Protocol J1I-MC-GZBU (d)

A Phase 2b, Double-Blind Study to Investigate the Effect of Retatrutide on Renal Function in Participants With Overweight or Obesity and Chronic Kidney Disease With or Without Type 2 Diabetes

NCT05936151

Approval Date: 10-Feb-2025

Title Page

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Protocol Title: A Phase 2b, Double-Blind Study to Investigate the Effect of LY3437943 on Renal Function in Participants with Overweight or Obesity and Chronic Kidney Disease with or without Type 2 Diabetes

Protocol Number: J1I-MC-GZBU

Amendment Number: d

Compound: Retatrutide (LY3437943)

Brief Title: A Study to Investigate the Effect of LY3437943 on Renal Function in Participants with Chronic Kidney Disease with or without Type 2 Diabetes

Study Phase: 2b

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, IN, USA 46285

Regulatory Agency Identifier Number(s)

EU trial number: 2023-504583-42-00

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

Document ID: VV-CLIN-120345

Medical Monitor Name and Contact Information will be provided separately.

Approved on 10 Feb 2025 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Amendment c	*17-Jun-2024*
Amendment b	*18-Oct-2023*
Amendment a	*24-Jun-2023*
Original Protocol	*17-Mar-2023*

Amendment d

This amendment is considered to be substantial.

The amendment is considered to be substantial because it is likely to have a significant impact on the safety or the rights of the study participants.

Overall rationale for the amendment:

The primary purpose of this amendment is to

- add new AESIs CCI [redacted]

The table below details these and other changes. Minor error corrections and formatting changes are not reflected in the table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	In the SoA table for the "Fasting Visit" row: Added "X" at Visit 5 and Visit 801.	Correction, since there is weight collection at these visits that should be carried out in the fasting state.
	In the SoA table for the "Concomitant medications" row: Updated comment for monitoring and routinely assessing the need to adjust or discontinue concomitant medications.	For consistency with recommendations in Sections 6.9.1, 5.3.1, 5.3.2, and 10.13.
	In the SoA table for the "Review diet and physical activity goals" row: Added a comment.	For consistency with recommendations in Section 5.3.1 and 5.3.2.
	In the SoA table for the "Urine pregnancy (local)" row: Changed Visits 16 and 24 to Visits 7 and 9 in the comments.	Correction.

Section # and Name	Description of Change	Brief Rationale
5.3.1. Meals and Dietary Restrictions	Specified in the subheading that individualized counseling for a healthy diet is "for the CKD population". Provided more detailed guidance for CKD.	To ensure the study site is aware of the minimum guidance on a healthy diet and hydration needs for individuals with CKD.
5.3.2. Monitoring Nutritional Needs	Updated to ensure consistency with the new guidance of meal and dietary restrictions and added more guidance to evaluate poor nutrition and dehydration.	To ensure the study site is aware of the minimum guidance to manage poor nutrition and dehydration.
6.6. Dose Modification	CCI [redacted]	CCI [redacted]
6.6.1. Management of Participants with Intolerable Gastrointestinal Symptoms	At the end of the section, updated a statement to state that all participants who permanently discontinue study intervention should be discontinued from the study.	Correction.
6.6.3. Management of Participants with Poor Nutrition or Dehydration 10.12. Appendix 12: Management of Poor Nutrition and Dehydration	Added a new section with an accompanying flow chart in the new Appendix 12.	To facilitate the management of participants with poor nutrition or dehydration.
7.1.1. Permanent Discontinuation of Study Intervention	Added 2 new discontinuation criteria.	To facilitate the management of participants with poor nutrition or dehydration and perceived excessive weight loss, despite good nutrition management.
8.3.4.16. CCI [redacted]	CCI [redacted]	To align the protocol with updated IB and risk profile.
8.3.4.17. CCI [redacted]	CCI [redacted]	To align the protocol with updated IB and risk profile.

Section # and Name	Description of Change	Brief Rationale
10.2. Appendix 2: Clinical Laboratory Tests	Added "Magnesium" under Clinical Chemistry Panel. Added new sub-section 10.2.3 to describe centrally available laboratory tests related to assessment of nutritional status and micronutrient levels.	To facilitate monitoring and management of participants with or at risk of poor nutrition or dehydration.
10.13. Appendix 13: Considerations for Concomitant Medications	Added a new section	To provide more detailed recommendations on the management of concomitant medications in the setting of weight management.
10.16. Appendix 16. Protocol Amendment History	Updated this section	To reflect the previous version of protocol amendment (c) summary of changes.

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 2b, Double-Blind Study to Investigate the Effect of LY3437943 on Renal Function in Participants with Overweight or Obesity and Chronic Kidney Disease with or without Type 2 Diabetes

Brief Title: A Study to Investigate the Effect of LY3437943 on Renal Function in Participants with Chronic Kidney Disease with or without Type 2 Diabetes

Regulatory Agency Identifier Number(s):

EU trial number: 2023-504583-42-00

Rationale:

Study GZBU is a Phase 2b study to investigate the mechanism(s) of action of retatrutide in the kidney, in participants with overweight or obesity and coexisting chronic kidney disease (CKD), with or without Type 2 diabetes (T2D).

Study GZBU will investigate the effects of 24 weeks of treatment with retatrutide on renal hemodynamics, including measured glomerular filtration rate (mGFR) using iohexol clearance, as well as renal blood flow (RBF), filtration fraction, renal oxygenation, renal injury, renal function, renal and abdominal adipose tissue, and renal diffusion, assessed using non-invasive, multimodal magnetic resonance imaging (MRI) techniques.

Findings from this study will help explain the effects of retatrutide on renal function and inform potential future kidney outcomes studies.

Objectives, Endpoints, and Estimands:

Objectives	**Endpoints**
Primary	
To compare the effect of retatrutide to placebo on mGFR from baseline to Week 24	Change in GFR (mL/min per 1.73 m^2) using iohexol clearance
Secondary	
To compare the effect of retatrutide to placebo on mGFR from baseline to Week 16	Change in GFR (mL/min per 1.73 m^2) using iohexol clearance
To compare the effect of retatrutide to placebo from baseline to Week 16 and baseline to Week 24 for	

Objectives	Endpoints
• Glomerular and tubular functional measurements	• change in o UACR[a] o creatinine-corrected FENa o filtration fraction estimated from mGFR and MRI-assessed renal mean arterial flow, corrected by hematocrit
• Renal hemodynamic measurements by MRI	• change in o mean arterial flow (MAF) o renal artery resistive index (RARI) o renal blood flow velocity (PSV and ESV) o global renal perfusion
• Renal volumetric measurements assessed by MRI	• change in o total renal parenchyma volume o renal cortex volume
• Renal injury and function by MRI	• change in o renal cortex T_1 (ms) o medulla T_1 (ms)
• Renal oxygenation measured by kidney BOLD MRI	• change in o renal cortex R_2* o medulla R_2*
• Body weight	• change in body weight
To compare the effect of retatrutide to placebo on glomerular and tubular functional measurements from baseline to Week 24	• change in 24-hr UAE (mg/24 h) • change in 24-hr urinary electrolytes (mg/24 h)

Abbreviations: BOLD MRI = blood oxygenation level-dependent magnetic resonance imaging; ESV = end-diastolic velocity; FENa = fractional urinary sodium excretion; GFR = glomerular filtration rate; mGFR = measured glomerular filtration rate; MRI = magnetic resonance imaging; PSV = peak systolic velocity; R_2* = the inverse of transverse relaxation time constant measured by MRI; UACR = urine albumin-to-creatinine ratio; UAE = urinary albumin excretion.

[a] Change in UACR will be analyzed in a subset of participants (those with baseline UACR ≥30 mg/g).

Primary Estimands

The primary analysis uses an estimand based on the hypothetical strategy to address intercurrent events (ICEs).

Hypothetical strategy

A scenario is envisaged in which the ICE would not occur. The value of the variable to reflect the clinical question of interest is the value that the variable would have taken in the hypothetical scenario defined.

The primary clinical question of interest is

> *What is the treatment difference in measured GFR (mGFR) change from baseline at 24 weeks between retatrutide and placebo in participants who meet the eligibility criteria if they would remain on their randomly assigned treatment for 24 weeks and would not initiate new sodium-glucose cotransporter-2 (SGLT2) inhibitor, angiotensin-converting enzyme (ACE) inhibitor, or angiotensin-receptor blocker (ARB)?*

Overall Design

Study J1I-MC-GZBU is a Phase 2b, double-blind, 24-week study that will investigate the effects of retatrutide compared with placebo on renal function, in participants with overweight or obesity and established CKD, with or without T2D.

This study includes a

- screening period
- dose escalation treatment period
- maintenance treatment period, and
- posttreatment safety follow-up period.

Brief Summary:

Study GZBU is a Phase 2b study to investigate the mechanism(s) of action of retatrutide in the kidney, in participants with overweight or obesity and coexisting CKD, with or without T2D.

Study GZBU will investigate the effects of 24 weeks of treatment with retatrutide on renal hemodynamics, including mGFR using iohexol clearance, as well as RBF, filtration fraction, renal oxygenation, renal injury, renal function, renal and abdominal adipose tissue, and renal diffusion, assessed using non-invasive, multimodal MRI techniques.

The study duration is approximately 33 weeks, including screening and follow-up.

The treatment duration will be approximately 24 weeks.

The treatment and follow-up visit frequency will be every 4 weeks.

Study Population:

In general, an individual may take part in this study if they

- Are 18 years of age or older or the legal age of consent in the jurisdiction in which the study is taking place at the time of signing the informed consent.
- Have a body mass index (BMI) ≥27 kg/m^2 at screening (Visit 1).
- Have either
    - no T2D diagnosis with an HbA1c <6.5% (<48 mmol/mol), as determined by the central laboratory at screening (Visit 1)

    OR

    - T2D diagnosis with an HbA1c ≤9.5% (≤80.34 mmol/mol), as determined by the central laboratory at screening (Visit 1); diagnosis of T2D must be confirmed using standard criteria.

      And

      are treated with diet and exercise only or with stable doses of up to 3 oral antihyperglycemic medications per local labeling, such as metformin, sulfonylurea, meglitinides, sodium-glucose cotransporter-2 inhibitors (SGLT2i),

or thiazolidinediones, with or without basal insulin, for at least 90 days before Visit 1.

- Have diagnosed CKD and eGFR ≥25 to ≤75 mL/min per 1.73 m^2, calculated using Cystatin-C-based CKD-EPI equation, as determined by central laboratory at screening (Visit 1).
- Are on stable treatment, for at least 90 days before Visit 1, with an ACE inhibitor or ARB that is considered the maximal appropriate dose per local label and by the investigator for treatment of CKD or hypertension. The use of SGLT2i is allowed in participants without T2D, in which case, the dose must be stable for at least 90 days before Visit 1.
  Note: Participants who are intolerant to ACE inhibitors or ARBs are allowed to enter the study.

Number of Participants:

Approximately 120 participants are planned to be randomly assigned to study intervention in a 1:1 ratio of 60 participants to retatrutide and 60 participants to placebo.

Intervention Groups and Duration:

Participants will be randomly assigned to receive either retatrutide, 12 mg, or placebo and will administer their dose once weekly by subcutaneous injection for up to approximately 24 weeks.

Participants randomized to retatrutide

The LY3437943 dose will be initiated at 2 mg once weekly and increased every 4 weeks until the 12 mg dose is reached.

Allowed maintenance dose levels

The target maintenance dose is 12 mg. If 12 mg is not tolerated, the 4 mg, 6 mg, or 9 mg dose is allowed.

Participants randomized to placebo

To maintain blinding, participants randomly assigned to the placebo treatment group will also receive study intervention once weekly. During the dose escalation period, participants will follow a sham dose escalation schedule by changing the volume administered every 4 weeks to match the retatrutide volume change.

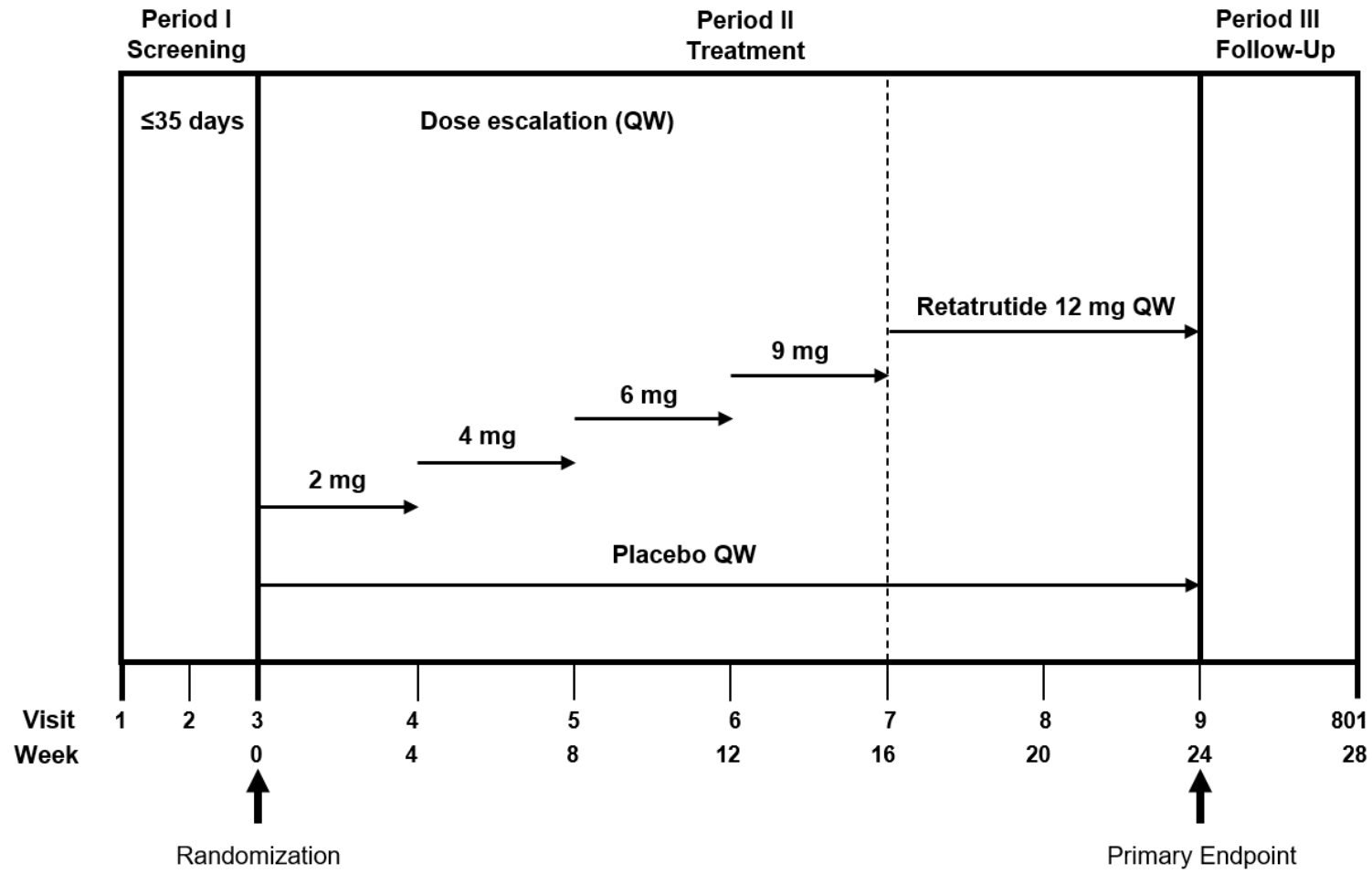
Retatrutide and the placebo to match are identical in appearance. Both materials are manufactured and packaged in the same vial and packaging configuration to maintain the blind.

Ethical Considerations of Benefit/Risk:

Considering the information available from previous completed clinical studies, and the measures taken to make sure the participants in this study are safe, the potential risks from taking retatrutide are justified by the potential benefits for adults living with obesity and chronic kidney disease.

Data Monitoring Committee: No

1.2. Schema



Abbreviation: QW = once weekly

1.3. Schedule of Activities (SoA)

Visit information

Visit procedures may be conducted over more than 1 day. Complete all activities within the allowed visit interval tolerance of each visit.

Telehealth or remote visits

T = telehealth visits may be by telephone or other technology, according to local laws and regulations.

Screening

All screening activities must take place within the 35-day window.

Visit 2 should not occur until Visit 1 results are received and initial assessments of eligibility are completed. At Visit 2, screening laboratory results will be reviewed to confirm eligibility.

Since some screening procedures need to be completed in the fasting state, Visit 1 may be conducted over more than 1 day to ensure necessary conditions are met. If not fasting at Visit 1, participants must return on another day in the fasted state, to complete all procedures that require fasting, including body weight measurement.

Fasting visits

For fasting clinic visits, study participants are required to report to the site in a fasting condition, after approximately 8 hours without eating, drinking anything except water, or performing any significant physical activity. Additionally, the participant should not take their study intervention or any antihyperglycemic medications before attending the fasting visit. If a participant is adversely affected by the fasting condition, they are allowed to eat; however, specific study procedures need to be completed while fasting.

If a participant attends a fasting visit in the non-fasting state, reschedule the visit at a time within the allowable visit interval.

Early discontinuation (ED)

If the participant is discontinuing the study during an unscheduled visit or a scheduled visit, that visit should be performed as an ED visit.

Unscheduled visits (UV)

Unscheduled visits may occur as needed. The SoA reflects some of the procedures that may occur during these visits.

An unscheduled visit may occur per investigator discretion for clinical oversight. The study site will determine if fasting status is needed prior to the visit. Concomitant medications, AEs, and endpoint events are required and should be recorded in the CRF.

Visit 801

A posttreatment safety follow-up visit will occur approximately 4 weeks following the last treatment period visit or final treatment visit. All participants are required to complete a safety follow-up visit.

J1I-MC-GZBU	**Period I Screening**		**Period II Treatment**									**Period III Follow-Up**	**Comments**
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
Informed consent, medical history, AEs													
Informed consent	X												The ICF must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3.
Inclusion and exclusion criteria, review and confirm	X	X											Confirm inclusion and exclusion criteria before treatment assignment and administration of first dose of study intervention.
Demographics	X												Includes year of birth, sex, ethnicity (where permissible), education level, and race.
Preexisting conditions and medical history, including relevant surgical history	X												Collect all ongoing conditions and relevant past surgical and medical history.
Prespecified medical history (indication and history of interest)	X												Collect diagnosis date for CKD, obesity, and T2D if applicable.
Prior treatments for indication	X												Includes medications used for CKD, chronic weight management, and T2D.
Substance use (alcohol, tobacco, and recreational drug use)	X												
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	Monitor closely and routinely assess the need to adjust or discontinue concomitant medications. Refer to Sections 6.9.1, 5.3.1, 5.3.2, and 10.13 for additional details..

J1I-MC-GZBU	Period I Screening		Period II Treatment									Period III Follow-Up	Comments
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
Level of medication intensity									X		X		
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	AE collection begins when the ICF is signed. See Section 8.3.1. Collect additional data for AESIs and other safety topics. See Section 8.3.4.
Physical evaluation													
Height	X												See Section 10.7 for details.
Weight	X		X	X	X	X	X		X		X	X	See Section 10.7 for details.
Waist circumference	X		X	X	X	X	X		X		X	X	See Section 10.7 for details.
Vital signs	X		X	X	X	X	X		X		X	X	See Section 8.2.2 for details.
Physical examination	X											X	The physical examination excludes pelvic, rectal, and breast examinations unless clinically indicated.
Symptom-directed physical assessment			X	X	X	X	X		X		X		Conduct at the discretion of the investigator or qualified personnel per local regulations, as indicated based on participant status and standard of care. Qualified personnel per local regulations will perform the examination.
12-lead ECG (single, local)	X		X						X		X		
Schedule MRI for next visit	X					X		X					

J1I-MC-GZBU	Period I Screening		Period II Treatment									Period III Follow-Up	Comments
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
MRI		X					X		X		X		**Visit 2:** The participant should meet all other eligibility criteria before performing the MRI. In the event that the centralized MRI vendor determines an MRI scan to have inadequate quality to obtain measures for secondary objectives, the participant can be scheduled for a repeat scan. **Visits 7 and 9:** conduct MRI ±7 days of the visit. See Section 8.5.2. In the event that the centralized MRI vendor determines an MRI scan to have inadequate quality to obtain measures for secondary objectives, the participant can be scheduled at the earliest possible time for a repeat scan. If such repeat scan is required, it can be performed outside of the visit window and would not be considered a protocol violation.
Participant diary (paper or electronic)													
Provide diary		X	X	X	X	X	X		X		X		See Section 5.3.
Return and review diary			X	X	X	X	X		X		X	X	Includes dosing information for all participants and hypoglycemia information for participants with T2D only.
Diet and Physical activity log			X	X	X	X	X	X	X		X		See Section 5.3.
Patient-reported outcomes													PROs will be translated into the native language of the region, linguistically validated, and administered according to the SoA.
PHQ-9	X		X			X			X		X	X	Collect AEs before the collection of PHQ-9.
Clinician-administered assessments (paper or electronic)													
C-SSRS screening/baseline	X												Collect AEs before the collection of the C-SSRS. See Section 8.3.4.13.

J1I-MC-GZBU	Period I Screening		Period II Treatment									Period III Follow-Up	Comments
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
C-SSRS since last assessed		X	X	X	X	X	X	X	X		X	X	Collect AEs before the collection of the C-SSRS. See Section 8.3.4.13.
Participant education and supplies as appropriate													
Lifestyle counseling		X											Lifestyle counseling may be repeated as needed.
Injection training		X											Repeat when needed.
Review diet and physical activity goals		X	X	X	X	X	X	X	X		X	X	Repeat training as needed to encourage participant compliance. Provide reinforcement and encouragement for lifestyle modifications. Monitor for and encourage adequate nutritional intake and hydration throughout the study. See Sections 5.3.1 and 5.3.2.
Diabetes education		X											Conduct as needed for participants who have or develop T2D during the study.
Dispense BG supplies as needed and collect any unused supplies		X	X	X	X	X	X		X		X	X	Dispense to participants who have or develop T2D. Participants without diabetes may, at the investigator's discretion, be given glucometers to assist in the evaluation of reported symptoms consistent with hypoglycemia or hyperglycemia.
Laboratory tests and sample collections													
Hematology	X						X		X		X		
Hemoglobin A1c (HbA1c)	X		X			X			X				
Clinical chemistry	X		X	X		X	X		X		X		
HCV screening test	X												If HCV antibody test is positive, perform an HCV RNA test.
HBV screening test	X												If HbcAb is positive, perform an HBV DNA test.

