

Protocol Amendment I8B-MC-ITTA (c)

A 26-Week, Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of
Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

NCT06370715

Approval Date: 03-Jan-2024

A 26-Week, Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

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Protocol Title: A 26-Week, Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

Protocol Number: I8B-MC-ITTA (c)

Compound: Lyumjev

Study Phase: 4

Short Title: A Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

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

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Amendment b</i>	<i>08-May-2023</i>
<i>Amendment a</i>	<i>03-Feb-2023</i>
<i>Original Protocol</i>	<i>24-Sep-2021</i>

Amendment [c]

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment

The primary rationale for this amendment is to introduce serum lipid profile screening in all participants of T2DM both during study screening and during final visit to assess their risk for cardiovascular events.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Added “Serum lipid profile” at Visits 1 and 10 under “Laboratory Assessments”	Serum lipid profile estimation is a routine investigation that is done for cardiac risk assessment of participants with T2DM.
10.2. Appendix 2: Clinical Laboratory Tests	Added lipid panel	
10.7. Appendix 7. Abbreviations	Added LDL, HDL, and VLDL	Tests included under lipid profile estimation
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol title: A 26-Week, Multicenter, Open-Label, Single-Arm, Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

Short title: A Phase 4 Study to Assess the Safety of Lyumjev in Adult Patients with Type 2 Diabetes Mellitus in India

Rationale: Rapid-acting insulins have a more rapid onset of action compared to human insulin; however, the general consensus is that they are not rapid enough to match carbohydrate absorption and many patients are thus unable to achieve optimal glycemic control. An ultra-rapid-acting prandial insulin with pharmacokinetic (PK) and glucodynamic profiles that demonstrate faster absorption and onset of action may better match carbohydrate absorption and lead to improved postprandial control.

Lyumjev® (insulin lispro ultrarapid injection 100 U/mL pen) is a new formulation of insulin lispro 100 U/mL developed as an ultra-rapid-acting insulin with a faster onset of action and shorter duration of action compared to commercially available insulin lispro 100 U/mL pen (Humalog®, Eli Lilly and Company). It will more closely mimic endogenous insulin action in healthy subjects. The changes in PK and pharmacodynamic characteristics are achieved by co-formulating insulin lispro with 2 enabling excipients, treprostinil and citrate. Treprostinil as an excipient enhances the absorption of insulin lispro through local vasodilatation rather than as an active pharmaceutical ingredient that elicits a systemic effect. Sodium citrate further enhance the absorption of insulin lispro. Sodium citrate and the other excipients in the Lyumjev formulation are listed in the FDA Generally Recognized as Safe food additives database and in the FDA Inactive Ingredients in Approved Drugs database.

Lyumjev® received marketing approval in India on 06 July 2021 for the treatment of adults with type 2 diabetes mellitus (T2DM) 18 years or older.

The aim of this study is to evaluate the safety of Lyumjev, as measured by incidence and rate of documented hypoglycemia from baseline to Week 26 in subjects with T2DM, when administered as a multiple daily injection (MDI) regimen in combination with basal insulin glargine 100 U/mL pen (Basaglar®).

Results of this study will **CCI** to provide safety and efficacy data in a minimum of 100 additional Indian subjects.

Objectives and endpoints

Objectives	Endpoints
Primary	
To assess the risk of hypoglycemia in adult subjects with T2DM in India who will be administered Lyumjev	Incidence (percent of subjects with at least 1 event) and rate (events/subject/year) of all documented hypoglycemia (BG<54 mg/dL) from baseline through Week 26

Objectives	Endpoints
Secondary	
To assess the adverse events and other safety parameters in adult subjects with T2DM in India	• SAEs and TEAEs from baseline through study follow-up • Incidence and rate (events/subject/year) of severe hypoglycemic events from baseline through Week 26 • Incidence and rate (events/subject/year) of nocturnal hypoglycemia (BG<54 mg/dL) from baseline through Week 26 • Incidence and rate (events/subject/year) of nocturnal and all documented hypoglycemic events (BG<70 mg/dL) from baseline through Week 26 • Change in body weight from baseline to Week 26 • Change in ITSQ scores from baseline to Week 26
To assess the efficacy of Lyumjev in adult subjects with T2DM in India	• Change in HbA1c from baseline to Week 26 • Percentage of subjects achieving HbA1c <7% at Week 26 • Change in 1- and 2-hour PPG (estimated from SMBG) values from baseline to Week 26 • Change in bolus insulin dose, basal insulin dose, and basal:bolus ratio from baseline to Week 26 • Change in 9-point SMBG values from baseline to Week 26

Abbreviations: BG = blood glucose; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; PPG = postprandial glucose; SAE = serious adverse event; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

Overall design

Study I8B-MC-ITTA (ITTA) is a Phase 4, prospective, open-label, single-arm, outpatient, multicenter study to assess the safety of Lyumjev in subjects with T2DM in India. The study includes a 1-week screening period, a 4-week lead-in period, followed by a 26-week treatment period, and a 2-week safety follow-up period.

The study is designed to evaluate the risk of hypoglycemia in adult subjects with T2DM during 26 weeks of Lyumjev treatment.

Lyumjev will be injected immediately (0 to 2 minutes) prior to each meal in a regimen with insulin glargine 100 U/mL once daily as basal insulin. Bolus insulin doses will be titrated to achieve protocol-specified glucose targets during the treatment period as determined by the principal investigator. It is expected that adjustments to prandial and basal insulin doses will continue throughout the 26-week treatment period to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia. Events of hypoglycemia and self-monitored blood glucose values will be recorded on a paper diary by the subjects as specified in the SoA. A hypoglycemia questionnaire will be completed after each event.

Disclosure statement: This is a single-arm treatment study and no blinding.

Number of subjects:

CCI

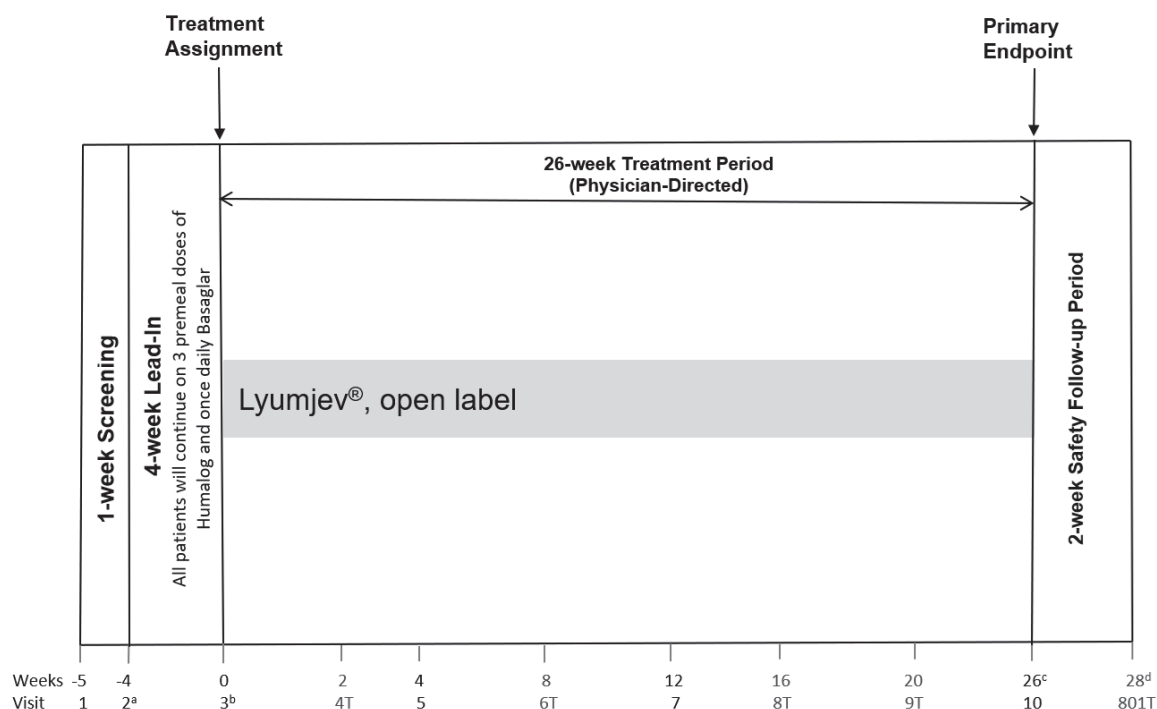
The target is to have a minimum of 100 subjects complete the study.

Intervention groups and duration:

This single-arm study includes the following study periods: 1-week screening, 4-week lead-in, 26-week treatment, and 2-week safety follow-up. All subjects will use open-label Lyumjev and Basaglar® during the treatment period.

Data monitoring committee: No

1.2. Schema



Abbreviation: T = telephone visit.

- ^a At Visit 2, subjects treated with insulin aspart, insulin glulisine, regular insulin, or premixed insulin will be transferred to insulin lispro 100 U/mL (Humalog) administered 0 to 2 minutes before meals 3 times a day. At Visit 2, subjects treated with a basal insulin regimen other than insulin glargine will be transferred to insulin glargine 100 U/mL once daily. Subjects will titrate basal insulin during the lead-in period.
- ^b At Visit 3, subjects will stop taking Humalog and will transition to Lyumjev unit-for-unit. Subjects will start treatment with Lyumjev administered 0 to 2 minutes before meals 3 times a day and continue once-daily Basaglar. Subjects will titrate Lyumjev during the 26-week treatment period.
- ^c Subjects will discontinue study insulins at Week 26 and be transferred to nonstudy insulin as determined by the principal investigator.
- ^d Subjects will return for a safety follow-up visit at Week 28.

Figure 1.1. Illustration of study design.

