Protocol 8M-MC-GN02(a)

A Phase 2, Parallel-Group, Double-Blind 4-arm Study to Investigate the Effects of Treatment with LY3549492 Tablets Compared with Placebo in an Obese or Overweight Population with Type-2 Diabetes (T2D)

NCT07030868

Approval Date: 02 April 2025

Title Page

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Master Protocol Title:

A Master Protocol for a Randomized, Controlled Clinical Trial of Multiple Interventions for Chronic Weight Management in Adult Participants with Obesity or Overweight

ISA Title:

A Phase 2, Parallel-Group, Double-Blind 4-arm Study to Investigate the Effects of Treatment with LY3549492 Tablets Compared with Placebo in an Obese or Overweight Population with Type-2 Diabetes (T2D)

Protocol Number: W8M-MC-GN02

Amendment Number: a

Compound: LY3549492

ISA Brief Title:

A Study to Investigate the effects of treatment with LY3549492 compared with placebo in adult participants who are obese or overweight with type-2 diabetes (T2D)

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number:

IND for CWMM master protocol: 163848

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

Document ID: VV-CLIN-184641

Medical Monitor Name and Contact Information will be provided separately.

Approved on 02 Apr 2025 GMT

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Original Protocol	15-Nov-2024

Amendment [a]

Overall rationale for the amendment

Based on regulatory feedback, the schema was updated and 2 exclusion criteria were added. Treatment of Overdoses text was also clarified. The changes are included in the table below.

Minor editorial or formatting changes are not included in this table.

Section # and Name	**Description of Change**	**Brief Rationale**
Section 1.2. Schema	Updated schema	To clarify that the treatment period extends to Week 32 with a posttreatment follow-up period from Week 32 to Week 40
Section 5.2. Exclusion Criteria	• added new exclusion criterion 528, and • added new exclusion criterion 529	To address regulatory feedback
Section 6.8. Treatment of Overdose	Added text	Clarification as regards to definition of potential overdose in this blinded study
Section 8.1.2. Bioelectrical Impedance Analysis	Changed “seca mBCA-544” to “seca mBCA-554”	Corrected typographical error
Throughout	Minor editorial revisions	Clarification

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1. Protocol Summary

1.1. Synopsis

Master Protocol Title:

A Master Protocol for a Randomized, Controlled Clinical Trial of Multiple Interventions for Chronic Weight Management in Adult Participants with Obesity or Overweight

ISA Title:

A Phase 2, Parallel-Group, Double-Blind 4-arm Study to Investigate the Effects of Treatment with LY3549492 Tablets Compared with Placebo in an Obese or Overweight Population with Type-2 Diabetes (T2D)

ISA Brief Title:

A study to investigate the effects of treatment with LY3549492 compared with placebo in adult participants who are obese or overweight with type-2 diabetes (T2D)

Regulatory Agency Identifier Number:

IND for CWMM master protocol: 163848

Rationale:

LY3549492 is an oral, non-peptide glucagon-like peptide-1 receptor agonist that is being developed as a daily oral adjunct therapy to diet and physical activity to improve weight management in adults who have obesity or are overweight.

Study W8M-MC-GN02 (GN02) is a 32-week, Phase 2 trial testing the treatment effects of 2 dose levels of once-daily (QD) administered LY3549492 tablets compared with QD administered placebo in the target population.

Objectives, Endpoints, and Estimands:

The W8M-MC-CWMM (CWMM) master protocol contains objectives and endpoints that will be evaluated for all study interventions evaluated under the CWMM master protocol.

Study GN02 includes the following LY3549492-specific features:

- primary analysis time point occurs at Week 32
- intervention is LY3549492, and
- control is a placebo.

The treatment period for Study GN02 is 32 weeks in duration, and the primary endpoint will be at Week 32. The secondary and exploratory objectives, and their respective endpoints specific to Study GN02 are listed in this table.

Objectives	Endpoints
Primary	
• To compare the treatment effect on weight reduction at Week 32 for the LY3549492 versus placebo	• Percent change from baseline in body weight
Secondary (in addition to secondary objectives listed in the CWMM master protocol)	

• To compare the treatment effects on other weight parameters at Week 32 for the LY3549492 versus placebo	• Change from baseline in body weight (kg)
	• Incidence of achieving body weight reduction of
	  ○ ≥5%
	  ○ ≥10%

• To assess treatment effects on glucose metabolism at 32 weeks for each LY3549492 dose versus placebo	• Change from baseline in
	  ○ hemoglobin A1c (HbA1c)
	  ○ fasting glucose
	• Incidence of achieving HbA1c
	  ○ <7%
	  ○ ≤6.5%
	  ○ ≤5.7%

• To characterize the pharmacokinetics (PK) of LY3549492	• PK parameters (average LY3549492 concentration)

Overall Design:

Study GN02 is a Phase 2, parallel-group, double-blind study to investigate the effects of treatment with orally administered once-daily LY3549492 compared with placebo. For convenience, the functional combination of the CWMM master protocol plus the Study GN02 intervention-specific appendix (ISA) will be simply described as "the study."

The study consists of a

- 6-week screening/lead-in period
- 32-week treatment period, and
- posttreatment follow-up period of approximately 8 weeks.

The primary endpoint will be at Week 32.

Brief Summary:

The purpose of Study GN02 is to evaluate the effects of treatment with LY3549492 compared to placebo in adult participants with obesity or who are overweight with T2D.

Study details include the following:

- The total study duration will be up to approximately 46 weeks, including the screening/lead-in period treatment and posttreatment follow-up periods.
- The treatment duration will be approximately 32 weeks.
- The visit frequency will be
  - every 3 weeks for Visits 0 to 24
  - every 6 weeks from Visit 24 to 30, and
  - every 2 weeks from Visits 30 to 32.

Study Population:

Eligibility for participation is based on inclusion and exclusion criteria specified in the CWMM master protocol, with additional criteria specific to the Study GN02 ISA as detailed below. Participants must first meet all criteria for the CWMM master protocol, and then must meet all criteria for Study GN02 ISA to be eligible to participate in Study GN02.

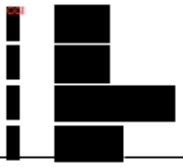
Number of Participants:

Approximately 150 participants will be randomly assigned to study intervention.

Intervention Groups and Duration:

Participants will be randomly assigned in a ratio of 2:2:1:1 (Arm 1: Arm 2: Arm 3: Arm 4), with

- approximately 50 participants in 1 treatment arm randomly assigned to receive placebo (Arm 1)
- approximately 50 participants in 1 treatment group randomly assigned to receive LY3549492 titrated to a CCI per day dose (Arm 2)
- approximately 25 participants in 1 treatment group randomly assigned to receive LY3549492 titrated (fast titration) to a CCI per day dose (Arm 3), and
- approximately 25 participants randomly assigned to receive LY3549492 titrated (slow titration) to a CCI per day dose (Arm 4).

Intervention Name	LY3549492	Placebo
Tablet Strength(s)		Matching placebo
Route of Administration	Oral	Oral
Authorized as Defined By EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

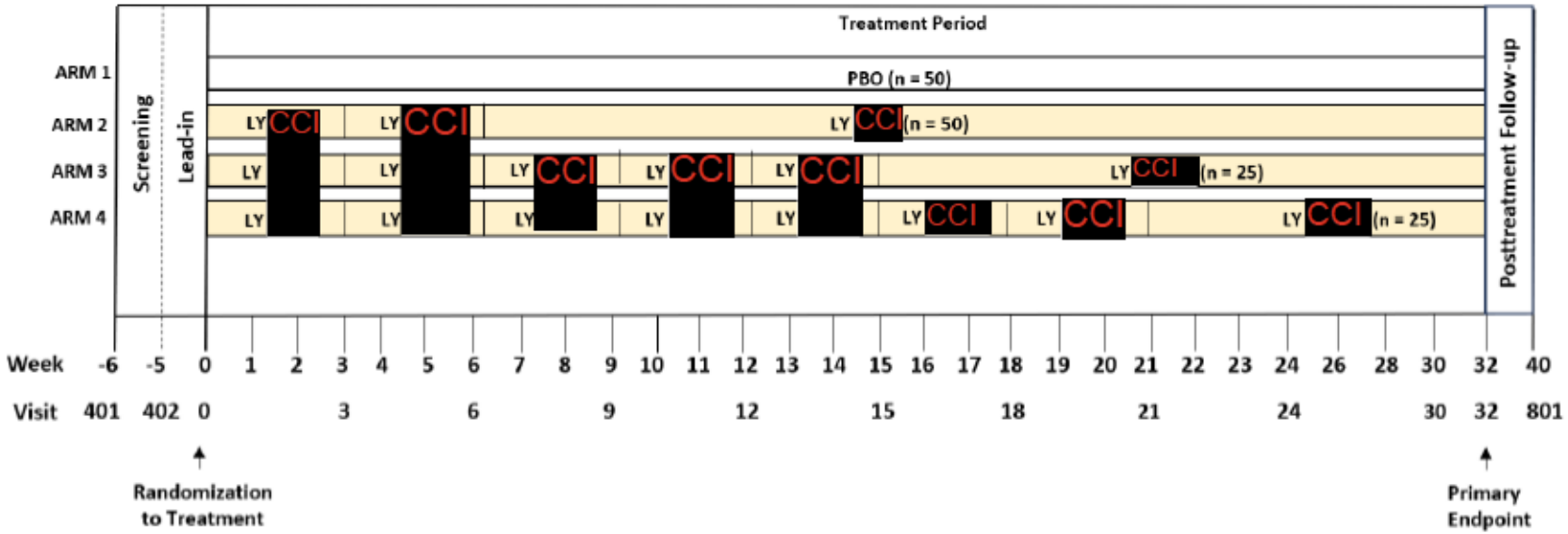
Ethical Considerations of Benefit/Risk:

The potential benefits from participation in this study, which include frequent expert medical care for up to 46 weeks and the chance for achieving body weight reduction and glycemic

control, are expected to outweigh the anticipated risks, which will be closely monitored and managed through the established procedures.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: LY = LY3549492; n = number of patients in the specified category; PBO = placebo.

1.3. Schedule of Activities (SoA)

In addition to activities required by the W8M-MC-CWMM (CWMM) master protocol, this SoA presents visits and procedures unique to the ISA, which is Study W8M-MC-GN02 (GN02) for the study intervention, LY3549492. Please refer to the CWMM master protocol SoA (Section 1.3) for information pertaining to screening (Visit 401).

Visit 402 (Lead-in)

Visit 402 may be used to accomplish Study GN02-specific activities, such as 7-point SMBG. If the time between this visit and Visit 0 takes shorter or longer than 5 weeks, it will not be considered a protocol deviation.

Visit 0 (Randomization to treatment)

Participants will be randomly assigned to a Study GN02-specific treatment arm at Visit 0 and will receive their first dose of study intervention.

Unscheduled visits

Unscheduled visits may occur as needed. The SoA reflects some of the procedures that may occur during these visits. Additional procedures will be performed at the investigator's discretion.

Early discontinuation (ED) visits

ED visits will be completed by participants permanently discontinuing early from the study. These participants should also complete the posttreatment follow-up. The SoA reflects the procedures that may occur during these visits.

Visit 801 (Posttreatment follow-up)

Visit 801 occurs approximately 8 weeks after a participant's last dose of study intervention. The SoA reflects the procedures that may occur during these visits.

