Protocol: I8B-MC-ITSZ(b)

An Exploratory Study Assessing Time in Target Glucose Range Using a New Titration Scheme of LY900014 and Insulin Degludec in Participants with Type 1 Diabetes

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Approval Date: 24-Nov-2020

Title Page

Protocol Title: An Exploratory Study Assessing Time in Target Glucose Range Using a New Titration Scheme of LY900014 and Insulin Degludec in Participants with Type 1 Diabetes

Protocol Number: I8B-MC-ITSZ

Amendment Number: (b)

Compound: LY900014

Study Phase: Phase 2

Short Title: Dose optimization study

Acronym: ITSZ

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

IND: 127210

Approval Date: Protocol Amendment (b) Electronically Signed and Approved by Lilly on date provided below.

Approval Date: 24-Nov-2020 GMT

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (a)	12-Jul-2020
Original protocol I8B-MC-ITSZ	08-Jun-2020

Amendment [b]

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to modify the inclusion criteria related to the type of rapid-acting insulin analog and the CGM system used at study entry.

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA), 4.1.1 Study visits	Updated language regarding use of personal CGM system at Visit 13	Clarification based on an update to inclusion criterion #12
1.3 Schedule of Activities (SoA), 4.1.1 Study visits	Updated the note that participants who enter the study on Novolog, Admelog, or Apidra will transition to Humalog at Visit 2	Clarification based on an update to inclusion criterion #6
5 Study population	Updated language regarding type of rapid-acting insulin analog used	Clarification based on an update to inclusion criterion #6
5.1 Inclusion Criteria	Updated criterion #6 regarding the types of rapid-acting insulin analog used	To update criterion to include Admelog and Apidra as rapid-acting insulin analog used
5.1 Inclusion Criteria	Updated criterion #12 to clarify the use of CGM system	To update criterion to include unblinded personal CGM use of at least 2 months in the prior 6 months
8.3 Adverse events and serious adverse events	Removed the term ‘legally authorized representative’	To remove the term ‘legally authorized representative’ as only study participants can provide informed consent
Appendix 10.1.3	Updated section regarding informed consent process	To remove the term ‘legally authorized representative’ as only study participants can provide informed consent
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized

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1. Protocol Summary

1.1. Synopsis

Protocol Title: An exploratory study assessing time in target glucose range using a new titration scheme of LY900014 and insulin degludec in participants with Type 1 Diabetes

Short Title: Dose Optimization study

Rationale: In clinical practice, prandial insulins are often titrated based on 'next pre-meal glucose'. For example, clinicians use the pre-lunch blood glucose value to assess the adequacy of the breakfast prandial dose. This commonly used titration scheme may not be fully optimized for the novel time-action profile of LY900014. An alternate approach of using peak post-prandial glucose (PPG) values or the change from pre-meal levels may be better-suited to titrating ultra-rapid acting prandial insulins. In particular, the 'faster on-faster off' profile of LY900014 might allow more aggressive prandial dosing that would further improve PPG without increasing the risk of late post-meal hypoglycemia.

The aim of this study is to evaluate the percentage of time with glucose values within target range (70 to 180 mg/dL, both inclusive) after 35 days of using a new titration scheme with LY900014 treatment and degludec.

Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the time that glucose values are within the target range 70 to 180 mg/dL from CGM use, after 35 days of using the study titration scheme with LY900014 treatment and degludec	Percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), with CGM use during the maintenance period
Secondary	
To evaluate ICR with LY900014 treatment	ICR at the end of the maintenance period
To evaluate the relationship between ICR and TDD with LY900014 treatment	ICR×TDD for the maintenance period
To evaluate total daily, basal, and prandial insulin dose with LY900014 treatment and degludec	Prandial: TDD ratio for the maintenance period

Abbreviations: CGM = continuous glucose monitoring; ICR = insulin-to-carbohydrate ratio; TDD = Total Daily Dose.

Overall Design

Study I8B-MC-ITSZ (ITSZ) is a multicenter, single-group, open-label, Phase 2 study that will be conducted in participants with type 1 diabetes (T1D) currently treated with insulin degludec and a rapid-acting insulin analog in a multiple daily injection (MDI) regimen. The objective of the study is to assess the percentage of time glucose values are within the target range of 70 to 180 mg/dL after 35 days of titration using the study titration scheme of LY900014 and insulin degludec in participants with type 1 diabetes.

Disclosure Statement: This is a single treatment group study with no masking.

Number of Participants

Approximately 34 participants will be assigned to study treatment intervention such that approximately 30 evaluable participants complete the study.

Intervention Groups and Duration

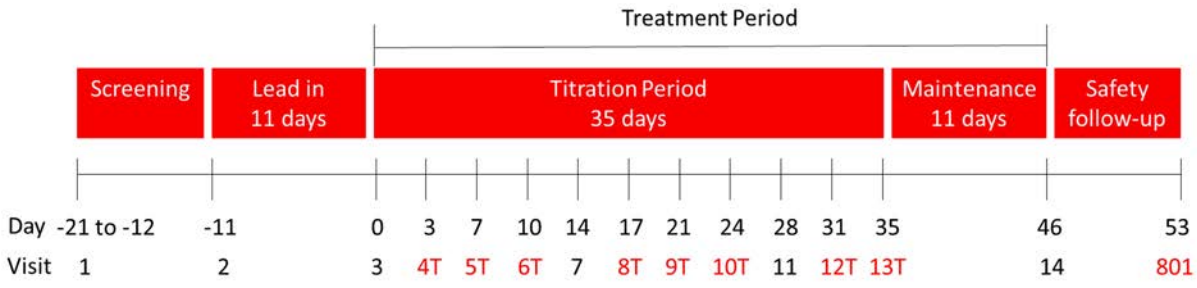
The total duration of study participation for each participant is approximately 74 days across the following study periods:

- Screening, up to 10 days
- Lead in period, 11 days
- Treatment period
  - Titration period, 35 days
  - Maintenance period, 11 days
- Safety follow-up period, 7 days

Data Monitoring Committee:

No.

1.2. Schema



T = Telephone visits

1.3. Schedule of Activities (SoA)

	Screen	Lead in Period -11 to -1	Treatment Period												Safety Follow-up	ET
			Titration Period Days 0 to 35											Maintenance Days 36 to 46	Days 47 to 53	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
Telephone visits are indicated by shaded columns. Telephone visits can become office visits. Site documentation will serve as the source for telephone visits.																
Informed Consent Signed	X															
Participant eligibility review	X	X														
IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Clinical Assessments																
Participant demographics	X															
Medical history and preexisting conditions	X															
Physical exam. /height	X															
Body Weight	X		X				X				X			X		X
	Note: Participants should be advised to remove their shoes/coats and empty their pockets before the body weight is obtained.															

	Screen	**Lead in Period -11 to -1**	**Treatment Period**												**Safety Follow-up**	**ET**
			Titration Period Days 0 to 35											**Maintenance Days 36 to 46**	**Days 47 to 53**	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
Vital signs blood pressure and heart rate	X		X				X				X			X		X
	Note: Vital sign measurements should be determined after participants have been seated quietly for at least 5 minutes in a chair with feet on the floor. The arm used for blood pressure measurement should be supported at heart level															
ECG (12-lead, local)	X															
	Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine, but awake, during ECG collection.															
Concomitant medications	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

	Screen	Lead in Period -11 to -1	Treatment Period												Safety Follow-up	ET
			Titration Period Days 0 to 35											Maintenance Days 36 to 46	Days 47 to 53	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
Participant Education and Management																
Diabetes education and nutrition counseling		X														
	Note: Diabetes education and nutrition counseling may be offered at additional visits if necessary.															
Confirmation of minimum baseline CGM data from SMS portal available before treatment assignment			X													
	Note: Investigator staff should determine before Visit 3 from the participant's Data Acceptability Report in the SMS portal that the participant will meet the minimum CGM requirements. The investigator should communicate to the participant whether he or she has met the minimum CGM requirements before treatment assignment at Visit 3. See Section 4.1.1 under Lead in period "CGM" for how to determine the minimum requirements.															
Treatment assignment			X													
Switch to morning administration of insulin degludec if applicable			X													
Review ambulatory glucose profile using		X	X	X	X	X	X	X	X	X	X	X	X	X		X

	Screen	**Lead in Period -11 to -1**	**Treatment Period**												**Safety Follow-up**	**ET**
			Titration Period Days 0 to 35											**Maintenance Days 36 to 46**	**Days 47 to 53**	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
CGM data in Clarity																
Print InPen report and review insulin doses. Retain InPen report as a part of the participant's medical chart			X	X	X	X	X	X	X	X	X	X	X	X		X
	Note: The investigator should confirm the receipt of the InPen report before each study visit.															
Keep degludec insulin dose, ICR, ISF, and DIA unchanged unless for safety reasons	X	X												X		
	Note: Insulin dose, ICR, ISF, and DIA should remain unchanged during the screening, lead-in, and maintenance period unless for safety reasons. At the end of the maintenance period (Visit 14), the investigator may adjust the participant's ICR to the value he or she had at study entry.															
Adjust DIA as needed			X	X	X	X	X	X	X	X	X	X	X			
	Note: The investigator is not required to adjust the DIA. However, if dose and CGM data indicate that a different duration of insulin action is necessary for participant safety or for optimizing glycemic control, the investigator should make the necessary changes.															
Adjust both basal and bolus insulin doses, ICR, and ISF as needed to achieve glucose target			X	X	X	X	X	X	X	X	X	X	X			
	Note: Please refer to Section 4.3 of the protocol for more details.															

	Screen	Lead in Period -11 to -1	Treatment Period												Safety Follow-up	ET
			Titration Period Days 0 to 35											Maintenance Days 36 to 46	Days 47 to 53	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
Start non-study rapid-acting insulin analog														X		X
Remind participant to bring their personal CGM system to Visit 14													X			
Participants return to their personal CGM device														X		X
Devices, Supplies, and IP																
Dispense CGM supplies		X					X				X					
Ensure that CGM mobile application is installed on participant's smart phone. Ensure participants activate and set up their account		X														
Grant site permission to access participant data		X														
	Note: The investigator should check the participant's eligibility before they request access to participant data in CLARITY.															