1.3. Schedule of Activities (SoA)

	Screen	Lead-In	Treatment Period									ED
Visit Number	1	2	3	4	5	6	7	8	9	10	801	ED
	O	O	O	P	O	P	O	P	P	O	P	O
Visit Window (± days)		3	3	3	3	3	3	3	3	3	7	
Time (weeks)	-5	-4	0	2	4	8	12	16	20	26	28	
Informed Consent Signed	X											
IWRS	X	X	X		X	X	X	X	X	X	X	X
Subject eligibility review	X											
Treatment assignment			X									
Clinical Assessments												
Subject demographics	X											
Medical history and preexisting conditions	X											
Physical examination/height, BMI	X											
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events and product complaints	X	X	X	X	X	X	X	X	X	X	X	X
Body weight	X	X	X		X		X			X		X
Vital signs, blood pressure, and heart rate	X	X	X		X		X			X		X
ECG (12-lead; local)	X											
Diabetes, hypoglycemia, and nutrition counselling		X										
Basal and prandial insulin dose assessments		X	X	X	X	X	X	X	X	X	X	X
ITSQ			X							X		
Supplies and IP												
Dispense study supplies		X	X		X		X					
Review/discuss hypoglycemia events		X	X	X	X	X	X	X	X	X	X	X

	Screen	Lead-In	Treatment Period									ED
Visit Number	1	2	3	4	5	6	7	8	9	10	801	ED
	O	O	O	P	O	P	O	P	P	O	P	O
Visit Window (± days)		3	3	3	3	3	3	3	3	3	7	
Time (weeks)	-5	-4	0	2	4	8	12	16	20	26	28	
Review 4-point SMBG profiles				X	X	X	X	X	X			X
Remind patient of 4-point SMBG and 9-point SMBG requirements ^a		X							X			
Review/discuss 9-point SMBG			X							X		X
Train on use of study paper diary for collection of insulin dose, SMBG, and hypoglycemia data		X										
Dispense study diary		X	X		X		X					
Remind subject of study diary requirements		X	X	X	X	X	X	X	X			
Collect/review study diary and transfer data to eCRF			X		X		X			X		X
Dispense Humalog [®]		X										
Dispense Basaglar [®]		X			X		X					
Stop Humalog [®]			X									
Dispense Lyumjev			X		X		X					
Subject returns unused study drug supplies					X		X			X		X
Drug accountability			X		X		X			X		X
Laboratory Assessments												
HbA1c	X		X				X			X		X
Chemistry panel	X											

	Screen	Lead-In	Treatment Period									ED
Visit Number	1	2	3	4	5	6	7	8	9	10	801	ED
	O	O	O	P	O	P	O	P	P	O	P	O
Visit Window (± days)		3	3	3	3	3	3	3	3	3	7	
Time (weeks)	-5	-4	0	2	4	8	12	16	20	26	28	
Hematology	X											
Serum lipid profile	X									X		
Serum pregnancy test (in WOCBP) ^b	X											
Urine pregnancy test ^b			X									
Follicle-stimulating hormone test ^c	X											

Abbreviations: BMI = body mass index; ECG = electrocardiogram; eCRF = electronic case report form; ED = early discontinuation; HbA1c = hemoglobin A1c; IP = investigational product; ITSQ = Insulin Treatment Satisfaction Questionnaire; IWRS = interactive web response system; O = office visit; P = phone visit; SMBG = self-monitored blood glucose; WOCBP = woman of childbearing potential.

- ^a Patients should be instructed to perform 4-point SMBG or 9-point SMBG profiles for at least 3 days during the week prior to the visit.
- ^b Serum pregnancy test must be performed in women of childbearing potential at Visit 1 followed by a urine pregnancy test within 24 hours prior to IP exposure at Visit 3 and at other times at the investigator's discretion.
- ^c Follicle-stimulating hormone test must be performed at Visit 1 for women at least 40 years of age with an intact uterus, not on hormone therapy, and who have had cessation of menses for at least 1 year without an alternative medical cause.

2. Introduction

Lyumjev® (insulin lispro ultrarapid injection 100 U/mL pen) is a new formulation of insulin lispro 100 U/mL developed as an ultra-rapid-acting insulin with a faster onset of action and shorter duration of action compared to commercially available insulin lispro 100 U/mL pen (Humalog®; Eli Lilly and Company). The active ingredient utilizes 2 enabling excipients with independent mechanisms to accelerate the absorption of insulin lispro from the site of injection or infusion resulting in a faster insulin time-action profile and in earlier glucose lowering when compared to Humalog. These 2 mechanisms include

- enhanced absorption of insulin lispro through increased local vasodilation, due to the addition of a microdose of treprostinil as an excipient in the formulation
- speeding absorption of insulin through enhanced local vascular permeability, which is achieved by addition of the excipient sodium citrate in the formulation

The accelerated absorption of insulin lispro demonstrated by the pharmacokinetic (PK) profile of Lyumjev, more closely mimics the profile of normal endogenous insulin secretion, when compared to Humalog, Novorapid, and Fiasp (Heise et al. 2020).

2.1. Study Rationale

An ultra-rapid-acting prandial insulin with PK and glucodynamic profiles that demonstrate faster absorption and onset of action may better match carbohydrate absorption and lead to improved postprandial control (Linnebjerg et al. 2020). The time-action profile of a rapid-acting insulin could be enhanced through the addition of excipients to an existing formulation to increase capillary blood flow and/or enhance vascular permeability.

The efficacy and safety of Lyumjev in subjects with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) have been evaluated in large, randomized, active-controlled, multicenter, multinational, Phase 3 clinical trials (I8B-MC-ITRN [ITRN] and I8B-MC-ITRM [ITRM]). Based on these clinical trials, Lyumjev received marketing approval in India on 06 July 2021 for the treatment of adults with diabetes mellitus 18 years or older. CCI

Lyumjev be studied in a minimum of 100 additional Indian subjects CCI

The aim of this study is to evaluate the safety and efficacy of Lyumjev with the primary endpoint of the incidence and rate of documented hypoglycemia from baseline to Week 26 in subjects with T2DM when administered as a MDI regimen in combination with basal insulin glargine 100 U/mL pen (Basaglar®).

2.2. Background

There have been many advances in the treatment of diabetes in the past 20 years; however, reaching and maintaining glycemic goals remain challenging even under intensive insulin therapy regimens. Only approximately 30% of insulin-requiring people with diabetes are able to

reach the goal hemoglobin A1c (HbA1c) target of <7% (Casagrande et al. 2013). Currently available, rapid-acting insulin analogs are unable to match the kinetics of physiological postmeal insulin secretion.

Lyumjev is a new formulation of insulin lispro developed as an ultra-rapid-acting insulin with a faster onset of action and shorter duration of action compared to currently available rapid-acting insulin analogs, and it more closely mimics endogenous insulin secretion in healthy subjects than rapid-acting insulin analogs (Heise et al. 2020).

Studies ITRM (subjects with T1DM) and ITRN (subjects with T2DM) evaluated safety and efficacy of Lyumjev and Humalog when administered as MDI, both in combination with basal insulin glargine or insulin degludec (Blevins et al. 2020; Klaff et al. 2020). The primary endpoint in these studies was HbA1c change from baseline to Week 26, with multiplicity-adjusted objectives for 1- and 2-hour postprandial glucose (PPG) excursions during 4-hour standardized meal tests. In both studies Lyumjev compared to Humalog demonstrated noninferiority for HbA1c change from baseline to endpoint and superiority in lowering 1- and 2-hour PPG excursions during standardized meal test. At Week 26, mean PPG excursions were statistically significantly lower in the Lyumjev group than in the Humalog group at all time points from 15 minutes to 4 hours in Study ITRM and from 30 minutes to 4 hours in Study ITRN.

The overall safety of Lyumjev was similar to Humalog in the Phase 3 trials. Overall hypoglycemia was similar between Lyumjev and Humalog, although differences in patterns of postprandial hypoglycemia were observed.

A detailed description of the chemistry, pharmacology, efficacy, and safety of Lyumjev is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

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

Subjects may experience the benefit of improved glycemic control with basal-bolus insulin treatment and dose titration.

2.3.1. Risk Assessment

The key risk for Lyumjev, similar to commercially available insulins, is hypoglycemia, especially severe hypoglycemia, which is the main limiting factor of insulin therapy in treatment of T1DM and T2DM.

Injection- and infusion-site reactions have been reported with all insulin therapies. In Phase 3 studies, injection- and infusion-site reactions were reported more frequently by subjects treated with Lyumjev compared to Humalog. A majority of these reactions were of mild severity and most resolved during study treatment.

The overall safety database for Lyumjev was sufficient in size and scope to adequately characterize the safety profile in adults with T1DM and T2DM using MDI therapy or T1DM on continuous subcutaneous insulin infusion (CSII) therapy. In general, the overall safety profile of Lyumjev observed in the Lyumjev Phase 3 and clinical pharmacology studies was similar to the

well-established safety profile of Humalog. Lilly maintains a global safety system, and postmarketing AEs will be monitored via routine pharmacovigilance.

2.3.2. Benefit Assessment

Lyumjev is an ultra-rapid-acting insulin formulation that demonstrates faster insulin absorption, earlier onset of appearance, and shorter duration of action, compared to Humalog.

As a prandial insulin, Lyumjev was developed to improve postprandial glycemic control. In the Phase 3 studies, mealtime Lyumjev was shown to reduce PPG levels using multiple, complementary modalities including:

- rigorous blood glucose (BG) measurement during a standardized liquid in the MDI studies
- measurements reflective of everyday life and typical meals, including self-monitored blood glucose (SMBG) monitoring in the MDI studies, as well as blinded continuous glucose monitoring assessment in the T1DM MDI study and unblinded continuous glucose monitoring in the T1DM CSII study.

The data consistently support that mealtime Lyumjev, when administered as a prandial insulin, has greater PPG lowering when compared to Humalog.

