Protocol: I8B-MC-ITSU (b)

Effectiveness of a Basal Rate Reduction With LyumjevTM Versus Humalog® on the Protection From Exercise-Induced Hypoglycemia in Individuals With Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion

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Approval Date: 09-May-2022

Title Page

Protocol Title: Effectiveness of a Basal Rate Reduction with Lyumjev™ versus Humalog® on the Protection from Exercise-Induced Hypoglycemia in Individuals with Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion

Protocol Number: I8B-MC-ITSU

Amendment Number: I8B-MC-ITSU (b)

Compound: LY900014 (Lyumjev)

Brief Title: A Study to Evaluate Protection from Exercise-Induced Hypoglycemia with Lyumjev™ Compared to Humalog® in Individuals with Type 1 Diabetes

Study Phase: 1

Acronym: ITSU

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Eli Lilly and Company, Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

Not Applicable

Approval Date: Protocol Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-028148

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment a	*09-Feb-2022*
Original Protocol	*27-Oct-2021*

Amendment (b)

Overall Rationale for the Amendment:

This protocol is being amended mainly to provide clarity for site implementation. Minor editorial changes have been done which are not reflected in the table below.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.3.1. Overall schedule	Removed row on COVID-19 temperature screening	Removed as this is not a study-related screening procedure
Section 1.3.1. Overall schedule	Reworded dosing day exclusion/withdrawal criteria as 'eligibility check/additional exclusion/withdrawal criteria'; Added 'X' mark for assessment day	Updated to align with naming of section 5.2.1
Section 1.3.1. Overall schedule	Removed 'X' on Day -1 for pump temporary basal rate reduction during prolonged exercise	Basal rate reduction is done on Day 1 and not Day -1
Section 1.3.2. Assessment schedule example for in-house visits	Reworded dosing day exclusion/withdrawal criteria as 'eligibility check/additional exclusion/withdrawal criteria'	Updated to align with section 1.3.1
Section 1.3.2. Assessment schedule example for in-house visits	Insert venous cannula prior to lunch; added 'removal of cannula' at 9:00 PM	Correction done as there are blood draws at 11:00 AM
Section 4.1.2. Assessment day	Insert venous cannula prior to lunch	Correction done as there is glucose sampling at -4 hours pre-exercise
Section 4.1.2. Assessment day	Updated text on pre-exercise glucose management	To provide clarity on site implementation
Section 4.1.2. Assessment day	Updated text on hypoglycemia during exercise	To provide clarity on site implementation

Section # and Name	Description of Change	Brief Rationale
Section 4.1.2. Assessment day	mM updated as mmol/L	Updated units to ensure consistency
Section 4.1.3. In-house visits	Insert venous cannula prior to lunch	Updated to align with Section 1.3.2
Section 4.1.3. In-house visits	Updated text on pre-exercise glucose management	To provide clarity on site implementation
Section 4.1.3. In-house visits	Updated text on hypoglycemia during exercise	To provide clarity on site implementation
Section 4.1.3. In-house visits	mM updated as mmol/L	Updated units to ensure consistency
Section 4.4. End of study definition	Term 'globally' has been removed	Single site for this study
Section 5.1. Inclusion criteria	Inclusion criteria 2 – added fasting C-peptide value in pmol/L	Added to align with laboratory reporting units
Section 5.1. Inclusion criteria	Inclusion criteria 2 – peak VO_2 of ≥35 for males and ≥32 for females	Updated peak VO_2 values
Section 5.2. Exclusion criteria	Exclusion criteria 23 – added details for over-the-counter or prescription medications	Clarification provided on the medications that should not be used within 14 days prior to dosing
Section 5.2. Exclusion criteria	Exclusion criteria 24 – added 'basal rate optimization'	Clarification provided to avoid acetaminophen during basal rate optimization visit
Section 5.2. Exclusion criteria	Exclusion criteria 28 – in house visits/ periods replaced by study treatment period	To clarify that this exclusion criteria is for all inpatient visits where study treatment is given
Section 5.2. Exclusion criteria	Separated criteria 34 into new Section 5.2.1.	Separate heading added to provide clarity that these criteria are for study treatment periods
Section 5.2.1. Additional exclusion criteria for study treatment periods	Added statement for rescheduling assessment day in case participants fulfill 1 or more of the	Clarification provided for participants who fulfill 1 or more of the additional criteria on assessment day and updated to be consistent with Section 1.3.1

Section # and Name	Description of Change	Brief Rationale
	additional criteria on assessment day	
Section 5.2.1. Additional exclusion criteria for study treatment periods	Alcohol consumption within 24 hours prior to each in-house period is not allowed and participants with positive drug screen are not allowed	Updated to be consistent with Section 5.3.2 and 1.3.1
Section 5.2.1. Additional criteria for study treatment periods	Sub criteria e – reference to exclusion criteria 22 removed	Updated as exclusion criteria includes medications which participants would not be taking based on screening criteria
Section 5.2.1. Additional criteria for study treatment periods	Added exclusion of participants who are unable to obtain glucose range [redacted] prior to initiation of exercise assessment	Updated to be consistent with Sections 4.1.2 and 4.1.3
Section 5.4. Screen failures	Term 'assent' removed	Assent is not required
Section 6.1.1. Noninvestigational medicinal products	mM updated as mmol/L	Updated units to ensure consistency
Section 6.5. Dose modification	Clinical pharmacologist, clinical research scientist added	Clarification provided on the sponsor roles
Section 6.8. Concomitant therapy	Added study periods when acetaminophen is to be avoided	Updated to align with exclusion criteria 24
Section 6.8. Concomitant therapy	Clinical research scientist added	Clarification provided on the sponsor roles
Section 7.2. Participant discontinuation/withdrawal from the study	Removed language on inadvertent enrollment	Updated as per harmonized clinical protocol template
Section 8.2.2. Vital signs	Vital sign measurements to include blood pressure, pulse rate, heart rate, and body temperature	To provide clarity on site implementation
Section 8.2.7.2. Treatment of hyperglycemia and	Updated text on hypoglycemia management	Updated to be consistent with Section 4.1.3

Section # and Name	Description of Change	Brief Rationale
hypoglycemia during in-house periods		
Section 8.2.7.2. Treatment of hyperglycemia and hypoglycemia during in-house periods	mM updated as mmol/L	Updated units to ensure consistency
Appendix 7: Protocol amendment history	New section added	Summary of changes table of amendment a have been moved to this section

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: Effectiveness of a Basal Rate Reduction with Lyumjev™ versus Humalog® on the Protection from Exercise-Induced Hypoglycemia in Individuals with Type 1 Diabetes on Continuous Subcutaneous Insulin Infusion

Brief Title: A Study to Evaluate Protection from Exercise-Induced Hypoglycemia with Lyumjev™ Compared to Humalog® in Individuals with Type 1 Diabetes

Rationale:

Study I8B-MC-ITSU (Study ITSU) will be conducted to compare the glycemic control during exercise achieved with Lyumjev™ versus Humalog® using different approaches on basal rate reductions in participants with type 1 diabetes on continuous subcutaneous insulin infusion (CSII) therapy.

Objectives and Endpoints:

Objectives	Endpoints
Primary	
• To compare changes in plasma glucose levels with Lyumjev versus Humalog from the start to the end of 60 minutes of moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates, set 60 minutes or 15 minutes before the onset of exercise, respectively	• Changes in plasma glucose from the start to the end of exercise
Secondary	
• To compare the glucodynamic response with Lyumjev versus Humalog during a dinner MMTT following moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates, set 60 minutes or 15 minutes before the onset of exercise, respectively	• Postprandial glucose excursion during the test meal (e.g., AUC0-4h)

• To compare the PK of insulin lispro between Lyumjev versus Humalog during an MMTT • To compare the PK of insulin lispro between Lyumjev versus Humalog during 60 minutes of moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates with Lyumjev or Humalog, set 60 minutes or 15 minutes before the onset of exercise, respectively	• Insulin lispro PK during the MMTT after exercise • Insulin lispro PK during the exercise

Abbreviations: AUC0-4h = area under the plasma concentration time curve from 0 to 4 hours post-meal; MMTT = mixed meal tolerance test; PK = pharmacokinetics.

Overall Design

Study ITSU will be a single center, randomized, double-blind, 4-period, crossover Williams design exercise and test meal study in physically active adult patients with type 1 diabetes using CSII. The study will consist of 2 active treatment arms, Lyumjev and Humalog. This study will include a screening visit (Visit 1), visits to optimize basal rates (optional based on investigator decision), an assessment day (Visit 2), 4 in-house study periods with study intervention administration (Visits 3, 4, 5, and 6), and a follow-up visit (Visit 7).

This is a participant- and investigator-blind study. On Day -1 of in-house period (Visit 3), participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to 1 of the 4 in-house study periods, according to the randomization schedule generated prior to the study by the statistics department at the sponsor/designee. Each participant will be dispensed blinded study intervention, labeled with the participant's unique randomization number, throughout the study. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the study. To maintain this blind, an otherwise uninvolved third party, such as a pharmacist, will be responsible for the dispensation of all study interventions and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

Brief Summary:

The purpose of this study is to measure the changes in plasma glucose levels with Lyumjev compared with Humalog from the start to the end of prolonged moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates in participants with type 1 diabetes mellitus on CSII.

Study details include

- The study duration will be approximately [redacted] weeks.
- The treatment duration will be approximately [redacted] weeks.

- The visit frequency during the in-house period will be 2 continuous days of stay (with 1 overnight) in clinical research unit for a total of 4 visits with a washout period of up to CCI days in between the visits.

Number of Participants:

A maximum of CCI participants will be enrolled to receive study intervention. Refer to Section 9.5 for details.

Intervention Groups and Duration:

Screening (Visit 1): CCI days prior to Visit 3

Assessment Day (Visit 2): CCI days prior to Visit 3; Humalog via standardized insulin pump.

In-house (Visits 3, 4, 5, 6): CCI days of stay in clinical research unit for a total of 4 visits with CCI days of washout period in between visits; Lyumjev or Humalog via standardized insulin pump, and 2 different basal insulin reduction rates to be administered at the 4 separate in-house visits based on randomization.

Follow-up (Visit 7): CCI days after Visit 6

Data Monitoring Committee: No

1.2. Schema

1.3. Schedule of Activities (SoA)

1.3.1. Overall Schedule

Procedure	**Screening Period**		**Study Period**			**Follow-up/ED**	**Comments**
Visit Number	**1**	**Optional visits**	**2**	**3, 4, 5, 6**		**7**	
	Screening	**Basal rate optimization**	**Assessment**	**In-house**			
Timing	**Within CCI days prior to Visit 3**	**First evaluation - Within CCI days of screening visit Second evaluation - Within CCI days of screening visit**	**CCI days prior to Visit 3**	**CCI days**		**CCI days after Visit 6**	
Day		CCI					
In-house stay				**X**	**X**		
Admission to CRU				X			
Discharge from CRU					X		At the discretion of investigator
Outpatient	X	X	X			X	
Informed consent	X						
Inclusion and exclusion criteria	X			X[a]			
Fasting	X				X		
Demographic data	X						
Smoking and alcohol consumption habits	X						
Medical history	X						
Weight, height, BMI	X			X[b]		X[b]	
Physical examination	X			X		X	
Vital signs	X			X		X	
12-lead ECG	X						Single

Procedure	**Screening Period**		**Study Period**			**Follow-up/ED**	**Comments**
Visit Number	**1**	**Optional visits**	**2**	**3, 4, 5, 6**		**7**	
	Screening	**Basal rate optimization**	**Assessment**	**In-house**			
Timing	**Within CCI days prior to Visit 3**	**First evaluation - Within CCI days of screening visit Second evaluation - Within CCI days of screening visit**	**CCI days prior to Visit 3**	**CCI days**		**CCI days after Visit 6**	
Day		CCI					
In-house stay				**X**	**X**		
Clinical Laboratory Tests	X						See Section 10.2
HbA1c	X						
Fasting C-peptide	X						
Pregnancy test (females only)	X			X		X	Serum test at screening; urine pregnancy test prior to study treatment and at follow-up; See Section 10.4.2
Urine drug screen and ethanol testing	X		X	X			Ethanol breath test on Day -1 and assessment day.
Perform pump basal rate assessment, review and titration if needed	X	X[c]					Collect and review the ambulatory glucose profile, pump settings, etc. Once established, these rates should be maintained for all study periods
Dispense study diaries and complete training	X						