	Screen	**Lead in Period -11 to -1**	**Treatment Period**												**Safety Follow-up**	**ET**
			Titration Period Days 0 to 35											**Maintenance Days 36 to 46**	**Days 47 to 53**	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
from CLARITY																
CGM training		X														
	Note: Additional CGM training may be performed as needed.															
Start Sponsor provided CGM sensor session		X														
	Note: See Section 4.1.1 for details.															
Dispense InPen and associated supplies		X														
Download InPen mobile app on smart phone. Ensure participants activate and set up their InPen account		X														
	Note: Smartphone encompasses Android and Apple iPhone with compatible operating system.															
InPen training		X														
	Note: Additional InPen training may be performed as needed.															
All participants		X														

	Screen	**Lead in Period -11 to -1**	**Treatment Period**												**Safety Follow-up**	**ET**
			Titration Period Days 0 to 35											**Maintenance Days 36 to 46**	**Days 47 to 53**	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
administer Humalog as rapid-acting insulin with the InPen during the lead in period	Note: Participants entering the study on Novolog, Admelog, or Apidra will transition to Humalog.															
Remind participant of required actions and study procedure with InPen and CGM		X	X	X	X	X	X	X	X	X	X	X	X			
	Note: The investigator should remind the participant of the following things: • LY900014 should be administered 0-2 minutes before the start of each meal and snack (not applicable for Visit 2). • InPen reports should be sent before each visit. • Mealtime and degludec dose should be entered into the Dexcom mobile app for Days -10 to -1 and Days 36 to 45.															
Dispense ancillary supplies		X														
Dispense IP			X								X					
Dispense pharmacy cards		X														
	Note: Participants will use pharmacy card to obtain Humalog 3 mL cartridge for use with the InPen during the lead-in period.															
Participant returns unused study drug							X				X			X		X

	Screen	Lead in Period -11 to -1	Treatment Period												Safety Follow-up	ET
			Titration Period Days 0 to 35											Maintenance Days 36 to 46	Days 47 to 53	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
Participant returns InPen device and associated supplies														X		X
Participant returns provided unused Dexcom G6 supplies to site														X		X
Remove access to participant's CLARITY account and SMS portal														X		X
	Note: If an investigator is the participant's primary care provider, the investigator may discuss with the participant whether they would like to retain the link to the CLARITY account.															
Drug accountability			X				X				X			X		X
Transfer data into eCRF																
Transcribe requested data into eCRF from participant's medical chart		X	X	X	X	X	X	X	X	X	X	X	X	X		X
	Note: **The following data are requested:** ICR, ISF, and DIA from the day before visit.															
Transcribe requested			X											X		X

	Screen	Lead in Period -11 to -1	Treatment Period												Safety Follow-up	ET
			Titration Period Days 0 to 35											Maintenance Days 36 to 46	Days 47 to 53	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
data into eCRF from InPen pdf report from each day of the lead in period (Days -10 to -1) and from the maintenance period (Days 36 to 45)	Note: Individual Humalog doses from each day during the lead-in period and LY900014 doses during the maintenance period are requested.															
Laboratory Assessments																
HbA1c	X													X		
Fructosamine	X													X		
1,5 AG	X													X		
Hematology	X															
Chemistry panel	X															
Urinalysis	X															
Serum Pregnancy test	X															
	Note: Serum pregnancy test must be performed in women of childbearing potential at Visit 1 and at other times at the investigator's															

	Screen	**Lead in Period -11 to -1**	**Treatment Period**												**Safety Follow-up**	**ET**
			Titration Period Days 0 to 35											**Maintenance Days 36 to 46**	**Days 47 to 53**	
Day	**-21 to -12**	**-11**	**0**	**3**	**7**	**10**	**14**	**17**	**21**	**24**	**28**	**31**	**35**	**46**	**53**	**ET**
Visit Window (days)	**0**	**+/-3**	**+3**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**-1/+2**	**+3**	**+/-3**	
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**801**	**ET**
	discretion.															
Urine Pregnancy test			X													
	Note: A urine pregnancy test must be performed in women of childbearing potential within 24 hours before IP exposure at Visit 3 and when required per local regulations and/or institutional guidelines, local pregnancy testing will occur at mandatory times during the study treatment period.															
Follicle stimulating hormone test	X															
	Note: Follicle-stimulating hormone test must be performed at Visit 1 for a post-menopausal woman who is at least 40 years of age with an intact uterus, not on hormone therapy, and who has had cessation of menses for at least 1 year without an alternative medical cause.															

Abbreviations: AG = anhydroglucitol; CGM = continuous glucose monitoring; DIA = Duration of Insulin Action; ECG = electrocardiogram; eCRF = electronic case report form; ET = Early Termination; HbA1c = hemoglobin A1c; ICR = insulin-to-carbohydrate ratio; IP = investigational product; ISF = insulin sensitivity factor; IWRS = interactive web-response system; SMS = Study management suite.

2. Introduction

LY900014 is an ultra-rapid-acting formulation of insulin lispro developed by Eli Lilly and Company (Lilly) for subcutaneous (SC) use and for intravenous (IV) use to improve glycemic control in participants with type 1 diabetes mellitus (T1D) or type 2 diabetes mellitus (T2D).

2.1. Study Rationale

Rapid-acting insulin analogs have been shown to have a more rapid onset of action compared with human insulin. However, the consensus is that they are not rapid enough to match carbohydrate absorption and many patients are unable to achieve optimal glycemic control.

An ultra-rapid-acting prandial insulin that would shift the pharmacokinetic (PK) and pharmacodynamic (PD) profiles of insulin to provide an even faster onset of action would better match carbohydrate absorption and allow for efficacious dosing immediately before meals. An ultra-rapid insulin would be useful in the treatment of T1D and T2D when delivered by MDI, continuous subcutaneous insulin infusion, or in closed loop and hybrid closed loop automated insulin delivery systems.

An ultra-rapid time-action profile has been achieved for LY900014 through the addition of 2 novel excipients: microdoses of treprostinil, a prostacyclin analog that increases local capillary blood flow, and citrate, which enhances vascular permeability. The Phase 3 PRONTO studies in patients with T1D and T2D on MDI regimens demonstrated that LY900014 was noninferior to Humalog in hemoglobin A1c (HbA1c) reduction when administered as prandial insulin in combination with basal insulin for 26 weeks (Klaff et al. 2019) (Blevins et al 2019). LY900014 also demonstrated superiority to Humalog in controlling 1-hour and 2-hour PPG excursions during mixed-meal tolerance tests in both patients with T1D and T2D. Improved time in range during daytime was observed in patients with T1D treated with LY900014.

In the PRONTO Diabetes studies, using individualized dose titration, mean bolus:basal insulin dose ratios at study endpoints were approximately 50:50 in both patients with T1D and T2D, which are typical for intensive insulin regimens. The design of the PRONTO Diabetes studies included an 8-week basal insulin optimization period in combination with prandial lispro before randomization, which might have favored aggressive titration of the basal insulin and likely limited titration of LY900014 and Humalog during the subsequent treatment period, as the mean HbA1c was 7.3% at the end of the lead-in period. The PRONTO Diabetes studies provide strong support for the efficacy and safety of LY900014 treatment as part of an MDI regimen. Despite this, it is possible that patient outcomes could be further optimized with alternate dosing regimens.

In clinical practice, the dosing formulas currently widely used by clinicians are as follows (DeWitt and Hirsch 2003, Bode 2004, Pickup 2009):

- Total Basal Dose (TBD)=0.5×Total Daily Dose (TDD)
- Insulin-to-Carbohydrate Ratio (ICR)=450~500/TDD (“450 Rule” or “500 Rule”)
- Correction Factor (CF) =1700~1800/TDD

These formulas originated from C-peptide kinetic studies of insulin secretion and from retrospective reviews of pump download in 'well-controlled' patients, which have some limitations. For example, TBD=0.5 × TDD came from c-peptide kinetic studies of insulin secretions in healthy volunteers and assumed that the basal insulin need is flat and constant throughout the entire day (Kruszynska et al. 1987, Polonsky et al. 1988). Recent prospective insulin titration studies, including studies using structured professional continuous glucose monitoring (CGM), demonstrate that current dosing formulas recommend too high of a dose for basal insulin and too low of a dose for bolus insulin (King and Armstrong 2007a, b, King 2010, Kuroda et al. 2012).

Prandial insulins are often titrated based on 'next pre-meal glucose' (for example, using pre-lunch value to assess adequacy of the breakfast prandial dose). This commonly used titration scheme may not be optimized for the novel time-action profile of LY900014. An alternate approach of using peak post-prandial glucose (PPG) values or the change from pre-meal levels may be better-suited to titrating ultra-rapid acting prandial insulins. In particular, the 'faster on-faster off' profile of LY900014 might allow more aggressive prandial dosing that would further improve PPG without increasing the risk of late post-meal hypoglycemia.

The aim of this study is to explore a new titration scheme of LY900014 to optimize glycemic control, when administered as prandial insulin, in combination with insulin degludec for 35 days. Insulin titration will be based on real-time Dexcom G6 CGM readings, which are approved by the Food and Drug Administration (FDA) for making clinical decisions.

2.2. Background

Type 1 diabetes is an autoimmune disease mediated by a combination of genetic and environmental triggers resulting in lymphocytic infiltration of pancreatic islets, destruction of beta cells, and lifelong dependency on exogenous insulin. The prevalence of T1D is near 1 in 300 and its incidence is steadily increasing worldwide (3% per year) (Gan et al. 2012]).

There have been many advances in the treatment of T1D in the last 20 years; however, reaching and maintaining glycemic goals remains 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% (Stark-Casagrande et al. 2013).

Recent prospective insulin titration studies using structured professional continuous glucose monitoring (CGM) demonstrate that current dosing formulas widely used in clinical practice promote under-dosing of mealtime insulin (Kuroda et al. 2012) (King 2012) (King and Armstrong 2007a, b). Using a new titration scheme for LY900014 might further improve glycemic control in patients with T1D on MDI regimen.

LY900014

LY900014 is composed of the active ingredient, insulin lispro, and 2 enabling excipients (treprostinil and citrate) that facilitate rapid absorption of insulin lispro into the blood stream. This novel formulation results in earlier glucose lowering when compared with Humalog. This faster glucose-lowering response, as demonstrated by the PK and PD profiles of LY900014 when compared with Humalog, more closely mimics the time-action profile of normal endogenous insulin secretion and may better match the speed of meal carbohydrate absorption. In previous

clinical pharmacology studies, LY900014 and Humalog were shown to be equipotent. In the completed Phase 3 studies, LY900014 and Humalog substituted generally on a unit-for-unit basis; LY900014 and Humalog doses at Week 26 were not statistically significantly different after titration. In addition, no significant difference between LY900014 and Humalog were observed in pump settings or bolus calculator settings in Phase 3 studies either.

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

InPen™

Companion Medical's InPen system is an FDA-approved class II device for use with Humalog, Novolog, or Fiasp. Lilly has determined that LY900014 is suitable for use with the InPen system under the conditions of the current investigational study. The InPen system consists of a manually controlled pen injector and an app containing a logbook and a dose (bolus) calculator.

The InPen is a home-use reusable pen injector for single-patient use by people with diabetes aged 12 years and older for the self-injection of a desired dose of insulin. The pen injector is compatible with Humalog U-100 3.0 mL cartridges, which have the same dimensions to LY900014 cartridges, and single-use detachable and disposable pen needles. Cartridges of the pen injector allow the user to dial the desired dose from 0.5 to 30 units in one-half unit increments.

The InPen app is designed to manage with the InPen injector a wireless transfer of

- insulin dose
- insulin dose time
- mealtime carbohydrates
- time of meal

The InPen app also provides a dose calculator to aid bolus insulin dose calculations. Before the use of the InPen app dose calculator, a health care professional (HCP) must provide the participant with specific target blood glucose, insulin-to-carbohydrate ratio, insulin sensitivity parameters, and duration of insulin action to be entered into the InPen app.