2.3.3. Overall Benefit: Risk Conclusion

Lyumjev, a new ultra-rapid-acting insulin formulation, is an advancement in diabetes treatment compared to rapid-acting insulin analogs. The safety and efficacy of insulin lispro are well established through the Humalog development program and more than 20 years of postmarketing experience. Glycemic control as measured by HbA1c was noninferior for Lyumjev and Humalog, as expected in a treat-to-target trial, with subjects in all treatment groups reaching good glycemic control. This allowed comparison of other attributes of these insulins at the same HbA1c and demonstration of differences in PPG control.

The general consensus is that the time-action profile of rapid-acting insulin analogs does not adequately mimic the postmeal insulin secretion pattern observed in people without diabetes. Due to the accelerated absorption of insulin lispro, Lyumjev more closely mimics the profile of normal endogenous insulin secretion, when compared to Humalog. The consequence of faster absorption is earlier insulin action. In Phase 3 trials, Lyumjev showed superiority of PPG lowering compared to Humalog due to faster absorption and earlier insulin action of Lyumjev.

The overall safety profile was similar between Lyumjev and Humalog. The key risk of hypoglycemia is a known risk of insulin therapy and is appropriately described in the labeling. Together, these studies support the use of Lyumjev as a prandial insulin in combination with basal insulins administered through MDI in adults with T1DM and T2DM or administered via CSII.

Considering the measures taken to minimize risk to subjects participating in this study, the potential risks identified in association with Lyumjev are justified by the anticipated benefits that may be afforded to subjects with diabetes.

3. Objectives, Endpoints and Estimands

Objectives	Endpoints
Primary	
To assess the risk of hypoglycemia in adult subjects with T2DM in India who will be administered Lyumjev	Incidence (percentage of subjects with at least 1 event) and rate (events/subject/year) of all documented hypoglycemia (BG<54 mg/dL) from baseline through Week 26
Secondary	
To assess the adverse events and other safety parameters in adult subjects with T2DM in India	- SAEs and TEAEs from baseline through study follow-up - Incidence and rate (events/subject/year) of severe hypoglycemic events from baseline through Week 26 - Incidence and rate (events/subject/year) of nocturnal hypoglycemia (BG<54 mg/dL) from baseline through Week 26 - Incidence and rate (events/subject/year) of nocturnal and all documented hypoglycemic events (BG<70 mg/dL) from baseline through Week 26 - Change in body weight from baseline to Week 26 - Change in ITSQ scores from baseline to Week 26
To assess the efficacy of Lyumjev in adult subjects with T2DM in India	- Change in HbA1c from baseline to Week 26 - Percentage of subjects achieving HbA1c <7% at Week 26 - Change in 1- and 2-hour PPG values (estimated from SMBG) from baseline to Week 26 - Change in bolus insulin dose, basal insulin dose, and basal:bolus ratio from baseline to Week 26 - Change in 9-point SMBG values from baseline to Week 26

Abbreviations: BG = blood glucose; HbA1c = hemoglobin A1c; ITSQ = Insulin Treatment Satisfaction Questionnaire; PPG = postprandial glucose; SAE = serious adverse event; SMBG = self-monitored blood glucose; T2DM = type 2 diabetes mellitus; TEAE = treatment-emergent adverse event.

4. Study Design

4.1. Overall Design

Study I8B-MC-ITTA (referred as Study ITTA henceforth) is a Phase 4, prospective, open-label, single-arm, outpatient, multicenter study to assess safety of Lyumjev in subjects with T2DM in India. The study includes a 1-week screening period, a 4-week lead-in period, followed by a 26-week treatment period, and a 2-week safety follow-up period.

The study is designed to evaluate risk of hypoglycemia in adult subjects with T2DM during 26 weeks of Lyumjev treatment.

Lyumjev will be injected immediately (0 to 2 minutes) prior to each meal in combination with insulin glargine 100 U/mL (Basaglar®) once daily as basal insulin.

The purpose of the lead-in period will be to titrate basal insulin, obtain preliminary diagnostic laboratory tests, and determine baseline hypoglycemia rates.

Subjects treated with MDI therapy will be eligible for inclusion in the trial. The subjects can be on

- a) basal insulin in combination with at least 1 prandial injection of bolus insulin OR
- b) premixed analog or human insulin regimens with any basal and bolus insulin combination injected at least twice daily, except for IDegAsp (insulin degludec + insulin aspart; Ryzodeg) injected once daily (Inclusion Criterion [4])

Subjects should use basal insulin glargine 100 U/mL (Basaglar) throughout the trial once daily. Subjects using other basal insulin regimens or premixed insulins will be transitioned at Visit 2 to an insulin glargine 100 U/mL. Subjects treated with 1 to 2 prandial injections a day, premixed insulin, or prandial insulin other than insulin lispro 3 times a day prior to study entry will be transitioned to 3 injections a day of insulin lispro (Humalog) at the beginning of the lead-in period. Basal insulin will be titrated during the 4-week lead-in period to allow the subject to reach the target fasting BG by the end of this period.

At Visit 3, subjects will stop taking Humalog and will transition to Lyumjev unit-for-unit. Subjects will start taking Lyumjev at each meal (breakfast, lunch, and dinner). Prandial insulin doses should be titrated as necessary to meet the target SMBG levels. It is expected that adjustments to prandial and basal insulin doses will continue throughout the 26-week treatment period to maintain glycemic control or for safety reasons such as hypoglycemia or unacceptable hyperglycemia.

The 26-week treatment period will be followed by a 2-week safety follow-up period.

Figure 1.1 (Section 1.2) illustrates the study design.

4.2. Scientific Rationale for Study Design

The 2 pivotal Phase 3 Studies ITRM and ITRN have proven the noninferiority of Lyumjev on glycemic control (noninferiority margin = 0.4% for HbA1c) in subjects with T1DM and T2DM, when administered as prandial insulin (0 to 2 minutes prior to the meal), in combination with basal insulin glargine or insulin degludec for 26 weeks.

Lyumjev received marketing approval in India as a mealtime insulin for the treatment of T2DM in adults aged 18 years or older on 06 July 2021. There were 150 subjects from India in the Studies ITRM and ITRN. CCI

Lyumjev be studied in a minimum of 100 additional Indian subjects.

Thus, Lilly designed a multicenter, open-label, single-arm, Phase 4 study to assess the safety and efficacy of Lyumjev in Indian subjects with T2DM.

4.3. Justification for Dose

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

4.4. End of Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study as shown in the Schedule of Activities (SoA; Section 1.3).

5. Study Population

This study will include subjects who have been diagnosed with T2DM and are being treated with basal insulin in combination with at least 1 prandial injection of bolus insulin or at least 2 injections of premixed insulin for at least 90 days (Section 5.1, Inclusion Criterion [4]), and have an HbA1c value of ≥ 7.0 at screening). Prior to screening, subjects may also be treated with up to 3 types of oral antihyperglycemic medications (OAMs) with stable dosing for 90 days prior to screening, as specified in Section 5.1, Inclusion Criterion [5].

Subjects' basal insulin may be insulin glargine 100 U/mL (Basaglar or Lantus) once or twice daily, insulin glargine 300 U/mL once daily, insulin degludec U-100 once daily, insulin detemir U-100 once or twice daily, or neutral protamine Hagedorn (NPH) once or twice daily. Subjects may be on any approved injectable rapid-acting insulin analog.

Subjects must give written informed consent (approved by Lilly or its designee and the Ethical Review Board governing the site) before being allowed to participate in the study and before any screening assessments are performed.

Study investigator(s) will review the subject's records and/or history and screening test results/measurements to determine if the subject meets all inclusion and no exclusion criteria to qualify for participation in the study. All screening activities must be completed and reviewed before the subject begins the lead-in period.

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

5.1. Inclusion Criteria

Subjects are eligible to be included in the study only if they meet all of the following criteria at screening:

Informed consent

1. Capable of giving signed informed consent (approved by the Ethical Review Board governing the site) as described in Appendix 1 (Section 10.1.3), which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol. Capable of, willing, and desirous to do the following during the study:
 - a. adhere to a basal-bolus insulin MDI regimen and use of the study-provided prandial and study-required basal insulin according to the protocol and as prescribed by the principal investigator,
 - b. follow a general daily pattern of administering prandial insulin doses with 3 main meals per day (breakfast, lunch, and dinner),
 - c. inject insulin with the use of an insulin pen injection device according to written instructions,
 - d. perform fingerstick SMBG as required by the study schedule using the study glucose meter provided, and
 - e. comply with scheduled visits and study requirements.

