

Protocol J3H-MC-GZNI(b)

A Parallel-Group, Double-Blind Study to Investigate the Safety and Tolerability of LY3549492 Compared With Placebo in Adult Participants Aged 55 to 80 Years With a BMI of 22 to 25 kg/m²

NCT07085468

Approval date: 26 Jun 2025

Title Page

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Protocol Title:

A Parallel-Group, Double-Blind Study to Investigate the Safety and Tolerability of LY3549492 Compared with Placebo in Adult Participants Aged 55 to 80 Years with a BMI of 22 to 25 kg/m²

Protocol Number: J3H-MC-GZNI

Amendment Number: (b)

Compound: LY3549492

Brief Title:

A Study to Investigate Safety and Tolerability of LY3549492 Compared with Placebo in Adult Participants 55 to 80 Years of Age and BMI within 22 to 25 kg/m²

Study Phase: 2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Number(s):

IND: 174606

Approval Date: Protocol electronically signed and approved by Lilly on date provided below.

Document ID: VV-CLIN-194092

Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
Amendment (b)	26-Jun-2025
Amendment (a)	06-Jun-2025
Original Protocol	21-Feb-2025

Amendment (b): 26-June-2025

This amendment is considered to be substantial.

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

- safety or the rights of the study participants

Overall rationale for the amendment

This amendment incorporates changes to dose modification for participants with GI AEs, discontinuation of study intervention, laboratory values (cystatin-c/eGFR), and addresses other minor protocol issues based on FDA feedback from amendment (a) review and Study May Proceed letter.

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities	For Physical assessment, added instances at Visits 10, 18, and 801.	Added in response to feedback received in the FDA Study May Proceed letter.
	For Symptom-directed physical assessment, removed instances at Visits 10, 18, and 801.	Removed in response to feedback received in the FDA Study May Proceed letter.
	For Vital signs assessment, added an instance at UV 997.	Added in response to feedback received in the FDA Study May Proceed letter.
	For Timed Up & Go (TUG) assessment, added a note to refer to Section 8.1.3.1.	For study site awareness and convenience.
	For cystatin-c assessment, added instances at Visits 3, 4, 5, 7, 8, and 9.	Added in response to feedback received in the FDA Study May Proceed letter to expand eGFR

Section # and Name	Description of Change	Brief Rationale
		assessment to match the frequency of clinical chemistry laboratory testing.
	For eGFR, added instances at Visits 3, 4, 5, 7, 8, and 9.	Added in response to feedback received in FDA Study May Proceed letter to expand eGFR assessment to match frequency of clinical chemistry laboratory testing.
Section 5.2 Exclusion Criteria	Changed subsection heading from “Autoimmune” to “Infections/Immune Abnormalities.”	Added in response to feedback received in FDA Study May Proceed letter to clarify category of exclusion criterion.
	In criterion 17, changed lower limit for hypertension from mean systolic BP ≥ 160 mm Hg to ≥ 150 mm Hg.	Added in response to feedback received in FDA Study May Proceed letter given that study population is older and vulnerable.
	In criterion 37, added examples of uncontrolled endocrine abnormality: “a history of recurrent severe hypoglycemia, impaired awareness of hypoglycemia, a history of orthostatic hypotension, and/or conditions associated with dysautonomia.”	Added in response to feedback received in FDA Study May Proceed letter to expand examples of uncontrolled endocrine abnormalities.
	In criterion 44, removed bullet point: “Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of	Removed in response to feedback received in FDA Study May Proceed letter to avoid selection bias and improve external validity.

Section # and Name	Description of Change	Brief Rationale
	efficacy should not be randomized.”	
Section 6.6.1 Management of Participants with GI Symptoms	Added table (Grading Scale and management for Assessment of Gastrointestinal-associated Adverse Events) listing Nausea/Vomiting and Diarrhea criteria. Also added guidance for investigators if participants report mild, moderate, or severe GI symptoms.	Added in response to FDA Question 1a and 1b to specify study intervention discontinuation criteria on the basis of GI-associated adverse events.
	Revised investigator guidance regarding study intervention interruption or resumption. In particular, removed the statement “resume intervention immediately” in Step 3.	Added Modified in response to FDA Question 1c to remove comments that convey an urgency to resume study intervention.
Section 7.1 Discontinuation of Study Intervention	Added 2 instances in which a participant should be permanently discontinued from the study intervention: Added: The participant’s eGFR decline to <45 mL/min/1.73 m², calculated per Chronic Kidney Disease Epidemiology Collaboration Cystatin-C method	Added in response to FDA Question 1c to clarify permanent discontinuation in the occurrence of Grade 4 GI events, and Question 2b to include eGFR threshold triggering study intervention discontinuation.

Section # and Name	Description of Change	Brief Rationale
	at any time during the treatment period • A participant experiences a Grade 4 GI adverse event (Section 6.6.1).	
Section 8.1.3.1 Assessment Timed Up and Go (TUG)	Added: “The timer starts when the person begins to stand and stops the moment they are seated again.”	Added to clarify the assessment procedure.
Section 8.2.2 Vital Signs	Modified instructions on timing and measurement of vital signs, including orthostatic measurements.	Added in response to feedback received in the FDA Study May Proceed letter to include orthostatic vital measurements.
Section 8.3.3.4 Acute Pancreatitis (Adjudicated) Subsection “Asymptomatic elevation of pancreatic amylase and/or lipase”	Added “The decision to perform diagnostic follow-up such as symptom-directed physical assessment, laboratory evaluation blood count, renal panel, liver tests, and/or abdominal imaging, should be guided by clinical judgment. Monitor and repeat pancreatic enzymes (lipase and/or p-amylase) tests and perform a symptom-directed physical assessment as per the SoA in Section 1.3 at each visit until amylase and lipase levels return to	Added in response to FDA Question 3 to provide frequency of pancreatic enzyme monitoring for participants with asymptomatic elevation of pancreatic enzymes (lipase and/or amylase $\geq 3x$ ULN).

Section # and Name	Description of Change	Brief Rationale
	baseline. If acute pancreatitis is suspected, follow Section 8.3.3.4 for further guidance.”	
Section 8.3.3.9 Acute Renal Events	Revised investigator guidance regarding discontinuation of participants with CKD who experience acute renal events.	Added in response to FDA Question 2a to clarify permanent discontinuation for participants with CKD experiencing acute renal events.
Section 10.4.2 Contraception Guidance	In the table entry titled Individuals AMAB with partner(s) who are IOCBP, added the term “highly” in “use condoms and at least 1 additional highly effective method of contraception.”	Added in response to feedback received in the FDA Study May Proceed letter to modify contraception guidance.
Section 10.7 Appendix 7: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	In the Vital sign measurements section, revised instructions on timing and measurement of vital signs, including orthostatic measurements.	Added in response to feedback received in the FDA Study May Proceed letter to include orthostatic vital measurements.
Section 10.13 Appendix 13: Protocol Amendment History	Added Summary of Events table listing amendment rationale and all changes made in protocol amendment J3H-MC-GZNI(a).	Document requirement.

Abbreviations: AMAB = assigned male at birth; BP = blood pressure; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; IOCBP = individuals of childbearing potential; ULN = upper limit of normal; UV = unscheduled visit.

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1. Protocol Summary

1.1. Synopsis

Protocol Title:

A Parallel-Group, Double-Blind Study to Investigate the Safety and Tolerability of LY3549492 Compared with Placebo in Adult Participants Aged 55 to 80 Years with a BMI of 22 to 25 kg/m²

Brief Title:

A Study to Investigate Safety and Tolerability of LY3549492 Compared with Placebo in Adult Participants 55 to 80 Years of Age and BMI within 22 to 25 kg/m²

Regulatory Agency Identifier Number(s):

IND: 174606

Rationale:

LY3549492 is an oral, non-peptide glucagon-like peptide-1 receptor agonist (GLP-1 RA) that is being developed as a daily oral adjunct therapy to diet and physical activity for weight management in adults with obesity or who are overweight with weight-related comorbidities.

GLP-1 RAs are known for improving glycemic control by increasing insulin and decreasing glucagon secretion in a glucose-dependent manner. Clinical trials and preclinical data suggest that GLP-1 RA may also offer cardiovascular and neuroprotective effects, improving outcomes in diseases associated with older age.

Study J3H-MC-GZNI (GZNI) is a parallel-group, double-blind study to investigate the safety and tolerability of LY3549492 once daily compared with placebo in adult participants aged 55 to 80 years with a body mass index (BMI) of 22 to 25 kg/m².

Participants will be randomly assigned to 48 weeks of LY3549492 (15 mg or 60 mg) or placebo to evaluate the safety and tolerability. The study will also explore the potential clinical effects of LY3549492 on additional outcomes, including body weight changes, waist circumference, body composition, physical mobility and balance, health-related quality of life, lipid levels, glycemic control, and cognitive health. The safety data from this study will support future clinical development of LY3549492 in indications associated with older age and occurring across different BMI categories, including those with a healthy BMI.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To compare the safety and tolerability of LY3549492 versus placebo	Incidence of TEAEs and SAEs

Secondary	
To characterize the effects of LY3549492 and placebo on body weight changes	• Percent change from baseline in body weight (kg) at Weeks 24 and 48 • Change from baseline in BMI at Weeks 24 and 48
To characterize the effects of LY3549492 and placebo on participant retention	Number of participants with AEs leading to permanent discontinuation of study intervention or withdrawal

Abbreviations: AE = adverse event; BMI = body mass index; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Primary estimand

The primary clinical question of interest is

What is the difference in the safety and tolerability of each regimen of LY3549492 and placebo, in participants who meet the eligibility criteria, regardless of adherence to study intervention?

Safety and tolerability assessments will be guided by an estimand comparing the safety of LY3549492 doses with placebo irrespective of adherence to the study intervention, including the data collected during the treatment period plus safety follow-up, from participants who are randomly assigned and exposed to at least 1 dose of study intervention.

Additional estimand

What is the treatment difference in discontinuation of study intervention due to malnutrition or excess weight loss between LY3549492 and placebo at 48 weeks, in participants who meet the eligibility criteria, if they would remain on their randomly assigned treatment for 48 weeks and would not initiate non-protocol weight loss management treatments?

An additional estimand for Study GZNI may also be used for secondary and exploratory endpoints and is defined by the attributes mentioned in Section 3 of the protocol.

Overall Design:

Study GZNI is a parallel-group, double-blind study to investigate the safety and tolerability of LY3549492 once daily compared with placebo in adult participants aged 55 to 80 years with a BMI of 22 to 25 kg/m².

Approximately 220 participants will be randomly assigned in a double-blind 1:5:5 ratio to placebo (approximately 20 participants), LY3549492 15 mg (approximately 100 participants), and LY3549492 60 mg (approximately 100 participants).

This study will consist of the following study periods:

- optional Visit 601: ≤3 weeks
- screening period (Visit 1): ≤5 weeks
- treatment period (Visit 2 to Visit 18): 48 weeks
- safety follow-up period: 4 weeks

The primary endpoint will be at Week 48.

Brief Summary:

The purpose of this study is to investigate the safety and tolerability of LY3549492 in adult participants aged 55 to 80 years with a BMI of 22 to 25 kg/m².

Study details include:

- The study duration will be up to 60 weeks, including the screening, treatment, and safety follow-up period.
- The treatment duration will be up to 48 weeks.
- During the treatment period, the visit frequency will be
 - 3 weeks – Optional Visit 601 to Visit 1
 - 5 weeks – Visit 1 to Visit 2
 - every 3 weeks – Visit 2 to Visit 18
 - 4 weeks – Visit 18 (or date of early discontinuation) to Visit 801

Study Population:

In general, an individual may take part in the Study GZNI if they

- are 55 to 80 years of age inclusive, at the time of signing the informed consent
- have a BMI within the range of 22 to 25 kg/m² (inclusive), and
- have had a stable body weight for the 3 months prior to randomization (<5% body weight gain and/or loss).

Number of Participants:

Approximately 220 participants will be randomly assigned in a double-blind 1:5:5 ratio to placebo (approximately 20 participants), LY3549492 15 mg (approximately 100 participants), and LY3549492 60 mg (approximately 100 participants).

Intervention Groups and Duration:

This table lists the interventions used in this clinical study.

Intervention Name	LY3549492	Placebo
Dosage Level(s)	CCI	Matching placebo QD
Route of Administration	Oral	Oral

Abbreviation: QD = once daily

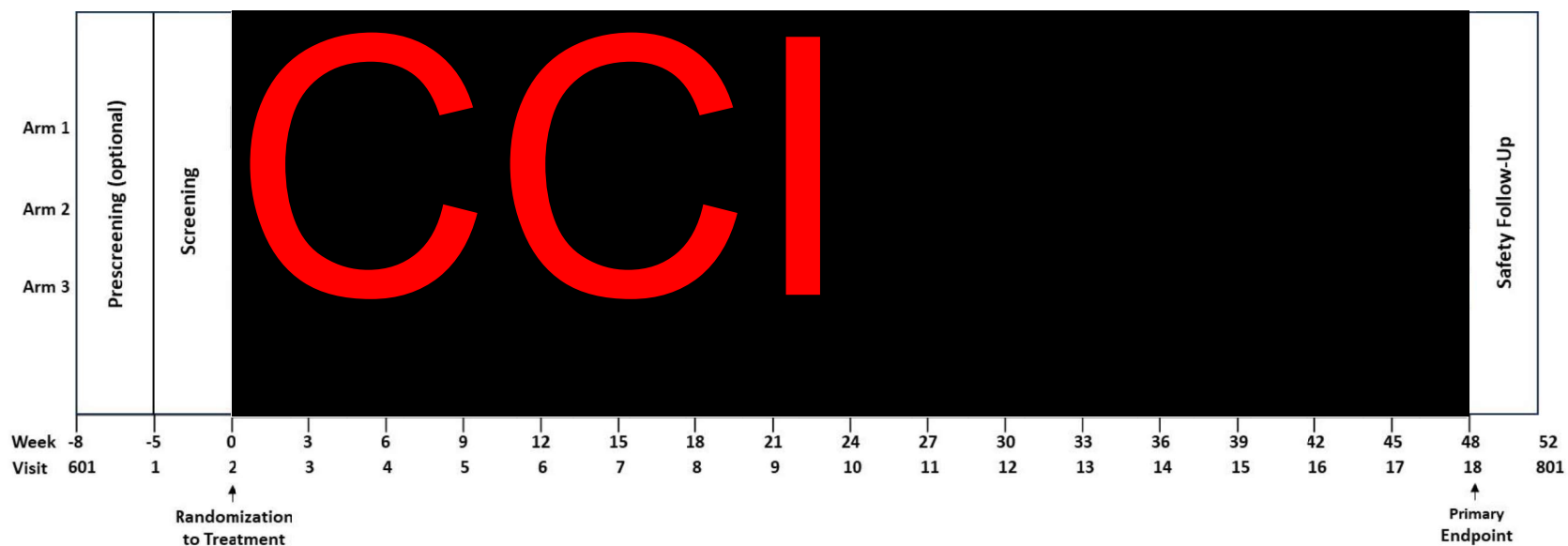
Ethical Considerations of Benefit/Risk:

There is no anticipated therapeutic benefit for the participants in this study.

