I8B-MC-ITSB (b) Protocol

A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes PRONTO-Peds

NCT03740919

Approval Date: 30-Apr-2020

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PRONTO-Peds

2018-002371-18 (EUDRA CTA)

Confidential Information

LY900014

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Protocol Electronically Signed and Approved by Lilly on 26 October 2018.
Protocol amendment (a) electronically signed and approved by Lilly on date provided below

Approval Date: 30-Apr-2020 GMT

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1. Synopsis

Title of Study:
A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes: PRONTO-Peds

Rationale:
The aim of this study is to demonstrate that an ultra-rapid formulation of insulin lispro, LY900014, is noninferior to Humalog on glycemic control as measured by change from baseline to Week 26 in hemoglobin A1c (HbA1c) in pediatric patients with type 1 diabetes (T1D), when administered in a double-blind manner as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin.

Objectives/Endpoints:

Objectives	Endpoints
Primary Objective	
1. To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (NIM=0.4% for HbA1c) in patients 1 to <18 years of age with T1D when administered as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin as part of a multiple daily injection regimen for 26 weeks	1. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Gated Objective	
2. To test the hypothesis that LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal (LY900014+20) is noninferior to Humalog, administered as prandial insulin (0 to 2 minutes prior to the meal), on glycemic control (NIM=0.4% for HbA1c)	2. Change from baseline to Week 26 in HbA1c
3. To test the hypothesis that LY900014 is superior to Humalog in improving glycemic control (HbA1c) when administered as prandial insulin (0 to 2 minutes prior to the meal)	3. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
4. To compare LY900014, LY900014+20, and Humalog with respect to the incidence and rate of documented post-dose hypoglycemia	4. Rate (events/patient/year) and incidence (percentage of patients with events) of documented post-dose hypoglycemic events within 1 and 2 hours after the prandial dose from Weeks 0 through 26
5. To compare LY900014, LY900014+20, and Humalog with respect to the incidence and rate of documented hypoglycemia	5. Rate (events/patient/year) and incidence (percentage of patients with events) of documented hypoglycemic events from Weeks 0 through 26

6. To compare LY900014, LY900014+20, and Humalog on the rate of severe hypoglycemic events	6. Rate (events/patient/100 years) of severe hypoglycemic events from Weeks 0 through 26
7. To compare LY900014, LY900014+20, and Humalog with respect to total, basal, and prandial insulin dose	7. Change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios at Week 26
8. To compare LY900014, LY900014+20, and Humalog with respect to the proportion of patients achieving HbA1c targets	8. The proportion of patients with HbA1c<7% and <7.5% at Week 26
9. To compare LY900014, LY900014+20, and Humalog with respect to 7-point SMBG	9. Change from baseline to Week 26 in 7-point SMBG values

Abbreviations: HbA1c = hemoglobin A1c; NIM = noninferiority margin; SMBG = self-monitored blood glucose; T1D = type 1 diabetes.

Summary of Study Design:

Study I8B-MC-ITSB (ITSB) is a Phase 3, prospective, randomized, outpatient, multinational, multicenter, parallel, active-controlled study conducted in children and adolescent patients with T1D currently using a multiple-daily-injection (MDI) regimen.

Treatment Arms and Duration:

The study includes a 1-week screening with a 4-week lead-in period, followed by a 26-week treatment period and a 2-week safety follow-up period. In 2 of the treatment groups, LY900014 and Humalog will be administered immediately (0 to 2 minutes) prior to each meal in a double-blind manner. A third open-label treatment group consists of LY900014 administered up to 20 minutes after the start of a meal (LY900014+20).

Number of Patients:

Approximately 945 participants will be screened to achieve 708 randomized and 600 patients completing 26 weeks of treatment for an estimated total of 240 completers per blinded treatment group and 120 completers for the open-label treatment group.

Statistical Analysis:

The primary analysis is for the treatment period through Week 26.

Efficacy analyses will be conducted on all randomized patients according to the treatment the patients are assigned. The analyses for the primary and gated objectives will be performed for the efficacy estimand, including data collected prior to permanent discontinuation of investigational product (IP) and for the intention-to-treat (ITT) estimand, including all data collected regardless of IP use. The primary endpoint will also be analyzed using the Per-Protocol (PP) and Completer populations.

Safety analyses will be conducted on the Safety population. Analyses of adverse events (AEs) will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data collected prior to permanent discontinuation of IP. The second set of analyses will include

all data collected during the course of the entire study, including the follow-up visit, regardless of IP use. Analyses of hypoglycemia will use data collected prior to permanent discontinuation of IP, while analyses for post treatment may be performed as needed. Analyses of safety laboratory measurements will be performed on all data during the planned treatment period regardless of IP use.

Baseline is defined as the last non-missing measurement at or before the randomization visit (Visit 4), unless otherwise specified.

For the United States (US) Food and Drug Administration (FDA) submission (using the ITT estimand), the missing endpoints will be imputed by the copy reference approach. The reference for each treatment group is from the retrieved dropout patients who discontinue IP but have the measurement at the primary endpoint in the same treatment group. If there are only a limited number of patients in the reference group that leads to a failure in performing the proposed multiple imputation analysis such that the model cannot converge, or the number of records in the reference group is less than the number of records with missing data, the missing endpoints will be imputed by the patient-level observed baseline value plus a noise, assuming a washout of any potential treatment effect (or "return to baseline"). The noise follows a normal distribution, with the variability estimated from the "washout HbA1c data". The "washout HbA1c data" will be derived by subtracting the corresponding treatment mean at Week 26 from individual non-missing HbA1c values at Week 26. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog from an analysis of covariance (ANCOVA). The model for the change from baseline to the Week 26 HbA1c endpoint will include treatment and strata (pooled country, type of basal insulin, and age group) as fixed effects and baseline HbA1c as a covariate. The final estimates will be the combined estimates from at least 1000 imputations.

For non-FDA submissions and publications, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog at Week 26 (Visit 15) from the mixed-effect model repeated-measure (MMRM) analysis of change from baseline in HbA1c, including data collected from all randomized patients prior to permanent discontinuation of IP through Week 26 (efficacy estimand).

For both primary analysis approaches, LY900014 will be declared noninferior to Humalog if the upper limit of the 2-sided 95% confidence interval (CI) for the least-squares (LS) mean difference in the change from baseline in HbA1c for LY900014 minus Humalog is below +0.4%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

A restricted maximum likelihood-based MMRM analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (pooled country, type of basal insulin, and age group), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. For analyses of variables other than HbA1c,

the HbA1c stratum (≤8.0%, >8.0%) will be included in the model. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on LS means and Type III tests.

An ANCOVA will also be used to analyze continuous variables. The model for the change from baseline to the Week 26 HbA1c endpoint will include treatment and strata (pooled country, type of basal insulin, and age group) as fixed effects and baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data. For analyses of variables other than HbA1c, the HbA1c stratum (≤8.0%, >8.0%) will be included in the model.

Hypoglycemia rates will be summarized for periods of 30 days, 1 year, and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method (details will be described in statistical analysis plan [SAP]). For each of the other categories of hypoglycemia, the number of hypoglycemia events during a specific period after randomization (for example, Weeks 0 to 12 of treatment period) will be analyzed by using a negative binomial regression model. The model will include treatment and age group as covariates. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days (or 30 days) will be included in the model to estimate the rate of hypoglycemia per year (or per 30 days). The proportion of patients with at least 1 hypoglycemic event in each category during a specific period after randomization will be analyzed using a logistic regression model including treatment and age group as covariates.

Continuous safety variables, as well as the change from baseline for these variables, will be analyzed by MMRM or ANCOVA models. For categorical variables, Fisher's exact test or Pearson's chi-square test will be used to compare treatment groups, unless otherwise specified.

2. Schedule of Activities

Table ITSB.1. Schedule of Activities

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[b]
eCRF Visit Number	**1**	**2**	**3[c]**	**4**	**5[c]**	**6[c]**	**7**	**8[c]**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14[c]**	**15**	**801[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Informed Consent/Assent (if applicable)	X																
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Patient eligibility review	X	X															
Randomization				X													
Clinical Assessments																	
Demographic data[e]	X																
Medical history, preexisting conditions	X																
Previous diabetes therapy	X																
Record Personal CGM/FGM use (yes/no)				X													
Height[f]	X			X						X					X		X
Weight	X	X		X			X			X		X			X		X
Vital signs (sitting SBP, DBP, and HR)[g]	X	X		X			X			X		X			X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Focused physical exam (including skin evaluation)[h]	X	X		X			X			X		X			X		X
Basal insulin dose assessment[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Basal insulin dose titration[j]		X	X	X	X	X	X	X	X	X							

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[b]
eCRF Visit Number	**1**	**2**	**3[c]**	**4**	**5[c]**	**6[c]**	**7**	**8[c]**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14[c]**	**15**	**801[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Prandial insulin dose assessment		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Prandial insulin dose titration[i]				X	X	X	X	X	X	X							
Ancillary Supplies/Diaries/IP																	
Dispense blood glucose meter and ancillary supplies and complete training[k,l]		X		X			X			X		X					
Diabetes education and nutrition counseling[l]		X															
Dispense study diaries and complete training[l]		X		X			X			X		X					
Collect study diaries				X			X			X		X			X		X
Dispense IP		X		X			X			X		X					
Train on collecting 4- and 7-point SMBG profiles[m]		X															
Remind patient of 7-point SMBG requirements			X						X					X			
Review and discuss SMBG (and/or CGM/FGM) and hypoglycemia data from patient study diary				X			X			X		X			X		
Discuss SMBG (and/or CGM/FGM) and hypoglycemia data with patient			X		X	X		X	X		X		X	X			
Review/discuss only severe hypo data after completion of study treatment																X	

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[b]
eCRF Visit Number	**1**	**2**	**3[c]**	**4**	**5[c]**	**6[c]**	**7**	**8[c]**	**9[c]**	**10**	**11[c]**	**12**	**13[c]**	**14[c]**	**15**	**801[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Patient returns unused study drug or open-label Humalog supplies				X			X			X		X			X		X
Drug accountability log				X			X			X		X			X		X
Laboratory Assessments																	
Pregnancy test, serum/urine (applicable females only)[n]	X			X													
Urinalysis (screening)	X																
HbA1c	X			X			X			X					X		X
Clinical chemistry	X														X		X
Hematology	X														X		X
Antilispro antibodies	X			X			X			X					X		X

Abbreviations: DBP = diastolic blood pressure; eCRF = electronic case report form; ED = early discontinuation; HbA1c = hemoglobin A1c; HR = heart rate; IP = investigational product; IWRS = interactive web-response system; SBP = systolic blood pressure; SMBG = self-monitored blood glucose; WHO = World Health Organization.

a Patients who rescreen will start at Visit 1.·

b Randomized patients who decide to discontinue will be asked to return for the ED visit. If a patient discontinues during an office visit that visit may be treated as the ED visit. If a patient discontinues via telephone, they will be asked to return for the ED visit.

c Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.

d V801 will be a telephone visit; this visit can become an office visit.

e Medical history to include investigator review of immunization status with patient and caregiver.

f In order to obtain accurate measurements, length should be measured using an infantometer and height should be measured using a stadiometer (WHO Child Growth Standards).

g Blood pressure measurements should be determined correctly, using the appropriate-sized cuff for the child's age and with the child seated and relaxed.

h A qualified medical professional must perform a medical assessment at each site visit. During each office visit, the skin surrounding the injection sites should be assessed.

i Basal insulin dose assessment should be made during the lead-in period and as needed during the study.

j Basal insulin should be adjusted during the lead-in period so as to achieve or maintain BG targets with a focus on the prebreakfast BG. Prandial insulin should be titrated with an emphasis during the first 12 weeks after randomization in order to reach optimal dosing and achieve BG targets. Adjustment of basal and prandial insulin doses may continue throughout the 26-week treatment period in order to achieve or maintain glycemic targets based on changes in lifestyle, individual circumstances or for safety reasons.

k Glucose monitoring supplies will be dispensed at each office visit, as needed.

l Initial training at Visit 2 may include diabetes education and nutrition counseling. Appropriate site personnel will administer training and education using locally approved diabetes education/training materials or other materials provided by the sponsor. Patients may be provided abbreviated training and education at visits following Visit 2, as appropriate.

m Patients who wear personal CGM/FGM approved for dosing decisions may be trained to use their sensor data for 4-point BG values and record in diary or download the BGs for investigator review.

n Serum pregnancy test must be performed in female patients of childbearing potential (see inclusion criterion [9]) at Visit 1 followed by a urine pregnancy test within 24 hours prior to IP exposure at randomization (Visit 4) and at other times at the investigator's discretion. When required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period.