Fasting visits

Participants should not eat or drink anything but water for a minimum of 8 hours before a fasting visit.

If a participant attends these visits in a non-fasting state, they should return in a fasting state for body weight measurement and sample collection within the visit interval tolerance specified in the SoA. Participants are required to fast at screening, baseline, and at visits specified as per the SoA.

A participant who attends Visits 3, 6, 9, 15, 18, or 21 in a non-fasting state does not need to return in a fasted state.

	Screening/ Lead-In	Treatment Period													Safety Follow-Up	Comments
CRF Visit Number	**402**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**	**UV 997**	**ED**	**801**	
Weeks	**-5 to 0**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**			**40**	
Visit Interval Tolerance (± days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**D**	**F**		**F**	**F**	F = Fasting D = Dispense Only
Consent and demographics																
Inclusion/Exclusion Criteria; Confirmation of Eligibility		X														Confirm inclusion and exclusion criteria prior to randomization and administration of the first dose of study intervention.
Concomitant Medications	X	X	X	X	X	X	X	X	X	X		X	X	X	X	
Adverse Events (AEs)	X	X	X	X	X	X	X	X	X	X		X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 10.3.1 of CWMM master protocol. Additional data are collected for certain AEs.
Physical evaluation																
Waist Circumference		X	X	X	X	X	X	X	X	X		X		X	X	
Weight		X	X	X	X	X	X	X	X	X		X		X	X	Weight should be obtained per guidance mentioned in Section 10.8 of CWMM master protocol and must be measured in the fasting status. If the participant is not fasting, the participant should return later within the visit window to have the fasting body weight measured.
Bioelectrical Impedance Analysis (BIA)		X	X	X	X	X	X	X	X	X		X		X	X	
Symptom-Directed Physical Assessment			X	X	X	X	X	X	X	X		X	X	X	X	Symptom-directed physical assessment may be conducted at the discretion of the PI or qualified personnel as indicated per local regulations based on participant status and standard of care.

	Screening/ Lead-In	Treatment Period													Safety Follow-Up	Comments
CRF Visit Number	**402**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**	**UV 997**	**ED**	**801**	
Weeks	**-5 to 0**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**			**40**	
Visit Interval Tolerance (± days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**D**	**F**		**F**	**F**	F = Fasting D = Dispense Only
Vital Signs		X	X	X	X	X	X	X	X	X		X		X	X	Includes pulse rate, (orthostatic - supine and standing) blood pressure (duplicate). Measured after participant has been sitting at least 5 minutes. Refer to Section 8.2.1.
ECG 12-lead (triplicate) (central)		X	X			X			X	X		X		X	X	Collect ECG at least 30 minutes before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. Refer to Section 8.2.3.
Participant Diary																
Dispense Diary	X															
Diary Review			X	X	X	X	X	X	X	X		X		X		
Diary Return												X		X		
Patient-reported Outcomes (Electronic)																
Short Form-36 Version 2 Health Survey acute form (SF-36 v2, Acute)		X										X		X		
Eating Behavior and Appetite Questionnaire (EBAQ)		X										X		X		Refer to Section 8.1.1.2
PGIS - Physical Function Weight		X										X		X		
PGIC - Physical Function Weight												X		X		
PGIS - Overall Eating Behavior		X										X		X		
PGIC - Overall Eating Behavior												X		X		

	Screening/ Lead-In	Treatment Period													Safety Follow-Up	Comments
CRF Visit Number	**402**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**	**UV 997**	**ED**	**801**	
Weeks	**-5 to 0**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**			**40**	
Visit Interval Tolerance (± days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**D**	**F**		**F**	**F**	F = Fasting D = Dispense Only
Patient Health Questionnaire-9 (PHQ-9)		X				X				X		X		X		AE collection should occur prior to the collection of the PHQ-9.
Clinician-administered assessments																
C-SSRS Since Last Assessed (Category Version)		X	X	X	X	X	X	X	X	X		X	X	X	X	AE collection should occur prior to the collection of the C-SSRS. This assessment will be paper based.
Participant education																
Diabetes Education	X	X														
Explain diet and physical activity plan	X	X														
Explain symptoms of hypoglycemic events (includes BG meter dispensing and SMBG training)	X															
Remind Participants about 7-point SMBG	X				X				X		X					The 7-point SMBG will be required prior to randomization. At all other times, the participant should be instructed to collect the 7-point SMBG during the week prior to the visit in which it is required. All 7-points of the SMBG should be completed in a single day. If a participant does not complete the entire profile on a single day, all 7-points must be collected on a subsequent day
Review 7-point SMBG values		X				X				X		X				

	Screening/ Lead-In	Treatment Period													Safety Follow-Up	Comments
CRF Visit Number	**402**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**	**UV 997**	**ED**	**801**	
Weeks	**-5 to 0**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**			**40**	
Visit Interval Tolerance (± days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**D**	**F**		**F**	**F**	F = Fasting D = Dispense Only
Review SMBG and hypoglycemia events collected in diary		X	X	X	X	X	X	X	X	X		X	X	X	X	
Review diet and physical activity goals			X			X				X						
Dietary Counseling			X			X				X						
Explain diet and physical activity plan	X	X														
Laboratory tests and sample collections																
Hematology		X				X				X		X		X	X	
Clinical Chemistry		X		X	X	X	X	X	X	X		X		X	X	
Urinalysis		X				X				X		X		X	X	
Lipids		X				X				X		X		X	X	
Lipase		X				X				X		X		X	X	
Calcitonin	X															
Pancreatic Amylase		X				X				X		X		X	X	

	Screening/ Lead-In	Treatment Period													Safety Follow-Up	Comments
CRF Visit Number	**402**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**	**UV 997**	**ED**	**801**	
Weeks	**-5 to 0**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**			**40**	
Visit Interval Tolerance (± days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**D**	**F**		**F**	**F**	F = Fasting D = Dispense Only
Hemoglobin A1c (HbA1c)		X				X				X		X		X	X	
Cystatin-C		X				X				X		X		X	X	
PK Samples - Random												X		X	X	
PK Samples - Predose			X		X		X	X								
PK Samples - Postdose		X	X	X	X	X	X	X	X	X						a. Week 0 and Week 24: collect PK samples 6 to 18 hours postdose. b. Weeks 3, 9, 15, and 18: collect PK samples 1 to 3 hours postdose. c. Week 12: collect PK samples 1 to 6 hours postdose. d. Weeks 6 and 21: collect PK samples 3 to 6 hours postdose.
Endpoint Biomarkers		X	X	X						X		X		X	X	
Longitudinal Biomarkers		X				X				X		X		X	X	
Calculation																
eGFR		X				X				X		X		X	X	Calculated using CKD-EPI Cystatin-C method (2012).
Urinary Albumin/Creatinine Ratio (UACR)		X				X				X		X		X	X	

	Screening/ Lead-In	Treatment Period													Safety Follow-Up	Comments
CRF Visit Number	**402**	**0**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**	**UV 997**	**ED**	**801**	
Weeks	**-5 to 0**		**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30**	**32**			**40**	
Visit Interval Tolerance (± days)			**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**	**3**			**3**	
Visit Detail		**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**F**	**D**	**F**		**F**	**F**	F = Fasting D = Dispense Only
Stored samples																
Genetics Sample		X														Sample can be obtained at or after the specified visit.
Exploratory Biomarker		X				X				X		X		X		
Epigenetic Sample		X										X				
Randomization and dosing related activities																
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X		X	X	
Randomization via IWRS		X														
Dispense study intervention via IWRS		X	X	X	X	X	X	X	X	X	X					
Dispense ancillary supplies to participant		X	X	X	X	X	X	X	X	X	X					
Participant returns unused study intervention and ancillary supplies			X	X	X	X	X	X	X	X	X	X		X		
Assess study intervention adherence			X	X	X	X	X	X	X	X	X	X		X		

Abbreviations: AE = adverse event; BG = blood glucose; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; EBAQ = Eating Behavior and Appetite Questionnaire; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; ISA = intervention-specific appendix; IOCBP = individuals of childbearing potential; IWRS = interactive web-response system; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of Severity; PHQ = Patient Health Questionnaire; PI = principal investigator; PK = pharmacokinetic(s); SMBG = self-monitored blood glucose; UV = unscheduled visit.

2. Introduction

2.1. Study Rationale

LY3549492 is an oral, non-peptide GLP-1 RA that is being developed as a daily oral adjunct therapy to diet and physical activity to improve weight management in adults who are obese or overweight and have T2D.

Study W8M-MC-GN02 (GN02) is a 32-week, Phase 2 trial testing the efficacy and safety of 2 dose levels of QD-administered LY3549492 compared with QD-administered placebo in the target population.

2.2. Background

LY3549492 is being investigated for its potential use in weight management. LY3549492 is a chemically synthesized molecule that shows agonist activity for the GLP-1 receptor. To date, no off-target toxicity has been identified.

The GLP-1 receptor belongs to the Class B family of G-protein-coupled receptors (Hoare 2005), specifically binding to the $G_{\alpha s}$ heterotrimeric G-protein. It is expressed in pancreatic beta-cells and other tissues, including

- various cell types of the GI tract, and
- neurons throughout the central and peripheral nervous systems.

GLP-1 RAs bind with specificity to GLP-1 receptor in the pancreas and elsewhere. Actions on the pancreatic islets include stimulation of glucose-dependent insulin release from the pancreatic beta-cells. GLP-1 RA actions that mimic the native GLP-1 include

- increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner
- decreasing appetite and increasing satiety, and
- slowing gastric emptying (Richards et al. 2014).

By these actions, GLP-1 RA drugs lower the glucose level and cause weight loss. GLP-1 RA drugs are generally considered to have a low risk of hypoglycemia, because they stimulate insulin secretion only in the presence of elevated BG levels (Frias et al. 2019). GLP-1 RA provides additional metabolic benefits, such as weight loss at doses higher than those effective for glycemic control (Davies et al. 2015; 2021).

Currently available GLP-1 RA therapies for T2D are large-molecular weight, peptide-based agents. Prior clinical trials in participants with T2D treated with such GLP-1 RA drugs demonstrated

- significant reduction in HbA1c levels from baseline
- reduction in fasting serum glucose levels from baseline
- reduction in self-monitored plasma glucose levels
- reduction in fasting glucagon levels, and
- significant reduction in body weight.

Furthermore, some of these GLP-1 RAs demonstrated a reduction in the risk of CV and renal complications (Caruso et al. 2019; Gerstein et al. 2019a and b; Holst 2020).

An important advance in GLP-1 RA therapy is the recent development of a tablet form of semaglutide (a peptide-based GLP-1 RA) co-formulated with the absorption enhancer, sodium N-(8-[2-hydroxybenzoyl] amino) caprylate, for oral delivery (Davies et al. 2017; Rybelsus package insert, 2020; Rybelsus EPAR product information, 2020).

However, orally administered semaglutide requires a time separation in dosing from food and fluid intake; therefore, the development of a GLP-1 RA non-peptide agonist with simpler oral dosing would offer more flexibility to patients.

Safety assessments of LY3549492 are based upon the completed Phase 1 clinical pharmacology study (Study J3H-MC-GZNA [GZNA]) and 2 studies (Studies J3H-MC-GZNB [GZNB]) and (J3H-MC-GZNC [GZNC]).

Study GZNA was a first-in-human single-ascending dose and multiple-ascending dose study involving 72 healthy participants. It evaluated the safety, tolerability, and PK/PD of LY3549492. Of these, 54 participants received LY3549492, and 18 participants received placebo.