Dexcom G6

Dexcom G6 CGM System is a real time, CGM device indicated for the management of diabetes in individuals aged 2 years and older. Dexcom G6 System is an FDA-approved class II device that can replace fingerstick blood glucose testing for diabetes treatment decisions.

Dexcom G6 CGM System has the following components:

- G6 CGM sensor
- G6 CGM transmitter
- G6 CGM receiver
- G6 System mobile app

The G6 CGM sensor continuously measures glucose concentration in interstitial fluid and can be worn for up to 10 days. When a new sensor is started, a code must be entered into the display device to use the G6 without fingerstick calibrations. Each sensor has its own code printed on the back of the adhesive patch. Calibration is not required if users enter a sensor code. The G6 CGM

transmitter contains a Bluetooth radio transceiver for communication with a compatible display device, either the G6 CGM receiver or a smart device. Participants in Study ITSZ will be using a smart device to receive data from the G6 CGM transmitter instead of the G6 CGM receiver.

The Dexcom G6 System mobile app is for iOS and Android. The mobile app provides an alternative display device to the receiver for users with compatible smart devices and behaves similarly to the receiver. The user has the ability to manually enter insulin dose and insulin dose time as well as meal carbohydrates and time into the mobile app. This dosing and meal information can also be entered retroactively.

2.3. Benefit-Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of LY900014 may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention (s) LY900014		
Hypoglycemia Hyperglycemia Hypersensitivity and Allergic reactions	See IB Section 6.2.2.5.1	Each participant will receive Diabetes education and counseling on how to avoid the risks of hypoglycemia and hyperglycemia at Visit 2. CGM alerts will be set up during Visit 2 for early detection of hypoglycemia and hyperglycemia. Participants with known hypersensitivity or allergy to any of the study medications or their excipients will be excluded from the study.
Study Procedures		
InPen and Mobile medical app (MMA)		
Errors of LY900014 dose delivery	LY900014 is not approved to be used with InPen; however, it is expected to perform similarly to Humalog due to the following reasons: • InPen is compatible with Humalog U-100 3.0 mL cartridges, which have the same dimensions to LY900014 cartridges • Lilly has internal data for LY900014 supporting in use stability for the container closure and fluid path (that is, needle), which are the same as Humalog • LY900014 and Humalog are shown to be equipotent in clinical pharmacology studies • LY900014 and Humalog substituted generally on a unit-for-unit basis in clinical pharmacology and Phase 3 studies • In the pivotal study of LY900014 in adult patients with T1D, Study ITRM, at study endpoint of 26 weeks, doses of LY900014 and Humalog were not significantly different after titration • There were no meaningful difference in safety observed between LY900014 and Humalog in Phase 3 studies (that is, incidence of adverse events and	• Lilly has completed preliminary testing of InPen supporting dose accuracy when used with LY900014. Definitive dose accuracy testing will be completed before study initiation • Real-time CGM guided insulin titration with hypo- and hyperglycemia alerts set up • Site selection: choose experienced primary investigators (PIs) and site staff with LY900014 and diabetes technology • Strict monitoring of patients through frequent interactions with investigators, who have 24/7 access to patient CGM data in CLARITY • Enrollment of technologically-competent and highly compliant patients • Carefully planned site training and patient training Based on the medical risk assessment, potential risks of using InPen with LY900014 off-label can be managed effectively upon the implementation of risk mitigation

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
	hypoglycemia) • There were no clinically meaningful difference between LY900014 and Humalog in pump settings or bolus calculator settings (including active insulin time) in Phase 3 studies	plans. Lilly Medical concluded that if InPen passes Lilly dose accuracy testing with LY900014, InPen can be safely used in Study ITSZ due to the expected similar performance between LY900014 and Humalog

Abbreviations: CGM = continuous glucose monitoring; T1D = type 1 diabetes.

2.3.2. Benefit Assessment

No direct clinical benefit is anticipated from participating in this trial due to the short nature of this study. However, some participants may benefit from improved glycemic control as a result of the dose titration strategy, frequent ICR, ISF, DIA, and insulin dose adjustments, and increased engagement with an HCP.

More detailed information about the known and expected benefits and risks of LY900014 along with its clinical and nonclinical development can be found in the IB.

More detailed information about the known and expected benefits and risks of degludec may be found in the USPI (Tresiba package insert, 2015).

2.3.3. Overall Benefit: Risk Conclusion

Considering the measures taken to minimize risk to participants involved in this study, the potential risks identified in association with LY900014 are justified by the potential benefits that may be afforded to participants with T1D.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the time that glucose values are within the target range 70 to 180 mg/dL from CGM use, after 35 days of using the study titration scheme with LY900014 treatment and degludec	Percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), with CGM use during the maintenance period
Secondary	
To evaluate ICR with LY900014 treatment	ICR at the end of the maintenance period
To evaluate the relationship between ICR and TDD with LY900014 treatment	ICR×TDD for the maintenance period
To evaluate total daily, basal, and prandial insulin dose with LY900014 treatment and degludec	Prandial: TDD ratio for the maintenance period
Tertiary/Exploratory	
To evaluate the safety of LY900014	Adverse events and vital signs
To explore the relationship between • ICR and TDD • ISF and TDD • ICR and ISF with LY900014 treatment	• Slope of the linear regression line of ICR or ISF on the reciprocal of TDD • Slope of the linear regression line of ICR on ISF, for the maintenance period
To explore ISF with LY900014 treatment	ISF at the end of the maintenance period
To explore glucose profiles, obtained from CGM use with LY900014 treatment	Actual and change from baseline in mean sensor glucose with CGM use during the maintenance period
To explore highest PPG level within 4 hours* after meal(s), obtained from CGM use, with LY900014 treatment	Actual and change from baseline in highest PPG level within 4 hours after meal(s), with CGM use during the maintenance period

Objectives	Endpoints
To explore the time from start of meal to highest PPG level within 4 hours* after meal(s), obtained from CGM use, with LY900014 treatment	Actual and change from baseline in minutes from start of meal to highest PPG level within 4 hours after meal(s), with CGM use during the maintenance period
To explore the percentage of time spent in hypoglycemic glucose ranges, obtained from CGM use, with LY900014 treatment	Actual and change from baseline in percentage of time with sensor glucose values <54 mg/dL, with CGM use during the maintenance period
To explore percentage of time spent in hyperglycemic glucose ranges, obtained from CGM use, with LY900014 treatment	Actual and change from baseline in percentage of time with sensor glucose values >250 mg/dL, with CGM use during the maintenance period
To explore within-day glucose variability, obtained from CGM use, with LY900014 treatment	Actual and change from baseline in within-day CV of sensor glucose, with CGM use during the maintenance period
To explore proportion of participants achieving CGM-based glycemic targets, with LY900014 treatment	The proportion of participants with percentage of time in • target glucose range, 70-180 mg/dL, >70% • hypoglycemia, <54 mg/dL, <1% • hyperglycemia, >250 mg/dL, <5%, with CGM use during the maintenance period
To explore fructosamine with LY900014 treatment	Fructosamine at the end of the maintenance period compared to baseline
To explore HbA1c with LY900014 treatment	HbA1c at the end of the maintenance period compared to baseline
To explore 1,5 Anhydroglucitol (AG) with LY900014 treatment	1,5 AG at the end of the maintenance period compared to baseline

Abbreviations: CGM = continuous glucose monitoring; CV = cardiovascular; HbA1c = hemoglobin A1c; ICR = insulin-to-carbohydrate ratio; ISF = insulin sensitivity factor; PPG = post-prandial glucose; TDD = Total Daily Dose.

* Excluding the glucose data from participants who have had the next meal event before the end of time interval.

4. Study Design

4.1. Overall Design

Study ITSZ is a multicenter, single-group, open-label, Phase 2, exploratory study that will be conducted in participants with T1D currently treated with insulin degludec and a rapid-acting insulin analog in an MDI regimen. The objective of the study is to assess the percentage of time glucose values are within the target range of 70 to 180 mg/dL after 35 days of titration using the study titration scheme.

The study will consist of the following periods:

- Screening and lead-in period
- Treatment period
  - Titration period
  - Maintenance period
- Safety follow-up period

4.1.1. Study Visits

Screening, Visit 1

The purpose of procedures at the screening visit is to establish eligibility for the study (see Sections 5.1 and 5.2). Participants will continue their pre-study rapid-acting insulin analog and their basal insulin dose. Insulin-to-carbohydrate ratio, insulin sensitivity factor (ISF), and DIA should not be changed unless for safety reasons during the screening period.

Lead-in Period, Visit 2

The lead-in period starts following Visit 2. During the lead-in period, all participants will administer Humalog as rapid-acting insulin with the InPen Pen Injector. Participants who enter the study on Novolog, Admelog, or Apidra will transition to Humalog at Visit 2. The dose of insulin degludec and the ICR, ISF, and DIA should not be changed unless for safety reasons.

Sponsor Provided CGM Session

At Visit 2, Dexcom G6 CGM sensors and transmitter will be dispensed to all participants who meet study entry criteria.

All participants will switch to a Lilly provided Dexcom G6 CGM system during Visit 2. Also, any participant using a personal Dexcom G6 will switch to a Lilly provided Dexcom G6 during Visit 2. All participants will use Dexcom G6 CGM from Visit 2 until Visit 14. Participants will grant permission to the site to access their CGM data.

At Visit 2, participants will insert a new Lilly provided sensor and transmitter. Between Day -11 and Day 46, participants will wear the study-provided G6 CGM system and change the sensor every 10 days or as needed. All participants should use the sensor code printed on the back of the adhesive patch to calibrate when starting a new sensor. Calibrating Dexcom G6 CGM using fingerstick meter values is prohibited in this study to avoid increased sensor measurement variability across participants caused by using different brands/models of glucose meters for calibration.

All participants will use the Dexcom mobile app on their smart phone to view their CGM data during the study. Participants who enter the study using Dexcom G6 CGM will not use their Dexcom G6 CGM receiver to view CGM data.

Sites will work with the participant to ensure:

- the Dexcom CGM mobile app is installed on the participant's smart phone
- participant has an active Dexcom mobile app business account
- CGM device and associated Mobile medical app (MMA) is set up so that
    - all alerts and notifications are enabled
    - alert levels are adjusted, if necessary
    - location services are enabled
- participant grants permission to the site to view his or her CGM data through CLARITY and SMS

During the lead-in period from Day -10 to Day -1, participants are required to enter the following data into the Dexcom mobile app every day:

- meal start time for breakfast, lunch, and dinner
- insulin degludec dose

Investigator staff should check CLARITY to ensure that participants are entering these data during the lead-in period.

Training related to the use of Dexcom G6 CGM and its associated mobile app will be provided at Visit 2. Abbreviated training following Visit 2 will be made available as deemed appropriate.

Minimum CGM Requirements

The CGM data collected during the lead-in period will be used as baseline CGM. Participants must have at least 5 days with a minimum of 70% CGM measures per day during the lead-in period to be eligible for treatment assignment. These 5 days do not need to be consecutive.