3. Introduction

3.1. Study Rationale

Young children with type 1 diabetes (T1D) are susceptible to glucose variability due to increased insulin sensitivity and unpredictable eating and physical activity. Often, their cognitive immaturity and inability to verbalize symptoms present a challenge for recognizing and treating hypoglycemia. It is well known that fear of hypoglycemia, particularly among parents of children with diabetes, impacts T1D management and quality of life. Children with T1D experience different insulin requirements due to increasing weight, height, and caloric needs, which poses challenges with glucose control and insulin therapy. The current rapid-acting insulin analogs are not as fast and as short-acting as needed to meet these challenges. A prandial insulin with faster onset and/or faster offset characteristics might reduce glycemic excursions and decrease the incidence of delayed postprandial hypoglycemia compared to currently available rapid-acting insulin analogs. LY900014 is an ultra-rapid-acting insulin lispro formulation with increased early absorption compared to Humalog®; Eli Lilly and Company. LY900014 aims to mimic the physiological prandial insulin secretion pattern, which may more effectively control postprandial glucose (PPG) excursions.

The aim of this study is to demonstrate that an ultra-rapid formulation of insulin lispro, LY900014, is noninferior to Humalog on glycemic control as measured by change from baseline to Week 26 in hemoglobin A1c (HbA1c) in pediatric patients with T1D, when administered in a double-blind manner as prandial insulin in combination with basal insulin.

3.2. Background

Regional evidence suggests that the incidence of T1D in youth is increasing in the United States (US; Lipman et al. 2013) and Europe (EURODIAB ACE Study Group 2000). Estimates of T1D prevalence in the pediatric population in the US come from the Centers for Disease Control and Prevention–sponsored SEARCH for Diabetes in Youth Study Group (SEARCH). The SEARCH study estimated that in 2011, the total number of youth in the US <20 years of age with T1D was 166,984 (Pettitt et al. 2014).

As with adults, intensive diabetes management through maintenance of tight glycemic control helps to delay onset and slow the progression of complications of the disease in youth (DCCT 1993). Tight glycemic control is achieved via intensive insulin therapy, which requires dietary discipline, frequent blood glucose (BG) 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 youth. Intensive insulin treatment in T1D should be initiated early in disease progression and the improved glycemic control may have a lasting impact on reducing the onset of diabetic complications.

There have been many advances in the treatment of T1D in the last 20 years; however, reaching and maintaining glycemic goals remain challenging even under intensive insulin therapy regimens. Only, approximately, 30% of insulin-requiring diabetes patients are able to reach the goal HbA1c target of <7% (Casagrande et al. 2013). Currently available rapid-acting insulin

analogs continue to be unable to match the kinetics of physiological postmeal insulin secretion. Thus, there remains a need to continue to develop formulations with a time-action profile that more closely approximates that of endogenous insulin secretion.

Ideally, currently available rapid-acting insulin analogs should be injected 10 to 15 minutes prior to meal consumption in order to optimally control PPG. However, many persons inject their rapid-acting insulin at the time of the meal or after the meal. This may be particularly true for children due to unpredictable eating patterns. According to survey data from the T1D Exchange on the timing of prandial insulin injection, 16.3% of patients indicated that they inject 15 minutes prior to meals, 33% inject 1 to 14 minutes prior to meals, 38.6% inject at the time of the meal, and 12.1% inject after the start of a meal. Because patients often inject later than recommended, there is a greater mismatch between insulin action and postprandial BG elevations. With postmeal dosing, the mismatch between the rise in BG and the onset of insulin action is even more pronounced. For the development of an ultra-rapid insulin, it will be important to understand the relationship between the time-action profile of the insulin, insulin injection timing, and meal timing in order to maximize improvements in postprandial glycemic control and minimize hypoglycemia risk. An insulin with higher early concentration and peak exposure along with a shorter duration should improve early postprandial control and limit postmeal hyperglycemia while reducing late postprandial hypoglycemia due to lower insulin exposure.

A new pharmaceutical innovation that may allow more effective control of PPG levels is LY900014, a new formulation of insulin lispro developed as an ultra-rapid-acting insulin with a faster onset of action and shorter duration of action compared to currently available rapid-acting insulin analogs. The changes in pharmacokinetic and pharmacodynamic (PK and PD) characteristics are achieved by coformulating insulin lispro with treprostinil and ingredients Generally Recognized as Safe by the Food and Drug Administration (FDA) as excipients. Treprostinil, as an excipient, enhances the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient that elicits a systemic effect. Treprostinil has been approved in the US since 2002 (Remodulin package insert, 2018) and in Europe since 2005 (PMR [WWW]). Sodium citrate, an excipient that speeds insulin absorption, is also included in the formulation to further enhance the absorption of insulin lispro. Furthermore, the excipient concentration in LY900014 is within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database.

Please refer to the Humalog local product labeling (for example, Humalog package insert, 2017; Humalog Summary of Product Characteristics, 2018) for more information regarding Humalog.

The Investigator's Brochure (IB) describes the clinical and nonclinical development of LY900014.

3.3. Benefit/Risk Assessment

The faster action profiles seen with rapid-acting insulins offer the potential to more safely and effectively simulate normal insulin profiles in patients with T1D with earlier and higher peaks and shorter duration of action. Yet, it is apparent that the absorption rates of currently available rapid-acting insulin analogs are still not fast enough to eliminate postmeal hyperglycemia and

attempts to correct this by increasing the dose often result in late postmeal hypoglycemia. An ultra-rapid insulin with a fast-in, fast-out profile will possibly reduce postprandial hyperglycemia and the frequency of hypoglycemia, easing the severe hypoglycemia anxiety for parents and patients, which often leads to under-dosing, overcorrecting, and overeating.

Heath Care Providers typically instruct patients to dose prandial insulin at the start of each meal, as it is assumed that this will provide the best postprandial glucose control under most conditions. However, patients with T1D and caregivers may administer insulin at different times relative to the start of a meal, depending on their experience and anticipated activities. In some cases, parents of young children may give the insulin dose after a child has eaten due to unpredictable dietary intake or low premeal BG to avoid potential hypoglycemia. It is often a balancing act, in which the risk of hypoglycemia (potentially severe in very young children) outweighs the risk of postmeal hyperglycemia in this population. Study ITSB will include an open-label treatment group to study dosing when given up to 20 minutes postmeal.

In Study ITSB, investigators and study sites will be experienced in the treatment of children, diabetes, and in the conduct of pediatric clinical trials. Frequent interaction with site staff will occur and allow for careful monitoring of BG values and hypoglycemic events. In order to minimize risk and discomfort for patients, the number of procedures (including blood draws) and office visits has been reduced to decrease time lost from work and school.

Across all doses in the Eli Lilly and Company (Lilly) clinical studies that have evaluated treprostinil as a local vasodilator with or without insulin lispro, there was no clinically significant increase in adverse events (AEs) associated with systemic absorption of treprostinil, as described in the Remodulin package insert (2018; that is, headache, diarrhea, nausea, jaw pain, vasodilatation, edema, and hypotension).

There are limited data on the use of treprostinil in pediatric patients. Pediatric assessments have not been required for treprostinil because of its orphan drug designation; thus, the safety and effectiveness of treprostinil in pediatric patients have not been established (Remodulin package insert, 2018; Tyvaso prescribing information, 2014; Orenitram prescribing information, 2016). Subcutaneous (SC) treprostinil has been evaluated in children with pulmonary artery hypertension (PAH) in an observational study (n=8). Six children had symptomatic and hemodynamic responses to the addition of SC treprostinil, with manageable control of local injection-site discomfort (Levy et al. 2011). A clinical study I8B-MC-ITSA (Study ITSA) is ongoing. The aim of Study ITSA is to evaluate PK, PD, safety, and tolerability of LY900014 in comparison with Humalog following a single subcutaneous (SC) dose administration immediately prior to a standardized liquid meal. Study ITSA is the first study to evaluate LY900014 in pediatric patients with T1D.

Preschool children often need proportionally larger bolus insulin doses, often constituting 60% to 80% of the total daily insulin dose (TDD; Sundberg et al. 2017). Study ITSB will allow a maximum TDD of 1.5 U/kg. Assuming a TDD of 1.2 U/kg and body weight of 80 kg, a total insulin bolus dose would be administered in 3 bolus insulin doses of 32U containing 320 ng of treprostinil. Following administration of 50 U of LY900014 by SC bolus injection in adult Phase

1b studies, treprostinil has been undetectable in the systemic circulation. In addition, there were no detectable treprostinil drug concentrations with continuous subcutaneous insulin infusion (CSII) therapy during the basal infusion or after the bolus dose samples from patients with T1D.

Thus, the expected treprostinil maximum drug concentration (C_{max}) following LY900014 administration would be below the assay quantitation limit of 0.010 ng/mL and would be approximately 200-fold lower than the average steady-state treprostinil levels in adult PAH patients treated with Remodulin. The exposures of treprostinil in LY900014 are expected to be substantially lower than those observed in the treatment of PAH.

Females of child-bearing potential can participate in this study if they test negative for pregnancy at study entry and agree to maintain sexual abstinence or use a highly effective method of contraception throughout the study. In a fertility and early embryonic development study in male and female rats, there were no adverse effects of treprostinil on sperm morphology, estrus cyclicity, mating, fertility, conception, implantation, and embryonic survival. Embryo-fetal development studies indicated that treprostinil was not teratogenic in rats or in rabbits. In a prenatal and postnatal development study in rats, there was no evidence of maternal toxicity or adverse effects on offspring growth, behavior, and reproductions.

More information about the known and expected benefits, risks, serious AEs (SAEs), and reasonably anticipated AEs of LY900014 can be found in the IB. More detailed information about the known and expected benefits and risks of Humalog may be found in the country-specific product labeling (for example, Patient Information Leaflet, Package Insert, or Summary of Product Characteristics).

4. Objectives and Endpoints

Table ITSB.2 shows the objectives and endpoints of the study.

Table ITSB.2. Objectives and Endpoints

Objectives and Endpoints

Objectives	Endpoints
Primary Objective	
1. To test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (NIM=0.4% for HbA1c) in patients 1 to <18 years of age with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal) in combination with basal insulin as part of a multiple daily injection regimen for 26 weeks	1. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Gated Objectives	
2. To test the hypothesis that LY900014 administered as postprandial insulin up to 20 minutes after the start of a meal (LY900014+20) is noninferior to Humalog, administered as prandial insulin (0 to 2 minutes prior to the meal), on glycemic control (NIM=0.4% for HbA1c)	2. Change from baseline to Week 26 in HbA1c
3. To test the hypothesis that LY900014 is superior to Humalog in improving glycemic control (HbA1c) when administered as prandial insulin (0 to 2 minutes prior to the meal)	3. Difference between LY900014 and Humalog in change from baseline to Week 26 in HbA1c
Other Secondary Objectives	
4. To compare LY900014, LY900014+20, and Humalog with respect to the incidence and rate of documented post-dose hypoglycemia	4. Rate (events/patient/year) and incidence (percentage of patients with events) of documented post-dose hypoglycemic events within 1 and 2 hours after the prandial dose from Weeks 0 through Week 26
5. To compare LY900014, LY900014+20, and Humalog with respect to the incidence and rate of documented hypoglycemia	5. Rate (events/patient/year) and incidence (percent of patients with events) of documented hypoglycemic events from Week 0 through Week 26
6. To compare LY900014, LY900014+20, and Humalog on the rate of severe hypoglycemic events	6. Rate (events/patient/100 years) of severe hypoglycemic events from Weeks 0 through 26
7. To compare LY900014, LY900014+20, and Humalog with respect to total, basal, and prandial insulin dose	7. Change from baseline in total, basal, and prandial insulin doses and prandial/total insulin dose ratios at Week 26
8. To compare LY900014, LY900014+20, and Humalog with respect to the proportion of patients achieving HbA1c targets	8. The proportion of patients with HbA1c <7% and <7.5% at Week 26
9. To compare LY900014, LY900014+20, and Humalog with respect to 7-point SMBG	9. Change from baseline to Week 26 in 7-point SMBG values
Tertiary/Exploratory Objectives	

10. To compare LY900014, LY900014+20, and Humalog with respect to changes in body weight	10. Change in weight (kg) from baseline to Week 26
11. To compare LY900014, LY900014+20, and Humalog with respect to glycemic variability	11. Within-day and between-day glycemic variability measured by the standard deviation and the coefficient of variation of 7-point SMBG profiles
12. To compare the incidence of treatment-emergent anti-insulin lispro antibodies for LY900014, LY900014+20, and Humalog	12. Incidence of treatment-emergent anti-insulin lispro antibodies

Abbreviations: HbA1c = hemoglobin A1c; NIM = noninferiority margin; SMBG = self-monitored blood glucose; T1D = type 1 diabetes.