Study GZNB evaluated multiple oral doses of LY3549492 or placebo in 79 participants with T2D. A total of 60 participants received LY3549492 and 19 participants received placebo.

Study GZNC was a 2-part study, evaluating the disposition of [^{14}C]-LY3549492 in 8 healthy participants and absolute bioavailability of [^{14}C]-LY3549492 with LY3549492 in 10 healthy participants.

Across the 3 studies, LY3549492 showed a tolerability profile consistent with the known tolerability profile of GLP-1 RA class members. No deaths were reported in all 3 studies until the data cutoff date (23 April 2024). One participant each in Studies GZNA and GZNB reported an SAE. Three participants discontinued due to AEs in Study GZNB.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs or SAEs of LY3549492 may be found in the Investigator's Brochure.

2.3.1. Risk Assessment

Study Intervention

LY3549492

The sponsor has evaluated the preclinical and clinical risks associated with LY3549492.

LY3549492 was studied in rats and monkeys. In monkeys, the drug effects observed were related to reduced food intake, decrease in body weight and body condition, and increases in HR and BP.

These changes are consistent with effects known to be associated with GLP-1 RAs. GI effects were also seen in the preclinical monkey studies with LY3549492.

In Studies GZNA and GZNB, AEs were generally consistent with the known pharmacology of GLP-1 RAs. The most common AEs observed in the LY3549492 clinical trials in healthy participants, and participants with T2D, have been GI disorders. These GI AEs have been mild to moderate in severity, and none were severe. Furthermore, events of headaches, as well as modest increases in HR, have also been observed.

Based on preclinical and clinical observations with LY3549492, with other GLP-1 RAs, and with GLP-1 containing multifunctional agonists, potential risks associated with LY3549492 include

- GI effects, such as nausea, vomiting, and diarrhea
- gallbladder disorder
- pancreatic safety
- effects on HR and BP
- hypoglycemic events
- thyroid safety
- developmental safety, and
- allergic/hypersensitivity reactions.

Refer to Section 8.3.2.2 for further details about AE of special interest for monitoring in the current development program in Phase 2. Please refer to Section 6 of the Investigator's Brochure for more details.

Management of risks for the study

Sections 5.1, 5.2, and 8.3 address known potential risks associated with LY3549492.

Participants will be closely monitored with scheduled medical assessments, vital signs, laboratory evaluations, and triplicate ECG measurements.

Section 6.6 addresses dose modifications based on participant safety and tolerability.

2.3.2. Benefit Assessment

LY3549492 is a GLP-1 RA in early clinical development. A full assessment of its potential benefits has not been completed. The purpose of this Phase 2 trial is to provide an initial efficacy assessment in adult obese and overweight participants with T2D, in addition to safety and PK/PD assessments.

Participants may benefit by receiving personal health information, routine safety assessments, and frequent engagement with healthcare providers during the study, which provide opportunities for coaching and support.

2.3.3. Overall Benefit Risk Conclusion

LY3549492 is being investigated as an oral tablet, QD therapy, administered as an adjunct to diet and physical activity to improve weight management in adult obese and overweight participants with T2D. At this time, no safety or efficacy issues have been identified which would constitute undue risk to study participants. The safety profile continues to be refined as more clinical safety data become available. The overall benefit-risk profile supports further development of LY3549492.

3. Objectives, Endpoints, and Estimands

The W8M-MC-CWMM (CWMM) master protocol contains objectives and endpoints that will be evaluated for all study interventions evaluated under the CWMM master protocol.

Study GN02 includes the following LY3549492-specific features:

- primary analysis time point occurs at Week 32
- intervention is LY3549492, and
- control is a placebo.

The treatment period for Study GN02 is 32 weeks in duration, and the primary endpoint will be at Week 32. The secondary and exploratory objectives, and their respective endpoints specific for GN02 are listed in this table.

Objectives	Endpoints
Primary	
To compare the treatment effect on weight reduction at Week 32 for LY3549492 versus placebo	Percent change from baseline in body weight
Secondary (in addition to secondary objectives listed in the CWMM master protocol)	

To compare the treatment effects on other weight parameters at Week 32 for LY3549492 versus the placebo	• Change from baseline in body weight (kg)
	• Incidence of achieving body weight reduction of
	  ○ ≥5%
	  ○ ≥10%

To assess treatment effects on glucose metabolism at 32 weeks for each LY3549492 dose versus placebo	• Change from baseline in
	  ○ HbA1c
	  ○ fasting glucose
	• Incidence of achieving HbA1c
	  ○ <7%
	  ○ ≤6.5%
	  ○ ≤5.7%

To characterize the PK of LY3549492	PK parameters (average LY3549492 concentration)
Exploratory (in addition to exploratory objectives listed in the CWMM master protocol)	

To compare the treatment effect at Week 32 for LY3549492 versus placebo	• Percent change from baseline BMI
	• Incidence of achieving BMI
	  ○ <30 kg/m^2
	  ○ ≤27 kg/ m^2
	  ○ ≤25 kg/ m^2

To compare the treatment effect at Week 32 for LY3549492 versus placebo	• Percent change from baseline
	  ○ waist circumference
	  ○ waist-to-height ratio

To compare the treatment effect at Week 32 for LY3549492 versus placebo	• Incidence of achieving body weight reduction of
	  ○ ≥15%
	  ○ ≥20%
	  ○ ≥25%

Objectives	Endpoints
	○ ≥30%
To compare the effects of LY3549492 versus placebo on health-related quality of life, emotional function, eating behavior, and appetite	• Change from baseline in: ○ SF-36v2 acute form domain and summary scores ○ EBAQ scores ○ PGIS – Physical Function Weight ○ PGIC – Physical Function Weight ○ PGIS – Overall Eating Behavior ○ PGIC – Overall Eating Behavior
To compare the effect LY3549492 versus placebo on mechanistic biomarkers at longitudinal time points from baseline to Week 32	Change from baseline in longitudinal and endpoint biomarkers
To assess the relationships between LY3549492 and LY3549492 doses and/or exposure and key safety and efficacy measures, as applicable	Dose-response or exposure-response analyses for key safety and efficacy endpoints, as applicable
To assess treatment effects on glucose metabolism at 32 weeks for each LY3549492 dose versus placebo	• Change from baseline in ○ fasting insulin ○ HOMA2-IR and HOMA2-B
To evaluate the effects of LY3549492 versus placebo on 7-point SMBG at 32 weeks	Change from baseline in 7-point SMBG values
To compare the effects of LY3549492 versus placebo on body composition at Week 32	• Percent change from baseline as determined by BIA in ○ total body fat mass, and ○ total body lean mass

Abbreviations: BIA = bioelectrical impedance analysis; BMI = body mass index; CWMM = W8M-MC-CWMM master protocol; BP = blood pressure; EBAQ = Eating Behavior and Appetite Questionnaire; HbA1c = hemoglobin A1c; HOMA2-B = homeostasis model assessment of beta-cell function; HOMA2-IR = homeostasis model assessment of insulin resistance; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PGIC = Patient's Global Impression of Change; PGIS = Patient's Global Impression of Severity; SF-36 v2 = Short Form-36 version 2 Health Survey.

Primary and additional estimands

The CWMM master protocol includes a description of the primary estimand and additional estimands that will be used for the primary and secondary efficacy objectives for comparisons between LY3549492 and placebo. The primary estimand is presented here for clarity.

Primary estimand

The clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at 32 weeks between LY3549492 and placebo, as an adjunct to healthy diet and physical activity, in participants who meet the eligibility criteria, if they would remain on their randomly assigned treatment for 32 weeks and would not initiate non-protocol weight management treatments?

The primary estimand for this protocol is the "efficacy" estimand defined by the following attributes:

- Population - Individuals who meet the eligibility criteria

- Endpoint - Percent change in body weight from baseline to 32 weeks
- Treatment condition - The randomized treatment, with allowance for potential dose interruptions and modifications
- Population-level summary and treatment effect of interest - difference in mean percent changes in body weight from baseline to Week 32 between LY3549492 and placebo
- Intercurrent events - Intercurrent events include permanent discontinuation of any study intervention and initiation of non-protocol weight management treatments, which is handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on the randomly-assigned treatment for 32 weeks and would not initiate non-protocol weight management treatments. Dose modifications and interruptions will not be considered as intercurrent events since dose modifications and interruptions are part of the treatment condition

Rationale for the efficacy estimand

This estimand aims to study the efficacy of LY3549492 under the ideal condition that all participants adhere to their randomly assigned treatment without being confounded by the initiation of other non-protocol weight management treatments.

4. Study Design

4.1. Overall Design

Study GN02 is a Phase 2, parallel-group, double-blind study to investigate efficacy with LY3549492 orally administered QD compared with placebo. For convenience, the functional combination of the CWMM master protocol plus the Study GN02 ISA will be simply described as "the study."

The study consists of a:

- 6-week screening/lead-in period
- 32-week treatment period, and
- posttreatment follow-up period of approximately 8 weeks after the last visit in the treatment period.

The primary endpoint will be at Week 32.

The study schema is presented in Section 1.2.

4.1.1. Overview of Study Periods

Screening period

The screening period consists of Visit 401 (screening) and Visit 402 and is split between the CWMM master protocol and Study GN02; Visit 401 occurs as part of the CWMM master protocol and Visit 402 occurs as part of Study GN02. Signing ICFs, completing screening procedures, and randomizing to the ISA all take place during Visit 401.

Visit 402 will be used to complete any Study GN02-specific baseline procedures including baseline procedures for Study GN02 appendices.

If the time between Visit 401 and randomization (Visit 0) takes more or less time than 6 weeks, it is not a protocol deviation.

Visit 401

Participant screening for the CWMM master protocol and Study GN02 occurs during the CWMM master protocol Visit 401 and is described in the CWMM master protocol Sections 1.3 (SoA) and 4.1. The ICF must be signed before any protocol-specific tests or procedures are performed at Visit 401.

Participants who successfully pass screening procedures and are assigned to participate in Study GN02 will proceed with Visit 402 as detailed below.

Participants who have not fasted at Visit 401 will need to return to the site for collection of fasting laboratory samples and other fasting parameters. This visit will be considered part of Visit 401.

Visit 402 (start of Study GN02 procedures)

Prior to Visit 402, all screening results, including laboratory results, will be reviewed to confirm participant eligibility for the CWMM master protocol and Study GN02.

Participants will complete procedures as indicated in the SoA (Section 1.3). Participants will receive education on recognizing the symptoms of hypoglycemic events.

Participant diaries will be dispensed, and their use explained.

Participants will meet with site personnel to discuss diet and physical activity goals (see Section 5.3 of the CWMM master protocol).

Participants will be registered in IWRS.

Treatment period

Visit 0 (randomization to treatment arm)

Study participants are required to report to the study site after approximately 8 hours without eating or drinking (except water) and should not have performed any significant physical activity.

At Visit 0, eligible participants, those who meet all applicable inclusion criteria and none of the applicable exclusion criteria for the CWMM master protocol and for Study GN02, will perform all required study procedures prior to randomization to a treatment arm (see SoA).