Age

2. Subject must be at least 18 years of age at the time of signing the informed consent.

Type of subject and disease characteristics

3. Subjects diagnosed (clinically) with T2DM for ≥ 1 year prior to screening.
4. Treated for ≥ 90 days prior to screening with MDI therapy
 - a. On basal insulin (insulin glargine 100 U/mL [Basaglar or Lantus] or insulin glargine 300 U/mL, insulin detemir, insulin degludec U-100, or NPH insulin) in combination with at least 1 prandial injection of bolus insulin (insulin lispro 100 U/mL or 200 U/mL, insulin aspart, insulin glulisine, regular insulin, Fiasp® fast-acting insulin aspart), OR
 - b. premixed analog or human insulin regimens with any basal and bolus insulin combination injected at least twice daily except for IDegAsp injected once daily
5. May have been treated with up to 3 OAMs including metformin, sodium-glucose cotransporter (SGLT)-2 inhibitor, dipeptidyl peptidase (DPP)-4 inhibitor, sulfonylurea, meglitinide, or alpha glucosidase inhibitor in accordance with local regulations. The dose of all OAMs must have been stable for ≥ 90 days prior to screening
6. Have an HbA1c value $\geq 7.5\%$ and $\leq 10\%$ according to the central laboratory at screening

Weight

7. Body mass index ≤ 45.0 kg/m²

Sex

8. Male or female
 - a. Male: no contraception required
 - b. Female: contraceptive use should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Contraception requirements for subjects are provided in Appendix 4 (Section 10.4)
 - c. Female subjects of childbearing potential, who were not breastfeeding, pregnant, or intending to become pregnant during the study and agreed to use a reliable method of birth control for the duration of the study

Other inclusions

9. Willing to fill in ITSQ at baseline and Week 26
10. Have access to a telephone, or alternative means for close monitoring/communications
11. Have refrigeration at home or have ready access to refrigeration for storage of insulin therapy
12. Have a regular wake-sleep schedule (awake-work during the day and sleep during the night)

5.2. Exclusion Criteria

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

Medical conditions

1. Having any other condition (including known drug or alcohol abuse, psychiatric disorder including eating disorder) that precludes the subject from following and completing the protocol
2. Have been diagnosed, at any time, with T1DM or latent autoimmune diabetes in adults
3. Have hypoglycemia unawareness as judged by the investigator
4. Have had any episode of severe hypoglycemia (defined as requiring assistance due to neurologically disabling hypoglycemia) within the 6 months prior to screening
5. Have had 1 or more episodes of diabetic ketoacidosis or hyperglycemic hyperosmolar state within the 6 months prior to screening
6. Have a known diagnosis of secondary diabetes (for example, diabetes caused by hemochromatosis, acromegaly, chronic pancreatitis, or pancreatectomy)
7. Excessive insulin resistance defined as having received a total daily dose of insulin >2.0 U/kg at the time of screening
8. Have a history of or are being evaluated for bariatric surgery including Roux-en-Y gastric bypass surgery, gastric banding, and/or gastric sleeve
9. Have cardiovascular disease, within the past 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
10. Renal:
 - a. History of renal transplantation
 - b. Currently receiving renal dialysis
 - c. Serum creatinine >2.0 mg/dL ($177 \mu\text{mol/L}$) at screening
11. Hepatic: Have obvious clinical signs or symptoms of liver disease (for example, acute or chronic hepatitis or cirrhosis), or elevated liver enzyme measurements as indicated below at screening:
 - a. Total bilirubin level (TBL) $\geq 2X$ the upper limit of normal (ULN [with the exception of Gilbert's disease]) as defined by the central laboratory, or
 - b. Alanine aminotransferase (ALT) $\geq 3X$ ULN as defined by the central laboratory, or

- c. Aspartate aminotransferase (AST) $\geq 3X$ ULN as defined by the central laboratory.
- 12. 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
- 13. Having any hypersensitivity or allergy to any of the insulins or excipients used in this trial
- 14. Hematologic: Have had a blood transfusion or severe blood loss within 90 days prior to screening or have known hemoglobinopathy, anemia, or any other traits known to interfere with measurement of HbA1c
- 15. Have presence of clinically significant gastrointestinal disease (for example, clinically active gastroparesis associated with wide glucose fluctuations) in the investigator's opinion

Prior/concomitant therapy

- 16. Have used thiazolidinediones, glucagon-like peptide 1 receptor agonist, or pramlintide within 90 days prior to screening
- 17. Have used CSII within 90 days prior to screening
- 18. Glucocorticoid therapy: receiving chronic (lasting longer than 14 consecutive days) systemic glucocorticoid therapy (including intravenous, intramuscular, subcutaneous, or oral, but excluding topical, intraocular, intranasal, intraarticular, and inhaled preparations) or have received such therapy within 8 weeks immediately prior to screening with the exception of replacement therapy for adrenal insufficiency
- 19. Have used any weight loss drugs (for example, prescription orlistat, or over-the-counter weight loss medications) within 90 days prior to screening
- 20. Have used Lyumjev within 90 days prior to screening

Prior/concurrent clinical trial experience

- 21. Are currently enrolled in any other clinical trial involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
- 22. Have participated, within the last 30 days in a clinical trial involving an IP. If the previous IP has a long half-life, 3 months or 5 half-lives (whichever is longer) should have passed
- 23. Have previously completed or withdrawn from this study after having signed the ICF or any other study investigating Lyumjev after receiving at least 1 dose of the IP

Other exclusions

24. 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
25. Are Lilly employees or representatives (including employees, temporary contract workers, or designees responsible for the conduct of the study)
26. Are unable and/or unwilling to provide informed consent, to make themselves available for the duration of the study, or to abide by study procedures

5.3. Lifestyle Considerations

Subjects will be suggested to continue their usual exercise habits and generally follow a healthy meal plan eating 3 main meals per day throughout the course of the study.

5.4. Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Retests are also not allowed, except for cases in which results are not available from the original sample.

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

6. Study Intervention

Study intervention is defined as any investigational interventions, marketed products, placebo, or medical devices intended to be administered to a study subject according to the study protocol.

6.1. Study Interventions Administered

Intervention Name	Lyumjev
Type	Drug
Dose Formulation	Solution
Unit Dose Strength	100 U/mL in 3 mL cartridge
Dosage Level	Individualized dosing
Route of Administration	Subcutaneous
Packaging and Labeling	Lyumjev will be provided in prefilled pens. Each pen will be labeled as required per country requirement.
Sourcing	Provided centrally by the sponsor, subsidiary, or designee

6.1.1. Packaging and Labeling

Clinical study materials will be labeled according to the country's regulatory requirements.

Lyumjev and Humalog (insulin lispro 100 U/mL) and insulin glargine 100 U/mL (Basaglar) prefilled pens will be supplied by Lilly, or its representative, in accordance with current good manufacturing practices, and will be supplied with clinical trial lot numbers. Instruction for use for the prefilled devices will be provided.

The open-label prefilled pens will contain a concentration of 100 U/mL in 3 mL cartridges.

6.1.2. Medical Devices

The medical devices provided for use in the study are prefilled pens.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only subjects enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

3. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (that is, receipt, reconciliation, and final disposition records).
4. Further guidance and information for the final disposition of unused study interventions are provided in the Pharmacy Manual.
5. All insulin products must be stored at the investigative site under refrigerated conditions (between 2°C and 8°C) in a locked and secure place. Insulin must not be frozen.
6. In-use insulin should be maintained at room temperature. In-use insulin must not be used after 28 days.

6.3. Measures to Minimize Bias: Randomization and Blinding

Not applicable. This is an open-label study.

6.4. Study Intervention Compliance

When subjects self-administer study interventions at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by reviewing the subject's glycemic control, adherence to the visit and treatment schedule, adjustment of prandial and basal insulin doses as appropriate, and completion of study diaries. Compliance will be documented in the source documents. No specific study data will be collected for analysis of treatment compliance.

Subjects who are deemed noncompliant will receive additional diabetes education and training, as required, and the importance of compliance with the protocol will be reinforced. Subjects who, in the opinion of the investigator, are deemed consistently noncompliant may be discontinued from the study

6.5. Concomitant Therapy

The following concomitant therapies will not be allowed during the study:

- any oral or injectable medication intended for the treatment of diabetes mellitus other than study insulins and those specified in Section 6.5.1. Exception: short-term use of nonstudy insulins is permissible as outlined in Section 7.1.2.
- chronic (lasting longer than 7 consecutive days) systemic glucocorticoid therapy excluding topical, intraocular, intranasal, inhaled, or intraarticular preparations.
- weight loss drugs (for example, prescription orlistat, or over-the-counter weight loss medications).

6.5.1. Management of Oral Antihyperglycemic Medications

- Subjects are eligible for the study if they are using up to 3 of the following OAMs for the treatment of T2DM: metformin, sulfonylurea, SGLT-2 inhibitor, DPP-4 inhibitor, meglitinide, or alpha glucosidase inhibitor, or TZDs. The dose of all OAMs must have been stable for 90 days prior to screening.
- Subjects are not eligible for the study if they are using glucagon-like peptide 1 receptor agonist and pramlintide within 90 days.

- During the study lead-in and treatment periods, patients may continue the use of up to 3 of the following OAMs: metformin, SGLT-2 inhibitor, and/or DPP-4 inhibitor. Please also refer to Section 5.2.
- Other prestudy OAMs including sulfonylurea, meglitinides, and alpha glucosidase inhibitor agents, and TZDs will be discontinued at the beginning of the lead-in period (Visit 2).
- OAM dosing is to remain stable during study lead-in and treatment, except with the development of contraindications or for safety reasons.
- During study lead-in and treatment, all glycemic management is to be conducted by adjustment of basal and prandial insulin doses.
- In emergency situations, it may be necessary for patients be treated with a nonstudy insulin. This will be allowed for up to 14 consecutive days based on the physician's discretion (Section 7.1.2).

6.6. Dose Modification

6.6.1. Target Glucose Values for Titration of Insulin Therapy

The overall glycemic control goals for all subjects enrolled in the study are similar to those recommended by the American Diabetes Association (American Diabetes Association 2021). Preprandial glucose and PPG target values used to reach the glucose goals and for determination of titration in insulin therapy are listed in Table 6.1. Subjects will record SMBG values in the paper diary for 3 days within the 7 days before each visit for review of investigator for use in insulin titration.

Table 6.1. Summary of Glycemic Recommendations for Adults with Diabetes

Time of Target Blood Glucose Measurement	Self-Monitored Blood Glucose (SMBG) Target (Range)
Preprandial capillary plasma glucose	80–130 mg/dL ^a (4.2–7.2 mmol/L)
Peak postprandial capillary plasma glucose [†]	<180 mg/dL ^a (10.0 mmol/L)

^a More or less stringent glycemic goals may be appropriate for individual patients. [†]Postprandial glucose may be targeted if hemoglobin A1c goals are not met despite reaching preprandial glucose goals. Postprandial glucose measurements should be made 1 to 2 hours after the beginning of the meal, generally peak levels in patients with diabetes.