5. Study Design

5.1. Overall Design

Study ITSB is a Phase 3, prospective, randomized, outpatient, multinational, multicenter, parallel, active-controlled study, conducted in children and adolescent patients with T1D currently using a multiple-daily-injection (MDI) regimen. In 2 of the treatment groups, LY900014 or Humalog will be administered immediately (0 to 2 minutes) prior to each meal in a double-blind manner. A third open-label treatment group consists of LY900014 administered up to 20 minutes after the start of a meal (LY900014+20). It is not possible to blind this treatment group as it uses a different injection timing. The study is designed to demonstrate noninferiority of LY900014 when compared with Humalog in change from baseline to Week 26 in HbA1c, when both are administered at the start of the meal. The study includes a 1-week screening with a 4-week lead-in period followed by a 26-week treatment period and a 2-week safety follow-up period.

The purpose of the lead-in period is to obtain blood glucose (BG) values along with basal and prandial insulin doses to assess basal and mealtime insulin dosing and to determine baseline hypoglycemia rates. Basal insulin should be titrated by the patient or caregiver during the lead-in period, in anticipation of increased activity or individual patient needs, so as to achieve or maintain glucose targets (Table ITSB.4) with an emphasis on the pre-breakfast BG. Investigators will have access to a patient's glucose values; so, they may assist patients and caregivers with appropriate basal adjustments. The lead-in will also allow patients and caregivers to become familiar with the patient study diary and the documentation required throughout the study. Patients treated with insulin glargine U-100 once a day (QD) or twice a day (BID), insulin detemir U-100 QD or BID or insulin degludec U-100 QD will be eligible for inclusion in the trial. At Visit 2, patients will continue their allowed study basal insulin regimen at the same dosing frequency (QD or BID). Patients should remain on the same basal insulin throughout the study; switching brands should be avoided when possible.

During the lead-in period, patients will be switched to open- label marketed insulin lispro (Humalog) using a unit for unit conversion or the dose may be determined based on the investigator's clinical judgement. Prandial insulin doses will be assessed at Visits 2 and 3. Adjustments to dose and dosing calculations may be necessary at randomization (Visit 4) to minimize the risk of hypoglycemia or hyperglycemia.

Diabetes education and nutrition counseling, including hypoglycemia recognition and management should be provided. Accuracy of carbohydrate counting should be assessed for those patients who dose mealtime insulin based on carb content. Appropriate site personnel will administer training and education as needed using locally approved diabetes education/training materials and programs or other materials that may be provided by the sponsor. Patients may be provided additional focused training and education at visits following Visit 2 based upon patient needs.

At Visit 4, patients will be randomized to either blinded LY900014 or Humalog to be given at mealtime (0 to 2 minutes prior to the meal) or open-label LY900014 given up to 20 minutes after

the start of the meal. Prandial insulin should be titrated with an emphasis during the first 12 weeks in order to reach optimal dosing and achieve glucose targets (Table ITSB.4). Adjustment of basal and prandial insulin doses may continue throughout the treatment period in order to achieve or maintain glycemic targets based on changes in lifestyle, individual circumstances or for safety reasons.

After completion of study treatment (Visit 15 or early discontinuation [ED]), it is recommended that patients return to their pre-study prandial insulin; however, the choice of insulin therapy should be made by the investigator in consultation with the patient or caregiver.

Study governance considerations are described in detail in Appendix 3. Figure ITSB.1 illustrates the study design.

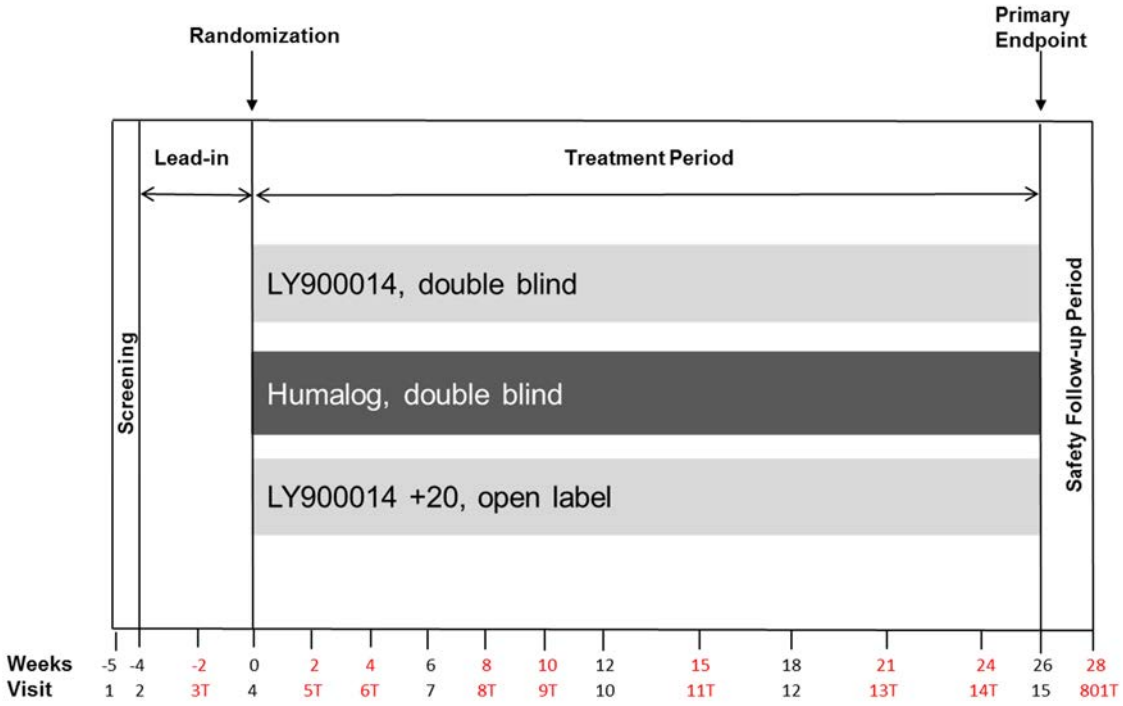

Figure ITSB.1. Illustration of study design for Clinical Protocol I8B-MC-ITSB.

5.2. Number of Participants

Approximately 945 participants will be screened to achieve 708 randomized and 600 patients completing 26 weeks of treatment for an estimated total of 240 completers per blinded treatment group and 120 completers in the open-label treatment group.

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, Table ITSB.1) for the last patient.

5.4. Scientific Rationale for Study Design

Study ITSB is a Phase 3 study designed to evaluate LY900014 compared to Humalog in combination with basal insulin in children and adolescent patients with T1D. The trial has 3 treatment groups, 2 of which are double-blind to allow comparison of LY900014 and Humalog when injected at the start of the meal. The third treatment group is open-label due to inability to blind postprandial injection timing of LY900014 (up to 20 minutes after the start of a meal) and will evaluate the efficacy and safety of postprandial dosing. The recommended time of administration of currently marketed rapid-acting insulins is before meals, but patients often inject later than recommended. The study is designed to compare a decrease in HbA1c as the primary endpoint. The HbA1c is a measure of glycemic control accepted by health care providers and regulatory authorities as a validated measure of BG control over time and is a marker for development and progression of diabetes complications. A 4-week lead-in period will provide the time needed for patients taking insulin aspart or insulin glulisine, or biosimilar insulin lispro at screening to switch to marketed insulin lispro (Humalog) with an emphasis on basal insulin adjustment and optimization. While basal insulin may continue to be adjusted to achieve FBG targets during the 26-week treatment period, prandial insulin should be titrated with an emphasis on achieving optimal dosing during the first 12 weeks so the primary endpoint HbA1c reflects glucose control during the 3-month time period when there are minimal changes. Adjustment of basal and prandial insulin doses may continue throughout the treatment period in order to achieve or maintain glycemic targets or for safety reasons.

5.5. Justification for Dose

LY900014 will have the same insulin lispro concentration (100 U/mL) as that of commercially available Humalog. The addition of treprostinil to the insulin lispro formulation does not modify the physical, chemical, or biological integrity of insulin lispro. The dosage of basal and prandial insulins used in this study should be determined based on the individual needs of each patient.

6. Study Population

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

6.1. Inclusion Criteria

Patients are eligible to be included in the study, only if they meet all the following criteria **at screening:**

Type of Patient and Disease Characteristics

[1] Male or female patients with T1D for at least 6 months and diagnosed by an endocrinologist (pediatric or adult), diabetes specialist, or a physician with expertise in treating pediatric patients with Type 1 diabetes.

Patient Characteristics

[2] Are at least 1 to <18 years of age.

[3] Are ≥16 lbs. (7.3 kg).

[4] Have been treated with only one of the following rapid-acting insulin analogs as part of an MDI regimen for at least the last 90 days:

a. insulin lispro U-100, or

b. insulin aspart

c. insulin glulisine or

d. Fast acting insulin aspart (must be approved for use in children in accordance with the local product label)

[5] Have been treated with only 1 of the following basal insulins for at least the last 90 days:

a. insulin glargine U-100 (QD or BID), or

b. insulin detemir U-100 (QD or BID), or

c. insulin degludec U-100 (QD)

[6] Use a total daily dose of insulin 0.3 to ≤1.9 U/kg.

a. TDD can be the average of previous 3 to 7 days

[7] Have a HbA1c value ≤9.9% according to the central laboratory.

[8] Male patients:

a. no male contraception required, except in compliance with specific local government regulations

[9] Female patients of childbearing potential:

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

b. if sexually active, must agree to use 1 highly effective form of contraception for the entirety of the study (Appendix 6)

c. not pregnant or intending to become pregnant

i. post pubertal females of childbearing potential must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure to investigational product (IP) at Visit 4

d. not breastfeeding

Other Study Requirements for Patient or Caregiver

[10] Has refrigeration in the home or has access to refrigeration for storage of insulin.

[11] Are capable and willing (as determined by the investigator) to do the following:

a. inject insulin with the use of an insulin pen injection device according to written instructions

b. perform fingerstick SMBG as required by the study schedule using the study glucose meter provided

EXCEPTION: patients using personal continuous glucose monitoring (CGM) or flash glucose monitoring (FGM) devices that are consistent with local country regulations and approved for use for insulin dosing decisions may use them for 4-point glucose testing during the study (see Section 9.1.5.2).

c. record all information in study diary as required by this protocol

d. follow instructions for basal insulin adjustment and individualized prandial insulin dosing using fixed-pattern adjustment or carbohydrate counting, as provided by the investigator

e. comply with the use of study insulin and scheduled visits

Informed Consent

[12] The child/adolescent and/or a parent or legal guardian are able to understand and willingly participate fully in the activities of the clinical trial and sign their age and developmentally appropriate assent and consent, as required per local guidelines.

6.2. Exclusion Criteria

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

Medical Conditions

[13] Have current hypoglycemic unawareness in the investigator's opinion or have had more than 1 episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia, indicated by coma or convulsion and/or use of intravenous glucose or glucagon) within 6 months prior to screening (Visit 1).

[14] Have had more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycemia or diabetic ketoacidosis) within 6 months prior to screening (Visit 1).

[15] Have any other clinically significant disorder or uncontrolled concomitant disease that, in the investigator's opinion, would preclude participation in the trial or pose a safety risk.

[16] Renal:

a. history of renal transplantation,

b. currently receiving dialysis, or

c. have a history of renal impairment (exclusion only if glomerular filtration rate [estimated GFR] <60 mL/minute/1.73 m^2 as defined by the central laboratory.

[17] Have obvious clinical signs or symptoms of liver disease in the opinion of the investigator (for example, acute or chronic hepatitis or cirrhosis) or elevated liver enzyme measurements as indicated below at screening:

a. total bilirubin ≥2× the upper limit of normal (ULN) (with the exception of Gilbert's disease) as defined by the central laboratory, or

b. alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase ≥3×ULN as defined by the central laboratory, or

c. aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase ≥3×ULN as defined by the central laboratory

[18] Active or untreated malignancy or in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years.

[19] Known hypersensitivity or allergy to any of the study insulins or their excipients.

[20] Blood transfusion or severe blood loss within 3 months prior to Visit 1 or have known hemoglobinopathy, anemia, hemolytic anemia, sickle cell anemia, or any other traits of hemoglobin abnormalities known to interfere with the HbA1c measurement.

[21] Have history of inpatient psychiatric treatment; emotional, behavioral, or other untreated conditions that, in the opinion of the investigator, would interfere with proper participation in routine diabetes control and management in the last 6 months.