The principal anticipated risks are those associated with the known pharmacologic effects of GLP-1 RAs, namely gastrointestinal tolerability and increased heart rate. In clinical studies to date, these risks have been monitorable, usually mild to moderate in severity, reversible, and readily manageable. Currently, there are no recognized adverse effects from LY3549492 other than those related to GLP-1 receptor agonism, and no safety or tolerability concerns have been identified that would constitute undue risk to study participants. The safety profile continues to be refined as more clinical safety data become available.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: LY = LY3549492; n = number of study participants; PBO = placebo.

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in Study J3H-MC-GZNI (GZNI). However, for those participants whose participation in this study is affected by exceptional circumstances, such as pandemics or natural disasters, please refer to Section [10.11](#).

Fasting visits

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

If a participant attends study Visits 1, 2, 3, 6, 10, 14, 18, or 801 in a non-fasting state, reschedule the visit to complete the required fasting activities within the allowable visit interval.

A participant who attends Visits 4, 5, 7, 8, 9, 11, 12, 13, 15, 16, or 17 in a non-fasting state does not need to return in a fasted state and the visit should be completed.

Visit 601 to Visit 1 - Screening

This study includes an optional screening visit (Visit 601), which will enable key eligibility factors associated with screen failures to be assessed at the earliest time point.

All screening activities must take place within the 5-week window. Since some screening procedures need to be completed in the fasting state, V1 may be conducted over more than 1 day to ensure necessary conditions are met.

If not fasting at V1, participants must return on another day in the fasted state to complete all procedures that require fasting.

Visit 2 - Randomization to treatment

Participants will be randomly assigned to a treatment arm at Visit 2 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

Participants who are unable or unwilling to continue the study treatment period for any reason will perform an ED visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit. These participants should also complete the safety follow-up.

The SoA reflects the procedures that may occur during these visits.

Participants should be fasting for the ED visit. If a participant arrives non-fasting at the time of weight measurement and sample collection, the visit should still be completed, and the non-fasting state should be recorded.

Visit 801 - Safety follow-up

Visit 801 occurs approximately 4 weeks after a participant's last dose of study intervention. All participants are required to complete a safety follow-up visit, according to the SoA.

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

		Screening	Treatment Period																		Safety Follow-Up	Comments	
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV 997	ED	801	
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52	
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7	
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting
Consent and demographics																							
Informed consent	X	X																					Participants completing V601 do not need to re-consent at V1.
Inclusion/Exclusion Criteria; Confirmation of Eligibility	X	X																					Confirm inclusion and exclusion criteria prior to randomization and administration of the first dose of study intervention.
Demographics	X	X																					Include ethnicity (US and outside of the US as allowable by local law), year of birth, gender (sex), and race. If demographics have been collected at V601, do not repeat collection at V1.
Preexisting conditions and medical history, including relevant surgical history		X																					All ongoing conditions and relevant past medical history should be collected.
Substance use (alcohol, caffeine, tobacco, nicotine)		X																					
Concomitant medications	X	X	X	X	X	X	X	X	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	X	X	X	X	X	X	X	X	Report only study procedure-related events for V601. Any events that occur after signing the informed consent are considered AEs, as defined in Section 10.3. Additional data are collected for certain AEs.

		Screening	Treatment Period																		Safety Follow-Up	Comments	
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV997	ED	801	
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52	
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7	
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting
Physical evaluation																							
Height		X																					Height should be obtained per guidance in Section 10.7.
Prescreening height	X																						Measured or self-reported.
Waist circumference			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Waist circumference should be obtained per guidance in Section 10.7.
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Weight should be obtained per guidance mentioned in Section 10.7.
Prescreening weight	X																						Measured or self-reported
Physical assessment		X									X								X			X	
Symptom-directed physical assessment			X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	X		Optional symptom-directed physical assessment may be conducted at any time during the study at the discretion of the investigator or qualified personnel, as indicated per local regulations based on participant status and standard of care.
Vital signs		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Includes pulse rate and blood pressure, measured in triplicate, after at least 5 minutes supine. Refer Sections 8.2.2 and 10.7.
ECG 12-lead (single) (central)		X	X	X				X			X								X		X	X	Collect ECG within 30 minutes before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. Refer Section 8.2.3.

		Screening	Treatment Period																			Safety Follow-Up	Comments	
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV997	ED	801		
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52		
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7		
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting	
DXA scan		X									X								X		X			
Participant Diary (paper)																								
Dispense diary		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Diary review			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Diary return			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			
Participant education																								
Explain 24-hour dietary recall		X																						
Hyperglycemia and hypoglycemia education		X																						
Explain symptoms of hypoglycemic events (includes BG meter dispensing and SMBG training)		X																					Refer to Section 5.3.5 .	
Review SMBG and hypoglycemia events collected in diary			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Lifestyle counseling			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		Should occur within 3 days after visit.	
Review nutrition goals		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X		Should occur within 3 days after visit.	
Patient-reported Outcomes (electronic)																								
Short-Form-36 version 2 Health Survey acute form (SF-36 v2, Acute)			X								X								X		X		Will also be administered at any visit when BMI reaches cutoffs. Refer Section 6.6.2 .	
Patient Health Questionnaire-9 (PHQ-9)		X	X				X		X		X				X				X		X		AE collection should occur prior to the collection of the PHO-9.	

		Screening	Treatment Period																		Safety Follow-Up	Comments	
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV 997	ED	801	
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52	
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7	
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting
Clinician-administered assessments																							
C-SSRS baseline and screening (Category Version) (paper)		X																					AE collection should occur prior to the collection of the C-SSRS.
C-SSRS since last assessed (Category Version) (paper)			X	X	X	X	X	X	X	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.
Timed Up & Go (TUG) assessment			X								X								X		X		Refer to Section 8.1.3.1.
MoCA cognitive assessment		X	X								X								X		X		
24-hour dietary recall			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	Should occur within 3 days after visit.
Laboratory tests and sample collections																							
Hematology		X	X	X			X				X				X				X		X	X	
Clinical chemistry		X	X	X	X	X	X	X	X	X	X				X				X		X	X	
Lipids		X					X				X								X				
Urinalysis			X				X				X				X				X		X	X	
HbA1c		X	X				X				X				X				X		X	X	
Fasting insulin		X		X			X				X				X						X	X	
OGTT (includes glucose, insulin, C-peptide at each time point)			X																X				OGTT may be done 4 days before baseline (V2). Refer to Section 8.1.5.
Calcitonin		X									X								X		X	X	Refer to Section 8.3.3.8 for Calcitonin Measurements Guidance table.
Cystatin-C		X	X	X	X	X	X	X	X	X	X				X				X		X	X	
Iron		X					X				X								X				
Vitamin B1		X					X				X								X				
Vitamin B12		X					X				X								X				

		Screening	Treatment Period																				Safety Follow-Up	Comments
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV 997	ED	801		
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52		
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7		
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting	
Vitamin A		X					X				X								X					
eGFR		X	X	X	X	X	X	X	X	X	X				X				X		X	X	eGFR calculation using the CKD-EPI Cystatin-C method (2012).	
HBV screening tests		X																					If HBsAg is negative and HbcAb is positive, further testing with HBV DNA is required. If the screening HBV DNA is negative, the participant is not excluded. See Section 8.2.9.	
HCV screening tests		X																					If HCV antibody test is positive, it must be followed by an HCV RNA test. See Section 8.2.10.	
HIV screening test		X																						
Thyroid-stimulating hormone (TSH)		X																						
Follicle-stimulating hormone (FSH)		X																					FSH will be assessed to confirm the postmenopausal status. For participants assigned female at birth (AFAB) with <12 months of cessation of menses, FSH should be >40 mIU/mL. For participants AFAB with ≥12 months of cessation of menses, FSH measurement is not needed.	

		Screening	Treatment Period																				Safety Follow-Up	Comments
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV997	ED	801		
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52		
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7		
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting	
Serum pregnancy test		X																					For IOCBP only.	
Urine pregnancy test (local)			X																				See Section 10.4.	
PK Samples - Random			X	X	X	X															X	X		
PK Samples - Predose								X											X					
PK Samples - Postdose								X		X		X			X								- Week 12: collect PK samples 1 to 6 hours postdose. - Weeks 18: collect PK samples 1 to 3 hours postdose. - Weeks 24: collect PK samples 3 to 6 hours postdose. - Week 36: collect PK samples 6 to 18 hours postdose.	
Endpoint biomarkers			X	X	X						X				X				X		X	X	Refer to Section 10.8.	
Longitudinal biomarkers			X				X				X				X				X		X	X	Refer to Section 10.8. Includes biomarkers related to insulin sensitivity, glucose metabolism, lipid metabolism, and others.	
Stored samples																								
Genetics sample			X																				Sample can be obtained at or after the specified visit.	
Exploratory biomarker			X				X				X				X				X		X			
Epigenetic sample			X												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	X	X	X	X		X	X		
Randomization via IWRS			X																					

		Screening	Treatment Period																				Safety Follow-Up	Comments
CRF Visit Number	Opt 601	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	UV997	ED	801		
Weeks	-8	-5 to 0	0	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48			52		
Visit Interval Tolerance (±days)				3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3			7		
Visit detail		F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F	F		F	F	F = Fasting	
Dispense study intervention via IWRS			X	X	X	X	X	X	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	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	X	X	X	X	X		X			
Assess study intervention compliance				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X			

Abbreviations: BG = blood glucose; BMI = body mass index; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CRF = case report form; C-SSRS = Columbia-Suicide Severity Rating Scale; DXA = dual-energy X-ray absorptiometry; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HbsAg = Hepatitis B surface antigen; HBV = Hepatitis B virus; HCV = Hepatitis C virus; HIV = human immunodeficiency virus; IWRS = interactive web-response system; MoCA = Montreal cognitive assessment; OGTT = oral glucose tolerance test; Opt = optional visit; PK = pharmacokinetic(s); RNA = ribonucleic acid; SMBG = self-monitored blood glucose; T2D = type 2 diabetes; 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 for weight management in adults with obesity or who are overweight with weight-related comorbidities.

GLP-1 RAs are known for improving glycemic control by increasing insulin and decreasing glucagon secretion in a glucose-dependent manner (Davies et al. 2017). Clinical trials and preclinical data suggest that GLP-1 RA may also offer cardiovascular and neuroprotective effects, improving outcomes in diseases associated with older age (Gerstein et al. 2019a; Cukierman-Yaffe et al. 2020; Nørgaard et al. 2022; Siddeeqe et al. 2024).

Study GZNI is a parallel-group, double-blind study to investigate the safety and tolerability of LY3549492 QD compared with placebo in adult participants aged 55 to 80 years with a BMI of 22 to 25 kg/m².

Participants will be randomly assigned to 48 weeks of LY3549492 (15 mg or 60 mg) or placebo to evaluate safety and tolerability. The study will also explore the potential clinical effects of LY3549492 on additional outcomes, including body weight changes, waist circumference, body composition, physical mobility and balance, health-related quality of life, lipid levels, glycemic control, and cognitive health. The safety data from this study will support future clinical development of LY3549492 in indications associated with older age and occurring across different BMI categories, including those with a healthy BMI.

2.2. Background

LY3549492 is an orally available non-peptide agonist of the GLP-1 receptor.

GLP-1 therapy

The GLP-1 receptor is expressed in pancreatic beta cells and other tissues, including various cell types of the GI tract and in neurons throughout the central and peripheral nervous systems.

GLP-1 RA binds with specificity to GLP-1 receptors 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 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 blood glucose levels (Frias et al. 2019).

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

GLP-1 R targeted treatment options

Clinical trials and preclinical data suggest that GLP-1 RA may offer benefits beyond weight and glucose management, including potential cardiovascular and neuroprotective effects which could improve outcomes in diseases commonly associated with older age (Gerstein et al. 2019a; Cukierman-Yaffe et al. 2020; Nørgaard et al. 2022; Siddeeqe et al. 2024). Therefore, it is important to study the effects of these therapies in participants with healthy BMI and who are above 55 years of age.

Currently available GLP-1 receptor-targeted treatments include liraglutide, exenatide, dulaglutide, and semaglutide. A significant drawback of these treatments is that they are high-molecular weight, peptide-based agents that generally require administration through subcutaneous injection.

An important advance in GLP-1 RA therapy is the recent development of a tablet form of semaglutide for oral delivery (Davies et al. 2017; Rybelsus package insert, 2020; Rybelsus EPAR product information, 2020). Although this approach has proven therapeutically feasible, orally administered semaglutide requires a time separation in dosing from food and fluid intake. Therefore, an oral GLP-1 receptor non-peptide agonist (GLP-1R NPA) with simpler oral dosing would offer more flexibility to the patients.

These considerations underlie the need to develop orally active GLP-1 R NPA therapies.

Clinical data for LY3549492

Safety assessments of LY3549492 are based upon completed studies J3H-MC-GZNA (GZNA), J3H-MC-GZNB (GZNB), and J3H-MC-GZNC (GZNC). The overview of these studies is presented in the table.

Study Identifier	Study Overview	Study Population	Serious Adverse Events
J3H MC GZNA	A randomized, double-blind, single-dose (Part A) and multiple-dose (Part B), placebo-controlled, 2-part study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of LY3549492 in healthy participants.	Seventy-two healthy participants, of which 54 received LY3549492 and 18 participants received placebo.	One participant reported appendicitis of serious intensity-considered as study treatment-related by the investigator
J3H-MC-GZNB	A randomized, double-blind, multiple-ascending dose, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of LY3549492 in patients with T2D.	Seventy-nine participants with T2D, of which 60 received LY3549492 and 19 participants received placebo.	Three participants reported SAEs of moderate severity • 1 participant experienced urinary retention – reported due to other medical condition • 1 participant experienced dizziness – reported due to other medical condition

Study Identifier	Study Overview	Study Population	Serious Adverse Events
			1 participant experienced atrial fibrillation – considered as study treatment-related by the investigator
J3H-MC-GZNC	An open-label, 2-part study in healthy participants, evaluating - disposition of [¹⁴C]-LY3549492 (Part A) - absolute bioavailability of [¹⁴C]-LY3549492 (Part B)	Eighteen healthy participants, which included 8 healthy participants (Part A), and 10 healthy participants (Part B).	One participant reported myocardial infarction (severe) before administering the study treatment – reported due to other medical condition

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.

Based on the available data from these studies, it is anticipated that target doses of 15 and 60 mg of LY3549492 will be reasonably tolerated by adult participants aged 55 to 80 years with healthy BMI in this study. The safety data from this study will allow future clinical development of LY3549492 in indications associated with older age and occurring across different BMI categories, including those with a healthy BMI.

2.3. Benefit/Risk Assessment

Detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3549492 may be found in the IB.