The investigator will have daily access to the SMS portal during the lead-in period and will print the participant's Data Acceptability Report to determine the participant's eligibility for treatment assignment. The investigator should determine before Visit 3 that the participant has met the minimum CGM eligibility requirements and then communicate to the participant their eligibility for treatment assignment. If the investigator becomes aware through SMS portal monitoring during the lead-in period that a participant will not meet the minimum CGM requirements before Visit 3, the site should advise the participant to re-schedule Visit 3 to a later date within the visit window.

InPen

During Visit 2, InPen Pen Injector and associated supplies will be dispensed to all participants who meet study entry criteria. The InPen mobile app will be downloaded onto the participants' smartphone.

Sites will work with the participant to ensure:

- InPen mobile app is installed on the participant's smart phone
- participant has an active InPen mobile app business account

- Participants have entered the following information in the InPen device and associated MMA:
    - Target blood glucose: this is the blood glucose value the participant is trying to achieve. It is prescribed by investigators and individualized for each participant in the study. The target blood glucose will be used by the dose calculator to calculate the correction bolus and is distinct from the glycemic targets used for insulin titration defined in Section 4.3.
    - ICR
    - ISF
    - DIA

Participants are required to enter meal or snack carbohydrates and current CGM glucose before each meal/snack into the InPen mobile app in order to use the bolus dose calculator during the study.

Training related to the use of InPen Reusable Pen Injector and its associated mobile app will be provided at Visit 2. Abbreviated training following Visit 2 will be made available as deemed appropriate.

Transcribing Data into the eCRF at Visit 2

At Visit 2, the investigator should transcribe the following data from the day before the visit into the eCRF:

- ICR
- ISF
- DIA

Diabetes Education

Initial training related to diabetes education and nutrition counseling will be provided at Visit 2 and other visits as needed. Appropriate site personnel will administer education using locally approved diabetes education materials and programs or by using other materials that may be provided by the Sponsor.

Treatment Period, Visit 3 to Visit 14

Treatment Assignment, Visit 3 (Day 0)

The investigator should determine eligibility for treatment assignment before Visit 3. There will be no early enrollment if a participant meets the minimum 5-day requirement of 70% CGM readings per day before Visit 3.

For participants who are eligible for treatment assignment, Humalog will be discontinued, and LY900014 will be initiated using their current ICR, ISF, and DIA at Visit 3. All participants who are not currently administering insulin degludec in the morning should switch to morning administration with the investigator's guidance. All participants should continue administering degludec in the morning throughout the treatment period.

Titration Period, Visit 3 through Visit 13 (Day 0 to Day 35)

Following treatment assignment at Visit 3, participants will enter a 35-day insulin titration period. The investigator may adjust the dose of insulin degludec, ICR, ISF, or DIA at any time from Visit 3 (Day 0) to Visit 13 (Day 35) to meet the glucose targets specified in Section 4.3.1.

Participant's ambulatory glucose profile will be reviewed using CGM data from CLARITY at each visit.

Participant's LY900014 dose will be reviewed using the InPen report. The investigator should confirm that the InPen report has been received before each study visit. Additionally, the investigator should confirm that the InPen report aligns with the clinical management of the participant. Based on these reports, insulin doses, ICR, ISF, and DIA will be adjusted as needed to reach the study specified glucose target (Sections 4.3.1 and 4.3.2).

Maintenance Period, Day 36 to Day 46

The maintenance period starts following Visit 13. Continuous glucose monitoring data collected during the maintenance period will be used as endpoint CGM data.

During the maintenance period, the investigator may not adjust the dose of insulin degludec, ICR, ISF, or DIA unless for safety reasons.

During the maintenance period from Day 36 to Day 45, participants are required every day to enter the following data into the Dexcom mobile app

- meal start time for breakfast, lunch, and dinner
- insulin degludec dose

Investigator staff should check CLARITY to ensure that participants are entering these data during the maintenance period.

Visit 14 (Day 46)

At Visit 14, participants will return to their non-study rapid-acting insulin analog regimen. Participants may decide to continue to administer degludec in the morning or switch to their pre-study dosing schedule. The investigator will determine basal and prandial insulin doses.

At Visit 14, participants will return to the personal CGM system that they were using before the study began. Participants should be reminded before Visit 14 that they will need to bring their personal CGM system to Visit 14.

Transcribing Data into the eCRF from Visit 3 to Visit 14

At every visit from Visit 3 to Visit 14 inclusive, the investigator should transcribe the following data from the day before the visit into the eCRF:

- ICR
- ISF
- DIA

Transcribing Data into the eCRF for Visit 3 and Visit 14 only

In addition to the ICR, ISF, and DIA, the investigator should transcribe the Humalog dose at Visit 3 (data from Day -10 to Day -1) and the LY900014 dose at Visit 14 (data from Day 36 to Day 45).

Safety Follow-up, Visit 801

All randomized participants who completed the treatment period should have a safety follow-up visit approximately 1 week after Visit 14.

Early Termination visit, ET Visit

Participants who discontinue investigational product (IP) permanently before completion of the treatment period for any reason will also be discontinued from the study. An (ET) visit should be conducted as soon as reasonably possible. After the ET visit, a safety follow-up assessment (Visit 801) should be conducted approximately 1 week after the ET Visit.

Transcribing Data into the eCRF at the ET Visit

At the early termination visit, the investigator should transcribe the following data from the day before visit into the eCRF:

- ICR
- ISF
- DIA
- LY900014 dose

4.2. Scientific Rationale for Study Design

This study will evaluate a new titration scheme of LY900014 in participants with T1D who use insulin degludec for basal glucose control in an MDI regimen. The study will last up to 73 days and include an intensive insulin titration period of 35 days followed by a 11-day maintenance period. The percentage of time glucose values are within the target range of 70 to 180 mg/dL after 35 days titration of using the study titration scheme will be evaluated.

4.3. Justification for Dose

In clinical practice, prandial insulins are often titrated based on the 'next pre-meal glucose'. For example, clinicians use the pre-lunch blood glucose value to assess the adequacy of the breakfast prandial dose. This commonly used titration scheme may not be optimized for the novel time-action profile of LY900014. An alternate approach of using peak PPG values or the change from pre-meal levels may be better-suited to titrating ultra-rapid acting prandial insulins. In particular, the 'faster on-faster off' profile of LY900014 might allow more aggressive prandial dosing that would further improve PPG without increasing the risk of late post-meal hypoglycemia.

The basal and bolus dosing of insulin in this study will be individually titrated based on real-time Dexcom G6 CGM readings and frequent interaction with investigators. The Dexcom G6 CGM system has been approved by the FDA to replace fingerstick blood glucose testing for diabetes treatment decisions.

4.3.1. Target Glucose Values for Titration of Insulin Therapy

The overall glycemic control goals for all participants enrolled in the study are generally similar to those recommended by the American Association of Clinical Endocrinologists (AACE) (Bailey et al. 2016). A target for overnight glucose excursion (the difference between bedtime and pre-breakfast glucose levels) is also provided to guide insulin titration.

Fasting glucose, overnight glucose excursion, and post-prandial glucose target values used to reach the glucose goals and for determination of titration in insulin therapy are listed as follows.

Time of Target Glucose Measurement	Glucose Target (Range)
Fasting glucose	100 mg/dL (range 80-110 mg/dL)
Overnight glucose excursion (the difference between bedtime and pre-breakfast glucose levels)	≤±30 mg/dL
Postprandial glucose peak	<140 mg/dL or <20% increase from premeal level

4.3.2. LY900014

Participants will perform carbohydrate counting for each meal and snack throughout the study. Participants should use the bolus calculator function on the InPen app to determine all meal/snack and correction doses. Prandial insulin dose is calculated based on the estimated carbohydrate content of the meal and investigator prescribed ICR. Participants are allowed to eat snacks during the study. However, each snack should be covered by bolus insulin (if applicable). Participants should routinely use correction boluses as needed for hyperglycemia management based on the investigator-prescribed ISF.

Treatment Period

During Visit 3, participants will receive instructions from the investigator to discontinue their pre-study rapid-acting insulin. LY900014 will be initiated unit-for-unit based on the pre-study ICR and ISF. LY900014 should be administered immediately (0 to 2 minutes) before the start of each meal and snack (if applicable).

During the insulin titration period (Visit 3 to Visit 13), ICR, ISF and DIA will be titrated by investigators based on Dexcom G6 CGM readings approximately twice per week as needed (see Section 1.3 SoA). Every effort should be made to reach the glycemic targets of:

- Post-prandial glucose peak<140 mg/dL **or**
- <20% rise from pre-meal level

During the maintenance period (Visit 13 to Visit 14), ICR, ISF, and DIA will remain unchanged unless for safety reasons. The insulin dose may be decreased at any time throughout the treatment period for safety reasons.

Safety follow-up period

At Visit 14, participants will switch back to the pre-study rapid-acting insulin. The dose will be prescribed by the investigator.

4.3.3. Insulin Degludec

Screening and lead-in period

During the screening and lead-in period, participants will continue their pre-study dose of insulin degludec and the dose should be kept stable unless for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

Treatment period

At Visit 3, participants who do not administer insulin degludec in the morning will follow the investigator's instructions to switch to morning dosing. All participants will administer insulin degludec in the morning from Visit 3 throughout the treatment period until the end of maintenance period, Visit 14.

During the insulin titration period (Visit 3 to Visit 13), the insulin degludec dose will be titrated by the investigator based on Dexcom G6 CGM readings approximately twice per week as needed (see Section 1.3 SoA) to reach the fasting glucose target of 100 mg/dL (range 80 to 110 mg/dL). Every effort should be made to reach the overnight glucose excursion target of ≤±30 mg/dL during the titration period.

During the maintenance period (Visit 13 to Visit 14), the dose of insulin degludec will be kept unchanged unless for safety reasons.

Safety follow-up period

During the safety follow-up period (Visit 14 to Visit 801), participants may choose to continue to dose insulin degludec in the morning or switch to a different dosing timing. The dose of insulin degludec will be prescribed by the investigator.

4.4. End of Study Definition

The end of the study is defined as the date of the last scheduled procedure for the last participant shown in the Schedule of Activities.

5. Study Population

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted. The study population will consist of participants with a diagnosis of T1D currently being treated with insulin degludec and a rapid-acting insulin analog in an MDI regimen.

Eligibility of participants will be based on the results of the assessments performed at screening as described in the Schedule of Activities (Section 1.3). All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria.

The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. The nature of any conditions present at the time of the initial screening and any preexisting conditions will be documented in the eCRF.

For screen failures and rescreening activities within the screening period, see Section 5.4.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

Informed Consent

1. Capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol

Age and Sex

2. Participant must be 18 to 65 years of age, inclusive, at the time of signing the informed consent.
3. Male or Female
    - Male: no contraception required
    - Female: A female participant is eligible to participate if she is not pregnant, intending to become pregnant, or breastfeeding, and at least one of the following conditions applies:
        - Is not a woman of childbearing potential (see Appendix 4, Section 10.4)

          OR
        - Is a woman of childbearing potential (WOCBP) and must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of two effective methods of contraception for the entirety of the study. Contraception requirements for participants are provided in Appendix 4 (Section 10.4).
        - A WOCBP 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 text within 24 hours prior to exposure to investigational product (IP) at Visit 3.