Procedure	**Screening Period**		**Study Period**			**Follow-up/ED**	**Comments**
Visit Number	**1**	**Optional visits**	**2**	**3, 4, 5, 6**		**7**	
	Screening	**Basal rate optimization**	**Assessment**	**In-house**			
Timing	**Within CCI days prior to Visit 3**	**First evaluation - Within CCI days of screening visit Second evaluation - Within CCI days of screening visit**	**CCI days prior to Visit 3**	**CCI days**		**CCI days after Visit 6**	
Day		CCI					
In-house stay				**X**	**X**		
Collect, review, and discuss entries in study diaries		X	X	X		X	
Peak VO_2, heart rate, and RPE assessment during progressive treadmill exercise test	X						RPE to be collected every 2 minutes during the progressive treadmill test; refer to Section 8.2.8 for further details
Prolonged exercise session at 45% to 55% of predetermined VO_2 peak			X		X		Heart rate and RPE (Section 8.2.8) will be collected at each 17-minute interval (the last 2 minutes of each interval) over the 1-hour exercise period (Sections 4.1.2 and 4.1.3)
Eligibility check/Additional exclusion/withdrawal criteria			X	X			
Randomization				X*			*Visit 3 only
Study intervention administration			X[d]	X	X		Administer study intervention bolus dose immediately (0-2 minutes) before meal

Procedure	**Screening Period**		**Study Period**			**Follow-up/ED**	**Comments**
Visit Number	**1**	**Optional visits**	**2**	**3, 4, 5, 6**		**7**	
	Screening	**Basal rate optimization**	**Assessment**	**In-house**			
Timing	**Within CCI days prior to Visit 3**	**First evaluation - Within CCI days of screening visit Second evaluation - Within CCI days of screening visit**	**CCI days prior to Visit 3**	**CCI days**		**CCI days after Visit 6**	
Day		CCI					
In-house stay				**X**	**X**		
Pump temporary basal rate reduction during prolonged exercise			X		X		50% or 100% basal rate reduction prior and during exercise period
MMTT			X		X		
PK[e]					X		
Glucose			X[f]		X[g]		
Study CGM				X	X		
Blood ketones/FFAs[h]					X		
Adverse events and product complaints			X	X	X	X	
Concomitant medications	X		X	X	X	X	
Standardized lunch			X		X		
Standardized dinner				X			
Standardized breakfast					X		

Abbreviations: BMI = body mass index; CGM = continuous glucose monitoring; CRU = clinical research unit; ECG = electrocardiogram; FFA = free fatty acid; HbA1c = glycosylated hemoglobin; MMTT = mixed meal tolerance test; PK = pharmacokinetics; RPE = rating of perceived exertion; VO_2 = oxygen uptake.

[a] Re-check of participant eligibility.

[b] Weight only.

[c] See Section 4.1.1 for further details.

[d] Humalog to be administered in pump on assessment day. Refer to Section 4.1.2 for initial bolus dose selection to be administered prior to MMTT.

[e] PK will be collected over CCI minutes after start of exercise and CCI

[f] Blood glucose (YSI) on assessment day at CCI minutes after start of exercise and CCI post-meal MMTT.

[g] Blood glucose (YSI) will be collected at CCI pre-exercise, and CCI after start of exercise and CCI post-meal MMTT.

[h] Ketones and FFAs will be collected at CCI after start of exercise.

1.3.2. Assessment Schedule Example for In-house Visits (Visits 3, 4, 5, 6)

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose	FFA/ Ketones	Other
Day -1						
CCI		Participant arrives at the CRU and continued eligibility will be checked				Weight, height, BMI, physical examination, vital signs, urine pregnancy test, alcohol breath test, eligibility check/ additional exclusion/withdrawal criteria, AEs, concomitant medications
		Randomization (Visit 3 only) Discontinue participant's own insulin pump Start study insulin pump with study intervention (participant's usual basal rate) Insert study CGM system				
		Standardized evening meal Administer individualized bolus dose immediately (0-2 minutes) before dinner meal				CCI
						Overnight stay in CRU with usual overnight basal infusion rates and glucose monitoring with CGM. Morning glucose target CCI mmol/L
Day 1						
CCI		Standardized breakfast meal				The meal should be completed within CCI Addition of correction bolus with mealtime bolus is allowed, if needed

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose	FFA/ Ketones	Other
		Administer individualized bolus dose immediately (0-2 minutes) before breakfast meal				
		Insert venous cannula (arm/hand) for insulin lispro PK, glucose, ketones, and FFA collection prior to lunch				
[redacted]	[redacted]	Standardized lunch meal Administer individualized bolus dose immediately (0-2 minutes) before lunch meal Set pump to individualized single hourly basal rate	X	X		The meal should be completed within [redacted] Addition of correction bolus with mealtime bolus is allowed, if needed. Collection of PK and glucose prior to meal
[redacted]	[redacted]	[redacted]	X	X	X	[redacted]
[redacted]	[redacted]	Basal rate reduction – 50%	X	X	X	For each period, either the 50% or 100% basal reduction will be used. Depending on the randomization for the participant. Sample collection to occur prior to basal reduction.
[redacted]	[redacted]	[redacted]	X	X	X	[redacted]
[redacted]	[redacted]	Basal rate reduction – 100%	X	X	X	[redacted]
[redacted]	[redacted]	Exercise (treadmill, brisk walking, or jogging at ~45%-55% of predetermined VO_2 peak) x 17 minutes x 3 with two 4-minute and 30-second breaks	X[a]	X[a]	X[a]	Heart rate and RPE to be recorded once within each 17-minute interval (within the last 2 minutes of each interval)

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose	FFA/ Ketones	Other
						Glucose sampling CCI during exercise period. Samples for FFAs, ketones, and PK will be collected CCI during exercise period
CCI		End of exercise assessment Reset pump basal rate to participant's usual rate (maintain individualized single hourly basal rate until the end of MMTT sampling)	X	X	X	Collection of glucose, PK, FFA, and ketones to occur prior to restart of usual basal rate
CCI		Post-exercise resting period				
		Dinner MMTT Administer individualized bolus dose immediately (0-2 minutes) before meal	X[a]	X[a]		CCI
			X[a]	X[a]		
			X[a]	X[a]		
			X[a]	X[a]		
		Following collection of PK and glucose samples, remove venous cannula, disconnect study pump, and remove study CGM system Participant resumes usual pump therapy	X[a]	X[a]		

Approx. hour	Nominal timing	Activity	Insulin (PK)	Plasma glucose	FFA/ Ketones	Other
Discharge from CRU		Participant may leave the CRU at the discretion of the investigator				AEs, product complaints, concomitant medication

Abbreviations: AE = adverse event; CGM = continuous glucose monitoring; CRU = clinical research unit; FFA = free fatty acids; MMTT = mixed meal tolerance test; PK = pharmacokinetics; RPE = rating of perceived exertion; VO_2 = oxygen uptake.

[a] Exact collection timing for PK and glucose samples is provided in footnote of table in Section 1.3.1.

2. Introduction

Lyumjev™ is a new formulation of insulin lispro developed as a more rapid-acting insulin with a faster onset of action and shorter duration of action compared to currently available rapid-acting insulin analogs, and it will more closely mimic endogenous insulin action in healthy subjects.

2.1. Study Rationale

Study I8B-MC-ITSU (Study ITSU) will be conducted to compare the glycemic control during exercise achieved with Lyumjev versus Humalog® using different approaches on basal rate reductions in participants with T1D on CSII therapy.

2.2. Background

Regular exercise in people with T1D can help in achieving targets related to their lipid profile, body composition, fitness, and glycemic control. It can improve the overall health and well-being. However, people with T1D and the healthcare providers face several challenges in the management of different forms of physical activity. These include fear of hypoglycemia, loss of glycemic control, inadequate knowledge around exercise management, etc. (Riddell et al. 2017).

Strategies for glycemic management during and after exercise include frequent glucose monitoring, intake of carbohydrates, and reductions in bolus and basal insulin doses. Following are the possible adjustment options for hypoglycemia risk reduction with prolonged (>30 minutes) aerobic exercise (Riddell et al. 2017):

- Bolus insulin dose reduction up to 75% at the meal before exercise, if the exercise is up to 2 hours after a meal
- Basal insulin dose reduction of approximately 20% in patients on multiple daily injections before exercise if the exercise is fasted or >2 to 3 hours after a meal
- Basal rate reduction of up to 100% pre-exercise (i.e., pump suspension) in patients on CSII, but ideally a 50% to 80% basal rate reduction set 60 to 90 minutes before exercise to reduce circulating insulin levels by exercise start time (Zaharieva et al. 2019; McGaugh et al. 2021)
- Basal nocturnal insulin dose reduction of approximately 20% in patients on multiple daily injections or CSII (for up to 6 hours in recovery) after exercise
- Intake of additional carbohydrates before, during, and after exercise without insulin bolus

Insulin lispro (*Humalog)*

The insulin analog insulin lispro (Humalog) has been shown to be absorbed more quickly than regular human insulin (Humalog product monograph, 2021). In healthy volunteers given subcutaneous doses of Humalog ranging from 0.1 to 0.4 units (U)/kg, peak serum levels were seen 30 to 90 minutes after dosing ([WWW] FDA 2015). However, the consensus is that rapid-acting insulin is still not rapid enough to match carbohydrate absorption profiles, which limit efficacy and dosing flexibility. An ultra-rapid-acting prandial insulin would shift the PK/GD of insulin analogs so that they have an even faster onset to better match carbohydrate absorption and also allow greater flexibility in the time of dosing relative to meals. The faster onset of

action in an ultra-rapid-acting prandial insulin would also be expected to be associated with a faster reduction in action after its administration (i.e. less of an insulin "tail" effect), which may offer better protection against exercise-induced hypoglycemia in post-absorptive settings or when individuals on CSII perform a basal rate reduction prior to exercise.

Lyumjev

Lyumjev is a novel formulation of insulin lispro that contains treprostinil, sodium citrate, and other excipients. This formulation involves the novel use of a microdose of treprostinil as an excipient to enhance the absorption of insulin lispro by local vasodilatation rather than as an active pharmaceutical ingredient to elicit a systemic effect. Sodium citrate, an excipient that speeds up insulin absorption (at least in part by enhancing vascular permeability), is also included in the formulation to further enhance the absorption of insulin lispro. Each of the other excipients (such as magnesium chloride) in the Lyumjev formulation is listed in the US FDA's Generally Recognized as Safe Food Additives database and in the FDA's Inactive Ingredients in Approved Drugs database ([WWW] FDA 2018; [WWW] FDA 2021a).

Lyumjev has received approval in Canada on 14 September 2021 for treatment of adult patients with diabetes mellitus (Lyumjev product monograph, 2021). Lyumjev also received FDA approval on 15 June 2020, and it was approved by the European Medicines Agency on 24 March 2020 ([WWW] EMA 2020; [WWW] FDA 2021b).

In the Phase 3 pivotal multiple daily injection studies, Lyumjev dosed at the start of a meal demonstrated noninferior overall glycemic control (HbA1c) in patients with T1D and type 2 diabetes and consistently better postprandial glucose control, compared to Humalog (Blevins et al. 2020; Jinnouchi et al. 2020; Klaff et al. 2020). Additionally, improved time in range during daytime was observed in patients with T1D treated with Lyumjev (Malecki et al. 2020). Safety profile was observed to be similar between the treatment groups in these trials. Injection-site reactions occurred at a higher incidence with Lyumjev compared to Humalog (2.7% versus 0.1%, respectively), but had an overall low incidence with <0.1% of patients discontinuing from trials due to injection site-related reactions (Lyumjev product monograph, 2021).

Lyumjev was efficacious, providing superior postprandial glucose control and less time in hypoglycemia compared with Humalog when administered through CSII (Warren et al. 2021). The incidence of patients reporting infusion site reaction and infusion site pain was higher in the Lyumjev group compared with the Humalog group (19.1% versus 7.4%, and 15.8% versus 2.8%, respectively) (Lyumjev product monograph, 2021). Of the 215 patients treated with Lyumjev, 7 discontinued treatment due to infusion site-related reactions (3.3%) (Lyumjev product monograph, 2021).

2.3. Benefit/Risk Assessment

This study will not offer any direct benefits to the participants in the study beyond the typical benefits derived from insulin pump use in T1D participants. The data from previous studies in patients with T1D on CSII therapy showed that Lyumjev was well tolerated, and overall safety profile was similar to that reported for Humalog (Warren et al. 2021).

Potential risks associated with Lyumjev and Humalog

- Hyperglycemia and/or hypoglycemia; severe or otherwise

- Hypokalemia
- Lipodystrophy
- Peripheral edema
- Severe, life-threatening generalized allergy, including anaphylaxis, to Humalog or Lyumjev insulin.
- Injection/infusion site-related reactions

The occurrence and severity of these events are not expected to be different from routine use of insulin injection systems. More detailed information about the known and expected risks and potential AEs may be found in the Lyumjev and Humalog product monographs (Lyumjev product monograph, 2021, Humalog product monograph, 2021).

Potential risks associated with CSII pump use

- Minor skin irritation, sensitization, or localized inflammatory response can occur if skin contacts bioincompatible materials.
- Pain, bruising, swelling, redness, and bleeding at the infusion set insertion site.