Patient-reported outcomes questionnaires should be administered according to the SoA. The preferred administration order of these questionnaires is:

- SF-36v2
- EBAQ
- PGIS – Physical Function Weight
- PGIC – Physical Function Weight
- PGIS – Overall Eating Behavior, and
- PGIC – Overall Eating Behavior
- PHQ-9
- C-SSRS

All study Visit 0 baseline measurements and assessments must be completed prior to the first dose of study intervention. Furthermore, triplicate ECGs should be collected prior to blood sample collection.

Study intervention dispensing and dosing

Beginning at randomization, all participants will receive study intervention according to the randomly-assigned treatment group for the duration of the 32-week treatment period (primary endpoint at 32 weeks) as per the SoA (Section 1.3).

The date and time of the first dose of study intervention will be recorded on an eCOA device (either provisioned or participant's own device).

Study intervention dosing

During the treatment period, the study drug will be returned per the SoA (Section 1.3) and according to local requirements. New supplies will be dispensed as needed. Participants should

be instructed to contact the investigative site for assistance as soon as possible if they experience any difficulties taking their study drugs.

Participants should also be advised about the appropriate course of action if study drugs are not taken at the required time (late/missing doses). Study participants will be permitted to use concomitant medications that they require during the study, except certain excluded medications that may interfere with the assessment of efficacy and safety characteristics of the study treatments.

Patient-reported outcomes

Patient-reported outcomes questionnaires should be administered according to the SoA.

The mental health questionnaires (PHQ-9 and C-SSRS) should be completed after the assessment for AEs.

The date and time of the doses of study intervention will be recorded on the eCOA device.

Safety and efficacy assessments and laboratory sample collections will be performed as specified in the SoA (Section 1.3) and as described in the CWMM master protocol.

Participants are also required to return any remaining diaries to the study site at Week 32.

Early discontinuation visit

Participants who discontinue study intervention but remain in the study do not need to undergo ED procedures but rather should continue to follow regularly scheduled visit procedures.

Participants unable or unwilling to continue the study for any reason will perform an ED of treatment visit (Section 7.1 of the CWMM master protocol). If the participant is discontinuing at the time of a scheduled visit, perform that visit as an ED visit. Procedures should be completed according to the SoA (Section 1.3).

Participants who withdraw from the study after signing the informed consent but who have not taken a dose of study intervention prior to randomization do not need to complete ED procedures on Visit 801.

Post treatment follow-up period

Visit 801

Visit 801, a posttreatment follow-up visit, will occur approximately 8 weeks following the last treatment period visit. All participants who have taken at least 1 dose of study intervention should complete Visit 801, according to the SoA (Section 1.3).

For participants who discontinue from the study early (regardless of whether they discontinue study intervention at the same time they discontinue from the study, or if they have discontinued study intervention at an earlier visit), an ED visit followed by the posttreatment follow-up visit (Visit 801) should be completed as per the SoA.

4.2. Scientific Rationale for Study Design

Study GN02 is a Phase 2 study designed to examine the body weight-lowering efficacy and safety of LY3549492 QD (dose ranging from CCI) compared with placebo during the

32-week treatment period (with the primary endpoint at Week 32), in adult participants who have obesity or are overweight and have T2D. This will allow for the selection of dose levels and dose escalation schemes for future studies. The planned treatment duration of 32 weeks will allow for a more robust evaluation of the body weight effects of LY3549492, as the putative mechanism of action of LY3549492 suggests that treatment with LY3549492 will result in continued weight loss beyond a 6-month period.

A primary study endpoint at Week 32 is considered sufficient duration for an adequate understanding of drug effect on body weight. Since participants in Study GN02 have T2D, they will receive training on the routine BG monitoring and eCOA diary completion required during the study. Participants should follow the investigator's instructions related to frequency of SMBG but should test their glucose a minimum of 3 times per week and as specified for determination of 7-point glucose profiles (See Section 8.2.12).

The effects of LY3549492 on other parameters, such as circulating biomarkers, HbA1c, lipids, and various safety-related assessments, will also be determined. The data from this trial will form the primary basis to assess the dose/exposure-response of LY3549492 efficacy for selecting doses and the dose escalation scheme to be included in Phase 3 testing. In addition, safety and tolerability over a wide dose range of LY3549492 versus placebo will be assessed to enable robust benefit-risk characterizations in this population.

The placebo comparison will provide efficacy and safety data to characterize the effects attributable to LY3549492.

Consistent with current guidelines for weight management, all participants will receive diet and physical activity counseling throughout the study. Clinical sites that have their own diet and physical activity programs may follow those programs. However, a suggested diet and physical activity program is provided in Section 10.9 of the CWMM master protocol for sites without specific programs.

In Section 10.9.1 of the CWMM master protocol, the diet recommendations are based on the WHO (WHO 2020a) diet recommendations for everyone which is based on a Mediterranean Diet eating pattern. In Section 10.9.2 of the CWMM master protocol, physical activity recommendations are based on WHO (WHO 2020b) and the United States Health and Human Services (HHS 2020) recommendations.

The primary efficacy measure, mean percent change in body weight, is an accepted Phase 2 endpoint for investigational drugs being developed for weight management (FDA 2007).

In addition, the study includes other parameters relevant to the assessment of the effects of LY3549492 on safety, BP, HR, lipids, PK parameters, and patient-reported outcomes. Further, safety and tolerability over a wide dose range of LY3549492 versus placebo will be assessed to enable robust benefit-risk characterizations in treatment of participants who have obesity or are overweight.

To minimize the potential confounding effect of changes in concomitant medications, participants will be permitted to use concomitant medications that do not interfere with the assessment of efficacy or safety characteristics of the study treatments.

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 question can be answered only if all the relevant data are collected.

4.3. Justification for Dose

LY3549492 doses of CCI administered orally and QD, were selected based on the following:

- safety and tolerability of LY3549492 in Phase 1 Studies GZNA and GZNB.
- PK/PD modeling of preliminary data from Studies GZNA and GZNB.

Most GLP-1 RAs require up-titration to the target dose to reduce incidence and severity of GI side effects like nausea and vomiting. We have, therefore, included 2 separate arms with different up-titration rates to a CCI target dose, in order to assess the tolerability of the different titration strategies.

The selected dose levels and dose range will support a dose/exposure-response analysis of multiple safety and efficacy measures, which will support the selection of the dose(s) of LY3549492 with the optimal benefit-risk ratio for further clinical development.

4.4. End of Study Definition

A participant is considered to have completed Study GN02 if the participant has completed all periods of the study, including the last scheduled procedure shown in the SoA.

The end of Study GN02 is defined as the date of the last visit of the last participant in Study GN02 or last scheduled procedure shown in the SoA for the last participant in Study GN02 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:

501. Are the following individuals who agree to abide by the reproductive and contraceptive requirements provided in Study GN02.

    - AMAB and
    - AFAB, who are of non-childbearing potential. Refer to Section 10.4 for further details.

    INOCBP (for definitions, see Section 10.6) and individuals AMAB may participate in this study considering the following:

    - AMAB participants who agree to use highly effective/effective methods of contraception may participate in this trial. Please refer to Section 10.4 (Appendix 4) for definitions and additional guidance related to contraception.

    All eligible participants must comply with the contraception requirements. 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 Appendix 10.4.

502. Have a clinical diagnosis of T2D based on the World Health Organization classification or other locally applicable diagnostic standards, on diet and exercise with or without a stable dose of metformin

503. Have HbA1c ≥7.0% (53 mmol/mol) to ≤10.5% (91 mmol/mol), as determined by the central laboratory at Visit 1 (screening).

5.2. Exclusion Criteria

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

Medical Related

504. Have a known clinically significant gastric emptying abnormality (for example, severe diabetic gastroparesis or gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take medications that directly affect GI motility

505. Have a history of acute or chronic pancreatitis. Patient with history of acute pancreatitis caused by gallstones may be included if they have had a cholecystectomy to resolve the problem.

Diabetes related

506. Have had more than 1 episode of severe hypoglycemia, as defined by the occurrence of neuroglycopenic symptoms requiring the assistance of another person for recovery, within 6 months prior to Visit 1, or has a history of hypoglycemia unawareness or poor recognition of hypoglycemic symptoms. Any participant that the investigator feels will not be able to communicate an understanding of hypoglycemic symptoms and the appropriate treatment of hypoglycemia should also be excluded.

507. Are currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema, for example, laser photocoagulation or intravitreal injections of antivascular endothelial growth factor inhibitors.

Cardiovascular

508. Have any of the following CV conditions within 6 months prior to screening:

- acute myocardial infarction
- cerebrovascular accident (stroke)
- unstable angina, or
- hospitalization due to congestive heart failure.

Note: This supersedes exclusion Criterion 16 in Section 5.1 of the CWMM master protocol

Prior/concomitant therapy

509. Have used insulin for diabetic control within the prior year. However, short-term use of insulin for acute conditions is allowed (≤14 days) in certain situations, such as during a hospitalization or perioperatively

510. On another OAM (including, but not limited to, sulfonylureas, DPP-4i, sodium-glucose cotransport 2 inhibitors, alpha-glucosidase inhibitors, meglitinides) may be randomized if the additional OAM treatment was discontinued at least 3 months prior to screening

Prior/concurrent clinical study experience

511. Have had any exposure to GLP-1 receptor analogs or RAs within the prior 3 months or any prior history of hypersensitivity/allergies to these medications. Have known or suspected hypersensitivity to trial product(s), selective GLP-1 RAs, or GIP/GLP-1 or GLP-1/GCG dual RAs.

512. Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of efficacy are not eligible.

513. Have known or suspected hypersensitivity to trial product(s).

Bioelectrical Impedance Analysis (for exclusion from BIA only – having any of the following criteria will not exclude a potential participant from the main study)

514. Bioimpedance measurements may not be performed on participants exhibiting the following characteristics:
    - Electronic implants, for example, cardiac pacemakers
    - Active prostheses.
515. Bioimpedance measurements may not be performed on persons who are connected to one of the following devices:
    - Electronic life-support systems, for example, artificial heart, artificial lung
    - Portable electronic medical devices for example, ECG devices or infusion pumps.
516. Bioimpedance measurements may only be performed on persons exhibiting the following characteristics after discussion with the attending physician:
    - Cardiac arrhythmias.

Other exclusions

517. Have a family or personal history of MTC or multiple endocrine neoplasia syndrome Type 2.
518. Have a serum calcitonin level at screening (at Visit 401 [screening] and Visit 402) of ≥35 ng/L (≥35 pg/mL).
519. Have, in the opinion of the investigator, evidence of significant, uncontrolled endocrine abnormality, for example, thyrotoxicosis or adrenal crisis.
520. Have difficulty swallowing tablets.
521. Have participated, within the last 90 days, in a clinical study and received treatment, whether active or placebo. If the study involved a study intervention, at least 5 elimination half-lives or 90 days, whichever is longer, should have passed.
522. Cannot be taking strong CYP3A inhibitors or strong CYP3A inducers and drugs that are P-gp/BCRP substrates with a narrow therapeutic index. See Appendix 10.5 for more details.
523. Have participated within the last 6 months, whether on active drug or placebo, in a clinical study that contained a GLP-1 RA
524. Are investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted.
525. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study that requires exclusion of their employees.
526. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

527. Are IOCBP. Please refer to Section 10.4 (Appendix 4) for definitions and additional guidance related to contraception.

Other medical exclusions

528. Has renal impairment, measured as estimated glomerular filtration rate less than 45 mL/min/1.73 m^2, calculated per Chronic Kidney Disease Epidemiology Collaboration as determined by the central laboratory.