2.3.1. Risk Assessment

Study intervention

The nonclinical pharmacology, PK, and toxicity of LY3549492 have been assessed in a battery of in vitro and in vivo studies. 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. At the highest dose, a prolongation in QTc also occurred in the monkey 4-week toxicity study. GI effects were also seen in the preclinical monkey studies with LY3549492.

Based on clinical trial experience with other GLP-1 RA drugs, GI AEs, such as nausea, vomiting, and diarrhea are reported as the most common TEAEs associated with the use of LY3549492.

Based on the nonclinical toxicology study results, nonclinical pharmacology, the known effects of GLP-1 RA in the class, and data from Studies GZNA, GZNB, and GZNC, potential risks for clinical study participants receiving LY3549492 may include

- GI effects, such as nausea, vomiting, and diarrhea
- gastroparesis
- gallbladder disorder
- acute pancreatitis
- effects on HR and BP
- hypoglycemic events
- thyroid safety
- developmental safety
- allergic/hypersensitivity reactions
- aspiration during general anesthesia or deep sedation, and
- malnutrition.

Refer to Section 8.3.3 for further details about AE of special interest for monitoring in the current development program in Phase 2.

Refer to Section 6 of the IB for detailed description of potential risks for LY3549492.

Management of risks for the study

The potential risks will be proactively monitored. Sections 5.1, 5.2, and 8.3 address mitigation, management, and monitoring of the known potential risks associated with LY3549492.

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

2.3.2. Benefit Assessment

LY3549492 is a small molecule GLP-1 RA in early clinical development. A full assessment of its potential benefits has not been completed.

In this study, there will be no anticipated therapeutic benefit for the participants. The purpose of this trial is to provide safety and tolerability assessment of LY3549492 in participants aged 55 to 80 years with a BMI of 22 to 25 kg/m² and a stable body weight for the 3 months prior to randomization (<5% body weight gain and/or loss). Additional outcomes, including body weight changes, waist circumference, body composition, physical mobility and balance, health-related quality of life, lipid levels, glycemic control, and cognitive health, will also be explored.

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

2.3.3. Overall Benefit Risk Conclusion

There is no anticipated therapeutic benefit for the participants in this study. The principal anticipated risks are those associated with the known pharmacologic effects of GLP-1 RAs, namely GI tolerability and increased heart rate. In clinical studies to date, these risks have been monitorable, usually mild to moderate in severity, reversible, and readily manageable. Currently,

there are no recognized adverse effects from LY3549492 other than those related to GLP-1 receptor agonism and no safety or tolerability concerns have been identified that would constitute undue risk to study participants. The safety profile continues to be refined as more clinical safety data become available.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To compare the safety and tolerability of LY3549492 versus placebo	Incidence of TEAEs and SAEs
Secondary	
To characterize the effects of LY3549492 and placebo on body weight changes	- Percent change from baseline in body weight (kg) at Weeks 24 and 48 - Change from baseline in BMI at Weeks 24 and 48
To characterize the effects of LY3549492 and placebo on participant retention	Number of participants with AEs leading to permanent discontinuation of study intervention or withdrawal
Exploratory	
To characterize the effects of LY3549492 and placebo on body weight changes	- Proportion of participants reaching BMI ≤ 20 kg/m² requiring dose de-escalation at or before Week 48 - Proportion of participants reaching BMI ≤ 18.5 kg/m² requiring study intervention discontinuation at or before Week 48 - Proportion of participants reaching BMI ≤ 20 kg/m² at or before Week 48 - Proportion of participants reaching BMI ≤ 18.5 kg/m² at or before Week 48 - Change from baseline in body weight (kg) at Weeks 24 and 48
To characterize the effects of LY3549492 and placebo on waist circumference and waist-to-height ratio	- Change from baseline in waist circumference at Weeks 24 and 48 - Change from baseline in waist-to-height ratio at Weeks 24 and 48 - Proportion of participants with a waist-to-height ratio < 0.4 at Weeks 24 and 48
To characterize the effects of LY3549492 and placebo on dietary intake	Change from baseline in total calorie and macronutrient intake (grams and % calories) based on 24-hour dietary recall at: - Week 12 - Week 24 - Week 48
To characterize the effects of LY3549492 and placebo on body composition	Percent change from baseline in the following (per DXA scan) at Weeks 24 and 48: - total body fat mass - total body lean mass, and - fat-to-lean mass ratio
To characterize the PK of LY3549492	Population PK parameters

To assess the relationship between LY3549492 dose and/or exposure and key safety and efficacy measures	Dose- and concentration-response analyses for key safety and efficacy parameters
To characterize the effect of LY3549492 and placebo on physical mobility and balance	Change from baseline in TUG score at Weeks 24 and 48
To characterize the retention of participants on the highest titration dose of LY3549492	Proportion of participants on the highest titration dose at Week 48
To characterize the effects of LY3549492 and placebo on health-related quality of life	Change from baseline in SF-36v2 acute form domain and summary scores at Week 48
To characterize the effects of LY3549492 and placebo on lipid parameters	Change from baseline in fasting lipids at Week 48
To characterize the effect of LY3549492 and placebo on glucose metabolism	• Change from baseline in HbA1c at Week 48 • Change from baseline in fasting blood glucose at Week 48 • Change from baseline in fasting insulin at Week 48 • Change from baseline in OGTT at Week 48
To characterize the effects of LY3549492 and placebo on cognition	• Change from baseline in MoCA scores at Weeks 24 and 48

Abbreviations: AE = adverse event; BMI = body mass index; DXA = dual-energy X-ray absorptiometry; HbA1c = hemoglobin A1c; MoCA = Montreal cognitive assessment; OGTT = oral glucose tolerance test; PK = pharmacokinetics; SAE = serious adverse event; SF-36v2 = short-form 36 version 2; TEAE = treatment-emergent adverse event; TUG = assessment timed up and go

Primary estimand

The primary clinical question of interest is

What is the difference in the safety and tolerability of each regimen of LY3549492 and placebo, in individuals who meet the eligibility criteria, regardless of adherence to study intervention?

Safety and tolerability assessments will be guided by an estimand comparing the safety of LY3549492 doses with placebo irrespective of adherence to the study intervention, including the data collected during the treatment period plus safety follow-up, from individuals who are randomly assigned and exposed to at least 1 dose of study intervention

Additional estimand

What is the treatment difference in discontinuation of study intervention due to malnutrition or excess weight loss between LY3549492 and placebo at 48 weeks, in individuals who meet the eligibility criteria, if they would remain on their randomly assigned treatment for 48 weeks and would not initiate non-protocol weight loss management treatments?

An additional estimand for Study GZNI may also be used for secondary and exploratory endpoints and is defined by the following attributes:

- **Population:** Individuals who meet the eligibility criteria, aged 55 to 80 years with a BMI of 22 to 25 kg/m².
- **Endpoint:** Incidence of treatment discontinuation due to BMI ≤ 18.5 kg/m² at or before Week 48.
- **Treatment condition:** The randomized treatment, with allowance for potential dose interruptions and modifications, including a planned dose de-escalation after reaching a BMI of ≤ 20 kg/m².
- **Population-level summary and treatment effect of interest:** The difference between LY3549492 and placebo in the proportion of individuals reaching the endpoint by Week 48.
- **Intercurrent events:** Intercurrent events include permanent discontinuation of any study intervention for reasons other than excess weight loss or malnutrition, as well as initiation of non-protocol weight loss management treatments. These intercurrent events are handled by the hypothetical strategy. The potential outcome of interest is the incidence of treatment discontinuation due to BMI ≤ 18.5 kg/m² if individuals remain on the randomly assigned treatment for 48 weeks and would not initiate non-protocol weight loss management treatments. Dose modifications and interruptions will not be considered as intercurrent events since dose modifications and interruptions are part of the treatment condition.

4. Study Design

4.1. Overall Design

Study GZNI is a parallel-group, double-blind study to investigate the safety and tolerability of LY3549492 QD compared with placebo in adult participants aged 55 to 80 years with a BMI of 22 to 25 kg/m².

Approximately 220 participants will be randomly assigned in a double-blind 1:5:5 ratio to placebo (approximately 20 participants), LY3549492 15 mg (approximately 100 participants), and LY3549492 60 mg (approximately 100 participants).

This study will consist of the following study periods:

- optional Visit 601: ≤3 weeks
- screening period (Visit 1): ≤5 weeks
- treatment period (Visit 2 to Visit 18): 48 weeks, and
- safety follow-up period: 4 weeks.

The primary endpoint will be at Week 48.

Study procedures and their timing are summarized in the SoA, Section [1.3](#).

4.2. Scientific Rationale for Study Design

The study is designed to investigate the safety and tolerability of LY3549492 15 mg QD and 60 mg QD in adult participants aged 55 to 80 years with a BMI of 22 to 25 kg/m² over a 48-week treatment period. The safety data from this study will allow the future clinical development of LY3549492 in indications associated with older age and occurring across different BMI categories, including those with a healthy BMI.

Choice of primary endpoint

The incidence of TEAEs and SAEs is a standard endpoint for studies with a primary objective of assessing the safety and tolerability of an intervention. Safety and tolerability over a wide dose range of LY3549492 versus placebo will enable robust benefit risk characterizations in this population. The data from this trial will support further clinical development in indications with healthy BMI.

In addition, the study includes other parameters relevant to the assessment of the effects of LY3549492 on body weight changes, waist circumference, body composition, physical mobility and balance, health-related quality of life, lipid levels, glycemic control, and cognitive health.

Choice of comparator

A placebo comparator was selected for this trial in accordance with regulatory guidance (FDA 2007a; EMA 2016). The use of placebo for 48 weeks during the double-blind portion of the study is considered appropriate to understand the safety and tolerability of LY3549492 in this population.

Study duration

The planned treatment duration of 48 weeks will allow for a robust evaluation of the effects of LY3549492 and thus a more robust assessment of safety and tolerability. Additionally, the anticipated uses in indications beyond weight loss will likely necessitate prolonged therapy, lasting 6 months or more. Consequently, it is essential to comprehend the safety and tolerability within the target population.

Concomitant medications

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.

Collection of race and ethnicity

In this study, the 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 dose levels of 15 mg QD and 60 mg QD were selected based on the following considerations:

- Dose levels of 15 mg and 60 mg will be attained through stepwise titrations CCI [REDACTED]. This starting dose, along with the planned titration steps, was selected based on the safety and tolerability data from Studies GZNA and GZNB and aims to minimize GI-related AEs.
- Both dose levels are well within the dose range of up to 360 mg that has been studied in healthy participants and the T2D population in Phase 1. The 15- and 60-mg doses are notably lower than the CCI [REDACTED] planned for investigation in Phase 2 for T2D and weight management indications, as the goal of this study is not to maximize the potential weight loss effect in the population aged 55 to 80 years with healthy BMI.
- The stepwise escalation will allow for the investigation of the time course of weight loss in the desired population with a healthy BMI of 22 to 25 kg/m².
- Data from this study will support a dedicated dose-exposure response analysis of multiple safety and efficacy measures to support the selection of dose(s) of LY3549492 for further clinical development in indications with healthy BMI.
- Most importantly, this study will be supported by extensive and timely safety assessments, which include weight loss and tolerability to ascertain that the safety profile is thoroughly monitored as outlined in Section 8.2.

4.4. End of Study Definition

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

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

5. Study Population

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

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

5.1. Inclusion Criteria

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

Age

1. Participant must be 55 to 80 years of age inclusive, at the time of signing the informed consent.

Weight

2. Have a BMI within the range of 22 to 25 kg/m² (inclusive).
3. Have had a stable body weight for 3 months prior to randomization (<5% body weight gain and/or loss).

Sex assigned at birth and contraceptive/barrier requirements

4. Are the following individuals who agree to abide by the reproductive and contraceptive requirements provided in this protocol.
 - assigned male at birth (AMAB) and
 - assigned female at birth (AFAB), who are of non-childbearing potential. Refer to Section 10.4 for further details.

Individuals not of childbearing potential (INOCBP) (for definitions, refer Section 10.4.1) 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 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 Section 10.4.

Informed Consent

5. Are capable of giving signed informed consent as described in Section 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical Conditions

Diabetes-related

6. Have type 1 diabetes, latent autoimmune diabetes in adults, or a history of ketoacidosis or hyperosmolar coma.
7. Have
 - T2D and are on antidiabetic therapy (except T2D being managed with diet and/or stable dose of metformin)
 - rare forms of diabetes mellitus, or
 - HbA1c >8% (64 mmol/mol), as determined by the central laboratory at Visit 1

Note: Patients with T2D are allowed ONLY if managed with diet and/or stable dose of metformin and have HbA1c ≤8.0%.

Note: Patients with a history of gestational diabetes are not excluded.

Obesity- and weight-related

8. Have had prior surgical, endoscopic, or device-based treatment for obesity.
9. Any condition or related treatment that is known to likely result in either weight loss or weight gain >5% of body weight.

Gastroenterological

10. Have a known clinically significant gastric emptying abnormality, e.g., severe gastroparesis or gastric outlet obstruction, or chronically take drugs that directly affect GI motility.
11. Have a significant history (within the past 6 months) of or current comorbidities capable of altering the absorption of nutrients.

Nutrition Status

12. Have clinical or biochemical evidence of significant nutritional deficiency that, in the investigator's judgment, poses a safety risk to the individual.

Neurological

13. Cognitive scores of MoCA assessment at screening that, in the investigator's judgment, would indicate moderate to severe cognitive impairment.

Malignancy

14. Have a history of cancer within the last 5 years.

Exceptions:

- non-metastatic basal and/or squamous cell carcinoma of the skin
- in situ cervical cancer
- nonprogressive prostate cancer, or
- other cancers with low risk of recurrence or spread.

Infections/Immune Abnormalities

15. Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or at screening, as determined by the central laboratory.

Renal

16. Has renal impairment, measured as estimated glomerular filtration rate <45 ml/min/1.73 m², calculated per Chronic Kidney Disease Epidemiology Collaboration Cystatin-C method, at screening, as determined by central laboratory.

Cardiovascular

17. Have poorly controlled hypertension, that is, mean systolic BP ≥ 150 mm Hg or mean diastolic BP ≥ 100 mm Hg at screening, renal artery stenosis, or evidence of labile BP, including symptomatic postural hypotension.
18. Have an elevated resting pulse rate (mean >100 bpm) at screening and baseline.
19. Have any of the following cardiovascular conditions within 12 months prior to screening:
 - acute myocardial infarction
 - stroke
 - unstable angina, or
 - hospitalization due to congestive heart failure.
20. Have a history of New York Heart Association Functional Classification III or IV congestive heart failure (Section 10.6).
21. Have triglyceride level >500 mg/dL, as determined by the central laboratory at screening (5.7 mmol/L). If the participant is on lipid-lowering therapies, doses must be stable for 3 months prior to screening.
22. Have a 12-lead ECG abnormality at screening that, in the opinion of the investigator, increases the risks associated with participating in the study or may confound ECG data analysis.
23. Have a personal or family history of long QT syndrome, a family history of sudden death in a first-degree relative (parents, siblings, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening.