J1I-MC-GZBU	Period I Screening		Period II Treatment									Period III Follow-Up	Comments
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
Lipid panel			X						X				
Dispense containers for 24-hr urine collection		X					X						Dispense containers before Visits 3 and 9.
24-h urine collection			X						X				Collect volume measurement. The collection should start in the morning of the day prior to Visits 3 and 9.
Urinalysis			X				X		X				Collect predose.
Urine chemistry	X		X				X		X				Collect predose.
Serum pregnancy	X												For women of childbearing potential only. Definition in Section 10.4.
Urine pregnancy (local)			X				X		X		X		For women of childbearing potential only. Visit 3: Results must be available before the first administration of study intervention Visits 3, 7, and 9: Results must be available before performing the iohexol procedure. Perform additional pregnancy tests at any time during the study if there is clinical suspicion of pregnancy, or as required by local law or regulation. If the urine pregnancy test is inconclusive at any visit, collect an additional serum pregnancy test. See Section 8.2.5.
Follicle-stimulating hormone	X												For women aged 40-55 years with ≥12 mo of cessation of menses, to determine menopausal status. See Section 10.4.
Thyroid-stimulating hormone	X												
Parathyroid hormone			X						X			X	
Urinary albumin/creatinine ratio (UACR)	X		X	X		X	X		X			X	

J1I-MC-GZBU	Period I Screening		Period II Treatment									Period III Follow-Up	Comments
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
Estimated glomerular filtration rate	X		X	X		X	X		X			X	Central lab will calculate using CKD-EPI Cystatin-C based equation (2012) and using CKD-EPI creatinine-based equation.
GFR assessment using iohexol clearance			X				X		X		X		
Cystatin-C	X		X	X		X	X		X			X	
Calcitonin	X								X				
Pancreatic amylase	X						X		X			X	
Pancreatic lipase	X						X		X			X	
Immunogenicity (ADA) samples (predose)			X	X		X			X		X	X	Collect samples before dosing, if applicable. Collect additional unscheduled samples if systemic drug hypersensitivity reactions (immediate or nonimmediate), or injection-site reactions occur. See Section 10.2.1.
PK sample for immunogenicity (predose)				X		X			X		X	X	Collect samples before dosing, if applicable.
Mechanistic biomarkers			X						X		X		See Section 10.2.2.
Stored Samples													
Genetics sample			X										Collect sample on or after the specified visit.
Exploratory biomarker samples			X				X		X		X		Collect samples predose, if applicable.
Randomization and Dosing													
Register visit in IWRS	X	X	X	X	X	X	X	X	X		X	X	
Randomization via IWRS			X										

J1I-MC-GZBU	Period I Screening		Period II Treatment									Period III Follow-Up	Comments
Visit Number	1	2	3	4	5	6	7	8	9	UV	ED	801	
Weeks from Randomization	≤35 days		0	4	8	12	16	20	24		—	4 weeks after end of treatment period	Dose escalation occurs every 4 weeks from Visit 3 to Visit 7.
Visit Interval Tolerance (days)	--	--	—	±3	±3	±3	±7	±3	±7	—	—	±5	
Fasting Visit	X		X	X	X	X	X		X	X	X	X	
Visit Details								T					T=telehealth
Dispense study intervention via IWRS			X	X	X	X	X						
Dispense supplies to participant for at-home dosing			X	X	X	X	X						
Observe participant administer study intervention			X										Repeat when needed.
Participant returns study intervention supplies				X	X	X	X		X		X		
Assess study intervention compliance				X	X	X	X	X	X		X		

Abbreviations: ADA = antidrug antibody; BG = blood glucose; C-SSRS = Columbia-Suicide Severity Rating Scale; CKD = chronic kidney disease; CKD-EPI = chronic kidney disease epidemiology collaboration; ECG = electrocardiogram; ED = early discontinuation; GFR = glomerular filtration rate; HBV = hepatitis B virus; HCV = hepatitis C virus; ICF = informed consent form; IWRS = interactive web-response system; MRI = magnetic resonance imaging; PHQ-9 = Patient Health Questionnaire-9; PK = pharmacokinetic; T2D = Type 2 diabetes.

2. Introduction

Obesity is a chronic disease, and its increasing prevalence is a public health concern associated with rising incidence of T2D, increased risk for premature death, and increased risk for some cancers (AMA 2013; CSAPH 2013; Lauby-Secretan et al. 2016).

Obesity is a complex, multicomponent metabolic disease of energy homeostasis involving central and peripheral mechanisms. Thus, once obesity is present, those mechanisms make it difficult to return to a lower weight (Aronne et al. 2021). As a result of this understanding, several guidelines now recommend treatment with anti-obesity medications for people with obesity or for those with overweight and weight-related complications (Apovian et al. 2015; Wharton et al. 2020).

One common and serious obesity-related comorbidity is CKD (Ejerblad et al. 2006; Kovesdy et al. 2017). Renal function and morphology in individuals with obesity are affected by coexisting hyperglycemia, hypertension, hyperlipidemia, and increased intracellular and extracellular fat infiltration in the kidney (D'Agati et al. 2016). Renal ectopic fat may result in reduced oxygen delivery, chronic hypoxia, and renal tissue damage through multiple pathophysiological pathways (Hesp et al. 2020; Spit et al. 2020).

Incretin-based medications such as GLP-1 receptor agonists have shifted the paradigm in the treatment of obesity and its comorbidities over the last decade. They have proven to be more effective in lowering body weight compared to previous generations of anti-obesity medications and offer additional benefits beyond body weight reduction, such as improvements in cardiometabolic risk factors and health-related quality of life (Jastreboff et al. 2022; Kirwan et al. 2022). Available exploratory data indicate that these agents may also have a reno-protective potential, and ongoing long-term clinical studies are examining this question (Marso et al. 2016; Gerstein et al. 2019; Heerspink et al. 2022).

Retatrutide

Retatrutide is a novel synthetic peptide which shows potent agonist activity at GIP, GLP-1, and glucagon receptors.

Potential benefits of retatrutide

GIP, GLP-1, and glucagon have roles in the regulation of carbohydrate and lipid metabolism, and energy balance. Each hormone carries unique metabolic regulatory actions, providing an opportunity to combine their receptor signaling in a single molecule. In addition, glucagon receptors are present in the kidney and liver, and glucagon receptor binding and activation may have potentially important physiological roles in regulation of renal function and hemodynamics.

Through its receptors in the distal sections of the tubular system, glucagon regulates the excretion of sodium, potassium, phosphate, and urea. Combined actions of glucagon and systemic cyclic adenosine monophosphate from the liver in the proximal sections of the glomerular tubular units increase the GFR. This is known as a pancreato-hepatorenal cascade, and this effect seems to be modulated by reduced insulin sensitivity, a common feature of obesity (Bankir et al. 2016, 2018).

The mechanism of retatrutide has the potential to deliver substantial body weight reduction across the spectrum of obesity severity, including for individuals with severe (Class 2 and Class 3) obesity. Beyond weight management, treatment with retatrutide is expected to result in related health benefits, including improved glucose homeostasis, and reduction in insulin resistance, lipids, blood pressure, and potentially preserving renal function.

2.1. Study Rationale

Study GZBU is a Phase 2b study that aims to investigate the mechanism(s) of action of retatrutide in the kidney, in participants with overweight or obesity and coexisting CKD, with or without T2D.

Study GZBU will investigate the effects of 24 weeks of treatment with retatrutide on renal hemodynamics, including mGFR using iohexol clearance, as well as renal blood flow, filtration fraction, renal oxygenation, renal injury, renal function, renal and abdominal adipose tissue, and renal diffusion, assessed using non-invasive, multimodal MRI techniques.

The hypothesis is that retatrutide improves or preserves GFR through direct effects on the kidney, as shown in Phase 2 Study GZBF (see Section 2.2). The attenuation of fatty kidney disease is also possible. By lowering intra- and extra-renal fat accumulation, retatrutide may also improve kidney perfusion through restoration of microvascular function. Furthermore, reductions in renal fat may attenuate RAAS activation and low-grade inflammation.

Findings from this study will help explain the effects of retatrutide on renal function and inform potential future kidney outcomes studies.

2.2. Background

Retatrutide

A detailed description of the chemistry, pharmacology, nonclinical and clinical efficacy, and safety of retatrutide is provided in the Investigator's Brochure.

Clinical studies

Three Phase 1 studies are completed, 1 in healthy participants and 2 in participants with T2D. Three additional Phase 1 studies are ongoing.

Two Phase 2 studies (GZBF and GZBD) have concluded, 1 in participants with obesity or overweight without T2D, and 1 in participants with T2D with BMI 25-50 kg/m^2.

Results from Phase 2 Studies GZBF and GZBD relevant for CKD

Study GZBF was a 48-week, Phase 2, multicenter, randomized, double-blind study of QW retatrutide compared with placebo in participants who have obesity, or overweight with weight-related comorbidities, without T2D. Four doses of retatrutide were evaluated in the study, 1, 4, 8, and 12 mg, with the primary outcome of change in body weight.

Study GZBF
Efficacy results and other measures change from baseline at 48 weeks
• Body weight reduction o 8.7%-24.2% for participants treated with retatrutide compared to o 2.1% for participants treated with placebo, and o 30% or more for approximately 26% of participants on retatrutide 12 mg • eGFR o -3.6 to +6.6 mL/min per 1.73 m^2 for participants treated with retatrutide compared to o -0.3 mL/min per 1.73 m^2 for participants treated with placebo • hs-CRP o -0.10 to -0.19 mg/dL (-30.5% to -55.3%) for participants on retatrutide compared to o -0.03 mg/dL (-8.9%) for participants treated with placebo
Safety results
• The most common AEs were GI related and were mild to moderate in severity

Study GZBD was a 36-week, Phase 2, multicenter, randomized, double-blind study of QW retatrutide compared with placebo and dulaglutide 1.5 mg in participants with T2D. Four maintenance doses of LY3437943 were evaluated in the study, 0.5, 4, 8, and 12 mg, with the primary outcome of change in HbA1c.

Study GZBD
Efficacy results and other measures change from baseline at 36 weeks
• HbA1c reduction from baseline o up to 2.2% for participants treated with retatrutide compared to o 1.4% for participants treated with dulaglutide and o 0.3% for participants treated with placebo • Body weight reduction o 3.2%-16.9% for participants treated with retatrutide compared to o 2% for participants treated with dulaglutide and o 3% for participants treated with placebo • eGFR -2.6 to +1.8 mL/min per 1.73 m^2 for participants treated with retatrutide compared to o -3.3 mL/min per 1.73 m^2 for participants treated with dulaglutide and o -1.3 mL/min per 1.73 m^2 for participants treated with placebo
Safety results
• The most common AEs were GI related and were mild to moderate in severity.

Additional parameters that may affect renal function or structure were also significantly reduced with retatrutide in both studies, including

- SBP
- DBP
- total cholesterol
- LDL cholesterol
- VLDL cholesterol, and
- triglycerides.

Overall conclusion from Phase 2 studies

The Phase 2 studies demonstrated that retatrutide administered once weekly in participants with obesity, or overweight with weight-related comorbidities, and in participants with T2D may affect several key CKD-related pathophysiological pathways. These data support the continued assessment of retatrutide as a potential therapy for treatment of individuals with CKD.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected adverse events of retatrutide may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Potential risks for this study

Information on AEs expected to be related to retatrutide are presented in Section 6.2 (Developmental Core Safety Information) of the IB.

Management of risks associated with retatrutide

Sections 5.1, 5.2, 8.2, and 8.3 address known potential risks associated with retatrutide.

Study procedures

Risks associated with GFR assessment using the iohexol clearance method

During the iohexol clearance method, participants will be exposed to administration of iohexol. See Section 10.10 for details.

The iohexol clearance method may cause

- hypersensitivity reactions to iohexol
- contrast-induced acute kidney injury
- preparatory dehydration leading to acute renal failure
- life-threatening or fatal cardiovascular reactions in people with underlying cardiovascular disease, or
- thyroid storm in people with hyperthyroidism or with an autonomously functioning thyroid nodule.

Risks associated with magnetic resonance imaging

Multimodal MRI scans will be performed during the study. AEs with MRI procedures are rare. However, the procedure involves a strong, magnetic pulsed gradient field that presents risks for participants with metal implants or other accessory medical devices, such as pacemakers, stents, and cochlear implants. Participants with such devices should not have an MRI procedure performed unless it has been confirmed that conditions are appropriate for safe use.

The confined space of the MRI testing environment may cause some participants to experience claustrophobia, and some participants may find remaining still to be difficult for the duration of the imaging process.

2.3.2. Benefit Assessment

Receiving study intervention during the study duration may have clinical benefit as described in Section 2 (Introduction) of the IB.

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for retatrutide supports the overall benefit risk for participants in this study. Considering the measures taken to minimize risk to participants in this study, the potential risks identified in association with retatrutide are justified by the anticipated benefits that may be afforded to participants living with obesity or overweight and CKD.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To compare the effect of retatrutide to placebo on mGFR from baseline to Week 24	Change in GFR (mL/min per 1.73 m^2) using iohexol clearance
Secondary	
To compare the effect of retatrutide to placebo on mGFR from baseline to Week 16	Change in GFR (mL/min per 1.73 m^2) using iohexol clearance
To compare the effect of retatrutide to placebo from baseline to Week 16 and baseline to Week 24 for	
• Glomerular and tubular functional measurements	• change in o UACR[a] o creatinine-corrected FENa o filtration fraction estimated from mGFR and MRI-assessed renal mean arterial flow, corrected by hematocrit
• Renal hemodynamic measurements by MRI	• change in o mean arterial flow (MAF) o renal artery resistive index (RARI) o renal blood flow velocity (PSV and ESV) o global renal perfusion
• Renal volumetric measurements assessed by MRI	• change in o total renal parenchyma volume o renal cortex volume
• Renal injury and function by MRI	• change in o renal cortex T_1 (ms) o medulla T_1 (ms)
• Renal oxygenation measured by kidney BOLD MRI	• change in o renal cortex R_2* o medulla R_2*
• Body weight	• change in body weight
To compare the effect of retatrutide to placebo on glomerular and tubular functional measurements from baseline to Week 24	• change in 24-hr UAE (mg/24 h) • change in 24-hr urinary electrolytes (mg/24 h)

Abbreviations: ESV = end-diastolic velocity; FENa = fractional urinary sodium excretion; GFR = glomerular filtration rate; mGFR= measured glomerular filtration rate; MRI = magnetic resonance imaging; PSV = peak systolic velocity; R_2* = the inverse of transverse relaxation time constant measured by MRI; T_1 = longitudinal relaxation time of tissue measured by MRI; UACR = urine albumin-to-creatinine ratio; UAE = urinary albumin excretion.

[a] Change in UACR will be analyzed in a subset of participants (those with baseline UACR ≥30 mg/g).

Estimand for primary objective

The primary analysis uses an estimand based on the hypothetical strategy to address ICEs.

Hypothetical strategy

A scenario is envisaged in which the ICE would not occur. The value of the variable to reflect the clinical question of interest is the value that the variable would have taken in the hypothetical scenario defined (ICH E9 [R1] 2019).

The primary clinical question of interest is:

> *What is the treatment difference in mGFR change from baseline at 24 weeks between retatrutide and placebo in participants who meet the eligibility criteria if they would remain on their randomly assigned treatment for 24 weeks and would not initiate new SGLT2 inhibitor, ACE inhibitor, or ARB?*

Estimand attributes

Population - Participants who are randomly assigned a study intervention and take at least 1 dose of study intervention

Measure - Change in GFR from baseline to 24 weeks

Treatment condition - The randomized treatment with allowance for potential dose interruptions and modifications

Intercurrent events – ICEs include permanent discontinuation of study intervention and initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB, which are handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned treatment for 24 weeks and would not initiate new SGLT2 inhibitor, ACE inhibitor, or ARB. Dose modification and interruption will not be considered as ICEs since dose modification and interruption are part of the treatment condition.

Population-level summary and treatment effect of interest – Difference in mean change in mGFR from baseline to 24 weeks between retatrutide and placebo.

Rationale for estimand

This estimand aims to study the mechanism of action of retatrutide under the ideal condition that all participants adhere to their randomly assigned treatment without being confounded by the initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB medications.

4. Study Design

4.1. Overall Design

Study J1I-MC-GZBU is a Phase 2b, double-blind, 24-week study that will investigate the effects of retatrutide compared with placebo on renal function, in participants with overweight or obesity and established CKD, with or without T2D.

This study includes a

- screening period
- dose escalation treatment period
- maintenance treatment period, and
- posttreatment safety follow-up period.

The study schema is in Section 1.2.

See the SoA for visit schedule, procedural, and assessment details (Section 1.3).

Participant population

All participants in the study will have a BMI ≥27 kg/m^2 and established CKD, with eGFR ≥25 to ≤75 mL/min per 1.73 m^2, inclusive, at screening.

Approximately 50% of the participants randomly assigned to study intervention will have T2D.

Approximately 20% to 30% of participants will be in each prespecified baseline eGFR category (≥25 to <45, ≥45 to <60, and ≥60 to ≤75 mL/min per 1.73 m^2).

At least 50% of the participants should have UACR ≥30 mg/g.

Section 9.5 provides details on the number of participants for the study.

4.1.1. Overview of Study Periods

Visit structure for clinic visits

For fasting clinic visits, study participants are required to report to the site in a fasting condition, after approximately 8 hours without eating, drinking anything except water, or performing any significant physical activity. Additionally, the participant should not take their study intervention or any antihyperglycemic medications before attending the fasting visit as they may interfere with study procedures or assessments.

Screening period

Visit 1

The purpose of screening procedures at Visit 1 is to establish initial eligibility and to obtain blood samples for laboratory assessments needed to confirm eligibility. The participant must sign the ICF before the study procedures are performed, as outlined in the SoA (Section 1.3).

Site staff should assess AEs before completing the PHQ-9 and the C-SSRS at screening/baseline.

Visit 2

At Visit 2, screening laboratory results will be reviewed to confirm eligibility. Visit 2 should not occur until Visit 1 results are received and initial assessments of eligibility are completed.

The participant should meet all other eligibility criteria before performing the MRI acquisition. Lilly-designated centralized MRI vendor should approve that the MRI scan has adequate quality to obtain measures for secondary objectives prior to randomization. However, if a repeat scan is required to obtain baseline measures for secondary objectives, it can be performed and quality reviewed by the centralized MRI vendor outside of the screening window and cause a delay in the randomization visit (Visit 3) which would not be considered a protocol violation.

Site staff should assess AEs before the collection of the C-SSRS.

All participants with T2D will receive their diary and glucometer to collect and record the baseline SMPG and hypoglycemia events. See Section 8.2.9 for instructions on SMPG. Site staff should train participants to record key study information, as appropriate.

Provide diabetes education as described in Section 5.3.5 to all participants with T2D.

Site staff will demonstrate study intervention preparation and injection technique using a vial and syringe. Training can be repeated anytime post-randomization as needed.

Randomization

Visit 3

A final review of eligibility will occur at Visit 3 before randomization can proceed.

At Visit 3, eligible participants will arrive at the clinic in the fasted state and complete all required baseline study procedures, including the collection of all baseline laboratory measures and questionnaires, before randomization and before taking the first dose of study intervention.

Following randomization, site staff will observe the study participant inject the first dose of retatrutide or placebo. The date, time, location, and volume of the first dose of study intervention will be recorded in the diary.

If a participant is currently taking concomitant insulin secretagogues (sulfonylureas) or basal insulin, site staff will need to reduce their dose at randomization, to reduce the potential risk of hypoglycemia, and safely introduce study intervention. See instructions in Section 6.9.4.

Treatment period

During the treatment period, participants will return study interventions and injection supplies per the SoA and according to local requirements. Site staff will dispense new supplies as needed.

Site staff should instruct participants to contact the investigative site for assistance as soon as possible if they experience any difficulties administering their study intervention.

Site staff should also advise participants about the appropriate course of action if study interventions are not taken at the required time (late or missed doses). See Section 6.1 for further details.

Dose-escalation treatment period (end of Visit 3 to Visit 7)

Study intervention dose escalation is double-blinded and will be managed via the interactive web-response system.

For retatrutide, the initial dose will be 2 mg injected subcutaneously once weekly and the weekly dose will be increased at 4-week increments until the 12 mg dose is achieved, as described in this table.

Treatment Group	Treatment Period Intervals				
	Weeks 0 to 4	Weeks 4 to 8	Weeks 8 to 12	Weeks 12 to 16	Week 16 Through end of treatment period
Retatrutide	2 mg	4 mg	6 mg	9 mg	12 mg

See Section 6.1 for dosing details.

See Section 6.6 for guidance and instructions on dose modifications.

See Section 7.1.2 for instructions on restarting treatment after temporary interruptions.

Visit 7 to Visit 9

MRI procedure

Conduct the MRI within 7 days before or after the visit and within 7 days of dosing. If a repeat scan is required to obtain measures for secondary objectives, it can be performed outside of the visit window, and would not be considered a protocol violation.

Early discontinuation visit

Randomized participants who are unable or unwilling to continue the study for any reason will perform an ED visit and should attend the posttreatment follow-up visit.

MRI procedure at early discontinuation visit

If MRI procedures cannot be performed on the same day as other activities planned for the ED visit as per SoA, it can be conducted on different days. However, all procedures should be completed within 7 days of the ED visit (± 7 days).

An MRI procedure on an ED visit should only be performed if it has been 4 weeks or more after the initial study intervention administration and if an MRI procedure has not been performed during the treatment period.

Posttreatment safety follow-up

Visit 801

A safety follow-up visit will occur approximately 4 weeks following the last treatment period visit or final treatment visit. All participants are required to complete a posttreatment safety follow-up visit.

Participants discontinuing the study early and performing an ED visit will also be asked to perform the posttreatment safety follow-up visit.

Participants are also required to return any remaining study diaries to the study site at the end of this period.

4.2. Scientific Rationale for Study Design

Overall design

Study GZBU is designed to investigate the effects of retatrutide compared with placebo on renal function, in participants with overweight or obesity and established CKD, with or without T2D. Treatment allocation is randomized to minimize bias in assignment to treatment.
Inclusion of a placebo comparator will allow for an assessment of the effect attributable to retatrutide, while a double-blind design will minimize participant and investigator bias. In addition, the parallel-group design for treatment comparison will avoid any interaction between treatments that may interfere with the interpretation of the study outcome.

Renal MRI assessments

Novel multimodal MRI techniques have the potential to non-invasively assess and quantify functional and pathophysiological changes in kidney diseases based on recent studies (Selby et al. 2018; Makvandi et al. 2022). The effects of retatrutide on longitudinal changes in RBF, filtration fraction (calculated using RBF, mGFR, and hematocrit), renal oxygenation, renal fat, renal injury, renal function, renal diffusion, and renal volume will be assessed using multiple MRI sequences and analysis techniques.

Treatment duration

In the concluded Phase 2 clinical studies, GZBD and GZBF, the full effect of retatrutide on kidney function (as determined by eGFR assessment) was observed by 24 weeks. The 24-week treatment period is expected to be appropriate to compare the effects of retatrutide and placebo in this study.

Study population

This study includes a population of participants with BMI ≥27 kg/m^2 and coexisting CKD, with or without T2D.

Participants with overweight or obesity are included to test if retatrutide affects renal function.