The occurrence and severity of these events are not expected to be different from routine use of the CCI [redacted] More detailed information on the use and about the known and expected risks and potential ADEs may be found in the manufacturer's label and Instructions for Use.

Potential risks associated with CGM use

- Pain, bruising, swelling, redness, and bleeding at the sensor insertion site
- Sensor breakoff where the sensor wire detaches and remains under the skin
- Minor skin irritation, sensitization, or localized inflammatory response can occur if skin contacts bioincompatible materials
- Inaccurate results due to use of meter that is out of calibration, malfunctioning, or rapidly changing glucose levels
- Loss of CGM connectivity (transient and permanent)
- Errors in the data transmitted to the software application
- Electric shock if the device is damaged

The occurrence and severity of these events are not expected to be different from routine use of CGM. More detailed information on the use and about the known and expected risks and potential ADEs may be found in the manufacturer's label and Instructions for Use.

The study includes in-house procedures during which participants will be continuously monitored.

3. Objectives and Endpoints

Objectives	Endpoints
Primary	
• To compare changes in plasma glucose levels with Lyumjev™ versus Humalog® from the start to the end of 60 minutes of moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates, set 60 minutes or 15 minutes before the onset of exercise, respectively	• Changes in plasma glucose from the start to the end of exercise
Secondary	
• To compare the glucodynamic response with Lyumjev versus Humalog during a dinner MMTT following moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates, set 60 minutes or 15 minutes before the onset of exercise, respectively	• Postprandial plasma glucose excursion during the test meal (e.g., AUC0-4h)
• To compare the PK of insulin lispro between Lyumjev versus Humalog during an MMTT	• Insulin lispro PK during the MMTT after exercise
• To compare the PK of insulin lispro between Lyumjev versus Humalog during 60 minutes of moderate-intensity aerobic exercise using either 50% or 100% reduction of basal infusion rates with Lyumjev or Humalog, set 60 minutes or 15 minutes before the onset of exercise, respectively	• Insulin lispro PK during the exercise
Exploratory	

Objectives	Endpoints
• To investigate tolerability and safety of Lyumjev and/or Humalog	• Incidence of TEAEs, SAEs, symptomatic hypoglycemia • Blood ketone levels
• To perform an exploratory comparison of glucose variability, time in range, hypoglycemia, and hyperglycemia using CGM profiles obtained from participants receiving Lyumjev and Humalog	• Overall variability (CV and SD) • Time in range (70 to 180 mg/dL) during exercise, MMTT assessment, overnight period, and for the entire in-house period • Time in hypoglycemia (<70 and <54 mg/dL) and hyperglycemia (>180 and 140 mg/dL) • Mean glucose levels

Abbreviations: AUC0-4h = area under the plasma concentration time curve from 0 to 4 hours postmeal; CGM = continuous glucose monitoring; CV = coefficient of variation; MMTT = mixed meal tolerance test; PK = pharmacokinetics; SAE = serious adverse event; SD = standard deviation; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study ITSU will be a single center, randomized, double-blind, 4-period, crossover Williams design exercise and test meal study in physically active adult participants with T1D using CSII. The study will consist of 2 active treatment arms, Lyumjev and Humalog. This study will include a screening visit (Visit 1), visits to optimize basal rates (optional based on investigator decision), an assessment day (Visit 2), 4 in-house study periods with study intervention administration (Visits 3, 4, 5, and 6), and a follow-up visit (Visit 7).

4.1.1. Screening Visit

Screening may occur up to CCI prior to Visit 3. Participants who are not enrolled within 28 days of screening prior to Visit 3 may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. In such instances, all the screening tests and procedures will be repeated.

During the screening visit, after obtaining informed consent, study participants will be assessed for eligibility (see Sections 5.1 and 5.2). An interview will be conducted to collect demographic details and medical history; examination, laboratory tests, and other assessments will be performed as mentioned in the SoA. Participant's insulin requirements (i.e pump) and ambulatory glucose profile (i.e. CGM downloads) will be examined. Participants will receive a study diary to document any AEs, hypoglycemic events, insulin doses, self-monitored blood glucose (SMBG) values, and meals (time, units of carbohydrate equivalent).

Prospective study participants will have their exercise capacity (i.e. peak VO_2), CCI Section 8.2.8), and heart rates evaluated during a progressive treadmill exercise test (i.e. a graded 2-minute stage test that maintains a constant running or jogging speed with increase in grade [2.5%] every 2 minutes) until volitional fatigue, as part of the study eligibility. Prospective study participants on a closed-loop pump system would switch their pump to "open-loop" or manual mode utilizing their programmed basal rates and allowing low glucose suspend via their personal CGM during the screening period. These participants would also agree to maintain their pump in open-loop mode for the entire study period.

For those prospective study participants who require basal rate titration based on investigator decision, participants will return to the CRU approximately CCI after their screening visit for a basal rate optimization visit. The ambulatory glucose profile from their CGM, personal pump data, and study diary will be reviewed. If further modification of pump settings is necessary, they will return to the CRU approximately a week later and their ambulatory glucose profile, personal pump data, and study diary will be reviewed. For those prospective study participants who are unable to get the basal rates optimized within this period (based on investigator decision), participants will not be eligible for the study. For those prospective study participants who do not require basal titration based on investigator decision at screening visit and are eligible for the study, they would return to the CRU on assessment day.

Once basal insulin rates are set, these should be fixed for the entire study period, unless a change is deemed necessary by the investigator.

4.1.2. Assessment Day

After screening, all eligible participants will have an assessment day (Visit 2) to undergo a prolonged exercise session at 45% to 55% of predetermined peak VO_2 and to determine the insulin bolus dose for the MMTT to be performed in the study.

Participants will arrive at the CRU in the morning by approximately CCI (Figure ITSU.1). Participants will be placed on a standardized insulin pump CCI with a new infusion set CCI After disconnecting the participant's own insulin pump, the study pump reservoir will be filled with Humalog by a qualified CRU staff. A standard infusion set and catheter will be inserted into the abdominal area, as per the manufacturer's instructions, after the region is inspected for lipodystrophy (Section 6.1.2). The participant's usual basal rate settings will be programmed in the pump and the basal rate infusion will be started.

A cannula will be inserted for venous access for glucose sampling prior to lunch. A standardized lunch will be provided CCI Section 5.3.1.3) and the bolus insulin dose will be individualized per participant to cover the carbohydrate content. No additional bolus insulin injection should be administered post-meal after lunch prior to the exercise period. The basal rate will be set to a single hourly rate at lunch based on the participant's usual basal rate for this time of day; this will be maintained until the basal rate reduction for the exercise period. The basal rate in the pump will be reduced by 50% at approximately CCI 1 hour prior to the exercise assessment. A pre-exercise glucose target of CCI will need to be achieved CCI prior to exercise. CCI prior to exercise, the assessment day will be rescheduled within the allowable time window mentioned in the SoA.

Four hours after lunch CCI, the participants will be instructed to walk or jog on the treadmill at 45% to 55% of their predetermined peak VO_2 using three 17-minute intervals with two 4-minute and 30-second rest periods in between intervals for a total duration of 1 hour CCI During the exercise period, heart rate will be monitored continuously using a chest strap heart rate monitor, and participants will be asked to rate their perceived exertion using CCI (Section 8.2.8) during the last 2 minutes of each 17-minute interval. Participants will be monitored for safety. If hypoglycemia ensues (plasma or whole blood glucose level CCI), the exercise will be terminated, and the participant will be treated with CCI of oral carbohydrates (dextrose tablets). If the glucose level continues to be below CCI after approximately CCI minutes, up to an additional CCI of oral carbohydrates can be provided. Repeat as necessary if glucose value remains below CCI mg/dL. If the exercise is terminated due to hypoglycemia during the first exercise interval, the assessment day will be rescheduled within the allowable time window mentioned in the SoA. If the exercise is terminated due to hypoglycemia during the second interval, the assessment day may not need to be rescheduled. If the exercise is terminated during the third interval, assessment day will not be rescheduled. Upon completion of the exercise period or once the participant recovers from hypoglycemia (blood glucose reaches CCI mg/dL or

CCI mmol/L) that occurred during the second or third interval, the pump basal rate will be returned to the participant's usual basal rate for this time of the day CCI and this basal rate will be maintained until the end of MMTT.

Participants will be instructed to rest for approximately 30 minutes. A standardized liquid dinner MMTT containing approximately CCI of carbohydrates CCI will be administered approximately CCI hour after the exercise assessment (Section 5.3.1.1). Participants are expected to complete each test meal within approximately CCI minutes of starting the meal. This meal will be the same as the meals that will be provided during Visits 3 to 6. The dose-finding assessment will use Humalog administered immediately (0 to 2 minutes) before the dinner MMTT using CCI. Selection of bolus dose will be as follows:

- Initial bolus dose selection will be based on discussion between participant and investigator using participant's usual dose requirements or insulin-to-carbohydrate ratio, insulin sensitivity index, and glycemic targets preprogrammed in their personal medical device along with a 25% reduction of the bolus dose to account for increased insulin sensitivity following exercise.
- Postprandial glucose profile over the 4-hour post-meal period will be measured every CCI minutes after administration of proposed insulin dose to verify that the initial bolus dose selected is appropriate using the following:

The selected bolus dose will be used during subsequent liquid dinner MMTT assessments in the study for both Lyumjev and Humalog.

Following completion of glucose sampling, the CCI will be removed and the participant's own insulin pump will be re-introduced using a new infusion set, if necessary, for pump compatibility.

Figure ITSU.1. Study activities during Assessment Day (Visit 2).

4.1.3. In-house Visits

After Visit 2, all eligible participants will undergo 4 in-house study periods (Visits 3 to 6). Each in-house period will comprise a CCI day stay at the CRU. The in-house period will be separated by a washout period of CCI days (e.g., between Visit 3, Day 1 and Visit 4, Day 1). Each participant will be randomly assigned to a treatment sequence consisting of 2 treatments (blinded), i.e., Lyumjev and Humalog, and 2 different basal insulin reduction rates to be administered at the 4 separate in-house visits in 4 by 4 crossover Williams design (Figure ITSU.2). Randomization will take place on Day -1 of Visit 3. An example of assessment schedule that will be carried out during the in-house visits is presented in Section 1.3.2.

Figure ITSU.2. Assessment schedule for in-house study periods (Visits 3 to 6).

Upon arrival at the site, participants will be placed on a standardized insulin pump CCI with a new infusion set CCI and a CGM system CCI on the evening before the exercise session (approximately CCI PM).

After disconnecting the participant's own insulin pump, the study pump reservoir will be filled with either Lyumjev or Humalog by a qualified CRU staff, and a standard infusion set and catheter will be inserted into the abdominal area, as per the manufacturer's instructions, after the region is inspected for lipodystrophy (Section 6.1.2). The catheter should stay at the same catheter insertion site location for the duration of each period. However, a catheter can be changed to a new location on the abdomen if an occlusion is suspected up to the breakfast meal on Day 1 (Section 6.1.3). The participant's usual basal rate settings will be programmed in the pump and the basal rate infusion will be started.

The participants will wear the CRU-provided pump and CGM device during all in-house days. The study CGM device will be calibrated on the morning of the exercise day in fasted state, if

needed, using the plasma glucose values obtained with a glucose analyzer by CRU staff (Section 8.5.2).

A standardized dinner will be provided at approximately CCI. On Day 1, a standardized breakfast CCI) and lunch CCI) will be provided prior to the scheduled exercise assessment (CCI (Figure ITSU.3). Details of standardized meals are provided in Section 5.3.1.3. A cannula will be inserted for venous access for insulin lispro, glucose, FFA, and ketones sampling prior to lunch. The insulin dose for these standardized meals (dinner, breakfast, and lunch) before exercise will be individualized per participant to cover the carbohydrate content (including any correction bolus) and will be administered immediately prior (0 to 2 minutes) to the meal using a CCI No additional bolus insulin injection should be administered post-meal after lunch prior to the exercise period. The basal rate will be set to a single hourly rate at lunch CCI based on the participant's usual basal rate for this time of day; this will be maintained until the basal reduction for the exercise period. A pre-exercise glucose target level of CCI mg/dL will need to be achieved CCI minutes prior to exercise. If glucose level is below 90 mg/dL, ~16 g of oral carbohydrates will be administered. CCI prior to exercise, the period will be rescheduled as mentioned in Section 5.2.1.