Hepatic

24. Have signs and symptoms of any other liver disease other than metabolic dysfunction-associated steatotic liver disease, or any of the following, as determined by the central laboratory during screening:
 - ALT or AST level $>2.0\times$ ULN for the reference range, as determined by the central laboratory at study entry
 - ALP level $>1.5\times$ ULN for the reference range, or

- TBL >1.5x ULN for the reference range, except for cases of known Gilbert's syndrome.
25. Have a history of clinically significant gallbladder disease; however, participants with cholecystectomy may be included in the study.
 26. Have a current infection with hepatitis B virus (HBV), that is,
 - positive for hepatitis B surface antigen, and/or
 - polymerase chain reaction positive for hepatitis B virus DNA (Section 8.2.9).
 27. Have a current infection with hepatitis C virus (HCV), that is, positive for HCV ribonucleic acid (RNA) (Section 8.2.10).

Psychobehavioral

28. Have a history of significant active or unstable major depressive disorder or other severe psychiatric disorder, for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder, within the last 2 years.
Note: Participants with major depressive disorder or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the investigator, may be considered for inclusion if they are not on excluded medications.
29. Have a PHQ-9 score of 15 or more at screening (Visit 1), prior to randomization.
30. Have a lifetime history of suicide attempts.
31. Are, in the judgment of the investigator, actively suicidal and, therefore, deemed to be at significant risk for suicide.
32. On the C-SSRS at Visit 1, prior to randomization, have
 - answered “yes” to either Question 4 or Question 5 on the “Suicidal Ideation” portion of the C-SSRS, and the ideation occurred within the past month,
 - OR**
 - answered “yes” to any of the suicide-related behaviors on the “suicidal behavior” portion of the C-SSRS, and the behavior occurred within the past month.
33. Have any other condition, including known drug or alcohol abuse, diagnosed eating disorder, or psychiatric disorder, that, in the opinion of the investigator, may preclude the participant from following and completing the protocol.

Endocrine

34. Have a history of acute or chronic pancreatitis. Participants with history of acute pancreatitis caused by gallstones may be included if they have a cholecystectomy to resolve the problem.
35. Have a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2).
36. Evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the investigator, would pose a risk to participant safety. Participants on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are

anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria.

37. Have, in the opinion of the investigator, evidence of a significant, uncontrolled endocrine abnormality, for example, thyrotoxicosis, adrenal crises, a history of recurrent severe hypoglycemia, impaired awareness of hypoglycemia, a history of orthostatic hypotension, and/or conditions associated with dysautonomia.
38. Have a calcitonin level determined by the central laboratory at screening (Visit 1) of ≥ 35 ng/L (≥ 35 pg/mL).

Other medical conditions

39. Current serious or unstable illnesses, including cardiovascular, hepatic, renal, gastroenterological, respiratory, endocrinologic, psychiatric, immunologic, or hematologic disease and other conditions that, in the investigator's opinion, could interfere with participation and the analyses in this study; or has a life expectancy of < 24 months.
40. Have a history of a transplanted organ (corneal transplants [keratoplasty] allowed).
41. Have had a blood donation of ≥ 500 mL within the previous 8 weeks of study screening or a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy (for example, hemolytic anemia or sickle cell anemia), or have a hemoglobin value < 11 g/dL (males) or < 10 g/dL (females) at screening.

Prior/Concomitant Therapy

42. Unless specified, all concomitant medications at stable dose for at least 3 months.
43. Have had any exposure to GLP-1 analogs or other related compounds within the prior 3 months.
44. Have known or suspected hypersensitivity/allergies to trial product(s), to selective GLP-1 RAs or GIP/GLP-1 or GLP-1/glucagon dual receptor agonists.
45. Are currently on prohibited medications - strong CYP3A inhibitors or strong CYP3A inducers and drugs that are P-gp/BCRP substrates with a narrow therapeutic index. Refer Section 10.9 for more details.
46. Have taken within 3 months prior to screening medications (prescribed or over-the-counter) or alternative remedies (including herbal/nutritional supplements) intended to promote weight loss or weight gain.
47. Are currently taking a central nervous system stimulant (for example, Ritalin-SR) with the exception of caffeinated beverages at screening.

DXA exclusion (for exclusion from DXA only - having the following criteria will not exclude a potential participant from the study)

48. Having a body weight, height, or width that prohibits the ability to obtain accurate measurements according to the DXA manufacturer's specification.
49. Having implants, hardware, devices, or other foreign materials in the measurement area that may interfere with the scan, according to the DXA manufacturer's specification.

Prior/Concurrent Clinical Study Experience

50. Are currently enrolled in any other clinical study, involving an investigational product or any other type of medical research judged not to be scientifically or medically compatible with this study.
51. Have participated, within the last 90 days, in a clinical study and received treatment, whether active or placebo. If the study involved an investigational product, at least 5 elimination half-lives or 90 days, whichever is longer, should have passed.
52. Have participated, within the last 12 months, in a clinical study of weight loss medication and received pharmacologic treatment, whether active or placebo.
53. Have previously completed or withdrawn from this study or any other study investigating LY3549492.
54. Have difficulty swallowing tablets.

Other Exclusion Criteria

55. Any condition where reduction in caloric intake could, in the investigator's opinion, lead condition to worsen or become unstable.
56. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) [1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits].
57. Evidence of regular use of known drugs of abuse in the opinion of the investigator.
58. Are individuals of childbearing potential (IOCBP).
59. Are individuals AFAB, acting as a surrogate, who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study intervention.
60. Are investigative 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.
61. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study, which requires exclusion of their employees.
62. Are, in the opinion of the investigator or sponsor, unsuitable for inclusion in the study.

5.3. Lifestyle Considerations**5.3.1. Meals and Dietary Restrictions**

For all assessments, the participants will be required to come to the site in a fasting state, after an overnight fast, except for water, of at least 8 hours as specified in the SoA.

Individualized counseling for a healthy dietary pattern

At Visit 2 and subsequent visits, study participants will receive individualized counseling regarding a healthy dietary pattern with the goal of maintaining adequate nutritional status while on pharmacotherapy. The counseling will be performed by a dietitian or nutritionist, or equivalent qualified designee trained in assessing needs, collecting and analyzing dietary intake,

and in providing individualized counseling, according to the local standard. During or coinciding with each visit, the participant's diet is reviewed via data collected during the 24-hour dietary recall, and advice to maximize adherence is provided, if needed.

Nutritional Counseling to Meet Nutrient and Fluid Needs

The focus of the counseling should be on the importance of meeting minimum intake goals for key nutrients and fluids, even in the setting of reduced appetite or GI adverse events. Participants should be reminded to eat or drink when they aren't feeling hungry or thirsty. This counseling should be completed according to the SoA and must be documented in the participant's study record.

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

Recommendations may include minimum daily intake goals, although individual goals will vary depending on age, sex, physical activity and other factors:

- a minimum of 50 g/day of carbohydrate intake
- a minimum of 60 g/day of protein intake
- a minimum of 15 g/day of fat intake (<10% saturated fat/day), and
- a minimum of 1000 kcal/day.

Principles in counseling sessions should consider:

- Participant education on the importance of meeting nutritional and hydration recommendations, even in cases of significantly reduced appetite or GI AEs.
- Encouraging participants to consume small nutrient-rich meals and fluids throughout the day at a slow pace, as the participants may not have typical hunger and thirst cues.
- Meal-replacement products (such as vitamin- and mineral-fortified protein shakes) and/or a complete multivitamin may be recommended in some cases to help individuals meet key nutritional needs.
- Avoid skipping meals to meet daily nutrition requirements.
- Focus on high-quality, nutrient-rich, minimally processed foods. Limit foods high in solid fats, added sugar, and salt.
- Include fiber-rich foods.
- For each meal (on an 8-10 inch [20-25 cm] plate), consider including approximately ½ plate of fruits/vegetables, ¼ plate of whole grains, and ¼ plate of protein. Incorporate 1 to 2 servings of healthy, unsaturated fats on most days (for example, nuts, avocado, olive oil, and salmon).
- Encourage participants to optimize daily protein intake to reach calculated daily protein goals based on ideal body weight and tailored to individual health and nutrition requirements. General daily recommended protein requirements are 60 to 120 g/day for women and 75 to 120 g/day for men. This should be individualized based on each participant's unique needs, such as medical conditions, physical activity levels, and so on.
- Drink enough water and/or unsweetened or decaffeinated fluids to stay well hydrated. Fluid intake of at least 2 L/day may be necessary for optimal hydration. Modifications to

daily fluid amount should be individualized based on each participant's unique needs, such as medical conditions, hydration status, physical activity levels, and so on.

5.3.2. Monitoring Nutritional Needs

LY3549492 acts, in part, by delaying gastric emptying and reducing appetite, leading to a decrease in food intake. There is potential that some participants will have significantly reduced caloric intake.

At each visit, the study site team should monitor the participant's nutritional and hydration status by history, targeted physical exam, and laboratory assessments, as appropriate. Attention should be given to ensure participants are eating high-quality foods that include adequate micronutrients and macronutrients. These recommendations should be personalized based on participants' comprehensive medical conditions at the investigator's discretion. If medical staff observes significantly reduced caloric intake, consider additional assessment, as described in Sections [8.2.11](#) and [10.2.2](#).

If any of the symptoms and signs of inadequate nutrition or hydration (presented in table below) are observed, please refer to the protocol for additional guidance and contact medical monitor to discuss management options, which may include:

- nutritional counseling
- dose interruption (dose interruption of 30 consecutive or non-consecutive days may impact a participant's ability to continue in the study, in each case the decision to continue in the study will be made on a case-by-case basis following discussion between the investigator and sponsor)
- dose de-escalation, for cases part way through the titration, and/or
- adjustment of concomitant medications, such as antihypertensives, anti-hyperglycemics, and diuretics.

Monitor for the following which could be risk factors/signs for poor nutrition or dehydration.

Potential concern	Early signs include, but are not limited to
Poor nutrition	• carbohydrate intake <50 g/day • protein intake <60 g/day • fat intake <15 g/day • caloric intake <1200 kcal/day, and • skipping multiple meals
Dehydration	• low fluid intake (<2000 ml/day) • volume loss (e.g. diuretic or laxative use, diarrhea, vomiting) • elevated pulse rate • decreased or low BP (including orthostatic symptoms), and • high blood urea nitrogen to creatinine (BUN:Cr) ratio

5.3.3. Substance Use: Caffeine, Alcohol, and Tobacco

Except when fasting is required, participants will be allowed to maintain their regular caffeine consumption throughout the study period.

Alcohol will not be permitted at least 24 hours prior to the study site visits.

Participants who use tobacco products will be instructed that use of nicotine-containing products (including nicotine patches) will not be permitted while they are at the site.

While not at the site, participants should not consume more than 10 cigarettes per day or the equivalent, including electronic cigarettes.

5.3.4. Other Restrictions

Study participants should be instructed not to donate blood or blood products during the study and for 8 weeks following the study.

5.3.5. Hyperglycemia and Hypoglycemia Education

Education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, BG meter and SMBG procedure, and management, according to American Diabetes Association Standards of Medical Care in Diabetes (ADA 2024) or local standards.

Provide education at screening (Visit 1) for participants who may develop hyperglycemic events during the study. Additional training may be provided during the study, as needed.

See Section [8.3.3.7](#) for management of hypoglycemia risk.

Self-monitored blood glucose (SMBG) training

Participants will receive a study-approved glucometer and related testing supplies for use during the study. Site personnel will train the participant on correct use of the glucometer for SMBG and reporting of hypoglycemia.

Participants should perform fasting BG measurements at least once daily as well as at any time they have symptoms suggestive of hypoglycemia (Section [8.3.3.7](#)). All SMBG results will be entered in the diary; these results will be used for glucose management only and for investigators to determine if rescue criteria are met (Section [6.9.1](#)).

5.3.6. 24-Hour Dietary Recall

A 24-hour dietary recall is a structured interview intended to obtain detailed information about all foods, beverages, and, if applicable, dietary supplements consumed by the participant in the past 24 hours. Most commonly, the 24-hour period is from midnight to midnight the previous day. A key feature of the 24-hour dietary recall is that the participant is asked for more detailed information than first reported.

An open-ended response structure is designed to prompt participants to provide a comprehensive and detailed report of all foods and beverages consumed. In addition to other detailed descriptors, such as time of day and source of food, portion size of each food and beverage is captured. Food models, pictures, and other visual aids may be used to help respondents judge and report portion size and may improve accuracy (Kesari and Noel 2023; National Cancer Institute [WWW]; National Cancer Institute 2024).

A multiple-pass method, such as the US Department of Agriculture's Automated Multiple-Pass Method, should be used to conduct all 24-hr dietary recalls in Study GZNI.

5.4. Screen Failures

A screen failure occurs when a participant who consents to participate in the clinical study is not subsequently assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened 1 time. Rescreened participants should be assigned a new participant number for every screening/rescreening event.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

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

6. Study Intervention(s) and Concomitant Therapy

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

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 240 ml) 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
Dosage Level(s)		Matching placebo QD
Route of Administration	Oral	Oral

Abbreviations: QD = once daily.

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 appropriate storage conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.

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

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

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

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

6.3. Assignment to Study Intervention

This is a parallel-group, double-blind study. Participants who meet all the criteria for enrollment will be randomly assigned to the study intervention using an IWRS. Before the study is initiated, the log-in information and directions for the IWRS will be provided to each site.

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

Participants will be randomly assigned in a double-blind 1:5:5 ratio to placebo (approximately 20 participants), LY3549492 15 mg (approximately 100 participants), and LY3549492 60 mg (approximately 100 participants). See study schema (Section 1.2).

LY3549492 15 mg and LY3549492 60 mg will be administered to the participants following a dose escalation schedule:

- CCI
-

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

- age (55 to 64 years, 65 to 80 years), and
- sex (AFAB, AMAB).

Additionally, each age group should constitute approximately no more than 60% of the total randomized population.

6.4. Blinding

This is a double-blind study. Investigators, site staff, clinical monitors, and participants will remain blinded to the treatment assignments until the study is complete.

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

Emergency unblinding

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

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

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

If an investigator, site staff performing assessments, or participant is unblinded, the participant must be permanently discontinued from study intervention but should continue in the study for efficacy and safety endpoint evaluations and monitoring for all visits.

6.5. Study Intervention Compliance

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

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, reviewing the diary, and documented in the source documents.

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.

Participants considered to be poorly compliant by the investigator with their study intervention and/or the study procedures will receive additional training and instruction, as required, and will be reminded of the importance of complying with the protocol.

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 1 step back in the assigned dosing group.

Dose modification is only allowed for the management of

- GI symptoms throughout the study for study intervention (Section 6.6.1)
- participants reaching a BMI of ≤ 20 kg/m² (Section 6.6.2), or
- perceived excessive weight loss (Section 6.6.3).