[22] Have significant lipohypertrophy.

[23] Retinopathy and maculopathy: have preproliferative and proliferative retinopathy, or maculopathy requiring treatment or not clinically stable in the last 6 months, or patients with active changes in subjective eye symptoms as determined by the investigator if an eye exam has not been performed in the last 6 months.

Note: Patients with a history of preproliferative retinopathy, proliferative retinopathy, or maculopathy that remains stable at least 6 months after photocoagulation, and who are enrolled based on investigator or subinvestigator's judgment should continue to attend appropriate periodical eye examinations with an ophthalmologist. If an eye examination has been performed no more than 6 months before screening, it will not have to be repeated; however, the investigator will need to confirm via interview that there is no change in subjective symptoms.

Prior/Concomitant Therapy

[24] Receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, and inhaled preparations) or have received such therapy within the last 90 days.

[25] Have been on a treatment regimen that includes regular human insulin, neutral protamine Hagedorn (NPH), Afrezza® (insulin human) inhalation powder, any premixed insulins or use of diluted insulins within the last 90 days.

[26] Receiving any oral or injectable medication intended for the treatment of diabetes mellitus other than insulins within the last 90 days.

[27] Have been treated by CSII regimen for ≥14 days within the last 90 days.

Prior/Concurrent Clinical Trial Experience

[28] Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged by the investigator to not to be scientifically or medically compatible with this study.

[29] Have participated, within the last 30 days, in a clinical study involving an IP, except for Study I8B-MC-ITSA (ITSA). Patients may be considered for screening in this trial immediately upon ED or completion of Study ITSA (Parts A and B). No additional waiting period is necessary between participation in ITSA and ITSB.

Other Exclusions

[30] The patient or caregiver are investigator site personnel directly affiliated with this study or a member of their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

[31] The patient or caregiver is an immediate family member of Lilly employees (including employees, temporary contract workers, or designees responsible for the conduct of the study). Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.

6.2.1. Rationale for Exclusion of Certain Study Candidates

The use of LY900014 in pediatric patients is anticipated; thus, this study will specifically examine the safety and efficacy in a pediatric population. Criterion [1] and Criterion [2] define the population needed for the purposes of this study. Therefore, patients not meeting these criteria are excluded.

6.3. Lifestyle Restrictions

Not applicable.

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) or were required to unexpectedly discontinue from the study during screening or lead-in period (e.g., due to enrollment pause related to the COVID-19 public health emergency) are allowed 1 rescreening.

All patients that rescreen will restart at Visit 1 and complete all screening procedures.

7. Treatments

7.1. Treatments Administered

This study involves a comparison of LY900014 and Humalog administered subcutaneously 0 to 2 minutes prior to the start of the meal for 26 weeks. In a third open-label treatment group, LY900014 will be administered up to 20 minutes after the start of a meal (LY900014+20) for 26 weeks.

Table ITSB.3 shows the treatment regimens.

Table ITSB.3. Treatment Regimens

Regimen	Dose Strength	Dose Administration	Route of Administration	Timing of Administration
LY900014	100 U/mL	Individualized dosing	Subcutaneous	0 to 2 minutes before start of the meal
Humalog	100 U/mL	Individualized dosing	Subcutaneous	0 to 2 minutes before start of the meal
LY900014+20	100 U/mL	Individualized dosing	Subcutaneous	Up to 20 minutes after the start of the meal

The investigator or his/her designee is responsible for

- explaining the correct use of the IP to the patient
  - including the importance of injection site rotation for both basal and prandial insulin
- explaining study diary requirements for recording insulin doses and injection times to the patient
- verifying that all study instructions are followed properly
- maintaining accurate records of IP dispensing and collection
- confirming that the patient returns all unused IP to the site

7.1.1. Packaging and Labeling

Clinical trial materials will be labeled as IP as appropriate and according to the country's regulatory requirements. Study insulins (LY900014 and Humalog) will be supplied by Lilly or its representative, in accordance with current good manufacturing practices, and will be supplied with clinical trial lot numbers. Instruction for Use for the prefilled pen devices will be provided.

The blinded prefilled pens will contain a concentration of 100 U/mL in 3-mL cartridges of either LY900014 or Humalog. The open-label prefilled pens will contain a concentration of 100 U/mL in 3-mL cartridges of LY900014.

During the lead-in period, marketed 100 U/mL insulin lispro (Humalog) will be provided using open-label prefilled pens.

7.1.2. Medical Devices

The medical devices provided for use in the study are disposable, prefilled insulin pens. Patients, caregivers and investigators will receive blinded pens in the blinded treatment arms and unblinded pens in the open label treatment arm. LY900014 prefilled pens are new investigational combination products. The prefilled pen allows for dosing in half-unit increments and can dose between 0.5 and 30 units per injection.

This study will also provide patients with FDA approved BG meters. The BG meter used in this study will be a meter that has received clearance from the FDA and meets the ISO 15197:2013 standard for blood glucose meters.

7.2. Method of Treatment Assignment

Patients who meet all criteria for enrollment will be randomized to double-blind treatment or open label treatment at Visit 4. Assignment to treatment groups will be determined by a computer-generated random sequence using an interactive web-response system (IWRS). Patients will be randomized to double-blind LY900014, double-blind Humalog, or open-label LY900014+20 in a 2:2:1 ratio. Stratification will be by country, HbA1c stratum (≤8.0%, >8.0%) based on HbA1c measured at Visit 1, type of basal insulin at randomization (insulin glargine, detemir, or degludec), and age group (1 to <12, 12 to <18 years).

The IWRS will be used to assign all IP (blinded and open-label) during the study. Site personnel will confirm that they have located the correct prefilled pens by entering a confirmation number found on the prefilled pen carton into the IWRS.

7.2.1. Selection and Timing of Doses

7.2.1.1. Target Glucose Values for Titration of Insulin Therapy

The overall glycemic control goals for all patients enrolled in the study are similar to those recommended by the International Society for Pediatric and Adolescent Diabetes (DiMeglio et al. 2018). The glucose target values shown in Table ITSB.4 are suggested guidelines that are required in order to achieve an HbA1c goal of <7.0% (53 mmol/mol) and may be used to determine insulin dose titration. Targets may be individualized, aiming for the lowest achievable HbA1c without undue exposure to severe hypoglycemia. A higher HbA1c goal (in most cases < 7.5% (58 mmol/mol) may be appropriate in younger children who are unable to articulate symptoms of hypoglycemia.

Table ITSB.4. Glucose Target Values

	Target Range
Before meals	70 - 130 mg/dL (4.0-7.0 mmol/L)
Postprandial (1 hr)	90 to 180 mg/dL (5.0 to 10.0 mmol/L)
Bedtime	80-140 mg/dL (4.4-7.8 mmol/L)
HbA1c	<7.0% (53 mmol/mol)

Abbreviations: HbA1c = hemoglobin A1c; w/out = without.

Source: DiMeglio et al. 2018

7.2.1.2. Timing of Doses

Marketed insulin lispro (Humalog) will be dispensed to all patients for use throughout the lead-in period. At randomization (Visit 4), patients study treatment (LY900014 or Humalog) starting dose may be initiated unit for unit however, investigators may consider reducing the prandial or correction doses based on patient's overall glycemic status or other considerations known to investigator in order to reduce risk of postprandial hypoglycemia. In the blinded treatment groups, LY900014 and Humalog will be administered immediately prior to each meal (0 - 2 minutes). The LY900014+20 open label treatment group will administer the dose up to 20 minutes after the start of a meal.

Patients will administer IP within the time instructed by the investigator as determined by treatment randomization (blinded LY900014 or blinded Humalog; 0-2 minutes before or open-label LY900014; up to 20 minutes after the start of the meal). An occasional change in the timing of injection may be warranted due to individual circumstances and will not be considered a protocol violation unless deemed by the investigator to be excessive and noncompliant to study procedures.

The patient's basal insulin during the study can be dosed at any time and should be taken at approximately the same time each day. Patients should use the same basal insulin regimen (type and dosing frequency) throughout the study. Patients will record all insulin doses in the study diary as instructed.

Patients will be required to collect glucose values at least 4 times (before meals and bedtime) each day using the BG meter provided or a personal CGM/FGM that is approved for non-adjunctive use; i.e. results may be used to make insulin dosing decisions per their local country regulations (Section 9.1.5). The investigator will review glucose values at office and telephone visits in order to determine any insulin dose adjustments. Once BG targets are achieved and basal and prandial dose titration has been optimized, daily 4-point glucose testing frequency and timing may be adjusted at the investigator's discretion in consultation with patient and caregiver. Effort should be made to reach the BG target recommendations provided (Table ITSB.4).

7.2.1.2.1. Basal Insulin Adjustment

Basal insulin should be adjusted during the lead-in period by the patient or caregiver in anticipation of increased activity, individual patient needs or to facilitate optimal prandial insulin dosing to achieve or maintain glucose targets with an emphasis on the pre-breakfast BG. Adjustment of basal insulin doses may continue throughout the study treatment period in order to achieve or maintain glycemic targets and for safety reasons. The prescribed basal insulin dose is determined by, and the responsibility of, the investigator in consultation with the patient or caregiver. Additional discussion between visits may be required to enable the patient to reach glycemic targets and will be determined by the investigator.

7.2.1.2.2. Prandial Insulin Adjustment

Prandial insulin should be titrated during the treatment period in order to reach optimal dosing and achieve glucose targets. Reasonable efforts should be made to achieve these targets during the first 12 weeks, however prandial insulin dose adjustments may continue throughout the treatment period in order to achieve or maintain glycemic targets or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. The prescribed prandial insulin dose is determined by, and the responsibility of, the investigator in consultation with the patient or caregiver. Modifications in the calculation of the insulin dose may be influenced by other clinical circumstances and safety considerations known to the investigator.

Additional postprandial glucose monitoring may be considered during the days following transition to study insulin at the discretion of the investigator. Patients may use their usual correction factor (CF) or insulin sensitivity factor (ISF) to determine dose needed to correct a high BG to their target level. This may be in addition to their meal-related dose. Investigators should instruct patients and caregivers of the potential for hypoglycemia if prandial insulin is given too frequently to a previous IP injection (insulin stacking).

Patients may determine their prandial IP dose by pattern adjustment or carbohydrate counting, but they should maintain the same dosing method throughout the study.

- Pattern adjustment: The patient is prescribed a fixed dose or dose range of insulin for each meal. The fixed insulin dose may be individualized for each meal.
- Carbohydrate counting: The patient performs carbohydrate counting for prandial insulin dosing; prandial insulin dose is based upon the estimated carbohydrate content of the meal (as unit of insulin per grams carbohydrate).

Based on the patient's individual needs and glucose values, the insulin to carbohydrate ratio and CF should be assessed and adjusted as often as needed in order to meet the target glucose values described in Table ITSB.4. Postprandial SMBG values from 7-point SMBG profiles should also be evaluated for optimization of prandial insulin dosing.

For patients who are using pattern adjustment, the prandial insulin dose should be assessed and adjusted as often as needed in order to achieve glucose targets.

Patients should attempt to eat 3 meals (morning, mid-day, and evening) with at least 3 doses of meal-related IP every day. Patients may also eat a snack and inject insulin to cover the carbohydrates eaten if that is their usual practice. Patients will administer IP to correct high BG using their usual method for determining a correction dose. Adjustments in insulin dosage should also take into account individual lifestyle changes (such as exercise, illness, or stressful events) that may affect the insulin dose needed.

7.3. Blinding

This is a double-blind study; both treatment arms, LY900014 and Humalog, will be administered immediately prior to each meal in a double-blind manner. Investigators, patients, and study site personnel will be blinded to assigned insulin regimen throughout the study. A third open-label treatment group consists of LY900014 administered up to 20 minutes after the start of a meal (LY900014+20). To preserve the blinding of the study, the Lilly study team will remain blinded throughout the study; only a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

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-labeling system. This option may be used ONLY if the patient's well-being requires knowledge of the patient's treatment assignment. 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 patient safety must always be the first consideration in making such a determination. If a patient's treatment assignment is unblinded, Lilly must be notified immediately. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale in the patient notes and notify Lilly as soon as possible.

7.4. Dosage Modification

See Section 7.2.1.

7.5. Preparation/Handling/Storage/Accountability

The investigator or his/her designee is responsible for confirming appropriate temperature conditions have been maintained during transit for all study treatments received and that any discrepancies are reported and resolved before use of the study treatment.

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

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

In-use insulins should be maintained at room temperature and refrigerated material should be warmed to near room temperature before injecting. In-use insulin must not be used after 28 days.