6.6.2. Basal Insulin Therapy and Titration

At Visit 2, subjects will be transferred to insulin glargine 100 U/mL (Basaglar) once daily if the subject enters the study on any other basal insulin regimen. The initial basal insulin dose may be unit-for-unit of the prestudy basal insulin regimen or 80% of the prior basal insulin daily dose if the patient was previously treated with insulin glargine 300 U/mL or twice-daily NPH insulin. At

Visit 2, subjects treated with 1 to 2 prandial insulin injections a day, premixed insulin, or prandial insulin other than Humalog 3 times a day will be transferred to Humalog administered 3 times a day, 0 to 2 minutes before meals. The total daily insulin dose should be divided between basal and bolus insulin doses at the discretion of the investigator. The initial basal insulin dose may be approximately 40% to 60% of the total daily dose.

Basal insulin should be adjusted during the lead-in period as instructed by the investigator in anticipation of increased activity and individual patient needs to achieve or maintain glucose targets with an emphasis on the prebreakfast BG. Reasonable efforts should be made to achieve these targets with basal insulin adjustment during the lead-in period. Adjustment of basal insulin doses may continue throughout the study treatment period to achieve or maintain glycemic targets and for safety reasons. The prescribed basal insulin dose is determined by, and the responsibility of, the principal investigator. Additional discussion between visits may be required to enable the subject to reach glycemic targets and will be determined by the investigator. The study basal insulin can be dosed at any time during the day and should be dosed at approximately the same time of day during study treatment. If there is a safety concern such as hypoglycemia, the dose timing of basal insulin may be changed per investigator discretion.

6.6.3. Study Prandial Insulin Therapy and Titration

At Visit 2, Humalog will be dispensed to all subjects for use throughout the lead-in period.

Subjects treated with 3 or more prandial injections a day of insulin lispro 100 U/mL or 200 U/mL, insulin aspart, insulin glulisine, regular insulin, or fast-acting insulin aspart will be transferred to Humalog (unit-for-unit). Subjects treated with 1 to 2 prandial insulin injections a day or premixed insulin will transition to 3 injections of Humalog per day with their 3 main meals. The initial distribution of prandial insulin may be equal (33% of total daily prandial dose prior to each meal). Otherwise, the investigator, in consultation with the subject, may alter the percentage of Humalog prescribed at each meal as clinically indicated such as by the subject's history of prandial insulin administration, SMBG levels, and meal pattern. The total daily insulin dose will be divided between basal and bolus insulin doses at the discretion of the investigator. The initial prandial insulin dose maybe approximately 40% to 60% of the total daily dose.

At Visit 3, subjects will stop taking Humalog and will transition to Lyumjev unit-for-unit. Subjects will administer their first dose of Lyumjev 0 to 2 minutes prior to the start of each meal (breakfast, lunch, and dinner). Subjects should have 3 doses of Lyumjev per day and eat 3 main meals per day (breakfast, lunch, and dinner) on a regular basis. Lyumjev should be titrated during the treatment period to reach optimal dosing and achieve glucose targets. The prescribed Lyumjev dose is determined by, and the responsibility of, the investigator. Modifications in the calculation of the insulin dose may be influenced by other clinical circumstances and safety considerations known to the investigator.

6.6.4. Transitioning off Study Prandial Insulin Therapy

Subjects will take their last doses of Lyumjev and basal insulin glargine prior to Visit 10 or at early discontinuation.

No special instructions for transition to nonstudy prandial insulin are necessary. The investigator, in consultation with the subject, will decide on the new prandial and basal insulin regimen, or other diabetes therapy, to be initiated.

6.7. Intervention after the End of the Study

Lyumjev will not be provided to the study subjects by the sponsor after completion of the study treatment period. Lyumjev will be marketed for use as prandial insulin. Other prandial and basal insulins, as well as other diabetes therapies, are available for the treatment of T2DM.

7. Discontinuation of Study Intervention and Subject Discontinuation/Withdrawal

7.1. Discontinuation of Study Treatment

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

7.1.1. Permanent Discontinuation of Study Treatment

Subjects will be discontinued from the IP under the following circumstances:

- The investigator may decide that the subject should stop IP. If this decision is made because of an AE, SAE, or a clinically significant laboratory value, the study drug is discontinued for that subject and appropriate measures are to be taken. Lilly or its designee is to be alerted.
- If the subject decides to stop IP.
- If the subject becomes pregnant.
- If the subject, for any reason, requires treatment with another basal insulin regimen or therapeutic agent (including addition of a second basal insulin injection) that has been demonstrated to be effective for treatment of the study indication. Discontinuation from IP should occur prior to introduction of the new agent.
- Use of prohibited concomitant medication, see Section 6.5.
- If the subject has not taken IP for more than 14 consecutive days.

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

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

7.1.2. Temporary Discontinuation from Study Treatment

During the study, subjects who temporarily discontinue the IP may be able to resume IP based on the following scenario:

Subject has not taken IP for 14 consecutive days or less:

- If the treatment regimen restarts within 14 days of when the subject initially stopped taking IP, subject may continue in the study and begin treatment again with IP. During this time, nonstudy insulins may have been used. If the subject decides to continue in the study, no early termination procedures will be completed. Subjects will continue study visits through the safety follow-up.

7.1.3. Discontinuation of Inadvertently Enrolled Subjects

If the sponsor or investigator identifies a subject who did not meet enrollment criteria and was inadvertently enrolled, a discussion must occur between the Lilly clinical research physician and the investigator to determine if the subject may continue in the study. If both agree it is medically appropriate to continue, the investigator must obtain documented approval from the Lilly clinical research physician to allow the inadvertently enrolled subject to continue in the study with or without treatment with IP.

7.2. Subject Discontinuation/Withdrawal from the Study

Some possible reasons that may lead to permanent discontinuation include

- Enrollment in any other clinical trial involving an IP or enrollment in any other type of medical research judged not to be scientifically or medically compatible with this study
- Participation in the study needs to be stopped for medical, safety, regulatory, or other reasons consistent with applicable laws, regulations, and good clinical practice (GCP)
- The investigator decides that the subject should be discontinued from the study
- The subject requests to be discontinued from the study
- The subject discontinues insulin lispro or study-allowed basal insulin regimen for >14 consecutive days in the lead-in period.

Patients who discontinue the study early but after randomization will have early discontinuation procedures performed as shown in the SoA (Section 1.3).

Subjects who discontinue during the lead-in period will have an early discontinuation visit and procedures.

If the subject 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 subject withdraws from the study, he or she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

A subject 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 subjects who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

8. Study Assessments and Procedures

- Study procedures and their timing are summarized in the SoA.
- Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study intervention.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

The efficacy measures will be evaluated as part of secondary objectives. The following are the secondary efficacy measures and samples will be collected for these measures at the times shown in the SoA (Section 1.3).

HbA1c

- Change in HbA1c from baseline to Week 26
- Percentage of subjects achieving HbA1c <7% at Week 26

PPG

- Change in 1- and 2-hour PPG values (estimated from SMBG) from baseline to Week 26

9-point SMBG

- Change in 9-point SMBG values from baseline at Week 26

Subjects will be trained to perform SMBG profiles as shown in the SoA (Section 1.3). The SMBG values are to be recorded in the diary with the time and date of measurement. It is expected that subjects will check SMBG 4 times a day (prior to each meal and bedtime, 4-point SMBG) routinely to aid in insulin titration. During the week prior to a study visit, subjects should record their SMBG 4 times a day on at least 3 days during the week.

The 9-point SMBG measurements should be collected at the beginning and end of the treatment period (Visit 3, and Visit 10, respectively) for at least 3 days during the week prior to the visit. The time points included in the 9-point SMBG measurements include:

- fasting
- 1 hour post breakfast
- 2 hours post breakfast
- pre lunch
- 1 hour post lunch
- 2 hours post lunch
- predinner

- 1 hour post dinner, and
- 2 hours post dinner.

Insulin dose

- Change in bolus insulin dose, basal insulin dose, and basal:bolus ratio from baseline to Week 26.

Doses of Lyumjev and Basaglar should be recorded in the diary at least 3 times during the week prior to a visit and should coincide with the 3 days that the 9-point SMBG values are recorded.

8.2. Safety Assessments

8.2.1. Primary Safety Assessment

Planned time points for all safety assessments are provided in the SoA (Section 1.3). The primary safety assessment is to check the risk of hypoglycemia from baseline through Week 26.

8.2.1.1. Hypoglycemia

Subjects should perform SMBG, whenever hypoglycemia may be suspected, either by symptoms experienced or perceived increased risk as related to dietary intake, physical activity, or inadvertent or atypical insulin dosing. All subjects will be instructed to treat a BG <70 mg/dL (3.9 mmol/L) as hypoglycemia. SMBG values should be recorded in the study diary and the questionnaire about hypoglycemia episodes should be completed for each event.

The subject should contact the site as necessary.

Hypoglycemia will be described using the following definitions:

- **Level 1 hypoglycemia:** glucose <70 mg/dL (3.9 mmol/L) and $\geq$ 54 mg/dL (3.0 mmol/L)
- **Level 2 hypoglycemia:** glucose <54 mg/dL (<3.0 mmol/L)
- **Level 3: Severe Hypoglycemia:** A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. Subjects have altered mental status and cannot assist in their own care, may be semiconscious or unconscious, or experience coma with or without seizures, and require assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of BG concentration to normal is considered sufficient evidence that the event was induced by a low BG concentration.

The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the subject to have required assistance and is not predicated on the report of a subject simply having received assistance.

All episodes of severe hypoglycemia must be reported as serious on the AE electronic case report form (eCRF) page and on the SAE eCRF page. Episodes of hypoglycemia not meeting the criteria for severe hypoglycemia should not be reported as an AE.