6.6.1. Management of Participants with GI Symptoms

The tables below provide grading scales and management guidance for assessment of GI-associated AEs for nausea/vomiting and for diarrhea.

Nausea/Vomiting

Nausea/Vomiting	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Definition	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient	Emergency room visit or hospitalization for hypotensive shock

Nausea/Vomiting	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
			intravenous hydration	
Management	Follow the steps in Section 6.6.1	Dietary modification Initiate symptomatic medication Temporary discontinuation until complete resolution (Step 3 in Section 6.6.1)	Dietary modification Initiate symptomatic medication Temporary discontinuation until complete resolution (Step 3 in Section 6.6.1)	Permanent discontinuation (Section 7.1)

Diarrhea

Diarrhea	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Definition	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or 800 g/24 hours or requires outpatient intravenous hydration	Emergency room visit or hospitalization
Management	Follow steps in Section 6.6.1	Dietary modification Initiate symptomatic medication Temporary discontinuation until complete resolution (Step 3 in Section 6.6.1)	Dietary modification Initiate symptomatic medication Temporary discontinuation until complete resolution (Step 3 in Section 6.6.1)	Permanent discontinuation (Section 7.1)

If a participant reports GI mild symptoms (see grading scale above) such as nausea, vomiting, or diarrhea, the investigator should follow the steps below sequentially. If a participant experiences moderate or severe symptoms, the investigator should begin with step 3 while completing steps 1 and 2 concurrently.

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 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 GI symptoms, temporary interruption of the study intervention until symptoms are completely resolved is permitted. If the study intervention interruption is **longer than 3 days**, the investigator should proceed to step 4.
4. If steps 1, 2, and 3 do not alleviate GI symptoms, follow guidance for temporary dose de-escalation and dose re-escalation upon symptom resolution. Only 1 de-escalation and re-escalation attempt for GI symptoms will be permitted per titration step.

In the event of persistent 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 (Section 7 and Section 10.3.4).

Once the resolution of GI AE occurs, restart the intervention.

Temporary dose de-escalation

If GI symptoms persist despite the measures outlined in Steps 1 to 3 above, the investigator should 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 GI symptoms persist during the first 3 weeks on the study intervention or anytime the participant is on the lowest titration step in the assigned dosing group, then interrupt the 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 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 GI symptoms or is not considered appropriate based on the investigator's assessment, then stop dose escalation and reduce the dose to the previous titration step. Only 1 dose reduction is allowed for 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 ≤ 20 kg/m²

If...	Then...
a participant has a BMI of ≤ 20 kg/m ² at any time during the study	- the investigator should consider a dose reduction to the previous titration step in a blinded fashion - no subsequent dose re-escalation is allowed, and - the participant will be closely monitored at the clinic on a weekly basis for at least 3 weeks, after which visits can be reduced based on the investigator's clinical judgment
a participant reaches a BMI of ≤ 18.5 kg/m ² at any time during the treatment period	- the investigator should discontinue the study intervention, and - the participant will continue to remain in the study, without intervention, to continue to follow BMI trend and nutritional intake.

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 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. The investigator should attempt to maintain participants on study intervention and restart the study intervention after any temporary interruption. 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 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, doses of study intervention may be omitted until acute symptoms have subsided. 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 the 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 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 study, an overdose of LY3549492 is considered any dose higher than the dose assigned through randomization. Treatment for overdose is supportive care.

In the event of an overdose, the investigator should

- contact the medical monitor immediately
- evaluate the participant to determine, in consultation with the medical monitor, whether study intervention should be interrupted or whether the dose should be reduced

- closely monitor the participant for any AE/SAE and laboratory abnormalities as medically appropriate until LY3549492 can no longer have a clinical effect or can no longer be detected systemically (at least 5 days).

6.9. Prior and Concomitant Therapy

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

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

Newly prescribed medications

Investigative site staff will inform participants that they must consult with the investigator or a designated site staff member upon being prescribed any new medications during the screening period. This may not be possible when initiated for treatment of medical emergencies, in which case the participant will inform the investigator or a designated site staff member as soon as possible.

If the need for additional concomitant medication arises, the participant may be continued in the study and on study intervention if, in the investigator's opinion, the addition of the new medication does not pose a safety risk and the medication is not excluded. If an additional concomitant medication is started, the sponsor should be informed as soon as possible.

Permitted medications

Participants will be permitted to use concomitant medications that they require during the study, except certain medications, for example, other medications for weight management, that may interfere with the assessment of the safety and efficacy characteristics of the study treatments. Metformin is an allowed concomitant medication if on stable dose for at least 3 months prior to screening.

Doses of other prescription medications for treatment of concurrent medical conditions should remain constant during the study unless an adjustment is medically indicated. For example, doses of antihypertensive medication may be reduced if the participant's BP declines significantly during the study.

Any medication or vaccine (including over-the-counter or prescription medicines and acetaminophen/paracetamol), vitamins, and/or herbal supplements that the participant is receiving at the time of enrollment or receives during the study must be recorded in CRF. Nonsteroidal anti-inflammatory medications (including ibuprofen and aspirin), acetaminophen (up to 3 g/day), cough suppressants, antihistamines, antibiotics, and topical ointments may be used on an as needed basis without notifying the sponsor and are not restricted by the stable dosing requirements listed earlier.

Prohibited medications

Treatment with or initiation of medications that are excluded in the entry criteria (Section 5.2) may not be used during the study.

The sponsor should be contacted if a participant starts treatment with a medication that is prohibited by the protocol.

Prescription or over-the-counter medications that are indicated for weight loss are exclusionary if used within 3 months prior to screening or between screening and randomization. These medications are also not allowed at any time during the treatment period. If started after randomization, the medications should be immediately withdrawn. Participants who refuse to withdraw the weight loss medications must be discontinued from the study intervention (Section 7.1).

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. Refer to Section 10.9 for more details.

6.9.1. Hyperglycemia Rescue Medicine

An additional therapeutic intervention should be considered in participants with T2D 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 fasting BG 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 fasting BG >240 mg/dL (>13.3 mmol/L) over any 2-week period or longer from Week 6 to Week 12 post-randomization, or
 - average fasting BG >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 intervention 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 the collection of efficacy measures.

7. Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

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

7.1. Discontinuation of Study Intervention

When necessary, a participant may be permanently discontinued from study intervention. If so, the participant will discontinue the study intervention (treatment) and will remain in the study and follow procedures for all remaining study visits, as shown in the SoA.

A participant should be permanently discontinued from study intervention if

- the participant is diagnosed with
 - acute pancreatitis, confirmed by adjudication
 - MTC or MEN2 (Section 8.3.3.8)
 - an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer), after randomization
 - type 1 diabetes or latent autoimmune diabetes, after randomization
- a BMI of ≤ 18.5 kg/m² is reached at any time during the treatment period.
- the participant initiates any other GLP-1 RA, GIP/GLP-1 RA, or GLP-1/glucagon dual receptor agonists, if the participant will not or cannot discontinue them.
- the participant becomes pregnant during the study.
- the participants
 - answered "yes" to Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS, **or**
 - answered "yes" to any of the suicide-related behaviors on the Suicidal Behavior portion of the C-SSRS.

A psychiatrist or appropriately trained professional may assist in the decision to discontinue the participant.

- the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified. If the investigator is uncertain about whether a systemic hypersensitivity reaction has occurred and whether discontinuation of the study intervention is warranted, the investigator may consult the sponsor.
- a participant develops any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent discontinuation of study intervention is the appropriate measure to be taken.
- in the opinion of the investigator, the participant should permanently discontinue the study intervention for safety reasons, or

- the participant develops any exclusion criterion during the course of the study, the investigator should call the sponsor to determine whether discontinuation of study intervention is necessary.
- the participant's eGFR decline to <45 mL/min/1.73 m², calculated per Chronic Kidney Disease Epidemiology Collaboration Cystatin-C method at any time during the treatment period.
- the participant experiences severe hypoglycemia (Level 3 according to Section 8.3.3.7) or persistent hypoglycemic events (Levels 1 and 2).
- a participant with CKD (chronic kidney disease) experiences acute renal events (according to Section 8.3.3.9).
- a participant experiences nonfatal MACE (according to Section 8.3.3.5)
- a participant experiences a Grade 4 GI adverse event (Section 6.6.1)
- HBV or HCV: the participant tests positive for HBV DNA (Section 8.2.9) or tests positive for HCV RNA (Section 8.2.10).

Note: The HBV DNA result is to be confirmed if the initial positive test result is positive but below the level of quantification. Prior to discontinuation of any immunomodulatory or immunosuppressive therapy (including study intervention), or both, the participant is to be referred to, evaluated, and managed by a specialist physician with expertise in evaluation and management of viral hepatitis. The timing of discontinuation from study intervention relative to the initiation of any antiviral treatment for hepatitis is to be based on the recommendation of the consulting specialist physician, in conjunction with the investigator, and aligned with medical guidelines and standard of care.

7.1.1. Hepatic Criteria for Study Intervention Interruption or Discontinuation

See Section 8.2.8.3 for hepatic criteria for study intervention interruption or discontinuation.

7.1.2. Cardiac Arrhythmia and QTc Stopping Criteria

If a clinically significant finding is identified (including, but not limited to changes from baseline in QTcF after enrollment), the investigator or qualified designee will determine if the participant can continue in the study and if any change in participant management is needed. This review of the ECG printed at the time of collection must be documented. Any new clinically relevant finding should be reported as an AE.

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

- QT interval corrected using Fridericia's formula (QTcF) >500 msec
- increase from baseline in QTc >60 msec, from at least 2 consecutive readings, if upon review the finding is confirmed by a cardiologist, or

- clinically significant arrhythmia (including but not limited to atrial fibrillation).

7.1.3. Temporary Discontinuation

During the treatment period, the investigator may interrupt a participant's study intervention, for example, due to an AE or a clinically significant laboratory value. The dates of study intervention interruption and restart must be documented.

7.2. Participant Discontinuation/Withdrawal from the Study

Discontinuation is expected to be uncommon.

A participant may withdraw from the study

- at any time at the participant's own request for any reason or without providing any reason
- at the request of the participant's designee, for example, parents or legal guardian
- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons, or
- if enrolled in any other clinical study involving an investigational product, or enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an ED visit and post-treatment follow-up, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. If a participant withdraws from the study, the participant may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the participant should continue or discontinue study intervention.

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

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

8.1. Efficacy Assessments

8.1.1. Efficacy Measures

The primary objective of the study is safety and tolerability. Efficacy will be assessed as exploratory objectives.

Exploratory

The following exploratory efficacy measures will be collected or calculated at the times shown in the SoA (Section 1.3):

- waist circumference and waist-to-height ratio
- dietary intake (total calorie and macronutrient intake [grams and % calories]; measured using 24-hour Dietary Recall)
- body composition (measured using DXA scan)
- serum lipids (measured through central laboratory; Section 10.2)
- HbA1c, fasting blood glucose, fasting insulin, and OGTT (measured through central laboratory; Section 10.2)
- patient-reported outcomes (Section 8.1.2), and
- clinician-administered assessments (Section 8.1.3).

8.1.2. Patient-Reported Outcome

8.1.2.1. Short-Form 36 Version 2 Health Survey, Acute Form (SF-36v2)

The SF-36v2 assesses the health-related quality of life. The SF-36v2 acute form is a 36-item generic, patient-completed measure designed to assess the following 8 health 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,” whereas the remaining domains assess functioning “in the past week.” Items are answered on Likert scales of varying lengths (3-point, 5-point, or 6-point scales).

Each domain is scored individually, and information from these 8 domains is further aggregated into 2 health component summary scores: Physical Component Summary and Mental Component Summary. 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).

8.1.3. Clinician-Administered Assessments

8.1.3.1. Assessment Timed Up and Go (TUG)

The TUG test assesses the physical mobility and balance in elderly participants and may be used to predict the likelihood of falls.

The TUG test is administered with the participant initially seated in a standard armchair. The participant will be required to stand up from the seated position, walk in a straight line to a marked point 3 meters (10 ft) from the chair, turn and walk back to the chair and return to the seated position. The timer starts when the person begins to stand and stops the moment they are seated again. Participants can wear their regular footwear and can use a walking aid, if needed.

The time taken to complete this task will be recorded in seconds using a stopwatch. Older adults requiring ≥ 12 seconds to complete the TUG test were identified as at risk for falling, as confirmed by Centers for Disease Control and Prevention.

8.1.3.2. Montreal Cognitive Assessment (MoCA)

The MoCA is a brief instrument used to assess cognitive function (Nasreddine et al. 2005). The instrument consists of 13 tasks organized into 8 cognitive domains including

- Visuospatial/Executive Function
- Naming
- Memory
- Attention
- Language
- Abstraction
- Delayed Recall, and
- Orientation.

A total score is generated by summing scores across the 8 domains. The range for the total MoCA score is 0 to 30, with lower scores indicating greater level of impairment.

8.1.4. Dual-Energy X-Ray Absorptiometry

DXA will be performed in participants who give consent and meet all DXA eligibility requirements to assess changes in body composition associated with weight reduction, including both fat and lean mass compartments.

Data collection and processing are explained in the Imaging Manual written and provided by the imaging contract research organization. DXA scans will be sent to the imaging contract research organization for central reading. Results must remain blinded to investigator and participant until database lock.

The risk associated with DXA scan is low, with a radiation exposure (effective dose) of about 5 μ Sv or 0.005 mSv (millisievert). The typical level of background radiation to which the general population is exposed, not including radiation due to medical procedures, has been estimated to be about 2.5 mSv/year (Lewiecki et al. 2016). Therefore, the exposure from a DXA scan is less than that from 1 day of background radiation.

8.1.5. Oral Glucose Tolerance Test

- OGTT of 120 minutes will be performed according to the SoA (Section 1.3).
- Participants should maintain adequate carbohydrate intake for 3 days prior to the scheduled 4-hour OGTT.
- In the 24 hours preceding the test, participants should refrain from drinking any alcohol or performing any extreme physical activity.
- Participants should fast for approximately 8 hours before the administration of the test and should not eat anything except water until the blood sampling is complete.
- Placement of a venous cannula, preferably in an antecubital vein, is recommended to simplify collection of multiple blood samples for glucose, insulin, and C-peptide at time 0, 30, 60, 90, and 120 minutes.
- Immediately after collection of the time 0 sample, a 75 g glucose dose will be given orally, using a commercial product approved for this use (and in a total volume of not more than 350 mL).
- The participant should consume the glucose load within 5 minutes.
- The participant should remain minimally active for the duration of the test.

8.2. Safety Assessments

Safety will be assessed as primary and secondary objectives.

Primary

The primary objective of the study is to evaluate and compare the overall safety and tolerability of LY3549492 with placebo. The primary safety endpoint is incidence of TEAEs and SAEs.

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.

Secondary

The following secondary safety measures will be collected or calculated at the times shown in the SoA (Section 1.3):

- body weight (measuring method is described in Section 10.7)
- BMI (derived using body weight in kilograms divided by the square of height in meters)
- participant retention (derived using number of participants with AEs leading to permanent discontinuation of the study intervention or withdrawal).