Reasons for including participants with or without T2D are

- CKD occurs in people with and without T2D
- hyperglycemia has an independent effect on the kidney and may accentuate the risk of renal tissue hypoxia
- both populations are included in the retatrutide Phase 3 studies and information from this population will inform the clinical program

Collection of demographic information

In this study, collection of demographic information includes race and ethnicity. The scientific rationale is based on the need to assess variable response in safety and/or efficacy based on race or ethnicity. This research question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

Participants randomly assigned to retatrutide will start with a 2 mg once weekly dose and a dose escalation every 4 weeks until the 12 mg dose is reached. The target dose is 12 mg. If 12 mg is not tolerated, the 4, 6, or 9 mg dose is allowed.

The 12 mg dose and associated escalation scheme were selected based on assessment of safety, efficacy, tolerability data, and PK/PD exposure-response modeling of data from Phase 1 and Phase 2 studies in participants with obesity, or overweight with weight-related comorbidity, and participants with T2D.

The dose escalation scheme is designed to minimize GI tolerability concerns.

The selected dose level will support an analysis of multiple safety and PD measures of retatrutide to determine an optimal benefit/risk ratio.

4.4. End of Study Definition

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

5. Study Population

Participant eligibility for enrollment in the study is based on the criteria listed in this section. The inclusion and exclusion criteria used to determine eligibility should only apply at screening or other specified visits, and not continuously throughout the study.

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

5.1. Inclusion Criteria

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

Age

1. Participants must be 18 years of age or older or the legal age of consent in the jurisdiction in which the study is taking place at the time of signing the informed consent.

Type of participant and disease characteristics

2. Have a BMI ≥27 kg/m^2 at screening (Visit 1).
3. Have either
   - no T2D diagnosis and with an HbA1c <6.5% (<48 mmol/mol), as determined by the central laboratory at screening (Visit 1)

   OR

   - T2D diagnosis with an HbA1c ≤9.5% (≤80.34 mmol/mol), as determined by the central laboratory at screening (Visit 1); diagnosis of T2D must be confirmed using the standard criteria provided in Section 10.8.
     and
     are treated with diet and exercise only or with stable doses of up to 3 oral antihyperglycemic medications per local labeling, such as metformin, sulfonylurea, meglitinides, sodium-glucose cotransporter-2 inhibitors (SGLT2i), or thiazolidinediones, with or without basal insulin, for at least 90 days before Visit 1.
4. Have diagnosed CKD and eGFR ≥25 to ≤75 mL/min per 1.73 m^2, calculated using Cystatin-C-based CKD-EPI equation, as determined by central laboratory at screening (Visit 1).
5. Are on stable treatment, for at least 90 days before Visit 1, with an ACE inhibitor or ARB that is considered the maximal appropriate dose per local label and by the investigator for treatment of CKD or hypertension. The use of SGLT2i is allowed in participants without T2D, in which case, the dose must be stable for at least 90 days before Visit 1.
   Note: Participants who are intolerant to ACE inhibitors or ARBs are allowed to enter the study.

Contraceptive and barrier requirements

6. Male and female participants may participate in this study.
   - Female participants must not be pregnant, intending to be pregnant, breastfeeding, or intending to breastfeed.

- Contraception for men with partners of childbearing potential is required.

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. For the contraception requirements of this protocol, see Section 10.4.

Study procedures

7. Are reliable and willing to make themselves available for the duration of the study and attend required study visits and are willing and able to follow study procedures as required, such as
   - self-inject study intervention
     Note: Persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study intervention
   - store and take provided study intervention as directed
   - maintain a paper or electronic study diary, and
   - complete required questionnaires.
8. Are willing to discontinue chronic use of NSAID medications, with the exception of daily low-dose aspirin for cardiovascular prophylaxis, for the duration of the study.
   Examples of NSAID medications include but are not limited to
   - ibuprofen
   - naproxen
   - diclofenac
   - celecoxib
   - mefenamic acid
   - etoricoxib
   - indomethacin, and
   - aspirin.

Informed consent

9. Are capable of giving signed informed consent as described in Appendix 1, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Obesity-related medical conditions

10. Have a self-reported change in body weight >5 kg (11 pounds) within 90 days before screening (Visit 1).
11. Have a prior or planned surgical treatment for obesity
    Exception: The following are allowed if performed >1 year before screening (Visit 1)
    - liposuction
    - cryolipolysis, or
    - abdominoplasty.

12. Have a prior or planned endoscopic procedure, for example, mucosal ablation or gastric artery embolization, and/or device-based, for example, lap band, intragastric balloon, or duodenal-jejunal endoluminal liner, therapy for obesity.
    Exception: Prior device-based therapy is acceptable if device removal was more than 6 months prior to screening (Visit 1).
13. Have obesity induced by other endocrinologic disorders, for example, Cushing Syndrome, or are diagnosed with monogenetic or syndromic forms of obesity, such as Melanocortin 4 Receptor deficiency or Prader Willi Syndrome.

Diabetes-related medical conditions for those without T2D

14. Are receiving treatment with a glucose-lowering agent initiated ≤90 days before screening (Visit 1).

Diabetes-related medical conditions for those with T2D

15. Have had 1 episode of severe hypoglycemia or hypoglycemia unawareness ≤6 months before screening (Visit 1).
16. Have a history of
    - proliferative diabetic retinopathy
    - diabetic macular edema, or
    - nonproliferative diabetic retinopathy that requires acute treatment.

Other medical conditions

Endocrine

17. Have T1D or history of
    - ketoacidosis
    - hyperosmolar state/coma, and
    - any other types of diabetes, for example, maturity onset diabetes of the young and diabetes induced by chronic pancreatitis.
18. Have a calcitonin level of ≥35 ng/L at screening (Visit 1).
19. Have TSH levels outside normal reference range for the central laboratory at screening (Visit 1).
    - Participants with hypothyroidism who are clinically euthyroid and on stable thyroid replacement therapy for at least 2 months prior to screening (Visit 1) and who are anticipated to remain on this dose throughout the study period are acceptable exceptions to this criterion.
20. Have a family or personal history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome Type 2.

Renal

21. Have a history of unstable or rapidly progressing renal disease according to investigator judgment, for example, active glomerulonephritis.
22. Have a history of a congenital or hereditary kidney disease, like polycystic kidney disease or congenital urinary tract malformations.

Hepatic

23. Have acute or chronic hepatitis, including a history of autoimmune hepatitis, signs or symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of these laboratory values during screening (Visit 1)
    - ALT or AST level ≥3.0x the ULN
      Note: Participants with nonalcoholic fatty liver disease may participate in the study if their ALT level is <3.0x the ULN.
    - ALP level ≥1.5x the ULN
    - TBL level ≥1.5x the ULN, except for participants with history of Gilbert's Syndrome
    - positive for both hepatitis B core antibody and HBV DNA
    - positive for hepatitis B surface antigen, or
    - positive for both hepatitis C antibody and HCV RNA.

Malignancy

24. Have a diagnosis or history of malignant disease within 5 years before screening (Visit 1).
    Exception:
    - basal cell or squamous cell skin cancer that has been resected with no evidence of metastatic disease, or
    - Stage 0 non-invasive cervical cancer.

Autoimmune

25. Have evidence of significant, active autoimmune abnormality, for example, lupus or rheumatoid arthritis, that, in the opinion of the investigator, is likely to require concurrent treatment with systemic glucocorticoids during the course of the study.

Psychobehavioral

26. Have a history of active or unstable major depressive disorder or other severe psychiatric disorder, such as schizophrenia, bipolar disorder, or other serious mood or anxiety disorder, within the last 2 years
    OR
    In the investigator's opinion, have any significant mental health disorder that may put the individual at higher risk of study participation.
    Note:
    In the investigator's opinion, individuals whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study may be considered for inclusion if they do not meet Exclusion Criterion #48 regarding weight gain-promoting concomitant medications.
27. Have a PHQ-9 score of 15 or more before randomization.
28. Have any lifetime history of a suicide attempt.
29. Are, in the judgment of the investigator, actively suicidal, and therefore deemed to be at significant risk for suicide.

30. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS and the ideation occurred within the past month
    OR
    Have answered "yes" to any of the suicide-related behaviors on the "suicidal behavior" portion of the C-SSRS and the behavior occurred within the past month.

Gastrointestinal

31. Have a known clinically significant gastric emptying abnormality, such as severe diabetic gastroparesis or gastric outlet obstruction, or chronically take drugs that directly affect GI motility.

Hematologic

32. Have any hematological condition that may interfere with HbA1c measurement, for example, hemolytic anemias, or sickle cell disease.

Cardiovascular

33. Have had within the past 90 days before screening (Visit 1)
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - coronary revascularization
    - hospitalization for unstable angina, or
    - hospitalization due to congestive heart failure.
34. Have New York Heart Association Class IV congestive heart failure.
35. Have a 12-lead ECG abnormality that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG data analysis, such as

    - a QT interval corrected using Fridericia's formula
      - >450 msec for males, or
      - >470 msec for females
    - short PR interval <120 msec, or PR interval >220 msec
    - second- or third-degree atrioventricular block
    - intraventricular conduction delay with QRS >120 msec
    - right bundle branch block
    - left bundle branch block, or
    - Wolff Parkinson-White syndrome.

    If an ECG parameter is out of range in the screening ECG, the site may perform 2 repeat ECGs and average the 3 results to assess eligibility.

Other

36. Have a history of chronic or acute pancreatitis.
37. Have had a transplanted organ or are awaiting an organ transplant.
    Exception: corneal transplants or keratoplasty is allowed.
38. At the time of screening have a planned surgery, except for minor surgical procedures, to occur during the study.

39. Have any contraindication for MRI according to standard checklist used in clinical routine, including claustrophobia that cannot be managed with low-dose sedatives, or metallic foreign bodies, metallic implants, internal electrical devices, or permanent makeup/tattoos that cannot be declared MRI compatible, or exceed the body size or weight limitations imposed by the MRI scanner machinery, or any condition or circumstance that, in the opinion of the investigator, would interfere with completion of MRI examinations.
40. Have any condition, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the participant's safety, for example, hypersensitivity or contraindication, or compliance with the protocol, for example, recreational drug use, alcohol abuse, or diagnosed eating disorder.

Prior or concomitant therapy

41. Are receiving chronic systemic glucocorticoid therapy for >14 days or have received such therapy within 90 days of screening (Visit 1)
    Exception: Treatment with
    - topical
    - intra-ocular
    - intranasal, or
    - inhaled preparations.
42. Have taken within 90 days before screening (Visit 1) any non-steroidal mineralocorticoid receptor antagonists.
43. Have known allergies or intolerance to GLP-1R agonists, GIP/GLP-1R agonist, or retatrutide.
44. Have known allergies, intolerance, or other contraindication to iohexol injection, such as iodine or contrast allergy.
45. Have taken within 90 days before screening (Visit 1) any of the following antihyperglycemic medications:
    - DPP-4 inhibitors
    - amylin analogs
    - GLP-1 receptor agonists
    - GIP/GLP-1 receptor agonist
    - any rapid-acting or short-acting insulin, or U-500 insulin.
46. Have taken within 90 days before screening (Visit 1), prescribed or over-the-counter medications, or alternative remedies, including herbal or nutritional supplements, intended to promote body weight reduction. Examples include, but are not limited to
    - tirzepatide
    - semaglutide
    - liraglutide
    - orlistat
    - sibutramine
    - phenylpropanolamine

- mazindol
- phentermine
- lorcaserin
- phendimetrazine
- phentermine/topiramate
- naltrexone/bupropion, and
- ingested material that transiently occupies space in the stomach, for example, hydrogel capsules made of cellulose and citric acid.

47. Have started treatment with or changed dose within 12 months before screening (Visit 1) any medications that are associated with significant weight gain, including but not limited to,
    - tricyclic and tetracyclic antidepressants, such as imipramine, amitriptyline, and mirtazapine
    - typical anti-psychotics, such as chlorpromazine and thioridazine
    - atypical anti-psychotics, such as clozapine, olanzapine, and quetiapine
    - mood stabilizers, such as lithium, valproic acid, and its derivatives
    - paroxetine, a selective serotonin reuptake inhibitor, or
    - phenelzine, a monoamine oxidase inhibitor.

    Exception: Selective serotonin reuptake inhibitors other than paroxetine are permitted.
48. Have started subcutaneous/intramuscular, implantable/injectable contraceptives, such as Depo-Provera®, Nexplanon, within 18 months before screening (Visit 1).
    Note: Intrauterine devices are acceptable.

Prior or concurrent clinical study experience

49. Are currently enrolled in any other clinical study involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
50. Within the last 90 days before screening (Visit 1), participated in a clinical study and received active treatment or unknown if they received active treatment.
51. Have previously completed or withdrawn from this study or any other study investigating retatrutide after receiving at least 1 dose of intervention.

Other exclusion criteria

52. Are investigator site staff directly affiliated with this study and/or their immediate family. Immediate family is defined as a spouse, legal partner, parent, child, or sibling, whether biological, or legally adopted.
53. Are Lilly employees or are employees of any third party involved in the study who require exclusion of their employees.

5.3. Lifestyle Considerations

Participant 3-day diet and physical activity log and study diary

Each participant will be responsible for entering information into a 3-day diet and physical activity log and a study diary.

The participant will enter information described in Sections 5.3.1 and 5.3.3 in the 3-day diet and physical activity log.

All participants will enter study intervention information, described in Section 6, in the study diary. In addition, participants with T2D or that develop T2D during the study will enter diabetes-related information, described in Section 5.3.5, in the study diary.

Lifestyle management counseling

Per the SoA (Section 1.3), participants will consult a dietitian, or equivalent qualified delegate, according to local standards, to receive lifestyle management counseling.

Healthy diet and physical activity goals established during the lifestyle consultation and the importance of adherence to the lifestyle component of the study will be reinforced at each visit by site staff.

To encourage adherence, it is recommended that the participant complete their 3-day diet and physical activity log before each counseling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed.

5.3.1. Meals and Dietary Restrictions

Individualized counseling for a healthy diet for the CKD population

At Visit 2 and subsequent visits, study participants will receive individualized counseling regarding a healthy diet with the goal of achieving weight reduction. The counseling will be performed by a dietitian or nutritionist, or equivalent qualified designee, according to local standard.

Counseling considerations

The focus of the counseling should facilitate healthier food choices and promote portion control through mindful eating.

It should include instruction on customized nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations.

Adequate nutritional intake and hydration recommendations, in the setting of weight management, may be individualized based on the participant's health status to optimize nutritional status and minimize risks imposed by comorbid conditions.

The nutritional therapy should be individualized based on the participant's CKD stage, age, comorbidities, and taking into consideration appetite, dietary intake, body weight changes, and GI tolerability during the study.

Recommendations should focus on prioritizing the appropriate intake of carbohydrates, fats, proteins, and fluids.

Consider the following advice:

- Intake approximately 25 to 35 kcal/kg body weight per day to optimize nutritional status.
- Intake approximately 0.8 g/kg body weight per day protein; consider adjusting per CKD stage.

- Limit intake of saturated and trans fats.
- Sodium intake to be <2 g per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in individuals with CKD.
- Consider recommending a plant-based diet that includes a higher consumption of fruits, vegetables, nuts, legumes, fish, olive oil, yogurt, and whole grains.
- Ensure that the right amount of fluid is consumed to avoid dehydration. Fluid recommendations may vary based on the stage of CKD, individual fluid intake, activity level, climate, and any comorbidities.
- Follow a diet that meets the Recommended Dietary Allowance for adequate intake of all vitamins and minerals.

Consider the following principles in counseling sessions:

- The importance of meeting nutritional and hydration recommendations.
- Eating smaller and more frequent meal/snacks every 3 to 4 hours and avoid skipping meals.
- Decreased appetite and increased fullness after eating typically drive a reduction in food intake. Additional voluntary food restriction, when appetite is reduced, is unnecessary and may be harmful.
- Focus on “eating enough” each day for optimal health.

In addition, if more frequent nutritional counseling is needed, either on-site or virtually, to facilitate adequate nutritional intake and hydration, contact the Lilly Medical team to discuss the implementation.

5.3.2. Monitoring Nutritional Needs

Retatrutide is an investigational, next-generation, anti-obesity medication with the potential for superior body weight reduction compared to established anti-obesity medications. Retatrutide acts, in part, by reducing appetite leading to a decrease in food intake, particularly during the weight reduction phase. There is potential that a portion of participants will have significantly reduced caloric intake.

Medical staff should consider clinical monitoring of the participant’s nutritional and hydration status if they observe significantly reduced caloric intake in comparison to what was recommended at Visit 2. By recognizing early signs of poor intake and dehydration, preventive actions can be taken to reduce the risk of potential complications.

Examples of clinical signals indicating poor nutrition or dehydration include

- age
- CKD stage

- medical history/comorbidities
- concomitant medications, and
- GI symptoms, for example, nausea, vomiting, diarrhea.

Clinically evaluate the nutritional and hydration status of participants and assess for any signs or symptoms of poor nutrition or dehydration, including vital signs, targeted physical exam, and recent laboratory data. See below some key aspects to potentially include in your routine evaluation.

Potential Concern	**Early signs include, but are not limited to:**
Poor nutrition	• carbohydrate intake <50 g/day • protein intake <0.8 g/kg body weight/day; consider adjusting per CKD stage • caloric intake lower than that recommended at the initial visit • skipping multiple meals
Dehydration	• fluid intake lower than that recommended for the individual participant volume loss (e.g., diuretic or laxative use, diarrhea, vomiting, and dizziness) • elevated pulse rate • decreased or low blood pressure • increased blood urea nitrogen/creatinine ratio

If there are concerns for poor nutrition or dehydration, mitigations are based on an assessment of the severity of the participant's status, potential underlying etiologies, and GI symptoms. See Sections 6.6.3 and 10.12 for the recommended steps to follow.

5.3.3. Healthy Physical Activity

Physical activity during the study

At Visit 3 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week if appropriate based on the participant's health condition.

To encourage adherence, it is recommended that the participant complete their 3-day diet and physical activity log before each counseling visit.

Activity before blood collection

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests.

5.3.4. Blood Donation

Study participants should not donate blood or blood products during the study or for 8 weeks following their last study visit.

5.3.5. Diabetes Education

Diabetes education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMPG, self-injection, and diabetes management, according to American Diabetes Association Standards of Medical Care in Diabetes (ADA 2023) or local standards.

Provide diabetes education at screening Visit 2 for participants who have diabetes and during the study for participants that develop T2D. Additional training may be provided during the study as needed.

Participants will enter diabetes-related information into the study diary.

See Section 6.9.6 for Management of Severe, Persistent Hyperglycemia.

See Section 6.9.7 for Management of Hypoglycemia Risk.

See Section 8.2.9 for Self-Monitoring of Plasma Glucose.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants 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, and any SAE.

Rescreening

Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreening once at the investigator's discretion and with medical monitor approval. If rescreening is performed, the participant must sign a new ICF and will be assigned a new identification number. Reconsenting and rescreening can occur no sooner than 30 days after the screen failure date. The screening procedures per the usual SoA should be followed, starting at the screening Visit 1, to ensure participant eligibility by the randomization at Visit 3.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Administration of Study Intervention of a Participant

This section is not applicable to this study. All entry criteria must be met within the specified intervals in the SoA.

6. Study Intervention(s) and Concomitant Therapy

Study intervention is defined as any medicinal product(s) or medical device(s) intended to be administered to or used by a study participant according to the study protocol. As this study is blinded, "dose" refers to placebo or retatrutide.

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	Retatrutide	Placebo	Iohexol
IMP and NIMP/AxMP	IMP	IMP	NIMP/AxMP
Use	Experimental	Placebo	Diagnostic
Type	Drug	Placebo	Marker for GFR
Dosage Level(s)	• 2 mg • 4 mg • 6 mg • 9 mg • 12 mg	Not applicable	3235 mg
Route of Administration	SC injection QW	SC injection QW	IV injection
Authorized as defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized	Authorized and not used according to EU authorization

Abbreviations: AxMP = auxiliary medicinal product; EU = European Union; GFR = glomerular filtration rate; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; QW = once weekly; SC = subcutaneous.

Participant training

Site staff will

- train the participant how and where to administer the study intervention
- observe the participant administer the study intervention
- explain what to do if the participant misses a dose
- explain what information the participant needs to record in the diary, and
- train the participant on the proper storage and handling of the study intervention.

Participants randomized to retatrutide

The retatrutide dose will be initiated at 2 mg once weekly and increased every 4 weeks until the 12 mg dose is reached. See Section 4.1.1 for further details.

Allowed maintenance dose levels

The target maintenance dose is 12 mg. If 12 mg is not tolerated, the 4, 6, or 9 mg dose is allowed (see Section 6.6.1).

Participants randomized to placebo

To maintain blinding, participants randomized to the placebo treatment group will also receive study intervention once weekly. During the dose escalation period, participants will follow a sham dose escalation schedule by changing the volume administered every 4 weeks to match the retatrutide volume change.

Retatrutide and the placebo to match are identical in appearance. Both materials are manufactured and packaged in the same vial and packaging configuration to maintain the blind.

Timing of dose administration

Participants should try to administer the SC injections on the same day of the week and similar time of day, but there are no restrictions on the time of day for each weekly dose.

The participant will record the actual date, time, location, and volume of all dose administrations in the diary.

Missed doses

If a dose is missed, the participant should

1. take it as soon as possible unless it is within 72 hours of the next dose, in which case that dose should be skipped, and the next dose should be taken at the appropriate time
2. record the date and the reason the dose was not taken in the diary

The day of weekly administration can be changed, if necessary, if the last dose was administered 72 hours or more before.

Anatomical location of injections

Acceptable locations for injection by the participant include the abdomen or thigh, or upper arm if another person gives the injection.

Participants should rotate injection sites from one injection to the next, even when injecting within the same region.

A new syringe will be used for each injection.

The participant will record the injection-site location of all dose administrations in the diary.

Packaging and labeling

Study interventions will be supplied by the sponsor in accordance with current Good Manufacturing Practice. Study interventions will be labeled as appropriate for country requirements.

6.2. Preparation, Handling, Storage, and Accountability

The investigator or designee must confirm appropriate storage conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply, prepare, or administer study intervention.

All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized study personnel.

The investigator or authorized study personnel are responsible for study intervention accountability, reconciliation, and record maintenance, that is, receipt, reconciliation, and final disposition records.

Further guidance and information for the final disposition of unused study interventions are provided in the study training materials.

Participant responsibilities

Study participants will be trained on the proper storage and handling of the study intervention and should follow in-use storage conditions according to the instructions for use provided by the sponsor.

6.3. Assignment to Study Intervention

Randomization

Participants who meet all enrollment criteria will be randomly assigned (1:1) in a double-blind fashion to either retatrutide or placebo.

Randomization will be stratified by

- T2D status at baseline (with T2D versus without T2D)
- eGFR category (≥25 to <45, ≥45 to <60, and ≥60 to ≤75 mL/min per 1.73 m^2), and
- treatment with SGLT2 inhibitors at baseline (Yes or No).