Type of Participant and Disease Characteristics

4. Have been clinically diagnosed with T1D for at least 1 year before screening, and continuously using intensive insulin therapy for at least 1 year.
5. Have been on stable insulin requirements at the discretion of the investigator's judgment with total daily dose (TDD) ≤1.2 U/kg/d according to the average TDD from the three days before Visit 1
6. Have been on the same type of rapid-acting insulin analog (Humalog U-100, Novolog, Admelog, or Apidra) for at least 30 consecutive days before screening
7. Are proficient, in the opinion of the investigator, in carbohydrate counting and are willing to use carbohydrate counting to calculate bolus doses throughout the study
8. Routinely use correction boluses as needed for hyperglycemia with stable correction factor in the opinion of the investigator
9. Have been treated for at least 30 consecutive days before screening with insulin degludec U-100
10. Have an HbA1c value ≥6.0 and ≤8.0%, according to the central laboratory at screening (Visit 1).
11. Have a body mass index (BMI) of ≤35.0 kg/m^2 at screening (Visit 1).
12. CGM system
    - Must be using unblinded personal CGM for diabetes management with total CGM use of 2 months in the prior 6 months
    - Must be willing and able to use a study-provided Dexcom G6 CGM system, including sensor and transmitter, during the study and must cease use of their personal CGM system, including Dexcom receiver if applicable
    - Must be willing and able to use the Dexcom mobile application and grant site permission to access their CGM data during the study
13. Must be willing to use InPen to inject rapid-acting insulin and share data with investigator via email
14. Have access to WiFi or a cellular data plan for transmission of data
15. Have an active email account
16. Have access to a Bluetooth enabled smart phone (either Android or iPhone) compatible with both the Dexcom and InPen mobile applications for transmission of the data
17. Have refrigeration in the home or have ready access to refrigeration for storage of insulin therapy
18. Have a regular sleep/wake cycle (for example, those who are awake during the day and sleep during the night)

19. Capable of and willing to do the following:
    a. Inject insulin with the use of an insulin injection device (insulin pen) according to manufacturer guidelines
    b. Follow the investigator's instructions to titrate insulin based on glucose targets
    c. Able to read and understand the language(s) available for devices and applications used in the study
    d. Comply with the use of the study insulin and scheduled visits
    e. Receive diabetes education

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions

20. Have had more than 1 episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within the last 90 days before screening
21. Have hypoglycemia unawareness as judged by the investigator
22. Have had more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycemia or diabetic ketoacidosis) within 6 months before screening (Visit 1)
23. Have a scheduled surgery or plastic surgery during the study
24. Have cardiovascular disease within the last 6 months before screening, defined as
    - stroke
    - decompensated heart failure New York Heart Association Class III or IV
    - myocardial infarction
    - unstable angina pectoris
    - coronary arterial bypass graft
25. Gastrointestinal
    - Have gastroparesis before screening
    - Undergone gastric bypass or sleeve gastrectomy (bariatric) surgery before screening
    - Undergone restrictive bariatric surgery (like Lap-Band®) before screening
26. Hepatic
    - Have acute or chronic hepatitis or cirrhosis

- Have obvious clinical signs or symptoms of any other liver disease EXCEPT non-alcoholic fatty liver disease (NAFLD). Those with NAFLD are eligible.
- Have elevated liver enzyme measurements, as determined by the central laboratory at screening according to the parameters are as follows:
    i. Total bilirubin ≥2 times the upper limit of normal (ULN; except for Gilbert's syndrome) as defined by the central laboratory, or
    ii. ALT/serum glutamic pyruvic transaminase (SGPT) ≥3 times ULN as defined by the central laboratory, or
    iii. Aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT) ≥3 times ULN as defined by the central laboratory

27. Renal
    - History of renal transplantation
    - Currently receiving renal dialysis
    - Serum creatinine >2.0 mg/dL (177 μmol/L) at screening as measured by the central laboratory
28. Cancer
    - Have active or untreated malignancy
    - Have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years
    - At increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator
29. Have any other serious disease or condition (for example, known drug or alcohol abuse or psychiatric disorder) that, in the opinion of the investigator, would pose a significant risk to the participant, preclude the participant from following and completing the protocol, or interfere with the interpretation of safety, efficacy, or PD data
30. Have vision or hearing loss that impairs recognition of CGM screens, alerts and alarms
31. Have experienced significant weight loss or gain (>5%) in body weight in the 3 months before screening
32. Have known hypersensitivity or allergy to any of the study medications or their excipients
33. Have had a blood transfusion or severe blood loss within 3 months before screening or have any hematologic condition that may interfere with HbA1c measurement (for example, hemoglobinopathy, hemolytic anemia, and sickle-cell disease)

Prior/Concomitant Therapy

34. Are taking drugs that may significantly affect glycemic control (for example, niacin [allowed if <1.0 g/day], bile acid sequestrants)
35. Glucocorticoid therapy
    - Are currently receiving chronic (lasting longer than 7 consecutive days) systemic glucocorticoid therapy through the following preparations
        i. Intravenous
        ii. IM
        iii. Subcutaneous
        iv. Oral
        v. Intra-articular
    - Have received such therapy within 4 weeks immediately before screening except for replacement therapy for adrenal insufficiency
36. Are currently taking, or have taken within the 3 months preceding screening, prescription or over-the-counter medications to promote weight loss
37. Are using any oral, injectable, or inhaled (except for the occasional, supplemental use of Afrezza) medication intended for the treatment of diabetes mellitus other than an MDI regimen including a rapid-acting insulin analog and a basal insulin analog in the 90 days before screening

Prior/Concurrent Clinical Study Experience

38. Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study
39. Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed

Other Exclusions

40. Per the principal investigator's discretion, is not technologically competent
41. Are unable and/or unwilling to provide informed consent, to make themselves available for the duration of the study, to comply with the use of a data collection device to directly record data, or to abide by study procedures
42. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
43. Are Lilly employees or representatives (including employees, temporary contract workers, or designees responsible for the conduct of the study)

5.3. Lifestyle Considerations

During the study, participants must avoid:

- donating blood or blood products
- major changes in diet or exercise

5.3.1. Meals and Dietary Restrictions

During the study, participants should avoid major changes in diet or exercise. Participants should have 3 doses of prandial insulin per day and eat 3 main meals per day (morning, midday, and evening) on a regular basis. Snacking is allowed if it is covered by a bolus dose of rapid-acting insulin (if applicable).

5.3.2. Activity

During the study, participants should continue their usual exercise habit and avoid major changes in exercise. Participants should not receive an intensive exercise program with the intent of reducing body weight at any time during the study.

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Individuals who were required to unexpectedly discontinue from the study during screening or the lead-in period (for example, due to enrollment pause related to the COVID-19 public health emergency) will be allowed one rescreening. All participants that rescreen will restart at Visit 1 and complete all screening procedures.

Retesting of laboratory samples is not allowed, except for cases in which results are not available from the original sample.

6. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

Intervention Name	LY900014	Degludec
Type	Drug	Drug
Dose Formulation	Solution	Solution
Unit Dose Strength(s)	100 units/mL	100 units/mL
Dosage Level(s)	Individualized dosing	Individualized dosing
Route of Administration	Subcutaneous	Subcutaneous
Use	Experimental prandial insulin (0-2 minutes before start of meal or snack [if applicable])	Basal insulin
IMP and NIMP	IMP	NIMP
Sourcing	Provided centrally by the Sponsor	Provided centrally by the Sponsor

Abbreviations: IMP = Investigational Medicinal Product; NIMP = Non-Investigational Medicinal Product

6.1.1. Medical Devices

The medical device for use in this study is the InPen.

Manufacturer instructions for use for InPen are available at www.companionmedical.com.

All device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 8.3.7) and appropriately managed by the sponsor.

6.2. Preparation/Handling/Storage/Accountability

- The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
- Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
- The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
- 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 insulin should be maintained at room temperature. In-use insulin must not be used after 28 days.

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a single-group, open-label study.

6.4. Study Intervention Compliance

Compliance for CGM will be assessed by the Clarity reports and SMS reports during all site visits. Compliance for prandial insulin administration will be assessed by the InPen report during all site visits. If the investigator deems that the participant is noncompliant with CGM or prandial insulin administration, the participant may be discontinued from the study.

Concomitant medication compliance and adherence to the visit window will be assessed by direct questioning during all site visits. If a participant is deemed noncompliant, he or she will receive additional diabetes education and training and the importance of compliance with the protocol will be reinforced. If the participant continues to be noncompliant in the opinion of the investigator, then the participant will be discontinued from the study.

A record of the number of LY900014 cartridges dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays and/or dose reductions will also be recorded in the CRF.

6.5. Concomitant Therapy

The following concomitant therapies

- Are NOT allowed at any time during the study:
  - Acetaminophen dosed in quantities greater than 1 gram every 6 hours

  - Non-study insulin (except for device failure when participants can switch to pre-existing rapid-acting insulin for a maximum of 48 hours)
  - Non-insulin injectables for the treatment of diabetes (for example, pramlintide, glucagon-like peptide-1 [GLP-1] agonists)
  - Oral antidiabetic medications: dipeptidyl peptidase-4 inhibitors, Sodium-glucose co-transporter-2 inhibitors, GLP-1 agonists, metformin, sulfonylureas, glinides, alpha-glucosidase inhibitors, and so on
  - Systemic glucocorticosteroids
  - Intra-articular steroid preparations
- ARE allowed at any time during the study
  - Inhaled, intranasal intraocular, and non-occlusive, limited topical steroid preparations

Lilly Medical should be contacted if there are any questions regarding concomitant or prior therapy.

6.6. Dose Modification

Dosing will be individualized based on readings from the study-provided Dexcom G6 CGM and through frequent interactions with investigators. See Section 4.3 for details of dose modification.

6.7. Intervention after the End of the Study

LY900014 will not be made available to participants after conclusion of the study. During the safety follow-up period, participants will return to the rapid-acting analog insulin regimen they had before the treatment period. Participants may choose to continue to dose insulin degludec in the morning or switch to an evening dose. The investigator will determine the dose for the rapid-acting analog insulin and for degludec.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants who need to permanently discontinue from study treatment will also be discontinued from the study. At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted. After the early discontinuation visit, a safety follow-up assessment (Visit 801) should be conducted approximately 1 week after the early termination visit.

Please see the SoA for the timing of these visits, for data to be collected at the time of study discontinuation and follow-up, and for any further evaluations that need to be completed.

Discontinuation is expected to be uncommon.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant will be withdrawn from the study in the following circumstances:

- if he or she uses a non-study rapid-acting insulin for a period greater than 48 hours during the treatment period.
- if he or she loses contact with the site for more than 10 days.
- if he or she uses prohibited concomitant medication during the study as specified in Section 6.5.

A participant may withdraw from the study:

- at any time at his or her own request
- at the request of his or her designee (for example, parents, or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- if the participant, 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 before introduction of the new agent
- if the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to study drug administration, the participant should be permanently discontinued from the investigational drug.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.2.1. Discontinuation of Inadvertently Enrolled Participants

If the sponsor or investigator identify a participant who did not meet enrollment criteria and was inadvertently enrolled, then the participant should be discontinued from study treatment unless there are extenuating circumstances that make it medically necessary for the participant 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 participant to continue in the study with or without treatment with investigational product.

