Protocol I8B-MC-ITTC(c)

A Study to Investigate Local Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

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Approval Date: 14-Oct-2021

Title Page

Protocol Title: A Study to Investigate Local Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

Protocol Number: I8B-MC-ITTC

Amendment Number: (c)

Compound: Citrate, Treprostinil (LSN3326777)

Study Phase: 1

Short Title: Investigation of Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s)

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

Approval Date: 14-Oct-2021 GMT

Medical Monitor Name and Contact Information will be provided separately

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	28-September-2021
Amendment (a)	08-September-2021
Original Protocol	18-May-2021

Amendment (c)

This amendment is considered to be non-substantial.

The protocol is amended to ensure that the infusion site location is documented following standard medical practice.

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
[redacted]		
6.1. Study Interventions Administered; 6.1.1. Administration Details	Pumps will be used to evaluate infusion sites [redacted]	To ensure that the infusion site location is documented following standard medical practice.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Study to Investigate Local Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

Short Title: Investigation of Infusion Site Pain after Infusion of Excipients across Infusion Sites and Infusion Depths

Rationale:

Local infusion site pain may vary between anatomical sites of infusion and between depths of infusion. This study will assess the contribution of infusion site and depth, as well as excipients such as sodium citrate and treprostinil, on local infusion site pain in patients with type 1 diabetes mellitus (T1D) on continuous subcutaneous insulin infusion (CSII).

Objectives and Endpoints

Objectives	Endpoints
Part A	
Primary	
To investigate local infusion site pain for infusions of sodium citrate and treprostinil in Humalog diluent with magnesium chloride (without insulin) in the abdominal, arm, thigh, and buttock areas in participants with T1D on CSII.	VAS pain score
Secondary	
To investigate local infusion site pain of 2 different cannula insertion depths (6 mm and 9 mm) in participants with T1D on CSII	VAS pain score
[redacted]	

Abbreviations: CSII = continuous subcutaneous insulin infusion; VAS = visual analog scale; T1D = type 1 diabetes mellitus.

Overall Design

Study I8B-MC-ITTC is a 1-/2-center, participant-(Part A CCI) and investigator-CCI blind, 2-part randomized crossover study in adults (18 to 69 years of age, inclusive) with T1D on CSII.

Part A of this study will be a 1-/2-center, randomized, 1 day 5-period crossover based on the order of infusion sites and depths, blinded (between infusion depths), open-label single-treatment study conducted in participants with T1D.

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Number of Participants:

Approximately 46 participants will be randomly assigned to study intervention such that approximately 40 evaluable participants complete Part A CCI of the study. CCI

Intervention Groups and Duration:

Interventions groups

Part A

- Following an informed consent and a screening visit, participants will come to the clinical research unit (CRU) the evening prior to Day 1 for Part A. Participants will continue use of their personal pump to administer insulin at the currently employed infusion site and infusion settings. Participants will be instructed to avoid the use of the central abdominal area for their personal infusion set (for at least 3 days) prior to arrival at the CRU. Thickness of the subcutaneous (SC) fat layer at the abdominal, arm, thigh, and buttock areas will be assessed by ultrasound.
- Each Medtronic™ MiniMed™ 770G pump reservoir will be filled with study treatment (sodium citrate and treprostinil in Humalog diluent with magnesium chloride [without insulin]) by a qualified site staff member, a MiniMed™ Mio™ Advance infusion set will be attached to the reservoir, the reservoir loaded into the pump, and the infusion set tubing primed until drops are seen at the tip. Six mm cannula will be inserted into each of these areas (abdomen [at least 5 cm away from the umbilicus in the left or right lower quadrants], posterior aspect of the upper arm, anterior or lateral thigh, and upper buttock), avoiding areas of lipohypertrophy and surgical scars. At the abdominal area only, a 9 mm cannula will also be inserted into the opposite side of the lower abdomen. The infusion set cannula will be filled with 0.6 unit for both 6 mm and 9 mm cannula (while no insulin will be infused by the study pumps, for simplicity, volumes and rates will be described in units and units/hour where 1 unit = 10 µL).
- Participants will be randomly assigned to a treatment sequence to indicate the order of the infusion sites being evaluated.

- The first infusion site will be initiated according to the treatment sequence and a basal infusion rate of 1 U/h will be started. The same procedure will occur at the subsequent infusion sites according to the treatment sequence with an approximate 30-minute interval between initiation of the previous infusion site.
- Approximately 3 hours after start of the basal infusion rate, a bolus dose of 15 U given at quick speed (15 U/min) will be delivered to each infusion site according to the treatment sequence with an approximate 30-minute interval between infusion sites.
- A second bolus dose of 15 U given at quick speed (15 U/min) will be delivered approximately 6 hours after the start of the basal infusion to each infusion site according to the treatment sequence with an approximate 30-minute interval between infusion sites.
- A third bolus dose of 15 U given at quick speed (15 U/min) will be delivered approximately 9 hours after the start of the basal infusion to each infusion site according to the treatment sequence with an approximate 30-minute interval between infusion sites.
- Participants will rate the pain at each infusion site with each bolus dose at the following approximate time points: 5 minutes before the administration of a bolus dose and 1 and 15 minutes after the start of each bolus dose. Study infusion sets and pumps will be removed, the infusion sites will be evaluated for acute infusion reactions, and the participant will be discharged.

Duration

The approximate duration of study participation for each participant may be up to 36 days, across the following study intervals:

- Screening, approximately 28 days
- Treatment period, 2 visits over 5 days (1 day for Part A[redacted])
- Follow-up period [redacted]

Data Monitoring Committee: No

1.2. Schema

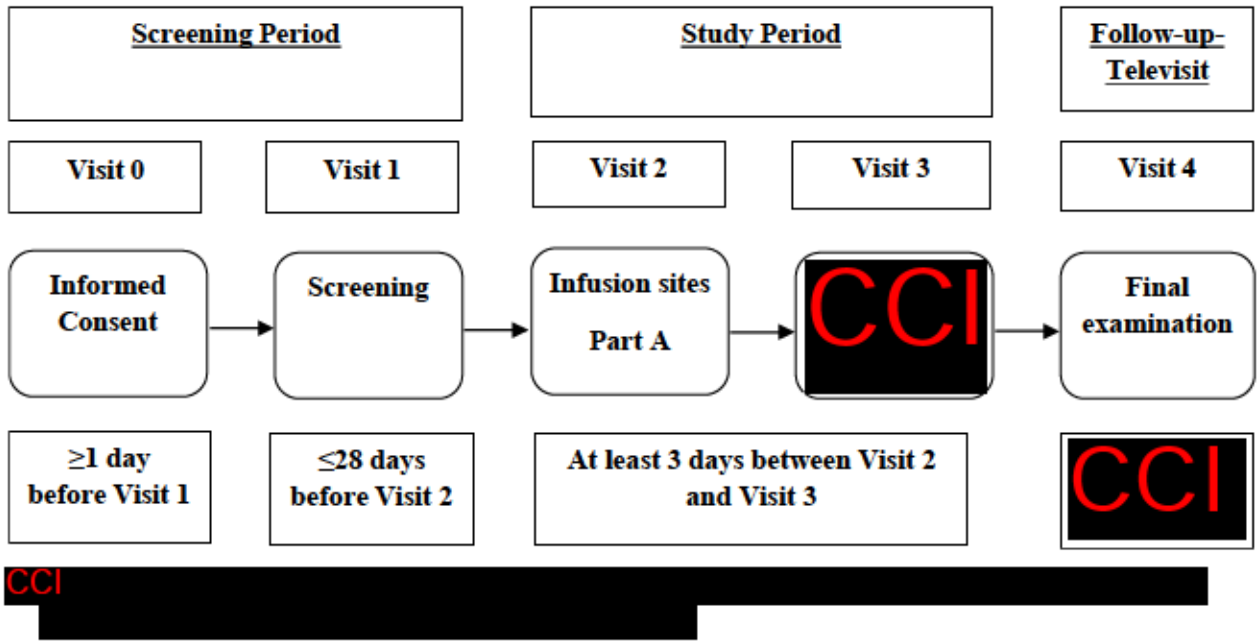

Figure 1 Schematic overview of the chronological structure of the trial.

1.3. Schedule of Activities (SoA)

Table 1 Trial Flow Chart

Trial Period	Screening Period		Study Period		Follow-up-Televisit/early discontinuation	Comments
Visit no.	0	1	2 (Part A) CCI		4	
Timing	≥1 day before Visit 1	≤28 days prior to Visit 2	at least 3 days between Visit 2 and Visit 3		CCI	
In-house Visit/Period			see Table 2	CCI		
Informed consent	X	X				At Visit 1, check that informed consent has been signed and dated
Fasting		X				
Inclusion/exclusion criteria		X				At Visit 2, confirm participant compliance
Demographic data		X				
Smoking and alcohol consumption habits		X				
Medical history/Pre-existing Conditions		X				
Weight		X	X			
Height		X				
Alcohol breath test/urine drug screen		X	X			
Physical examination		X				
Vital signs		X	X			
12-lead ECG		X				
Haematology		X				
Biochemistry		X				
Coagulation		X				
Urinalysis		X				
Infectious serology		X				

Trial Period	Screening Period		Study Period		Follow-up-Televisit/early discontinuation	Comments
Visit no.	0	1	2 (Part A) CCI		4	
Timing	≥1 day before Visit 1	≤28 days prior to Visit 2	at least 3 days between Visit 2 and Visit 3		CCI	
In-house Visit/Period			see Table 2	CCI		
Pregnancy test		X	X			Only required for women of childbearing potential Serum at the screening visit and urine at Visits 2 and 3
FSH		X				This is only for women with both more than 12 months of amenorrhea and age of ≤55 (see Sections 10.2 and 10.4)
HbA1c		X				
Ultrasound			X			Thickness of the subcutaneous (SC) fat layer will be assessed at the abdominal areas (lower right and left), arm, thigh, and buttock.
Local Infusion site pain (VAS)			X			See Table 2 and Table 3 for collection times
Local Infusion site reactions			X			After removal of each infusion set
CCI Platform			X			Collect image of each local infusion site prior to insertion and after removal of each infusion set
AEs/Product Complaints		X	X		X	
Concomitant Medications		X	X		X	

Trial Period	Screening Period		Study Period		Follow-up-Televisit/early discontinuation	Comments
Visit no.	0	1	2 (Part A) CCI		4	
Timing	≥1 day before Visit 1	≤28 days prior to Visit 2	at least 3 days between Visit 2 and Visit 3		CCI	
In-house Visit/Period			see Table 2	CCI		
Meals (breakfast, lunch, and dinner)			X			Breakfast will be provided prior to study activities. Lunch will be provided after completion of the first bolus assessments. Dinner will be provided after completion of the second bolus assessments

Abbreviations: AE = adverse event; BMI = body mass index; ECG = electrocardiogram; HbA1c = hemoglobin A1c; no. = number; VAS = visual analog scale.