Based on the randomization, the pump basal rate will be reduced either 60 minutes or 15 minutes prior to the start of exercise period, scheduled for approximately CCI in the following manner:

- 50% basal insulin reduction 60 minutes prior to exercise until end of exercise CCI
- 100% basal insulin reduction 15 minutes prior to exercise until end of exercise CCI

Participants will begin the exercise assessment at approximately 4 hours after lunch CCI They will be instructed to walk or light jog on the treadmill at approximately 45% to 55% of their predetermined peak VO_2 using three 17-minute intervals with two 4-minute and 30-second rest periods in between the intervals for 1 hour. During this period, samples will be collected for glucose, insulin lispro, ketones and FFAs per the SoA (Section 1.3). Heart rate will be monitored, and participants will be asked to rate their perceived exertion using 6-20 Borg RPE scale (Section 8.2.8) during the last 2 minutes of each 17-minute interval, as per the assessment day visit. If hypoglycemia ensues (plasma or whole blood glucose level CCI the exercise will be terminated, and the participant will be treated with ~CCI of oral carbohydrates. If the glucose level continues to be below CCI after approximately CCI minutes, up to an additional CCI of oral carbohydrates can be provided. Repeat as necessary if glucose value remains below CCI /dL.

Upon completion of the exercise period (or once the participant recovers from hypoglycemia [blood glucose reaches CCI the pump basal rate will be returned to the participant's usual rate for this time of the day CCI and this basal rate will be maintained until the end of MMTT. Participants will be instructed to rest for approximately 30 minutes.

A standardized liquid dinner MMTT containing approximately CCI of carbohydrate with a fixed nutrient composition CCI will be administered approximately 1 hour after the exercise assessment (Section 5.3.1.1). The same individualized insulin bolus dose determined from the dose assessment will be used for both arms (Lyumjev or Humalog) for all 4 in-house visits, unless it is required to be changed to protect participant safety (see Section 4.1.2). The insulin bolus dose will be administered immediately prior (0 to 2 minutes) to the meal using a CCI The meal is to be consumed within 15 minutes.

Participants will be without further oral food intake from the start of each test meal to completion of blood collection 4 hours after the start of the meal (approximately 240 minutes) unless required to treat Level 1 hypoglycemia with symptoms or Level 2 hypoglycemia. Refer to Section 8.2.7.1 and 8.2.7.2 for details. If a participant's plasma glucose concentration rises above CCI for more than CCI hour, CCI will be administered. In both situations, blood samples for plasma glucose (for safety and PD) will be taken, and PK samples will be collected as planned during this period per the SoA (Section 1.3). Following completion of study procedures, the study pump will be disconnected and the study CGM system will be removed. The participant's own insulin pump will be re-introduced using a new infusion set, if necessary, for pump compatibility. Participants may leave the CRU at the discretion of the investigator.

Appropriately trained staff must be available until the participants complete the study procedures. The pump can be reused after disinfection, according to the local procedure.

Figure ITSU.3. Study activities during In-house Periods (Visits 3, 4, 5, and 6).

4.1.4. Between In-house Visits

During the time between visits, participants will continue their CSII therapy with their own pre-study insulin, pump, and CGM or FGM. Participants will be instructed

- to perform regular blood glucose monitoring consisting of a minimum of daily 4-point SMBG (pre-prandial for 3 meals [that is, breakfast, lunch, and dinner] and at bedtime) using their own CGM and

- to use a diary to document any AEs, hypoglycemic events, meals (time, units of carbohydrate equivalent), insulin bolus doses, and basal rates, and the SMBG values.

Upon return to the CRU, the diary will be reviewed and checked for hypoglycemic events and AEs. Only data related to AEs, will be entered into the eCRF. Additionally, as determined by the investigator, interim telephone visits may occur at any time during the outpatient periods to review the safety and well-being of the participant.

4.1.5. Follow-Up Visit

Participants will be required to visit CRU 3 to 7 days after Visit 6 and will undergo assessments as mentioned in Section 1.3.1. The diary will be reviewed and checked for hypoglycemic events and AEs.

4.2. Scientific Rationale for Study Design

The study has a 4-period crossover Williams design to reduce the variability of insulin PK and GD as each participant serves as his or her own control. The total number of participants needed with a crossover design is less than the number needed with a parallel group design. Williams design will achieve the balance and maximize the comparisons with the smaller number of participants and will require fewer sequences and periods. A maximum duration of CCI weeks is allowed for participants to complete all 4 assigned periods to minimize the risk of insulin resistance/changes in mean glycemic control during the study, provided no rescheduling is required.

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

Prior to the study periods, participants will undergo an assessment day to determine an appropriate, individualized insulin lispro dose of Lyumjev or Humalog to be administered with the MMTT.

A minimum of approximately CCI of washout between the in-house periods allows for a complete washout of study interventions administered with the MMTT and glucose response and prevents carryover effects.

4.3. Justification for Dose

The bolus dose of insulin lispro (Lyumjev or Humalog) will be individualized per participant to cover the carbohydrate content of both the standardized meals while in-house at the CRU and will be based on the participant's individually calculated dose and/or insulin: carbohydrate ratio. For each participant, the individualized prandial insulin lispro dose for the dinner liquid MMTT and basal rates must be kept identical throughout the in-house periods.

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last participant in the study or last scheduled procedure shown in the SoA (Section 1.3) for the last participant in the trial.

5. Study Population

Eligibility of participants for enrollment in the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, diabetes device downloads, and ECG. The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented.

The inclusion and exclusion criteria used to determine eligibility should be applied at screening only unless otherwise specified, and not continuously throughout the trial.

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

5.1. Inclusion Criteria

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

Age

1. Participant must be aged 18 to 55 years, inclusive, at the time of signing the informed consent and of an acceptable age to provide informed consent according to local law.

Type of participant and disease characteristics

2. Participants with a diagnosis of T1D based on medical history with a fasting C-peptide ≤0.30 nmol/L (≤300 pmol/L) and the following:
    a. HbA1c ≤8.5%
    b. diabetes duration of at least 1 year
    c. using CSII and stable insulin regimen with a rapid-acting insulin analog for at least 6 months prior to inclusion into the trial
    d. currently on CSII therapy, with a total insulin dose >0.25 U/kg/day and ≤1.2 U/kg/day
    e. have had no episodes of severe hypoglycemia in the past 6 months (severe hypoglycemia is defined as having neurological symptoms consistent with neuroglycopenia and required assistance in treatment by a second party)
    f. have clinical laboratory test results within normal reference range with acceptable deviations that are judged to be not clinically significant by the investigator.
    g. a peak VO_2 of ≥35 for males and ≥32 for females
    h. able to undergo at least 1 hour of moderate-intensity treadmill exercise (walking or jogging depending on baseline fitness)
    i. exercise regularly (≥3 times per week of moderate or vigorous exercise)
    j. are using a personal CGM or FGM to self-monitor glucose
        i. are capable of, and willing, to do the following: Perform 4-point SMBG, prior to designated visits (participants using a personal CGM or FGM
        ii. keep records in participant study diaries required by this protocol

Weight

3. Participants with a body mass index within the range 18.5 to 29.0 kg/m^2 (inclusive).

Sex and contraceptive/barrier requirements

4. Male and female

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

a. Male participants:
Males may participate in this trial.
No male contraception is required except in compliance with specific local government study requirements.
b. Female participants:
1. Women of childbearing potential may participate in this trial as long as they follow the contraception guidance outlined in Section 10.4.
2. Women not of childbearing potential may participate in this trial.
Please refer to Appendix 4 (Section 10.4) for definitions and additional guidance related to contraception

Informed consent

5. Participants whom are capable of giving signed informed consent as described in Appendix 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

Other inclusions

6. Participants who have venous access sufficient to allow for blood sampling as per protocol.
7. Participants who are reliable and willing to make themselves available for the duration of the study and are willing to follow study procedures.

5.2. Exclusion Criteria

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

Medical conditions

8. Participants who are lactating.
9. Women of childbearing potential who are not following contraception guidance as mentioned in Section 10.4.
10. Participants who have known allergies to study intervention, related compounds, or any components of the formulation
11. Participants who have an abnormal blood pressure and/or pulse rate as determined by the investigator.

12. Participants who have significant previous or current history of comorbidities capable of significantly altering the absorption, metabolism, or elimination of drugs; of constituting a risk when taking the investigational product; or of interfering with the interpretation of data
13. Participants who have a current psychiatric disorder that may prevent them from being compliant with study procedures
14. Participants who regularly use known drugs of abuse or show positive findings on drug screening.
15. Participants who show evidence of human immunodeficiency virus infection and/or positive human immunodeficiency virus antibodies.
16. Participants who have spontaneously cleared hepatitis C virus infection, defined as
    a. a positive hepatitis C virus antibody test and
    b. a negative hepatitis C virus RNA test.
17. Participants who show evidence of possible chronic or active hepatitis B, including hepatitis B core antibody and hepatitis B surface antigen positivity or both.
18. Participants who have donated blood of more than 500 mL within the previous 4 weeks of study screening.
19. Participants with clinically significant cardiac or pulmonary disease (e.g., angina, clinically significant cardiac arrhythmias, exercise-induced bronchospasm that requires bronchodilators or would preclude completing exercise).
20. Participants with severe neuropathy, in particular autonomic neuropathy, as judged by the investigator.
21. Participants who have had lymphoma, leukemia, or any malignancy within the past 5 years except for basal cell or squamous epithelial carcinomas of the skin that have been resected with no evidence of metastatic disease for 3 years.

Prior/concomitant therapy

22. Participants with current use of any glucose-lowering agents other than insulin that might impact outcome measures:
    a. any agents that affect hepatic glucose production, including all beta-adrenergic agonists or antagonists, all xanthine derivatives
    b. beta blockers
    c. any noninsulin diabetes therapy, (i.e., pramlintide. etc.).
23. Participants who intend to use over-the-counter or prescription medication including herbal medications and traditional medications that affect blood glucose level or the body's sensitivity to insulin, or that promote weight loss within 14 days prior to dosing. Specific medications listed in Section 6.8, Concomitant Medications, may be allowed.
24. Participants who intend to use acetaminophen CCI during the basal rate optimization, assessment day, or study periods.

Prior/concurrent clinical study experience

25. Participants who have previously completed or withdrawn from this study.

26. Participants who have participated, within the past 30 days, in a clinical study involving an investigational product. If the previous investigational product has a long half-life, 5 half-lives or 30 days (whichever is longer) should have passed.

Other exclusions

27. Participants who have an average weekly alcohol intake that exceeds 21 units per week (males aged ≤55 years) and 14 units per week (females).
28. Participants who are unwilling to stop alcohol consumption for 24 hours prior to each study treatment and during the study treatment periods.
29. Participants who smoke more than 10 cigarettes per day or the equivalent including electronic cigarettes or are unable to abide by CRU smoking restrictions.
30. Participants who are unwilling to comply with the dietary restrictions required for this study.
31. Participants who in the opinion of the investigator or sponsor, are unsuitable for inclusion in the study.
32. Participants who do not achieve the optimal basal rates, at the discretion of the investigator, at second evaluation of basal rate optimization visits.
33. Individuals following a very low-carbohydrate diet, defined as ≤50 g per day of carbohydrates or ≤10% carbohydrates as a proportion of calories

5.2.1. Additional criteria for study treatment periods

For participants who fulfill 1 or more of the following criteria prior to the in-house periods, the in-house period can be rescheduled 1 to 14 days later. For the assessment day, rescheduling will be within the allowable time window mentioned in the SoA. Each of the study treatment periods can only be rescheduled once.

a. consumption of alcohol within 24 hours prior to each in-house period, or a positive result for the alcohol or drug test
b. consumption of coffee, tea, chocolate, cola, energy drinks and/or energy drinks containing methylxanthine within 8 hours prior to start of dosing with study intervention during each in-house period
c. strenuous exercise within the past 24 hours prior to each in-house period.
d. any medical condition or AE that could interfere with glucose metabolism, as judged by the investigator
e. any use of prescription or nonprescription medication as per exclusion criteria 23 and 24
f. hypoglycemia CCI [redacted] posing a safety problem as judged by the investigator, or
g. participant is unable to obtain glucose range (CCI [redacted] prior to initiation of exercise assessment.

5.3. Lifestyle Considerations

Throughout the study, participants must adhere to lifestyle restrictions as outlined by the CRU and in the study procedures. Participants will be assessed for compliance with requirements before continuing in the study. When not resident in the CRU, participants may resume their regular diet.

5.3.1. Meals and Dietary Restrictions

- While resident at the CRU, participants may not consume any food or caloric drinks other than that provided by the CRU. While not resident at the CRU, participants may resume their regular diet.
- The time of meal start and completion, the total calories, and grams of carbohydrates consumed in the MMTT (Section 5.3.1.1), and the standardized meals (Section 5.3.1.3) during the assessment day and Day 1 of in-house period will be captured in the study eCRF.