529. Triglycerides greater than 500 mg/dL (5.7 mmol/L), as determined by the central laboratory. If the participant is on lipid-lowering therapies, doses must be stable for 3 months prior to screening.

5.3. Lifestyle Considerations

Refer to Section 5.3 of the CWMM master protocol.

5.4. Screen Failures

Refer to Section 5.4 of the CWMM master protocol.

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

This section is not applicable to this study.

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. LY3549492 or placebo will be administered orally on each dosing day.

6.1. Study Intervention(s) Administered

Participants are recommended to take their dose at approximately the same time each day with a sufficient amount of water (around 240ml) without meal restrictions.

On days of fasting visits, participants are recommended to fast for at least 8 hours and withhold their dose prior to the visit, and instead take the dose on site as directed.

This table lists the interventions used in this clinical study.

Intervention Name	LY3549492	Placebo
Tablet Strength(s)	• CCI • • •	Matching placebo
Route of Administration	Oral	Oral
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized in EU

Packaging and labeling

Study interventions will be supplied by the sponsor or its designee 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 that appropriate storage conditions have been maintained during transit for all study interventions received and that any discrepancies are reported and resolved before the intervention is used.

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

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

The Pharmacy Manual or another specified location provides further guidance and information on the final disposition of unused study interventions.

6.3. Assignment to Study Intervention

Participants who meet all criteria for enrollment will be randomly assigned to study intervention using an IWRS.

Study interventions will be dispensed at the study visits summarized in the SoA. Returned study interventions should not be re-dispensed to the participants.

Participants will be randomly assigned in a ratio of 2:2:1:1 (Arm 1: Arm 2: Arm 3: Arm 4); refer to Section 1.2 for an illustration of each arm, with

- approximately 50 participants in 1 treatment group randomly assigned to receive placebo (Arm 1)
- approximately 50 participants in 1 treatment group randomly assigned to receive LY3549492 (Arm 2), and
- approximately 25 participants per remaining treatment groups (Arms 3 and 4) randomly assigned to receive CCI of LY3549492 using alternative dose escalation schemes.

All doses of study intervention tablets appear the same. Furthermore, placebo tablets look like study intervention tablets to maintain blinding. Participants in the placebo group will be randomly assigned to a dosing regimen which matches one of the active dose arms.

Stratification

The randomization will be stratified by

- sex (AFAB, AMAB), and
- HbA1c (≤8.5%, >8.5%).

6.4. Blinding

This is a double-blind study.

To maintain the blind, a minimum number of Lilly personnel will see the randomization table and treatment assignments before the study is complete.

Refer to Section 6.3 of the CWMM master protocol for emergency unblinding and additional information on minimizing bias.

6.5. Study Intervention Compliance

When the individual dose for a participant is prepared from a bulk supply, a second member of the study site staff will confirm the preparation.

When participants self-administer study intervention(s) at home, compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning, counting returned tablets, etc., and documented in the source documents. Compliance may also be assessed using dosing diary information, if available.

A record of the number of LY3549492 tablets dispensed to and taken by each participant must be maintained and reconciled with study intervention and compliance records. Intervention start and stop dates, including dates for intervention delays or dose reductions where allowed, will also be recorded in the CRF, diary, and source documents.

6.6. Dose Modification

All dose adjustments will be managed through IWRS in a blinded fashion.

All dose modifications have to be implemented through IWRS by moving one step back in the assigned dosing group.

Dose modification is only allowed for the management of

- intolerable GI symptoms throughout the study for study interventions (Section 6.6.1)
- participants reaching a BMI of ≤22 kg/m^2 (Section 6.6.2), or
- perceived excessive weight loss (Section 6.6.3).

6.6.1. Management of Participants with GI 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.
2. If symptoms persist, prescribe symptomatic medication, such as an 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 up to 3 days** is permitted, if the participant has taken the last 2 weeks of dosing. Resume study intervention immediately, when possible, either alone or in combination with symptomatic medication.
4. If Steps 1, 2, and 3 do not alleviate intolerable GI symptoms, follow guidance for temporary dose de-escalation and dose re-escalation. Only 1 de-escalation and re-escalation attempt for intolerable GI symptoms will be permitted per titration step.

In the event of persistent intolerable GI symptoms, the investigator can advise on Steps 1 and 2 above (in other words, changes in dietary behaviors or consider prescribing symptomatic medication) before stopping the treatment permanently.

Temporary dose de-escalation

If intolerable GI symptoms persist despite the measures outlined in Steps 1 to 3 above, the investigator should contact the sponsor to consider temporarily de-escalating the study intervention to the previous titration step for at least 3 weeks and then re-escalate. De-escalation may be performed during an unscheduled dispensing visit.

If intolerable GI symptoms persist during the first 3 weeks on study intervention, or anytime the participant is on the lowest titration step in the assigned dosing group, then interrupt study intervention for 1 to 3 doses and then restart at the same titration step before the interruption. If the rechallenge is not tolerated, the participant is permanently discontinued from the study intervention.

Dose re-escalation

If intolerable GI symptoms stop with the dose de-escalation, the investigator must resume the dose re-escalation according to the assigned dosing group after at least 3 weeks and only at a scheduled visit.

Dose reduction

If the dose re-escalation results in the return of intolerable GI symptoms or is not considered appropriate based on the investigator's assessment, then stop dose escalation and dose reduce to the previous titration step. Only 1 dose reduction is allowed for intolerable GI symptoms. No subsequent dose re-escalation is allowed.

All participants who discontinue study intervention are encouraged to continue to attend the remaining scheduled study visits (Section 7.1).

6.6.2. Management of Study Intervention in Participants with BMI ≤22 kg/m2

If…	Then…
a participant has a body mass index of ≤22 kg/m^2 at any time during the study	the investigator should contact the sponsor to consider a dose reduction to the previous titration step in a blinded fashion. No subsequent dose re-escalation is allowed.
body weight continues to decline despite a dose reduction to the previous titration step or BMI is ≤18.5 kg/m^2 at any time during the treatment period	the investigator should contact the sponsor for further discussion.

6.6.3. Management of Participants with Perceived Excessive Weight Loss

If there are concerns that the degree of body weight reduction outside of the situation described in Section 6.6.2 may lead to a decision to discontinue from study intervention, the investigator should contact the sponsor to consider dose reduction to the previous titration step, provided a prior dose reduction was not done for perceived excess weight loss. No subsequent dose re-escalation is allowed.

6.6.4. Temporary Discontinuation

In certain situations, after randomization, study intervention may need to be temporarily interrupted. 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 appropriate to do so. A participant may experience multiple events that require dosing interruption; each event should be addressed individually per guidance provided in this section.

For example, participants may need to temporarily interrupt study intervention due to

- occurrence of intolerable GI AEs
- other AEs that warrant dosing interruption determined by the investigator, or
- reasons unrelated to AEs.

If the reason for temporary dosing interruption is related to poor participant tolerability, for example, when protracted GI events of vomiting and/or diarrhea trigger a request from the participant and/or from the investigator for temporary discontinuation of dosing, 1 to 3 doses of

study intervention may be omitted. A longer interruption may be needed at the discretion of the investigator.

In other situations when participant safety is compromised, for example due to an SAE, more than 1 dose may need to be skipped.

The decision to interrupt dosing in any of these situations will not be considered a protocol deviation.

If the participant interrupts dosing for other reasons that are not related to the tolerability or safety of the participant, dosing interruption will be considered a protocol deviation.

The dates and number of skipped doses related to temporary interruption of study treatment will be documented.

Other situations of study intervention interruption that are not described in this section should be discussed between the primary investigator or designee and Lilly study physician or research scientist to decide on an appropriate dosing plan for any participant with such events.

6.6.4.1. Restarting Study Intervention After a Temporary Interruption

If the number of consecutive missed doses of study intervention is

- ≤7, the treatment can be restarted at the same titration step before the interruption or escalate as required, if the drug was well tolerated prior to the interruption. If the participant is on the lowest titration step in the assigned dosing group, treatment can be restarted on the lowest titration step in the assigned dosing group.
- ≥8 (or fewer doses if the study intervention was not well tolerated before any interruption) when the dose interruption occurred, then the treatment should be restarted as described below.

If the dose interruption occurs

- during the first 3 weeks of dosing (that is, the starting dose level), the participant should be restarted on the first titration step, or
- after the first 3 weeks, restart study intervention at the titration step prior to the last dose received before the interruption and resume this dose for at least 3 weeks before continuing to dose escalate every 3 weeks according to the titration schedule assigned to the participant. If the participant is on the lowest titration step in the assigned dosing group, treatment can be restarted on the lowest titration step in the assigned dosing group. When the restart dose escalation is initiated at an unscheduled visit, the subsequent step in the escalation will occur after at least 3 weeks have passed and only at a scheduled visit.

Refer to Section 6.6.1 for guidance on dose escalation or maintenance for participants who do not tolerate a dose level of study intervention.

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

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

6.8. Treatment of Overdose

For the purposes of this blinded study, a potential overdose of LY3549492 is considered any dose higher than the dose assigned through IWRS. Treatment for potential overdose is supportive care.

In the event of a potential 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, and
- closely monitor the participant for any AE or SAE and laboratory abnormalities until LY3549492 no longer has a clinical effect or can no longer be detected systemically (at least 5 days). Refer to Section 8.2.1 for reporting details.

6.9. Prior and Concomitant Therapy

Refer to Section 6.8 of the CWMM master protocol.

Participants cannot be taking strong CYP3A inhibitors or strong CYP3A inducers and drugs that are P-gp/BCRP substrates with a narrow therapeutic index. In order to be eligible for screening into this study, those drugs need to be washed out for at least 2 weeks and the participant should be on a stable dose of alternative medications for at least 2 weeks prior to screening. See Appendix 10.5 for more details.

Metformin is an allowed concomitant medication if on stable dose for at least 3 months prior to screening.

6.9.1. Hyperglycemia Rescue Medicine

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 32-week treatment period. An additional therapeutic intervention should be considered in participants who meet the following criteria:

- the participants are fully compliant with the assigned therapeutic regimen

AND

- in the absence of any acute condition that raises BG either of the following occurs:
  - during the first 6 weeks post-randomization, an average FBG level above 270 mg/dL (15.0 mmol/L) occurs over at least a 2-week period (at least 4 values per week must be available)
  - average FBG >240 mg/dL (>13.3 mmol/L) over any 2-week period or longer from Week 6 to Week 12 post-randomization, or
  - average FBG >200 mg/dL (>11.1 mmol/L) over any 2-week period or longer after Week 12.

If these conditions are met, then participants may begin treatment with another antihyperglycemic agent as determined by their physician. If treatment with another antihyperglycemic agent is instituted, then study drug should be permanently discontinued.

Participants may remain in the study for safety follow-up, but the date at which they begin rescue therapy will be the last date for collection of efficacy measures.

Approved on 02 Apr 2025 GMT

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

Refer to Section 7 of the CWMM master protocol.

7.1. Discontinuation of Study Intervention

In addition to the reasons stated in Section 7.1 of the CWMM master protocol, participants in Study GN02 should be permanently discontinued from study intervention if

- the participant is diagnosed with pancreatitis
- the participant is diagnosed with MTC or multiple endocrine neoplasia type 2 syndrome
- the participant's BMI reduces below ≤18.5 kg/m^2 at any time during the treatment period.

7.1.1. Liver Chemistry Stopping Criteria

Refer to Section 7.1.1 of the CWMM master protocol.