Table 2 Assessment Schedule for Visit 2 (Part A)

Approx. hour	Nominal timing	Activity	Other
Day -1		Participant arrives after dinner for overnight stay at the trial site and continued eligibility will be checked. The participant will continue personal diabetes management care. Participants will be instructed to avoid the use of the central abdominal area for their personal infusion set (for at least 3 days) prior to arrival at the CRU and continue insulin infusion with their personal insulin pump.	SARS-CoV-2 test may be performed according to the site general procedures AEs, concomitant medication, alcohol breath test, vital signs, urine pregnancy test
Day 1		Breakfast	
		Measure and record adipose thickness by ultrasound at infusion sites Collect image of each local infusion site prior to insertion of the corresponding infusion set using CCI Platform	These measurements may be performed at any time after the subject's arrival on Day -1 until infusion set insertion. Each local infusion site should be labeled and have a unique identifier for CCI Platform image acquisition
		Study pumps loaded with study treatment	
+0 h		Insert infusion set cannula into infusion site 1 and start pump at a basal rate of 1 U/h	
+0.5 h (±5 min)		Insert infusion set into infusion site 2 and start pump at a basal rate of 1 U/h	
+1 h (±5 min)		Insert infusion set into infusion site 3 and start pump at a basal rate of 1 U/h	
+1.5 h (±5 min)		Insert infusion set into infusion site 4 and start pump at a basal rate of 1 U/h	
+2.0 h (±5 min)		Insert infusion set into infusion site 5 and start pump at a basal rate of 1 U/h	
+3.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 1	
	0 min	Administer 15 U bolus to infusion site 1 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 1	
	+15 min[b]	Collect VAS score for infusion site 1	
+3.5 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 2	

Approx. hour	Nominal timing	Activity	Other
	0 min	Administer 15 U bolus to infusion site 2 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 2	
	+15 min[b]	Collect VAS score for infusion site 2	
+4.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 3	
	0 min	Administer 15 U bolus to infusion site 3 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 3	
	+15 min[b]	Collect VAS score for infusion site 3	
+4.5 h (±3 min)	-5 min[b]	Collect VAS score for site 4	
	0 min	Administer 15 U bolus to infusion site 4 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 4	
	+15 min[b]	Collect VAS score for infusion site 4	
+5.0 h (±3 min)	-5 min[b]	Collect VAS score for site 5	
	0 min	Administer 15 U bolus to infusion site 5 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 5	
	+15 min[b]	Collect VAS score for infusion site 5	
		Lunch	
+6.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 1	
	0 min	Administer 15 U bolus to infusion site 1 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 1	
	+15 min[b]	Collect VAS score for infusion site 1	
+6.5 h (±3 min)	-5 min[b]	Collect VAS score for site 2	
	0 min	Administer 15 U bolus to infusion site 2 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 2	
	+15 min[b]	Collect VAS score for infusion site 2	
+7.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 3	
	0 min	Administer 15 U bolus to infusion site 3 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 3	
	+15 min[b]	Collect VAS score for infusion site 3	
+7.5 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 4	

Approx. hour	Nominal timing	Activity	Other
	0 min	Administer 15 U bolus to infusion site 4 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 4	
	+15 min[b]	Collect VAS score for infusion site 4	
+8.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 5	
	0 min	Administer 15 U bolus to infusion site 5 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 5	
	+15 min[b]	Collect VAS score for infusion site 5	
		Dinner	
+9.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 1	
	0 min	Administer 15 U bolus to infusion site 1 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 1	
	+15 min[b]	Collect VAS score for infusion site 1	
+9.5 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 2	
	0 min	Administer 15 U bolus to infusion site 2 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 2	
	+15 min[b]	Collect VAS score for infusion site 2	
+10.0 h (±3 min)	-5 min[b]	Collect VAS score for site 3	
	0 min	Administer 15 U bolus to infusion site 3 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 3	
	+15 min[b]	Collect VAS score for infusion site 3	
+10.5 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 4	
	0 min	Administer 15 U bolus to infusion site 4 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 4	
	+15 min[b]	Collect VAS score for infusion site 4	
+11.0 h (±3 min)	-5 min[b]	Collect VAS score for infusion site 5	
	0 min	Administer 15 U bolus to infusion site 5 at quick bolus speed (15 U/min)	
	+1 min[a]	Collect VAS score for infusion site 5	
	+15 min[b]	Collect VAS score for infusion site 5	

Approx. hour	Nominal timing	Activity	Other
+11.5 h (±3 min)		Remove infusion sets, evaluate local infusion sites Collect image of each local infusion site after removal of the corresponding infusion set using CCI Platform	Each local infusion site should be labeled and have a unique identifier for CCI Platform image acquisition that is the same as prior to infusion
+12.5 h (±30 min)		Participant discharge from CRU	Following the final evaluation, the participants will have the option to spend the night or be discharged from the CRU

Abbreviations: AE = adverse event; Approx. = approximately; CRU = clinical research unit; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; VAS = visual analog scale.

[a] The VAS time point of 1- minute (+1 min) is to be collected from the start of bolus infusion.

[b] The VAS time points of -5 (±2 min), and 15 (±2 min) minutes are to be collected from start of bolus infusion.

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2. Introduction

LY900014 (Lyumjev®) is an ultra-rapid-acting formulation of insulin lispro for subcutaneous (SC) and intravenous use that employs excipients, citrate and treprostinil, to accelerate time action, along with magnesium to enhance insulin stability, resulting in improved glycemic control in participants with type 1 diabetes mellitus (T1D) or type 2 diabetes mellitus.

2.1. Study Rationale

In the Phase 3 pivotal multiple daily injection studies (Blevins et al. 2020; Jinnouchi et al. 2020; Klaff et al. 2020), LY900014 dosed at the start of a meal demonstrated noninferior overall glycemic control (hemoglobin A1c [HbA1c]) in patients with T1D and type 2 diabetes mellitus, and superior overall glycemic control in patients with T1D, and consistently better postprandial glucose (PPG) control, compared to Humalog. Injection site reactions occurred at a higher incidence with LY900014 compared to Humalog (2.7% versus 0.1%, respectively), but had an overall low incidence.

LY900014 was efficacious, providing superior PPG control and less time in hypoglycaemia but with more frequent infusion site reactions (ISRs) compared with Humalog when administered by continuous subcutaneous insulin infusion (CSII) (Warren et al. 2021). Infusion site reactions were reported by 37.7% of T1D patients treated with LY900014 using CSII for 16 weeks in the PRONTO-Pump-2 study (Warren et al. 2021). Typically, local infusion site pain is noted immediately after infusion of a bolus dose, subsiding over 20-30 minutes thereafter.

This study aims to investigate whether local infusion site pain is dependent on the site of infusion and/or the depth of the infusion. In addition, the study will investigate the contribution of two of the excipients of LY900014 to local infusion site pain.

2.2. Background

Type 1 diabetes mellitus is an autoimmune disease resulting in destruction of beta cells, and lifelong dependency on exogenous insulin. The prevalence of T1D is near 1 in 300 and its incidence is steadily increasing worldwide (3% per year) (Gan et al. 2012).

Many advances in the treatment of T1D have occurred in the last 20 years; however, reaching and maintaining glycemic goals remains challenging even under intensive insulin therapy regimens. Rapid-acting insulin analogs, such as insulin lispro, aspart, and glulisine, were developed to be absorbed more rapidly and have a faster onset of insulin action compared with regular human insulin. Despite these improvements, the current formulations are not rapid enough to match carbohydrate absorption, limiting their efficacy in controlling PPG. LY900014 is a novel insulin lispro formulation developed to more closely match physiological insulin secretion and improve PPG control. In a recent publication comparing the pharmacokinetics and glucodynamics of LY900014 with Humalog, Fiasp®, and NovoRapid®, LY900014 showed greater numeric glucose lowering during a mixed meal tolerance test in patients with T1D and more closely matched the early glucose lowering of endogenous insulin secretion in healthy individuals (Heise et al. 2020; Leohr et al. 2020). Phase 3 clinical studies of LY900014 have demonstrated superiority of LY900014 to Humalog in controlling PPG excursions, with a similar

overall safety profile in patients with T1D (Klaff et al. 2020) and T2D (Blevins et al. 2020; Jinnouchi et al. 2020).