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

7.6. Treatment Compliance

The investigator or designee will assess patient compliance at each visit, based on a review of the patient's glycemic control using available glucose values and HbA1c results, adherence to the visit and treatment schedule, and completion of the study diary. Patients who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Patients who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from IP or from the study. No specific study data will be collected for analysis of treatment compliance.

7.7. Concomitant Therapy

All concomitant therapies that are part of routine care are allowed and can be used during the study. Those listed in the exclusion criteria cannot be used. The subject should be encouraged to report any new concomitant medications after initiating the medication. Please check with the study team if you have any concerns or questions about a medication the subject is taking. Prohibited and restricted concomitant medications are listed below.

The following concomitant medications are NOT allowed at any time during the study

- Insulin glargine U-300, insulin degludec U-200,
- Afrezza® (inhaled insulin)
- premixed human or analog insulin
- Any noninsulin diabetes treatment therapy

The following concomitant medications ARE allowed for up to a total of 14 days during the study

- Regular human insulin, NPH or a nonstudy rapid analog insulin
- Systemic glucocorticosteroid
    - Including; intravenous, intramuscular, SC, or oral

7.8. Treatment after the End of the Study

LY900014 will not be made available to patients after conclusion of the study. Rapid-acting insulin analogs are available in all countries for use as prandial insulin.

After discontinuation of IP at the end of the treatment period or earlier, it is recommended that patients return to their pre-study basal and prandial insulin; however, the choice of insulin therapy should be made by the investigator in consultation with the patient or caregiver.

Investigators should provide patients with appropriate guidance for glucose monitoring and insulin dose adjustment throughout the follow-up period in order to maintain glycemic control.

8. Discontinuation Criteria

8.1. Discontinuation from Study Treatment

In the event that a patient is discontinued from the study treatment, the investigator should encourage the patient to remain in the study for continued safety monitoring. If the patient decides to continue in the study without IP, no early termination procedures will be completed. Patients will continue study visits through the safety follow-up.

Lilly recognizes the importance of complete data collection. This study includes elements to minimize missing data. Randomized patients who are discontinued from IP before study completion are encouraged to remain in the study for continued monitoring. For patients who remain in the study after early discontinuation of IP, both efficacy (including HbA1c) and safety data will be collected at scheduled visits. The difference between stopping IP and discontinuing the study will be explained to patients as part of the informed consent, and patients will be encouraged to continue in the study even if they stop study drug. In addition, study site investigators will be trained on the importance of complete data collection, with additional re-education of sites and patients as necessary.

8.1.1. Permanent Discontinuation from Study Treatment

Possible reasons leading to permanent discontinuation of IP are:

- **Subject Decision**
  - The patient/or the patient's designee, for example, parents or legal guardian requests to discontinue IP.
- The investigator may decide that the patient should stop IP. If this decision is made because of an AE, SAE, or a clinically significant laboratory value, the study drug is discontinued for that patient and appropriate measures are to be taken. Lilly or its designee is to be alerted.
- The patient becomes pregnant.
- An investigator, study site personnel performing assessments, or patient is unblinded, the patient must discontinue IP.
- The patient, for any reason, requires treatment with another therapeutic regimen or therapeutic agent that has been demonstrated to be effective for treatment of the study indication with the exception of those described in Section 7.7. Discontinuation from IP should occur prior to introduction of the new agent.
- Frequent use of prohibited concomitant medication, see Section 7.7.
- Patient has not taken IP for more than 14 consecutive days.
- Patient discontinuation is recommended by the DMC.
- **Discontinuation due to a hepatic event or liver test abnormality.** Patients who are discontinued from the IP due to a hepatic event or liver test abnormality should have additional hepatic safety data collected via case report form (CRF).

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

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

8.1.2. Temporary Discontinuation from Study Treatment

Patients who temporarily discontinue the IP may have used non-study insulins. The patient will be allowed to resume IP if they have not taken IP for up to a total of 14 days on up to two occasions.

8.1.3. Discontinuation of Inadvertently Enrolled Patients

If the sponsor or investigator identifies a patient who did not meet enrollment criteria and was inadvertently enrolled, then the patient should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the patient to continue on study treatment. If the investigator and the sponsor clinical research physician (CRP) agree that it is medically appropriate to continue, the investigator must obtain documented approval from the sponsor CRP to allow the inadvertently enrolled patient to continue in the study with or without treatment with IP. Safety follow-up is as outlined in Section 2 (Schedule of Activities Table ITSB.1), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of the protocol.

8.2. Discontinuation from the Study

Patients will be discontinued in the following circumstances:

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

- investigator decision
  - the investigator decides that the patient should be discontinued from the study
  - if the patient, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent
- patient decision
  - the patient or the patient's designee, for example, parents or legal guardian requests to be withdrawn from the study

Patients discontinuing from the study prematurely for any reason should complete ED and other safety follow-up per Section 2 (Schedule of Activities Table ITSB.1.), Section 9.2 (Adverse Events), and Section 9.4 (Safety) of this protocol.

8.3. Lost to Follow-Up

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

9. Study Assessments and Procedures

Section 2 lists the Schedule of Activities in Table ITSB.1.

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 the 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 and Safety Assessments

9.1.1. Primary Efficacy Assessments

The primary efficacy measure is the change from baseline to Week 26 in HbA1c.

9.1.2. Secondary Efficacy Assessments

The following secondary efficacy measures will be collected at the times shown in the Schedule of Activities (Section 2, Table ITSB.1).

- Prandial, basal, and total insulin doses (units and units/kg) and prandial/total insulin ratio
- Proportion of patients with HbA1c<7.0% and <7.5%
- SMBG 7-point profiles (fasting, 1-hour post morning meal, pre midday meal, 1-hour post midday meal, pre evening meal, 1 hour post evening meal, and bedtime)
    - 1-hour PPG excursions
    - within- and between-day glucose variability measured by the coefficient of variation and standard deviation (SD).

9.1.3. Safety Assessments

- Rate and incidence of hypoglycemia:
    - documented post-dose
    - documented
    - severe
- Adverse events
- Laboratory value assessments
- Weight.

9.1.4. Appropriateness of Assessments

All efficacy and safety assessments included in this study are generally regarded as reliable and accurate with respect to diabetes mellitus.

9.1.5. Study Procedures

During this study, the patient or caregiver will be responsible for the following:

Every day

- Answering study diary questions for all hypoglycemia events
- Obtaining glucose value before meals and at bedtime

At least 3 days before all visits (telephone and office)

- Recording daily basal dose, including date
- Recording prandial doses, including date and time

At least 3 days during the 2 weeks before Visits 4, 10, and 15

- Collecting 3 separate 7-point SMBG profiles using the study provided meter and recording in study diary

9.1.5.1. Self-Monitored Blood Glucose

A study BG meter will be provided to all patients who meet screening criteria and should be used to obtain all 7-point SMBG values throughout the study. Patients will be required to collect glucose values at least 4 times (before meals and bedtime) each day using the BG meter provided or a personal CGM/FGM that is approved for non-adjunctive use, (i.e. results may be used to make insulin dosing decisions) per their local country regulations (Section 9.1.5.2).

Patients who do not wear a personal CGM/FGM will use the study provided BG meter;

- to perform all 4-point and 7-point glucose values,
- to record glucose values in their study diary, and
- to perform the glucose assessment for hypoglycemia events.

These glucose values are used by the investigator for dose titration as well as to assess patient safety during the study. Once BG targets are achieved and basal and prandial dose titration has been optimized, daily 4-point glucose testing frequency and timing may be adjusted at the investigator's discretion (in consultation with patient and caregiver) to allow for individual patient needs and lifestyle changes. Missing values in SMBG profiles will not be considered protocol deviations unless, in the opinion of the investigator, they are excessive and reflect noncompliance with the protocol. Patients should be encouraged to eat 3 meals on the days that the 7-point SMBG is monitored.

Patients should perform SMBG with the study provided BG meter whenever hypoglycemia is experienced or suspected (with or without symptoms), when there is perceived increased risk as related to changes in dietary intake, physical activity, or inadvertent or atypical insulin dosing. Patients who wear personal CGM/FGM should use the study provided BG meter to confirm hypoglycemia symptoms or a CGM value ≤ 70mg/dL (3.9 mmol/L).

Collection Schedule for Glucose Values

Glucose Value	How Many	When	
4-point (SMBG or CGM/FGM)	Daily	Daily	
7-point (SMBG)	9 total	3× during the 2 weeks prior to Visits 4, 10, and 15.	
		Glucose Values	
Timing		4-Point (SMBG or CGM/FGM)	7-Point (SMBG)
Fasting (pre morning meal)		X	X
1 Hour post morning meal			X
Pre midday meal		X	X
1 Hour post midday meal			X
Pre evening meal		X	X
1 Hour post evening meal			X
Bedtime		X	X

9.1.5.2. Use of Personal CGM or FGM

Patients will be allowed to use their personal CGM or FGM. Patients who choose to wear their personal CGM/FGM device should make every attempt to wear it throughout the entire study. Personal CGM/FGM use (yes/no) will be recorded at Visit 4.

Patients who wear a personal CGM/FGM:

- will collect 4-point glucose values using study provided BG meter OR from the personal CGM device if approved for non-adjunctive use. BG values from a personal device are to be entered into the study diary OR investigators have the discretion to download glucose data from a personal CGM/FGM device as per usual practice
- should perform 7-point glucose values by fingerstick using study-provided BG meter, and
- should use the study-provided BG meter to confirm hypoglycemia symptoms or a CGM value ≤ 70mg/dL (3.9 mmol/L).

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 healthcare option, AEs that are serious or otherwise medically important, considered related to the IP or the study, or that caused the patient to discontinue the IP before completing the study. The patient should be followed until the event resolves, stabilizes with appropriate diagnostic evaluation, or is

reasonably explained. The frequency of follow-up evaluations of the AE is left to the discretion of the investigator.

Lack of drug effect is not an AE in clinical studies, because the purpose of the clinical study is to establish treatment effect.

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. In addition, site personnel will record any change in the condition(s) and any new conditions as AEs. Investigators should record their assessment of the potential relatedness of each AE to protocol procedure and/or IP, via electronic data entry.

The investigator will interpret and document whether or not an AE has a reasonable possibility of being related to study treatment, study device, or a study procedure, taking into account the disease, concomitant treatment, or pathologies.

A "reasonable possibility" means that there is a cause-and-effect relationship between the IP, study device and/or study procedure, and the AE.

The investigator answers yes/no when making this assessment.

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

If a patient's IP is discontinued as a result of an AE, study site personnel must report this to Lilly or its designee via electronic data entry, clarifying, if possible, the circumstances leading to any dosage modifications or discontinuations of treatment.

9.2.1. Serious Adverse Events

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

- death
- initial or prolonged inpatient hospitalization
- a life-threatening experience (that is, immediate risk of dying)
- persistent or significant disability/incapacity
- congenital anomaly/birth defect
- important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

- when a condition related to the prefilled pen 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
- severe hypoglycemia events: episodes of severe hypoglycemia as determined by the investigator according to the definition provided in Sections 9.4.1 and 9.4.2 must be reported as SAEs.

All AEs occurring after signing the ICF are recorded in the CRF and assessed for serious criteria. The SAE reporting to the sponsor begins after the patient has signed the ICF and has received IP. However, if an SAE occurs after signing the ICF, but prior to receiving an IP, the SAE should only be reported to the sponsor as per SAE reporting requirements and timelines if it is considered reasonably possibly related to study procedure.

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

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

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

9.2.1.1. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are serious events that are not listed in the IB and that the investigator identifies as related to IP or procedure. United States 21 CFR 312.32, European Union Clinical Trial Directive 2001/20/EC, and the associated detailed guidances or national regulatory requirements in participating countries require the reporting of SUSARs. Lilly has procedures that will be followed for the identification, recording, and expedited reporting of SUSARs that are consistent with global regulations and the associated detailed guidances.

9.2.2. Complaint Handling

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

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

- Complaints must be reported by site staff within 24 hours of notification to the clinical site/study personnel or within 24 hours of study/site personnel becoming aware of a product issue, regardless of the availability of the complaint sample.
- Retain the IP under appropriate storage conditions, if available or when obtained, until instructed to return it to Lilly.
- Product complaints for non-Lilly products (including concomitant drugs) that do not have a Lilly Product Batch or Control number are reported directly to the manufacturer per product label.
- Follow the instructions outlined in the Product Complaint Form for other reporting requirements.

9.3. Treatment of Overdose

Excess insulin administration may result in hypoglycemia. Refer to the IB for LY900014 and product label for Humalog.