Safety follow-up is as outlined in Section 1.3 (Schedule of Activities), Section 8.2 (Safety Assessments), and Section 8.3 (Adverse Events and Serious Adverse Events) of the protocol.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she loses contact with the study site for more than 10 days. Site personnel are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

8.1.1. Primary Efficacy Assessments

The primary efficacy measure is the change from baseline in percentage of time with sensor glucose values between 70 and 180 mg/dL (both inclusive), from CGM use in the maintenance period.

8.1.2. Secondary Efficacy Assessments

Secondary efficacy assessments for this study are

- Change from baseline in ICR at the end of the maintenance period
- ICR×TDD for the maintenance period
- Prandial:TDD ratio for the maintenance period

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA Section 1.3.

The actual and change from baseline in percentage of time with sensor glucose values <54 mg/dL will be evaluated with CGM as an exploratory objective.

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems. Height and weight will also be measured and recorded.

Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the Schedule of Activities (Section 1.3).

8.2.3. Electrocardiograms

Single 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT.

8.2.4. Clinical Safety Laboratory Assessments

See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency. See Section 10.5 (Appendix 5) for clinical laboratory testing for close hepatic monitoring and see Section 10.2.1 for clinical laboratory testing for hypersensitivity.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participants' condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal or baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2 (Appendix 2) and the assessments described in Section 10.5 (Appendix 5) and Section 10.2.1, must be conducted in accordance with the laboratory manual and the SoA.

If laboratory values from non-protocol-specified laboratory assessments performed at the institution's local laboratory require a change in participant management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then the results must be recorded in the CRF.

8.2.5. Self-monitoring of Blood Glucose

Self-monitoring of blood glucose is optional in this study. Insulin titration will be guided by real-time CGM readings from the Dexcom G6 CGM during this study. Dexcom G6 CGM has been approved by FDA for making clinical decisions. In case glucose alerts and readings from Dexcom G6 CGM do not match participant's symptoms, the participant can use a finger stick blood glucose value to make treatment decisions.

All participants will wear Dexcom G6 CGM throughout the study until the end of maintenance period. Calibrating Dexcom G6 CGM using finger stick measurement is not allowed. All participants should use the sensor code printed on the back of adhesive patch to calibrate when starting a new sensor.

8.2.6. Hypoglycemia

Participants will be trained about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and how to discuss hypoglycemic events with investigators.

Hypoglycemia will be described using the following definitions:

- **Level 1:** Glucose <70 mg/dL (3.9 mmol/L) and ≥54 mg/dL (3.0 mmol/L)
- **Level 2:** Glucose <54 mg/dL (3.0 mmol/L)
- **Level 3: Severe hypoglycemia:**

  A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Participants have 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. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of blood glucose concentration to normal is considered sufficient evidence that the event was induced by a low blood glucose concentration.

  - The 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 participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
  - All episodes of severe hypoglycemia must be reported as SAEs on the AE eCRF page and on the SAE eCRF page.

Any events of severe hypoglycemia categorized as level 3 per the evaluation of investigators will be collected from ICF signing to Visit 801.

Episodes of hypoglycemia categorized as level 1 or level 2 will be analyzed based on data from the CGM sensor session. Therefore, level 1 and level 2 hypoglycemic events do not need to be reported as an AE.

8.2.7. Safety Monitoring

The principle investigator will monitor safety and laboratory data throughout the study and should discuss safety concerns with the sponsor immediately upon occurrence or awareness of the concern to determine whether the participant should continue or discontinue study drug.

8.2.7.1. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, the event will be reported as a spontaneous AE. Additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per the local standard of care.

In the case of generalized urticaria or anaphylaxis, additional blood, or urine samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

8.2.7.2. Hepatic Monitoring

If a participant develops symptoms that warrant liver function assessment, liver function tests as detailed in Section 10.5 should be performed. If these tests are abnormal, clinical and laboratory monitoring should be initiated by the investigator.

8.3. Adverse Events and Serious Adverse Events

Adverse events will be reported by the participant, or when appropriate, by a caregiver or surrogate..

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention or the study (See Section 7).

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

All AEs occurring after signing the ICF are recorded in the AE eCRF and assessed for serious criteria.

The SAE reporting to sponsor begins after the participant has signed the ICF and has received study drug. However, if an SAE occurs after signing the ICF, but before receiving LY900014, it needs to be reported ONLY if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Section 10.3 (Appendix 3). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Section 10.3 (Appendix 3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE or SAE report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs, and AEs of special interest (as defined in Section 8.3.6), will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is provided in Section 10.3 (Appendix 3).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

Pregnancy (maternal or paternal exposure to study treatment) does not meet the definition of an AE. However, to fulfill regulatory requirements, any pregnancy should be reported following the SAE process described in Section 10.4 (Appendix 4) to collect data on the outcome for both mother and fetus.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected after the start of study intervention and until a period that is at least 5 terminal half-lives after the last dose.

If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Section 10.4 (Appendix 4).

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Adverse Events of Special Interest

There are no adverse events of special interest (AESIs) in Study ITSZ.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of products provided in the study.

Sponsor collects product complaints on investigational products 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.

Participants will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the investigational product so that the situation can be assessed.

Product complaints will be reported by the investigator to the sponsor per the Product Complaint Form.

Note: Adverse events or SAEs that are associated with a product complaint will also follow the processes outlined in Section 8.3.3 and Section 10.3 (Appendix 3) of the protocol.

8.3.7.1. Time Period for Detecting Product Complaints

Product complaints that result in an AE will be detected, documented, and reported to the sponsor during all periods of the study in which the drug or device is used.

If the investigator learns of any product complaint at any time after a participant has been discharged from the study, and such incident is considered reasonably related to a drug or device provided for the study, the investigator will promptly notify the sponsor.

8.3.7.2. Prompt Reporting of Product Complaints to Sponsor

The Product Complaint Form will be available to the investigator on an investigator site portal and all product complaints will be reported according to the instructions on the form. Additionally, the investigator will be supplied with product complaint reporting training materials.

8.3.7.3. Follow-up of Product Complaints

Follow-up applies to all participants, including those who discontinue study intervention. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the product complaint. New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator and submitted to the sponsor.

8.4. Treatment of Overdose

In the event of an overdose, refer to the IB for LY900014, or to the product label for degludec.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Not applicable.

8.6. Pharmacodynamics

Not applicable.

8.7. Genetics

Not applicable

8.8. Biomarkers

Not applicable.

8.9. Immunogenicity Assessments

Not applicable.

8.10. Health Economics

Not applicable.

9. Statistical Considerations

9.1. Statistical Hypotheses

As an exploratory pilot dose optimization study, the primary objective of Study ITSZ is to evaluate the percentage of time with glucose values within target range (70 to 180 mg/dL, both inclusive) after 35 days of using the study titration scheme with LY900014 treatment and degludec.

The study will investigate if a more aggressive ICR is needed with LY900014 treatment for participants to reach the study-specific glucose target, compared to the "500 Rule" that is currently used in clinical practice.

9.2. Sample Size Determination

Approximately 34 participants will be assigned to study treatment such that 30 evaluable participants will complete the maintenance period, assuming a 10% dropout rate.

The study is not strictly powered to demonstrate a statistically significant change from baseline in the primary endpoint (percentage of time with glucose within 70 to 180 mg/dL) because of the exploratory nature of the study.

Using a standard deviation of 12%, the sample will provide approximately 80% coverage probability that the half-width of the 95% confidence interval of the change from baseline in the primary endpoint falls within 4.93%.

9.3. Populations for Analyses

The following populations are defined:

Population	Description
Entered	All participants who give informed consent
Enrolled	All participants who continue the study after Visit 2
Treated	All assigned participants who receive at least 1 dose of the assigned study treatment after Visit 3

9.4. Statistical Analyses

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 statistical analysis plan (SAP) or the clinical study report. Additional exploratory analyses of data will be conducted, as deemed appropriate.

9.4.1. General Considerations

Unless otherwise specified, all efficacy and safety analyses will be conducted on the Treated Population. Unless otherwise noted, all tests will be conducted at a 2-sided alpha level of 0.05, and confidence intervals will be calculated at 95%, 2-sided. Comparison between baseline and

endpoints will be performed at the full significance level of 0.05. No multiplicity adjustment will be made. Baseline is defined as the last non-missing measurement at or before the treatment assignment (Visit 3) unless otherwise specified.

An analysis of covariance (ANCOVA) will be used to analyze continuous variables that are planned to be collected only for baseline and endpoint. The model will include baseline as a covariate.

A restricted-maximum-likelihood-based, mixed model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables collected only at baseline and more than one scheduled post-baseline visits according to SoA in Section 1.3. All the longitudinal observations at each scheduled post-baseline visit will be included in the analysis. The model for the analysis of the primary efficacy endpoint will include the fixed class effect of visit, and the random effect of patient. 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. If the analysis still does not converge with Compound symmetry without heterogeneous variances, only summary statistics will be provided.

For continuous measures, summary statistics will include sample size, mean, standard deviation, median, minimum, and maximum for both the actual and the change from baseline measurements. Least-square (LS) means and standard errors derived from the analysis models will also be displayed for the actual and the change from baseline measurements.

For categorical measures, summary statistics will include sample size, frequency, and percentages. No statistical analyses will be conducted for baseline and endpoint comparison.

All CGM outcome variables will only be derived for Visit 3 (baseline) and Visit 14 (endpoint) based upon the CGM data collected from valid CGM days, excluding data (if any) that are collected while patients are temporarily off Humalog during the lead-in period or temporarily off IP during the maintenance period. A valid CGM day to be counted into the calculation for a visit must have at least 70% of the total measures that are supposed to be obtained.

9.4.2. Primary Endpoint(s)

The primary objective of this study is to evaluate the percentage of time with glucose values within target range (70 to 180 mg/dL, both inclusive) after 35 days of using the study titration

scheme with LY900014 treatment and degludec. Both actual and change from baseline will be derived and analyzed by the ANCOVA model as described in Section 9.4.1.

The primary analyses will be conducted based upon the CGM data collected for Visit 3 (baseline) and Visit 14 (endpoint), excluding data (if any) that are collected while patients are temporarily off Humalog during the lead-in period or temporarily off IP during the maintenance period.

9.4.3. Secondary Endpoint(s)

Additional continuous secondary efficacy variables, as well as the change from baseline for these variables, will be analyzed by the MMRM or ANCOVA model as described in Section 9.4.1.

Relationships between ICR and TDD will be evaluated through regression lines (ICR versus 1/TDD) and compared with the "500 Rule," which is currently used in clinical practice where ICR = 500/TDD (Section 2.1).

9.4.4. Exploratory Endpoints

Additional continuous exploratory efficacy variables, as well as the change from baseline for these variables, will be analyzed by the MMRM or ANCOVA model described in Section 9.4.1, unless otherwise specified.