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

8.2.1. Physical Examinations

For each participant, measurements, including height, weight, and waist circumference, should be recorded as per the SoA. The study-specific recommendations for performing these measurements are included in Section 10.7.

A complete physical examination will be performed at the times shown in the SoA and will include, at a minimum, the following assessments:

- skin, including feet
- cardiovascular system
- respiratory system
- GI system
- neurological system, and
- thyroid.

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

8.2.2. Vital Signs

BP (supine and standing) and pulse rate will be measured when specified in the SoA and as clinically indicated. Additional vital signs may be measured during study visits if warranted, as determined by the investigator.

Vital signs should be measured after participant has been supine at least 5 minutes before obtaining an ECG tracing and collection of blood samples for laboratory testing when feasible. For orthostatic measurements, participants should be supine for at least 5 minutes and stand for at least 3 minutes. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. BP may be remeasured within 30 minutes at investigator discretion.

When possible, measurements of BP and pulse rate should be performed at approximately the same time of day at each scheduled time point.

Any clinically significant findings from vital sign measurement that result in a diagnosis and that occur after the participant receives the first dose of the study intervention should be reported to Lilly or its designee as an AE via CRF.

8.2.3. Electrocardiograms

A single 12-lead digital ECG will be collected for each participant according to the SoA (Section 1.3) using centrally provided ECG equipment. All single ECGs recorded should be stored at the investigational site. ECGs (single) may be obtained at additional times when deemed clinically necessary.

ECGs must be recorded within 30 minutes before collecting any blood samples for laboratory testing, including PK samples. Participants must be supine for at least 5 to 10 minutes before ECG collection and remain supine and awake during ECG collection.

ECGs will be interpreted by the investigator (a physician or qualified designee) at the site as soon after the time of ECG collection as practical, and ideally while the participant is still present for immediate participant management, should any clinically relevant findings be identified. The investigator or qualified designee must document their review of the ECG printed at the time of evaluation.

Any clinically significant findings from ECGs that result in a diagnosis and that occur after the participant receives the first dose of the study intervention should be reported to the sponsor or its designee as an AE via the eCRF.

All digital ECGs will be electronically transmitted to a central ECG laboratory. The central ECG laboratory will perform a basic quality control check (for example, demographics and study details) and then store the ECGs in a database. At a future time, the stored ECG data may be overread by a cardiologist at the central ECG laboratory for further evaluation of machine-read measurements or to meet regulatory requirements.

The machine-read ECG intervals and HR may be used for data analysis and report writing purposes, unless a cardiologist overread of the ECGs is conducted prior to completion of the final study report (in which case the overread data would be used).

8.2.4. Clinical Safety Laboratory Tests

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

The investigator must review the laboratory results, document this review, and report any clinically relevant changes occurring during the study as an AE. The laboratory results must be retained with source documents unless a Source Document Agreement or comparable document cites an electronic location that accommodates the expected retention duration. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by investigator to be more severe than expected for participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study after the last dose of study intervention should be repeated until the values return to

normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

All protocol-required laboratory assessments, as defined in Section 10.2, must be conducted in accordance with the SoA, standard collection requirements, and laboratory manual.

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

8.2.5. Pregnancy Testing

Pregnancy testing will occur as outlined in the SoA. Serum pregnancy test will be performed at screening.

If the specified visit includes administration of study intervention, the pregnancy test must be “negative” within 24 hours before the study intervention is administered.

Pregnancy testing at any time during the study

Additional pregnancy testing may be performed at any time in the study, at the discretion of the investigator, if there is clinical suspicion of pregnancy or as required by local law or regulation.

Discontinuation of participants who are pregnant

Participants who are pregnant will be permanently discontinued from the study intervention (Section 7.1). Participants who become pregnant will complete procedures for an ED visit and safety follow-up, as shown in the SoA.

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS captures the occurrence, severity, and frequency of suicidal ideation and behavior during the assessment period via a semi-structured interview by a trained rater.

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

Timing of collection and AE monitoring

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

Only report a suicide-related event discovered during the collection of the C-SSRS on the AE form if it is an AE that leads to discontinuation or an SAE.

Follow standard procedures for reporting SAEs.

8.2.7. Depression Monitoring

Study site personnel should monitor participants receiving study intervention for depression or any other unusual changes in behavior, especially at the beginning and the end of the course of treatment or at the time of dose changes, either increases or decreases.

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 is a validated, participant-reported instrument that assesses the specific diagnostic symptoms that determine the presence and severity of a clinical depressive disorder per the Diagnosis and Statistical Manual for Mental Disorders, 5th Edition (APA [WWW]) (Spitzer et al. 1999; Kroenke et al. 2001; Moriarty et al. 2015). This scale is validated for use in individuals 18 years of age and older.

The recall period of the questionnaire is the past 2 weeks.

The PHQ-9 assesses 9 diagnostic symptoms:

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

Each question has 4 response options, with scores ranging from 0 to 3, corresponding to categories of “not at all” to “nearly every day.” Higher numbers indicate greater dysfunction.

This table describes the interpretation of the results. The total score is the sum of scores for the 9 items.

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

8.2.8. Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation

The following tables summarize actions to take based on abnormal hepatic laboratory or clinical changes.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)

If this laboratory value is observed...	Then...		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study intervention
ALT or AST ≥ 3 x ULN	X		
ALP ≥ 2 x ULN	X		
TBL ≥ 2 x ULN ^a	X		
ALT or AST ≥ 5 x ULN	X	X	
ALP ≥ 2.5 x ULN	X	X	X
ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^b	X	X	X
ALT or AST ≥ 5 x ULN for more than 2 weeks	X	X	X
ALT or AST ≥ 8 x ULN	X	X	X
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5	X	X	X

^a In participants with Gilbert's syndrome, the threshold for TBL may be higher.

^b Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

Participants with elevated baseline (ALT, AST, or ALP ≥ 1.5 x ULN)

If this laboratory value is observed...	Then...		
	Initiate or continue close hepatic monitoring	Initiate comprehensive evaluation	Interrupt or discontinue study intervention
ALT or AST ≥ 2 x baseline	X		
ALP ≥ 2 x baseline	X		
TBL ≥ 2 x ULN ^a	X		
ALT or AST ≥ 3 x baseline or ≥ 250 U/L (whichever occurs first)	X	X	
ALP ≥ 2.5 x baseline	X	X	X
ALT or AST ≥ 2 x baseline or ≥ 250 U/L (whichever occurs first) with hepatic signs or symptoms ^b	X	X	X
ALT or AST ≥ 3 x baseline or ≥ 250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥ 4 x baseline or ≥ 400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥ 2 x baseline or ≥ 250 U/L (whichever occurs first) and TBL ≥ 2 x ULN ^a or INR ≥ 1.5	X	X	X

- ^a In participants with Gilbert's syndrome, the threshold for TBL may be higher.
- ^b Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

8.2.8.1. Close Hepatic Monitoring

If a participant develops any one of these changes, initiate close hepatic monitoring:

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)
ALT or AST ≥3x ULN or	ALT or AST ≥2x baseline
ALP ≥2x ULN or	ALP ≥2x baseline
TBL ≥2x ULN ^a	TBL ≥2x ULN ^a

- ^a In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Close hepatic monitoring should include these actions:

- Laboratory tests (Section 10.2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyltransferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2-3 times weekly until levels normalize or return to approximate baseline values. Subsequently, the frequency of monitoring may be lowered to once every 1 to 2 weeks if the participant's clinical condition and lab results stabilize.
- In addition to lab tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including
 - current symptoms
 - recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
 - recent travel
 - concomitant medications, including over-the-counter
 - herbal and dietary supplements
 - history of alcohol drinking, and
 - other substance abuse.

8.2.8.2. Comprehensive Hepatic Evaluation

If a participant develops any one of the following laboratory or clinical changes, initiate a comprehensive hepatic evaluation:

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)
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ALT or AST ≥ 5 x ULN or	ALT or AST ≥ 3 x baseline or ≥ 250 U/L (whichever occurs first) or
ALP ≥ 2.5 x ULN or	ALP ≥ 2.5 x baseline or
ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^a or	ALT or AST ≥ 2 x baseline or ≥ 250 U/L (whichever occurs first) with hepatic signs or symptoms ^a or
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5	ALT or AST ≥ 2 x baseline or ≥ 250 U/L (whichever occurs first) and TBL ≥ 2 x ULN ^b or INR ≥ 1.5

^a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia $>5\%$.

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined in Sections 1.3 and 8.2.1, as well as tests for prothrombin time-international normalized ratio; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan). Remaining samples collected for hepatic evaluation may be stored as exploratory biomarker samples. These stored samples will be used for the limited purpose of additional hepatic evaluations for up to 15 years.
- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for
 - hepatitis D virus
 - cytomegalovirus
 - Epstein-Barr virus
 - acetaminophen levels
 - acetaminophen protein adducts
 - urine toxicology screen
 - Wilson's disease
 - blood alcohol levels
 - urinary ethyl glucuronide, and
 - blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation and additional tests, including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and test results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.8.3. Study Intervention Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study-drug and continue close monitoring and comprehensive hepatic evaluation, as described in Sections 8.2.8.1 and 8.2.8.2.

Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥1.5x ULN)
ALT or AST ≥3x ULN with hepatic signs or symptoms ^a or	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms ^a or
ALT or AST ≥5x ULN for more than 2 weeks or	ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks or
ALT or AST ≥8x ULN or	ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first) or
ALT or AST ≥3x ULN and TBL ≥2x ULN ^b or INR ≥1.5 or	ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN ^b or INR ≥1.5 or
ALP ≥2.5x ULN	ALP ≥2.5x baseline

^a Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

^b In participants with Gilbert's syndrome, the threshold for TBL may be higher.

Interruption or discontinuation of study intervention should include these actions:

- While the participant is not receiving the study intervention, clinical and laboratory monitoring should continue at a frequency of 1 to 3 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock), the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, the data lock date).
- All the medical information and test results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study intervention after interruption for a hepatic reason can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results returned to near baseline and if a self-limited nonstudy-drug etiology is identified. Otherwise, the study intervention should be permanently discontinued.

8.2.9. Hepatitis B Testing and Monitoring

As specified in the SoA (Section 1.3), initial testing for HBV infection includes HbsAg and hepatitis B core antibody (HbcAb).

- If HbsAg is positive, the participant is excluded.
- If HbsAg is negative and HbcAb is negative, the participant is not excluded.
- If HbsAg is negative and HbcAb is positive, further testing for HBV DNA is required.
 - If the screening HBV DNA is positive, the participant is excluded.

- If the screening HBV DNA is negative, the participant is not excluded. Repeat testing for HBV DNA is required at least every 3 months during the study.

Management of enrolled participants with detectable HBV DNA during the study

If HBV DNA is detected, study intervention will be temporarily withheld or permanently discontinued, as described in Section 7.1, and the participant should receive appropriate follow-up medical care.

8.2.10. Hepatitis C Testing

As specified in the SoA (Section 1.3), initial testing for HCV infection includes testing for anti-HCV.

- If anti-HCV is positive, a test for circulating HCV RNA is required.
- If HCV RNA test is negative, the participant is not excluded.
- If HCV RNA test is positive, the participant is excluded.

Participants who have had HCV infection and have been successfully treated (defined as HCV RNA by PCR negative for at least 24 weeks following treatment completion), are not excluded on the basis of HCV as long as an HCV RNA is negative at screening.

If HCV RNA is detected during the study, the study intervention will be discontinued (Section 7.1) and the participant should receive appropriate follow-up medical care.

8.2.11. Malnutrition

Malnutrition is a term broadly used to describe deficiencies or excesses in the intake of macronutrients, micronutrients, or energy, as well as the physiological changes that can result. Investigators should monitor participants for signs and symptoms of malnutrition.

A table of signs and symptoms associated with common nutrient deficiencies is included in Section 10.10. In cases of suspected malnutrition, the nutritional panel described in Section 10.2.2 should be collected. Additionally, the site investigator should consider temporary interruption of study intervention pending assessment of nutritional panel and totality of evidence on the nutritional status of a participant should be assessed to determine if dosing can be resumed or permanently discontinued. A clinical assessment of dietary intake and nutritional status should also be completed. Nutritional guidance and, as needed, supplementation should be considered.

For severe or persistent cases, study intervention should be discontinued and management of the participant should be discussed with the medical monitor, including appropriate medical treatment and follow-up of suspected condition. The treatment of deficiencies should be managed in line with local clinical guidelines. If additional guidance is required, reach out to the Lilly-designated medical monitor.

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

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

- AEs

- SAEs, and
- PCs.

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

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

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits or contacts. All SAEs and AEs of special interest (as defined in Section 8.3.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3).

For PCs, the investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature or causality. Further information on follow-up procedures is provided in Section 10.3.

8.3.1. Timing and Mechanism for Collecting Events

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

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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE CRF	SAE paper form
SAE ^a – after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in participants and partners of participants	After the start of study intervention	90 days or 13 weeks after last participant visit	Within 24 hours (Section 8.3.2)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

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

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

8.3.2. Collection of Pregnancy Information

8.3.2.1. Participants Who Become Pregnant

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

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

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

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

Any post-study pregnancy-related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, the investigator may learn of an SAE through spontaneous reporting.

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

8.3.2.2. Participants with Partners Who Become Pregnant

When to collect pregnancy information

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 a 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 outcome of the pregnancy. 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 these circumstances

- the partner of the study participant was not exposed to the study intervention via semen during conception or pregnancy, or
- the participant did not contribute the spermatozoid or ova that resulted in the pregnancy.

8.3.3. Adverse Events of Special Interest

The AEs of special interest include

- severe GI AEs
- hepatic disorders, including drug-induced liver injury
- gallbladder and biliary tract disorders
- acute pancreatitis
- major adverse cardiovascular events
- supraventricular arrhythmias and cardiac conduction disorders
- hypoglycemia
- thyroid malignancies and c-cell hyperplasia
- acute renal events
- hypersensitivity reactions
- suicidal ideation and behavior monitoring
- depression, and
- deaths.

The details of analysis will be provided in the SAP.

8.3.3.1. 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.

8.3.3.2. 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. Hepatic events will include drug-induced liver injury, which will be adjudicated by an independent CEC. In cases of elevated liver laboratory tests, hepatic monitoring should be initiated, as outlined in Section 8.2.8.

8.3.3.3. 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.

8.3.3.4. Acute Pancreatitis (Adjudicated)

Diagnosis of acute pancreatitis

Acute pancreatitis is a 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 $\geq 3\times$ 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.
- Perform imaging studies, such as abdominal CT scans with or without contrast or abdominal MRIs.
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/gallbladder disease, hypertriglyceridemia, and concomitant medications.

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue the use of the study intervention. If acute pancreatitis is ruled out, the participant should resume study intervention based on the 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 (Section 7.1). If the case is not confirmed, then the participant can restart study intervention if the investigator deems it as clinically appropriate.