9.4. Safety

9.4.1. Hypoglycemia

Patients are encouraged to perform SMBG whenever hypoglycemia may be suspected, either by symptoms experienced or perceived increased risk as related to dietary intake, physical activity, or inadvertent or atypical insulin dosing. All patients will be instructed to treat a BG level ≤70 mg/dL (3.9 mmol/L) as hypoglycemia.

If a hypoglycemia event is suspected, patients should measure the BG value using the study provided meter and record the BG value in the diary, any associated symptoms, and the treatment administered in the study diary. The patient should contact the site as necessary. All hypoglycemia events (severe and non-severe) must be reported on the hypoglycemia electronic case report form (eCRF); see below and Section 9.4.2. All episodes of severe hypoglycemia must be reported as SAEs on the AE eCRF page and on the SAE eCRF page. Reports of hypoglycemia will be classified by the investigator as "severe" or "not severe" based upon data collected in the patient diary and in consultation with the patient. Episodes of hypoglycemia not meeting the criteria for severe hypoglycemia should not be reported as an AE.

Hypoglycemia will be described using the following definitions:

- **Documented Glucose Alert; BG≤70 mg/dL (3.9 mmol/L):**
  - **Documented symptomatic hypoglycemia:** an event with typical symptoms of hypoglycemia.
  - **Documented asymptomatic hypoglycemia:** an event without typical symptoms of hypoglycemia.
  - **Documented unspecified hypoglycemia:** with no information about symptoms of hypoglycemia available (this has also been called unclassifiable hypoglycemia).
- **Documented Clinically Significant Hypoglycemia with similar criteria as above, except for threshold BG<54 mg/dL (3.0 mmol/L)**
  - **Documented symptomatic hypoglycemia**
  - **Documented asymptomatic hypoglycemia**
  - **Documented unspecified hypoglycemia**
- **Severe Hypoglycemia:** during these episodes, patients have an altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Blood glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration (BG≤70 mg/dL [3.9 mmol/L]).
  - **Note:** Young children will frequently require assistance with treatment of hypoglycemia but are not experiencing signs of altered mental status or cognitive impairment. Final determination should be made by the investigator and based on a severe hypoglycemia event meeting the description provided above.
- **Other Hypoglycemia:**

- **Nocturnal hypoglycemia:** any documented hypoglycemic event (including severe hypoglycemia) that occurs between bedtime and waking.
- **Probable symptomatic hypoglycemia:** an event during which symptoms are present, but BG measurement was not reported.
- **Overall (or total) hypoglycemia:** this category combines all cases of hypoglycemia (documented hypoglycemia and probable symptomatic hypoglycemia, including severe hypoglycemia) excluding the events of relative hypoglycemia. Nocturnal and severe hypoglycemia are special cases of documented or probable hypoglycemia. If an event of hypoglycemia falls into multiple subcategories, the event is only counted once in this category.

9.4.2. Severe Hypoglycemia

Young children, because of their age, will frequently require assistance with treatment of hypoglycemia, but are not experiencing signs of changes in mental status. The final determination of a hypoglycemic event as an episode of severe hypoglycemia as defined above is made by the investigator based on the medical need of the child to have required assistance (that is, altered mental status or cognitive impairment) and is not predicated on the report of a child simply having received assistance.

9.4.3. Vital Signs, Height, and Weight

For each patient, vital signs, height, and weight measurements should be conducted according to the Schedule of Activities (Section 2, Table ITSB.1) and following the study-specific recommendations.

Any clinically significant findings from vital sign measurement that result in a diagnosis and that occur after the patient receives the first dose of study treatment should be reported to Lilly or its designee as an AE via electronic data entry.

9.4.4. Laboratory Tests

For each patient, laboratory tests detailed in Appendix 2 should be conducted according to the Schedule of Activities (Section 2, Table ITSB.1).

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

Any clinically significant findings from laboratory tests that result in a diagnosis and that occur after the patient receives the first dose of IP should be reported to Lilly or its designee as an AE via electronic data entry.

9.4.5. Immunogenicity Assessments

Blood samples for immunogenicity testing will be collected for the assessment of anti-insulin lispro antibodies as specified in the Schedule of Activities (Section 2, Table ITSB.1). This assessment will be performed using a validated assay at a laboratory approved by the sponsor.

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

9.4.6. Safety Monitoring

In compliance with international regulations and Good Clinical Practice guidelines, Lilly actively monitors and evaluates safety information for investigational drugs on an ongoing basis during the clinical trial program.

In the event that safety monitoring uncovers an issue that needs to be addressed by unblinding at the group level, only members of the data monitoring board (an advisory group for this study formed to protect the integrity of data; refer to Interim Analyses section [Section 10.3.8]) can conduct additional analyses of the safety data.

The data and safety monitoring committee (DMC) consisting of pediatric experienced members external to the study team will review safety results at least once during the study. The DMC comprises those individuals responsible for the evaluation and interpretation of the results from the interim analysis. The DMC for this study will be conducted as an independent DMC. Therefore, the members of the DMC are external to Lilly. Further details pertaining to the DMC activities may be found in the DMC charter. Unblinding details are specified in the unblinding plan section of the statistical analysis plan (SAP).

Only the DMC is authorized to evaluate unblinded interim safety analyses. Study sites will receive information about interim results ONLY if they need to know for the safety of their patients.

9.4.6.1. Hepatic Safety Monitoring

If a study patient experiences elevated ALT≥3×ULN, ALP≥2×ULN, or elevated TBL≥2×ULN, liver testing (Appendix 4) should be repeated within 3 to 5 days, including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase to confirm the abnormality and to determine if it is increasing or decreasing. If the abnormality persists or worsens, clinical and laboratory monitoring should be initiated by the investigator and in consultation with the study medical monitor. Monitoring of ALT, AST, TBL, and ALP should continue until levels normalize or return to approximate baseline levels.

Hepatic Safety Data Collection

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

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

- hepatic event considered to be a SAE.

9.5. Pharmacokinetics

Not applicable.

9.6. Pharmacodynamics

Not applicable.

9.7. Pharmacogenomics

Not applicable.

9.8. Health Economics

Not applicable.

10. Statistical Considerations

10.1. Sample Size Determination

Approximately 708 patients will be randomized in order that 600 patients complete the study through the primary endpoint at Week 26.

Patients will be randomized in a 2:2:1 ratio to double-blind LY900014 dosed 0 to 2 minutes before meals, double-blind Humalog dosed 0 to 2 minutes before meals, or open-label LY900014 dosed up to 20 minutes after the start of a meal. Stratification will be by country, HbA1c stratum (≤8.0%, >8.0%), type of basal insulin (insulin glargine, insulin detemir, or insulin degludec), and age group (1 to <12 years, 12 to <18 years).

Assuming a NIM of 0.4%, no true difference between treatment groups and an SD of 1.1%, 240 completers for each double-blind treatment group will provide greater than 95% power to show noninferiority between LY900014 and Humalog using the upper limit of a 2-sided 95% CI (LY900014−Humalog). This sample size also has more than 80% power to show noninferiority between LY900014 and Humalog using a 0.3% NIM at 26 weeks.

With the assumption a difference no larger than 0.07% between treatment groups and a SD of 1.1%, 240 completers of double-blind Humalog dosed 0 to 2 minutes before meals and 120 completers of open-label LY900014 dosed up to 20 minutes after the start of a meal will provide approximately 76% power to show noninferiority between open-label LY900014+20 and double-blind Humalog using a NIM of 0.4%. .

Assuming a 15% dropout rate during 26 weeks of treatment, approximately 708 patients (283 patients in each double-blind treatment group and 142 patients in the open-label treatment group) will need to be randomized.

10.2. Populations for Analyses

For purposes of analysis, the following populations are defined:

Population	Description
Entered	All patients who give informed consent.
Randomized	All patients who are randomly assigned to study treatment at Visit 4. Treatment group will be defined on the basis of the treatment the patients are assigned.
Safety	All randomized patients who receive at least 1 dose of the randomly assigned investigational product (IP). Treatment group will be defined on the basis of the treatment the patients are assigned.
Completer	Patients included in the randomized population who have completed Week 26 of study treatment without permanent discontinuation of IP. Treatment group will be defined on the basis of the treatment the patients are assigned.
Per Protocol	Patients included in the randomized population who have completed Week 26 of study treatment without permanent discontinuation of IP and without significant protocol deviations through Week 26 that would significantly impact the primary objective. Treatment group will be defined on the basis of the treatment the patients actually receive.

10.3. Statistical Analyses

10.3.1. General Statistical Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the clinical study report (CSR). Additional exploratory analyses of data will be conducted, as deemed appropriate.

The primary analysis is for the treatment period through Week 26.

Efficacy analyses will be conducted on all randomized patients according to the treatment the patients are assigned. The analyses for the primary and gated objectives will be performed for the efficacy estimand, including data collected prior to permanent discontinuation of IP and for the ITT estimand, including all data collected regardless of IP use. The primary endpoint will also be analyzed using the PP and Completer populations.

Unless otherwise specified, the efficacy analyses for other secondary objectives and exploratory objectives will be performed for the efficacy estimand. When change from baseline is included as a response variable of analysis models, the patient will be included in the analysis only if a baseline and at least 1 postbaseline measurement are available.

Safety analyses will be conducted on the Safety population. Analyses of AEs will include 2 sets of analyses, unless otherwise specified. The first set of analyses will include data collected prior to permanent discontinuation of IP. The second set of analyses will include all data collected during the course of the entire study, including the follow-up visit, regardless of IP use. Analyses of hypoglycemia will use data collected prior to permanent discontinuation of IP, while analyses for post treatment may be performed as needed. Analyses of safety laboratory measurements will be performed on all data during the planned treatment period regardless of IP use.

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. All tests of interactions between treatment groups and other factors will be conducted at a 2-sided alpha level of 0.10. Countries in similar geographic regions with fewer than 10 patients, based on all randomized population, will be pooled to achieve a pooled country of at least 10 patients. All analyses using country in the model will use a pooled country, unless otherwise specified. The final pooling by country and geographic region will be finalized prior to data lock.

Baseline is defined as the last non-missing measurement at or before the randomization visit (Visit 4), unless otherwise specified.

A restricted maximum likelihood-based, mixed-effect model repeated-measure (MMRM) analysis will be used to analyze continuous longitudinal variables. All the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model for

the analysis of the primary efficacy endpoint of change from baseline in HbA1c will include the fixed class effects of treatment, strata (pooled country, type of basal insulin, and age group), visit, and treatment-by-visit interaction, as well as the continuous, fixed covariate of baseline value. For analyses of variables other than HbA1c, the HbA1c stratum (≤8.0%, >8.0%) will be included in the model. An unstructured covariance structure will be used to model the within-patient errors. Significance tests will be based on least-squares (LS) means and Type III tests. SAS PROC MIXED will be used to perform the analysis. If this analysis fails to converge, the following covariance structures will be tested, in order:

- Toeplitz with heterogeneity
- Autoregressive with heterogeneity
- Compound symmetry with heterogeneous variances
- Toeplitz
- Autoregressive
- Compound symmetry without heterogeneous variances.

The first covariance structure that converges will be used. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

An analysis of covariance (ANCOVA) will also be used to analyze continuous variables. The model for the change from baseline to the Week 26 HbA1c endpoint will include treatment and strata (pooled country, type of basal insulin, and age group) as fixed effects and baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward (LOCF) approach, using only postbaseline data. For analyses of variables other than HbA1c, the HbA1c stratum (≤8.0%, >8.0%) will be included in the model.

For continuous measures, summary statistics will include sample size, mean, SD, median, and minimum and maximum for both the actual and the change from baseline measurements. The LS means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences along with the p-values for the treatment comparisons.

For categorical measures, summary statistics will include sample size, frequency, and percentages. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons.

10.3.2. Treatment Group Comparability

10.3.2.1. Patient Disposition

A detailed description of patient disposition will be provided. Frequency counts and percentages of all patients entered, randomized, completing, and/or discontinuing from the study will be presented for each treatment group. Reasons for discontinuation from study treatment and from

the study during the treatment period will be summarized and compared between treatment groups using Fisher's exact tests.

10.3.2.2. Patient Characteristics

Standard baseline characteristics of age, age group (Age Group 1: 1 to <12, 12 to 18 years and Age Group 2: 1 to <6, 6 to <12, 12 to <18 years), sex, ethnicity, race, height, weight, and body mass index (BMI) will be summarized for all randomized patients. Summary statistics will include sample size, mean, SD, median, minimum and maximum for continuous measures and sample size, frequency, and percent for categorical measures. Comparisons between treatment groups will be performed using Fisher's exact test or Pearson's chi-square test for categorical data and an analysis of variance with treatment in the model for continuous data for all patients. Baseline diabetes characteristics will be summarized in a similar manner.