Relationships between the following endpoints will be explored through regression lines (King et al. 2007a, 2007b).

- ISF and 1/TDD
- ICR and ISF
- TBD and weight

9.4.5. Other Safety Analyses

Safety measures will include AEs, vital signs, and treatment exposure. Events that are newly reported after the first dose of IP used or reported to worsen in severity from baseline (details will be described in SAP) will be considered TEAEs.

Analyses of AEs will be descriptive and include all data collected during the treatment period. AEs during the lead-in period and the safety follow-up period will be provided in a listing.

Serious AEs, AEs reported as the reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term sorted by decreasing frequency. Treatment-emergent AEs will also be summarized by preferred term sorted by decreasing frequency within the SOC for all TEAEs and by maximum severity. For events that are gender-specific (as defined by MedDRA), the denominator and computation of the percentage will include only patients from the given gender. The number and proportion of patients with at least 1 event for each type of event will also be summarized.

In addition, time in hypoglycemic ranges will be assessed by CGM analyses.

9.4.6. Other Analyses

Analysis details for additional exploratory endpoints will be described in the SAP.

9.5. Interim Analyses

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary, the appropriate Lilly medical director, or designee, will be consulted to determine whether it is necessary to amend the protocol.

9.6. Data Monitoring Committee

No Data Monitoring Committee is planned for this study.

10. Supporting Documentation and Operational Considerations

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

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

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the participant and answer all questions regarding the study.

Participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.

The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.

Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor. Any participant records, datasets or tissue samples that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent.

The participant must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

Reports

The sponsor will disclose a summary of study information, including tabular study results, on publicly available website where required by local law or regulation.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the United States (US) and European Union (EU) and after the primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank, or annotated case report forms, will be provided in a secure data sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.clnicalstudydatarequest.com.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

- The sponsor or designee is responsible for the data management of this study including quality checking of the data.

- The sponsor assumes accountability for actions delegated to other individuals (for example, Contract Research Organizations).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the period outlined in the Clinical Trial Agreement (CTA) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

- In addition, Sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by Sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

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 system (EDC) 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.

Data collected via the sponsor-provided data capture system will be stored at a single third-party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system. Before 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 Sponsor data warehouse.

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

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site and Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines

- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

10.1.9. Publication Policy

In accordance with the sponsor's publication policy the results of this study will be submitted for publication by a peer-reviewed journal if the results are deemed to be of significant medical importance.

10.1.10. Investigator Information

Physicians with a specialty in endocrinology or primary care physicians specializing in endocrinology or internal medicine will participate as investigators in this clinical trial.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed below will be performed by the central laboratory except where indicated. Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol. Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations. Investigators must document their review of each laboratory safety report.

For the timing and frequency of the tests refer to the Schedule of Activities in Section 1.3.

Clinical Laboratory Tests[a]

Hematology	**Clinical Chemistry (Serum Concentrations of)**
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Chloride
Neutrophils, segmented	Blood urea nitrogen (BUN)
Lymphocytes	Creatinine
Monocytes	Glucose
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
Platelets	Magnesium
	Uric acid
Pregnancy Test (females only)[b]	Total protein
Follicle-stimulating hormone[c]	Albumin
	Calcium
Urinalysis	Creatine kinase (CK)
Specific gravity	1,5 Anhydroglucitol
pH	Fructosamine
Protein	
Glucose	**HbA1c**
Ketones	
Blood	
Urine leukocyte esterase	
Bilirubin	
Nitrite	

[a] All laboratory tests will be assayed by a Lilly-designated central laboratory, unless otherwise noted.

[b] Serum pregnancy test must be performed in women of childbearing potential at Visit 1 followed by a urine pregnancy test within 24 hours before IP exposure at randomization and at other times at the investigator's discretion.

[c] Follicle-stimulating hormone test must be performed at Visit 1 for women at least 40 years of age with an intact uterus, not on hormone therapy, and who has had cessation of menses for at least 1 year without an alternative medical cause.

10.2.1. Hypersensitivity Clinical Laboratory Tests

Laboratory testing should be performed at the time of a Systemic Hypersensitivity Event. Important information about why, when, and what to test for are provided as follows. The management of the AE may warrant laboratory testing beyond that described below and should be performed as clinically indicated.

Laboratory testing during a Systemic Hypersensitivity Event is not performed for diagnostic purposes. Its intent is several fold:

- To help characterize and classify systemic hypersensitivity reactions
- To meet regulatory expectations
- To improve subsequent clinical management by helping to distinguish between the various mechanistic bases of anaphylaxis

When should labs be obtained?

- In the presence of generalized urticaria or if anaphylaxis is suspected
- After the subject has been stabilized, obtain a sample within 1 to 2 hours of the event; however, samples may be obtained as late as 12 hours after the event as analytes can remain altered for an extended period of time. Record the time at which the sample was collected.
- Obtain a follow-up sample at the next regularly scheduled visit or after 4 weeks, whichever is later.

What labs* should be obtained?

- Tryptase**
- ADA and LY concentration (PK)
    - ADA testing should include drug-specific immunoglobulin E (IgE) or the basophil activation test (BAT)#. These tests are not routinely available and need to be developed for individual molecules based on their evolving safety profile. Samples are collected, and testing conducted once the assay is available, as appropriate. Please consult an immunologist within GPS for further guidance.
- Complement
    - C3, C3a, and C5a
- Cytokines
    - Interleukin (IL)-6, IL-1β, IL-10 (or any cytokine panel that includes these 3 cytokines)

* These laboratories are bundled in the Clinical Laboratory Operations Hypersensitivity Lab Testing Kit

** If a tryptase sample is obtained more than 2 hours after the event (that is, within 2 to 12 hours), or is not obtained because more than 12 hours have lapsed since the event, obtain urine for *N*-methylhistamine (NMH) testing. Note that for tryptase serum samples obtained within 2 to 12 hours of the event, urine NMH testing is performed in addition to tryptase testing. Collect the first void urine following the event. Obtain a follow-up urine for NMH testing at the next regularly scheduled visit or after 4 weeks, whichever is later.

[#] The BAT is an *in vitro* cell based assay that only requires a serum sample. It is a surrogate assay for drug-specific IgE but is not specific for IgE.

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (that is, ECG, radiological scans, and vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. Such a finding includes an episode considered to be related to hypoglycemia categorized as either level 1 or level 2 based on plasma glucose levels.
  - Level 1: <70 mg/dL (3.9 mmol/L) and glucose ≥54 mg/dL (3.0 mmol/L)
  - Level 2: <54 mg/dL (3.0 mmol/L)
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (for example, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Is categorized as level 3 hypoglycemia: a severe event characterized by altered mental and/or physical status requiring assistance

b. Results in death

c. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

d. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization' occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

e. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

f. Is a congenital anomaly/birth defect

g. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participants' medical records to Sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to Sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

  An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as 'severe.'

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A 'reasonable possibility' of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB and/or Product Information, for marketed products, in his or her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to Sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to Sponsor or designee.
- The investigator may change his or her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs
• The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. • New or updated information will be recorded in the originally completed CRF. • The investigator will submit any updated SAE data to Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool
• The primary mechanism for reporting an SAE will be the electronic data collection tool. • If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the electronic system as soon as it becomes available. • After the study is completed at a given site, the electronic data collection tool will be taken offline to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken offline, then the site can report this information on a paper SAE form (see next section) or to Lilly Medical by telephone. • Contacts for SAE reporting can be found at 1.800.LillyRx.

SAE Reporting via Paper CRF
• Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Lilly Medical. • Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames. • Contacts for SAE reporting can be found at 1.800.LillyRx.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile. If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women <u>not</u> of childbearing potential

1. Premenarchal
2. Premenopausal female with one of the following:
    - Documented hysterectomy
    - Documented bilateral salpingectomy
    - Documented bilateral oophorectomy

    For individuals with permanent infertility due to an alternate medical cause other than the above, (for example, Mullerian agenesis and androgen insensitivity), investigator discretion should be applied to determining study entry.

    Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female is defined as, women with:
    - 12 months amenorrhea for women aged >55 years, with no need for follicle stimulating hormone (FSH)
    - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (for example, oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that induced amenorrhea)

Contraception Guidance

Male Participants

No male contraception required.

Female Participants

A female participant is eligible to participate if she is not pregnant, intending to become pregnant, or breastfeeding, and at least one of the following conditions applies:

- Is not a woman of childbearing potential

  OR
- Is a WOBCP with the following study requirements:
    - A WOCBP 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 text within 24 hours prior to exposure to investigational product (IP) at Visit 3.

- WOCBP who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.
- WOCBP (who are not abstinent or in a same-sex relationship) must agree to use one highly effective method (less than 1% failure rate) of contraception, or a combination of two effective methods of contraception for the entirety of the study.

CONTRACEPTIVES ALLOWED DURING THE STUDY INCLUDE:
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 pounds or 90Kg
• Total Abstinence
• Vasectomy
• Fallopian tube implants (Essure) [if confirmed by hysterosalpingogram]
Effective methods of contraception (must use two forms combined)[a]
• Male condom with spermicide[b]
• Female condom with spermicide[b]
• Diaphragm with spermicide
• Cervical sponge
• Cervical cap with spermicide

a Participants may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide.

b Male and female condoms should not be used in combination as a double barrier method due to the high failure rate when these methods are combined.

Collection of Pregnancy Information

Female Participants Who Become Pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at >20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 10.3.4. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue from study intervention and from the study.

10.5. Appendix 5: Hepatic Safety: Suggested Actions and Follow-up Assessments

Close Hepatic Monitoring

Laboratory tests including ALT, AST, ALP, TBL, D. Bil, GGT, and CK, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if one or more of these conditions occur.

If a participant with baseline results of ...	Develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN
ALP <1.5x ULN	ALP ≥2x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥2x baseline (except for participants with Gilbert's syndrome)

If the abnormality persists or worsens, clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking and other substance abuse.

Initially, monitoring of symptoms and hepatic biochemical tests should be done at a frequency of 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and lab results stabilize. Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive Hepatic Evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if one or more of these conditions occur:

If a participant with baseline results of...	Develops the following elevations:
ALT or AST <1.5x ULN	ALT or AST ≥3x ULN with hepatic signs/symptoms,* or ALT or AST ≥5x ULN
ALP <1.5x ULN	ALP ≥3x ULN
TBL <1.5x ULN	TBL ≥2x ULN (except for participants with Gilbert's syndrome)
ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline with hepatic signs/symptoms,* or ALT or AST ≥3x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline (except for participants with Gilbert's syndrome)

* **Hepatic signs/symptoms are severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.**

At a minimum, this evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for PT-INR; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus (HDV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and serum phosphatidylethanol. Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection in study participants who have abnormal liver tests during the study

Additional hepatic safety data collection in hepatic safety case report forms (CRF) should be performed in study participants who meet one or more of the following 5 conditions:

1. Elevation of serum ALT to ≥5x ULN on 2 or more consecutive blood tests (if baseline ALT <1.5x ULN)
    - In participants with baseline ALT ≥1.5x ULN, the threshold is ALT ≥3x baseline on 2 or more consecutive tests
2. Elevated TBL to ≥2x ULN (if baseline TBL <1.5x ULN) (except for cases of known Gilbert's syndrome)

- In participants with baseline TBL ≥1.5x ULN, the threshold should be TBL ≥2x baseline

3. Elevation of serum ALP to ≥2x ULN on 2 or more consecutive blood tests (if baseline ALP <1.5x ULN)
    - In participants with baseline ALP ≥1.5x ULN, the threshold is ALP ≥2x baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be a serious adverse event (SAE)
5. Discontinuation of study drug due to a hepatic event

Note: the interval between the two consecutive blood tests should be at least 2 days.