LY900014 is composed of the active ingredient insulin lispro and two locally acting excipients, treprostinil to induce local vasodilation and citrate to increase vascular permeability, thereby accelerating insulin lispro absorption. The LY900014 formulation also differs from the Humalog formulation in that it includes magnesium to stabilize the insulin. Treprostinil is a prostacyclin analog used in the treatment of pulmonary arterial hypertension. Treatment with high-dose continuous SC or intravenous infusion of treprostinil with clear systemic effects is known to be associated with injection/infusion site pain and injection/infusion site reactions (Remodulin SPC 2016). The clinically relevant doses of LY900014 administered via the SC route contain microdoses of treprostinil that are not detectable in the systemic circulation or associated with any systemic effects. However, local vasodilation at the injection site could potentially be a contributing factor to local erythema or discomfort. In addition, prostacyclins may be involved as endogenous mediators of inflammation and pain (Murata et al. 1997). CCI [redacted]

Citrate has been associated with injection site pain in other injectable products (Humira Prescribing Information 2021; Kaiser et al. 2012; Nash et al. 2016). The specific role of citrate in LY900014 injection/infusion site reaction events is unknown, but increased local vascular permeability with injection/infusion of LY900014 could potentially contribute to injection/infusion site reactions. Further, evidence suggests that citrate chelation of endogenous divalent metal ions may lead to injection/infusion site pain, and reintroduction of magnesium can mitigate this discomfort (Krasner et al. 2012). CCI [redacted]

CCI [redacted]

In the PRONTO-Pump-2 study, most ISRs with LY900014 started in the first 4 weeks after randomization (Warren et al. 2021). The reported ISRs were primarily mild in severity (approximately 75%) and lasted a median of 2 to 6 days in this study. While individual ISRs resolved during the study, other events could occur with a different infusion set/site. Additional analysis determined there were no significant treatment-by-subgroup interactions for the incidence of ISRs for sex, age, body mass index (BMI), ethnicity, race, infusion set model, bolus speed, total daily dose, duration of diabetes, or duration of CSII use.

The Investigator's Brochure (IB) describes the clinical and nonclinical development of LY900014. Additional details are also available in the LY900014 package insert (Lyumjev SPC 2020).

2.3. Benefit/Risk Assessment

There is no direct clinical benefit anticipated from participation in this trial.

The treatments (sodium citrate, magnesium chloride, Humalog diluent, or treprostinil) within this study are administered below approved therapeutic levels and are considered placebo treatments. No known potential risks are associated with the use of small amounts of treprostinil, sodium citrate, magnesium chloride, or Humalog diluent. Furthermore, these study treatments are well characterized, and the description of each treatment relative to a therapeutic use is described in Section 8.4.

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 Medtronic™ MiniMed™ 770G pump. More detailed information about the known and expected risks and potential adverse events may be found in the manufacturer's instructions.

3. Objectives and Endpoints

Objectives	Endpoints
Part A	
Primary	
To investigate local infusion site pain for infusions of sodium citrate and treprostinil in Humalog diluent with magnesium chloride (without insulin) in the abdominal, arm, thigh, and buttock areas in participants with T1D on CSII.	VAS pain score
Secondary	
To investigate local infusion site pain of 2 different cannula insertion depths (6 mm and 9 mm) in participants with T1D on CSII	VAS pain score
Exploratory:	
To assess local infusion site reactions using the exploratory CCI Platform	Characterization and measurement of incidence and severity of local infusion site reaction data
CCI	

Abbreviations: CSII = continuous subcutaneous insulin infusion; VAS = visual analog scale; T1D = type 1 diabetes mellitus.

4. Study Design

4.1. Overall Design

Study I8B-MC-ITTC is a 1-/2-center, participant-(Part A CCI) and investigator-CCI blind, 2-part randomized crossover study in adults (18 to 69 years of age, inclusive) with T1D on CSII. Approximately 46 participants will be randomly assigned to study intervention such that approximately 40 evaluable participants complete Part A CCI of the study. CCI

Part A of this study will be a 1-/2-center, randomized, 1 day 5-period crossover based on the order of infusion sites and depths, blinded (between infusion depths), open-label single-treatment study conducted in adults with T1D.

CCI

For CCI Part A CCI , the participant will continue using his or her personal insulin pump system at the currently employed infusion site and will be responsible for performing the required actions to maintain its functionality. Participants will be instructed to avoid the use of the central abdominal area for their personal infusion sets during the CCI and prior to arrival at the clinical research unit (CRU).

For Part A

1. Following an informed consent and a screening visit, participants will come to the CRU in the evening (after dinner) of Day -1 for Part A.

2. Prior to the insertion of the first infusion set, the thickness of the SC adipose tissue layer at the abdomen, arm, thigh, and buttock areas will be assessed by ultrasound and recorded in the electronic case report form (eCRF). The evaluated site should be identified with a unique identifier.

3. The infusion sites will be assessed, and an image of each local infusion site will be collected using the CCI Platform (Section 8.2.5.3.1) prior to insertion of the corresponding infusion set.

4. Each Medtronic™ MiniMed™ 770G pump reservoir will be filled by a qualified site staff member with 3 mL of study treatment (sodium citrate and treprostinil in Humalog diluent with magnesium chloride [without insulin]). The pump and infusion set will be set up as described in Section 6.1.1.

5. Five pumps will be used for each participant to assess infusions into the abdominal, arm, thigh, and buttocks areas. Participants will be randomly assigned to 1 of 5 infusion site sequences as shown in Table 4 to indicate the order of the infusion sites being evaluated.

6. Six mm cannula will be inserted into each of the designated areas (abdomen [at least 5 cm away from the umbilicus in the left or right lower quadrants], posterior aspect of the upper arm,

anterior or lateral thigh, and upper buttock), avoiding areas of lipohypertrophy or surgical scars. At the abdominal area only, a 9 mm cannula will also be inserted into the opposite side of the lower abdomen.

7. The first infusion site will be initiated, and a basal infusion rate of 1 U/h will be started. The same procedure will occur at the subsequent infusion sites according to the randomly assigned sequence with an approximately 30-minute interval between initiation of the previous infusion site. In case of immediate infusion set intolerance, a new infusion set can be inserted within the first 10 minutes of initiation of the infusion site.

Table 4 Infusion Site Sequences for Part A

	Infusion 1	Infusion 2	Infusion 3	Infusion 4	Infusion 5
Sequence 1	Arm	Thigh	Abdomen 6 mm	Abdomen 9 mm	Buttock
Sequence 2	Abdomen 6 mm	Abdomen 9 mm	Thigh	Buttock	Arm
Sequence 3	Abdomen 9 mm	Arm	Buttock	Abdomen 6 mm	Thigh
Sequence 4	Thigh	Buttock	Abdomen 9 mm	Arm	Abdomen 6 mm
Sequence 5	Buttock	Abdomen 6 mm	Arm	Thigh	Abdomen 9 mm

Note: This is an example table based on a 5x5 Latin square design; participants will be assigned an infusion sequence according to the actual schedule provided to the site.

8. Approximately 3 hours after the start of the basal infusion at 1 U/hr, a bolus dose of 15 U will be delivered at quick bolus speed (15 U/min) to each infusion site according to the treatment sequence with an approximately 30-minute interval between infusion sites.

9. A second bolus of 15 U given at quick speed (15 U/min) will be delivered approximately 6 hours after the start of the basal infusion to each infusion site according to the treatment sequence with an approximately 30-minute interval between infusion sites.

10. A third bolus dose of 15 U given at quick speed (15 U/min) will be delivered approximately 9 hours after the start of the basal infusion to each infusion site according to the treatment sequence with an approximately 30-minute interval between infusion sites.

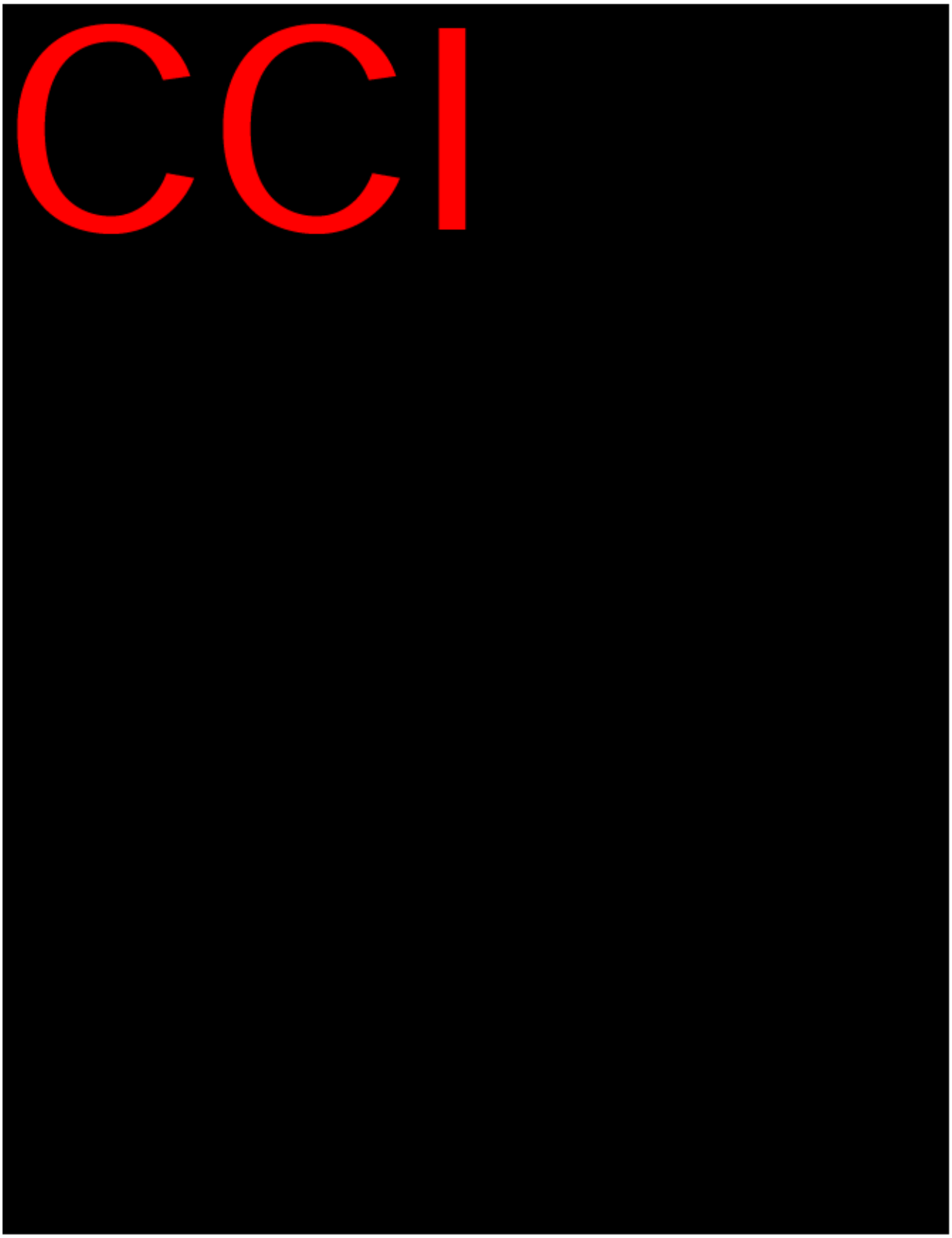
11. Participants will rate the pain at each infusion site after each bolus dose at the following approximate time points: 5 minutes before the administration of a bolus dose and 1 and 15 minutes after the start of each bolus dose.