Case adjudication and data entry

An independent CEC 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 the asymptomatic elevation of pancreatic enzymes (lipase and/or p-amylase $\geq 3\times$ ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

The decision to perform diagnostic follow-up such as symptom-directed physical assessment, lab evaluation blood count, renal panel, liver tests and/or abdominal imaging should be guided by clinical judgment. Monitor and repeat pancreatic enzymes (lipase and/or p-amylase) tests and perform a symptom-directed physical assessment as per the SOA in Section 1.3 at each visit until amylase and lipase levels return to baseline. If acute pancreatitis is suspected, follow Section 8.3.3.4 for further guidance.

8.3.3.5. Major Adverse Cardiovascular Events (Adjudicated)

Nonfatal cardiovascular 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 cardiovascular 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.

8.3.3.6. 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, must be reported as SAEs.

8.3.3.7. Hypoglycemia

Upon signing of the ICF, participants will be educated by the authorized study personnel 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.

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 2023).

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. Participants should be advised to recheck their glucose 15 minutes after ingesting carbohydrates and to repeat carbohydrate ingestion for ongoing hypoglycemia. 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 2 hypoglycemia can alert a person to take action, such as treatment with fast-acting carbohydrates. Participants should be advised to recheck their glucose 15 minutes after ingesting carbohydrates and to repeat carbohydrate ingestion for ongoing 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).

8.3.3.8. Thyroid Malignancies and C-Cell Hyperplasia

Participants who are diagnosed with MTC or MEN2 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 will include reporting any case of thyroid malignancy, including MTC and papillary carcinoma, and measuring calcitonin. Calcitonin measurements will be used to assess the potential of LY3549492 to affect thyroid C-cell function, which may indicate the development of C-cell hyperplasia and medullary thyroid neoplasms.

Data will be captured in specific CRFs.

Calcitonin Measurements

If...	Then...
a participant's laboratory serum calcitonin results meet any of the criteria described below	- record the laboratory result as an AE, and - record the additional data from the follow-up assessment in the specific section of the CRF. Note: The participant should remain in the trial, but all concomitant medications that could potentially be linked to this condition must be stopped until a diagnosis is confirmed or ruled out.
Criterion 1: Serum calcitonin value ≥ 100 ng/L (≥ 100 pg/mL)	- Permanently discontinue study intervention (Section 7.1). - The participant should - promptly undergo additional endocrine assessments for further investigation, and - have longer-term follow-up by a thyroid specialist or an endocrinologist. - The investigator can perform imaging studies if clinically indicated.
Criterion 2: Serum calcitonin value ≥ 35 ng/L (≥ 35 pg/mL) AND $\geq 50\%$ over the screening value	Repeat the calcitonin measurement in 4 weeks for confirmation. If the increased calcitonin level still meets Criterion 2 in the confirmatory measurement, then take these steps: Step 1: The participant should continue the study intervention and be referred to a thyroid specialist or an endocrinologist for further investigation. The thyroid specialist or endocrinologist will determine whether the study intervention should continue based on the thyroid assessment. Step 2: Measure calcitonin levels every 4 weeks thereafter, and take the following actions: If the value increases to ≥ 100 ng/L (≥ 100 pg/mL), then follow guidance for Criterion 1

	OR If the value decreases to <35 ng/L (<35 pg/mL), then follow the calcitonin measurements as defined in the SoA.
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Abbreviations: AE = adverse event, AESI = adverse event of special interest, CRF = case report form, SoA = schedule of activities.

8.3.3.9. 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.

If the investigator determines that an acute renal event has occurred, the participant with CKD must be permanently discontinued from the study intervention, and the sponsor's designated medical monitor should be notified (Section 7.1). For participants without CKD experiencing acute renal event, the investigator should follow Section 7.1.

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

If the investigator determines that a systemic hypersensitivity reaction has occurred related to study intervention administration, the participant may be permanently discontinued from the study intervention and the sponsor's designated medical monitor should be notified (Section 7.1).

The investigator can use Common Terminology Criteria for Adverse Events Version (CTCAE) 5.0 (NCI 2018) to assign AE severity grades.

8.3.3.11. Suicidal Ideation or Behavior Monitoring

Refer to Section 8.2.6 for information on suicidal ideation and behavior risk monitoring.

8.3.3.12. Depression

Refer to Section 8.2.7 for information on depression monitoring.

8.3.3.13. Deaths (Adjudicated)

All deaths will be adjudicated by a committee of physicians external to Lilly. This committee will be blinded to treatment assignment.

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

PK 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 the 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.

Sample retention is described in Section [10.1.12](#).

8.5. Pharmacodynamics

Pharmacodynamic assessments are evaluated as part of the efficacy measures and biomarkers (Section [8.7](#)) in this study and will be collected in accordance with the SoA (Section [1.3](#)).

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, exploratory biomarker research on stored non-pharmacogenetic samples may be performed to address questions of

- relevance to drug disposition
- target engagement
- pharmacodynamics
- 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 nonpharmacogenetic 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.

Sample retention is described in Section [10.1.12](#).

8.8. Immunogenicity Assessments

Immunogenicity assessments are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

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

9.1. Statistical Hypothesis

The primary hypothesis tested in this study is that LY3549492 doses of 15 or 60 mg administered QD are different from placebo with regard to safety and tolerability evaluated at Week 48 in adult participants.

9.1.1. Multiplicity Adjustment

No adjustment for multiplicity will be performed.

9.2. Analyses Sets

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

Participant Analysis Set	Description
Full analysis set (FAS)	All randomized participants who meet the inclusion criteria.
Safety analysis set (SAS)	All participants who are exposed to investigational intervention.

The following data point sets are defined:

Data Point Sets (DPS)	Description
DPS1	Data points obtained during treatment period at or after randomization up to the date of discontinuation of any study intervention or intercurrent events (ICEs) described in Section 3.
DPS2	Data points obtained during treatment period at or after randomization to study intervention.
DPS3	Data points obtained during treatment period plus safety follow-up period regardless of adherence to study intervention.

Note:

FAS and DPS1 will be used to estimate the additional estimand for secondary objectives.

FAS and DPS2 may be used to estimate the additional estimands for the secondary objectives.

SAS and DPS3 will be used to present safety data.

For the efficacy analyses, participants will be included in the analyses according to the planned investigational intervention; whereas for safety analyses, participants will be included in the analyses according to the investigational intervention they actually received.

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

All tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, unless otherwise stated, and all confidence intervals will be given at a 2-sided 95% level. In statistical summaries and analyses, participants will be analyzed as randomized.

The summary statistics for continuous measures will include sample size, mean, standard deviation, median, minimum, and maximum. The analysis model to make comparisons among treatment groups relative to continuous measurements assessed over time (in addition to the baseline and end of treatment measurements) will be the mixed-effects models for repeated measures (MMRM). Further specification of the model will be included in the SAP, including selection of covariance structure. Analysis of covariance may be used to make comparisons among treatment groups for continuous measurements with only 1 postbaseline assessment.

Summary statistics for categorical measures (including categorized continuous measures) will include sample size, frequency, and percentages. Fisher's exact test will be used to examine the treatment difference in categorical outcomes. Logistic regression may be used to examine the treatment difference in binary efficacy outcomes. The negative binomial regression model may be used for the treatment comparison of discrete count measures if deemed appropriate.

Participant-specific random effects may be added to the logistic and the negative binomial regression models if longitudinal measurements are available.

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

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 will be described in the final CSR.

9.3.2. Primary Endpoint Analysis

Primary endpoint analysis on binary outcomes will be conducted on the safety analyses set via logistic regression, which will include the fixed effects of treatment group (if applicable); stratification factors, including age (55 to 64 years and 65 to 80 years) and sex (AFAB and AMAB); and fixed effects of age and sex, visit, treatment-by-visit interaction, baseline weight value, and baseline weight-by-visit interaction.

The model will assume an unstructured variance-covariance matrix on the residuals to model within-subject correlations due to repeated measures, if appropriate. Additional covariates or

fixed effect terms and details of the variance-covariance matrix assumption may be added in the SAP.

9.3.3. Secondary Endpoint(s) Analysis

The secondary analysis on percent change from baseline in body weight (kg) at Weeks 24 and 48 and change from baseline in BMI at Weeks 24 and 48 will be conducted using the safety analysis set and DPS3. The analysis model will be an MMRM, which will include the fixed effects of treatment group; stratification factors, including age (55 to 64 years and 65 to 80 years) and sex (AFAB and AMAB); and fixed effect of visit, treatment-by-visit interaction, baseline weight value, and baseline weight-by-visit interaction. The model will also assume an unstructured variance-covariance matrix on the residuals to model within-subject correlations due to repeated measures, if appropriate. Additional covariates or fixed effect terms and details of the variance-covariance matrix assumption may be added in the SAP.

9.3.4. Exploratory Endpoint(s) Analysis

Details of the analyses will be provided in the SAP.

9.3.5. Safety Analyses

All safety analyses will be conducted on the safety analysis set and DPS3. Safety assessments will be guided by an estimand comparing the safety of the primary intervention to the primary control irrespective of adherence to the study intervention.

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported with preferred terms and system organ class. Summary statistics will be provided for the incidences of TEAEs, SAEs, study discontinuation due to AEs, study intervention discontinuation due to AEs, deaths, and other cardiovascular endpoints. Counts and proportions of participants experiencing AEs will be reported for each treatment group and each dose escalation subgroup, and Fisher's exact test will be used to compare the primary intervention dose groups with the primary control.

9.3.6. Other Analyses

Other safety analyses and sub-group analyses may be conducted. The details will be provided in the SAP.

Analysis of C-SSRS Data

Suicide-related thoughts and behaviors will be summarized based on responses to the C-SSRS consistent with the C-SSRS Scoring and Data Analysis Guide (C-SSRS WWW).

Depression

In addition to the summary of TEAEs, depression-related symptoms will be assessed using PHQ-9.

The analysis details will be provided in the 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.

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 pharmacodynamic parameters may be examined.

9.4. Interim Analysis

At least 1 interim analysis may be conducted after at least 50% of participants enter treatment to support planning activities associated with the clinical development program and to aid in the development of PK/PD models. The SAP will describe any interim analysis. At the discretion of the sponsor, the prespecified interim analysis may not be conducted.

Only the IAC is authorized to evaluate unblinded interim efficacy and safety analyses. Study sites will receive information about interim results only if they need to know for the safety of their participants.

9.5. Sample Size Determination

The study sample size of approximately 220 participants will be randomly assigned to the study intervention in a randomization ratio of 1:5:5 as follows:

- approximately 20 participants to placebo
- approximately 100 participants to LY3549492 15 mg, and
- approximately 100 participants to LY3549492 60 mg.

Assuming a 20% dropout rate, this results in 16 completers per 20-participant arm and 80 completers per 100-participant arm.

Sample size determination was done to detect percent change in body weight from baseline to Week 48 for each LY3549492 arm and within each age group. Assuming a standard deviation of 10% and a 2-sided type I error rate of 0.05, 40 completers for the LY3549492 treatment group within an age group can provide over 95% power, assuming a treatment effect of -6%.

10. Supporting Documentation and Operational Considerations

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

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable ICH GCP Guidelines
- International Organization for Standardization 14155
- Applicable laws and regulations.

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents, for example, advertisements, must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

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

The investigator will be responsible for the following:

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

Investigator sites are compensated for participation in the study as detailed in the clinical trial agreement.

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after the completion of the study.

10.1.3. Informed Consent Process

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

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

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

Revised consents must be appropriately obtained using the correct approved ICFs for applicable study participants in accordance with sponsor and Ethical Review Boards consenting guidance.

A copy of the ICF(s) must be provided to the participant and is kept on file.

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

10.1.4. Data Protection

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

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

The participant must be informed through the informed consent by the site personnel that their medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The sponsor has processes in place to ensure information security, data integrity, and data protection. These processes address management of data transfer, and prevention and management of unauthorized access, disclosure, dissemination, alteration or loss of information

or personal data. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

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

10.1.5. Committees Structure

10.1.5.1. Internal Assessment Committee (IAC)

In addition to the safety reviews routinely performed by the blinded study team, as described in Section 8.2, an IAC may exist for the purpose of reviewing safety data in an unblinded fashion periodically or on an ad hoc basis, if needed. The IAC may determine whether any changes to the study, for example, dose reductions or other protocol modifications, should be made.

The IAC will be independent from the study team and include, at a minimum, a Lilly medical physician, a statistician, and a representative from the Lilly Global Patient Safety organization. Details about IAC membership, purpose, responsibilities, and operation will be described in an IAC charter, which will be approved prior to the first unblinding.

If an efficacy interim analysis is conducted, the IAC will be responsible for review of the efficacy data. See Section 9.4 for general information about interim analyses. Details of interim analyses will be provided in the SAP.

Investigator sites will receive information about interim analyses results only if such information is relevant regarding the safety of their study participants.

10.1.5.2. Clinical Event Committee (CEC)

An independent CEC with membership external to the sponsor will be responsible for event adjudication in a blinded fashion.

The independent CEC will adjudicate drug-induced liver injury, acute pancreatitis events, death and major adverse cardiovascular events, as listed in Section 8.3.3. The CEC charter will contain the final detailed event definitions used for adjudication.

10.1.6. Dissemination of Clinical Study Data

Reports

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

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

Data

The sponsor provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data.

Data are available to request 6 months after the indication studied has been approved in the US and EU and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available.

Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data-sharing agreement.

Data and documents, including the study protocol, SAP, CSR, and blank or annotated CRFs, will be provided in a secure data-sharing environment for up to 2 years per proposal.

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

10.1.7. Data Quality Assurance

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

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

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

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

Quality tolerance limits will be predefined to identify systematic issues that can impact participant safety and/or reliability of study results. These predefined parameters will be monitored during the study and important excursions from the quality tolerance limits and remedial actions taken will be summarized in the CSR.

Monitoring details describing strategy, for example, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring, methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques are provided in the Monitoring Plan.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

The sponsor assumes accountability for actions delegated to other individuals, for example, contract research organizations.

The sponsor or designee will perform monitoring to confirm that data transcribed into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that

the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

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

In addition, the sponsor or its representatives will periodically check a sample of the participant data recorded against source documents at the study site. The study may be audited by the sponsor or its representatives, or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data Capture System

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor.

Electronic data capture system

An electronic data capture system will be used in this study for the collection of CRF data. The investigator maintains a separate source for the data entered by the investigator or designee into the sponsor-provided electronic data capture system. The investigator is responsible for the identification of any data to be considered source and for the confirmation that data reported are accurate and complete by signing the CRF.

Clinical outcome assessments

COA data (participant-focused outcome instrument) will be collected by the participant and/or authorized study personnel, via a paper source document and will be transcribed by the authorized study personnel into the electronic data capture system and will serve as the source documentation.

Additionally, electronic COA data (participant-focused outcome instrument) will be directly recorded by the participant and/or investigator site personnel into an instrument for example, hand-held smart phone or tablet. The electronic COA data will serve as the source documentation, and the investigator does not maintain a separate written or electronic record of these data.