5.3.1.1. Mixed Meal Tolerance Test

On assessment day and on Day 1 of in-house periods, a dinner liquid MMTT will be administered 1 hour after the exercise assessment as mentioned in Sections 4.1.2 and 4.1.3 and as outlined in Section 1.3. The standardized liquid test meal will use CCI [redacted] The macronutrient composition of the meal will contain approximately 50 g of carbohydrates, approximately CCI of protein, and approximately CCI of fat. Participants will be fasted, except for water, for 4 hours before each test meal and are required to consume the MMTT within approximately CCI [redacted]. The MMTT meals will be kept consistent across the assessments in the study. Participants will not be allowed to consume water for CCI after dosing apart from fluid provided with the meal. However, water may be consumed freely after CCI [redacted] post-dose.

5.3.1.2. Standardized Lunch Meal

On assessment day and on Day 1 of in-house periods, a standardized lunch will be administered prior to the exercise assessment as mentioned in Sections 4.1.2 and 4.1.3 and as outlined in Section 1.3. The macronutrient composition of the lunch should be targeted to provide approximately CCI of the calories from carbohydrate CCI [redacted], CCI of the calories from fat, and CCI [redacted] the calories from protein. The standardized lunch for each participant will be kept consistent for all assessment periods. Participants will consume the meal within approximately CCI [redacted].

5.3.1.3. Standardized Breakfast and Dinner Meals

Participants will be provided individualized standardized meals during the in-house periods and assessment day, as outlined in Section 1.3. The macronutrient composition of the meals should be targeted to provide approximately CCI of the calories from carbohydrate, CCI of the calories from fat, and CCI of the calories from protein. Participants will consume each meal within approximately CCI [redacted] minutes. Breakfast and dinner meals for each participant during the in-house periods will be kept consistent with regard to calories and nutrient content.

5.3.1.4. Snacks

Snacks with CCI of carbohydrates are allowed at bedtime during in-house periods unless otherwise specified in the protocol.

5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco

- During the in-house period, participants will abstain from ingesting caffeine- or xanthine-containing products (e.g., coffee, tea, cola drinks, and chocolate) for 8 hours before the start of dosing with study intervention until after collection of the final PK sample, excluding the MMTT when CCI Plus may be given.
- During each dosing session, participants will abstain from alcohol for 24 hours before the start of dosing until after collection of the final PK sample.
- Participants who use tobacco products will be instructed to abide by the smoking restrictions while they are in the CRU.

5.3.3. Activity

Participants will be encouraged to maintain their regular exercise and insulin regimen adaptation related to exercise during the outpatient period; however, they should not undertake vigorous or prolonged exercise at least 24 hours before each dosing day at the CRU.

Participants will be instructed to perform exercise on assessment day and on Day 1 of in-house periods as mentioned in Sections 4.1.2 and 4.1.3. On Day 1, a pre-exercise glucose target of CCI will need to be achieved CCI prior to exercise as mentioned in Section 4.1.3.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened only once. Rescreened participants will be required to undergo all screening assessments and procedures. The interval between rescreening should be at least 28 days. Each time rescreening is performed, a new informed consent form (see Section 10.1.2 for details) must be signed and participants will be assigned a new identification number.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

Intervention Name	Lyumjev™	Humalog®
Type	Drug	Drug
Dose Formulation	10-mL vial	10-mL vial
Unit Dose Strength(s)	100 U/mL	100 U/mL
Dosage Level(s)	Basal and bolus infusion based on individual needs	Basal and bolus infusion based on individual needs
Route of Administration	Subcutaneous infusion via CSII	Subcutaneous infusion via CSII
Use	Experimental	Active comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	The study intervention will be provided to the CRU in unblinded vials. All clinical study materials provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained staff. Detailed records of the amounts of the study intervention received, dispensed, and remaining at the end of the study will be maintained. The study intervention will be	The study intervention will be provided to the CRU in unblinded vials. All clinical study materials provided to the investigator will be stored in a secure place and allocated and dispensed by appropriately trained staff. Detailed records of the amounts of the study intervention received, dispensed, and remaining at the end of the study will be maintained. The study intervention will be

	labeled according to the country's regulatory requirement	labeled according to the country's regulatory requirement

Abbreviations: CRU = clinical research unit; IMP = investigational medicinal product; NIMP = noninvestigational medicinal product.

6.1.1. Noninvestigational Medicinal Products

During the in-house periods, if a participant's plasma glucose concentration rises above CCI for more than CCI hour during the liquid MMTT dinner, commercially available CCI will be administered. CCI or intravenous glucose/oral dextrose can also be administered during the complete in-house period outside of the MMTT procedures if required to treat hyperglycemia or hypoglycemia, respectively, at the discretion of the investigator.

The doses of CCI and glucose administered during the in-house periods of the study must be recorded in the eCRF.

All NIMPs will be sourced locally by the site and will be used from their original packaging.

6.1.2. Administration Details

During in-house periods (Day –1, starting prior to the administration of the standardized dinner, to Day 1), all study interventions will be administered using a CCI A standardized catheter with a CCI needle length will be inserted on the day before the dinner meal is administered (Day –1) during each period, and the catheter site must remain the same until completion of study procedures on Day 1.

For each pump, a 3-mL reservoir will be filled with 3 mL of study treatment by a qualified CRU staff; a CCI will be attached to the filled reservoir and the reservoir will be loaded into the pump. The infusion set tubing CCI) will be primed, and a cannula fill with CCI unit will be completed. CCI cannula will be inserted into the central abdominal area (at least 5 cm away from the umbilicus) avoiding areas of lipohypertrophy and surgical scars. Infusion sites will be alternated among 4 sites (that is, right and left upper quadrants and right and left lower quadrants) on the abdominal wall. Catheter insertions should be performed by a limited number of qualified and appropriately trained CRU staff as designated by the investigator for consistency. Whenever possible, study intervention administration should be carried out by the same staff.

The insulin pump reservoir will be filled with either Lyumjev or Humalog by qualified CRU staff while maintaining the blinding for the investigator and participant. For each standardized meal and the MMTT, the doses will be administered immediately before the start of a test meal. The meals will be given at approximately the same time for each in-house study period. The actual time and dose level of all doses during the assessment day and in-house periods will be recorded in the participant's eCRF.

6.1.3. Pump Occlusion Alarms and Accidental Infusion Set Discontinuations

If a pump occlusion alarm occurs during basal infusion, the infusion set tubing should be inspected for kinks or crimps and the basal infusion rate restarted. If the occlusion alarm persists, the infusion site will be discontinued, a catheter can be changed to a new location on the

abdomen if an occlusion is suspected up to the breakfast meal on Day 1. If a suspected occlusion occurs during the breakfast meal or afterwards, the period will be terminated for the participant and that study period will be repeated at another time.

If a catheter occlusion alarm occurs during a bolus infusion or <5 hours after the start of the MMTT, the data will not be used for analysis. Data related to these events will be recorded in the eCRF.

6.2. Preparation, Handling, Storage, and Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention. Only authorized study staff may supply, prepare, or administer study intervention. All study interventions 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 study staff.
3. The investigator or authorized study staff are responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Study Reference Manual.

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

6.3. Measures to Minimize Bias: Randomization and Blinding

This is a participant- and investigator-blind study. Blinding will be maintained throughout the conduct of the study until all data are cleaned to an acceptable level of quality and locked. The details are included in the blinding/unblinding plan.

To preserve the blinding of the study, only a minimum number of staff at the CRU will see the randomization table and codes before the study is complete. Those individuals with access to the randomization table and codes will not be involved in the conduct of the study or subject care.

On Day -1 of in-house period (Visit 3), participants will be assigned a unique number (randomization number) in ascending numerical order. The randomization number encodes the participant's assignment to 1 of the 4 sequences for the in-house study periods, according to the randomization schedule generated prior to the study by the statistics department at the sponsor/designee. Each participant will be dispensed blinded study intervention, labeled with the participant's unique randomization number, throughout the study.

Participants will be randomly assigned in a 1:1 ratio to receive study intervention. Investigators will remain blinded to each participant's assigned study intervention throughout the course of the

study. To maintain this blind, an otherwise uninvolved third party, such as a pharmacist, will be responsible for the dispensation of all study interventions and will endeavor to ensure that there are no differences in time taken to dispense following randomization.

This third party will instruct the participant to avoid discussing dosing frequency, or packaging of the study intervention with the investigator.

In the event of a quality assurance audit, the auditor(s) will be allowed access to unblinded study intervention records at the site(s) to verify that randomization/dispensing has been done accurately.

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

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. Where feasible and when timing of the emergent situation permits, the investigator should attempt to contact the Lilly medical monitor before unblinding a participant's treatment assignment. If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

If an investigator, site staff performing assessments, or participant is unblinded, the participant must be discontinued from the study. In cases where there are ethical reasons to have the participant remain in the study, the investigator must obtain specific approval from Lilly clinical pharmacologist or CRP for the participant to continue in the study. During the study, emergency unblinding should occur only by accessing the study participant's emergency code.

Upon completion of the study, all codes must be returned to Lilly or its designee.

6.4. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, the preparation of the dose will be confirmed by a second member of the CRU staff.

Study intervention will be administered under medical supervision by the investigator or designee. The dose of study intervention and study participant identification will be confirmed prior to the time of dosing. The date and time of each dose administered will be recorded in the source documents and in the eCRF.

6.5. Dose Modification

For the in-house period, there will be no dose modifications of insulin lispro for the MMTT and basal rates unless medically indicated and confirmed between the sponsor clinical pharmacologist/CRP/CRS and the investigator.

6.6. Continued Access to Study Intervention after the End of the Study

Study completion will occur following the final analysis of primary and secondary objectives, as determined by Lilly. Investigators will continue to follow SoA (Section 1.3) for all participants until notified by Lilly that study completion has occurred.

No intervention is allowed following the end of the trial. Participants will return to their pre-study interventions and devices.

6.7. Treatment of Overdose

In the event of an overdose, refer to the Humalog or Lyumjev package insert.

Excess insulin administration may cause hypoglycemia and hypokalemia.

Mild episodes of hypoglycemia can usually be treated with oral glucose. Adjustments in drug dosage, meal patterns, or exercise may be needed. More severe episodes with coma, seizure, or neurologic impairment may be treated with intramuscular or subcutaneous glucagon or concentrated intravenous glucose. Sustained carbohydrate intake and observation may be necessary because hypoglycemia may recur after apparent clinical recovery.

Hypokalemia must be corrected appropriately.

6.8. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) other than study intervention that the participant is receiving at the time of enrollment or receives during the study must be recorded along with

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency for concomitant therapy of special interest

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Participants on stable concomitant medication at the time of study entry should continue their regular, unchanged dose throughout the study. Participants will continue their basal insulin infusion rate during the entire study except when presenting safety issues and prior to and during the exercise assessment period when the basal insulin rate is reduced as defined in Section 4.1.3. In case of safety-driven indications for a basal rate adaptation, the investigator will discuss a change of the regimen of insulin basal rate to prevent any medical problems. Any change in the basal rate will be captured in the participant diary and eCRF.

Participants should not use over-the-counter or prescription medication (other than their current regimen of insulin therapy and concomitant medication [e.g., antihypertensives, lipid-lowering agents] at enrollment) or nutritional supplements that affect blood glucose level or the body's sensitivity to insulin or that promote weight loss within 14 days before dosing (apart from vitamin/mineral supplements, ibuprofen, hormone/thyroid-replacement therapy, or hormonal contraceptives) or throughout the study.

Participants should not use over-the-counter or prescription medications containing acetaminophen (paracetamol) during the basal rate optimization, assessment day, or study periods because it is known to interfere with CGM sensing, impacting the accuracy of the CCI

Participants should not apply any creams or lotions to the abdominal skin on the morning of the catheter insertion or during the in-house study procedure.

If the need for concomitant medication arises (e.g., to treat an AE or infusion-site pain), inclusion or continuation of the patient may be at the discretion of the investigator, preferably after consultation with a Lilly clinical pharmacologist or CRS/CRP. Any additional medication used during the course of the study must be documented.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1).

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue (definitive discontinuation) study intervention. If study intervention is definitively discontinued, for any reason, participants should report AEs and product complaints and complete other safety follow-up at exit visit, in accordance with this protocol. Safety follow-up should be performed as outlined in Sections 1.3 and 8.3.

The sponsor shall be notified of any instance of participant withdrawal or discontinuation. Any data collected up to the point of withdrawal or discontinuation may be used in the study.

See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention and for any further evaluations that need to be completed.

7.1.1. Liver Chemistry Stopping Criteria

Not applicable.

7.1.2. QTc Stopping Criteria

Not applicable.

7.1.3. Hypoglycemia

Discontinuation of the study intervention should be considered by the investigator for participants with severe hypoglycemia (Level 3 according to Section 8.2.7.1) or persistent hypoglycemic events (Level 2).

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee (e.g., parents or legal guardian)
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- 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 prior to introduction of the new agent.

Discontinuation is expected to be uncommon.