12. Study infusion sets with cannula and pumps will be removed.

13. Infusion sites will be evaluated for acute local infusion site reactions as described in Section 8.2.5.3 and an image of each local infusion site will be collected using the CCI Platform (Section 8.2.5.3.1).

14. Following the final evaluation, the participants will have the option to spend the night or be discharged from the CRU.

CCI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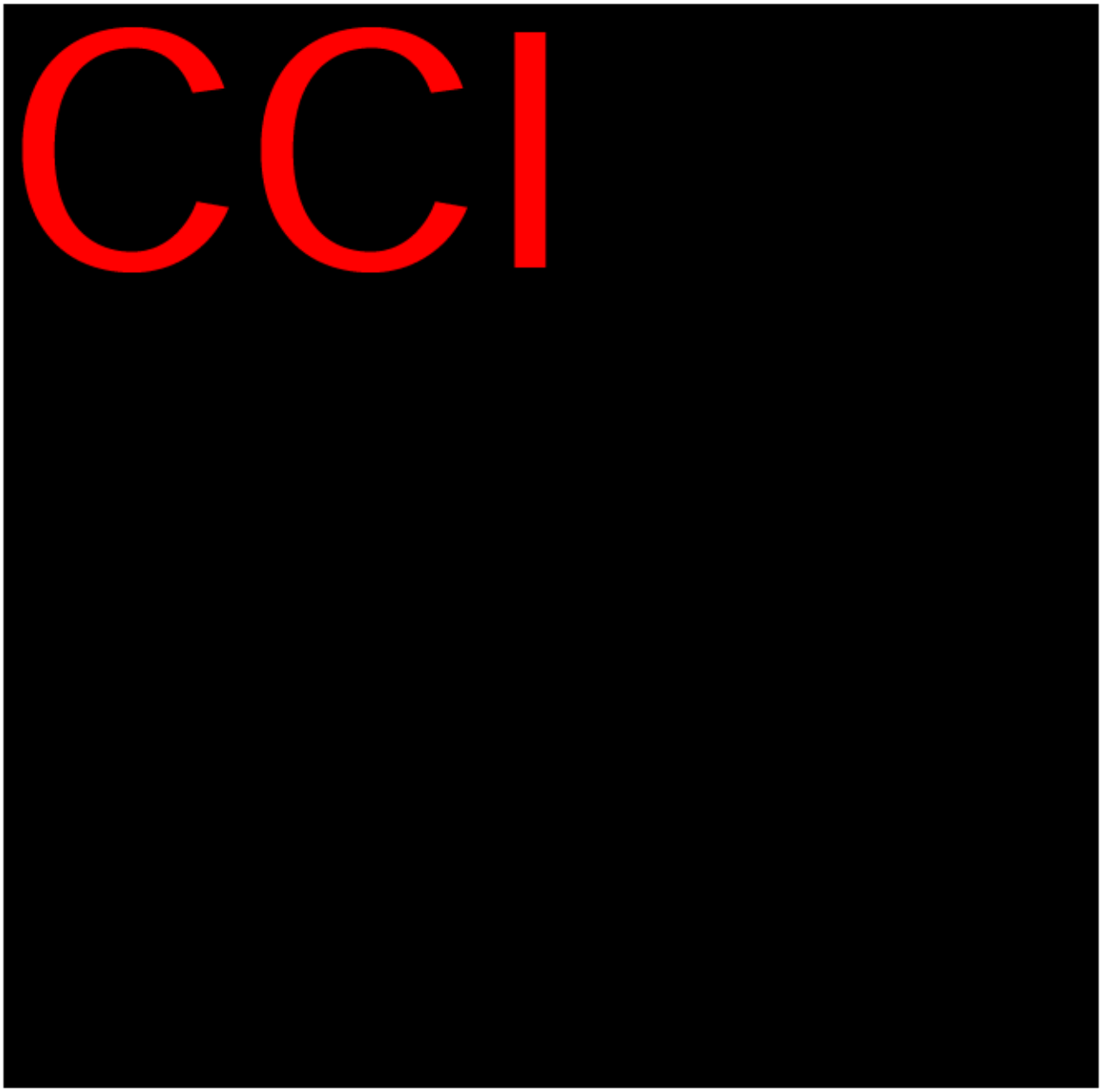

4.2. Scientific Rationale for Study Design

Each study part consists of a cross-over design to allow each participant act as his/her own control. The total number of participants needed for this design is less than the number needed for a parallel group design.

The bolus dose is delivered to each infusion site 3 times and provides intra-subject variability in the local infusion pain score in each study part.

Randomization and blinding are used to avoid bias introduced through an association between allocation order of CCI injection site.

4.3. Justification for Dose

The concentrations of these excipients were based on the formulation of LY900014. Basal and bolus doses were selected based on what is typically used for LY900014 and Humalog in participants with T1D.

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 Schedule of Activities (SoA; Section 1.3) for the last participant in the trial.

5. Study Population

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

Eligibility of participants for the study will be based on the results of screening medical history, physical examination, vital signs, clinical laboratory tests, and electrocardiograms (ECGs). The nature of any conditions present at the time of the physical examination and any preexisting conditions will be documented. Screening may occur up to 28 days prior to enrollment. Participants who are not enrolled within 28 days of screening may undergo an additional medical assessment and/or clinical measurements to confirm their eligibility.

5.1. Inclusion Criteria

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

Informed Consent

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

Age and Sex

2. Participant must be between 18 and 69 years of age, inclusive, at the time of signing the informed consent.
3. Male or Female

    - Male: no contraception required.
    - Female: contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraception requirements for participants are provided in Section 10.4.

Type of Participant and Disease Characteristics

4. Have been clinically diagnosed with T1D for at least 1 year before screening and have continuously been using intensive insulin therapy for at least 1 year.
5. Have been using an insulin pump for at least 6 months.
6. Have an HbA1c value ≤9.0% at screening.
7. Have a BMI of 18.5 to 35.0 kg/m^2, inclusive.
8. Have clinical laboratory test results within normal reference range with acceptable deviations that are judged to be not clinically significant by the investigator.
9. Have venous access sufficient to allow for blood sampling.
10. 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

11. Hemophilia or any other bleeding disorder.

12. A condition, which in the opinion of the investigator or designee, would put the participant or study at risk.
13. Have a pathologic tuning fork test as assessed with a Rydel-Seiffer tuning fork.
14. Have had more than 1 episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within the last 90 days before screening.
15. Have had more than 1 emergency room visit or hospitalization due to poor glucose control (hyperglycemia or diabetic ketoacidosis) within 6 months before screening (Visit 1).
16. Have a scheduled surgery during the study.
17. Have cardiovascular disease within 6 months prior to screening, defined as stroke, decompensated heart failure (New York Heart Association Class III or IV), myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft.
18. Renal:
    a. History of renal transplantation
    b. Currently receiving renal dialysis
    c. Serum creatinine >2.0 mg/dL (177.0 µmol/L) at screening.
19. Hepatic: Have obvious clinical signs or symptoms of liver disease (excluding nonalcoholic fatty liver disease), acute or chronic hepatitis, cirrhosis, or elevated liver enzyme measurements as indicated below at screening (Visit 1):
    a. Total bilirubin level (TBL) ≥2× the upper limit of normal (ULN) (except for Gilbert's syndrome) or
    b. Alanine aminotransferase (ALT) ≥3× ULN or
    c. Aspartate aminotransferase (AST) ≥3× ULN.
20. Malignancy: Have active or untreated malignancy, have been in remission from clinically significant malignancy (other than basal cell or squamous cell skin cancer) for less than 5 years, or are at an increased risk for developing cancer or a recurrence of cancer in the opinion of the investigator.
21. Have any hypersensitivity or allergy to any of the diluents or excipients used in this trial.
22. Hematologic: Have had a blood transfusion or severe blood loss within 90 days prior to screening (Visit 1) or have known hemoglobinopathy, hemolytic anemia, sickle cell anemia, or any other traits known to interfere with the measurement of HbA1c.
23. Have any other condition (including known drug or alcohol abuse [consuming more than an average 24.0 grams alcohol/day for males and 12.0 grams alcohol/day for females], or psychiatric disorder including eating disorder) that precludes the participant from following and completing the protocol at the investigator's discretion or positive alcohol and/or urine drug screen at the screening visit.
24. Show evidence of human immunodeficiency virus (HIV) infection and/or positive human HIV antibodies.
25. Show evidence of hepatitis C and/or positive hepatitis C antibody (Presence of hepatitis C antibodies will not lead to exclusion if liver function tests are normal and a hepatitis C polymerase chain reaction is negative).
26. Show evidence of hepatitis B and/or positive hepatitis B surface antigen.
27. Inability or unwillingness to refrain from smoking, vaping and any use of nicotine substitute products one day before and during the inpatient period.