The assignment of a participant's treatment group is determined by the IWRS using a computer-generated permuted block randomization table. Only a minimal number of Lilly personnel, and separate to the main study team, will see the randomization records before the double-blind study period is completed.

6.4. Blinding

This is a double-blind, randomized study in which study participants and study personnel are blinded to study intervention. Retatrutide and the placebo to match are identical in appearance. Both materials are manufactured and packaged in the same vial and packaging configuration to maintain the blind. Blinding will be maintained throughout the conduct of the study, as described in the separate Blinding and Unblinding Plan.

Emergency unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's treatment assignment is warranted for medical management of the event. The participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately.

If the investigator decides that unblinding is warranted, it is the responsibility of the investigator to promptly document the decision and rationale and notify Lilly as soon as possible.

Emergency unblinding for AEs may be performed through the IWRS. This option may be used ONLY if the participant's well-being requires knowledge of the participant's treatment assignment. All emergency unblinding events are recorded and reported through the IWRS.

Discontinuation from the study in case of unblinding

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be discontinued from the study.

6.5. Study Intervention Compliance

Participant compliance with study intervention will be assessed at visits summarized in the SoA. Compliance will be assessed by direct questioning and counting of unused study intervention returned. Study intervention compliance will be determined by the following:

- Study intervention administration data will be recorded by the participant and reviewed by the investigator at each study visit.
- The participants will be instructed to return any unused study intervention at the next visit to the study site for the purpose of performing study intervention accountability.

Treatment compliance is defined as taking at least 75% of the required SC doses of study intervention. Similarly, a participant will be considered significantly noncompliant if the investigator determines that they have intentionally or repeatedly taken more than the prescribed amount of medication (more than 125%).

Other aspects of compliance with the study interventions will be the participant's adherence to the visit schedule, study diaries, and any other parameters the investigator considers necessary.

Participants considered poorly compliant will receive additional training and instruction as required. Additional unscheduled visits may be scheduled if study site staff determine that a participant requires additional training.

6.6. Dose Modification

Allowed dose modifications

Dose modification is only allowed for the management of

- intolerable GI symptoms during the first 20 weeks (see Sections 6.6.1 and 10.9)
- any other intolerable AEs
- participants reaching a BMI <22 kg/m^2 (see Section 6.6.2), or

CCI [redacted]

6.6.1. Management of Participants with Intolerable Gastrointestinal Symptoms

Follow these steps if a participant reports intolerable GI symptoms, such as nausea, vomiting, or diarrhea:

1. Counsel the participant on dietary behaviors that may help mitigate nausea and vomiting, for example
   - eating smaller meals
   - splitting 3 daily meals into 4 or more smaller ones
   - stopping eating when they feel full, and
   - avoiding foods that trigger symptoms.

   See Sections 5.3.1 and 5.3.2 for Monitoring Nutritional Needs.
2. If symptoms persist, prescribe symptomatic medication, for example, antiemetic, or antidiarrheal medication, per local country availability and individual participant needs. Record these medications as concomitant medications in the CRF.
3. If Steps 1 and 2 do not alleviate intolerable GI symptoms, temporary interruption of study intervention for 2 or less doses is permitted. Resume study intervention immediately according to the planned dosing schedule, when possible, either alone or in combination with symptomatic medication.
4. If Steps 1, 2, and 3 do not alleviate intolerable GI symptoms **during the first 20 weeks of the study**, follow guidance for temporary dose de-escalation and dose re-escalation.

CCI [redacted]

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

CCI

If a participant …	Then …
CCI	

CCI

CCI

CCI		

6.6.3. Management of Participants with Poor Nutrition or Dehydration

Follow the following steps (and refer to Section 10.12) if a participant is at risk of poor nutrition or dehydration based on clinical judgement and criteria described in Sections 5.3.1, 5.3.2, and 10.12:

1. Assess if there is an intercurrent illness (e.g., systemic infection, cholecystitis, etc.) that could be causing or contributing to the inadequate oral intake.

a. If yes, consider temporary interruption of study intervention per Section 7.1.2.
b. If no, go to Step 2.

2. Assess if increased oral intake may likely trigger GI symptoms.

   a. If no,

      i. Provide nutritional counseling and consider strategies to increase oral intake. Refer to Sections 5.3.1 and 5.3.2.
      ii. Assess concomitant medications and consider adjustment as appropriate; consider laboratory tests as appropriate (see Sections 6.9.1, 10.2.3, and 10.13).

   b. If yes,

      i. Temporarily interrupt study intervention for 1 to 2 doses.
      ii. Provide nutritional counseling and consider strategies to increase oral intake. Refer to Sections 5.3.1 and 5.3.2.
      iii. Assess concomitant medications and consider adjustment as appropriate; consider laboratory tests as appropriate (see Sections 6.9.1, 10.2.3, and 10.13).

   c. Reassess if nutritional and hydration concerns persist

      i. If no, restart the study intervention per Section 7.1.2.
      ii. If yes, contact the sponsor for possible discontinuation of study intervention per Section 7.1.1.

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

Study intervention will not be available to participants after completion of the study.

6.8. Treatment of Overdose

For this study, any total dose of study intervention within a 72-hour period greater than the dose assigned by IWRS for that participant will be considered an overdose and should be assessed for AE reporting as per criteria described in Section 10.3.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced
- closely monitor the participant for any AE or SAE and laboratory abnormalities as medically appropriate.

6.9. Prior and Concomitant Therapy

6.9.1. General Considerations

Participants are permitted to use concomitant medications that they require during the study except medications that may interfere with the assessment of efficacy and safety characteristics of the study interventions.

Participants must consult with the investigator or a designated site staff member if they are prescribed any new medications during the study. If this is not possible due to treatment of medical emergencies, the participant will inform the investigator or a designated site staff member as soon as possible.

The initiation of weight gain-promoting medications is not permitted, and alternate therapies not associated with weight gain should be considered whenever possible.

In this study population, many study participants will be taking medications to treat weight-related comorbidities, including hypertension, dyslipidemia, and T2D. Since weight reduction is expected to improve these comorbidities, study participants may require a dose reduction or complete withdrawal of certain concomitant medications.

Investigators should closely monitor the need for adjustment of concomitant medications throughout the study, especially antihypertensives, as substantial weight reduction may be associated with a reduction in blood pressure. See Section 10.13 for concomitant medication considerations.

Recording concomitant medications

Site staff will record concomitant medication CRF throughout the study. Site staff will also assess and record changes in intensity of medications of special interest on the level of medication intensity CRF at intervals specified in the SoA. Categories for medications of special interest that should be recorded in both CRFs include

- antihypertensive
- antihyperglycemic, and
- lipid-lowering medications.

Any medication or vaccine, over-the-counter or prescription medicine, including hormonal contraceptives, vitamins or herbal supplements, or other specific categories of interest that the participant is receiving at the time of enrollment or receives during the study must be recorded in the CRF along with

- reason for use

- dates of administration, including start and end dates, and
- dosage information, including dose and frequency only for concomitant medications of special interest, for example antihypertensive, antihyperglycemic, and lipid-lowering medications.

Non-study medications taken by participants who are screened but not randomly assigned to treatment will not be reported to the sponsor unless an SAE or AE occurs that the investigator believes may have been caused by a study procedure.

6.9.2. Use of Medications that May Affect the Primary Objective Measure (mGFR)

General restrictions

Participants must not use NSAIDs chronically during the study with the exception of daily low-dose aspirin for cardiovascular prophylaxis. This includes, but is not limited to

- ibuprofen
- naproxen
- diclofenac
- celecoxib
- mefenamic acid
- etoricoxib
- indomethacin, and
- aspirin.

Participants must not use NSAIDs for incidental use within 48 hours prior to MRI or iohexol procedures.

Additional prohibited medications that must not be used within 48 hours of the iohexol procedure are medications containing

- ephedrine
- phenylephrine
- pseudoephedrine
- phenylpropanolamine, and
- medications that lower seizure threshold, especially phenothiazine derivatives, including those used for their antihistaminic properties.
- metformin, participants with T2D using metformin may pause use of medication prior to iohexol procedure and resume after the completion of the test according to country specific guidance or prescribing information of iohexol (ACR 2023, van der Molen et al, 2018).

6.9.3. Prohibited Surgical Treatments, Procedures, or Medications for Weight Management

Any planned elective major surgery during the study should be discussed with the sponsor.

Prohibited bariatric surgical treatments include gastric bypass or sleeve gastrectomy.

Prohibited procedures for weight management include liposuction, abdominoplasty, or cryolipolysis.

Endoscopic or device-based therapy for obesity are prohibited. Examples include

- mucosal ablation
- lap band
- gastric artery embolization
- intragastric balloon, or
- duodenal-jejunal endoluminal liner.

Prohibited medications include those intended to promote weight loss, including prescribed, over-the-counter, or alternative remedies.

6.9.4. Use of Antihyperglycemic Medications at Randomization in Participants with T2D

If a participant with T2D is taking concomitant antihyperglycemic medications that could cause an increased risk of hypoglycemia, then adjust the medications at Visit 3 (Week 0) to reduce the potential risk of hypoglycemia and safely introduce study intervention.

CCI [redacted]

It is recommended to have these participants appropriately monitor their blood glucose during this time.

For all other antihyperglycemic medications, participants should maintain their current dose at randomization throughout the study, unless they meet the criteria for severe, persistent hyperglycemia defined in Section 6.9.6.

See Section 6.9.6 for guidance on Management of Severe, Persistent Hyperglycemia.

See Section 6.9.7 for Management of Hypoglycemia Risk.

6.9.4.1. Prohibited Antihyperglycemic Medications

Regardless of indication of use, these medications are prohibited during the study, including after permanent discontinuation of study intervention, as rescue therapy, or during the posttreatment safety follow-up period

- amylin analogs/agonists
- GLP-1R agonists
- GIP/GLP-1R agonists
- DPP-4 inhibitors, or
- any rapid-acting and short-acting insulin, or U-500 insulin.

6.9.5. Initiation of New Antihyperglycemic Medication during the Study

The initiation of new antihyperglycemic medications other than study intervention may occur during the study ONLY in the following situations:

- a participant develops T2D during the study
- a participant requires antihyperglycemic medication as a rescue therapy for the management of hyperglycemia, rescue therapy is mandated when severe, persistent hyperglycemia occurs as defined in Section 6.9.6, or
- during the posttreatment safety follow-up period for participants with T2D.

6.9.6. Management of Severe, Persistent Hyperglycemia

Criteria for initiation of glycemic rescue therapy

Investigators will be trained on how to apply decision criteria for the timing and method of intervention in participants who do not reach glycemic targets during the treatment period. Glycemic rescue criteria will be primarily determined from fasting SMPG values recorded in the participant's glucometer and diary.

Participants should continue administering assigned study intervention.

The investigator or the participant's usual care physician may initiate rescue therapy to manage hyperglycemia that is above the pre-specified targets for individual participants. Rescue intervention is mandated if a participant has

- more than 2 confirmed fasting SMPG values over at least 2 consecutive weeks that are
  - more than 270 mg/dL (15.0 mmol/L) at any time from Week 0 and prior to Week 9
  - more than 240 mg/dL (13.3 mmol/L) at any time from Week 9 to Week 16, or
  - more than 200 mg/dL (11.1 mmol/L) at any time after Week 16.

Investigators should first confirm that the participant is fully compliant with the assigned study intervention and their diabetes management regimen and that they do not have an acute condition causing severe hyperglycemia.

Recommended glycemic rescue therapy

Participants who develop severe persistent hyperglycemia during the treatment period may be candidates for glycemic rescue and should be considered for addition of or dose increase in antihyperglycemic therapies.

The choice of new antihyperglycemic therapy or amount of dose increase will be at the discretion of the investigator or the participant's usual diabetes care physician. Follow national standards of care for diabetes management in respective participating countries or the guidelines for T2D management (ADA/EASD 2022), but avoid the prohibited medications listed in Section 6.9.4.1.

Insulin rescue therapy can be initiated based on the discretion of the investigator. Insulin therapy should be administered according to ADA guidelines (2023) and for as short of a duration as possible.

The use of rescue therapy should be recorded on the concomitant medication CRF page as rescue therapy.

Short-term treatment with insulin not as rescue therapy

Short-term treatment with insulin for less than 14 days is allowed for certain clinical situations, such as elective surgery, during hospitalization, hyperosmolar states, or acute illness.

This is not considered as rescue therapy, and it should be recorded in the concomitant medications CRF as general concomitant medication.

6.9.7. Management of Hypoglycemia Risk

Moderate or severe CKD, defined as eGFR < 60 mL/min per 1.73 m^2, is a risk factor for developing hypoglycemia. Patients with both diabetes and CKD carry a 2-fold risk of developing hypoglycemia compared with patients with diabetes, but without CKD (Moen et al. 2009).

Participants will be trained on the signs and symptoms of hypoglycemia and its treatment and instructed to record pertinent information about hypoglycemic events in their study diary.

Participants who develop persistent or recurrent unexplained hypoglycemia during the treatment period will be asked to reduce the dose of or discontinue any concomitant antihyperglycemic medications, starting preferably with the ones commonly associated with hypoglycemia, for example, sulfonylurea or insulin.

Monitoring for hypoglycemia includes capture of events as described in Sections 8.3.4.3 and 10.2.2. See Section 8.2.9 for SMPG information.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

7.1.1. Permanent Discontinuation of Study Intervention

A participant must be permanently discontinued from study intervention if

- the participant requests to permanently discontinue study intervention
- the participant becomes pregnant during the study
- the participant is diagnosed during the study with
    - T1D
    - proliferative diabetic retinopathy or macular edema or requires acute treatment for ocular changes
    - acute or chronic pancreatitis confirmed by adjudication
    - medullary thyroid cancer or multiple endocrine neoplasia Type 2 syndrome, and
    - an active or untreated malignancy.

  Exception:
    - basal cell or squamous cell skin cancer, or
    - Stage 0 non-invasive cervical cancer.
- the participant has a significant elevation of calcitonin levels (see Section 8.3.4.7.1)
- the participant develops any other TEAE, SAE, or clinically significant laboratory value or other safety reasons for which the investigator believes that permanent study intervention discontinuation is appropriate
- the participant receives or needs prohibited medications during the study described in Section 6.9.1, and the participant will not or cannot discontinue them, or
- if an investigator, site staff performing assessments, or participant is unblinded.

Other possible reasons that may lead to permanent discontinuation of study intervention:

- If the participant is unable to maintain adequate nutrition or hydration despite management as described in Section 6.6.3.
- The participant has perceived excessive body weight loss, despite good nutrition management.
- the participant has intolerable GI symptoms despite management as described in Section 6.6.1.
- the participant has a BMI ≤18.5 kg/m^2 at any time during the treatment period

  Note: The investigator should contact the sponsor to discuss whether it is medically appropriate for the participant to continue study intervention (see Section 6.6.2)
- the participant has bariatric surgery, body weight reduction procedures, or medications for weight management described in Section 6.9.3
- the participant has a systemic hypersensitivity reaction (see Section 8.3.4.11)

Note: If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of study intervention is warranted, the investigator may consult the sponsor.

- PHQ-9 score ≥15
- C-SSRS
    - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
    - answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS.

Note: In the event either the PHQ-9 score or C-SSRS conditions above are met, participants should be referred to a mental health professional for consultation. If a participant's psychiatric disorder can be adequately treated with psycho- or pharmacotherapy (see Section 6.9.1 for restricted use medications), then the participant, at the discretion of the investigator (in agreement with the mental health professional), may be continued in the study on study intervention.

If a participant permanently discontinues study intervention for any reason, they will discontinue participation after attending the ED visit and posttreatment follow-up visit.

7.1.2. Temporary Interruption of Study Intervention

In certain situations, the investigator may need to temporarily interrupt study intervention, for example, if the participant experiences an acute illness, has surgery, or requires hospitalization.

Every effort should be made by the investigator to maintain participants on study intervention and to restart study intervention after any temporary interruption, as soon as it is safe to do so. If dose interruption occurs after first 20 weeks, the participant will be discontinued from study intervention and from the study.

Guidance for restarting study intervention

1. If the number of consecutive missed doses is ≤2, and the dose was well tolerated prior to the interruption, then restart study intervention at the same dose the participant received before the interruption and dosing will continue as planned, per protocol.
2. If the number of consecutive missed doses is 3, then
    - if the missed doses were the initial 2 mg dose level, the participant will restart on the 2 mg dose and subsequently escalate as required by protocol, or
    - if the missed doses were 4 mg or more, the participant will restart study intervention at 4 mg, regardless of the dose the participant received before the interruption and subsequently escalate as required by protocol.

3. If the number of consecutive missed doses is 4 or more, then discontinue the participant from the study.

7.1.3. Liver Chemistry Stopping Criteria

Interrupting study intervention based on liver test elevations in participants with normal or near-normal baseline liver tests

In study participants with normal or near-normal baseline liver tests of ALT, AST, ALP <1.5x ULN, the study intervention should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.7) if 1 or more of the conditions in this table occur.

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x 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%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN
ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.	

Interrupting study intervention based on elevated liver tests in participants with abnormal baseline liver tests

In study participants with abnormal baseline liver tests of ALT, AST, ALP ≥1.5x ULN, the study intervention should be **interrupted** if 1 or more of the conditions in this table occur.

Elevation	Exception
ALT or AST >4x baseline	
ALT or AST >3x baseline for more than 2 weeks	
ALT or AST >2x baseline and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL>2x ULN
ALT or AST >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >2.5x baseline, when the source of increased ALP is the liver	
ALP >2x baseline and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for drug interruption decisions rather than TBL >2x ULN
ALP >2x baseline with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications.	

Resuming study intervention after elevated liver tests

Resumption of the study intervention can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results return to baseline and if a self-limited, non-drug etiology is identified. Otherwise, the study intervention should be discontinued.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon. To minimize the amount of missing data and to enable assessment of study objectives as planned in the study protocol, every attempt will be made to keep participants in the study regardless of study intervention use.

A participant may withdraw from the study

- at any time at the participant's own request
- at the request of the participant's designee, for example, parents or legal guardian
- if the number of consecutive missed retatrutide doses is 4 or more
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or

- if enrolled in any other clinical study involving an investigational product or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

Female participants will be withdrawn from the study if the participant becomes pregnant (see Section 8.3.2).

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and posttreatment follow-up, as shown in the SoA.

If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

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

Participants discontinuing from the study prematurely for any reason should complete AE and other posttreatment safety follow-up per the SoA and Section 8.2 (Safety Assessments) of this protocol.

7.3. Lost to Follow-Up

A participant will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site. Site personnel or designee are expected to make diligent attempts to contact participants who fail to return for a scheduled visit or were otherwise unable to be followed up by the site.

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 participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

8.1. Efficacy Assessments

This section is not applicable for this study.

See Section 3 for specific measures.

See Section 8.5 for descriptions of pharmacodynamic measures.

See Sections 8.2 and 8.3 for descriptions of safety-related measures.

8.2. Safety Assessments

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

8.2.1. Physical Examinations

A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems. Height and weight will also be measured and recorded as per the SoA (Section 1.3). Refer to Section 10.7 for further details on the height and weight measurements.

A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).

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

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3). If warranted, additional vital signs may be measured.

Guidance for vital sign measurements of blood pressure and heart rate

- measure vital signs before obtaining an ECG tracing and before collection of blood samples for laboratory testing
- have the participant sit quietly for about 5 minutes before vital signs measurements are taken
- when possible, measure blood pressure and pulse rate at approximately the same time of day at each scheduled time point

- participant should have blood pressure measurements with both feet on the floor
- for each parameter, take 3 subsequent measurements from the same arm, preferably the nondominant arm
- measure the recordings at least 1 minute apart
- blood pressure must be taken with an automated BP instrument with the appropriate size cuff on the upper arm
- heart rate is measured by pulse
  Note: In the event pulse measurement cannot be taken via an automated BP instrument, the preferred location for measurement of pulse is the radial artery, and
- if BP and pulse measurements are taken separately, pulse should be taken prior to BP.

Each measurement of sitting pulse and BP needs to be recorded in the CRF.

8.2.3. Electrocardiograms

Single 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3). ECGs may be obtained at additional times, when deemed clinically necessary. Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. Collect ECG before blood samples for laboratory testing.

ECGs will initially be interpreted by the investigator or qualified designee at the site as soon after the time of ECG collection as possible, and ideally while the participant is still present for immediate participant management, should any clinically relevant findings be identified. Any clinically relevant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of study intervention should be reported as an AE via CRF.

The investigator, or qualified designee, must document their review of the ECG printed at the time of evaluation and any alert reports.

8.2.4. Clinical Safety Laboratory Tests

See Section 10.2 (Appendix 2) for the list of clinical laboratory tests to be performed and the SoA for the timing and frequency.

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration.

Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 4 weeks after the last dose of study intervention 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 Section 10.2 (Appendix 2), must be conducted in accordance with the SoA, standard collection requirements.

If laboratory values from non-protocol-specified laboratory assessments performed at an investigator-designated local laboratory require a change in participant management or are considered clinically significant by the investigator, for example, SAE or AE or dose modification, then report the information as an AE.

8.2.5. Pregnancy Testing

On-site pregnancy testing will occur as outlined in the SoA.

Female participants of childbearing potential will be supplied with home testing kits to perform additional pregnancy tests at any time during the study. Participants should notify the investigator as soon as possible if they test positive for pregnancy.

Details of all pregnancies in female participants and, if indicated, female partners of male participants will be collected as outlined in Sections 8.3.1 and 8.3.2.

See Section 10.4 for additional information for pregnancy.

8.2.6. Suicidal Ideation, and Behavior Risk Monitoring

Baseline assessment of SIB/intervention emergent SIB will be monitored using the C-SSRS and PHQ-9. See Section 8.3.4.13 for more details.

Participants should be monitored appropriately and observed closely for SIB or any other unusual changes in behavior throughout the study.

Participants who experience signs of SIB should undergo a risk assessment. All factors contributing to SIB should be evaluated, and consideration should be given to discontinuation of the study intervention (Section 7.1).

8.2.7. Hepatic Safety Monitoring

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests (Section 10.6), 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 the conditions in this table occur.

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

ALT or AST ≥1.5x ULN	ALT or AST ≥2x baseline
ALP ≥1.5x ULN	ALP ≥2x baseline
TBL ≥1.5x ULN	TBL ≥1.5x baseline, except for participants with Gilbert's syndrome

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, the investigator, in consultation with the Lilly-designated medical monitor, should initiate clinical and laboratory monitoring, and evaluation for possible causes of abnormal liver tests. 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, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

Initially, monitoring of symptoms and hepatic biochemical tests should be done 1 to 3 times weekly, based on the participant's clinical condition and hepatic biochemical tests.

Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks, if the participant's clinical condition and laboratory results stabilize.

Monitoring of ALT, AST, ALP, and TBL should continue until levels normalize or return to approximate baseline levels.

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of the conditions in this table occur.