7.1.2. Cardiac Arrhythmia and QTc Stopping Criteria

Discontinuation of study intervention should be considered by the investigator and sponsor if any of the following occurs in a participant:

- QTc ≥500 msec or change in QTc ≥60 msec from baseline, or
- clinically significant arrhythmia (that is, atrial fibrillation).

Refer to Section 7.1.2 of the CWMM master protocol.

7.2. Participant Discontinuation/Withdrawal from the Study

Refer to Section 7.2 of the CWMM master protocol.

7.3. Lost to Follow-Up

Refer to Section 7.3 of the CWMM master protocol.

8. Study Assessments and Procedures

Refer to Section 8 of the CWMM master protocol.

8.1. Efficacy Assessments

Primary

The primary efficacy measure is to compare the effect of the primary intervention (LY3549492) versus the primary control (placebo) for weight reduction at the primary analysis time point (Week 32). Body weight measurements will be collected at specific clinic visits as summarized in the SoA (Section 1.3). Methods for measuring body weight are described in Section 10.8 of the CWMM master protocol.

Secondary

Refer to Section 3 of the CWMM master protocol and Section 3 of Study GN02 ISA for specific secondary efficacy endpoints. Secondary efficacy measures will characterize the

- secondary comparisons of body weight
- treatment effects on glucose metabolism, and
- PK of LY3549492.

Exploratory

Refer to Section 3 of the CWMM master protocol and Section 3 of Study GN02 ISA for specific exploratory efficacy endpoints. The following exploratory efficacy measures will be collected or calculated at the times shown in the SoA:

- To compare the treatment effect at Week 32 for LY3549492 versus placebo
- To compare the effects of LY3549492 versus placebo on health-related quality of life, function, and appetite
- To assess the relationships between LY3549492 and LY3549492 doses and/or exposure, and key safety and efficacy measures, as applicable
- To assess treatment effects on glucose metabolism at 32 weeks for each LY3549492 dose versus placebo
- To evaluate the effects of LY3549492 versus placebo on 7-point SMBG at 32 weeks
- To compare the effects of LY3549492 versus placebo on body composition at Week 32

8.1.1. Patient-Reported Outcomes

8.1.1.1. SF-36 v2 Acute Form

The SF-36 v2 acute form, 1-week recall version is a 36-item, generic, participant-completed measure designed to assess the following 8 domains:

- physical functioning
- role-physical
- bodily pain
- general health
- vitality

- social functioning
- role-emotional, and
- mental health.

The physical functioning domain assesses limitations due to health "now," while the remaining domains assess functioning "in the past week." Each domain is scored individually and information from these 8 domains are further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales). Scoring of each domain and both summary scores are norm based and presented in the form of T-scores, with a mean of 50 and standard deviation of 10; higher scores indicate better levels of function and/or better health (Maruish 2011).

8.1.1.2. Eating Behavior and Appetite Questionnaire

The Easting Behavior and Appetite Questionnaire is a 21 item, patient-reported measure that assesses appetite, eating behavior, and experience with food in the past 7 days which can be used in weight management clinical studies. All items are rated on a 5-point frequency scale that ranges from "never" to "always." Scores for each domain are transformed to a 0 to 100 scale and the total score is the mean of the 3 domain scores. Higher scores indicate better outcomes (reduced appetite, more eating control, less impact of cravings and emotions on eating).

8.1.1.3. Patient Global Impression of Severity - Physical Function due to Weight

The PGIS - Physical Function Weight questionnaire is designed to assess the participants' overall perception of their condition. This is a single-global item that asks participants to rate how their weight limited their ability to perform physical activities in the past 7 days on a 5-point scale, ranging from "not at all limited" to "extremely limited."

8.1.1.4. Patient Global Impression of Change - Physical Function due to Weight

The PGIC - Physical Function Weight questionnaire assesses the participants' overall perception of the efficacy of treatment. This is a single-global item that asks participants to rate the overall change in their ability to perform physical activities due to their weight since starting the study medication. The responses are based on a 5-point scale, ranging from "much better" to "much worse."

8.1.1.5. Patient Global Impression of Status - Overall Eating Behavior

The PGIS Overall Eating Behavior is a single-global item that asks participants to rate their eating habits overall in the past 7 days on a 5-point scale ranging from "Excellent" to "Poor."

8.1.1.6. Patient Global Impression of Change- Overall Eating Behavior

The PGIC Overall Eating Behavior is a single-global item that asks participants to rate the overall change in their eating habits since starting the study medication. The responses are based on a 5-point scale ranging from "much worse" to "much better."

8.1.2. Bioelectrical Impedance Analysis

A whole-body bioimpedance analyzer will be used in this study to assess exploratory endpoints related to body composition. The measurement is quick and noninvasive. BIA is measured using the 8-point method which includes weight, height, waist circumference values, and a low alternating current introduced via foot and hand electrodes. BIA is currently used in diverse settings, including private clinicians' offices, health clubs, and hospitals, and across a spectrum of ages, body weights, and disease states. An estimate of total body water is derived by measuring electrical properties of body tissues, from which fat-free mass, lean (muscle) mass, and body fat (adiposity) are estimated. The seca mBCA-554 is 510(k) exempt.

8.2. Safety Assessments

Planned time points for safety assessments are provided in the Study GN02 SoA (Section 1.3).

Lilly will periodically review evolving aggregate safety data within the study. The study team will review safety reports in a blinded fashion (for applicable blinded study period) according to the schedule provided in the Trial-Level Safety Review plan. Lilly will also review SAEs within time frames mandated by company procedures. The Lilly-designated medical monitor will, as appropriate, consult with the functionally independent Global Patient Safety therapeutic area physician or clinical scientist.

Refer to Section 8.2 of the CWMM master protocol for safety assessments and safety monitoring activities required for all ISAs.

Procedures specified in the following subsections of Study GN02 must be followed in addition to those described in the CWMM master protocol.

8.2.1. Vital Signs

Refer to Section 8.2.1 of the CWMM master protocol.

8.2.2. Physical Examinations

Refer to Section 8.2.2 of the CWMM master protocol.

8.2.3. Electrocardiograms

Refer to Section 8.2.3 of the CWMM master protocol.

Triplicate 12-lead ECGs will be collected at visits specified in the relevant ISA and at additional visits or time points when deemed clinically necessary.

8.2.4. Clinical Safety Laboratory Tests

Laboratory assessments are performed per the SoA (Section 1.3). Refer to Section 8.2.4 of the CWMM master protocol for information on reporting, review and recording, and repeating laboratory tests.

Refer to Section 1.3 of the Study GN02 ISA, and Section 10.2 of the CWMM master protocol for the list of clinical laboratory tests.

8.2.5. Major Adverse Cardiovascular Events

Refer to Section 8.2.5 of the CWMM master protocol.

8.2.6. Deaths

Refer to Section 8.2.6 of the CWMM master protocol.

8.2.7. Hepatobiliary Disorders

Refer to Section 8.2.7 of the CWMM master protocol.

8.2.8. Acute Renal Events

Refer to Section 8.2.8 of the CWMM master protocol.

8.2.9. Pregnancy Testing

Refer to Section 8.2.9 of the CWMM master protocol.

8.2.10. Hepatic Monitoring

Refer to Section 8.2.10 of the CWMM master protocol.

8.2.11. Suicidal Ideation and Behavior Risk Monitoring

8.2.11.1. Columbia-Suicide Severity Rating Scale

Refer to Section 8.2.11.1 of the CWMM master protocol.

8.2.11.2. Patient Health Questionnaire-9

Refer to Section 8.2.11.2 of the CWMM master protocol.

8.2.12. Self-Monitoring of Blood Glucose

8.2.12.1. Glucometer for Participant Use during the Study

All participants 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 SMBG and reporting of hypoglycemia data in the study diary. 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
- as directed by the investigator, or
- for the 7-point SMBG profiles per SoA.

The frequency of SMBG can be increased at the discretion of the investigator.

8.2.13. Additional Safety Data and Sample Collections

8.2.13.1. Major Adverse Cardiovascular Events

Nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise. This committee will be blinded to treatment assignment. The nonfatal CV AEs to be adjudicated include

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

8.2.13.2. Supraventricular Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be submitted to the central reading center. Additional diagnostic tests to determine exact diagnosis should be performed, as needed. The specific diagnosis will be recorded as an AE. Events that meet criteria for serious conditions as described in Section 10.3 of the CWMM master protocol must be reported as SAEs.

8.2.13.3. Hypoglycemia

Upon signing of the ICF, all participants will be educated about signs and symptoms of hypoglycemia and how to treat hypoglycemia.

Hypoglycemia may be identified by spontaneous reporting of symptoms from participants (whether confirmed or unconfirmed by simultaneous glucose values) or by BG samples collected during study visits.

All participants will be provided with glucometers for use during the study (Section 8.2.12.1). Participants will be trained on the correct use of the glucometer and will be instructed to record relevant information, for example, glucose values and symptoms.

In the event that participants develop persistent or recurrent unexplained hypoglycemia during the treatment period, participants may be asked to reduce the dose or discontinue any concomitant glucose-lowering medication.

If a hypoglycemic event meets severe criteria (see definition below), it should be recorded as serious on the AE and SAE CRFs and reported to Lilly as an SAE.

Investigators should use the following definitions and criteria when diagnosing and categorizing an episode considered to be related to hypoglycemia (the BG 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 2020 American Diabetes Association position statement on glycemic targets (ADA 2020). Level 2 and Level 3 hypoglycemic events are considered as safety topics of special interest.

Level 1 hypoglycemia

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 hypoglycemia:

Glucose <54 mg/dL (3.0 mmol/L): Level 2 hypoglycemia is also referred to as documented or BG-confirmed hypoglycemia with glucose <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia:

Severe hypoglycemia (in adults): A severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia. For example, participants had altered mental status and could not assist in their own care, or were semiconscious or unconscious, or experienced coma with or without seizures, and the assistance of another person was needed to actively administer carbohydrate, glucagon, or other resuscitative actions. Glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of glucose concentration to normal is considered sufficient evidence that the event was induced by a low glucose concentration.

- The determination of a hypoglycemic event as an episode of severe hypoglycemia, as defined above, is made by the investigator based on the medical need of the participant to have required assistance and is not predicated on the report of a participant simply having received assistance.
- If a hypoglycemic event meets the criteria of severe hypoglycemia, the investigator must record the event as serious on the AE CRF and report it to Lilly as an SAE.

Nocturnal hypoglycemia:

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

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

8.2.13.4. Severe Gastrointestinal Adverse Events

LY3549492 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 electronic CRF/AE and Concomitant Medications forms, respectively. For detailed information concerning the management of GI AEs, please refer to Section 6.6.1.

8.2.13.5. 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 chronic renal failure. GI AEs have been reported with LY3549492, including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 receptors (Aroda and Ratner 2011). These events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure. Participants should be advised to notify investigators in case of severe nausea, frequent vomiting, or symptoms of dehydration.

8.2.13.6. Pancreatitis

Diagnosis of acute pancreatitis

Acute pancreatitis is safety topic of interest in all studies with LY3549492, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi et al. 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) and/or lipase ≥3x ULN, and
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the investigator should ensure that the following steps are taken:

- obtain appropriate laboratory tests, including pancreatic amylase (p-amylase) and lipase, and
- perform imaging studies, such as abdominal CT scan with or without contrast, or abdominal MRI.