Prior/Concomitant Therapy

28. Are taking anesthetics or pain medication regularly or intermittently which could interfere with interpretation of pain scale.
29. Have used or are currently using Lyumjev® as part of their standard insulin therapy.

Prior/Concurrent Clinical Study Experience

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

Other Exclusions

31. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
32. Are Eli Lilly and Company (Lilly) employees or representatives (including employees, temporary contract workers, or designees responsible for the conduct of the study).

5.3. Lifestyle Considerations

Participants must adhere to lifestyle restrictions as outlined by the CRU throughout the duration of the stay in the CRU.

While in the CRU, participants will use their own insulin pump and glucose sensor and bring extra supplies including insulin, infusion set and reservoir, glucose sensor, batteries, blood glucose monitor and test strips, insulin syringe in case of pump failure, and fast-acting glucose tablets or gel to treat hypoglycemia. Participants should avoid hypoglycemia and prolonged hyperglycemia during the study procedures.

5.3.1. Meals and Dietary Restrictions

Meals and snacks will be provided in the CRU at appropriate times.

5.3.2. Caffeine, Alcohol, and Tobacco

Caffeine will be permitted during the study. No alcohol will be allowed at least 24 hours before CRU admission, including screening, and throughout the duration of the stay in the CRU. No tobacco, vaping and any nicotine products use will be permitted while in the CRU.

5.3.3. Activity

Participants may be required to remain recumbent or sitting throughout the duration of the stay in the CRU.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently assigned to study intervention or enrolled in the study.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened. Rescreened participants should be assigned a new participant number. When

rescreening, the screening tests and procedures should be repeated based on the exclusion criteria. Individuals may be rescreened 1 time at the discretion of the principal investigator. The interval between the screenings should be at least 2 weeks. Before rescreening is performed, the individual must sign a new ICF. Repeating of laboratory tests during the screening period or repeating screening tests to comply with the protocol designated screening period does not constitute rescreening.

6. Study Intervention

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

6.1. Study Interventions Administered

Part A of this study involves administration of sodium citrate and treprostinil in Humalog diluent with magnesium chloride (without insulin) to each participant at 4 different infusion sites (abdomen [at least 5 cm away from the umbilicus in the left or right lower quadrant], posterior aspect of the upper arm, anterior or lateral thigh, and upper buttock) and at 2 different cannula insertion depths (6 mm and 9 mm in abdomen only) (see Table 6 for details).

CCI

Table 6 Treatment Administered

ARM Name	Part A	CCI
Intervention Name	Sodium citrate and treprostinil in Humalog diluent with magnesium chloride (without insulin)	
Type	Excipients	
Dose Formulation	Solution	

Unit Dose Strength(s)	15 mM sodium citrate and 1 µg/mL treprostinil in Humalog diluent with 5 mM magnesium chloride (without insulin)	CCI
Dosage Level(s)	1 U/hr basal infusion rate at each infusion site (abdomen [at least 5 cm away from the umbilicus in the left and right lower quadrants], posterior aspect of the upper arm, anterior or lateral thigh, and upper buttock). 15 U bolus dose at quick bolus speed of 15 U/min 3 times (3-hr, 6-hr, and 9-hr intervals) at each infusion site	
Route of Administration	SC infusion using 6 mm cannula in abdomen, arm, thigh, and buttock. SC infusion using 9 mm cannula in abdomen only	
Use	Experimental	
IMP and NIMP	IMP	
Sourcing	Provided by the sponsor	
Packaging and Labeling	Study intervention will be provided in container. Each container will be labeled as required per country requirement	

Abbreviations: IMP = investigational medicinal product; NIMP = non-investigational medicinal product; SC = subcutaneous.

6.1.1. Administration Details

Study treatment will be administered via CSII at a basal infusion rate of 1 U/hr and 15 U bolus doses will be delivered at quick bolus speed (15 U/min) per the SoA (Section 1.3). Medtronic™ MiniMed™ 770G pumps will be used in manual mode for infusion of all study treatments. The

pump requires 1 new AA (1.5 V) battery. For best results, use a new AA lithium (FR6) battery. The pump also accepts an AA alkaline (LR6). MiniMed™ 3-mL reservoirs and MiniMed™ Mio™ Advance infusion sets will be used with the pumps.

Pumps will be programmed with the following settings:

- Preferred language
- Current date and time
- Single basal pattern of 1 U/hr with start time 12:00AM and end time 12:00AM
- Bolus increment of 0.1 U
- Bolus speed quick (15 U/min)
- Bolus type normal
- Bolus entry method manual

In Part A, 5 pumps will be used for each participant. For each pump, a 3-mL reservoir will be filled by a qualified site staff member with 3 mL of study treatment, a MiniMed™ Mio™ Advance infusion set will be attached to the filled reservoir and the reservoir will be loaded into the pump. The infusion set tubing will be primed, and a cannula fill with 0.6 unit for both 6 mm and 9 mm cannula will be completed. Six mm cannula will be inserted into each of the designated areas (abdomen, arm, thigh, and buttock), avoiding any areas of lipohypertrophy or surgical scars. At the abdominal area only, 9 mm cannula will be used in addition to the 6 mm cannula. In case of immediate infusion set intolerance or insulin flow block alarm occurs, a new infusion set can be inserted within the first 10 minutes of initiation of the infusion site. CCI

[redacted]

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

6.1.2. 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 restarted. If the occlusion alarm persists, the infusion site will be discontinued, and data related to this site will not be used in the analysis. If a pump occlusion alarm occurs during a bolus infusion, the infusion site will be discontinued, and data related to this site will not be used in the analysis. If an infusion set cannula is accidentally pulled out of an infusion site, the infusion site will be discontinued, and data related to that site will not be used in the analysis. Data related to these events will be recorded on the eCRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention 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 personnel may supply, prepare, or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual

or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

3. The investigator or authorized study personnel 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

Randomization and blinding will be used in order to avoid bias introduced through an association between allocation order and participant characteristics.

In Part A of this study, participants will be randomly assigned to 1 of 5 infusion site sequences to indicate the order of the infusion sites being evaluated. The infusion depths will be blinded.

CCI [redacted]

The CRU personnel who will prepare the pump reservoirs for each treatment period will not be blinded and will be separate and distinct from those who are involved in subject care. The sponsor including the Lilly study team will be unblinded. Blinding will be maintained throughout the conduct of the study.

Treatment assignment will be kept strictly confidential and accessible only to authorized persons until after the time of unblinding. Codes with treatment assignment will, however, be readily available to the blinded personnel in case of an emergency.

If an investigator, site personnel 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 a sponsor clinical pharmacologist or clinical research physician (CRP)/clinical research scientist (CRS) for the participant to continue in the study.

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 study site staff.

The infusion of the excipients will be administered in the CRU under medical supervision by the investigator or designee. The study excipients and infusion depths and study participant identification will be confirmed prior to the time of infusion. The date and time of each infusion administered will be recorded in the source documents and in the case report form (CRF).

A record of the number of excipients administered to each participant must be maintained and reconciled with study intervention and compliance records. Infusion start and stop dates,

including dates for infusion delays and/or infusion rate reductions, will also be recorded in the CRF.

6.5. Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements or other specific categories of interest) 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 taking analgesics including non-steroidal anti-inflammatory drugs within 24 hours before the first infusion will be rescheduled.

The investigator must check if any pre-medications affect the participants' current ongoing treatment for T1D.

6.6. Dose Modification

Dose modification for the excipients or infusion rate are not planned in this study.

6.7. Intervention after the End of the Study

Not applicable.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1. Discontinuation of Study Intervention

Participants discontinuing from the study prematurely for any reason must complete adverse event (AE) and follow-up procedures per Section 1.3 of this protocol.

If the investigator, after consultation with the sponsor-designated medical monitor, determines that a systemic hypersensitivity reaction has occurred related to the excipients administration, the participant should be permanently discontinued from the infusion of the excipients.

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

If an infusion site is unable to be initiated after several attempts, the participant should be discontinued from the study and a replacement subject may be enrolled.

7.1.1. Hepatic Criteria for Discontinuation

Not applicable.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

- at any time at his/her own request
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons
- if the participant becomes pregnant during the study
- if enrollment in any other clinical study involving an investigational product or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study

At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA (Section 1.3). See the 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 both from the study intervention and from 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.

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 study site. Site personnel 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.

Site personnel, or an independent third party, will attempt to collect the vital status of the participant within legal and ethical boundaries for all participants randomized, including those who did not receive investigational product. Public sources may be searched for vital status information. If vital status is determined to be deceased, this will be documented, and the participant will not be considered lost to follow-up. Sponsor personnel will not be involved in any attempts to collect vital status information.