8.2.2. Secondary Safety Assessments

Secondary safety assessments include

- SAEs and treatment-emergent adverse events (TEAEs) from baseline through study follow-up
- Incidence and rate (events/subject/year) of severe hypoglycemia from baseline through Week 26
- Incidence and rate (events/subject/year) of nocturnal hypoglycemia (BG<54 mg/dL) from baseline through Week 26
- Incidence and rate (events/subject/year) of nocturnal and all documented hypoglycemic events (BG<70 mg/dL) from baseline through Week 26
- Change in body weight from baseline to Week 26
- Change in ITSQ scores from baseline to Week 26

Nocturnal hypoglycemia: any hypoglycemic event (documented hypoglycemia or probable symptomatic hypoglycemia, including severe hypoglycemia) that occurs between bedtime and waking (11:59 PM to 5:59 AM).

8.2.3. Other Safety Assessments

8.2.3.1. Physical Examinations

- A complete physical examination with measurement and record of height and weight

8.2.3.2. Vital Signs

- For each subject, vital sign measurements should be conducted according to the SoA (Section 1.3) including the study-specific requirements.

8.2.3.3. Electrocardiograms

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

8.2.3.4. Clinical Safety Laboratory Assessments

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

- All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.
 - If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
 - All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2) and Appendix 5 (Section 10.5), must be conducted in accordance with the SoA (Section 1.3), 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 subject management or are considered clinically significant by the investigator (for example, SAE or AE or dose modification), then report the information as an AE.

8.2.3.5. Safety Monitoring

8.2.3.5.1. Hypersensitivity Reactions

Many drugs, but particularly biologic agents, carry the risk of systemic hypersensitivity reactions.

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

8.2.3.5.2. Hepatic Monitoring

If a subject develops symptoms that warrant liver function assessment, liver function tests as detailed in Appendix 5 (Section 10.5) should be performed. If these tests are abnormal, clinical and laboratory monitoring should be initiated by the investigator.

Laboratory tests including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur.

8.2.3.6. Subject-Reported Outcomes

Subject-reported outcomes will be measured using the ITSQ at baseline and Week 26.

The ITSQ is a validated instrument containing 22 items that assess treatment satisfaction for subjects taking insulin. Items are measured on a 7-point scale, in which lower scores reflect better outcomes. The items that constitute the 5 domains of satisfaction are categorized as

- Inconvenience of Regimen (5 items)
- Lifestyle Flexibility (3 items)
- Glycemic Control (3 items)

- Hypoglycemic Control (5 items), and
- Insulin Delivery Device (6 items).

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Change at Week 26 from Week 0 will be analyzed using the ANCOVA model, with the Week 0 value of the response variable as covariate.

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

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

- AEs
- SAEs
- product complaints

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

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

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

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

8.3.1. Timing and Mechanism for Collecting Events

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

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

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

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

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

8.3.2. Method of Detecting AEs and SAEs

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

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

8.3.3. Follow-up of AEs and SAEs

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

8.3.4. Trial Level Safety Review

Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. Details for Trial Level Safety Review are found in the Trial Level Safety Review Plan.

8.3.5. Regulatory Reporting Requirements for SAEs

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

- The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs), and investigators.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.6. Pregnancy

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

- If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).
- Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.7. Product Complaints

A product complaint is any written, electronic, or oral communication that alleges a deficiency related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a Lilly product after it is released for distribution. When the ability to use the product safely is impacted, the following are also product complaints:

- a. deficiencies in labeling information, and
- b. use errors for device or combination products due to ergonomic design elements of the product

The sponsor collects product complaints on IPs, medical devices, and drug delivery systems used in clinical studies to ensure the safety of study subjects, monitor quality, and to facilitate process and product improvements. Complaints are also collected on comparators and other clinical trial material supplied, as required.

Subjects will be instructed to contact the investigator as soon as possible if he or she has a complaint or problem with the IP or device, so that the situation can be assessed.

Product complaints will be reported by the investigator to the sponsor per instructions provided on the study-specific Product Complaint Form.

As required by local regulations, and per instructions on the Product Complaint Form, the investigator will report to the sponsor and to their IRB/IEC any unanticipated adverse device effect or unanticipated problem that resulted in an SAE, or any device-related product complaint that could have led to an SAE had precautions not been taken.

8.4. Treatment of Overdose

Excess insulin administration may result in hypoglycemia and will be managed as discussed in Section 8.2.1.1.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the subject.

8.5. Pharmacokinetics

PK 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 will not be assessed in this study.

8.10. Medical Resource Utilization and Health Economics

Medical resource utilization parameters will not be evaluated in this study.

9. Statistical Considerations

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

9.1. Statistical Hypotheses

The primary objective is to estimate the incidence and rate of all documented hypoglycemia with BG <54 mg/dL. There will be no statistical hypothesis tested.

9.1.1. Multiplicity Adjustment

Not applicable.

9.2. Analyses Sets

For the purposes of analysis, the following analysis sets are defined:

Subject Analysis Set	Description
Full analysis set	All <i>enrolled subjects who are exposed to study intervention.</i>

The full analysis set will be used for all analyses.

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

Unless otherwise specified, all efficacy and safety analyses will be conducted on the full analysis set. Confidence intervals will be calculated at 95%, 2-sided. Baseline is defined as the last nonmissing measurement at or before the treatment assignment (Visit 3) unless otherwise specified. An ANCOVA will be used to analyze continuous variables that are planned to be collected only for baseline and endpoint, and a restricted-maximum-likelihood-based, mixed model repeated measures (MMRM) analysis will be used to analyze continuous longitudinal variables collected at baseline and more than 1 scheduled postbaseline visits.

For the MMRM analyses, all the longitudinal observations at each scheduled postbaseline visit will be included in the analysis. The model will include fixed class effect of visit and the covariate of baseline. An unstructured covariance structure will be used to model the within-subject errors. Significance tests will be based on least-squares means and Type III tests. SAS® PROC MIXED will be used to perform the analysis. The Kenward-Roger approximation will be used to estimate denominator degrees of freedom.

The ANCOVA model will include baseline as a covariate. Unless otherwise stated, missing endpoints will be imputed using the last-observation-carried-forward approach, using only postbaseline data.

9.3.2. Primary Endpoint

The proportion of patients with at least 1 documented hypoglycemic event with BG < 54 mg/dL (incidence) will be summarized. The 1-year rate of documented hypoglycemia will be summarized. The aggregate rate will be calculated using the total number of hypoglycemia episodes divided by the cumulative days on treatment from all patients, multiplied by 365.

9.3.3. Secondary Endpoint

The secondary endpoints of the incidence and rate of all documented hypoglycemia with BG < 70 mg/dL, nocturnal hypoglycemia, and severe hypoglycemia will be summarized as described for the primary endpoint.

The analyses of HbA1c, dose, SMBG values, and weight will be performed using the MMRM and ANCOVA models described above.

9.3.4. Safety Analyses

Safety measures will include AEs, vital signs, and treatment exposure. Events that are newly reported after the first dose of IP used or reported to worsen in severity from baseline (details will be described in the SAP) will be considered TEAEs. Analyses of AEs will be descriptive and include all data collected during the treatment period. AEs during the lead-in period and the safety follow-up period will be provided in a listing. SAEs, AEs reported as the reason for discontinuation from the IP or study, and TEAEs will be summarized in tables using the Medical Dictionary for Regulatory Activities Preferred Term sorted by decreasing frequency. TEAEs will also be summarized by preferred term sorted by decreasing frequency within the system organ class for all TEAEs and by maximum severity. For events that are gender specific (as defined by Medical Dictionary for Regulatory Activities), the denominator and computation of the percentage will include only patients from the given gender. The number and proportion of patients with at least 1 event for each type of event will also be summarized.

Continuous safety variables, as well as the change from baseline for these variables, will be summarized either using MMRM or ANCOVA models.

Subject responses to the ITSQ will be reported as overall and domain scores at Weeks 0 and 26. These scores will be summarized by descriptive statistics (mean, median, standard deviation, standard deviation, minimum, and maximum) by visit. Change at Week 26 from Week 0 will be analyzed using the ANCOVA model, with the Week 0 value of the response variable as covariate, after applying the appropriate method to missing values described in Section 8.2.3.6.

9.4. Interim Analysis

An interim analysis of baseline characteristics will be done when all patients have been administered at least 1 dose of the investigational product. Limited information is available on baseline characteristics of patients in India with T2DM on basal bolus insulin therapy. This analysis will help understand this missing information.

9.5. Sample Size Determination

Assuming a 30% screen failure rate, approximately 215 subjects will be screened to achieve approximately 150 enrolled to study intervention and evaluable subjects. Assuming a drop-out rate of 30%, CCI [REDACTED]

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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 Council for Harmonisation (ICH) GCP guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, IB, and other relevant documents (for example, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- 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 subjects.
- 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 subjects under their responsibility and adherence to requirements of 21 Code of Federal Regulations, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

No financial disclosure information will be collected.

10.1.3. Informed Consent Process

- The investigator or his or her representative will explain the nature of the study, including the risks and benefits, to the subject or his or her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 Code of Federal Regulations 50, local regulations, ICH guidelines, 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 subject 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.
- Subjects 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 subject or the subject's legally authorized representative and is kept on file.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the sponsor. Any subject records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only; subject names or any information that would make the subject identifiable will not be transferred.
- The subject must be informed that his or her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject who will be required to give consent for his or her data to be used as described in the informed consent.
- The subject must be informed that his or her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- 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.

10.1.5. Committees Structure

No data monitoring committee is planned for this study.

10.1.6. Dissemination of Clinical Study Data

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 provides access to all individual subject data collected during the trial, after anonymization, except for PK or genetic data. Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

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

10.1.7. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or eCRF unless transmitted to the sponsor or designee electronically (for example, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the case report form (CRF).
- The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.
- The sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The sponsor assumes accountability for actions delegated to other individuals (for example, contract research organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for the time period outlined in the clinical trial agreement unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.
- In addition, the sponsor or its representatives will periodically check a sample of the subject 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 system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the subject 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 [10.1.7](#).

10.1.9. Study and Site Start and Closure

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

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 subjects 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 subject and assures appropriate subject therapy and/or follow-up.