***Note*:** Abdominal ultrasound may be used as an alternative method only if CT and MRI cannot be performed.

- evaluate possible causes of acute pancreatitis, including alcohol use, gallstone/gall bladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention. If acute pancreatitis is ruled out, the participant should resume study intervention based on investigator's clinical judgment.

If pancreatitis is confirmed by the adjudication committee, the study intervention must be permanently discontinued, and the participant should be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart study intervention, if the investigator deems it as clinically appropriate, as described in the Section 7.1.

Case adjudication and data entry

An independent Clinical Endpoint Committee will adjudicate all suspected cases of acute pancreatitis. Relevant data from participants with acute pancreatitis will be entered into a

specifically designed CRF page. The adjudication committee representative will enter the results of adjudication in a corresponding CRF page.

Asymptomatic elevation of pancreatic amylase and/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 pancreatic 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.

8.2.13.7. Thyroid Malignancies and C-Cell Hyperplasia

Individuals who are diagnosed with MTC or multiple endocrine neoplasia syndrome type 2 during the study will be discontinued from study intervention (Section 7.1). The investigator should keep the participant in the study, and also refer the participant to a thyroid specialist or an endocrinologist for follow-up.

The assessment of thyroid safety during the trial will include reporting of any case of thyroid malignancy including MTC, and papillary carcinoma. These data will be captured in specific CRFs.

Data will be captured in specific CRFs.

8.2.13.8. Gallbladder and Biliary Tract Disorders

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

8.2.13.9. Depression

Refer to Section 8.2.11.1 of the CWMM master protocol for information on depression monitoring.

8.2.13.10. Suicidal Ideation or Behavior Monitoring

Refer to Section 8.2.11 of the CWMM master protocol for information on suicidal ideation and behavior risk monitoring.

8.2.13.11. Hepatic Disorders

All events of hepatic disorders or other suspected events related to hepatic disorders should be evaluated and additional diagnostic tests performed as needed. In cases of elevated liver laboratory tests, hepatic monitoring should be initiated as outlined in Section 8.2.10.

8.2.13.12. 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 10.2.2. Laboratory results are provided to the sponsor via the central laboratory.

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

Refer to Section 10.3 of the CWMM master protocol for AE, SAE, and product complaint definitions.

8.3.1. Timing and Mechanism for Collecting Events

Refer to Section 8.3.1 of the CWMM master protocol.

8.3.2. Collection of Pregnancy Information

Refer to Section 8.3.2 of the CWMM master protocol.

8.3.2.1. Participants Who Become Pregnant

AFAB participants who become pregnant

The investigator will collect pregnancy information on any male participant's female partner 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, the investigator may learn of an SAE through spontaneous reporting.

Any participant who becomes pregnant while participating in the study will discontinue study intervention

8.3.2.2. Participants With Partners Who Become Pregnant

When to collect pregnancy information

AMAB participants with partners who become pregnant.

In most circumstances, the investigator will attempt to collect pregnancy information from a participant's partner who becomes pregnant while the participant is in this study.

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

- will obtain consent to release information from the pregnant 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 partner will be followed to determine the pregnancy's outcome. Information on the status of the mother and neonate will be forwarded to the sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks after 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.

When not to collect pregnancy information

It is not necessary to collect information about a pregnancy in the partner of a study participant in the following circumstances:

- the partner of the study participant was not exposed to the study intervention, or
- the participant did not contribute the sperm that resulted in the pregnancy.

8.3.3. Adverse Events of Special Interest

The AEs of special interest include

- major adverse CV events
- arrhythmias and cardiac conduction disorders
- hypoglycemia
- severe GI AEs
- acute renal events
- pancreatitis
- thyroid malignancies and c-cell hyperplasia
- hepatobiliary disorders
- depression
- suicidal ideation or behavior monitoring, including C-SSRS and PHQ-9 for chronic weight management, and
- drug-induced liver injury.

Refer to Section 8.2.13 for any additional samples and data collections when certain AEs occur.

The details of analysis will be provided in the SAP.

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 LY3549492 will be analyzed for drug concentration.

A maximum of 3 samples may be collected at additional time points during the study if warranted and agreed upon between the investigator and the sponsor. The timing of sampling may be altered during the course of the study based on newly available data, for example, to obtain data closer to the time of peak plasma concentrations, to ensure appropriate monitoring.

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.

8.4.1. Bioanalysis

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

Concentrations of LY3549492 will be assayed using a validated liquid chromatography with tandem mass spectrometry method. Samples collected from participants receiving placebo will be retained and analyzed only for LY3549492 if required to confirm participant dosing records.

Bioanalytical samples collected to measure study intervention concentrations, including placebo samples, will be retained for a maximum of 1 year following last participant visit for the study. During this time, samples remaining after the bioanalyses may be used for exploratory analyses, such as metabolism and/or protein binding work.

8.5. Pharmacodynamics

PD parameters are not evaluated in this study.

8.6. Genetics

While genetic samples will be collected, no study-specific genetic analyses are planned.

8.7. Biomarkers

In addition to the planned biomarker research, as indicated in the SoA and Section 8.7, exploratory biomarker research on stored non-pharmacogenetic samples may be performed to address questions of

- relevance to drug disposition
- target engagement
- PD
- mechanism of action

- variability of participant response, including safety, and
- clinical outcome.

Sample collection is incorporated into clinical studies to enable the examination of these questions through the measurement of biomolecules, including, proteins, lipids, and other cellular elements.

Serum and plasma samples for non-pharmacogenetic biomarker research will be collected at the times specified in the SoA where local regulations allow. Samples may be used

- for research on the
  - drug targets
  - disease process
  - variable response to LY3549492
  - pathways associated with obesity
  - related clinical traits or complications, including chronic kidney disease and nonalcoholic steatohepatitis
  - mechanism of action of LY3549492, and/or
  - research methods, or
- for validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, related traits, or complications.

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 personnel. Samples will be retained at a facility selected by Lilly or its designee, for a maximum of 15 years after the last participant visit for the study, or for a shorter period if local regulations and Ethical Review Boards impose shorter time limits. This retention period 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 LY3549492 or after LY3549492 becomes commercially available.

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Health Economics OR Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

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

9.1. Statistical Hypothesis

The primary hypothesis that is being tested in this study is that LY3549492 doses of CCI administered QD are superior to placebo with regard to percent change in body weight from baseline to Week 32, in participants with T2D who are obese or overweight.

9.1.1. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

9.2. Analyses Sets

The analysis sets are defined in Section 9.2 of the CWMM master protocol.

9.3. Statistical Analyses

9.3.1. General Considerations

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. Adjustments to the planned analyses are described in the final clinical study report.

9.3.2. Primary Endpoint(s)/Estimand(s) Analysis

Refer to Section 9.3.2 of the CWMM master protocol for an outline of the primary endpoint analyses. Details will be provided in the Study GN02 SAP.

9.3.3. Secondary Endpoint(s)/Estimand(s) Analysis

Details of the secondary endpoints analyses will be provided in the Study GN02 SAP.

9.3.4. Exploratory Endpoint(s)/Estimand(s) Analysis

Details of the exploratory endpoints analyses will be provided in the Study GN02 SAP.

9.3.5. Safety Analyses

Refer to Section 9.3.5 of the CWMM master protocol for a description of the safety analyses.

9.3.6. Other Analyses

Refer to Section 9.3.6 of the CWMM master protocol and its subsections for a description of other safety analyses which may be conducted. Details of these analyses will be provided in the Study GN02 SAP.

9.3.7. Pharmacokinetic/Pharmacodynamic Analyses

Concentration data of LY3549492 may be analyzed using descriptive analyses approaches and/or analyzed using a population PK approach using nonlinear mixed-effects modeling techniques implemented with the NONMEM® software.

The relationships between LY3549492 dose and/or concentration and selected efficacy, tolerability, and safety endpoints will be evaluated. Additionally, the impact of intrinsic and extrinsic participant factors, such as age, weight, gender, and renal function on LY3549492 PK and/or PD parameters may be examined.

9.4. Interim Analyses

The interim analyses of safety and/or efficacy may be conducted after data from approximately 100% of participants have been obtained at Week 24 of the treatment period to support planning activities associated with the clinical development program and to aid in the development of PK/PD models. An IAC will be formed to review the interim analyses for the safety and efficacy reports in an unblinded manner. The timing of dissemination of data summaries based on interim analyses is addressed in Section 10.1 of the CWWM master protocol.

The SAP will describe the planned interim analyses in greater detail. Only the IAC is authorized to evaluate unblinded interim efficacy and safety analyses. Refer to Section 10.1.5 of the CWMM master protocol for information on the IAC.

Study sites will receive information about interim results only if they need to know for the safety of their participants.

Unblinding details are specified in the unblinding plan section of the SAP or in a separate unblinding plan document.

9.5. Sample Size Determination

The study sample size of approximately 150 participants will be randomly assigned to study drug in a randomization ratio of 2:2:1:1 as follows:

- 50 participants to placebo
- 50 participants to LY3549492 CCI
- 25 participants to LY3549492 CCI (slow titration)
- 25 participants to LY3549492 CCI (fast titration)

Upper limits of approximately 60% enrollment for males and approximately 60% for females will be used to ensure sufficient representation of both populations across the randomized arms. There are 2 arms for the CCI dose, with slow or fast dose titration, to assess tolerability of dose escalation.

Assuming a constant 20% dropout rate, this results in 40 completers per 50-participant arm and 20 completers per 25-participant arm.

Sample size selection is guided by the objective of establishing superiority of each LY3549492 dose to placebo relative to the percent change from baseline in body weight at Week 32.

Assuming a standard deviation of 10%, a 2-sided type I error rate of 0.05, 40 completers for the LY3549492 CCI treatment arm and 40 completers for the placebo arm can provide over 90% power, assuming a treatment difference of -8%. Under similar assumptions, 20 completers for an individual LY3549492 CCI treatment arm and 40 completers for the placebo arm can provide over 95% power, assuming a treatment difference of -12%.

10. Supporting Documentation and Operational Considerations

This section provides information specific to the Study GN02 ISA. For supporting documentation and operational considerations applicable to all ISAs, refer to Section 10 of the CWMM master protocol.

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

Refer to Section 10.1.5 of the CWMM master protocol for information on the IAC.

Refer to Section 9.4 for information on efficacy interim analyses and the IAC.

10.2. Appendix 2: Clinical Laboratory Tests

Sections 1.3 (SoA), 10.2 (Clinical Laboratory Tests), and 10.13 (Requirements for ISA Design) of the CWMM master protocol describe laboratory tests that may be performed at additional times from those noted in the Study GN02 SoA (Section 1.3).

This table describes tests unique to Study GN02 ISA.

10.2.1. Clinical Laboratory Tests Performed Starting at Visit 0

Clinical Laboratory Tests	Comments
Calculations	Generated by Lilly-designated laboratory
eGFR (CKD-EPI) calculated using cystatin-C	
Pharmacokinetics	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
PK samples – LY concentration	
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Longitudinal biomarkers	Refer to Section 10.3 (Mechanistic Biomarkers) for specific laboratory tests.
Endpoint biomarkers	Refer to Section 10.3 (Mechanistic Biomarkers) for specific laboratory tests.
Genetics	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Genetic sample	
Stored samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Serum	
Plasma (EDTA)	
Whole-blood epigenetics	

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; EDTA = ethylenediaminetetraacetic acid; LY = 3549492; PK = pharmacokinetic(s).