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

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

What a comprehensive evaluation should include

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above
- tests for
    - prothrombin time, INR
    - viral hepatitis A, B, C, or E, and
    - autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or CT scan.

Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for

- hepatitis D virus
- cytomegalovirus
- Epstein-Barr virus
- acetaminophen levels
- acetaminophen protein adducts
- urine toxicology screen
- Wilson's disease
- blood alcohol levels
- urinary ethyl glucuronide, and
- blood phosphatidylethanol.

Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.

Additional hepatic data collection (hepatic safety CRF) in study participants who have abnormal liver tests during the study

Collect additional hepatic safety data in hepatic safety CRFs if a study participant develops a hepatic event considered to be an SAE or discontinues study intervention due to a hepatic event or meets 1 of the conditions described in this table.

If a participant with baseline results of...	Develops the following elevations…
ALT <1.5x ULN	ALT to ≥5x ULN on 2 or more consecutive blood tests
ALT ≥1.5x ULN	ALT ≥3x baseline on 2 or more consecutive blood tests
TBL <1.5x ULN	TBL ≥2x ULN, except for participants with Gilbert's syndrome
TBL ≥1.5x ULN	TBL ≥2x baseline
ALP <1.5x ULN	ALP ≥2x ULN on 2 or more consecutive blood tests
ALP ≥1.5x ULN	ALP to ≥2x baseline on 2 or more consecutive blood tests

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

8.2.8. Renal Safety Monitoring

Investigators should ensure to monitor participants and manage renal safety, blood pressure, lipids, and diabetes by following The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF KDOQI™), Kidney Disease: Improving Global Outcomes (KDIGO®), or according to local clinical guidelines for treatment of CKD as applicable.

8.2.9. Self-Monitoring of Plasma Glucose (SMPG) for Participants with Diabetes or Who Develop Diabetes during the Study

Glucometer for participant use during the study

All participants with T2D or who develop T2D during the study will be provided with glucometers and related testing supplies for use during the study.

Site staff will train the participant on correct use of the glucometer for SMPG and reporting of hypoglycemia data in the diary. See Section 8.3.4.3 for information on hypoglycemia.

Participants should use the glucometer

- whenever hypoglycemia is experienced or suspected
- when there is awareness of increased risk of hypoglycemia related to changes in dietary intake or physical activity
- to check for hyperglycemic events, or
- as directed by the investigator.

Measuring daily glucose

Participants with a confirmed T2D diagnosis should collect daily fasting glucose to assist with participant clinical management.

If participant condition or type of therapy needs an assessment of a daily glucose profile, then the participant should collect 4-point SMPG before assigned visits. The frequency of these measures is determined by the investigator for participant clinical management.

A 4-point SMPG consists of these measurements within the same day

- a fasted measurement before breakfast, and
- measurements 2 hours after breakfast, lunch, and dinner.

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

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

- AEs
- SAEs, and
- PCs.

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

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet these definitions and remain responsible for following up events that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention (see Section 6.9.2).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For product complaints, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality. Further information on follow-up procedures is provided in Section 10.2.2.

8.3.1. Timing and Mechanism for Collecting Events

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
Adverse Event					
AE	Signing of the informed consent form (ICF)	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention **and** deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hr of awareness	SAE CRF	SAE paper form

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-Up Method of Reporting
SAE[a] – after participant's study participation has ended **and** the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	Until 1 mo after the last dose of study intervention	Within 24 hr (see Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hr of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (after participant's study participation has ended and if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

[a] Serious adverse events should not be reported unless the investigator deems them to be possibly related to study treatment or study participation.

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

After learning of a pregnancy in the female partner of a study participant, the investigator

- will obtain a consent to release information from the pregnant female partner directly, and
- within 24 hours after obtaining this consent will record pregnancy information on the appropriate form and submit it to the sponsor.

The female partner will also be followed to determine the outcome of the pregnancy. Information on the status of the mother and child will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

Female participants who become pregnant

The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.

The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies), or indication for the procedure.

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.

Any 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 participants, he or she may learn of an SAE through spontaneous reporting.

Any female participant who becomes pregnant while participating in the study will be discontinued from the study. If the participant is discontinued from the study, follow the standard discontinuation process and continue directly to the follow-up phase. The follow-up on the pregnancy outcome should continue independent of intervention or study discontinuation.

8.3.3. Adjudicated Clinical Events

Cardiovascular events

Adjudicated cardiovascular events include

- death (CV and non-CV)
- myocardial infarction
- hospitalization for unstable angina
- hospitalization for heart failure, and
- coronary revascularization.

Neurologic events

Adjudicated neurologic events include stroke and transient ischemic attack.

Pancreatic events

Adjudicated pancreatic events include

- pancreatitis (acute or chronic)
- pancreatic hyperenzymemia with symptoms
- pancreatic hyperenzymemia that undergoes further diagnostic follow-up, and
- severe or serious abdominal pain of unknown etiology.

8.3.4. Adverse Events of Special Interest and Other Safety Topics

Adverse events of special interest and other safety topics are prospectively defined in this section. If these events are reported, investigators may be prompted to collect additional data about the event.

8.3.4.1. Major Adverse Cardiovascular Events

Nonfatal cardiovascular AEs or deaths will be adjudicated by a committee of physicians external to Lilly with cardiology expertise (Section 10.1.5). This committee will be blinded to treatment assignment. The adjudicated nonfatal cardiovascular AEs include

- myocardial infarction
- hospitalization for unstable angina
- hospitalization for heart failure event
- coronary revascularization procedure, such as coronary artery bypass graft or percutaneous coronary intervention, and
- cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

8.3.4.2. Arrhythmias and Cardiac Conduction Disorders

Participants who develop any event from these groups of disorders should undergo an ECG performed locally. ECGs will be interpreted by the investigator or qualified designee in accordance with applicable local regulations. Additional diagnostic tests to determine exact diagnosis should be performed, as needed.

Record the specific diagnosis as an AE.

Record events that meet criteria for serious conditions as described in Section 10.3.2 as SAEs.

8.3.4.3. Hypoglycemia

Distribution of glucometers and study diaries

All participants who have T2D at randomization or develop T2D during the study will be provided with glucometers.

Participants without diabetes may, at the investigator's discretion, be given glucometers to assist in the evaluation of reported symptoms consistent with hypoglycemia.

All participants with glucometers will receive a study diary. Participants will be trained about the signs and symptoms of hypoglycemia and its treatment and instructed to record relevant information about hypoglycemic events in their study diary.

Responding to recurrent hypoglycemia in participants taking concomitant antihyperglycemic medication

If a participant develops recurrent unexplained hypoglycemia during the treatment period, the investigator should consider reducing the dose of or discontinuing any concomitant antihyperglycemic medication commonly associated with hypoglycemia, for example, sulfonylurea or insulin. See Section 6.9.4.

Recording hypoglycemic episodes

Participants will be trained to record hypoglycemic episodes in the study diary.

Site staff should ONLY record hypoglycemia as an AE if the event meets serious criteria. A hypoglycemic event meets serious criteria if it meets the Level 3 severe definition stated below.

If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE and SAE CRFs and report it to the sponsor as an SAE.

To avoid duplicate reporting, all consecutive blood glucose values <70 mg/dL (3.9 mmol/L) occurring within a 1-hour period are considered a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013).

Hypoglycemia definitions and categories

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia. The blood glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine blood-equivalent glucose meters and strips in accordance with the 2023 American Diabetes Association position statement on glycemic targets (ADA 2023).

Level 1 - Glucose <70 mg/dL (3.9 mmol/L) and ≥ 54 mg/dL (3.0 mmol/L)

Level 1 hypoglycemia can alert a person to take action such as treatment with fast-acting carbohydrates. Providers should continue to counsel participants to treat hypoglycemia at this glucose alert value.

Level 2 - Glucose <54 mg/dL (3.0 mmol/L)

Level 2 hypoglycemia is also referred to as documented or blood glucose-confirmed hypoglycemia. This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 - Severe hypoglycemia in adults

A severe event characterized by altered mental or physical status requiring assistance for treatment of hypoglycemia. Examples of severe hypoglycemia events are

- a participant with altered mental status that could not assist in their own care, or
- a participant who becomes semiconscious or unconscious, or
- a participant who experiences coma with or without seizures, and
- the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions.

Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

The investigator determines if a hypoglycemic event is severe based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.

Nocturnal hypoglycemia
Any hypoglycemic event that occurs between bedtime and waking.

8.3.4.4. Severe Gastrointestinal Adverse Events

Retatrutide may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe GI AEs as well as antiemetic/antidiarrheal use will be collected in the AE and concomitant medication CRFs, respectively. For detailed information concerning the management of GI AEs, please refer to Section 6.6.1.

8.3.4.5. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute renal failure or worsening of preexisting CKD.

Retatrutide may cause severe GI AEs, such as nausea, vomiting, and diarrhea, consistent with other GLP-1 receptor agonists (Aroda and Ratner 2011). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure.

Participants should notify investigators in case of severe nausea, frequent vomiting or diarrhea, or symptoms of dehydration.

8.3.4.6. Pancreatitis

Diagnosis of acute pancreatitis

The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006).

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting
- serum amylase (total, pancreatic, or both) or lipase ≥3x ULN, and
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the investigator should:

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase, via the central laboratory (and locally, if needed)
- perform imaging studies, such as abdominal CT scan with or without contrast, abdominal MRI, or abdominal ultrasound.
  Note: Abdominal ultrasound may be used as an alternative method only if CT scan and MRI cannot be performed, and
- evaluate for possible causes of acute pancreatitis, including
  - alcohol use
  - gallstone or gall bladder disease
  - hypertriglyceridemia, and
  - concomitant medications.

Case adjudication and reporting

An independent CEC will adjudicate all suspected cases of acute or chronic pancreatitis (see Section 10.1.5.1).

Cases of pancreatic hyperenzymemia with symptoms or asymptomatic cases of pancreatic hyperenzymemia that undergo additional diagnostic follow-up will be submitted for adjudication.

AEs of severe or serious abdominal pain of unknown etiology will also be submitted to the adjudication committee to assess for possible pancreatitis or other pancreatic disease.

Each AE of pancreatitis must be reported. If typical signs or symptoms of pancreatitis are present and confirmed by laboratory values (lipase or amylase [total and/or pancreatic]) and imaging studies, the event must be reported as an SAE. For a potential case that does not meet all of these criteria, it is up to the investigator to determine the seriousness of the case (AE or SAE) and the relatedness of the event to study intervention. If the event meets SAE criteria (see Section 10.3.2) report it as an SAE.

See Sections 8.3.1 and 10.3 for further information on AE and SAE definitions and reporting.

Asymptomatic elevation of pancreatic amylase or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic

enzymes (lipase and/or p-amylase ≥3x ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

Discontinuation for acute pancreatitis

If the investigator suspects acute pancreatitis, the participant must temporarily discontinue study intervention. If the case is confirmed as acute pancreatitis by the adjudication committee, the participant must permanently discontinue study intervention and the participant needs to be followed throughout the duration of the study. If the case is not confirmed, then the investigator determines if the participant may restart study intervention.

8.3.4.7. Thyroid Malignancies and C-Cell Hyperplasia

Participants who are diagnosed with medullary thyroid carcinoma or multiple endocrine neoplasia syndrome Type 2 during the study will be discontinued from study intervention. The participant should continue in the study but should also follow up with an endocrinologist.

The assessment of thyroid safety will include reporting of any case of thyroid malignancy, including medullary thyroid carcinoma and papillary carcinoma, and measurements of calcitonin. Calcitonin measurements will be used to assess the potential of retatrutide to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Data will be captured in specific CRFs.

8.3.4.7.1. Calcitonin Measurements

If an increased calcitonin value is observed in a participant who received a medication that is known to increase serum calcitonin, then stop the medication and repeat the calcitonin measurement after an appropriate washout period.

For participants who require additional endocrine assessment because of increased calcitonin value, record data from the follow-up assessment in the specific section of the CRF.

If a participant's laboratory serum calcitonin results meet any of the criteria described below, then record the clinically significant laboratory results as an AE.

Calcitonin measurements in participants with eGFR ≥60 mL/min per 1.73 m^2

Serum calcitonin value ≥20 ng/L and <35 ng/L AND ≥50% increase from the screening value

If a participant has this value, repeat the calcitonin measurement within 1 month.

If the repeat value increases ≥10%, then permanently discontinue study intervention.

Site staff should encourage the participant to undergo additional endocrine assessment and longer term follow-up by an endocrinologist to exclude any serious adverse effects on the thyroid.

Serum calcitonin value ≥35 ng/L AND ≥50% increase from the screening value

If the increased concentration of calcitonin is confirmed, permanently discontinue study intervention.

Participants should immediately undergo additional endocrine assessments and longer term follow-up by an endocrinologist to exclude any serious adverse effects on the thyroid.

Calcitonin measurement in participants with eGFR <60 mL/min per 1.73 m^2

Serum calcitonin value ≥35 ng/L AND ≥50% increase from the screening value

If the increased concentration of calcitonin is confirmed, permanently discontinue study intervention.

Participants should immediately undergo additional endocrine assessments and longer term follow-up by an endocrinologist to exclude any serious adverse effects on the thyroid.

8.3.4.8. Malignancies

Evaluate all events of malignancy or other suspected events related to malignancy and perform additional diagnostic tests as needed.

8.3.4.9. Hepatic Disorders

In cases of elevated liver laboratory tests, initiate hepatic monitoring as outlined in Section 8.2.7.

8.3.4.10. Gallbladder and Biliary Tract Disorders

All events of TE biliary colic, cholecystitis, cholelithiasis, or other suspected events related to gallbladder disease should be evaluated and additional diagnostic tests performed, as needed.

8.3.4.11. Hypersensitivity Reactions

Many drugs, including oral agents and biologic agents, carry the risk of systemic hypersensitivity reactions. If such a reaction occurs, additional data should be provided to the sponsor in the designated CRFs.

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

In the case of a suspected systemic hypersensitivity event, additional blood samples should be collected as described in Section 10.2.1. Laboratory results are provided to the sponsor via the central laboratory.

8.3.4.12. Injection-Site Reactions

Symptoms and signs of a local injection-site reaction may include erythema, induration, pain, pruritus, and edema.

If an injection-site reaction is reported by a participant or site staff, it should be recorded as an AE, and the ISR CRF will be used to capture additional information about this reaction, for example, injection-site pain, degree and area of erythema, induration, pruritis, and edema.

At the time of AE occurrence, samples will be collected for measurement of retatrutide ADA and retatrutide concentration.

8.3.4.13. Depression and Suicidal Ideation or Behavior Monitoring

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the C-SSRS and the PHQ-9 questionnaires. Scores of the questionnaires must be reviewed by the investigator at the time of each visit and appropriate actions as described below should be taken.

Timing of collection and AE monitoring

Nonleading AE collection should occur prior to the collection of PHQ-9 and the C-SSRS.

If a suicide-related event is discovered *during the C-SSRS* but was not captured during the nonleading AE collection, sites should not change the AE form.

If an AE is serious or leads to discontinuation, it needs to be included on the AE form and the process for reporting SAEs is followed.

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (C-SSRS 2013) is a scale that captures the occurrence, severity, and frequency of SIB during the assessment period via a questionnaire. The scale was developed by the National Institute of Mental Health trial group for the purpose of being a counterpart to the Columbia Classification Algorithm of Suicide Assessment categorization of suicidal events.

For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Spitzer et al. 1999; Moriarty et al. 2015) is a validated, participant-reported instrument that assesses the specific diagnostic symptoms that determine the presence of a clinical depressive disorder per the Diagnosis and Statistical Manual for Mental Disorders, 5th Edition (DSM-5).

The questionnaire assesses the previous 2 weeks.

The PHQ-9 assesses 9 diagnostic symptoms:

- mood
- anhedonia
- appetite change
- sleep disturbance
- psychomotor agitation or retardation
- loss of energy
- feelings of worthlessness or guilt
- diminished concentration, and
- suicidal thoughts or attempts.

Each question has 4 response options, with scores ranging from 0 to 3. Higher numbers indicate greater dysfunction.

This table describes the interpretation of results.

Interpretation of Depression	Total Score
Minimal to none	0-4
Mild	5-9
Moderate	10-14
Moderately severe	15-19
Severe	20-27

8.3.4.14 Abuse Potential

All events of abuse potential should be evaluated, and additional investigations performed as needed.

CCI [redacted]

CCI [redacted]

CCI [redacted]

8.4. Pharmacokinetics

At the visits and times specified in the SoA, PK blood samples will be collected for all participants. Only samples from participants assigned to treatment with retatrutide will be analyzed for drug concentration.

Instructions for the collection and handling of blood samples will be provided by the sponsor.

The actual date and time (24-hour clock time) of each sampling will be recorded.

Drug concentration information that would unblind the study will not be reported to study sites or blinded personnel while the study is blinded.

Samples may be used for exploratory analyses, such as metabolism, protein binding, or bioanalytical cross-validation purposes.

Bioanalytical

Samples will be analyzed at a laboratory designated by the sponsor and stored at a facility designated by the sponsor. Concentrations of retatrutide will be assayed using a validated bioanalytical method.

Sample retention is described in Section 10.1.12.

Individual PK data will not be reviewed by the investigator to avoid unblinding until the study is complete.

8.5. Pharmacodynamics

See Section 3 for specific measures and Section 10.2.2 for exploratory mechanistic markers. This section includes general information about these measures:

- GFR assessment using iohexol clearance procedure
- renal MRI procedures
- creatinine-corrected FENa
- filtration fraction estimated from GFR and MRI assessed renal blood flow
- UACR
- 24-hour urine collection, UAE
- urinary electrolytes, and
- body weight.

The SAP will define additional exploratory measures.

Individual PD data will not be reviewed by the investigator to avoid unblinding until the study is complete.

8.5.1. GFR Assessment using Iohexol Clearance Procedure

The iohexol clearance procedure will be used to measure the GFR. A single injection of iohexol will be followed by multiple blood sample collections for iohexol measurement and GFR calculation. See Section 10.10 for details.

The iohexol clearance procedure in this study has been modified for individuals with obesity and CKD, referring to observations reported by Clerte et al. (2017), Friedman et al. (2010), Åsberg et al. (2020), Cherney et al. (2020), and Delanaye et al. (2016).

It is recommended that the iohexol procedure and MRI acquisitions be done on separate days. If both procedures need to be conducted on the same day because of logistical circumstances, it is recommended that MRI acquisitions be done prior to the iohexol clearance procedure.

If a participant discontinues the study early, the investigator will decide if it is safe and medically appropriate to perform the procedure during an ED visit.

8.5.2. Pharmacodynamic Parameter Estimation through Renal Multimodal Magnetic Resonance Imaging

Renal imaging procedures include multimodal MRI at all sites during scheduled visits as listed in the SoA.

After the participant has given consent and met all protocol eligibility requirements, renal imaging procedures at baseline must be performed before the participant receives the first dose of study intervention.

Time courses of absolute and percentage change from baseline in MRI markers will be summarized and plotted for retatrutide and placebo groups. All of the acquired MRI sequences should be sent to centralized MRI vendor. In the event that Lilly-designated centralized MRI vendor determines an MRI scan to have inadequate quality to obtain measures for the study secondary objectives, the participant can be scheduled at the earliest possible time for a repeat scan (more than 1 repeat scan would require the sponsor’s approval). If such repeat scan is requested, it can be performed outside of the visit window and would not be considered a protocol violation.

The procedures for acquisition and image handling will be provided in the MRI training manual provided by the Lilly-designated centralized MRI vendor.

PD parameters	Assessment methods
Renal hemodynamics • mean arterial flow (MAF) • peak systolic and end-diastolic velocity • renal arterial resistive index (RARI) • global renal perfusion • filtration fraction (FF)	• PC-MRI • FF will be estimated from measured GFR and renal blood flow, corrected by hematocrit
Renal injury and function	• T_1 mapping scan o renal cortex T_1 (ms) o medulla T_1 (ms)
Renal volumetric measures • renal parenchymal volume • renal cortex volume	• T_1 mapping scan
Renal cortex and medulla oxygenation	• kidney BOLD MRI o renal cortex R_2* o medulla R_2*
Renal fat metrics • sinus fat volume • perirenal fat volume • parenchyma PDFF	• Dixon technique and MRI-PDFF
Renal cortex and medulla diffusion	• ADC maps obtained from DWI-MRI
Aortic flow	• PC-MRI
Abdominal VAT and SAT volumes	• Dixon technique

Abbreviations: ADC = apparent diffusion coefficients; BOLD = blood oxygenation level-dependent; DWI-MRI = diffusion-weighted imaging MRI; GFR = glomerular filtration rate; PC-MRI = phase contrast MRI; PDFF = proton density fat fraction; R_2* = the inverse of transverse relaxation time constant measured by MRI; SAT = subcutaneous adipose tissue; VAT = visceral adipose tissue.

Mean arterial flow (MAF)

MAF is the mean blood flow (mL/min) in the renal arteries calculated using PC-MRI.

Peak systolic velocity (PSV) and end-diastolic velocity (EDV)

PSV is the highest velocity (cm/s) measurement within the systole of the cardiac cycle. EDV is the lowest measured velocity (cm/s) within the diastole of the cardiac cycle. Both parameters will be measured using PC-MRI and cardiac gating to time systole and diastole.

Mean renal artery resistive index (RARI)

RARI (no units) will be calculated using the equation below:

RARI = (PSV – EDV) / PSV

PSV and EDV will be measured using PC-MRI. A high RARI value might indicate the presence of renal artery stenosis or other renal vascular diseases.

Global renal perfusion

Global renal perfusion will be assessed as the mean renal flow per 100 g of kidney tissue as measured by MRI (mL/min/100 g).

Renal injury and function

Renal function and renal injury will be assessed using T_1 mapping scans. Renal microstructural changes will be assessed for cortex and medulla separately using image masks. Higher T_1 (ms) values and lesser corticomedullary differentiation on T_1 maps were associated with worsened renal function (Wolf et al. 2018).

Renal volumetric measures

Total kidney, cortical, and medulla volume (cm^3) will be measured by delineating corresponding region-of-interests from T_1 maps.

Renal oxygenation

An indirect assessment of renal oxygenation will be conducted based on the paramagnetic properties of endogenous deoxyhemoglobin based on BOLD MRI-measured R_2* parameter (s^{-1}). R_2* increases with the increase in deoxyhemoglobin levels and associates with reduced tissue oxygenation. Cortex and medulla oxygenation will be assessed separately from BOLD images.

Renal fat metrics

The renal fat measures will be acquired to support exploratory objectives provided in the SAP. Increased renal sinus fat and perirenal fat are associated with metabolic disease, CKD, impaired renal function, and blood hypertension (Favre et al. 2017; Notohamiprodjo et al. 2020).

Renal sinus fat and perirenal fat volumes (cm^3) will be measured utilizing MRI scans acquired using Dixon technique (Ma 2008).

Parenchymal proton density fat fraction (PDFF) will be assessed using MRI-PDFF maps to measure the relative amount of fat in renal parenchyma (%). The region-of-interests will be placed on parenchymal tissues to calculate PDFF values.