Preexisting conditions will be summarized by treatment group using preferred term (PT) within system organ class (SOC). No p-values will be reported.

10.3.2.3. Concomitant Therapy

Concomitant medications used during the treatment period will be summarized and compared between treatment groups using Fisher's exact test. The type of insulin therapy at study entry will be compared between treatment groups using Fisher's exact tests.

10.3.3. Efficacy Analyses

10.3.3.1. Primary Analyses

The primary objective of this study is to test the hypothesis that LY900014 is noninferior to Humalog on glycemic control (NIM=0.4% for HbA1c) in patients 1 to <18 years of age with T1D, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin for 26 weeks. There will be 2 primary analysis methods, each tested at the full significance level of 0.05.

For the US FDA submission (using the ITT estimand), the missing endpoints will be imputed by the copy reference approach. The reference for each treatment group is from the retrieved dropout patients who discontinue IP but have the measurement at the primary endpoint in the same treatment group. If there is only a limited number of patients in the reference group that leads to a failure in performing the proposed multiple imputation analysis such that the model cannot converge, or the number of records in the reference group is less than the number of records with missing data, the missing endpoints will be imputed by the patient-level observed baseline value plus a noise, assuming a washout of any potential treatment effect (or "return to baseline"). The noise follows a normal distribution with the variability estimated from the "washout HbA1c data". The "washout HbA1c data" will be derived by subtracting the corresponding treatment mean at Week 26 from individual non-missing HbA1c values at Week 26. After imputation, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog from an ANCOVA. The model for the change from baseline to the Week 26 HbA1c endpoint will include treatment and strata (pooled country, type of basal

insulin, and age group) as fixed effects and baseline HbA1c as a covariate. The final estimates will be the combined estimates from at least 1000 imputations.

For non-FDA submissions and publications, the primary efficacy comparison will be based on the contrast between LY900014 and Humalog at Week 26 (Visit 15) from the MMRM analysis of change from baseline in HbA1c, including data collected from all randomized patients prior to permanent discontinuation of IP through Week 26 (efficacy estimand). The analysis model and selection of covariance structure are described in Section 10.3.1.

For both primary analysis approaches, LY900014 will be declared noninferior to Humalog if the upper limit of the 2-sided 95% CI for the LS mean difference in the change from baseline in HbA1c for LY900014 minus Humalog is below +0.4%. In addition, the 95% CI for the treatment difference will be compared to an alternative NIM of +0.3%. Both estimands will be tested at the full significance level of 0.05.

10.3.3.1.1. Sensitivity Analyses for Missing Data

A missing-not-at-random-based analysis will be performed for both the efficacy and ITT estimands to assess sensitivity to departures from the missing-at-random (MAR) assumption. The tipping point approach that will be used is similar to progressive stress test (Ratitch et al. 2013). The basic idea is to impute the missing values and add a value (delta) to the imputed values of the experimental group and perform an analysis for the primary endpoint on the delta-adjusted data set to see whether the conclusion of the primary analysis is overturned. If not, a larger delta is chosen and the process is repeated until the primary result is overturned. If the delta required to overturn the primary result is not a plausible departure from MAR, then the primary result is robust to plausible departures from MAR. Imputation under the noninferiority null method, in which delta equals the NIM, will be included as a special case of the progressive stress test.

For the ITT estimand, the imputation of missing data will be as described for the FDA primary analysis and ANCOVA on the change from baseline to Week 26 in HbA1c will be used.

For the efficacy estimand, the copy reference approach will be used to impute missing data and the reference group will be the Humalog treatment group. Imputation will be for all longitudinal visits.

10.3.3.1.2. Additional Analyses for the Primary Endpoint

The primary MMRM analysis model will be repeated using the PP and Completer populations to check the sensitivity of the analysis. If the conclusion differs from that of all randomized patients, the data and analyses will be further investigated.

A secondary analysis model for the efficacy estimand will be an ANCOVA for HbA1c change from baseline to Week 26 (Visit 15), using the model described in Section 10.3.1. Missing endpoints will be imputed using the LOCF approach using postbaseline data only.

10.3.3.2. Secondary Analyses

Following the successful claim of the primary objective, the assessment of noninferiority between LY900014+20 and Humalog and superiority between LY900014 and Humalog in

controlling HbA1c will use gatekeeping strategy. The noninferiority between LY900014+20 and Humalog will be evaluated first with the significant level of 0.05 (from the primary objective). Once the noninferiority is achieved, the superiority test between LY900014 and Humalog will be performed with the significant level of 0.05 (from the gated noninferiority objective). Both the assessments will be based on the analysis approaches used for the primary objective (ITT estimand for FDA submission and efficacy estimand for non-FDA submissions).

HbA1c and change from baseline in HbA1c at all timepoints will be analyzed by the same MMRM model used for the primary analysis for the efficacy estimand. The noninferiority in change from baseline in HbA1c for LY900014+20 to Humalog will be based on the same model.

Additional continuous secondary efficacy variables, as well as the change from baseline for these variables, will be analyzed either by the MMRM or ANCOVA models described in Section 10.3.1 for the efficacy estimand.

Treatment comparisons for the proportion of patients with HbA1c<7.0% and <7.5% will be analyzed using a longitudinal logistic regression with repeated measurements conducted by a generalized linear mixed model including independent variables of treatment, baseline HbA1c value, visit, baseline HbA1c by visit interaction, and treatment by visit interaction. An unstructured covariance structure will be used. As a sensitivity analysis, the proportion of patients with HbA1c<7.0% and <7.5% at Week 26 (Visit 15), imputed using LOCF, will be compared using a logistic regression model including treatment and baseline HbA1c value in the model.

10.3.3.3. Tertiary/Exploratory Analyses

Continuous variables and the change from baseline for these variables will be analyzed either by the MMRM or ANCOVA models described in Section 10.3.3.1. Categorical variables will be analyzed either by model (for example, logistic regression) or by Fisher's exact test or Pearson's chi-square test. Analysis details for the tertiary endpoints will be described in the SAP.

10.3.4. Safety Analyses

Safety measures will include AEs, hypoglycemia, vital signs and weight, treatment exposure, laboratory measures, and antibodies to insulin lispro. Analyses will be performed on data collected from randomization through Visit 801 for both treatment groups.

Events that are newly reported after the first dose of IP or reported to worsen in severity from baseline will be considered treatment-emergent AEs (TEAEs). The Medical Dictionary for Regulatory Activities (MedDRA) lowest level term (LLT) will be used in the treatment-emergent assessment. The maximum severity for each LLT during the baseline period will be used as baseline severity.

The SAEs, AEs reported as reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the MedDRA PT, sorted by decreasing frequency within the LY900014 treatment group. The TEAEs will also be summarized by PT sorted by decreasing frequency within SOC for all TEAEs and by maximum severity. For events that are specific to only 1 sex, the denominator and computation of the percentage will include only patients from

the given sex. The number and proportion of patients with at least 1 event for each type of event will be summarized and compared between treatment groups using Fisher's exact test.

Hypoglycemia rates will be summarized for periods of 30 days, 1 year, and 100 years (severe hypoglycemia only). The rate of severe hypoglycemia per 100 years will be compared between treatment groups using the empirical method (details will be described in SAP). For each of the other categories of hypoglycemia, the number of hypoglycemia events during a specific period after randomization (for example, Weeks 0 to 12 of treatment period) will be analyzed by using a negative binomial regression model. The model will include treatment and age group as covariates. An offset defined as the log transformation of treatment exposure in the specific period (days)/365.25 days (or 30 days) will be included in the model to estimate the rate of hypoglycemia per year (or per 30 days). The proportion of patients with at least 1 hypoglycemic event in each category during a specific period after randomization will be analyzed using a logistic regression model including treatment and age group as covariates.

Continuous safety variables, as well as the change from baseline for these variables, will be analyzed by MMRM or ANCOVA models. For categorical variables, Fisher's exact test or Pearson's chi-square test will be used to compare treatment groups, unless otherwise specified.

10.3.5. Pharmacokinetic/Pharmacodynamic Analyses

Not applicable.

10.3.6. Evaluation of Immunogenicity

The treatment-emergent anti-insulin lispro antibody (denoted as treatment-emergent antidrug antibody [TEADA] throughout this document) is based on the change from baseline to postbaseline in the anti-insulin lispro antibody level (percent binding). The TEADA can be sub-classified as either treatment-induced (not detected anti-insulin lispro antibody at baseline) or treatment-boosted (detected anti-insulin antibody at baseline):

- treatment-induced response: change from not detected anti-insulin lispro at baseline to postbaseline detected anti-insulin lispro and
- treatment-boosted response: change from detected anti-insulin lispro at baseline to postbaseline detected anti-insulin lispro antibody level (percent binding) at least 157% of the baseline value.

The summary of TEADA will be provided by treatment group. Fisher's exact test will be used for the treatment comparison.

The relationship between the presence of TEADA and selected efficacy and safety measures will also be evaluated. Analyses details will be documented in the SAP.

10.3.7. Other Analyses

10.3.7.1. Subgroup Analyses

The following subgroups will be analyzed using the efficacy estimand to evaluate consistency of treatment effects on the primary efficacy measure if there are sufficient numbers of patients in each treatment by subgroup (for example, 10%):

- Age (Age Group 1: 1 to <12, 12 to <18 years and Age Group 2: 1 to <6, 6 to <12, 12 to <18 years)
- HbA1c stratum (≤8.0%, >8.0%)
- Type of basal insulin at randomization (insulin glargine, detemir, or degludec)
- Sex (male or female)
- BMI (<25, ≥25 kg/m^2 and <30, ≥30 kg/m^2)
- Duration of diabetes (using the median as the cutoff)
- Race
- Ethnicity
- Country
- Region
- Prandial insulin dosing plan (carbohydrate counting, pattern adjustment).

Analyses for HbA1c and change from baseline in HbA1c will be performed using an MMRM model that includes the same fixed effects given for the primary analysis model plus factors of subgroup, 2-way interaction of subgroup and treatment, 2-way interaction of subgroup and visit, and 3-way interaction of treatment, visit, and subgroup. The interaction of subgroup and treatment at the primary endpoint (Week 26) will be evaluated to assess the treatment by subgroup interaction.

Additional subgroup analyses may also be performed.

10.3.8. Interim Analyses

There will be no interim analysis, but safety will be monitored by a DMC. A limited number of pre-identified individuals may gain access to the limited unblinded data for DMC review, as specified in the DMC charter. Information that may unblind the study during the analyses will not be reported to study sites or the blinded study team until the study has been unblinded.

Unblinding details are specified in the unblinding plan section of the SAP and the DMC charter or in a separate unblinding plan document.

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12. Appendices

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 adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
BID	twice daily (twice a day)
Blinding/masking	A single-blind study is one in which the investigator and/or his staff are aware of the treatment but the patient is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/his staff and the patient are not. A double-blind study is one in which neither the patient nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the patients are aware of the treatment received.
BMI	body mass index
CGM	continuous glucose monitoring
CI	confidence interval
C_{max}	maximum drug concentration
Product complaint	Product complaints are a customer's written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution.
CRF	case report form
CRP/CRS	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
CSR	clinical study report
DMC	data and safety monitoring committee
eCRF	electronic case report form
ED	early discontinuation
Enroll	The act of assigning a patient to a treatment. Patients who are enrolled in the trial are those who have been assigned to a treatment.
Enter	Patients entered into a trial are those who sign the informed consent form directly or through their legally acceptable representatives.
ERB	ethical review board
FDA	Food and Drug Administration
FGM	flash glucose monitoring
GFR	glomerular filtration rate
HbA1c	hemoglobin A1c
IB	Investigator's Brochure
ICF	informed consent form
IP	investigational product: A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
ITT	Intention-to-treat: The principle that asserts that the effect of a treatment policy can be best assessed by evaluating on the basis of the intention to treat a patient (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that patients allocated to a treatment group should be followed up, assessed, and analyzed as members of that group irrespective of their compliance to the planned course of treatment.
IWRS	interactive web response system
LLT	lowest level term
LOCF	last observation carried forward
LS	least-squares

MAR	missing-at-random
MDI	multiple-daily-injection
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
NIM	noninferiority margin
NPH	neutral protamine Hagedorn
PAH	pulmonary artery hypertension
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
PP	per-protocol
PPG	postprandial glucose
PT	preferred term
QD	once a day
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
Screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SD	standard deviation
SMBG	self-monitored blood glucose
SOC	system organ class
SUSARs	suspected unexpected serious adverse reactions
T1D	type 1 diabetes
TBL	total bilirubin level
TDD	total daily insulin dose

TEADA	treatment-emergent antidrug antibody
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
US	United States
WHO	World Health Organization

Appendix 2. Clinical Laboratory Tests

Clinical Laboratory Tests

Hematology[a]	**Clinical Chemistry**[a]
Hemoglobin	**Serum Concentrations of:**
Hematocrit	Sodium
Erythrocyte count (RBC)	Potassium
Mean cell volume	Total bilirubin
Mean cell hemoglobin concentration	Direct bilirubin
Leukocytes (WBC)	Alkaline phosphatase (ALP)
Neutrophils, segmented	Alanine aminotransferase (ALT)
Lymphocytes	Aspartate aminotransferase (AST)
Monocytes	Blood urea nitrogen (BUN)
Eosinophils	Creatinine
Basophils	Uric acid
Platelets	Calcium
	Chloride
HbA1c[a]	Magnesium
	Cholesterol
Urinalysis[a]	Glucose (nonfasting)
Specific gravity	Albumin
pH	Total protein
Protein	
Glucose	**Pregnancy Test** (females only)
Ketones	Serum pregnancy test[a]
Blood	Urine pregnancy test[b]
Urine leukocyte esterase	
Nitrite	**Serology**[a]
	Anti-insulin lispro antibodies

Abbreviations: HbA1c = hemoglobin A1c; RBC = red blood cells; WBC = white blood cells.