Discontinuation of specific sites or of the study as a whole are handled as described in Section 10.1 Appendix 1.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA (Section 1.3).
- 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 (Section 1.3), 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.
- Unless otherwise stated in subsections below, all samples collected for specified laboratory tests will be destroyed within 60 days of receipt of confirmed test results. Certain samples may be retained for a longer period, if necessary, to comply with applicable laws, regulations, or laboratory certification standards.

8.1. Efficacy Assessments

Not applicable.

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 physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal and peripheral nervous system' systems. Height and weight will also be measured and recorded.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

- For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3).

Blood pressure and pulse rate should be measured after at least 5 minutes in a 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

For each participant, a single 12-lead ECG will be collected according to the SoA (Section 1.3). Electrocardiograms 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. Electrocardiograms may be obtained at additional times when deemed clinically necessary. All ECGs recorded should be stored at the investigational site.

Electrocardiograms will be interpreted by a qualified physician (the investigator or qualified designee).

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 Assessments

- See Section 10.2 Appendix 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 and document this review. 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 or other abnormal safety assessments 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 Section 10.2 Appendix 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., serious adverse event [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. Safety Monitoring

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

8.2.5.1. Hepatic Safety

Not applicable.

8.2.5.2. Hypersensitivity Reactions

Many drugs, or their excipients particularly biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data describing each symptom should be provided to the sponsor in the eCRF.

Sites should have appropriately trained medical staff and appropriate medical equipment available when study participants are receiving study drug. It is recommended that participants who experience a systemic hypersensitivity reaction be treated per national and international guidelines.

In the case of generalized urticaria or anaphylaxis, additional blood and urine samples should be collected as described in Section 10.2 Appendix 2. Laboratory results are provided to the sponsor via the central laboratory.

8.2.5.3. Local Infusion Site Reactions

Symptoms or signs of local infusion site reactions may include erythema, induration, pain, pruritus, and edema.

Pre-specified local infusion site reaction assessments will be performed and collected at the time points indicated in the SoA (Section 1.3).

In addition, if a spontaneous ISR is reported by a participant or site staff at a non-prespecified time point, the local infusion site reaction eCRF will be used to capture additional information about this reaction (e.g., infusion site pain, erythema, induration, pruritis, and edema).

Local infusion site reactions, whether recorded as a result of the prespecified (or solicited) assessment or spontaneously reported reactions, will be recorded as AEs as clinically indicated.

Investigational site staff will be provided with separate instructions/training on how to evaluate local infusion site reactions and their severity in a consistent manner.

8.2.5.3.1. Exploratory Assessment using CCI Platform

8.2.6. Local Pain Measurements Using the Visual Analog Scale

Local pain measurements during bolus application will be assessed using the 100-mm validated VAS for pain. The VAS is a well-validated tool (Williamson and Hoggart 2005) to assess catheter insertion site pain. The VAS is presented as a 10-cm (100-mm) line, anchored by verbal descriptors, usually "no pain" and "worst imaginable pain." The participant is asked to mark the 100-mm line to indicate pain intensity. The participant will be asked to rate any pain associated during each inpatient infusion on a scale of 0 to 100 mm at times specified in the SoA (Section 1.3).

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

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.

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

- AEs
- SAEs
- 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 on events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the excipients infusion (see Section 7).

Care will be taken not to introduce bias when detecting events. Open-ended and non-leading 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 each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). 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 Section 10.3 Appendix 3.

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 informed consent form (ICF)	Follow-up visit	As soon as possible upon site awareness	AE eCRF	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related with study procedures	Signing of the informed consent form (ICF)	Start of intervention	Immediately, without undue delay	SAE paper form	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Immediately, without undue delay	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	Immediately, without undue delay	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants	After the start of study intervention	10 hours after the last dose	Within 24 hours of learning of the pregnancy	SAE paper form	SAE paper form
Product Complaints					
Product complaint 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
Product complaint not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
Updated product complaint information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
Product complaint (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; N/A = not applicable; SAE = serious adverse event.

Serious adverse events, including death, caused by disease progression should not be reported unless the investigator deems them to be possibly related to study treatment.

8.4. Treatment of Overdose

There is a low risk of an overdose from either sodium citrate, magnesium chloride, Humalog diluent or treprostinil within this study.

The largest planned total dose of study treatment will be administered in Part A of the study when each participant will have 5 pumps and will receive a total dose of 270 U/day. The total amount of study treatment (sodium citrate, magnesium chloride, Humalog diluent or treprostinil) provided would be comparable to Humalog or Lyumjev administration to individuals with diabetes who are highly-insulin resistant and require more than 200 U of insulin per day. Likewise, Reznik (2010) reviewed the data from 4 patients with type 2 diabetes with insulin resistance who were placed on CSII therapy with a concentrated insulin to address their daily insulin requirements (192U-630U). Although rare, patients with extreme insulin resistance requiring 10,000 U of insulin per day have been reported (Lalej-Bennis et al. 1997).

Additionally, the total dose for each study treatment is well below any therapeutic level:

- Sodium citrate as it is listed in the FDA Generally Recognized as Safe (FDA 2015a) food additives database and total amount given (11.9 mg as trisodium citrate dihydrate) is within the limits identified for approved drug products in the FDA Inactive Ingredients in Approved Drugs database (FDA 2015b).
- Magnesium chloride is a cation primarily intracellular. The total planned dose in Part A is 13.5 µmol magnesium (or 2.74 mg magnesium chloride hexahydrate) and is below the therapeutic use (Lavoisier magnesium chloride 2004):

Therapeutic Indication	Administration
Curative treatment of torsades de pointe (TdP)	Intravenous bolus in 8 mmol of magnesium cation
Treatment of acute hypokalemia associated with hypomagnesemia	Intravenous infusion from 24 to 32 mmol of magnesium cation daily
Magnesium supplement during electrolyte rebalance and parenteral nutrition	Intravenous infusion from 6 to 8 mmol of magnesium cation over 24 hours
Preventive and curative treatment of eclampsia crisis	Intravenous infusion of 16 mmol of magnesium cation, i.e. 3.5 g of magnesium chloride for 20 to 30 minutes.

Based on the drug label (Lavoisier magnesium chloride 2004), the first signs of overdose of hypermagnesemia include inhibition of knee jerks, feeling of heat, drowsiness, spoken speech disorders, muscular paralysis with respiratory disorders and at the most, respiratory and cardiac arrest.

- Treprostinil is approved in many European Member States for use in the treatment of pulmonary arterial hypertension (PAH) and is known as Remodulin® for SC administration (Remodulin SPC 2016). In Part A, participants will be administered a planned total dose of treprostinil of 2700 ng. The maximum total daily dose of treprostinil in the study will be a small fraction of the average Remodulin® therapeutic dose (53- to 1707-fold less; Table 7). Based on the drug label, the signs and symptoms of overdose with Remodulin® during clinical trials are extensions of its dose-limiting pharmacologic effects and include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Most events were self-limiting and resolved with reduction or withholding of Remodulin®.

Table 7 Maximum Estimated Treprostinil Dose in Diabetes Relative to Treprostinil Doses for Pulmonary Arterial Hypertension

Treprostinil Therapeutic Indication	Treprostinil Dose		Treprostinil dose in PAH patients vs Treprostinil Dose in study[b]
	ng/kg/min	ng/kg/day	
Total Dose in Part A			
• Maximum dose [a]	-	33.75	-
PAH (Remodulin®)[c]			
• Lowest starting dose	1.25	1800	53-fold
• Average dose	9.3	13392	397-fold
• High dose	40	57600	1707-fold

Abbreviations: PAH = pulmonary arterial hypertension.

[a] Total Treprostinil dose in Part A (2700ng/80kg) assuming 80 kg body weight for an adult with T1DM

[b] Treprostinil dose in study vs PAH patients = treprostinil dose for PAH ÷ maximum treprostinil dose in study (Part A)

[c] Remodulin SPC 2016.

The sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator/treating physician should:

1. Turn off all study pumps immediately.
2. Contact the medical monitor immediately.
3. Closely monitor the participant for any AE/SAE until study infusion no longer has a clinical effect or at least until the end of each visit. Refer to Section 10.3 Appendix 3 for reporting details.
4. Document the quantity of the excess dose, as well as the duration of the overdose, in the CRF.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization and health economics are not evaluated in this study.

9. Statistical Considerations

9.1. Statistical Hypotheses

The hypotheses being tested are as follows:

- Part A: To test for differences between infusion sites and depth of infusion in pain as measured by the VAS pain score.
- CCI [redacted]

9.2. Analyses Sets

The following analysis sets are defined:

Participant Analysis Set	Description
Full analysis set	All randomized participants. Participants will be included in the analyses according to the randomly assigned sequences.
Safety analysis set	All randomized participants who receive at least 1 infusion. Participants will be analyzed according to the infusions they actually received.

Data related to a site where an infusion set cannula is accidentally pulled out of an infusion site will not be used in the analysis.

9.3. Statistical Analyses

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

Any change to the data analysis methods described in the protocol will require an amendment only if it changes a principal feature of the protocol. Any other change to the data analysis methods described in the protocol, and the justification for making the change, will be described in the statistical analysis plan (SAP) and the clinical study report. Additional exploratory analyses of the data will be conducted as deemed appropriate.

9.3.1. General Considerations

Unless otherwise specified, these general considerations will apply to all analyses. Continuous variables will be summarized by the number of observations, mean, standard deviation, minimum, median, and maximum values. Categorical variables will be summarized by counts and percentages. Summaries will be provided by infusion site locations, including cannula depths, and study treatments (excipients).