Renal diffusion

The renal diffusion measures will be acquired to support exploratory objectives provided in the SAP. Renal diffusion will be assessed by ADC maps obtained from DWI-MRI. ADC estimates the water molecule motion in the tissue and is associated with changes in renal microstructure, renal fibrosis, cellular infiltration (inflammatory or tumorous) or edema, and changes in renal perfusion. A decrease in ADC values (mm^2/s) in cortex and medulla might reflect a decrease in renal function, increase in tissue fibrotic changes, and inflammation (Caroli et al. 2018).

Aortic flow

The aortic flow will be acquired to support exploratory objectives provided in the SAP. The mean aortic flow, PSV, and EDV will be assessed using PC-MRI.

Abdominal visceral/subcutaneous adipose tissue

The adipose tissue measures will be acquired to support exploratory objectives provided in the SAP. Volumes of abdominal visceral adipose tissue and subcutaneous adipose tissue will be measured using MRI scans acquired using Dixon technique.

All MRI PD parameters will be assessed by the MRI vendor designated by Lilly. Additional analysis may be performed if warranted upon review of the data. Details on MRI procedures are presented in the training material from the centralized MRI vendor.

8.5.3. Other Measures

Creatinine-corrected FENa

Sponsor statisticians will calculate the creatinine-corrected FENa using creatinine and sodium values from blood and urine sample collections summarized in the SoA using the equation (Espinel 1976)

100 × [(Serum creatinine (mg/dL) × Urine sodium (mEq/L)) / (serum sodium (mEq/L) × urine creatinine (mg/dL)]

Filtration fraction estimated from mGFR and MRI-assessed renal blood flow

Sponsor statisticians will calculate the filtration fraction using the equation (Villa et al. 2020)

mGFR (mL/min) / renal plasma flow (RPF) (mL/min)

where RPF is MRI-measured RBF x (1 - hematocrit).

UACR

The central laboratory will calculate UACR using urinary albumin and creatinine values from the clinical chemistry sample collections summarized in the SoA.

24-hour UAE

Sponsor statisticians will calculate UAE using the 24-hour urine sample collections summarized in the SoA.

Urinary electrolytes

The urine chemistry sample collections include the urinary electrolytes as summarized in Section 10.2.

Body weight

See Section 10.7 for methods for measuring body weight.

8.6. Genetics

A whole blood sample will be collected at times specified in the SoA, where local regulations allow.

See Section 10.5 for information regarding genetic research and Section 10.1.12 for details about sample retention and custody.

8.7. Biomarkers

Stored samples for exploratory biomarker research will be collected at times specified in the SoA, where local regulations allow. Stored sample test type is specified in Section 10.2.

Samples may be used for research on the drug targets, disease process, variable response to retatrutide, pathways associated with obesity, diabetes mellitus, and related clinical traits, or comorbidities, mechanism of action of retatrutide or research method, or for validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, or related clinical traits, or comorbidities, including CKD.

All samples will be coded with the participant number. These samples and any data generated can be linked back to the participant only by the investigative site staff.

See Section 10.1.12 for details about sample retention.

8.8. Immunogenicity Assessments

At the visits and times specified in the SoA (Section 1.3), venous blood samples will be collected to determine antibody production against retatrutide. Antibodies may be further characterized for cross-reactive binding to endogenous counterparts (native GIP, GLP-1, and glucagon), and their ability to neutralize the activity of the retatrutide and endogenous counterparts.

To interpret the results of immunogenicity, a venous blood sample will be collected at the same time points to determine the plasma concentrations of retatrutide. All samples for immunogenicity should be taken predose when applicable and possible.

Immunogenicity will be assessed by a validated assay designed to detect ADA in the presence of retatrutide at a laboratory approved by the sponsor.

Treatment-emergent ADA are defined in Section 9.3.7.5. In the event of drug hypersensitivity reactions (immediate or nonimmediate), additional samples may be collected as described in Section 10.2.1.

See Section 10.1.12 for details about sample retention.

Individual ADA data will not be reviewed by the investigator to avoid unblinding until the study is complete.

8.9. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

The statistical analysis plan will be finalized prior to database lock, and it will include a more technical and detailed description of the statistical analyses described in this section. This section is a summary of the planned statistical analyses of the most important measures, including primary and key secondary measures.

9.1. Statistical Hypotheses

The null hypothesis for the primary objective is the following:

> H_0: retatrutide QW is not different from placebo with respect to the mean change in GFR (iohexol) from baseline at 24 weeks in participants with overweight or obesity and CKD with or without T2D.

This hypothesis will be tested at 2-sided significant level of 0.05.

9.2. Analyses Sets

For the purpose of analysis, the following populations are defined.

Analysis Set	Description
Enrolled Participants	All participants who sign informed consent.
Randomized Participants	All participants who are randomly assigned to study intervention.
Safety Participants	All participants who are randomly assigned to a study intervention and take at least 1 dose of double-blind study intervention.
Completed Participants	All participants who are randomly assigned to a study intervention, remain on treatment, and have evaluable data collected at 24 weeks, without discontinuation of study intervention or initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB.

For the purpose of analysis, the following data points sets are defined:

Data Points Set	Description
Primary Estimand Data Points Set	Data points obtained during the treatment period at or after randomization up to the earliest date of discontinuation of study intervention or initiation of new SGLT2 inhibitor, ACE inhibitor, or ARB.

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 statistical methods described in the protocol will require a protocol amendment only if it changes a principal feature of the protocol. Any other change to the statistical analyses and the justification for the change will be documented in the SAP and/or clinical study report. Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data. Additional exploratory analyses of data may be conducted as deemed appropriate without further changes made to the protocol or SAP. Analyses will be fully detailed in the SAP.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided.

Unless otherwise noted, in statistical summaries and analyses, the statistical treatment comparisons will only be performed between retatrutide and placebo.

Unless specified otherwise, baseline will be defined as the last available non-missing measurement prior to taking the first dose.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of retatrutide with placebo irrespective of adherence to study intervention. Thus, safety analyses will be conducted using the safety participants during the treatment period or during the treatment period plus the posttreatment safety follow-up period.

Summary statistics for continuous measures will include sample size, mean, SD, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time will include an MMRM, with terms of treatment, visit, and treatment-by-visit interaction, stratification factors, and baseline measurement as a covariate. ANCOVA with robust inference (Ye et al. 2022) may be used to make comparisons among treatment groups for continuous measurements with only 1 postbaseline assessment.

Other statistical methods may be used, as appropriate, and details will be described in the SAP.

Handling of missing and unused data is addressed by the use of the hypothetical strategy and described by the Primary Estimand Data Points Set; efficacy analyses will use data points up to the date of discontinuation of study intervention or the introduction of concomitant medications (SGLT2 inhibitor, ACE inhibitor or ARB) and any missing data is treated as missing at random by the MMRM model. Safety analyses will use all data points for Safety Participants regardless of discontinuation or new concomitant medication. Imaging data from MRI scanning is reviewed individually and with previous images from the same participant to ensure reliability, with rescans requested for any spurious result.

Adjustments to the planned analyses are described in the final CSR.

9.3.2. Treatment Arm Comparability

9.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided at the end of the study.

Frequency counts and percentages of all participants screened, randomly assigned, and receiving at least 1 dose of study intervention will be presented by treatment groups.

A listing of randomized participants not receiving study intervention will be provided.

All participants who discontinue the study intervention and study will be identified, and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment.

9.3.2.2. Participant Characteristics

Demographics and other baseline characteristics will be summarized by treatment group for all randomized participants.

9.3.2.3. Concomitant Therapy

Concomitant medications, including previous therapy, will be summarized by treatment group for the safety participants during the treatment period.

9.3.2.4. Treatment Compliance

Treatment compliance is defined as taking at least 75% and no more than 125% of required injections of study intervention during the treatment period. Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment groups using the safety participants during treatment period.

9.3.3. Primary Analysis

The primary analysis aligned to the estimand based on hypothetical strategy will analyze change in GFR (iohexol) from baseline at 24 weeks using a mixed model for repeated measures. The safety participants with primary estimand data points set will be used. Details of the statistical modeling will be provided in the SAP.

9.3.4. Secondary Analysis

Secondary measures with repeated postbaseline assessments will be analyzed similarly to the primary analysis in the primary estimand data points set, guided by the estimand based on hypothetical strategy. For continuous measurements with only 1 postbaseline assessment, ANCOVA with robust inference (Ye et al. 2022) may be used to make comparisons among treatment groups.

Analysis details for all secondary measures will be provided in the SAP.

No adjustments for multiplicity will be performed, as these data are considered hypothesis generating.

9.3.5. Supplementary Analysis

Supplementary analyses will be conducted to analyze change in GFR (iohexol) from baseline at 24 weeks between retatrutide to placebo on completed participants. Details and additional supplementary analyses will be provided in the SAP.

9.3.6. Exploratory Analysis

Additional exploratory analyses will be conducted, and details will be provided in the SAP.

9.3.7. Safety Analyses

Safety endpoints in this section are exploratory and full analysis details will be provided in the SAP.

9.3.7.1. Study Intervention Exposure

Exposure to each study treatment will be calculated for each participant and summarized by treatment group.

9.3.7.2. Adverse Events

Adverse events will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported with preferred terms and system organ class. Counts and proportions of participants experiencing events will be reported for each treatment group, and Fisher's exact test will be used to compare the treatment groups.

The proportion of participants experiencing TEAE, SAE, and discontinuation due to AE will be summarized by treatment group.

9.3.7.3. Adverse Event of Special Interest

The list of AESI in this study is provided in Section 8.3.3. Summaries and analyses for incidence of AESIs may be provided by treatment.

The details of analysis of AESI will be provided in the SAP.

9.3.7.4. Other Adverse Event Assessments

9.3.7.4.1. Gastrointestinal Events

Summaries and analyses for incidence and severity of nausea, vomiting, and diarrhea will be provided for each treatment.

9.3.7.4.2. Depression, Suicidal Ideation, and Behavior

In addition to the summary of TEAEs, suicidal ideation and behavior will be assessed by C-SSRS, and depression-related symptoms will be assessed using the PHQ-9.

The analysis details will be provided in the SAP.

9.3.7.4.3. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual values and change from baseline to postbaseline values of central laboratory measures and vital signs will be summarized at each scheduled visit. Change from baseline to postbaseline value will be summarized for participants who have both a baseline and at least 1 postbaseline result.

The percentages of participants with treatment-emergent abnormal, high, or low measures, including laboratory parameters and vital signs will be summarized and compared between treatment groups using Fisher's exact test.

The analysis details will be provided in the SAP.

9.3.7.4.4. Pharmacokinetic/Pharmacodynamic Analyses

No formal PK data analysis will be performed. PK data will be summarized.

9.3.7.5. Evaluation of Immunogenicity

The frequency and percentage of participants with preexisting ADA and with retatrutide TE ADA may be reported.

TE ADA are defined as

- treatment-induced ADA - those with a titer 2-fold (1 dilution) greater than the minimum required dilution if no ADAs were detected at baseline, or
- treatment-boosted ADA - those with a 4-fold (2 dilutions) increase in titer compared to baseline if ADAs were detected at baseline.

For the TE ADA+ participants, the distribution of maximum titers may be reported.

The frequency of neutralizing antibodies against retatrutide, if performed, may be reported in TE ADA+ participants.

If cross-reactivity to native GLP-1, GIP, and glucagon, or neutralizing antibodies against native GLP-1 and GIP, and glucagon assays are performed, the frequency of each may be reported.

The relationship between the presence of antibodies and the retatrutide concentrations and PD response, including safety and efficacy to retatrutide, may be assessed.

Additional details may be provided in the SAP.

9.3.8. Other Analyses

9.3.8.1. Subgroup Analyses for the Primary Objective Measure

Details of the subgroup analyses will be shown in the SAP.

The following subgroup variables for the primary measure may be considered, but are not limited to

- age (<65 years and ≥65 years)
- sex (female and male)
- baseline eGFR and mGFR (≥45 and <45 mL/min per 1.73 m^2)
- baseline UACR (<30 and ≥30 mg/g)
- baseline BMI (<35 and ≥35 kg/m^2)
- diabetes status (with diabetes and without diabetes)
- race
- ethnicity, and
- baseline SGLT2 inhibitor use (Yes and No).

9.3.8.2. Supportive Analysis

Relationship between kidney oxygenation, renal sinus fat, and GFR measured using iohexol clearance may be explored. The relationship will be explored at baseline and after 24 weeks of intervention with retatrutide.

Details will be provided in the SAP.

9.4. Interim Analysis

Primary analyses will be conducted as described in Section 9.3, when all applicable participants have completed the Week 24 visit or have discontinued study intervention.

Potential prespecified interim analyses

Two interim analyses prior to the primary database lock may be conducted when approximately 25% and 50% of participants have completed Week 24, or have discontinued intervention, for the purpose of evaluating PD and safety analyses, and supporting planning activities associated with the retatrutide clinical development program. The primary goal is that of safety and PD; investigation of endpoints will not result in any changes to the trial and hence no adjustment to final alpha levels will be made due to these interim analyses. Full details will be given in SAP and AC charter.

Changes in the number of interim analyses and the timing of conducting the interim analyses due to the change of enrollment rate will not require an amendment.

Assessment of unblinded interim data

The unblinded interim data will be reviewed by an Assessment Committee. The planned interim analysis and data review process will be described in the assessment committee charter. Study sites will receive information about interim safety results only if they need to know for the safety of their participants.

Interim analyses will use the same statistical analysis methods as those described for the relevant endpoints in Section 9.3, but will be descriptive in nature.

9.5. Sample Size Determination

Approximately 120 participants are planned to be randomly assigned to study intervention in a 1:1 ratio of 60 participants to retatrutide and 60 participants to placebo. Assuming a 15% dropout rate, approximately 51 participants will complete each of the retatrutide and placebo arms.

Sample size selection is guided by the objective of establishing a significantly different change in measured GFR, of retatrutide compared to placebo, from baseline to Week 24. The chosen sample size provides at least 80% power to establish a significant difference in change of GFR between retatrutide and placebo, based on a 2-sided 2-sample t-test with significance level of 0.05, a standard deviation (SD) of 8.1 and a mean change in GFR of 4.56 mL/min per 1.73 m^2 at Week 24 from baseline compared to placebo.

The effect size is calculated from Ph2 studies of retatrutide assuming 50% T2D subjects and 50% non-T2D subjects based on the estimand with hypothetical strategy, where the mean change in eGFR was 1.50 mL/min per 1.73 m^2 for T2D participants and 7.61 mL/min per 1.73 m^2 for non-T2D participants yielding a mean across all participants of 4.56 mL/min per 1.73 m^2. In these same studies, the standard deviation of eGFR change was 7.1 in the T2D population and 8.9 in the non-T2D population, yielding an average of 8.0 for the 2 groups combined. To leverage the use of a measured GFR endpoint which is known to be less prone to variability than estimated GFR, the more conservative SD = 8.1 was adopted from the results of external trial,

MB102035, comparing the effect of SGLT-2 inhibitor dapagliflozin on measured GFR in participants with T2D (Lambers Heerspink et al. 2013).

Sample size calculations were conducted using nQuery Version 8.

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 CIOMS International Ethical Guidelines
- applicable ICH GCP Guidelines, and
- 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 participants.

Protocols and any substantial amendments to the protocol will require health authority approval prior to initiation except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations, and
- reporting to the sponsor or designee significant issues related to participant safety, participant rights, or data integrity.

Investigator sites are compensated for participation in the study as detailed in the Clinical Trial Agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are

responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

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

Potential participants must be informed that their participation is voluntary. Participants will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, privacy, and data protection requirements, where applicable, and the IRB/IEC or study center.

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

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and Ethical Review Board consenting guidance. A copy of the ICF(s) must be provided to the participant and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor to protect the participant's personal data. Any participant information, such as records, datasets, or tissue samples that are transferred to the sponsor will contain the identifier only. Participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that the participant's personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant who will be required to give consent for their data to be used as described in the informed consent. This is done by the site personnel through the informed consent process.

The participant must be informed through the informed consent by the site personnel that their 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 information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration, or loss of information or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

The transfer of personal data is subject to appropriate safeguards through contractual agreements and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation.

10.1.5. Committees Structure

10.1.5.1. Adjudication Committee

An independent committee of physicians external to Lilly, with the appropriate expertise, will be responsible for adjudication of clinical events described in Section 8.3.3 in a blinded fashion.

10.1.5.2. Assessment Committee

An internal AC will be responsible for reviewing unblinded data during the study.

The committee will include, at a minimum, a clinical research physician, global patient safety physician with appropriate expertise, and a statistician, all external to the study team.

Access to the unblinded data may be provided to the data monitoring safety committees on other retatrutide trials.

Details about the membership, purpose, responsibilities, and operation will be included in the AC charter.

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.

The summary of results will be posted within the time frame specified by local law or regulation. If the study remains ongoing in some countries and a statistical analysis of an incomplete dataset would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic 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, statistical analysis plan, clinical study report, and blank or annotated case report forms, will be provided in a secure data-sharing environment for up to 2 years per proposal.

For details on submitting a request, see the instructions provided at www.vivli.org.

10.1.7. Data Quality Assurance

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

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF. This includes laboratory tests, medical records, and clinical notes.

The investigator must review and confirm that data entries are accurate and complete throughout the duration of the study, by physically or electronically signing the CRF, as instructed by the sponsor. All completed CRFs must be signed prior to archival.

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

QTLs will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study, and important excursions from the QTLs and remedial actions taken will be summarized in the CSR.

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.

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

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

In addition, sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, 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 EDC system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided EDC system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Additionally, clinical outcome assessment data (participant-focused outcome instrument) for suicidality assessments will be collected by the authorized study personnel as well as the C-SSRS and PHQ-9 via paper source documents or via electronic data collection tool at site and will be transcribed by the authorized study personnel into the EDC system if paper is used. Other data (Study Drug Administration and Hypoglycemia information) will be collected by the participant, via a paper source document or electronic participant diary, and paper will be, if collected by paper source, transcribed by the authorized study personnel into the EDC system and will serve as the source documentation. If the data is collected via electronic data collection by the participant or site, then the eCOA data will serve as the source documentation and the investigator does not maintain a separate written or electronic record of these data.

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in the central vendor's database system, and reports/electronic transfers will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

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

Data reported on or entered in the CRF and 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 the site confirmation of source data.

10.1.9. Study and Site Start and Closure

First act of recruitment

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

Study or site termination

The sponsor or sponsor's 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

- study termination due to discontinuation of further study intervention development
- site termination due 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, evaluated after a reasonable amount of time, of participants by the investigator, or
    - total number of participants included earlier than expected.

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

10.1.10. Publication Policy

In accordance with the sponsor's publication policy, the results of this study will be submitted for publication by a peer-reviewed journal.

10.1.11. Investigator Information

Researchers with appropriate education, training, and experience, as determined by the sponsor, will participate as investigators in this clinical study.

10.1.12. Long-Term Sample Retention

Sample retention enables use of new technologies, response to regulatory questions, and investigation of variable response that may not be observed until later in the development of the intervention or after the intervention becomes commercially available.

This table describes the retention period for potential sample types.

Sample Type	Custodian	Retention Period after Last Participant Visit[a]
Genetics	Sponsor or designee	Up to 15 years
Exploratory biomarker	Sponsor or designee	Up to 15 years
Immunogenicity	Sponsor or designee	15 years
Pharmacokinetic	Sponsor or designee	1 year

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by the central laboratory.

Local laboratory results are only required in the event that the central laboratory results are not available in time for either study intervention administration and/or response evaluation. If a local sample is required, it is important that the sample for central analysis is obtained at the same time.

In circumstances where the sponsor approves local laboratory testing in lieu of central laboratory testing (in the table below), the local laboratory must be qualified in accordance with applicable local regulations.

Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.

Additional tests may be performed at any time during the study as determined necessary by the investigator or required by local regulations.

Investigators must document their review of the laboratory safety results.

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

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs – red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs – white blood cells)	
Differential	
Neutrophils	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs), if indicated	
Clinical Chemistry	Assayed by Lilly-designated laboratory
Sodium	
Potassium	
Magnesium	
Chloride	

Clinical Laboratory Tests	Comments
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Additional Testing	Assayed by Lilly-designated laboratory
Iohexol	Results will not be provided to investigative sites
HbA1c (hemoglobin A1c)	
Calcitonin	
Pancreatic amylase	
Pancreatic lipase	
Cystatin-C	
Thyroid-stimulating hormone (TSH)	
Mechanistic biomarkers (see table in Section 10.2.2)	Results will not be provided to the investigative sites
Lipid Panel	Assayed by Lilly-designated laboratory
High-density lipoprotein (HDL)	
Low-density lipoprotein cholesterol (LDL-C)	Results will be calculated by the central laboratory. If triglyceride level exceeds maximum value for calculation, LDL will be directly measured.
Very low-density lipoprotein cholesterol (VLDL-C)	
Cholesterol	
Triglycerides	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	

Clinical Laboratory Tests	Comments
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment, if indicated	
Urine Chemistry	Assayed by Lilly-designated Laboratory
Albumin	
Creatinine	
Sodium	Results will not be provided to the investigative sites
Potassium	Results will not be provided to the investigative sites
Chloride	Results will not be provided to the investigative sites
Calcium	Results will not be provided to the investigative sites
Phosphate	Results will not be provided to the investigative sites
Bicarbonate	Results will not be provided to the investigative sites
Urea	Results will not be provided to the investigative sites
Glucose	
24-Hour Urine Chemistry	Assayed by Lilly-designated Laboratory
Albumin	Results will not be provided to the investigative sites
Creatinine	Results will not be provided to the investigative sites
Sodium	Results will not be provided to the investigative sites
Glucose	Results will not be provided to the investigative sites
Hormones (Female)	
Serum pregnancy	Assayed by Lilly-designated laboratory
Urine pregnancy	Evaluated locally
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory
Calculations	Generated by Lilly-designated Laboratory
eGFR calculated using CKD-EPI Cystatin-C-based equation	
eGFR calculated using CKD-EPI creatinine-based equation	
Urinary albumin/creatinine ratio (UACR)	
Pharmacokinetic Samples – retatrutide concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Genetic Sample	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Stored Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites

Clinical Laboratory Tests	Comments
Exploratory biomarker samples:	
Serum	
Plasma (EDTA)	
Plasma (P800)	
Urine	
Urine sampling for metabolomics	
Immunogenicity Samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Anti-retatrutide antibodies	
Anti-retatrutide antibodies neutralization	

Abbreviation: EDTA = ethylenediaminetetraacetic acid.

10.2.1. Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory test results from these samples to characterize hypersensitivity events across the clinical development program.

When to collect samples after a systemic hypersensitivity event occurs

Collect the samples listed below if a systemic hypersensitivity event is suspected. The timing should be as designated in the table, assuming the participant has been stabilized.

Obtain follow-up predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return-to-baseline values.