[a] Assayed by Lilly-designated laboratory.

[b] Assayed by local- or investigator-designated laboratory.

Appendix 3. Study Governance Considerations

Appendix 3.1. Regulatory and Ethical Considerations, Including the Informed Consent Process

Appendix 3.1.1. Informed Consent

The investigator is responsible for the following:

- 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 investigational product.
- 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.
- Ensuring that a copy of the ICF is provided to the participant or the participant's legal representative and is kept on file.
- Ensuring that the medical record includes a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

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

Appendix 3.1.2. Recruitment

Lilly or its designee is responsible for the central recruitment strategy for patients. Individual investigators may have additional local requirements or processes.

Appendix 3.1.3. Ethical Review

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

Documentation of ERB approval of the protocol and the ICF 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, including any changes made by the ERBs, before it is used at the investigative site(s). All ICFs must be compliant with the ICH guideline on Good Clinical Practice (GCP).

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

- the protocol and related amendments and addenda, current Investigator Brochure (IB) Package Insert, or Summary of Product Characteristics and updates during the course of the study
- informed consent form and Assent Form
- other relevant documents (for example, curricula vitae, advertisements)

Appendix 3.1.4. Regulatory Considerations

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

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

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

Appendix 3.1.5. Investigator Information

Pediatric endocrinologist or diabetologist, adult endocrinologist or diabetologist, internal medicine, or primary care physicians with experience in the care of pediatric patients with T1D will participate as investigators in this clinical trial.

Appendix 3.1.6. 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.

Appendix 3.1.7. Final Report Signature

The CSR coordinating investigator will sign the final CSR for this study, indicating agreement that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

An investigator will be selected by the Lilly study team to serve as the CSR coordinating investigator. The sponsor's responsible medical officer and statistician will approve the final CSR for this study, confirming that, to the best of his or her knowledge, the report accurately describes the conduct and results of the study.

Appendix 3.2. 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 sponsor start-up training to instruct the investigators and study coordinators. This training will give instruction on the protocol, the completion of the CRFs, and study procedures
- make periodic visits to the study site
- be available for consultation and stay in contact with the study site personnel by mail, telephone, and/or fax
- review and verify data reported to detect potential errors

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 or its representatives 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. These 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 original source documents.

Appendix 3.2.1. Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

An electronic data capture (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data (questionnaires and self-reported diary data) will be collected by the subject, via a paper source document and will be transcribed by the investigator-site personnel into the EDC system.

Data collected via the sponsor-provided data capture system(s) will be stored at third-party sites. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports will be provided to the investigator for review

and retention. Data will subsequently be transferred from the central vendor to the Lilly data warehouse.

Data from complaint forms submitted to Lilly will be encoded and stored in the global product complaint management system.

Appendix 3.3. Study and Site Closure

Appendix 3.3.1. Discontinuation of Study Sites

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

Appendix 3.3.2. Discontinuation of the Study

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

Appendix 3.4. Publication Policy

The publication policy for Study I8B-MC-ITSB is described in the Clinical Trial Agreement.

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 the Lilly or its designee clinical research physician.

Hepatic Monitoring Tests

Hepatic Hematology[a]	**Haptoglobin[a]**
Hemoglobin	
Hematocrit	**Hepatic Coagulation[a]**
RBC	Prothrombin Time
WBC	Prothrombin Time, INR
Neutrophils, segmented	
Lymphocytes	**Hepatic Serologies[a,b]**
Monocytes	Hepatitis A antibody, total
Eosinophils	Hepatitis A antibody, IgM
Basophils	Hepatitis B surface antigen
Platelets	Hepatitis B surface antibody
	Hepatitis B Core antibody
Hepatic Chemistry[a]	Hepatitis C antibody
Total bilirubin	Hepatitis E antibody, IgG
Direct bilirubin	Hepatitis E antibody, IgM
Alkaline phosphatase	
ALT	**Anti-Nuclear Antibody[a]**
AST	
GGT	**Alkaline Phosphatase Isoenzymes[a]**
CPK	
	Anti-Smooth Muscle Antibody (or Anti-Actin Antibody)[a]

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

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

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

Appendix 5. Sampling Summary

This table summarizes the approximate volumes for all standard laboratory and immunogenicity tests during the study. Fewer samples may actually be taken, but this will not require a protocol amendment.

Protocol I8B-MC-ITSB Sampling Summary

	Study Visit						
	V1[a]	**V4**	**V7**	**V10**	**V15**	**ED**	**Total**
Estimated blood volume[b], mL	10	6.5	6.5	6.5	10	10	39.5
Hepatic monitoring[c]	3-30 mL						

Abbreviation: ED = early discontinuation; V = visit.

[a] For rescreening patients, an additional Visit 1 blood volume draw is required.

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

[c] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Appendix 6. Classification of Contraceptive Methods

Post pubertal females of childbearing potential are defined as children and adolescents ≥12 years of age or <12 years of age who have onset of menses. Females of childbearing potential must use 1 highly effective method of contraception.

Methods of Contraception

Highly Effective Methods of Contraception
• Combined oral contraceptive pill and mini-pill • NuvaRing® • Implantable contraceptives • Injectable contraceptives (such as Depo-Provera®) • Intrauterine device (such as Mirena® and ParaGard®) • Contraceptive patch – ONLY women <198 lb. or 90 kg • Total abstinence • Vasectomy

Females who are not of childbearing potential include those who have undergone or who have:

a. Female sterilization
b. Hysterectomy
c. Menopause
d. Mullerian agenesis (Mayer-Rokitansky-Küster-Hauser syndrome [also referred to as congenital absence of the uterus and vagina])

Appendix 7. Protocol Amendment History

Protocol I8B-MC-ITSB (a) A Prospective, Randomized, Double-Blind Comparison of LY900014 to Humalog with an Open-Label Postprandial LY900014 Treatment Group in Children and Adolescents with Type 1 Diabetes; PRONTO-Peds has been amended. The new protocol is indicated by amendment (b) and will be used to conduct the study in place of any preceding version of the protocol.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol I8B-MC-ITSB Amendment (b)

Section # and Name	Description of Change	Brief Rationale
Table ITSB.1 Schedule of Activities	Added new footnote to Screen	Clarification for restart at Visit 1 for those patients who need to rescreen.
6.1 Inclusion Criteria	Changed insulin daily dose range and HbA1c acceptable values	Changes allow for younger and active children using smaller doses and adolescents who require more insulin during puberty. Will allow broader range of patients including those who are in good control.
6.1 Inclusion Criteria	Added language defining postpubertal females	Change clarified definition of postpubertal females already noted in Appendix 6.
6.4 Screen Failures	Added 1 rescreen allowed	Change made to allow1 rescreen to patients who who had a screen fail or unexpectedly had to discontinue due to COVID-19 enrollment pause.
Appendix 5 Sampling Summary	Added footnote on V1	Change made to include information on rescreening.

Revised Protocol Sections

Note:	Deletions have been identified by ~~strikethroughs~~. Additions have been identified by the use of underscore.

Table ITSB.1. Schedule of Activities

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[a] [b]
eCRF Visit Number	**1**	**2**	**3[b][c]**	**4**	**5[b][c]**	**6[b][c]**	**7**	**8[c][b]**	**9[b][c]**	**10**	**11[b][c]**	**12**	**13[b][c]**	**14[b][c]**	**15**	**801[ed]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Clinical Assessments																	
Demographic data-[c][d]	X																
Medical history, preexisting conditions	X																
Previous diabetes therapy	X																
Record Personal CGM/FGM use (yes/no)				X													
Height[e][f]	X			X						X					X		X
Weight	X	X		X			X			X		X			X		X
Vital signs (sitting SBP, DBP, and HR)[f][g]	X	X		X			X			X		X			X		X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Focused physical exam -(including skin evaluation)[g][h]	X	X		X			X			X		X			X		X
Basal insulin dose assessment[i][h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Basal insulin dose titration[i][j]		X	X	X	X	X	X	X	X	X							

	Screen[a]	Lead-In		Treatment Period												Safety Follow-Up	ED[~~a~~ b]
eCRF Visit Number	**1**	**2**	**3~~b~~[c]**	**4**	**5~~b~~[c]**	**6~~b~~[c]**	**7**	**8~~c~~[b]**	**9~~b~~[c]**	**10**	**11~~b~~[c]**	**12**	**13~~b~~[c]**	**14~~b~~[c]**	**15**	**801~~e~~[d]**	**ED**
Weeks from Randomization	**−5**	**−4**	**-2**	**0**	**2**	**4**	**6**	**8**	**10**	**12**	**15**	**18**	**21**	**24**	**26**	**28**	
Visit Window (±days)		**3**	**3**	**3**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	**7**	
Ancillary Supplies/Diaries/IP																	
Dispense blood glucose meter and ancillary supplies and complete training[~~i~~,~~k~~,l]		X		X			X			X		X					
Diabetes education and nutrition counseling[~~k~~l]		X															
Dispense study diaries and complete training[~~k~~l]		X		X			X			X		X					
Collect study diaries				X			X			X		X			X		X
Dispense IP		X		X			X			X		X					
Train on collecting 4- and 7-point SMBG profiles[~~l~~m]		X															
Laboratory Assessments																	
Pregnancy test, serum/urine (applicable females only)[~~m~~n]	X			X													

a Patients who rescreen will start at Visit 1.·

6.1. Inclusion Criteria

Patients are eligible to be included in the study, only if they meet all the following criteria **at screening:**

[5] Have been treated with only ~~one~~ 1 of the following basal insulins for at least the last 90 days:

a. insulin glargine U-100 (QD or BID), or

b. insulin detemir U-100 (QD or BID), or

c. insulin degludec U-100 (QD)

[6] Use a total daily dose of insulin 0.3~~5~~ to ≤1.9~~5~~ U/kg.

a. TDD can be the average of previous 3 to 7 days

[7] Have a~~n HbA1c value ≥6.5% and ≤9.5%,~~ HbA1c value ≤9.9% according to the central laboratory.

[8] Male patients:

a. no male contraception required, except in compliance with specific local government regulation

[9] Female patients of childbearing potential:

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

6.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) ~~may not be rescreened. Retests are also not allowed, except for cases when results are not available from the original sample.~~or were required to unexpectedly discontinue from the study during screening or lead-in period (e.g., due to enrollment pause related to the COVID-19 public health emergency) are allowed 1 rescreening.

All patients that rescreen will restart at Visit 1 and complete all screening procedures.

Appendix 5. Sampling Summary

Protocol I8B-MC-ITSB Sampling Summary

	Study Visit						
	V1[a]~~V1~~	V4	V7	V10	V15	ED	Total
Estimated blood volume~~,~~[ab]~~,~~ mL	10	6.5	6.5	6.5	10	10	39.5
Hepatic monitoring~~[b]~~[c]	3-30 mL						

Abbreviation: ED = early discontinuation; V = visit.

[a] For rescreening patients, an additional Visit 1 blood volume draw is required.

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

~~[b]~~[c] Based on laboratory safety values, unscheduled hepatic monitoring testing may be performed as part of patient follow-up, in consultation with Lilly-designated Medical Monitor.

Leo Document ID = 6ec65f49-6319-4aff-8f32-73e9b233e460

Approver: PPD

Approval Date & Time: 30-Apr-2020 19:17:05 GMT

Signature meaning: Approved

Approver: PPD

Approval Date & Time: 30-Apr-2020 19:33:05 GMT

Signature meaning: Approved