9.3.2. Primary Endpoints

Infusion site pain assessed using the VAS pain score will be listed and summarized using standard descriptive statistics by bolus time (3, 6, and 9 hours after initiation of basal infusion) and VAS assessment time point (5 minutes prior to bolus and 1 and 15 minutes after bolus). For Part A, the summary will also be by infusion site location. The 5 infusion site locations include the assessment of 2 cannula depths at the abdominal site. CCI [redacted]

CCI [redacted]

A mixed effects model will be used to analyze from the log transformed VAS pain score for each bolus time and VAS time point. The statistical model for Part A will include terms for infusion site location, period (order of infusions), bolus time, VAS time point, the 2- and 3-way interactions between infusion site location, bolus time, and VAS time point as fixed effects and participant as a random effect. Comparisons will be made between infusion site locations and between cannula insertion depths for the abdominal infusion site for each bolus time and VAS time point. CCI [redacted] Least-squares means (LSMeans), infusion site location/treatment differences in LSMeans, and the corresponding 95% confidence intervals (CIs) for the infusion site location/treatment differences will be estimated and back-transformed from the log scale to provide estimates of the ratio of geometric LSMeans and 95% CI for the ratio of these means. It is possible that VAS scores will be 0; if so, all scores may be updated to log (VAS+1) to allow for the inclusion of the 0 values in the analysis.

The same model will also be used to analyze the change from the pre-bolus time point (5 minutes prior to the bolus) to the post-bolus time points of (1 and 15 minutes after bolus).

9.3.3. Secondary Endpoints

The comparison of cannula depths at the abdominal infusion site location will be analyzed as part of the mixed effects model described in Section 9.3.2.

9.3.4. Exploratory Endpoints

Local infusion site reaction data will be listed and summarized by infusion site location (Part A) CCI [redacted] in frequency tables.

9.3.5. Safety Analyses

All treatment- and protocol procedure-related AEs will be listed, and if the frequency of events allows, safety data will be summarized using descriptive methodology. CCI [redacted] Symptoms reported to occur prior to enrolment will be distinguished from those reported as new or increased in severity during the study. Each symptom will be classified by the most suitable term from the Medical Dictionary for Regulatory Activities.

9.4. Interim Analysis

No interim analyses are planned for this study. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, the protocol must be amended.

9.5. Sample Size Determination

Approximately 46 participants with T1D will be enrolled in Study I8B-MC-ITTC so that approximately 40 participants complete Part A CCI of the study. CCI [redacted] Forty completing participants will provide approximately 80% power to demonstrate approximately a 55% increase in the VAS pain score between the infusion site locations in Part A CCI [redacted]. Testing will be done at alpha-level of 0.05 with a 2-sided CI. The variability was estimated by analyzing a Lilly internal study that showed a log-scale standard deviation of within-subject difference in VAS pain scores of 0.95.

Participants who discontinue the study before completing the assessments may be replaced at the discretion of the sponsor and investigator to ensure that approximately 40 participants complete the study. The replacement participant will be assigned to the same treatment sequence as the discontinued participant.

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 International Conference for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
    - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/Independent Ethics Committee (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 (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement (CTA).

10.1.2. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study, including the risks and benefits, to the participant or his/her legally authorized representative and answer all questions regarding the study.
- Participants must be informed that their participation is voluntary. Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was entered in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participants must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant or the participant's legally authorized representative 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 his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for his/her data to be used as described in the informed consent.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- 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. Committees Structure

No committees are planned for this study.

10.1.5. Dissemination of Clinical Study Data

Communication of suspended for terminated dosing

If a decision is taken to suspend or terminate infusion of the excipients in the trial due to safety findings, this decision will be communicated by the sponsor 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 the sponsor personnel prior to any further planned dosing. If an infusion is planned imminently, the sponsor personnel 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.

10.1.6. Data Quality Assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (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.
- 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.
- Source data may include laboratory tests, medical records, and clinical notes.
- 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 personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the CTA unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by 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 (EDC) system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Data collected via the sponsor-provided data capture systems will be stored by third parties. The investigator will have continuous access to the data during the study and until decommissioning of the data capture systems. Prior to decommissioning, the investigator will receive an archival copy of pertinent data for retention.

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system and reports/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.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in Section 10.1.6.

10.1.8. Study and Site Start and Closure

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

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

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

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

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further study intervention development.

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

10.1.9. Publication Policy

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed in the Safety Laboratory Tests table below will be performed by the central laboratory or by the local laboratory.
- Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time. Additionally, if the local laboratory results are used to make either a study intervention decision or response evaluation, the results must be entered into the CRF.
- In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.
- 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 personnel.

Safety Laboratory Tests

Hematology [a]	Clinical Chemistry [a]
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
Absolute counts of:	Glucose
Neutrophils	Blood urea nitrogen (BUN)
Lymphocytes	Creatinine
Monocytes	Uric acid
Eosinophils	Total protein
Basophils	Albumin
Platelets	Total bilirubin
Urinalysis [a]	Alkaline phosphatase (ALP)
Specific gravity	Aspartate aminotransferase (AST)
pH	Alanine aminotransferase (ALT)
Protein	
Glucose	
Ketones	Hepatitis B surface antigen[a]
Bilirubin	Hepatitis C antibody[a]
Urobilinogen	HIV [a]
Blood	Pregnancy test
Nitrite	FSH[a, b]
Coagulation	HbA1c[a]
International normalized ratio (INR)	

Abbreviations: FSH = follicle-stimulating hormone; HbA1c = hemoglobin A1c; HIV = human immunodeficiency virus; RBC = red blood cells; WBC = white blood cells.

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] Performed at screening only.

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

10.2.1. Blood Sampling Summary

Approximately 100 mL blood sampling per participant is expected in this study. Blood sampling estimate will be provided in the ICF.

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

10.3.1. Definition of AE

AE Definition
• An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavourable 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., ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though they 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 overdose should be reported regardless of sequelae.

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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- Pain experienced at the infusion site during scheduled VAS assessments is not to be documented as an AE.

10.3.2. Definition of SAE

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

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

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

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

10.3.3. 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 in order 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. Adverse event/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 a SAE. Severe is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The investigator will also consult the IB and Product Information in his/her 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 his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by 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 the SAE Report.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

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

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/IECs, and investigators.
- An investigator who receives an investigator safety report describing a 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 IB and will notify the IRB/IEC, if appropriate according to local requirements.

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

Definitions:

Woman of Childbearing Potential (WOCBP)
A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

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

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

   Note: Determination can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

3. Postmenopausal female is defined as, women with:
   - 12 months of amenorrhea for women >55, with no need for follicle-stimulating hormone (FSH)
   - 12 months of amenorrhea for women >40 years old with FSH ≥40 mIU/mL and no other medical condition such as anorexia nervosa and not taking medications during the amenorrhea (e.g. oral contraceptives, hormones, gonadotropin releasing hormone, anti-estrogens, selective estrogen receptor modulators [SERMs], or chemotherapy that induced amenorrhea).

Contraception Guidance:

Male Participants:

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

Female Participants:

Females of childbearing potential agree to either remain abstinent or use at least one effective contraception until study completion.

Examples of Different Forms of Contraception:

Highly effective contraception

- combination oral contraceptive pill and mini-pill
- implanted contraceptives
- injectable contraceptives
- contraceptive patch (only women <198 lb 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
- condom with spermicide
- diaphragm with spermicide, or
- 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

Collection of Pregnancy Information

Male participants with partners who become pregnant

- The investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive excipients infusion.

- After obtaining the necessary signed informed consent from the pregnant female partner directly, the investigator will record pregnancy information on the appropriate form and submit it to the sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

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

10.5. Appendix 5: Genetics

Not applicable.

10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments

Not applicable.

10.7. Appendix 7: Medical Device Adverse Events (AEs), Adverse Device Effects (ADEs), Serious Adverse Events (SAEs) and Device Deficiencies: Definition and Procedures for Recording, Evaluating, Follow-Up, and Reporting

Not applicable.

10.8. Appendix 8: Country-Specific Requirements

Not applicable.

10.9. Appendix 9: Provisions for Changes in Study Conduct During COVID-19 Pandemic

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.

COVID-19 pandemic

Individual, site, or regional restrictions due to the COVID-19 pandemic may cause disruptions to the conduct of the study. 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 during the COVID-19 pandemic

The sponsor will first submit a substantial amendment to IRB/IEC, regulatory bodies, and any other relevant local authorities for approval, should there be a need to implement the provisional changes outlined in this appendix. Should these measures need to be implemented immediately to protect the safety of study participants, then they will be implemented as urgent safety measures, and reported as soon as possible following implementation. All approvals and notifications must be retained in the study records.

After receiving the sponsor's written approval, sites may implement changes if permitted by local regulations. 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 for the following reasons, if required:

- 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 the COVID-19 pandemic

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.

To ensure the quality of data and the well-being of participants, it will be ensured that the investigator sites and their staff are following GCP principles and are meeting the sponsor responsibilities of Section 5 of ICH-GCP. Throughout these activities the participant remains under the care of the primary investigator.

Safety monitoring will be followed as per the Schedule of Activities.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at the 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 the COVID-19 pandemic:

- If screening is paused for less than 42 days from screening visit to randomization visit: the participant will proceed to the next study visit per the usual Schedule of Activities, provided that the randomization visit is conducted within 42 days from the first 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 Schedule of Activities 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 the study 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-Televisit**	**Visit Interval Tolerance**
Visit no.	**0**	**1**	**2 (Part A)** CCI	**4**	
Timing	≥ 1 day before Visit 1	≤28 days prior Visit 2	At least 3 days between Visit 2 and Visit 3	CCI	
In-house Visit/Period			See Table 2 CCI		
	On-site only	On-site only	On-site only	Televisit	Same as shown in SoA, but flexibility can be considered following consultation with, and 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 and conducted activities were affected by the COVID-19 pandemic. Relevant communications, including delegation, should be filed with site study records.