Timing	Laboratory Test[a]
Collect from 30 min to 4 hr after the start of the event. ***Note:*** The optimal collection time is from 1 to 2 hr after the start of event.	Total tryptase
Collect only if not already collected on the same day as the event. ***Note:*** If collecting, collect up to 12 hr after the start of the event.	Retatrutide antidrug antibodies (ADA)
	Retatrutide concentration

[a] All samples for hypersensitivity testing will be assayed by Lilly-designated laboratory. Results will not be provided to the study site. If samples are not collected or are collected outside the specified period, this will not be considered a protocol deviation.

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management.

10.2.2. Mechanistic Biomarkers

Biomarkers	Results will not be provided to the investigative sites
Amino acid panels (alanine, arginine, glutamine, proline, serine, threonine, lysine, asparagine, histidine, isoleucine, leucine, methionine, phenylalanine, tryptophan, valine)	To assess GCGR-mediated amino acid metabolism
Adiponectin (total), HOMA2-IR (computed with insulin or C-peptide), insulin, C-peptide	To assess changes in insulin sensitivity
Aldosterone (serum), plasma renin activity, angiotensin 1, angiotensin 2, angiotensinogen	To assess the renin/angiotensin axis
Copeptin	To assess vasopressin activity
hs-CRP	To assess inflammation
FFA, beta-hydroxybutyrate	To assess fatty acid metabolism and oxidation
Lactate	To assess anaerobic glycolysis
Intact PTH, 25-hydroxyvitamin D, vitamin D1, Calcium, Phosphate	To assess regulation of calcium and phosphate metabolism
Plasma metanephrines	To assess catecholamine production
ApoB, ApoC3, and NT-proBNP	To assess markers of cardiovascular risk
Urinary metabolomics panels	To assess changes in renal carbohydrate, lipid, protein and mitochondrial metabolism
Serum large-scale proteomics panels	To assess changes in protein metabolism

Abbreviations: ApoB = apolipoprotein B; ApoC3 = apolipoprotein C3; FFA = free fatty acids; GCGR = glucagon receptor; HOMA2-IR = homeostasis model assessment-2 insulin resistance; hs-CRP = high-sensitivity C-reactive protein; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PTH = parathyroid hormone.

10.2.3. Centrally Available Laboratory Tests Related to the Assessment of Nutritional Status and Micronutrient Levels

The following are additional tests available through the central laboratory that may be assessed per investigator's discretion if there is concern for poor nutrition or specific micronutrient deficiencies.

Category	Laboratory Test
Special tests	Vitamin A
	Vitamin B1 (Thiamine)
	Vitamin B9 (Folate)
	Vitamin B12
	Vitamin D (25-hydroxy vitamin D)[a]
Hematology	Complete blood count[b]
Clinical Chemistry	Clinical chemistry panel[c]
	Zinc
	Pre-albumin
	Intact PTH[a]
	TSH reflex to free T4
Iron Panel	Serum iron
	TIBC
	Transferrin saturation (%)
	Ferritin

Abbreviations: PTH = parathyroid hormone; TIBC = total iron-binding capacity; TSH = thyroid stimulating hormone.

[a] Refer to Section 10.2.2 for mechanistic biomarkers.

[b] Refer to section 10.2 contents of the complete blood count panel.

[c] Refer to Section 10.2 for the contents of clinical chemistry panel.

Note: Tests will be assayed by a Lilly-designated laboratory and results will be provided to the investigative sites where allowed (or appropriate).

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

The investigator may perform additional tests locally, if clinically indicated, for acute study participant management or if a test is not available centrally.

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

10.3.1. Definition of AE

Definition

- An AE is any untoward medical occurrence in a participant administered a pharmaceutical product and which does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal (investigational) product, or investigational combination product whether or not related to the medicinal (investigational) product or investigational combination 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, and vital sign measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.

Events <u>NOT</u> meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease or disorder being studied or expected progression, signs, or symptoms of the disease or disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure, for example, endoscopy and appendectomy. The condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

- Results in death
- Is life-threatening
    - The term *life-threatening* in the definition of *serious* refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization
    - In general, hospitalization signifies that the participant has been admitted to hospital or emergency ward (usually involving at least an overnight stay) for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
    - Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.
- 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.
- Is a congenital anomaly/birth defect
    - Abnormal pregnancy outcomes, for example, spontaneous abortion, fetal death, stillbirth, congenital anomalies, and ectopic pregnancy, are considered SAEs.
- Other situations:
    - Medical or scientific judgment should be exercised by the investigator in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
    - Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood

dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

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

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

AE, SAE, and product complaint recording

- When an AE/SAE/product complaint occurs, it is the responsibility of the investigator to review all documentation, 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 participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page, and product complaint information is reported on the Product Complaint form.
- Note: An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint form for product complaints.
- There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Moderate: A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research participant.
- Severe: A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with an SAE. Severe is a category utilized for rating the intensity of an event, and both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least one of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

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

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible.

This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide 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 SAE paper form (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 participant 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 an SAE paper form (see next section) or to the sponsor by telephone.
- Contacts for SAE reporting can be found on the SAE paper form.

SAE reporting via paper form

- Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.
- 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 on 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 participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. Investigator safety reports will be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (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.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with an FSH >40 mIU/mL or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women should not be taking medications during amenorrhea, such as oral contraceptives, hormones, gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea.

10.4.2. Contraception Guidance

10.4.2.1. Guidance for Women

WOCBP and WNOCBP may participate in this study.

WOCBP who are completely abstinent as their preferred and usual lifestyle or in a same-sex relationship as their preferred and usual lifestyle must adhere to the rules in this table.

Must…	Must not…

agree to either remain abstinent or stay in a same-sex relationship without sexual relationships with males	• use periodic abstinence methods
	  ○ calendar
	  ○ ovulation
	  ○ symptothermal, or
	  ○ post-ovulation
	• declare abstinence just for the duration of a study, or
	• use the withdrawal method.

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle must adhere to the rules in this table.

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to first dose of study intervention. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 60 days after the last dose of the study intervention.

10.4.2.2. Guidance for Men

Males may participate in this study.

The table below describes contraception guidance for all men.

Topic	Guidance
For all men	should refrain from sperm donation for the duration of the study and for 4 months after the last dose of the study intervention
Contraception for men with partners of childbearing potential	• either remain abstinent, if this is their preferred and usual lifestyle, or • must use condoms during intercourse for the duration of the study and • for 4 months after the last dose of study intervention

Contraception for men in exclusively same-sex relationships, as their preferred, and usual lifestyle	are not required to use contraception

10.4.2.3. Examples of Different Forms of Contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives[a] • injectable contraceptives[a] • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices.

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

Ineffective forms of contraception whether used alone or in any combination	• spermicide alone • immunocontraceptives • periodic abstinence • fertility awareness (calendar method, temperature method, combination of above 2, cervical mucus, or symptothermal) • withdrawal • postcoital douche, or • lactational amenorrhea.

[a] Participants that have started implantable or injectable contraceptives (such as Depo-Provera®) within 18 months prior to screening are excluded from this study.

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to retatrutide or obesity, diabetes, and related complications and diseases, including chronic kidney disease. Samples may be used to investigate variable response to retatrutide, including evaluation of AEs or differences in pharmacodynamic, mechanistic, safety, or efficacy measures. They may also be used to develop tests/assays, including diagnostic tests related to retatrutide or obesity, diabetes, or related complications. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome, as appropriate.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to retatrutide or study interventions of this or related classes of medications to understand study disease or related conditions.

The results of genetic analyses may be reported in the CSR or in a separate study summary.

The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on retatrutide continues but no longer than 15 years or other period as per local requirements.

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

Hepatic evaluation testing

See Section 8.2.7 for guidance on appropriate test selection.

The Lilly-designated central laboratory should complete the analysis of all selected testing except for testing listed in the investigator-designated local laboratory table. The central laboratory will report results if a validated test or calculation is available.

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

The local laboratory must be qualified in accordance with applicable local regulations.

Tests assayed by Lilly-designated central laboratory	
Hepatic Hematology Panel	**Hepatitis A virus (HAV) testing:**
Hemoglobin	HAV total antibody
Hematocrit	HAV IgM antibody
Erythrocytes (RBCs - red blood cells)	**Hepatitis B virus (HBV) testing:**
Leukocytes (WBCs - white blood cells)	Hepatitis B surface antigen (HBsAg)
Differential:	Hepatitis B surface antibody (anti-HBs)
Neutrophils, segmented	Hepatitis B core total antibody (anti-HBc)
Lymphocytes	Hepatitis B core IgM antibody
Monocytes	HBV DNA[a]
Basophils	**Hepatitis C virus (HCV) testing:**
Eosinophils	HCV antibody
Platelets	HCV RNA[a]
Cell morphology (RBC and WBC)	**Hepatitis D virus (HDV) testing:**
Hepatic Clinical Chemistry Panel	HDV antibody
Total bilirubin	HDV IgM antibody
Direct bilirubin	**Hepatitis E virus (HEV) testing:**
Alkaline phosphatase (ALP)	HEV IgG antibody
Alanine aminotransferase (ALT)	HEV IgM antibody
Aspartate aminotransferase (AST)	HEV RNA[a]
Gamma-glutamyl transferase (GGT)	**Anti-nuclear antibody (ANA)**
Creatine kinase (CK)	**Anti-smooth muscle antibody (ASMA)**[b]
Hepatic Coagulation Panel	**Anti-actin antibody**[c]
Prothrombin time, INR (PT-INR)	**Immunoglobulin IgA (quantitative)**
Urine Chemistry	**Immunoglobulin IgG (quantitative)**
Drug screen	**Immunoglobulin IgM (quantitative)**
Haptoglobin	

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody
Alkaline phosphatase isoenzymes	CMV DNA[a]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA[a]
Phosphatidylethanol (PEth)	Liver kidney microsomal Type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV antibody	
EBV DNA[a]	

[a] Reflex/confirmation dependent on regulatory requirements or testing availability, or both.

[b] Not required if anti-actin antibody is tested.

[c] Not required if anti-smooth muscle antibody (ASMA) is tested.

10.7. Appendix 7: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Calculation of BMI

The following information has been adapted from standardized physical measurement protocols for the World Health Organization's STEPwise approach to Surveillance (STEPS) (WHO 2017).

Measuring height

Step 1. Ask the participant to remove their footwear and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when their height is measured).

Step 2. Ask the participant to stand on the calibrated height-measuring board (stadiometer) or against a wall with their feet together and their knees straight with their heels against the backboard, the stadiometer, or the wall.

Step 3. Ask the participant to look straight ahead without tilting their head up.

Step 4. Ask the participant to breathe in and stand tall. Measure and record the participant's height in **centimeters.**

Measuring weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in **kilograms to 1 decimal place.**
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Body weight should be measured in fasting state.

Step 1. Ask the participant to empty their pockets, remove their footwear, outerwear (coat, jacket, etc.), and any headgear (light headgear worn for religious reasons can remain, but this should be worn by the participant at every clinic visit when weight is measured).

Step 2. Make sure the scale is placed on a firm, flat, even surface (not on carpet, on a sloping surface, or a rough, uneven surface).

Step 3. Ask the participant to step onto the scale with 1 foot on each side of the scale.

Step 4. Ask the participant to stand still with arms by sides and then record weight in kilograms to the nearest one-tenth kilogram.

Measuring waist circumference

- Waist circumference should be measured in the horizontal plane and at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest.
- Measurements should be taken at the end of a normal expiration using a non-stretchable measuring tape. The tape should lie flat against the skin without compressing the soft tissue.

- The waist circumference should be measured twice, rounded to the nearest 0.5 cm. The measuring tape should be removed between the 2 measurements. Both measurements will be recorded in the CRF. If the difference between the 2 measurements exceeds 1 cm, this set of measurements should be discarded and the 2 measurements repeated.

Step 1: Ask the participant to wear little clothing (if available, garments could also be used).

Step 2: Ask the participant to stand with their feet close together, arms at their side, body weight evenly distributed.

Step 3: Ask the participant to relax and measure the participant's waist circumference.

Calculation of BMI

Round to 1 decimal point. For example, a BMI of 26.6 kg/m^2 should **not** be rounded to 27.0 kg/m^2.

10.8. Appendix 8: Definition and Management of Diabetes

Criteria for diagnosis of diabetes

Diabetes is defined when any 1 of the following occurs after randomization (American Diabetes Association 2023):

- a participant with classic symptoms of hyperglycemia or hyperglycemic crisis has a random serum glucose ≥200 mg/dL (11.1 mmol/L) or
- HbA1c ≥6.5% (48 mmol/mol) confirmed by repeat laboratory measurement or
- fasting serum glucose ≥126 mg/dL (7.0 mmol/L) confirmed by repeat laboratory measurement (fasting is defined as no caloric intake for at least 8 hours) or
- 2-hour glucose ≥200 mg/dL (11.1 mmol/L) by a 2-hour oral glucose tolerance test confirmed by repeat laboratory measurement.

The abnormal test should be confirmed within 4 weeks to confirm diagnosis of diabetes and to ensure that diabetes management is initiated without delay.

Recording of diabetes events

- Diabetes diagnosis and the onset date as assessed by investigator will be recorded in the AE CRF.
- If the diagnosis of diabetes is based on laboratory results, the date of the first abnormal HbA1c or glucose value above the defined glycemic thresholds should be indicated as the date of diagnosis, unless, in the investigator's opinion, a different date is more appropriate. If the diagnosis is based on initiation of any medication for the treatment of diabetes, the investigator should indicate the most probable date of diagnosis in the CRFs.

Management of diabetes

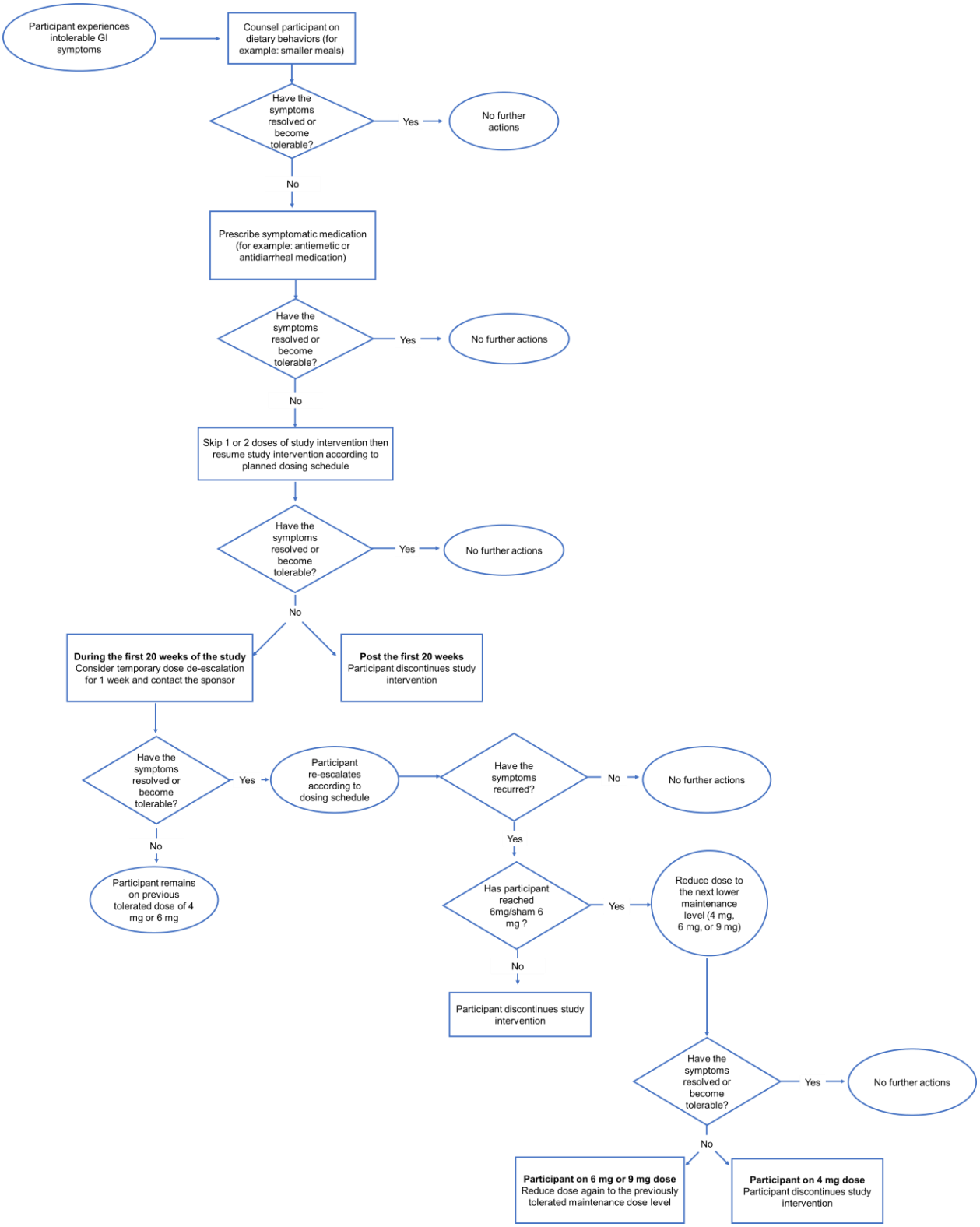
Participants who develop T2D during the study will

- be provided and trained to use a glucometer (the frequency of self-monitoring of blood glucose will be at the discretion of the investigator)
- be educated on the signs and symptoms of hypoglycemia and its treatment, and
- record hypoglycemic episodes in the provided diary per Section 8.3.4.3.

Participants will be provided with a letter showing the study results indicative of diabetes and will be referred to their usual care provider. The decision to initiate glucose-lowering medication and the choice of glucose-lowering medication will be at the discretion of the participant's usual care provider. Refer to Section 6.9.5 for further instructions.

Monitoring for hypoglycemia includes capture of events as defined in Section 8.3.4.3. If participants are diagnosed with T1D (rather than T2D), discontinuation of study intervention should occur as noted in Section 7.1.

10.9. Appendix 9: Management of Intolerable Gastrointestinal Symptoms



10.10. Appendix 10: Iohexol Clearance Method

Preparation before the procedure

- Perform the procedure in the morning after an overnight fast.
    - Participants should abstain from any food, caffeine, and medications from 22:00 the evening before, unless the investigator advises otherwise
- Participants with T2D using metformin may pause use of medication prior to iohexol procedure and resume after the completion of the test according to country-specific guidance or prescribing information of iohexol.
- Perform a physical examination focusing on signs and symptoms of dehydration before iohexol administration (see Section 5.3.2).
    - Participants should not use laxatives or diuretics on the day of the procedure, prior to iohexol administration.
    - Participants should drink at least 500 mL of water before arriving at the site.
    - Participants should drink water before, during, and after the procedure to prevent dehydration.
    - Study staff should not perform the iohexol clearance method on participants who show signs and symptoms of dehydration.
- Iohexol can cause hypersensitivity reactions Most severe reactions develop shortly after the start of the injection (within 3 minutes), but reactions can occur up to hours later. Premedication with antihistamines or corticosteroids does not prevent serious life-threatening reactions but may reduce both their incidence and severity. See iohexol country-specific prescribing information.

Iohexol procedure

1. Study staff will insert 2 peripheral intravenous cannulas, 1 for iohexol injection and 1 for the blood sampling.
2. Before administering iohexol, collect a blood sample as a control sample.
3. Determine the exact dose of iohexol by weighing the syringe before and after administration, with an accuracy of 0.01 g. For example, iohexol 300 mg I/mL weighs 1.35 g/mL and provides 647 mg iohexol/mL.
4. Administer 3235 mg of iohexol slowly over 2 minutes through the dedicated intravenous cannula.
5. Flush cannula with 10 mL of saline.
6. After saline flush is complete, record as time 0 for the iohexol clearance.
7. Weigh syringe to determine exact dose.
8. Observe participants for 30 minutes after iohexol administration for adverse reactions.

9. Collect blood samples at 120, 150, 180, 210, and 240 minutes after iohexol administration.
10. Process all blood samples according to standard operating procedures.

Information about iohexol

Iohexol is a non-ionic, monomeric, tri-iodinated, water-soluble substance mostly used as X-ray contrast medium.

Iohexol absorption, distribution, metabolism, and excretion

The maximum urinary concentration of iohexol appears within approximately 1 hour after injection. No metabolites have been detected. The protein binding of iohexol is very low (less than 2%). Close to 100% of the intravenously injected iohexol is excreted unchanged through the kidneys within 24 hours in patients with normal renal function.

Risk of hypersensitivity reactions

The risk of serious reactions related to the iohexol use is regarded as minor. However, iodinated contrast media may provoke serious, life-threatening, fatal anaphylactic/anaphylactoid reactions or other manifestations of hypersensitivity.

10.11. Appendix 11: Magnetic Resonance Imaging Procedure and Preparation

Magnetic resonance imaging of the kidney will be performed according to the SoA and as clinically indicated. The same scanner and imaging acquisition should be used for all time points (including repeat scans) for a particular participant. Any exceptions must be approved in advance of scanning by the Lilly-designated centralized MRI vendor.

All MRI acquisitions will be transmitted to Lilly-designated centralized MRI vendor for independent central review. It is recommended that these scans be transmitted as soon as possible (within 1 to 2 days) to allow for rapid quality review of the images and repeat scanning if necessary.

Specific imaging acquisition protocols designed to ensure consistency across sites will be provided in training material from the centralized MRI vendor. The scanning technologists will be blinded to participants' treatment assignments.