10.5.1. Hepatic Evaluation Testing

If the investigator has confirmed liver test abnormality, he or she should select further appropriate tests. For the selected testing, analysis is required to be completed by the Lilly designated central laboratory except for microbiology.

Local testing may be performed in addition to central testing when required for immediate participant management.

Results will be reported if a validated test or calculation is available.

Hematology	**Clinical Chemistry**
Hemoglobin	Total bilirubin
Hematocrit	Direct bilirubin
Erythrocytes (RBCs - Red Blood Cells)	Alkaline phosphatase (ALP)
Leukocytes (WBCs - White Blood Cells)	Alanine aminotransferase (ALT)
Differential:	Aspartate aminotransferase (AST)
Neutrophils, segmented	Gamma-glutamyl transferase (GGT)
Lymphocytes	Creatine kinase (CK)
Monocytes	**Other Chemistry**
Basophils	Acetaminophen
Eosinophils	Acetaminophen Protein Adducts
Platelets	Alkaline Phosphatase Isoenzymes
Cell morphology (RBC and WBC)	Ceruloplasmin
Coagulation	Copper
	Ethyl Alcohol (EtOH)
Prothrombin Time, INR (PT-INR)	Haptoglobin
Serology	Immunoglobulin IgA (Quantitative)
Hepatitis A Virus (HAV) Testing:	Immunoglobulin IgG (Quantitative)
HAV Total Antibody	Immunoglobulin IgM (Quantitative)
HAV IgM Antibody	Phosphatidylethanol (PEth)
Hepatis B Virus (HBV) Testing:	**Urine Chemistry**
Hepatitis B surface antigen (HBsAg)	Drug Screen
Hepatitis B surface antibody (Anti-HBs)	Ethyl glucuronide (EtG)
Hepatitis B core total antibody (Anti-HBc)	**Other Serology**
Hepatitis B core IgM antibody	Anti-nuclear antibody (ANA)
Hepatitis B core IgG antibody	Anti-smooth muscle antibody (ASMA) [a]
HBV DNA [d]	Anti-actin antibody [b]
Hepatis C Virus (HCV) Testing:	Epstein-Barr Virus (EBV) Testing:
HCV antibody	EBV antibody
HCV RNA [d]	EBV DNA [d]
Hepatitis D Virus (HDV) Testing:	Cytomegalovirus (CMV) Testing:
HDV antibody	CMV antibody
Hepatitis E Virus (HEV) Testing:	CMV DNA [d]
HEV IgG antibody	Herpes Simplex Virus (HSV) Testing:
HEV IgM antibody	HSV (Type 1 and 2) antibody
HEV RNA [d]	HSV (Type 1 and 2) DNA [d]
Microbiology [c]	Liver Kidney Microsomal Type 1 (LKM-1) Antibody
Culture:	
Blood	
Urine	

[a] This is not required if Anti-Actin Antibody is tested.

[b] This is not required if Anti-smooth muscle antibody (ASMA) is tested.

[c] Assayed by Investigator-designated local laboratory ONLY; no Central Testing available.

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

10.6. Appendix 9: Abbreviations

Term	Definition
AACE	American Association of Clinical Endocrinologists
ADA	Anti-drug Antibodies
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BAT	basophil activation test
CF	Correction Factor
CFR	Code of Federal Regulations
CGM	continuous glucose monitoring
CIOMS	Council for International Organizations of Medical Sciences
CK	creatine kinase
CMV	cytomegalovirus
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRP	clinical research physician: Individual responsible for the medical conduct of the study. Responsibilities of the CRP may be performed by a physician, clinical research scientist, global safety physician or other medical officer.
CT	computed tomography
D. Bill	direct bilirubin
Device Deficiencies	Equivalent to product complaint
DIA	Duration of Insulin Action
DMC	data monitoring committee
EBV	Epstein-Barr virus

ECG	electrocardiogram
enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
ERCP	endoscopic retrograde cholangiopancreatography
FSH	follicle stimulating hormone
GCP	good clinical practice
gestational age	The estimated age of the fetus calculated from the first day of the last menstrual period to the delivery of the fetus. It is expressed in the number of completed weeks. This is based on 40 weeks or 10 months.
GGT	Gamma-glutamyltransferase
GLP-1	glucagon-like peptide 1
HCP	health care professional
HDV	Hepatitis D virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICR	insulin-to-carbohydrate ratio
IEC	Independent Ethics Committees
IgE	immunoglobulin E
IL	interleukin
IMP	Investigational Medicinal Product
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INR	international normalized ratio
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

investigational product (IP)	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.
IRB	Institutional Review Boards
ISF	insulin sensitivity factor
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 participant (that is, the planned treatment regimen) rather than the actual treatment given. It has the consequence that participant 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.
IV	intravenous
IWRS	interactive web-response system
MedDRA	Medical Dictionary for Regulatory Activities
MDI	multiple daily injections
MMA	mobile medical app
MMRM	mixed model repeated measures
MRCP	magnetic resonance cholangiopancreatography
NAFLD	non-alcoholic fatty liver disease
NIMP	Non-investigational Medicinal Product
NMH	*N*-methylhistamine
participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PIs	primary investigators
PK/PD	pharmacokinetics/pharmacodynamics
PT	prothrombin time
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.

SMS	Study management suite
T1D	type 1 diabetes
T2D	type 2 diabetes
TBL	total bilirubin
TBD	Total Basal Dose
TDD	Total Daily Dose
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
USPI	United States Prescribing Information
WOCBP	woman of childbearing potential

10.7. Appendix 10: Protocol Amendment History

Amendment [a]

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.3 Schedule of Activities (SoA)	Removal of Visit 7 for investigational product (IP) dispensing	Study IP will not be dispensed at Visit 7. IP will be dispensed at Visits 3 and 11.
1.3. Schedule of Activities (SoA), 4.1.1. Study Visits	Addition of language to clarify data capture on insulin dosing	Clarification for transcribing data into eCRF for insulin dosing at Visit 3 and Visit 14
5.1. Inclusion Criteria	Addition of language to align with Lilly guidance	Clarification of inclusion criteria for females regarding pregnancy, breastfeeding and contraceptive guidance
9.4.1. General Considerations	Add analysis details if mixed model repeated measures (MMRM) does not converge	Clarification of analysis details if MMRM does not converge
	Addition of language for continuous glucose monitoring (CGM) data analysis for Visit 3 and Visit 14	Clarification of study interventions data during study periods
9.4.2. Primary Endpoint(s)	Replace analysis method with analysis of covariance (ANCOVA)	Change was made because CGM data will only be derived for Visit 3 and Visit 14
	Addition of language for CGM data analysis for Visit 3 and Visit 14	Clarification of study interventions data during study periods
10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information	Addition of language to align with Lilly guidance	Clarification of contraceptive guidance
Throughout	Minor editorial and document formatting revisions	These are minor changes; therefore, they have not been summarized

11. References

Bailey TS, Grunberger G, Bode BW, Handelsman Y, Hirsch IB, Jovanovič L, Roberts VL, Rodbard D, Tamborlane WV, Walsh J. American Association of Clinical Endocrinologists and American College of Endocrinology 2016 Outpatient Glucose Monitoring Consensus Statement. *Endocrine Practice*. 2016; 22(2): 231-261.

Blevins T, Zhang Q, Frias JP, Jinnouchi H, Chang AM. Ultra Rapid Lispro (URLi) Improves Postprandial Glucose (PPG) Control vs. Humalog (Lispro) in Patients with Type 2 Diabetes (T2D): PRONTO-T2D [abstract]. In: American Diabetes Association 4 June 2019; 68(1).

Bode BW. Insulin pump therapy in *Therapy for Diabetes Mellitus and related disorders*, Fourth edition. In: Lebovitz HE, editor. American Diabetes Association; 2004.

DeWitt DE, Hirsch IB. Outpatient insulin therapy in type 1 and type 2 diabetes. *JAMA*. 2003;289:2254-2264.

Gan MJ, Albanese-O'Neill A, Haller MJ. Type 1 diabetes: current concepts in epidemiology, pathophysiology, clinical care, and research. *Curr Probl Pediatr Adolesc Health Care*. 2012;42(10):269-291

Insulin pump therapy and continuous glucose monitoring. Pickup J, editor. London: Oxford University Press; 2009.

King AB, Armstrong DU. A prospective evaluation of insulin dosing recommendations in patients with type 1 diabetes at near normal glucose control: basal dosing. *J Diabetes Sci Technol*. 2007a;1(1):42-46.

King AB, Armstrong DU. A prospective evaluation of insulin dosing recommendations in patients with Type 1 Diabetes at near normal glucose control: bolus dosing. *J Diabetes Sci Technol*. 2007b;1(1):42-46.

Allen King. How Much Do I Give? Reevaluation of Insulin Dosing Estimation Formulas Using Continuous Glucose Monitoring. *Endocrine Practice*. 2010;16(3):428-432.

King AB. Continuous glucose monitoring-guided insulin dosing in pump-treated patients with type 1 diabetes: a clinical guide. *J Diabetes Sci Technol*. 2012;16(3):191-203.

Klaff L, Cao D, Dellva MA, Tobian J, Miura J, Dahl D, Bue-Valleskey JM. Ultra Rapid Lispro (URLi) Improves Postprandial Glucose (PPG) Control vs. Humalog (Lispro) in T1D: PRONTO T1D Study [abstract]. In: American Diabetes Association; 4 June 2019; 68(1).

Kruszynska YT, Home PD, Hanning I, Alberti KGMM. Basal and 24-hour C-peptide and insulin secretion rate in normal man. *Diabetologia*. 1987;30:16-21.

Kuroda A, Yasuda T, Takahara M, Sakamoto F, Kasami R, Miyashita K, Yoshida S, Kondo E, Aihara K, Endon I, Matsuoka T, Kaneto H, Matsumoto T, Shimomura I, Matsuhisa M. 300–400 Divided by total daily insulin dose in type 1 diabetes patients who use the insulin pump. *Diabetes Technol Ther*. 2012;14(11):1077-1080.

Polonsky KS, Given BD, Van Cauter E. Twenty-four-hour profiles and pulsatile patterns of insulin secretion in normal and obese subjects. *J Clin Invest*. 1988;81:442-448.

Stark-Casagrande S, Fradkin JE, Saydah SH, Rust KF, Cowie CC. The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988-2010. *Diabetes Care*. 2013;36(8):2271-2279.

Tresiba [package insert]. DK-2880 Bagsvaerd, Denmark, Novo Nordisk A/S; 2015.

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