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, an interim analysis based on the baseline characteristics of the study population and later the completed results of this study may be submitted for publication in a peer-reviewed journal.

10.1.11. Investigator Information

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

10.2. Appendix 2: Clinical Laboratory Tests

- The tests detailed below will be performed by the central laboratory unless designated as local in the SoA and in the table below.
- 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 subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.
- Investigators must document their review of each laboratory safety report.
- Pregnancy testing will be done as specified in Section 1.3.

Clinical Laboratory Tests^a

Hematology	Clinical Chemistry (Serum Concentrations of)
Hemoglobin	Sodium
Hematocrit	Potassium
Erythrocyte count (RBC)	Total bilirubin
Mean cell volume	Direct bilirubin
Mean cell hemoglobin concentration	Alkaline phosphatase
Leukocytes (WBC)	Chloride
Neutrophils, segmented	Blood urea nitrogen (BUN)
Lymphocytes	Creatinine
Monocytes	Glucose
Eosinophils	Alanine aminotransferase (ALT)
Basophils	Aspartate aminotransferase (AST)
Platelets	Magnesium
	Uric acid
Pregnancy Test (females only)^b	Total protein
Follicle-stimulating hormone^c	Albumin
	Calcium
	Creatine kinase (CK)
	HbA1c
	Lipid Panel
	High-density lipoprotein (HDL)
	Low-density lipoprotein (LDL)
	Very low-density lipoprotein (VLDL)
	Cholesterol
	Triglycerides

Abbreviations: HbA1c = hemoglobin A1c; IP = investigational product; RBC = red blood cell; WBC = white blood cell.

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

^b Serum pregnancy test must be performed in women of childbearing potential at Visit 1 followed by a urine pregnancy test within 24 hours prior to IP exposure at Visit 3 and at other times at the investigator's discretion.

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

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

Events Meeting the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease). • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New 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. • The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE. Also, “lack of efficacy” or “failure of expected pharmacological action” also constitutes an AE or SAE.

Events <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 subject’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 subject's condition.
- Medical or surgical procedure (for example, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

SAE is defined as any untoward medical occurrence that, at any dose:	
a. Results in death	
a. Is life threatening	The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject 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.
b. Requires inpatient hospitalization or prolongation of existing hospitalization	• In general, hospitalization signifies that the subject 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 preexisting condition that did not worsen from baseline is not considered an AE.
c. Results in persistent disability/incapacity	• The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (for example, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
d. Is a congenital anomaly/birth defect	

Abnormal pregnancy outcomes (for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.
e. 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 subject or may require medical or surgical intervention to prevent 1 of the other outcomes listed in the above definition. These events should usually be considered serious. - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product Complaint
- A product complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also product complaints: - Deficiencies in labeling information, and - Use errors for device or drug-device combination products due to ergonomic design elements of the product. - Product complaints related to study interventions used in clinical trials are collected to ensure the safety of subjects, monitor quality, and to facilitate process and product improvements. - Investigators will instruct subjects 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 (for example, 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 subject's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate (e) 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 subject's medical records to the sponsor or designee in lieu of completion of the (e) 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 subject identifiers, with the exception of the subject 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 subject.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- 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 Product Information, for marketed products, in his or her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he or she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred, and the investigator has minimal information to include in the initial report to 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 or her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is 1 of the criteria used while 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.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken

off-line, then the site can report this information on a paper SAE form (see next section).

- Contacts for SAE reporting can be found in the paper SAE form.

SAE Reporting via Paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to Lilly (Global Patient Safety).
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in the SAE paper form.

10.3.6. Regulatory Reporting Requirements

SAE Regulatory Reporting

- Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities toward the safety of subjects 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 an SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the Product Information 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 postmenopausal unless permanently sterile (see below).

If fertility is unclear (for example, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the 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 subject's medical records, medical examination, or medical history interview.

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

Contraception guidance:

Male subjects

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

Female subjects

WOCBP and women not of childbearing potential are eligible to participate according to the definitions above and the following contraception criteria:

1. WOCBP who are abstinent (if this is complete abstinence, as their preferred and usual lifestyle) or in a same-sex relationship (as part of their preferred and usual lifestyle) must agree to either remain abstinent or stay in a same-sex relationship without sexual

relationships with males. Periodic abstinence (for example, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence just for the duration of a trial, and withdrawal are not acceptable methods of contraception.

2. Otherwise, WOCBP participating must agree to use 1 highly effective method (<1% failure rate) of contraception, or a combination of 2 effective methods of contraception for the entirety of the study.
 - a. WOCBP participating must test negative for pregnancy prior to initiation of treatment as indicated by a negative serum pregnancy test at the screening visit followed by a negative urine pregnancy test within 24 hours prior to exposure. (Any pregnancy testing subsequent to this initial test should be based on compound-specific concerns and is not mandated by this guidance.)
 - b. Either 1 highly effective method of contraception (such as combination oral contraceptives, implanted contraceptives, or intrauterine device) or a combination of 2 effective methods of contraception (such as male or female condoms with spermicide, diaphragms with spermicide, or cervical sponges) will be used. The subject may choose to use a double-barrier method of contraception. Barrier protection methods without concomitant use of a spermicide are not a reliable or acceptable method. Thus, each barrier method must include use of a spermicide. It should be noted that the use of male and female condoms as a double-barrier method is not considered acceptable due to the high failure rate when these methods are combined.

Collection of pregnancy information

Female subjects who become pregnant

- The investigator will collect pregnancy information on any female subject 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 subject's pregnancy.
- The subject will be followed up to determine the outcome of the pregnancy. The investigator will collect follow-up information on the subject 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 poststudy 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 subjects, he or she may learn of an SAE through spontaneous reporting.
- Any female subject who becomes pregnant while participating in the study be withdrawn from the study.

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

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

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

Clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver test results, should be initiated by the investigator in consultation with the Lilly-designated medical monitor.

At a minimum, this evaluation should include physical examination and a thorough medical history, including symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, history of concomitant medications (including over-the-counter), herbal and dietary supplements, history of alcohol drinking, and other substance abuse.

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

Comprehensive hepatic evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

If a subject with baseline results of...	Develops the following elevations:
ALT or AST <1.5X ULN	ALT or AST ≥3X ULN with hepatic signs/symptoms ^a , <u>or</u> ALT or AST ≥5X ULN
ALP <1.5X ULN	ALP ≥3X ULN
TBL <1.5X ULN	TBL ≥2X ULN (except for subjects with Gilbert's syndrome)
ALT or AST ≥1.5X ULN	ALT or AST ≥2X baseline with hepatic signs/symptoms, ^a <u>or</u> ALT or AST ≥3X baseline

If a subject with baseline results of...	Develops the following elevations:
ALP $\geq 1.5X$ ULN	ALP $\geq 2X$ baseline
TBL $\geq 1.5X$ ULN	TBL $\geq 1.5X$ baseline (except for subjects with Gilbert's syndrome)

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; TBL = total bilirubin level; ULN = upper limit of normal.

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

At a minimum, this evaluation should include a physical examination and a thorough medical history, as outlined above, as well as tests for prothrombin time, international normalized ratio; tests for viral hepatitis A, B, C, or E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or computed tomography scan).

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

Additional hepatic data collection

Additional hepatic safety data collection in hepatic safety CRFs should be performed in study subjects who meet 1 or more of the following 5 conditions:

1. Elevation of serum ALT to $\geq 5X$ ULN on 2 or more consecutive blood tests (if baseline ALT $<1.5X$ ULN)
 - a. In subjects with baseline ALT $\geq 1.5X$ ULN, the threshold is ALT $\geq 3X$ baseline on 2 or more consecutive tests
2. Elevation of TBL to $\geq 2X$ ULN (if baseline TBL $<1.5X$ ULN) (except for cases of known Gilbert's syndrome)
 - a. In subjects with baseline TBL $\geq 1.5X$ ULN, the threshold should be TBL $\geq 2X$ baseline
3. Elevation of serum ALP to $\geq 2X$ ULN on 2 or more consecutive blood tests (if baseline ALP $<1.5X$ ULN)
 - a. In subjects with baseline ALP $\geq 1.5X$ ULN, the threshold is ALP $\geq 2X$ baseline on 2 or more consecutive blood tests
4. Hepatic event considered to be an SAE
5. Discontinuation of study drug due to a hepatic event

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

Hepatic monitoring laboratory tests

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

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

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

Blood	
Urine	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio.

- a This is not required if anti-actin antibody is tested.
- b Reflex/confirmation dependent on regulatory requirements and/or testing availability.
- c This is not required if antismooth muscle antibody (ASMA) is tested.
- d Assayed by investigator-designated local laboratory ONLY; no central testing available.

10.6. Appendix 6: Provisions for Changes in Study Conduct during Exceptional Circumstances

Implementation of this appendix

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

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

Additional consent from the subject will be obtained, if required, for:

- participation in remote visits, as defined in Section "Remote Visits"
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in study conduct during exceptional circumstances

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

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

Remote visits***Types of remote visits***

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, concomitant medications, symptom-directed physical examination through verbal assessment, AE/SAEs, and review of subject diary (including insulin dose assessment, hypoglycemic event review and study compliance).

Other alternative locations: Procedures that may be done at an alternate location, other than those listed above, include laboratory draws.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including subject diaries)

When a subject is unable to go to the site to receive study supplies during normal on-site visits, the site should work with the sponsor to determine appropriate actions. These actions may include

- asking the subject to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the subject's designee to go to the site and receive study supplies on a subject's behalf, and
- arranging delivery of study supplies

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of subject's receipt of study supplies.
- While delivering supplies to a location other than the study site (for example, subject's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).