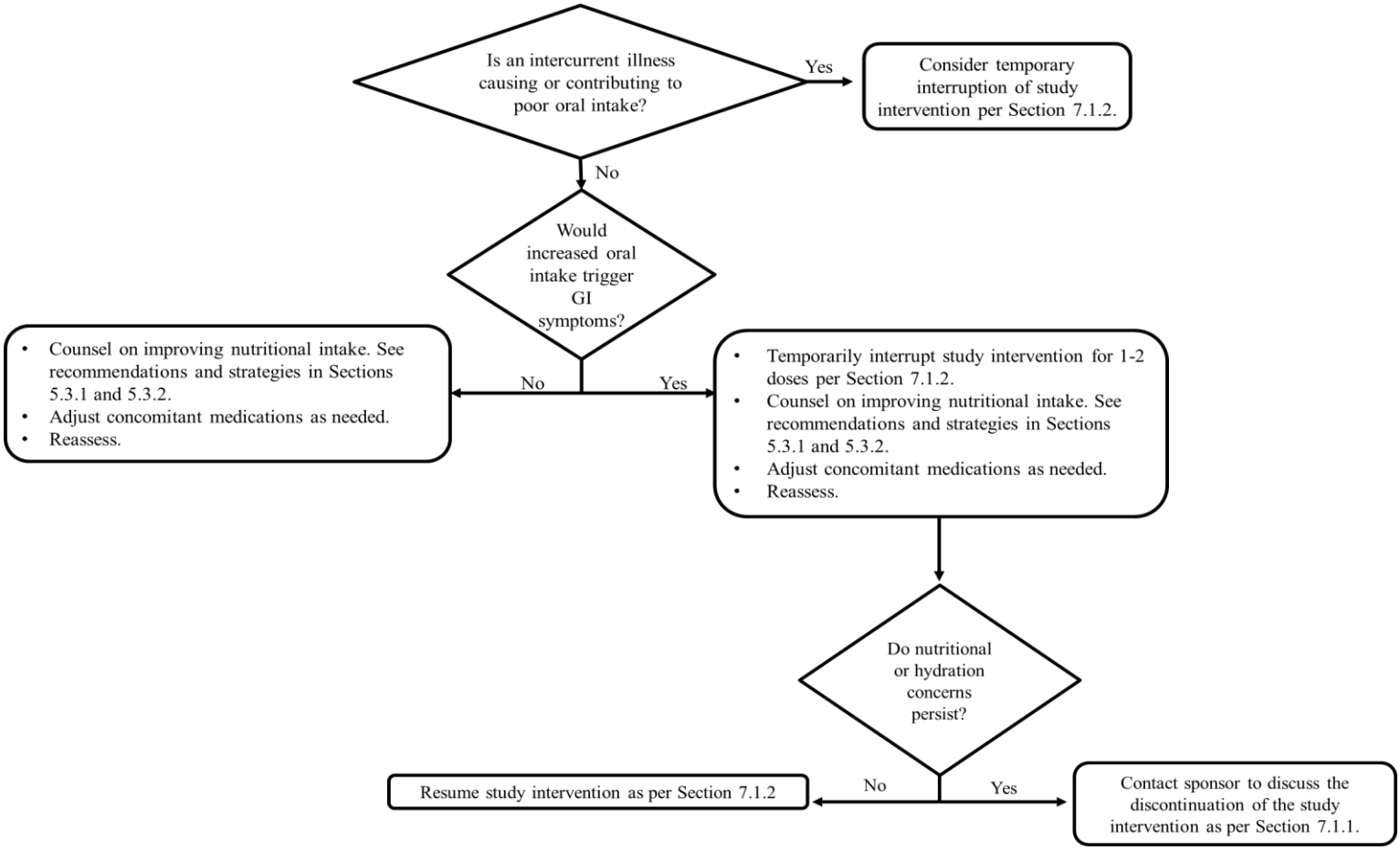
Preparation before the procedure

- Participants should drink at least 250 ml (8.5 oz) of water within 1 hour before the scan.
- Participants should avoid excess intake of sodium during the 3 days before the MRI scan.
- Participants should abstain from caffeine, nicotine, alcohol, and protein-rich meals within 6 hours of the MRI scan.

Participants must minimize movement during each MRI procedure, which can last 40-60 minutes for each scan.

10.12. Appendix 12: Management of Poor Nutrition and Dehydration

Follow the guidance in the flow chart and see Section 6.6.3 if there are concerns about poor nutrition or dehydration. Note that this flow chart does not preclude taking any other necessary steps for participant safety per the investigator's discretion.



10.13. Appendix 13: Considerations for Concomitant Medications

The table below provides considerations for adjusting concomitant medications in the setting of weight management. See Section 6.9.1 for general considerations on documenting changes in concomitant medications.

Concomitant Medication	Consider adjusting or discontinuing if …
Antihypertensives (including diuretics)	the participant is at risk of low blood pressure (e.g., in the setting of ongoing weight reduction or signs/symptoms of dehydration, if blood pressure is within or below normal range)
Diuretics and laxatives	the participant is at risk of dehydration (e.g., based on decreased fluid intake, increased fluid losses, or clinical signs or symptoms of dehydration)
Stimulant and osmotic laxatives	the participant has hyperuricemia or electrolyte abnormalities, such as hypernatremia or hypokalemia
Anti-hyperglycemics	the participant is at risk of hypoglycemia
Anti-emetics, such as domperidone and those with serotonin receptor agonism, such as, ondansetron, granisetron, palonosetron, and dolasetron	the participant has electrolyte abnormalities, such as hypokalemia or hypomagnesemia
Medications with weight-based dosing, such as thyroid medications	the participant is experiencing weight changes

10.14. Appendix 14: 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 or participants, or both, to attend on-site visits or to conduct planned study procedures.

Implementing changes under exceptional circumstances

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

After approval by local Ethical Review Boards, regulatory bodies, and any other relevant local authorities, implementation of these exceptional circumstance changes will not typically require additional notification to these groups, unless they have specific requirements in which notification is required, 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 participants. Additional important considerations for making a change are compliance with GCP, enabling participants to continue safely in the study and maintaining the integrity of the study.

Informed consent

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

- participation in remote visits, as defined 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
- AEs
- administer C-SSRS since last assessed
- review diary, or
- review diet and physical activity goals.

Mobile healthcare - Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits may include, but are not limited to

- weight measurement
- taking blood and urine samples
- conducting physical assessments, and
- collecting health information.

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 PCs remain unchanged.

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing for safety and participant management. However, central laboratory testing must be retained for Visits 1, 3, 9, ED, and Visit 801. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

When a participant 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 participant to go to the site and receive study supplies from site staff without completion of a full study visit
- asking the participant's designee to go to the site and receive study supplies on a participant'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 does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, participant's home), the investigator or 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 participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at V1 are valid for a maximum of 35 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

- If screening is paused for less than 35 days, the participant will proceed to the next study visit per the usual SoA, provided the randomization Visit 3 is conducted within 35 days from screening Visit 1.
    - The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
    - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 35 days, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreening once at the investigator's discretion and with medical monitor approval. If rescreening is performed, the participant must sign a new ICF and will be assigned a new identification number. Reconsenting and rescreening can occur no sooner than 30 days after the screen failure date. The screening procedures per the usual SoA should be followed, starting at the screening Visit 1, to ensure participant eligibility by the randomization at Visit 3.

Adjustments to visit windows

Whenever possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Screening Visits 1 and 2	Within 35 days before the intended date
Visit 3 and Visit 8	Within ±6 days of the intended date
Visit 9	Within ±10 days of the intended date

For participants 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 participants, visit types, and conducted activities were affected by exceptional circumstances. Dispensing or 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.

10.15. Appendix 15: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AC	assessment committee
ACE	angiotensin-converting enzyme
ADA	antidrug antibodies
ADC	apparent diffusion coefficient
AE	adverse event
AESI	adverse events of special interest
AHM	anti-hyperglycemic medication
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin II receptor blockers
AST	aspartate aminotransferase
authorized IMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
authorized AxMP	*Applicable to the EU only*: a medicinal product authorized in accordance with Regulation (EC) No 726/2004, or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an auxiliary medicinal product
AxMP	auxiliary medicinal product (see also NIMP): A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment. AxMP does not include investigational medicinal product (IMP) or concomitant medications. Concomitant medications are medications unrelated to the clinical trial and not relevant for the design of the clinical trial
BG	blood glucose
BKD	burden of kidney disease

blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received
BMI	body mass index
BMR	basal metabolic rate
BOLD MRI	blood oxygenation level-dependent magnetic resonance imaging
BP	blood pressure
CEC	clinical events committee
CFR	Code of Federal Regulations
CKD	chronic kidney disease
CKD-EPI	chronic kidney disease epidemiology collaboration
CIOMS	Council for International Organizations of Medical Sciences
Complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system
Compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CV	cardiovascular
DBP	diastolic blood pressure
DNA	deoxyribonucleic acid
DPP-4	dipeptidyl peptidase 4
DWI-MRI	diffusion-weighted imaging magnetic resonance imaging
ECG	electrocardiogram
eCOA	electronic clinical outcome assessments
ED	early discontinuation

EDC	electronic data capture
EDV	end-diastolic velocity
EKD	effects of kidney disease
Enroll	The act of assigning a participant to a treatment. Participants who are enrolled in the study are those who have been assigned to a treatment
Enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives
ESRD	end-stage renal disease
ESV	end-systolic volume
FDA	the United States Food and Drug Administration
FENa	fractional excretion of sodium
FSH	follicle-stimulating hormone
GCP	good clinical practice
GFR	glomerular filtration rate
GFR/eGFR	glomerular filtration rate/estimated glomerular filtration rate
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide 1- receptor agonist
GLP-1/GIP	glucagon-like peptide-1/glucose-dependent insulinotropic polypeptide
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HR	heart rate
hs-CRP	high-sensitivity C-reactive protein
IB	Investigator’s Brochure
ICE	intercurrent event

ICF	informed consent form
ICH	International Council for Harmonisation
IMP	investigational medicinal product (see also "investigational product"): A medicinal product, which is being tested or used as a reference, including as a placebo, in a clinical trial
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked
INR	International normalized ratio
IRB/IEC	Institutional Review Boards/Independent Ethics Committees
ISR	injection-site reaction
IWRS	interactive web-response system
LDL	low-density lipoproteins
LOCF	last observation carried forward
MAF	mean arterial flow
mGFR	measured glomerular filtration rate
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold 1 or more of the 5 "rights" of medication use: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core 5 rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription

MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MRI-PDFF	magnetic resonance imaging-estimated proton density fat fraction
NIMP	non-investigational medicinal product (see also See AxMP) A medicinal product used for the needs of a clinical trial as described in the protocol, but not as an investigational medicinal product. Examples include rescue medication, challenge agents, agents to assess endpoints in the clinical trial, or background treatment
NSAID	non-steroidal anti-inflammatory drugs
participant	Equivalent to Clinical Data Interchange Standards Consortium term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PBO	placebo
PC	product complaint
PC-MRI	Phase contract magnetic resonance imaging
PD	pharmacodynamics
PDFF	proton density fat fraction
PK	pharmacokinetics
PHQ-9	Patient Health Questionnaire-9
PSV	peak systolic velocity
QTLs	Quality tolerance limits
QW	once weekly
R2*	the inverse of transverse relaxation time constant measured by MRI
RAAS	renin-angiotensin-aldosterone system
RARI	renal artery resistive index
RBC	Red blood cell
RBF	renal blood flow
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

SC	subcutaneous
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study
SD	standard deviation
SGLT2	sodium-glucose cotransporter-2
SIB	suicidal ideation and behavior
SMPG	Self-monitoring of plasma glucose
SoA	schedule of activities
SS	safety analysis set
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBL	total bilirubin level
TE ADA	treatment-emergent antidrug antibodies
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
TSH	thyroid-stimulating hormone
UACR	urine albumin-to-creatinine ratio
UAE	urinary albumin excretion
ULN	upper limit of normal
VLDL	very low-density lipoproteins
WBC	white blood cell
WOCBP	women of childbearing potential
WNOCBP	women not of childbearing potential

10.16. Appendix 16. Protocol Amendment History

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

Amendment [c] (17-Jun-2024)

This amendment is considered to be nonsubstantial.

Overall rationale for the amendment:

The primary purpose of this amendment is to revise the exclusion criteria and implement rescreening.

These and other changes are detailed in the table below. Minor error corrections and formatting changes are not reflected in the table.

Section # and Name	Description of Change	Brief Rationale
1.3. Schedule of Activities (SoA)	Physical evaluation – MRI row: Updated text under Visit 2: "…In the event that the centralized MRI vendor determines an MRI scan to have inadequate quality <u>to obtain measures for secondary objectives</u>, the participant can be scheduled for a repeat scan."	Revised to be consistent with description for Visits 7 and 9.
5.2. Exclusion Criteria	Simplified Exclusion Criterion 18 on calcitonin level to state "Have a calcitonin level of ≥35 ng/L at screening (Visit 1)."	Data from completed studies with tirzepatide and other incretins have not indicated that calcitonin levels are associated with eGFR, except for patients with end-stage renal disease, that is, GFR <15 ml/min. Thus, the calcitonin screening strategy has been modified accordingly.
	Updated Exclusion Criterion 46 to include tirzepatide as one of the medications taken to promote body weight reduction.	Updated the list to reflect recent global approvals of tirzepatide in weight management.

Section # and Name	Description of Change	Brief Rationale
5.4. Screen Failures	Deleted the following sentence at the end of the section: "Rescreening of participants who have had a screen failure is not allowed." Added the following text at the end of the section: "Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreening once at the investigator's discretion and with medical monitor approval. If rescreening is performed, the participant must sign a new ICF and will be assigned a new identification number. Reconsenting and rescreening can occur no sooner than 30 days after the screen failure date. The screening procedures per the usual SoA should be followed, starting at the screening Visit 1, to ensure participant eligibility by the randomization at Visit 3."	Rescreening is a standard practice across trials and is implemented in this trial to facilitate enrolment.
8.3.4.2. Arrhythmias and Cardiac Conduction Disorders	Revised the first paragraph to read: "Participants who develop any event from these groups of disorders should undergo an ECG performed locally. ECGs will be interpreted by the investigator or qualified designee in accordance with applicable local regulations."	Correction to reflect use of local procedure instead of central laboratory collection. Revisions are consistent with description of ECG assessment in the SoA.
9.3.7.4.3. Central Laboratory Measures, Vital Signs, and Electrocardiograms	Updated the text in the first and second paragraphs to remove reference to ECG parameters.	Correction and provides consistency with the SoA.
9.3.8.1. Subgroup Analyses for the Primary Objective Measure	Updated the text in the third bullet to include both eGFR and mGFR.	For clarification.
10.2. Appendix 2: Clinical Laboratory Tests	Lipid Panel row in the table: Revised the text to allow the central laboratory to use their individual validated cutoffs for calculation versus direct measure.	For clarification.
10.7. Appendix 7: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Calculation of BMI	Measuring height subsection: Deleted the following text at the end under Step 4 "to 1 decimal place".	Revised to ensure consistency in height measurement across sites.

Section # and Name	Description of Change	Brief Rationale
10.12. Appendix 12: Provisions for Changes in Study Conduct during Exceptional Circumstances	Screening period guidance subsection: Deleted the following sentence at the end of the subsection: "Rescreening of participants who have had a screen failure is not allowed." Added the following at the end of the subsection: "Individuals who do not meet the criteria for participation in this study (screen failure) may be considered for rescreening once at the investigator's discretion and with medical monitor approval. If rescreening is performed, the participant must sign a new ICF and will be assigned a new identification number. Reconsenting and rescreening can occur no sooner than 30 days after the screen failure date. The screening procedures per the usual SoA should be followed, starting at the screening Visit 1, to ensure participant eligibility by the randomization at Visit 3."	Rescreening is a standard practice across trials and is implemented in this trial to facilitate enrolment.
Throughout	Corrected the presentation of eGFR unit to mL/min per 1.73 m^2.	For clarification
	Replaced LY3437943 with the generic name, retatrutide.	To ensure consistency.
	Minor editorial and document formatting revisions.	Minor, therefore, have not been summarized.

Amendment [b]: (18-Oct-2023)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to make changes to inclusion criteria and provide clarity of statistical methods.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	In "Study Population", changed the upper limit for HbA1c from ≤10.5% (≤91 mmol/mol) to ≤9.5% (≤80.34 mmol/mol)	Edits done to reflect the protocol changes described below.
	In "Study Population", added "meglitinides,"	
	Added "Retatrutide and the placebo to match are identical in appearance. Both materials are manufactured and packaged in the same vial and packaging configuration to maintain the blind." to "Participants randomized to placebo"	
5.1. Inclusion Criteria	In inclusion criterion 3, changed the upper limit for HbA1c from ≤10.5% (≤91 mmol/mol) to ≤9.5% (≤80.34 mmol/mol)	The decrease in the upper limit of HbA1c is to ensure a smaller glucose variability for participants with Type 2 diabetes, as high glucose values are known to increase eGFR measures

Section # and Name	Description of Change	Brief Rationale
	In inclusion criterion 3, added "meglitinides,"	Addition of meglitinides class to reflect the common therapy used by participants as requested by regulatory feedback
6.1. Study Intervention(s) Administered	Added "Retatrutide and the placebo to match are identical in appearance. Both materials are manufactured and packaged in the same vial and packaging configuration to maintain the blind." to "Participants randomized to placebo".	Clarification on language to ensure the blind of retatrutide and placebo.
6.3 Assignment to Study Intervention	Deleted "Assignment to treatment groups will be determined by a computer-generated random sequence using the IWRS." Added "The assignment of a participant's treatment group is determined by the IWRS using a computer-generated permuted block randomization table. Only a minimal number of Lilly personnel, and separate to the main study team, will see the randomization records before the double-blind study period is completed."	Included additional details on method of randomization and measures taken to preserve protection of assignment sequence to ensure clarity of the process as requested.
6.4. Blinding	Added "Retatrutide and the placebo to match are identical in appearance. Both materials are manufactured and packaged in the same vial and packaging configuration to maintain the blind."	Clarification on language to ensure the blind of retatrutide and placebo.
6.9.4. Use of Antihyperglycemic Medications at Randomization in Participants with T2D	Added "or meglitinides"	Addition of meglitinides class to reflect the common therapy used by participants as requested by regulatory feedback
9.3.1. General Considerations	The following sentence "Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate" was expanded and modified to "Handling of missing and unused data is addressed by the use of the hypothetical strategy and described by the Primary Estimand Data Points Set; efficacy analyses will use data points up to the date of discontinuation of study intervention or the introduction of concomitant medications (SGLT2 inhibitor, ACE inhibitor or ARB) and any missing data is treated as missing at random by the MMRM model. Safety analyses will use all data points for Safety Participants regardless of discontinuation or new concomitant medication. Imaging data from MRI scanning is reviewed individually and with previous images from the same	To ensure clarity of the statistical methods which are aligned with the hypothetical strategy.

Section # and Name	Description of Change	Brief Rationale
	participant to ensure reliability, with rescans requested for any spurious result."	
9.3.7. Safety Analyses	Added "Safety endpoints in this section are exploratory and full analysis details will be provided in the SAP."	To ensure safety analysis are planned as exploratory endpoints
9.4. Interim Analysis	Added "applicable"	Clarified that the main purpose of interim analysis is safety and PD analyses with no intended change to trial conduct as a result.
	Removed "supporting sample size reassessment"	
	Added "supporting"	
	Added "The primary goal is that of safety and PD; investigation of endpoints will not result in any changes to the trial and hence no adjustment to final alpha levels will be made due to these interim analyses. Full details will be given in SAP and AC charter."	
	Added "Interim analyses will use the same statistical analysis methods as those described for the relevant endpoints in Section 9.3, but will be descriptive in nature"	
harmo9.5 Sample Size Determination	Added "measured"	Added additional detail to explain the choice of effect size and standard deviation chosen to derive sample size.
	Added ", where the mean change in eGFR was 1.50 mL/min/m^2 for T2D participants and 7.61 mL/min/m^2 for non-T2D participants yielding a mean across all participants of 4.56 mL/min/m^2. In these same studies, the standard deviation of eGFR change was 7.1 in the T2D population and 8.9 in the non-T2D population, yielding an average of 8.0 for the 2 groups combined. To leverage the use of a measured GFR endpoint which is known to be less prone to variability than estimated GFR, the more conservative SD = 8.1 was adopted from the results of external trial, MB102035, comparing the effect of SGLT-2 inhibitor dapagliflozin on measured GFR in participants with T2D (Lambers Heerspink et al. 2013)."	
	Removed "Sample size reassessment may be performed during interim analysis. Details will be specified in the SAP."	

Amendment [a]: (24-Jun-2023)

Overall Rationale for the Amendment:

The primary rationale for the current amendment is to address regulatory feedback and to resolve certain inconsistencies observed in the original protocol.

Section # and Name	Description of Change	Brief Rationale
1.1. Synopsis	In brief summary, changed "31" to "33" weeks	Updated study duration for a more precise total duration
	In brief summary, added "treatment and follow-up"	For clarification
	Updated the section to align with the changes in the main body of the protocol	For consistency
1.3. Schedule of Activities (SoA)	Added ", according to local laws and regulations" for telehealth visits	For clarification
	Added "Level of medication intensity" row	For consistency with the text in the protocol
	Added hematology test at "16 weeks (Visit 7)"	This test is needed for assessment of study objectives at the corresponding study visit at Week 16
2.3.1. Risk Assessment	Removed the reference citation of Omnipaque package insert, 2017	"Omnipaque" is a proprietary name. Iohexol may be supplied under other brands or unbranded
4.1.1. Overview of Study Periods	Removed "with MRI of adequate quality for assessment as confirmed by the centralized MRI vendor"	For consistency with the text in the inclusion criteria
5.1. Inclusion Criteria	In inclusion criterion 5, added "The use of SGLT2i is allowed in participants without T2D, in which case, the dose must be stable for at least 90 days before Visit 1"	Updated information about use of SGLT2i at study entry in non T2D participants
	Removed the inclusion criterion 8. Subsequent criteria have been renumbered	If this procedure (MRI) would not yield a report of needed quality, the patient should continue in the trial, since the primary objective in this case would not be affected; potential negative impact on patient retention was also considered
5.2. Exclusion Criteria	In exclusion criterion 45, removed "insulin pump,"	Insulin administration system is not relevant
6.1. Study Intervention(s) Administered	Added "not" and "EU"	Correction
6.6. Dose Modification	Added "any other intolerable AEs, or"	For clarification
6.9.2. Use of Medications that May Affect the Primary Objective Measure (mGFR)	Added • bullet point regarding metformin • 2 reference citations	Updated text to align with new information added to Section 10.10
6.9.4.1. Prohibited Antihyperglycemic Medications	Removed "insulin pump"	Insulin administration system is not relevant

Section # and Name	Description of Change	Brief Rationale
7.1.1. Permanent Discontinuation of Study Intervention	Added “during the study”	Clarification
8.2.2. Vital Signs	Removed “blood pressure should be measured after a participant is seated and awake in a quiet environment for at least 15 minutes”	This statement was redundant.
8.5.1. GFR Assessment using Iohexol Clearance Procedure	Added 2 new reference citations	Updated information
10.2.2. Mechanistic Biomarkers	Removed “(Metabolon)” and “(SomaScan®)	To avoid brand names
10.10. Appendix 10: Iohexol Clearance Method	Added “Participants with T2D using metformin may pause use of medication prior to iohexol procedure and resume after the completion of the test according to country-specific guidance or prescribing information of iohexol.”	Updated in response to Regulatory Agency advice. New text includes additional details from the product labels to protect participant safety
	• Added “at least”, “and after”, and “to prevent dehydration” • replaced “may” with “should”	• For clarification • Addition to make text clear and reinforce hydration recommendation based on Regulatory Agency advice.
	Removed “Omnipaque package insert, 2017”, and added “See iohexol country-specific prescribing information”	Change made in accordance with the change in 2.3.1. Risk Assessment
	Replaced “Omnipaque” with “iohexol”; Removed “, which corresponds with a 5 mL solution of Omnipaque 300 mg I/mL,”	Removed information specific to Omnipaque in accordance with the change in 2.3.1. Risk Assessment
	Removed the storage conditions	Correction
11. References	Removed Omnipaque package insert reference	Change made in accordance with the change in 2.3.1. Risk Assessment
	Added 4 new references	Updated information
Throughout the protocol	Minor formatting and editorial changes	Minor, therefore, not detailed

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