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. The participant will be permanently discontinued from both the study intervention and the study at that time.

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/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

Participants will be discontinued under the following circumstances:

- enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws and regulations
- the investigator decides that the participants should be discontinued from the study
- participant becomes pregnant during the course of the study
- participant did not meet the enrollment criteria and was inadvertently enrolled
- any episode of diabetic ketoacidosis occurring in the past 6 months
- any episode of severe hypoglycemia occurring in the past 6 months, and
- the study is discontinued.

Participants discontinuing from the study prematurely for any reason should return to the CRU. Concomitant medications, AEs, and product complaints will be reviewed. CRU staff should document details regarding the reason for discontinuation when available. Participants will return all appropriate sponsor-provided study materials per sponsor instructions. A point-of-care HbA1c measurement will be taken that may be used to inform decision making for end-of-study insulin regimen. Participants will begin non-study insulin.

Lilly shall be notified of any instance of participant withdrawal or discontinuation. Any data collected up to the point of withdrawal or discontinuation may be used in the study.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the CRU. CRU staff or designee 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

- 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.

Section 1.3 lists the SoA, detailing the study procedures and their timing (including tolerance limits for timing). The specifications in this protocol for the timings of safety and sample collection are given as targets to be achieved within reasonable limits. Modifications may be made to the time points based upon emerging clinical information. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF.

Section 10.2 (Appendix 2) lists the laboratory tests that will be performed for this study.

Section 10.2.1 provides a summary of the maximum number and volume of invasive samples, for all sampling, during the study.

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

8.1. Efficacy Assessments

There are no efficacy assessments within this study.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and peripheral 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 sign measurements (blood pressure, pulse rate, heart rate, and body temperature) should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations included in Manual of Operations for the study.
- Blood pressure and pulse rate should be measured after at least 5 minutes in supine position.
- If orthostatic measurements are required, participants should be supine for at least 5 minutes and stand for at least 3 minutes.
- If the participant feels unable to stand, supine vital signs only will be recorded.
- Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. Additional vital signs may be measured during each study period if warranted.

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, QT, and corrected QT intervals.
- ECGs must be recorded before collecting any blood samples. Participants must be supine for approximately 5 to 10 minutes before ECG collection and remain supine but awake during ECG collection. ECGs may be obtained at additional times, when deemed clinically necessary. All ECGs recorded should be stored at the CRU.
- ECGs will be interpreted by a qualified physician (the investigator or qualified designee) as soon after the time of ECG collection as possible, and ideally while the participant is still present, to determine whether the participant meets entry criteria at screening visit and for immediate participant management, should any clinically relevant findings be identified.
- If a clinically significant finding is identified the investigator will determine if the participant can be enrolled in the study.

8.2.4. Clinical Safety Laboratory Tests

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.
- The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those that are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.
- If laboratory values from non-protocol specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator (e.g., SAE or AE or dose modification), then report the information as an AE.

If a central vendor is used for the study, Lilly or its designee will provide the investigator with the results of laboratory tests analyzed by a central vendor, unless the safety laboratory test results may unblind the study.

8.2.5. Pregnancy Testing

Pregnancy test will be carried out as outlined in SoA (Section 1.3).

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Not applicable.

8.2.7. Safety Monitoring

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

8.2.7.1. Hypoglycemia

Glucose level will be monitored for safety throughout the study according to the SoA using YSI and using CGM. Participants will be trained by CRU staff about signs and symptoms of hypoglycemia and the manner of treating hypoglycemia. Investigators should use the following classification of hypoglycemia:

- Level 1 hypoglycemia (glucose CCI [redacted] - It can alert a person to take action, such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.
- Level 2 hypoglycemia (glucose CCI [redacted] - This is also referred to as documented or blood glucose confirmed hypoglycemia with glucose CCI [redacted]. This glucose threshold is clinically relevant regardless of the presence of absence of symptoms of hypoglycemia.
- Level 3 hypoglycemia (severe hypoglycemia [in adults]) - A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status, and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed 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

glucose concentration to normal is considered sufficient evidence that the event was induced by a low 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. If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE eCRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia is a hypoglycemic event (including severe hypoglycemia) that occurs at night and presumably during sleep.

8.2.7.2. Treatment of Hyperglycemia and Hypoglycemia during In-house Periods

Hypoglycemia during MMTT:

Participants will be without food intake from the start of the MMTT to completion of blood collection (approximately 240 minutes) unless required to treat Level 1 hypoglycemia with symptoms or Level 2 hypoglycemia. If it occurs, treatment is to be done with either rapidly absorbable oral carbohydrates or intravenous glucose.

Hypoglycemia during Exercise:

If hypoglycemia ensues [redacted], the exercise will be terminated, and the participant will be treated initially with ~[redacted] of oral carbohydrates. If the glucose level continues to be below [redacted] after approximately [redacted] minutes, up to an additional [redacted] of oral carbohydrates can be provided. Repeat as necessary if glucose value remains below [redacted] mg/dL. The same approach should be used if hypoglycemia ensues after completion of the exercise prior to the MMTT. The administration of the MMTT could be given [redacted] minutes earlier to prevent hypoglycemia at the discretion of the investigator.

If carbohydrates are administered and consumed during the in-house periods, it must be captured in the eCRF.

If a patient is experiencing hyperglycemia (glucose level [redacted] for more than [redacted] hour, insulin glulisine will be administered intravenously.

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

8.2.8. Rating of Perceived Exertion

The RPE scale will be used during each of the exercise periods as outlined in the SoA (Section 1.3). The [redacted] is a well-validated tool [redacted] to assess perceived physical effort during exercise; it is presented as a scale [redacted] anchored by verbal descriptors. This scale describes different efforts: [redacted] is no exertion at all and [redacted] the maximal exertion or hardest possible effort. Participants will be asked to point to a number that best describes their feelings of the exercise at that moment.

8.3. Adverse Events, Serious Adverse Events, and Product Complaints

The definitions of the following events can be found in Appendix 3 (Section 10.3):

- AEs
- SAEs, and
- product complaints

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study (see Section 7).

Care will be taken not to introduce bias while detecting events. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about event occurrences.

After the initial report, the investigator is required to proactively follow up each participant at subsequent visits/contacts. All SAEs will be followed up until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Appendix 3 (Section 10.3).

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

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

8.3.1. Timing and Mechanism for Collecting Events

This table describes the timing, deadlines, and mechanism for collecting events.

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Adverse Event					
AE	Signing of the ICF	The follow-up visit	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	participation in study has ended	Within 24 hours of awareness	SAE paper form	SAE paper form
SAE* – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	10 hours after the last dose	Within 24 hours of learning of the pregnancy (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End-of-study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End- of-study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; CRF = case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

* SAEs should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

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 up 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.
- Any poststudy pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in Section 8.3.1. 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 study intervention. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adverse Events of Special Interest

Not applicable.

8.4. Pharmacokinetics

At the visits and times specified in the SoA (Section 1.3), venous samples will be collected to determine the serum concentrations of insulin lispro. Instructions for the collection and handling of blood samples will be provided by the sponsor. The actual date and time (24-hour clock time) of each sampling will be recorded.

Samples collected for analyses of insulin lispro concentration may also be used to evaluate safety or pharmacology aspects related to concerns arising during the study.

Drug concentration information that would unblind the study will not be reported to CRU or blinded staff until the study has been unblinded.

8.4.1. Bioanalysis

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

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

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

8.5. Pharmacodynamics

8.5.1. Glucose Values

Blood will be collected for glucose values via CCI [redacted] at visits and times specified in the SoA (Section 1.3). These values will be used in statistical analyses, and the actual date and time (24-hour clock time) of each sampling will be recorded in the eCRF.

8.5.2. Exploratory CGM Values

For the CGM, a standard system (e.g., CCI [redacted]) will be used in this study. The study CGM sensor will be inserted by qualified CRU staff, and the participants will be instructed to always carry the receiver with them. The CGM device will be calibrated, if required, using the plasma glucose values obtained with the CCI [redacted] by qualified CRU staff. Participants will not be allowed to view their glucose levels during the exercise or the liquid MMTT assessments. The participants will wear this device before the start of a standardized dinner (at CCI [redacted] on Day -1 until completion of MMTT assessment on Day 1 for each in-house period. The monitor will record continuous glucose measurements. At the end of the recording, the study CGM sensor will be removed, and the receiver will be used to download the glucose data.

8.5.3. Exploratory Blood Ketones and Free Fatty Acids

Blood will be collected for ketones via CCI [redacted] at visits and times specified in the SoA (Section 1.3). The actual date and time (24-hour clock time) of each sampling will be recorded in the eCRF.

Blood will be collected to determine concentration of free fatty acid levels at visits and times specified in the SoA (Section 1.3) using a validated method. The actual date and time (24-hour clock time) of each sampling will be recorded in the eCRF. Instructions for the collection and handling of these samples will be provided by the sponsor.

8.6. Genetics

Genetics are not evaluated in this study.

8.7. Biomarkers

Biomarkers are not evaluated in this study.

8.8. Immunogenicity Assessments

Not applicable.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

Health economics or medical resource utilization and health economics parameters are not evaluated in this study.

9. Statistical Considerations

The SAP will be finalized prior to the first participant first visit, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important endpoints, including primary and key secondary endpoints.

9.1. Statistical Hypotheses

This study will evaluate if there is a significant difference in the change in plasma glucose level during exercise between Lyumjev and Humalog using either 50% or 100% reduction of basal infusion rates.

9.1.1. Multiplicity Adjustment

There is no multiplicity adjustment in this study.

9.2. Analyses Sets

Participant Analysis Set	Description
Full analysis set	Participants who receive at least 1 dose of IP and have completed at least 1 MMTT procedure will be included in the analysis set for the PD analyses. Participants who receive at least 1 dose of insulin during the in-house period and have measurable insulin lispro concentrations will be included in the PK analysis dataset
Modified full analysis set	All participants who receive both treatments (Lyumjev and Humalog) for at least 1 basal rate reduction (either 50% or 100%) and receive the same dose and meal consumption. Participants who do not keep identical insulin lispro doses for Lyumjev and Humalog or have difference in the consumption of the meal for each visit/period will be excluded from the statistical analysis of the PK* and glucodynamic parameters
Safety analysis set	All participants who are exposed to at least 1 dose of IP. Participants will be analyzed according to the intervention they actually received

Abbreviations: IP = investigational product; MMTT = mixed meal tolerance test; PD = pharmacodynamics; PK = pharmacokinetics.

*For the MMTT PK parameters analysis, all participants who receive both treatments with an identical insulin lispro doses for Lyumjev and Humalog will be included.

9.2.1. Study Participant Disposition

A detailed description of the participant's disposition will be provided.

9.2.2. Study Participant Characteristics

The participant's age, sex, weight, body mass index, height, race/subrace, duration of diabetes, smoking habits, or other demographic characteristics will be recorded.

9.2.3. Treatment Compliance

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

The specifications in this protocol for the timings of safety, PK, and PD sampling are given as targets, to be achieved within the time windows described in the study specific CRF completion guidelines. Modifications may be made to the time points based upon the safety and PK information obtained. The scheduled time points may be subject to minor alterations; however, the actual time must be correctly recorded in the eCRF. Failure to obtain samples and perform protocol-specific procedures outside the allowable time window because of clinical issues, such as problems with venous access, technical problems with equipment, or problems with participant no-show for scheduled procedures, will not be considered a protocol deviation but the site will still be required to notify the sponsor in writing. Written documentation (e.g., a note-to-file) will have to be provided to the sponsor for all missing or delayed samples and procedures (regardless of reasons) to facilitate data reconciliation before study completion.

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

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analysis of this study will be the responsibility of Lilly or its designee. Any change to the data analysis methods described in the protocol will require an amendment ONLY if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the SAP or the CSR.

Additional exploratory analyses of the data will be conducted as deemed appropriate. Analyses will be fully detailed in the SAP.

Insulin lispro concentration will be used for population PK analysis. Additionally, the study results may be pooled with the results of other studies for population PK analysis. This analysis and output will not be captured in the final CSR.

Insulin lispro concentration may be pooled with the results of other studies for population PK analysis purposes. This analysis and output will not be captured in the final CSR.

9.3.2. Glucodynamic Analysis

9.3.2.1. Glucodynamic Parameter Estimation

Participants who receive at least 1 dose of study intervention and have completed at least 1 MMTT procedure will be included in the analysis set for the PD analyses.

Data will be analyzed for the participants during each exercise and MMTT assessment.

During the exercise period, the change from baseline values CCI [redacted] for each participant will be calculated to derive the change in plasma glucose level from start to end of exercise.

The rate of plasma glucose during the exercise, the nadir plasma glucose, decremental AUC, for each exercise assessments will be calculated.