- Instructions may be provided to the subject or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

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

- If screening is paused for less than 42 days from Visit 1: the subject will proceed to Visit 2 per the SoA.
 - The site should conduct the next visit if the subject'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 subject's consent and document this confirmation in the source documentation.
- If screening is paused for more than 42 days from Visit 1: The subject must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The subject can reconsent and be rescreened as a new subject. The screening procedures per the SoA should be followed.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, subjects should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study. The primary endpoint visit (Visit 10) should be completed as per the usual SoA whenever possible and safe to do so.

This table describes the allowed adjustments to visit windows upon approval from the sponsor

Visit Number	Tolerance
Visit 2 through Visit 4	Visit window for these visits may be adjusted to within 7 days (before or after) of the visit as represented by the SoA.
Visits 5-10, 801, ED	Visit window for these visits may be adjusted to within 14 days (before or after) of the visit as represented by the SoA.

For subjects whose visits have extended windows, additional study intervention may need to be provided to avoid interruption and maintain overall integrity of the study.

Documentation*Changes to study conduct will be documented*

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

Source documents at alternate locations

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

10.7. Appendix 7: Abbreviations

Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
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.
companion diagnostic	An in vitro diagnostic device (assay or test) that provides information that is essential for the safe and effective use of a corresponding therapeutic product
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
CSII	continuous subcutaneous insulin infusion
ECG	electrocardiogram
eCRF	electronic case report form
enroll	The act of assigning a subject to a treatment. Subjects who are enrolled in the study are those who have been assigned to a treatment.
enter	Subjects entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
HbA1c	hemoglobin A1c
HDL	high-density lipoprotein
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation

informed consent	A process by which a subject 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 subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form.
IP	investigational product. A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form.
IRB	Institutional Review Board
ITSQ	Insulin Treatment Satisfaction Questionnaire
LDL	low-density lipoprotein
MDI	multiple daily injection
MMRM	mixed model repeated measures
OAM	antihyperglycemic medication
NPH	neutral protamine Hagedorn
PK	pharmacokinetics
SAE	serious adverse event
SAP	statistical analysis plan
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.
SGLT	sodium-glucose cotransporter
SMBG	self-monitored blood glucose
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	upper limit of normal
VLDL	very-low-density lipoprotein
WOCBP	women of childbearing potential

10.8. Appendix 8: Protocol Amendment History

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

Amendment b

This amendment was created to capture changes that were not captured in amendment a. This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to incorporate Insulin Treatment Satisfaction Questionnaire (ITSQ) as a secondary safety endpoint.

Changes and rationale are summarized in the following table. Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Inclusion of change in ITSQ scores from baseline to Week 26	To estimate the impact of flexible dosing of mealtime insulin on the quality of life in patients with T2DM in India
1.3 Schedule of Activities	Inclusion of ITSQ assessment at Week 0 (Visit 3) and Week 26 (Visit 10)	To estimate the impact of flexible dosing of mealtime insulin on the quality of life in patients with T2DM in India
2.1 Study Rationale	Inclusion of reference Linnebjerg et al. 2020	Reference to text on PK of insulin
2.2 Background	Inclusion of references, Blevins et al. 2020 and Klaff et al. 2020 Addition of basal to insulin glargine Deleted text about no new safety issues being identified in the Phase 3	Reference to publication related to Phase 3 Studies ITRM and ITRN Based on Phase 3 studies Based on Phase 3 study results
3 Objectives, Endpoint and Estimands	Inclusion of change in ITSQ scores from baseline to Week 26 in the secondary endpoints	To estimate the impact of flexible dosing of mealtime insulin on the quality of life in patients with T2DM in India
5 Inclusion criteria	Inclusion of willingness to fill in ITSQ at baseline and Week 26	Based on inclusion of ITSQ as a secondary endpoint
8.2.2 Secondary	Change in ITSQ scores from baseline to Week 26	Based on inclusion of ITSQ as a secondary endpoint

Section # and Name	Description of Change	Brief Rationale
Safety Assessments		
8.2.3.6 Subject-Reported Outcomes	Inclusion of a description of the ITSQ instrument and calculation of the ITSQ scores	Based on inclusion of ITSQ as a secondary endpoint
8.3.4 Trial Level Safety-Review	Inclusion of details for trial level safety review	As per template
9.3.4 Safety Analyses	Inclusion of ITSQ statistical analyses	Based on inclusion of ITSQ as a secondary endpoint
Sec 9.4 Interim Analysis	Inclusion of interim analysis timing and rationale	Limited information is available on baseline characteristics of patients in India with T2DM on basal bolus insulin therapy
10.1.10 Publication Policy	Inclusion of publication of interim analysis based on baseline characteristics of the study population	Based on inclusion of interim analysis
10.7 Abbreviations	Inclusion of ITSQ	Abbreviation is used throughout the protocol amendment
10.8 Protocol Amendment History	Inclusion of protocol amendment history	As per the template
11 References	Included new references	References are cited in the study rationale and background section

Amendment a

This amendment is considered to be nonsubstantial.

Overall Rationale for Amendment a

The primary rationale for this amendment is to include ITSQ as a secondary safety endpoint. Changes and rationale are summarized in the table below. Minor editorial changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	Inclusion of change in ITSQ scores from baseline to Week 26	Currently available analog bolus insulin needs to be given 15 to 20 minutes before meals whereas, ultra rapid insulin lispro (URLi) has the flexibility of dosing up to 2 min before meals, and in some cases after meals as well. The objective was to estimate the impact of this flexible dosing of mealtime insulin on the quality of life in patients with T2DM in India. Compared with Humalog, URLi had a 10-min faster onset of action, a 3-fold greater insulin action in the first 30 min, a 35% reduction in insulin action beyond 4 h, and a 44-min shorter duration of action across all populations and dose range. (reference: Leohr J, Dellva MA, Carter K, et al. Ultra Rapid Lispro (URLi) accelerates insulin lispro absorption and insulin action vs Humalog® consistently across study populations: a pooled analysis of pharmacokinetic and glucodynamic data. <i>Clin Pharmacokinet.</i> 2021;60:1423-1434)
1.3 Schedule of Activities	Inclusion of ITSQ assessment at Week 0 (Visit 3) and Week 26 (Visit 10)	To estimate the impact of flexible dosing of mealtime insulin on the quality of life in patients with T2DM in India.
2.1 Study Rationale	Inclusion of reference Linnebjerg et al. 2020	Reference to text on PK of insulin
2.2 Background	Inclusion of references Blevins et al. 2020 and Klaff et al. 2020 Addition of basal to insulin glargine	Reference to publication related to Phase 3 Studies ITRM and ITRN Based on Studies ITRM and ITRN Based on Phase 3 study results

Section # and Name	Description of Change	Brief Rationale
	Deleted text about no new safety issues being identified in the Phase 3	
3 Objectives, Endpoints and Estimands	Inclusion of change in ITSQ scores from baseline to Week 26 in the secondary endpoints	To estimate the impact of flexible dosing of mealtime insulin on the quality of life in patients with T2DM in India
5 Inclusion criteria	Inclusion of willingness to fill in Insulin Treatment Satisfaction Questionnaire (ITSQ) at baseline and Week 26	Based on inclusion of ITSQ as a secondary endpoint
8.2.2 Secondary Safety Assessments	Change in ITSQ scores from baseline to Week 26	Based on inclusion of ITSQ as a secondary endpoint
8.2.3.6 Subject-Reported Outcomes	Included the following: Subject-reported outcomes will be measured using the ITSQ at baseline and Week 26. The ITSQ is a validated instrument containing 22 items that assess treatment satisfaction for subjects taking insulin. Items are measured on a 7-point scale, in which lower scores reflect better outcomes. The items that constitute the 5 domains of satisfaction are categorized as • Inconvenience of Regimen (5 items) • Lifestyle Flexibility (3 items) • Glycemic Control (3 items) • Hypoglycemic Control (5 items), and • Insulin Delivery Device (6 items).	Based on inclusion of ITSQ as a secondary endpoint

[illegible]

Section # and Name	Description of Change	Brief Rationale
	CCI Change at Week 26 from Week 0 will be analyzed using the analysis of covariance (ANCOVA) model, with the Week 0 value of the response variable as covariate.	
8.3.4 Trial Level Safety-Review	Included the following: Lilly will periodically review evolving aggregate safety data within the study by appropriate methods. Details for Trial Level Safety Review are found in the Trial Level Safety Review Plan	As per the template
9.3.4 Safety Analyses	Included the following: Subject responses to the ITSQ will be reported as overall and domain scores at Weeks 0 and 26. These scores will be summarized by descriptive statistics (mean, median, standard deviation, standard deviation, minimum, and maximum) by visit. Change at Week 26 from Week 0 will be analyzed using the ANCOVA model, with the Week 0 value of the response variable as covariate, after applying the appropriate method to missing values described in Section 8.2.3.6.	Based on inclusion of ITSQ as a secondary endpoint
9.4 Interim Analysis	Included the following: An interim analysis of baseline characteristics will be done when all patients have been administered at least 1 dose of the investigational product. Limited information is available on baseline characteristics of patients in India with T2DM on basal bolus insulin therapy. This	Limited information is available on baseline characteristics of patients in India with T2DM on basal bolus insulin therapy

Section # and Name	Description of Change	Brief Rationale
	analysis will help understand this missing information.	
10.1.10 Publication Policy	Included the following: In accordance with the sponsor's publication policy, an interim analysis based on the baseline characteristics of the study population and later the completed results of this study may be submitted for publication in a peer-reviewed journal.	Based on inclusion of interim analysis
10.7 Abbreviations	Inclusion of ITSQ	Abbreviation is used throughout the protocol amendment
10.8 Protocol Amendment History	Inclusion of protocol amendment history	As per the template
11 References	Included new references	References are cited in the study rationale and background section

11. References

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Approval	PPD Medical Director 03-Jan-2024 11:37:04 GMT+0000
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Approval	PPD Statistician 03-Jan-2024 12:16:20 GMT+0000
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