10.2.2. Laboratory Samples to be Obtained at Time of 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 tests 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 minutes to 4 hours after the start of the event. • Note: The optimal collection time is from 1 to 2 hours after the start of event.	Total tryptase

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

10.3. Appendix 3: Mechanistic Biomarkers

Mechanistic biomarkers will be measured at longitudinal intervals (longitudinal biomarkers) or less frequently to correspond with primary and/or interim analysis endpoints (endpoint biomarkers). To explore potential mechanisms of action related to changes in glucose, lipid or nutrient metabolism, or target receptor-related functions, the following markers will be assessed:

- biomarkers related to insulin sensitivity: fasting BG, fasting insulin, fasting C-peptide, homeostasis model assessment of insulin resistance (computed with fasting BG and fasting insulin or C-peptide), insulin-like growth factor 1, total adiponectin, and leptin
- biomarkers related to glucose metabolism: HbA1c and fasting BG
- biomarkers related to lipid metabolism: fasting cholesterol, triglycerides, LDL-C, HDL-C, VLDL-C, and non-HDL-C
- biomarkers related to regulation of BP and fluid balance: sodium, potassium, plasma renin activity, and aldosterone
- biomarkers related to regulation of calcium and bone metabolism: calcium, phosphate, 25-OH vitamin D, parathyroid hormone, procollagen 1 intact N-terminal propeptide, and collagen cross-linked C-telopeptide, and
- biomarker related to inflammation: high-sensitivity C-reactive protein.

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Insulin sensitivity	• Fasting glucose • Fasting insulin[a] • Fasting C-peptide[a] **Calculation:** HOMA2-IR[a] (computed with fasting glucose and fasting insulin or fasting C-peptide)	Total adiponectin[a] IGFBPs[a] Leptin[a]
Glucose metabolism	• Fasting glucose • HbA1c **Calculation:** • HOMA2-B[a] (computed with fasting glucose and fasting insulin or fasting C-peptide)	
Regulation of blood pressure and fluid balance	• Plasma renin activity[a] • Aldosterone[a] • Sodium • Potassium	

Lipid metabolism	• Apolipoprotein B[a]
	• Fasting lipid panel:
	  ○ total cholesterol
	  ○ Calculated LDL cholesterol (LDL-C) – LDL direct measure if triglycerides exceed maximum calculation limit
	  ○ HDL cholesterol (HDL-C)	

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
	○ non-HDL cholesterol (non-HDL-C) ○ triglycerides ○ VLDL cholesterol (VLDL-C)	
Bone and calcium metabolism	Calcium Phosphate	Intact PTH[a] 25-OH vitamin D[a] CTX-1[a] P1NP[a]
Inflammation	hsCRP[a]	

Abbreviations: CTX-1 = collagen cross-linked C-telopeptide; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HOMA2-B = homeostasis model assessment of beta-cell function; HOMA2-IR = homeostasis model assessment of insulin resistance; hsCRP = high-sensitivity C-reactive protein; IGFBP = insulin-like growth factor-binding protein; LDL = low-density lipoprotein; P1NP = procollagen 1 intact N-terminal propeptide; PTH = parathyroid hormone; VLDL = very low-density lipoprotein.

[a] Results will not be provided to site.

Note: Fasting glucose, calcium, phosphate, sodium, and potassium will be measured within the clinical chemistry panel.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Individuals assigned female at birth (AFAB)	Individuals assigned the female sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are potentially capable of gestating a fetus, and thus are capable of exposing an egg, embryo, or fetus to study drug or drug effects.
Individuals assigned male at birth (AMAB)	Individuals assigned the male sex based on external genitalia and/or genetic or medical information. In addition, if these individuals are of reproductive potential, they are not capable of gestating a fetus, but are capable of exposing a fetus to study drug or drug effects via their semen. Individuals AMAB are considered to be not of reproductive potential if they have had orchiectomy (orchidectomy) with or without penectomy, confirmed by operative note.
Individuals of childbearing potential (IOCBP)[a]	Adult individuals AFAB are considered IOCBP unless they are INOCBP. Note: Adolescent or adult individuals AFAB who are receiving hormone therapy as part of gender transition are considered IOCBP unless they meet the conditions outlined below for INOCBP.
Individuals not of childbearing potential (INOCBP)[b]	Individuals AFAB are considered INOCBP if they are not capable of producing ova or embryo, and/or are not capable of potentially gestating a fetus. Such individuals include those who • have a congenital anomaly such as Müllerian agenesis, resulting in confirmed infertility • are infertile due to surgical sterilization, or • are menopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Menopausal state[c]	The menopausal state is defined as an individual: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[c], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle-stimulating hormone ≥40 mIU/mL • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or

Word/Phrase	Definition
	• aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy.

[a] IOCBP is inclusive of the concept of women of childbearing potential (WOCBP or WCBP), a term often used in literature and regulatory guidance documents.

[b] INOCBP is inclusive of the concept of women not of childbearing potential (WNOBCP).

[c] The individual **should not** be taking medications during amenorrhea, such as oral contraceptives, hormone replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy, that could induce transient amenorrhea. Individuals on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of menopausal status before study enrollment.

10.4.2. Contraception Guidance

1. IOCBP are excluded from the trial.
2. INOCBP may participate in this trial.
3. Please see Section 10.4.1 for definitions.
4. Individuals AMAB may participate in this trial.

The table below describes contraception guidance for individuals AMAB.

Participant Population	**Contraception Guidance**
All individuals AMAB…	should refrain from sperm donation for the duration of the study and for 90 days or 13 weeks after the last dose of the study intervention.
Individuals AMAB with partner(s) who are IOCBP[a]…	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms and at least 1 additional effective method of contraception for the duration of the study and for 90 days or 13 weeks after the last dose of the study intervention.
Individuals AMAB with partner(s) who are pregnant[a]…	must • remain abstinent (if this is their preferred and usual lifestyle), or • use condoms for the duration of the study and for 90 days or 13 weeks after the last dose of the study intervention.
Individuals AMAB who exclusively engage in sexual relations with other individual(s) who are AMAB, as their preferred and usual lifestyle.	are not required to use contraception.

[a] Individuals AMAB who have undergone orchiectomy but not penectomy must use condoms during sex, but the partner who is IOCBP is not required to use an additional form of contraception. Individuals AMAB who have

undergone orchiectomy and penectomy are not required to use condoms.

Examples of different methods of contraception:

Methods	Examples

Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the INOCBP definition above.
	• combined (estrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
	  ○ oral
	  ○ intravaginal (vaginal ring)
	  ○ transdermal/contraceptive patch (only individuals <198 pounds or 90 kg)
	• progestogen-only hormonal contraception associated with inhibition of ovulation:
	  ○ oral
	  ○ injectable
	  ○ implantable
	• sexual relationships exclusively between individuals who are assigned the same sex at birth
	• vasectomy – for individuals AMAB in clinical trials and for the partner of an individual AFAB (if only sexual partner)
	• fallopian tube implants (if confirmed by hysterosalpingogram), or
	• intrauterine devices (IUD) with or without hormone-releasing system

Effective contraception	• progestogen-only hormonal contraception where inhibition of ovulation is not the primary mode of action • penile condom with spermicide • vaginal condom with spermicide • diaphragm with spermicide • cervical sponge with spermicide • cervical cap with spermicide Note: Penile and vaginal condoms should not be used in combination.
Ineffective methods of contraception whether used alone or in any combination	• spermicide alone • periodic abstinence • fertility awareness (calendar method, temperature method, cervical mucus, or symptothermal) • withdrawal

	• postcoital douche, or • lactational amenorrhea

10.5. Appendix 5: List of Prohibited Drugs (Strong CYP3A Inhibitors or Strong CYP3A Inducers and Drugs That Are P-gp/BCRP Substrates)

This list is intended to be exhaustive, but with available information continually evolving, the status of every relevant drug cannot be guaranteed.

Strong CYP3A4 inhibitors or Strong CYP3A4 inducers	**Indication**	**Excluded medications**
	COVID-19 therapy	• nirmatrelvir and ritonavir (Paxlovid™)
	Antibiotics	• clarithromycin[a] • telithromycin[a] • josamycin[a] • rifamycins
	Antifungals	• ketoconazole[b] • itraconazole[b] • posaconazole[b] • voriconazole[b] (topical use is allowed)
	Antiepileptics	• carbamazepine • phenytoin • fosphenytoin • phenobarbital
	Antiretrovirals (HIV infection)	• certain protease inhibitors[c]
	Chemotherapy	• certain kinase inhibitors[c] • certain androgen receptor inhibitors[c] • mitotane
	Antidepressant	• nefazodone
	Herbal	• St. John's Wort
	Progesterone receptor inhibitor	• mifepristone
P-gp substrates for which small increases in exposure may result in serious AEs	Antiarrhythmics	• digoxin • quinidine
	Antimalarial	• quinine
	Immunosuppressant	• tacrolimus • cyclosporine
	Antipsychotic	• pimozide

	Anticoagulant	• Dabigatran etexilate
BCRP substrates for which small increases in exposure may result in serious AEs	HMG-CoA reductase inhibitors	• rosuvastatin

[a] For participants taking these medications, azithromycin may be substituted (if appropriate) at least 2 weeks prior to randomization.

[b] For participants taking these medications, miconazole may be substituted (if appropriate) at least 2 weeks prior to randomization.

[c] lists of specific medications of concern are available upon request

10.6. Appendix 6: Abbreviations and Definitions

Term	Definition
AE	adverse event
AFAB	assigned female at birth
AMAB	assigned male at birth
BCRP	breast cancer-resistance protein
BG	blood glucose
BIA	bioelectrical impedance analysis
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BMI	body mass index
BP	blood pressure
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.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CV	cardiovascular
CYP	cytochrome
DPP-4i	dipeptidyl peptidase-4
ECG	electrocardiogram
eCOA	electronic Clinical Outcome Assessment

ED	early discontinuation
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.
GCG	glucagon
GI	gastrointestinal
GIP	glucose-dependent insulinotropic peptide
GLP-1	glucagon-like peptide-1
HOMA2-B	homeostasis model assessment of beta-cell function
HOMA2-IR	homeostasis model assessment of insulin resistance
HbA1c	hemoglobin A1c
HDL-C	high-density lipoprotein cholesterol
HR	heart rate
IAC	internal assessment committee
ICF	informed consent form
IND	investigational new drug
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.
IOCPB	individuals of childbearing potential
INOCBP	individuals not of childbearing potential
ISA	intervention-specific appendix
IWRS	interactive web-response system
LDL-C	low-density lipoprotein cholesterol
MRI	magnetic resonance imaging
MTC	medullary thyroid cancer
OAM	oral antihyperglycemic medication

participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PD	pharmacodynamics
PGIC	Patient’s Global Impression of Change
PGIS	Patient’s Global Impression of Severity
P-gp	P-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetics
QD	once-daily
QTc	corrected QT interval
RA	receptor agonist
SAE	serious adverse event
SAP	statistical analysis plan
screen	The act of determining if an individual meets minimum requirements to become part of a pool of potential candidates for participation in a clinical study.
SF-36 v2	Short Form 36 Version 2 Health Survey
SMBG	self-monitored blood glucose
SoA	Schedule of Activities
T2D	type 2 diabetes mellitus
ULN	upper limit of normal
VLDL-C	very low-density lipoprotein cholesterol

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