During the MMTT, the change from baseline values CCI [redacted] for each participant will be calculated. The area under the baseline subtracted plasma glucose concentration versus time curve (incremental) (iAUC) will be calculated during the MMTT for each in-house period.

- The AUC from time zero to 30 minutes postmeal (iAUC0-30min)
- The AUC from time zero to 1-hour postmeal (iAUC0-1hour)
- The AUC from time zero to 2 hours postmeal (iAUC0-2hours)
- The AUC from time zero to 3 hours postmeal (iAUC0-3hours)
- The AUC from time zero to 4 hours postmeal (iAUC0-4hours)

In addition, the change from baseline maximum plasma glucose observed during the 4 hours postmeal (ΔPGmax) and change from baseline 1-hour plasma glucose (ΔPG1h and 2-hour plasma glucose after the start of the meal (ΔPG2h) will be calculated. Other partial iAUCs may be calculated, as deemed appropriate.

The mean data will be presented by summary statistics and presented by treatment for those participants who received both treatments (Lyumjev and Humalog) with the same insulin dose (bolus dose for the MMTT or basal reduction) and meal consumption.

9.3.2.2. Glucodynamic Statistical Inference

Statistical analyses comparing PD parameters (described in Section 9.3.2.1) of Lyumjev versus Humalog during exercise with a basal reduction of either 50% or 100% and after the MMTT will be conducted on the modified full analysis set. The exercise and MMTT will be analyzed separately.

9.3.2.2.1. Statistical Analysis of the Primary Endpoint Change in Plasma Glucose during Exercise

Changes in plasma glucose will be compared between Lyumjev versus Humalog from the start to the end of exercise during either 50% or 100% reduction of basal infusion rates.

For the primary endpoint, the change in plasma glucose will be analyzed using a mixed-effect model that includes treatment (Lyumjev, Humalog), sequence, period, and treatment as fixed effects and participant within sequence as a random effect. LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance.

9.3.2.2.2. Statistical Analysis of the Secondary GD Endpoints

Changes in GD parameters during exercise and MMTT will be compared between Lyumjev versus Humalog during exercise with either 50% or 100% reduction of basal infusion rates.

Log-transformed iAUCs, ΔPG_{max}, ΔPG1h, and ΔPG2h will be evaluated to estimate geometric means, ratios of geometric means of insulin lispro within Lyumjev to Humalog, and their corresponding 90% CIs of the ratios using the mixed-effects model that includes treatment (Lyumjev, Humalog), sequence, period, and treatment as fixed effects and subject as a random effect. Analysis of iAUCs during the MMTT and AUCs during exercise will be based on untransformed endpoints, if negative values occurred. In this case, LSmeans, treatment differences in LSmeans, and corresponding 90% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance. The treatment ratios and 90% CIs for the ratios will be calculated using Fieller's theorem. Additionally, treatment differences in LSmeans, and corresponding 90% CIs may be estimated from the model for ΔPG_{max} , ΔPG1h , and ΔPG2h based on untransformed data.

The same model without log transformation will be used for the analysis of the rate of change in PG during the exercise period and exploratory GD time parameters. LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance. The treatment ratios and 90% CIs for the ratios will be calculated using the Fieller's theorem (Chow and Liu 2009).

Additionally, exploratory analysis may be conducted and will be defined in the SAP.

9.3.3. Pharmacokinetic Analysis

9.3.3.1. Pharmacokinetic Parameter Estimation

Participants who receive at least 1 dose of insulin during the in-house period and have measurable insulin lispro concentrations will be included in the PK analysis dataset.

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

Free serum insulin lispro concentrations will be used to calculate several PK parameters following the meal bolus for the MMTT, including time to early half-maximal drug concentration (early 50% t_{max}), time to late half-maximal drug concentration (late 50% t_{max}), maximum observed drug concentration (C_{max}), time of maximum observed drug concentration (t_{max}), and area under the plasma concentration time curve (AUC) from zero to 15 minutes (AUC[0-15min]), AUC from time zero to 30 minutes (AUC[0-30min]), AUC from time zero to 1 hour (AUC[0-1h]), AUC from time zero to 4 hours (AUC[0-4h]), and AUC from time zero to infinity (AUC[0-∞]). Other parameters may be calculated as deemed appropriate. Additional partial AUCs may be computed as necessary. If the pre-bolus insulin lispro concentrations differ between Lyumjev and Humalog, the average of the two samples collected immediately prior to the correction bolus will represent as the 0-hour time point for each subject and will be used to subtracting the baseline value from all post-dose insulin lispro measurements to calculate the PK parameters.

Additionally, an analysis will be conducted to assess the insulin lispro PK during the basal insulin suspension period. PK parameters that were used included the terminal half-life ($t_{1/2}$), time of the last concentration prior to dose (t_{last}) and AUC from time of suspension to the time of the last detectable concentration (AUC[0-t_{last}]). The insulin lispro concentration versus time profile will be compared between Lyumjev and Humalog during this time.

Although attempts will be made to adhere to the scheduled collection times (Section 1.3), failure to collect PK samples due to legitimate clinical issues will not be considered as protocol deviations.

Parameters will be individually calculated for each participant based on actual collection times. The mean data will be presented by summary statistics and presented by treatment for those participants who received both treatments (Lyumjev and Humalog) with the same insulin dose (bolus dose for the MMTT or basal reduction) and meal consumption.

9.3.3.2. Pharmacokinetic Statistical Inference

The statistical analyses comparing PK parameters (described in Section 9.3.3.1) following Lyumjev and Humalog for the exercise period and MMTT for test condition of either 50% or 100% reduction of basal infusion rates during exercise will be conducted on the modified full analysis set. The statistical analyses of the PK parameters for the MMTT will be conducted on those participants who receive both treatments with an identical insulin lispro doses for Lyumjev and Humalog. The exercise and MMTT will be analyzed separately.

9.3.3.2.1. Statistical Analysis of the Secondary PK Endpoints during MMTT

Log-transformed AUCs and C_{max} for insulin lispro were evaluated to estimate geometric means, ratios of geometric means of insulin lispro within Lyumjev to Humalog, and their corresponding 90% CIs of the ratios using the mixed-effects model that includes treatment (Lyumjev, Humalog) and period as fixed effects and participant as a random effect.

The same model without log transformation was used for the analysis of the PK time parameters (early 50% t_{max}, late 50% t_{max}, and t_{max}). LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences were estimated from the model. The 2-sided p-value on the difference between LSmeans was used to determine statistical significance. The treatment ratios and 90% CIs for the ratios were calculated using the Fieller's theorem (Chow and Liu 2009).

9.3.3.2.2. Statistical Analysis of the Secondary PK Endpoints during Exercise

A mixed-effects model without log transformation that includes treatment (Lyumjev, Humalog), sequence, period, and treatment as fixed effects and subject as a random effect may be used for the exploratory PK endpoints during the exercise period. LSmeans, treatment differences in LSmeans, and the corresponding 90% CIs for the treatment differences will be estimated from the model. The p-value on the difference between LSmeans will be used to determine statistical significance. The treatment ratios and 90% CIs for the ratios will be calculated using the Fieller's theorem (Chow and Liu 2009).

9.3.4. Exploratory Analysis

9.3.4.1. Exploratory CGM Parameter Estimation

The following variables will be derived from the CGM for each participant for the analysis periods during the exercise, test meal assessments, overnight periods (Day -1 from CCI on Day 1), as duration (in minutes) and percentage of time with glucose values between 70 and 180 mg/dL (3.9 and 10.0 mmol/L) (both inclusive).

- duration (in minutes) and percentage of time with glucose values <54 and <70 mg/dL (3.0 and 3.9 mmol/L)
- duration (in minutes) and percentage of time with glucose values >180 and >250 mg/dL (10.0 and 13.9 mmol/L)
- mean glucose
- overall variability (coefficient of variation and standard deviation).

9.3.4.2. CGM Statistical Inference

Statistical analyses comparing of CGM parameters (described in Section 9.3.4.1) of Lyumjev and Humalog for test condition of either 50% or 100% reduction of basal infusion rates will be conducted on the modified full analysis set for the analysis periods of exercise, test meal assessments, overnight periods, and for the duration of in-house period. The same model as described in Section 9.3.2.2.1 is used for the CGM parameter analysis.

9.3.5. Safety Analyses

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

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

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

9.3.5.1. Statistical Evaluation of Safety

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

9.3.6. Other Analyses

Other analyses will be provided in the SAP.

9.4. Interim Analysis

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

The Lilly clinical pharmacologist/CRP/Lilly study team is unblinded. Data may be accessed and analyzed while the trial is ongoing, but no changes to the study design are planned. The results may help Lilly expedite final delivery and enable planning of future studies. Information that may unblind the study during the analyses will not be reported to the CRU until the study has been unblinded. An assessment committee will not be formed.

9.5. Sample Size Determination

Approximately CCI participants may be enrolled to ensure that at least CCI participants complete the study.

This sample size will provide approximately CCI power to demonstrate a CCI mg/dL difference in the change in plasma glucose level from start to the end of the exercise between Lyumjev and Humalog, assuming no true difference in the change in plasma glucose level between Lyumjev and Humalog and a standard deviation of CCI mg/dL with a 2-sided alpha-level of 0.1. Discontinued participants may be replaced to ensure that CCI subjects complete the trial. A replacement participant will be assigned to the same treatment sequence as the participant being replaced.

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 International Ethical Guidelines
    - applicable ICH GCP guidelines
    - applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (e.g., 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.
- Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation 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 study conduct for participants under their responsibility and adherence to requirements of 21 Code of Federal Regulations, 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. Informed Consent Process

- The investigator or the investigator's 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. Participant will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, privacy and data protection 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 reconsented 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 and is kept on file.

Participants who are rescreened are required to sign a new ICF.

10.1.3. 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 that would make the participant identifiable will not be transferred.
- The participant must be informed that the participant's 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 their medical records may be examined by Clinical Quality Assurance auditors or other authorized staff appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- The sponsor has processes in place to ensure data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

10.1.4. Dissemination of Clinical Study Data

Communication of suspended or terminated dosing

If a decision is taken to suspend or terminate dosing in the trial due to safety findings, this decision will be communicated by Lilly to all investigators (e.g., through phone and/or email) as soon as possible. It will be a requirement that investigators respond upon receipt to confirm that they understand the communication and have taken the appropriate action prior to further dosing any participants with study intervention. Any investigator not responding will be followed up by Lilly staff prior to any further planned dosing. If a dose is planned imminently, Lilly staff will immediately, and continually, use all efforts to reach investigators until contact is made and instructions verified.

Reports

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

Data

The sponsor does not proactively share data from Phase 1 clinical trials. Requests for access to Phase 1 clinical trial data are evaluated on a case-by-case basis taking into consideration the ability to anonymize the data and the nature of the data collected.

10.1.5. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or eCRFs unless transmitted to the sponsor or designee electronically (e.g., 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. Source data may include laboratory tests, medical records, and clinical notes.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the quality tolerance limits and remedial actions taken will be summarized in the CSR.
- Monitoring details describing strategy (e.g., 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 (e.g., contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site staff 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 time period outlined in the clinical trial agreement 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, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the CRU. The study may be audited by the 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 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 electronic data capture 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(s) will be stored at third party. The investigator will have continuous access to the data during the study and until decommissioning of the data capture system(s). Prior to decommissioning, the investigator will receive or access 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/electronic transfers 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 the sponsor will be encoded and stored in the global product complaint management system.

10.1.6. 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 or entered in the CRF and 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 10.1.5.

10.1.7. Study and Site Start and Closure

First act of recruitment

The study start date is the date on which the clinical study will be open for recruitment of participants.

Study or site termination

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

For study termination:

- Discontinuation of further study intervention development

For site termination:

- 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 (evaluated after a reasonable amount of time) of participants by the investigator
- Total number of participants included earlier than expected.

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.

10.1.8. 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.

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the following table will be performed by the local laboratory.
- 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.
- Pregnancy testing will occur as indicated in the SoA (Section 1.3).

Investigators must document their review of the laboratory safety results.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded staff.

Safety Laboratory Tests at Screening

Hematology	Clinical Chemistry
Hematocrit	Sodium
Hemoglobin	Potassium
Erythrocyte count (RBC)	Bicarbonate
Mean cell volume	Chloride
Mean cell hemoglobin	Calcium (ionized/total)
Mean cell hemoglobin concentration	Phosphorus/Phosphate
Leukocytes (WBC)	Magnesium
	Glucose, fasting
Absolute counts of:	Blood urea nitrogen (BUN)
Neutrophils	Creatinine
	Uric acid
Lymphocytes	Total cholesterol
Monocytes	Total protein
Eosinophils	Albumin
Basophils	Total bilirubin
	Alkaline phosphatase (ALP)
Urinalysis	Aspartate aminotransferase (AST)
Specific gravity	Alanine aminotransferase (ALT)
pH	
Protein	
Glucose	
Ketones	Ethanol testing[a]
Bilirubin	Urine drug screen[a]
Urobilinogen	Hepatitis B surface antigen[b]
Blood	Hepatitis C antibody[b]
Nitrite	HIV[b]
	Pregnancy test
	FSH[c]
	HbA1c, C-peptide

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

Note: Results of these assays will be validated by the local laboratory at the time of testing. Additional tests may be performed or auto calculated by the laboratory as part of its standard panel that cannot be removed. Some of the above parameters are calculated from measured values. Omission of calculated values will not be considered as a protocol violation.