10.10. Appendix 10: Abbreviations

Term	Definition
ADE	adverse device effects
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
blinding/masking	A single-blind study is one in which the investigator and/or his 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/his 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.
BMI	body mass index
CFR	Code of Federal Regulations
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
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
CTA	Clinical Trial Agreement
device deficiencies	equivalent to product complaints
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture

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.
ERB	ethical review board
FSH	follicle-stimulating hormone
GCP	good clinical practice
HbA1c	hemoglobin A1c
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISR	infusion site reaction
Informed consent	A process by which a participant voluntarily confirms his or her willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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.
LSMeans	Least-squares means
PAH	pulmonary arterial hypertension
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
PPG	postprandial glucose
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.

SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SERM	selective estrogen receptor modulator
SoA	Schedule of Activities
T1D	type 1 diabetes mellitus
TBL	total bilirubin
ULN	upper limit of normal
VAS	visual analog scale
WOCBP	woman/women of childbearing potential

10.11. Appendix 11: Protocol Amendment History

DOCUMENT HISTORY	
Document	**Date**
Amendment (b)	28-September-2021
Amendment (a)	08-September-2021
Original Protocol	18-May-2021

Amendment (a)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- scientific value of the trial,
- conduct or management of the trial

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis; 4.1. Overall design; 9.5. Sample Size Determination	Amended statement "approximately 40 evaluable participants complete both Part A and Part B of the study". Removed word "both" throughout.	Corrected error.
1.1. Synopsis; 1.3. Schedule of Activities; 4.1. Overall design	Adipose thickness will be measured by ultrasound. Option to measure by caliper deleted.	Clarification.
1.3. Schedule of Activities (Part A)	Time windows for VAS score collection updated.	Clarification.
CCI		
1.3. Schedule of Activities (Part A CCI)	On Day -1, deleted the dosing day exclusion/withdrawal criteria check as continued eligibility will be checked	Corrected error.
2.2. Background	Deleted "depending on the type of reaction" from section detailing the reported ISRs in the PRONTO-Pump-2 study.	Clarification.
5.2. Exclusion Criteria	Criterion 13: amended from severe neuropathy to have a pathologic tuning fork test. Criterion 18: serum creatinine value in µmol/L unit updated to 1 decimal place. Criterion 29: added new criterion to exclude use of Lyumjev.	Criteria 13 and 29: ethics committee request. Criterion 18: clarification.
8.2.5.3. Local Infusion Site Reactions	Amended to state local infusion site reactions will be recorded as AEs as	BfArM request.

Section # and Name	Description of Change	Brief Rationale
	clinical indicated and not only if they qualify as SAEs.	
8.3.1. Timing and Mechanism for Collecting Events	Timing for reporting SAEs to Sponsor amended to "Immediately, without undue delay, and under no circumstances later than 24 hours of awareness".	BfArM request.
10.2. (Appendix 2) Clinical Laboratory Tests	Ethanol testing and urine drug screen deleted from table of laboratory tests as this table refers to local and central testing only. These tests will be performed at site using a breathalyzer or dip stick.	Clarification.
10.3. (Appendix 3) Adverse Events	Deleted statement that infusion site reactions are not be documented as an AE.	BfArM request.
10.9. (Appendix 9) Provisions for Changes in Study Conduct	Appendix changed from "Provisions for Changes in Study Conduct During Exceptional Circumstances" to "Provisions for Changes in Study Conduct During COVID-19 Pandemic". Appendix updated to include procedures to manage impact of COVID-19.	BfArM request.

Amendment (b)

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the

- safety or physical or mental integrity of the study participants,
- scientific value of the trial,
- conduct or management of the trial

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
8.3.1. Timing and Mechanism for Collecting Events	Timing for reporting SAEs to Sponsor amended by removing “under no circumstances later than 24 hours of awareness”.	BfArM request.

11. References

Blevins T, Zhang Q, Frias JP, et al. Randomized double-blind clinical trial comparing ultra rapid lispro with lispro in a basal-bolus regimen in patients with type 2 diabetes: PRONTO-T2D. *Diabetes Care*. 2020;43(12):2991-2998. https://doi.org/10.2337/dc19-2550

Gan MJ, Albanese-O'Neill A, Haller MJ. Type 1 diabetes: current concepts in epidemiology, pathophysiology, clinical care, and research. *Curr Probl Pediatr Adolesc Health Care*. 2012;42(10):269-291. https://doi.org/10.1016/j.cppeds.2012.07.002

[FDA] United States Food and Drug Administration. 2015a. SCOGS (Select Committee on GRAS Substances). Available at: http://www.accessdata.fda.gov/scripts/fdcc/?set=SCOGS. Accessed December 15, 2015.

[FDA] United States Food and Drug Administration. 2015b. Inactive Ingredient Search for Approved Drug Products. Available at: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm. Accessed December 15, 2015.

Heise T, Linnebjerg H, Coutant D, et al. Ultra rapid lispro lowers postprandial glucose and more closely matches normal physiological glucose response compared to other rapid insulin analogues: A phase 1 randomized, crossover study. *Diabetes Obesity Metab*. 2020;22(10):1789-1798. https://doi.org/10.1111/dom.14094

Humira Prescribing Information. 2021. AbbVie Inc. North Chicago, IL 60064, USA; 2021. https://www.rxabbvie.com/pdf/humira.pdf.

Jinnouchi H, Imori M, Nishiyama H, Imaoka T. Ultra-rapid lispro efficacy and safety compared to Humalog® in Japanese patients with type 2 diabetes: PRONTO-T2D subpopulation analysis. *Diabetes Ther*. 2020:11(9):2075-2088. https://doi.org/10.1007/s13300-020-00890-2

Kaiser C, Knight A, Nordström D, et al. Injection-site reactions upon Kineret (anakinra) administration: experiences and explanations. *Rheumatol Int.* 2012;32:295-299. https://doi.org/10.1007/s00296-011-2096-3

Klaff L, Cao D, Dellva MA, et al. Ultra rapid lispro improves postprandial glucose control compared with lispro in patients with type 1 diabetes: Results from the 26-week PRONTO-T1D study. *Diabetes Obes Metab.* 2020;22(10):1799-1807. https://doi.org/10.1111/dom.14100

Krasner A, Pohl R, Simms P, et al. A review of a family of ultra-rapid-acting insulins: formulation development. *J Diabetes Sci Technol.* 2012;6(4):786-796. https://doi.org/10.1177/193229681200600408

Lalej-Bennis D, Selam JL, Fluteau-Nadler S, et al. Extreme insulin resistance: clinical management by external subcutaneous insulin infusion. *Diabetes Metab.* 1997;23(6):533-536. PMID: 9496561

Lavoisier magnesium chloride. Lavoisier magnesium chloride 10 % (1 g/10 ml), iv injectable solution. CDM LAVOISIER, Laboratoires Chaix et Du Marais - 7, rue Labie - 75017 PARIS – FRANCE. 2004. http://www.lavoisier.com/fic_bdd/pdf_en_fichier/12133479260_Magnesium_Chlorhide_10_En.pdf.

Leohr J, Dellva MA, LaBell E, et al. Pharmacokinetic and glucodynamic responses of ultra rapid lispro vs lispro across a clinically relevant range of subcutaneous doses in healthy subjects. *Clin Ther.* 2020;42(9):1762-1777.e1764. https://doi.org/10.1016/j.clinthera.2020.07.005

Lyumjev SPC, Lyumjev Summary of Product Characteristics. Eli Lilly and Company, Indianapolis, IN, USA; 2020. https://www.ema.europa.eu/en/documents/product-information/lyumjev-previously-liumjev-epar-product-information_en.pdf.

Murata T, Ushikubi F, Matsuoka T, et al. Altered pain perception and inflammatory response in mice lacking prostacyclin receptor. *Nature.* 1997;388:678-682. https://doi.org/10.1038/41780

Nash P, Vanhoof J, Hall S, et al. Randomized Crossover Comparison of Injection Site Pain with 40 mg/0.4 or 0.8 mL Formulations of Adalimumab in Participants with Rheumatoid Arthritis. *Rheumatol Ther.* 2016;3:257-270. https://doi.org/10.1007/s40744-016-0041-3

Remodulin SPC. United Therapeutics - Remodulin Solution for Infusion: Summary of Product Characteristics. United Therapeutics Europe Ltd., Chertsey, KT16 9FG, UK. 2016. https://mri.cts-mrp.eu/Human/Downloads/FR_H_0278_001_FinalSPC.pdf.

Reznik Y. Continuous subcutaneous insulin infusion (CSII) using an external insulin pump for the treatment of type 2 diabetes. *Diabetes Metab.* 2010;36(6 Pt 1):415-21. https://doi.org/10.1016/j.diabet.2010.08.002

Shin H-J, Na H-S, Do S-H. Magnesium and Pain. *Nutrients.* 2020;12(8):2184. https://doi.org/10.3390/nu12082184

Srebro D, Vuckovic S, Milovanovic A, et al. Magnesium in Pain Research: State of the Art. *Curr Med Chem.* 2017;24(4):424-434. https://doi.org/10.2174/0929867323666161213101744

Warren M, Bode B, Cho JI, et al. Improved postprandial glucose control with ultra rapid lispro versus lispro with continuous subcutaneous insulin infusion in type 1 diabetes: PRONTO-Pump-2. [published online March 8, 2021] *Diabetes Obes Metab*. https://doi.org/10.1111/dom.14368

Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. *J Clin Nurs*. 2005;14(7):798-804. https://doi.org/10.1111/j.1365-2702.2005.01121.x

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