[a] Urine drug screen and ethanol level may be repeated prior to admission to the clinical research unit and at other times indicated in the schedule of activities.

[b] These tests may be waived if performed within 6 months prior to screening, and if test results are available for "review" for hepatitis B and C and HIV.

[c] Follicle-stimulating hormone test must be performed at screening for a woman who is aged less than 55 years with an intact uterus, not on hormone therapy and has had 12 months of spontaneous amenorrhea.

10.2.1. Blood Sampling Summary

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

Protocol I8B-MC-ITSU Sampling Summary

Purpose	Blood Volume per Sample (mL)	Number of Blood Samples	Total Volume (mL)
Screening tests[a]	CCI		
CCI			
Pharmacokinetics			
Ketones			
FFAs			
Blood discard for cannula patency			
Total			492.1
Total for clinical purposes (rounded up to nearest 10 mL)			500

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

10.3. Appendix 3: Adverse Events and Serious 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 participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECGs, radiological scans, 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 preexisting condition including either an increase in frequency and/or intensity of the condition. • New condition 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. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an 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 <u>NOT</u> Meeting the AE Definition
• Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition. • 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 (e.g., endoscopy, 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 1 or more of the criteria listed:

a. Results in death

b. 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.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) 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 preexisting condition that did not worsen from baseline is not considered an AE.

d. 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 (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

f. Other situations:

- Medical or scientific judgment should be exercised by the investigator 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 1 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. Definition of Product Complaints

Product Complaint

- 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 a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints:
  - Deficiencies in labeling information, and
  - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.
- Investigators will instruct participants to contact the site as soon as possible if he or she has a product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

10.3.4. Recording and Follow-Up of AE and/or SAE and Product Complaints

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/product complaint information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and product complaint information is reported on the Product Complaint Form.

Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the 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 the 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 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an 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. The investigator will use clinical judgment to determine the relationship/
- 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.
- 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 Investigator's Brochure and/or Product Information, for marketed products in their assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/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 the 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 the sponsor or designee.
- The investigator may change their 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 1 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 the 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.

10.3.5. Reporting of SAEs

SAE reporting via SAE report

- Facsimile transmission of the SAE report is the preferred method to transmit this information to the sponsor or designee.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE report within the designated reporting time frames.
- Contacts for SAE reporting can be found in SAE report.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward 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, IRB/IEC, and investigators.

- An investigator who receives an investigator safety report describing an SAE or other specific safety information (e.g., summary or listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential	Females are considered women of childbearing potential if • they have had at least 1 cycle of menses, or • they have Tanner 4 breast development. Any amount of spotting should be considered menarche. If Tanner staging of breasts is performed as part of study procedures, please refer to the Reproductive, Pregnancy and Pediatrics Safety Committee Safety Guidance for Children in Clinical Trial regarding Tanner staging.
Women not of childbearing potential	Females are considered women not of childbearing potential if • they have a congenital anomaly such as Mullerian agenesis • they are infertile due to surgical sterilization, or • they are postmenopausal. Examples of surgical sterilization include hysterectomy, bilateral oophorectomy, tubal ligation.
Postmenopausal state	The postmenopausal state should be defined as 1. a woman at any age at least 6 weeks postsurgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or 2. a woman aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy*, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND With a follicle-stimulating hormone >40 mIU/mL; or 3. A woman aged 55 years or above not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or 4. A woman aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy * Women should not be taking medications during amenorrhea such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.
Reproductive toxicology studies	Embryo-fetal studies are toxicity studies in pregnant animals designed to identify abnormalities in the development of fetuses, which could indicate potential for teratogenicity in humans. The relevant dosing period is during organogenesis.

10.4.2. Contraception Guidance

WOCBPs who are completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

Must…	Must not…

agree to either remain abstinent, or	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a trial, or

stay in a same-sex relationship without sexual relationships with males	• use the withdrawal method

WOCBPs who are NOT completely abstinent as their preferred and usual lifestyle, or in a same-sex relationship, as part of their preferred and usual lifestyle

Topic	Explanation
Pregnancy testing	Negative serum result at screening followed by a negative urine result prior to study treatment and at follow-up.
	Note: subsequent pregnancy testing is compound specific
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective (less than 1% failure rate)

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception	• combination oral contraceptive pill and mini pill • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  o condom with spermicide
	  o diaphragm with spermicide, or
	  o female condom with spermicide
	
	Note: The barrier method must include use of a spermicide (i.e., condom with spermicide, diaphragm with spermicide, female condom with spermicide) to be considered effective.

Ineffective forms of contraception	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, symptothermal) • withdrawal • post-coital douche • lactational amenorrhea

10.5. Appendix 5: Provisions for Changes in Study Conduct during Exceptional Circumstances

Implementation of this appendix

The changes to procedures described in this appendix are temporary measures intended to be used only during specific time periods as directed by the sponsor in partnership with the investigator.

Exceptional circumstances

Exceptional circumstances are rare events that may cause disruptions to the conduct of the study. Examples include pandemics or natural disasters. These disruptions may limit the ability of the investigators, participants, or both to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

In an exceptional circumstance, after receiving the sponsor's written approval, sites may implement changes if permitted by local regulations.

After approval by local ethical review boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required (e.g., upon implementation and suspension of changes). All approvals and notifications must be retained in the study records.

If the sponsor grants written approval for changes in study conduct, the sponsor will also provide additional written guidance, if needed.

Considerations for making a change

The prevailing consideration for making a change is ensuring the safety of study participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

Additional consent from the participant will be obtained, if required, for

- participation in remote visits, as defined below in "Remote visits"
- a change in the method of study intervention administration
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

Changes in study conduct not described in this appendix, or not consistent with applicable local regulations, are not allowed.

The following changes in study conduct will not be considered protocol deviations.

Remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable only for optional basal optimization visits or follow-up visit to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, safety monitoring, etc.

Data capture

In source documents and the CRF, the CRU should capture the visit method, with a specific explanation for any data missing because of missed in-person site visits.

Safety reporting

Regardless of the type of remote visits implemented, the protocol requirements regarding the reporting of AEs, SAEs, and product complaints remain unchanged.

Return to on-site visits

Every effort should be made to enable participants to return to on-site visits as soon as reasonably possible, while ensuring the safety of both the participants and the CRU staff.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 42 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 42 days from screening to randomization visit: the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 42 days from screening visit.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 42 days from screening visit to randomization visit: the participant must undergo an additional medical assessment and/or clinical measurements to confirm their eligibility. The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by the randomization visit.

Adjustments to visit windows

Adjustments to visit windows will not be considered protocol deviations. Missing data will be captured as protocol deviations.

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as

on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

Trial Period	**Screening Period**		**Study Period**			**Follow-up**	**Visit Interval Tolerance**
Visit no.	**1**	**Optional visits**	**2**	**3, 4, 5, 6**		**7**	
Timing	Within [redacted] days prior to Visit 3	First evaluation - Within [redacted] days of screening visit Second evaluation - Within [redacted] days of screening visit	[redacted] days prior to Visit 3	[redacted]		[redacted] days after Visit 6	
Day				[redacted]			
In-house stay				X	X		
	On-site only	On-site	On-site only	On-site only	On-site only	Televisit	Same as shown in SoA, but flexibility can be considered following consultation with, land with prior approval by, the sponsor

Abbreviations: no. = number; SoA = schedule of activities.

Documentation

Changes to study conduct will be documented

Sites will identify and document the details of how participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing/shipment records of study intervention and relevant communications, including delegation, should be filed with site study records.

Source documents at alternate locations

Source documents generated at a location other than the CRU should be part of the investigator's source documentation and should be transferred to the site in a secure and timely manner.

10.6. Appendix 6: Abbreviations and Definitions

Term	Definition
ADE	adverse device effect
AE	adverse event
AUC	area under the plasma concentration time curve
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment, but the participant is not, or vice versa, or when the sponsor is aware of the treatment, but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CGM	continuous glucose monitoring
CI	confidence interval
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form: a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
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.
CRS	clinical research scientist
CRU	clinical research unit
CSII	continuous subcutaneous insulin infusion
CSR	clinical study report
ECG	electrocardiogram
eCRF	electronic case report form
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.
FGM	flash glucose monitoring
GCP	good clinical practice
GD	glucodynamics
HbA1c	glycosylated hemoglobin
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	institutional ethics committee
informed consent	A process by which a participant voluntarily confirms their 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.
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	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 board
LSmean	least-square mean
MMTT	mixed meal tolerance test
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
PK/PD	pharmacokinetics/pharmacodynamics
SAE	serious adverse event
SAP	statistical analysis plan
SMBG	self-monitored blood glucose
SoA	schedule of activities
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.
T1D	type 1 diabetes

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.
VO_2	oxygen uptake

10.7. Appendix 7: Protocol Amendment History

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

Amendment a: 09 February 2022

Overall Rationale for the Amendment

This protocol is being amended mainly to clarify the language related to pregnancy testing. Minor editorial changes have been done and are not provided in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 1.3.1. Overall Schedule	Added pregnancy testing on assessment day; serum test at screening; urine pregnancy test prior to study treatment and at follow-up	For clarification, updated timing and type of pregnancy testing
Section 1.3.1. Overall Schedule	Added urine drug screen and ethanol breath testing on assessment day	For clarification, updated timing of urine drug screen and ethanol testing
Section 1.3.1. Overall Schedule	CGM mentioned as 'study CGM' and removed 'X' from assessment day for study CGM	Clarified that CGM will be study CGM; participant will be placed on study CGM during in-house period
Section 1.3.1. Overall Schedule, footnote	Footnotes e, f, g, and h updated	Clarification on timings provided and correction done to be consistent with collections in Section 1.3.2
Section 1.3.2. Assessment Schedule Example for In-house Visits	CGM mentioned as 'study CGM'	Clarified that CGM will be study CGM
Section 1.3.2. Assessment Schedule Example for In-house Visits	Clarified timing of sample collection, updated nominal timing as -4 hours at 11:00 AM	Clarified the timing of the samples relative to the study activities and made nominal timing consistent between Sections 1.3.1 and 1.3.2
Section 4.1.3. In-house Visits	CCI [redacted]	Corrected typo. Platinum is not part of the name of CGM.
Section 4.1.3. In-house Visits	CGM mentioned as 'study CGM'	Clarified that CGM will be study CGM

Section # and Name	Description of Change	Brief Rationale
Section 5.3.1.4. Snacks	Removed the term “uncovered’	Removed due to lack of clarity
Section 5.3.2. Substance Use: Caffeine, Alcohol, and Tobacco	Added the following text to the first bullet point excluding the MMTT when chocolate-flavored Ensure® Plus may be given	Clarification provided regarding the use of chocolate-flavored Ensure® Plus in the MMTT
Section 6.3. Measures to Minimize Bias: Randomization and Blinding	Added 1 of the 4 ‘sequences for the’ in-house study periods	Clarified that participants will be assigned to 1 of the 4 ‘sequences for the’ in-house study periods
Section 6.8. Concomitant therapy	Medications mentioned should not be used within 14 days prior to dosing	Correction done to be consistent with Exclusion Criteria Number 23
Section 8.5.2. Exploratory CGM Values	CCI [redacted]	Correction done. Platinum is not part of the name of CGM
Section 8.5.2. Exploratory CGM Values	CGM mentioned as ‘study CGM’	Clarified that CGM will be study CGM
Section 9.3.2.1. Glucodynamic Parameter Estimation	The change from baseline values is the average of -15 minutes and 0 minute	Corrected typo of -10 minutes to -15 minutes to be consistent with schedule of activities (Section 1.3.2)
Section 9.3.3.1. Pharmacokinetic parameter estimation	LY900014 replaced as Lyumjev	Correction done to be consistent with document (LY900014 and Lyumjev refer to the same product)
Section 10.4.2. Contraception guidance	Negative serum result at screening followed by a negative urine result prior to study treatment and at follow-up	Updated language on pregnancy testing in women of childbearing potential who are not completely abstinent or in a same-sex relationship to be consistent with schedule of activities
Section 10.2.1	Updated number of blood samples for glucose and pharmacokinetics and updated total blood volume	Corrected table to be consistent with Sections 1.3.1 and 1.3.2 for glucose and pharmacokinetic samples

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