Data storage and access

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

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

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

10.1.8. Source Documents

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

Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the site confirmation of source data.

10.1.9. Study and Site Start and Closure

Study start

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

First act of recruitment

The first act of recruitment is the opening of the first site.

Study or site termination

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

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

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

- for study termination due to discontinuation of further study intervention development
- for site termination due to
 - failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
 - inadequate recruitment, evaluated after a reasonable amount of time of participants by the investigator, or
 - total number of participants included earlier than expected.

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

10.1.10. Publication Policy

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

Sample retention enables the 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.

Sample Type	Custodian	Retention Period After Last Participant Visit ^a
Genetics	Sponsor or designee	7 years
Exploratory biomarkers	Sponsor or designee	7 years
Pharmacokinetics	Sponsor or designee	1 year

^a Sample retention periods may differ dependent upon local regulations.

10.2. Appendix 2: Clinical Laboratory Tests

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

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

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

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

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

Investigators must document their review of the laboratory safety results.

Laboratory results that could unblind the study will not be reported to investigative sites or other blinded personnel until the study has been unblinded.

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

Clinical Laboratory Tests	Comments
Chloride	
Bicarbonate	
Total bilirubin (TBL)	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Pancreatic amylase	
Lipase	
Glucose	
Lipid Panel	Assayed by Lilly-designated laboratory
High-density lipoprotein (HDL)	
Low-density lipoprotein (LDL-C)	LDL will be directly measured if triglycerides exceed maximum value for calculation.
Very low-density lipoprotein (VLDL-C)	
Total cholesterol	
Triglycerides	
Urinalysis	Assayed by Lilly-designated laboratory
Specific gravity	
pH	
Protein	
Glucose	
Ketones	
Bilirubin	
Urobilinogen	
Blood	
Nitrite	
Urine leukocyte esterase	
Microscopic examination of sediment (performed only if clinically indicated)	
Hormones (individual AFAB only)	
Serum pregnancy (beta-HCG)	Assayed by Lilly-designated laboratory
Follicle-stimulating hormone (FSH)	Assayed by Lilly-designated laboratory

Clinical Laboratory Tests	Comments
Calculations	Generated by Lilly-designated Laboratory
eGFR (CKD-EPI) calculated using cystatin-C	
Hepatitis serology screening	Assayed by Lilly-designated laboratory
HIV screening test	
Hepatitis B virus (HBV) screening tests	
HBV DNA	Performed only for participants who test positive for anti-HBc.
Hepatitis B core antibody (HBc-Ab)	
Hepatitis B surface antigen (HBsAg)	
Hepatitis C virus (HCV) screening tests	
HCV antibody	
HCV RNA	Performed only for participants who test positive for HCV antibody.
Additional Testing	Assayed by Lilly-designated laboratory
Cystatin-C	Results will not be provided to investigative sites.
Calcitonin	
Thyroid-stimulating hormone (TSH)	
Fasting insulin	Results will not be provided to investigative sites.
HbA1c	
C-Peptide	Results will not be provided to sites
Pharmacokinetics	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
PK samples – LY3549492 concentration	
Biomarkers	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites
Endpoint biomarkers	Refer to Section 10.8 (Mechanistic Biomarkers) for specific laboratory tests.
Longitudinal biomarkers	Refer to Section 10.8 (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: AFAB = assigned female at birth; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; EDTA = Ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; OGTT = oral glucose tolerance test; PK = pharmacokinetics; RBC = red blood cell; WBC = white blood cell.

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

Purpose of collecting samples after a systemic hypersensitivity event

The samples listed in this appendix are not collected for acute study participant management. The sponsor will use the laboratory 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 the event.	Total tryptase

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

10.2.2. Nutritional Monitoring Panel to be Obtained in Case of Suspected Malnutrition

Purpose of collecting samples in case of suspected malnutrition

Investigators should monitor participants for signs and symptoms of malnutrition. Refer to Section [8.2.11](#).

Nutritional guidance and, as needed, supplementation should be considered. For severe or persistent cases, consider study intervention discontinuation and discuss management of the participant with the Lilly-designated medical monitor.

When to collect samples in case of suspected malnutrition

Collect the samples listed below if malnutrition is suspected.

Category	Laboratory Test
Special tests	Vitamin A
	Vitamin B1 (Thiamine)
	Vitamin B9 (Folate)

Category	Laboratory Test
	Vitamin B12
	Vitamin D (25-hydroxy vitamin D)
	Vitamin E
	Vitamin K ₁
Hematology	Complete blood count ^a
Clinical chemistry	Clinical chemistry panel ^b
	Magnesium
	Zinc
	Phosphorous
Iron panel	Serum iron
	Total iron binding capacity (TIBC)
	Transferrin saturation (%)
	Ferritin

^a Refer to Section 10.2 for contents of complete blood count panel.

^b Refer to Section 10.2 for contents of clinical chemistry panel.

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

10.3.1. Definition of AE

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

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments, for example, ECG, radiological scans, and vital signs measurements, including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator, that is, not related to progression of underlying disease.
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT meeting the AE definition

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

10.3.2. Definition of SAE

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

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

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

10.3.3. Definition of Product Complaints

Product complaint

A PC is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness or performance of a study intervention. When the ability to use the study intervention safely is impacted, the following are also PCs:

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

Product complaints related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements.

If the participant identifies a PC or a problem with the study intervention, investigators will instruct participants to contact the site as soon as possible so that the situation can be assessed.

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

Device deficiencies are PCs.

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

AE, SAE, and PC recording

When an AE/SAE/PC occurs, it is the responsibility of the investigator to review all documentation (for example, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.

The investigator will then record all relevant AE/SAE/PC information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.

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

It is **not** acceptable for the investigator to send photocopies of the participant's medical records to the sponsor or designee in lieu of completion of the CRF page for AE/SAE and the Product Complaint Form for PCs.

There may be instances when copies of medical records for certain cases are requested by the sponsor or designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the sponsor or designee.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

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

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

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

Grading Scale for Assessment of Gastrointestinal-associated Adverse Events

Systemic (General)	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Nausea/vomiting	No interference with activity or 1-2 episodes/24 hours	Some interference with activity or >2 episodes/24 hours	Prevents daily activity, requires outpatient IV hydration	ER visit or hospitalization for hypotensive shock
Diarrhea	2-3 loose stools or <400 g/24 hours	4-5 stools or 400-800 g/24 hours	6 or more watery stools or 800 g/24 hours or requires outpatient IV hydration	ER visit or hospitalization
Headache	No interference with activity	Repeated use of non-narcotic pain reliever >24 hours or some interference with activity	Significant; any use of narcotic pain reliever or prevents daily activity	ER visit or hospitalization
Fatigue	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization
Myalgia	No interference with activity	Some interference with activity	Significant; prevents daily activity	ER visit or hospitalization

Illness or clinical AE (as defined according to applicable regulations)	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	ER visit or hospitalization
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Abbreviations: AE = adverse event, ER = emergency room, IV = intravenous.

Source: FDA, 2007b

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.

A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.

Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

The investigator will also consult the IB, in their assessment.

The investigator **must** review and provide an assessment of causality for each AE/SAE and document this in the medical notes.

There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor or designee.

The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.

The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide the sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

The primary mechanism for reporting an SAE will be the electronic data collection tool.

If the electronic system is unavailable, then the site will use the SAE paper form (see next section) in order to report the event within 24 hours.

The site will enter the SAE data into the electronic system as soon as it becomes available.

After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.

If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a SAE paper form (see next section) or to the sponsor by telephone.

Contacts for SAE reporting can be found in study training material.

SAE reporting via paper form

Facsimile transmission of the SAE paper form is the preferred method to transmit this information to the sponsor.

Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE CRF pages within the designated reporting time frames.

Contacts for SAE reporting can be found in study training material.

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will evaluate the reported SAEs, including confirmation of relatedness and assessment of expectedness. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC, and investigators.

An investigator who receives an investigator safety report describing a SAE or other specific safety information (for example, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
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 bilateral orchiectomy (orchidectomy) with or without penectomy.
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 postmenopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state ^c	The postmenopausal state is defined as an individual • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy; or • 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; or • 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 (WNOCBP).
- ^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 postmenopausal 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 postmenopausal status before the study enrollment.

10.4.2. Contraception Guidance

For individuals assigned AFAB

- IOCBP are excluded from the trial.
- INOCBP may participate in this trial.

See Section 10.4.1 for definitions.

For individuals assigned AMAB

Individuals AMAB may participate in this trial. See Section 10.4.1 for definitions and additional guidance related to contraception.

This table 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 highly 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.

Participant Population	Contraception Guidance
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^a:

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 (for example, contraceptive patch) (only for 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 (IUDs) 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 or without spermicide - Vaginal condom with or without spermicide - Diaphragm with spermicide

Methods	Examples
	• 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

^a Ablation (endometrial or uterine) is not considered a form of contraception.

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

Hepatic evaluation testing

See Section 8.2.8 for guidance on appropriate test selection from this table. Note that testing for some analytes may not be available from the central lab or local lab in certain regions due to local availability of assay or regulatory requirements. If testing is not available, this will not be considered a protocol deviation.

Local testing may be performed *in addition to central testing* when necessary for immediate participant management. If local testing is performed in lieu of central testing, the results should be recorded in the appropriate local lab CRF. For example, if immediate participant management circumstances preclude collection of central lab samples – for example, emergency room visit or hospitalization. The local laboratory must be qualified in accordance with applicable local regulations.

TESTS AVAILABLE FROM LILLY-DESIGNATED CENTRAL LABORATORY	
Hepatic Clinical Chemistry Panel	Hepatitis A virus (HAV) testing:
Total bilirubin	HAV total antibody ^a
Direct bilirubin	HAV IgM antibody
Alkaline phosphatase (ALP)	Hepatitis B virus (HBV) testing:
Alanine aminotransferase (ALT)	Hepatitis B surface antigen (HBsAg)
Aspartate aminotransferase (AST)	Hepatitis B core total antibody (anti-HBc)
Gamma-glutamyl transferase (GGT)	Hepatitis B core IgM antibody
Creatine kinase (CK)	HBV DNA ^b
Hepatic Coagulation Panel	Hepatitis C virus (HCV) testing:
Prothrombin time, INR (PT-INR)	HCV total antibody ^a
Hepatic Hematology Panel	HCV RNA ^b
Hemoglobin	Hepatitis E virus (HEV) testing:
Hematocrit	HEV IgG antibody
Erythrocytes (RBCs - red blood cells)	HEV IgM antibody
Leukocytes (WBCs - white blood cells)	HEV RNA ^b
Differential:	Anti-nuclear antibody (ANA)
Neutrophils	Anti-smooth muscle antibody (ASMA) or anti-actin antibody
Lymphocytes	Haptoglobin
Monocytes	Immunoglobulin IgA, IgG, IgM (quantitative)
Basophils	Urine Chemistry
Eosinophils	Drug Screen
Platelets	
Cell morphology (RBC and WBC)	

TESTS TO BE PERFORMED BY INVESTIGATOR-DESIGNATED LABORATORY, AS NEEDED	
Acetaminophen	Hepatitis D virus (HDV) testing^c
Acetaminophen protein adducts	HDV total antibody ^a
Alkaline phosphatase isoenzymes	HDV IgM antibody
Ceruloplasmin	HDV RNA ^b
Copper	Herpes simplex virus (HSV) testing:
Cytomegalovirus (CMV) testing:	HSV (Type 1 and 2) antibody
CMV antibody	HSV (Type 1 and 2) DNA ^b
CMV DNA ^b	Liver kidney microsomal type 1 (LKM-1) antibody
Ethyl alcohol (ethanol, EtOH)	Phosphatidylethanol (PEth)
Ethyl glucuronide (EtG)	Microbiology Culture:
Epstein Barr virus (EBV) testing:	Blood
EBV antibody	Urine
EBV DNA ^b	

^a If lab does not offer total antibody testing, IgG and/or IgM are acceptable substitutes

^b Reflex/confirmation dependent on regulatory requirements, testing availability, or both.

^c If HDV testing is not available, HBV testing may be sufficient. If HBV testing is positive, consult with the Lilly-designated medical monitor.

10.6. Appendix 6: New York Heart Association Functional Classification of Heart Failure

Class	Symptomatology
I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea.
II	Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea.
III	Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes fatigue, palpitation, or dyspnea.
IV	Unable to carry on any physical activity without discomfort. Symptoms of heart failure at rest. If any physical activity is undertaken, discomfort increases.

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

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

Measuring height

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

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

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

Step 4. Ask the participant to breathe in and stand tall. Measure the participant's height in centimeters and record to 1 decimal place.

Measuring weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in kilograms.
- All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.
- Body weight must be measured in fasting state. If the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting body weight measured.

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

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

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

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

Measuring waist circumference

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

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

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

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

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

Vital sign measurements

- Vital signs should be measured after participant has been supine at least 5 minutes, and before obtaining an ECG tracing and collection of blood samples for laboratory testing when feasible. For orthostatic measurements, participants should be supine for at least 5 minutes and standing for at least 3 minutes before each of the measurements. Unscheduled orthostatic vital signs should be assessed, if possible, during any AE of dizziness or posture-induced symptoms. BP may be remeasured within 30 minutes at investigator discretion.
- BP must be taken with an automated BP instrument.
- If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

Step 1. The participant should rest quietly for 5 minutes before vital signs measurements are taken.

Step 2. For each parameter, 3 measurements will be taken using the same arm, preferably the nondominant arm.

Step 3. The recordings should be taken at least 1 minute apart. Each measurement of pulse and BP needs to be recorded in the CRF.

Note: In the event pulse measurement cannot be taken via an automated BP instrument, the preferred location for measurement of pulse is the radial artery.

10.8. Appendix 8: 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 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
- biomarkers related to lipid metabolism: fasting cholesterol, triglycerides, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, and non-high-density lipoprotein-cholesterol
- biomarkers related to regulation of BP and fluid balance: plasma renin activity and aldosterone
- biomarkers related to regulation of calcium and bone metabolism: 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 C-peptide^a Calculation: HOMA2-IR ^a (computed with fasting glucose [part of clinical chemistry panel] and fasting insulin or fasting C-peptide)	Total adiponectin ^a IGF-1 ^a Leptin ^a
Glucose metabolism	Calculation: • HOMA2-B^a (computed with fasting glucose [part of clinical chemistry panel] and fasting insulin or fasting C-peptide)	
Regulation of blood pressure and fluid balance	• Plasma renin activity^a • Aldosterone^a	
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) ○ non-HDL cholesterol (non-HDL-C) ○ triglycerides ○ VLDL cholesterol (VLDL-C)	

Mechanism	Longitudinal Biomarkers	Endpoint Biomarkers
Bone and calcium metabolism		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; IGF-1 = insulin-like growth factor 1; 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.

10.9. Appendix 9: 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.

Prohibited Drugs	Indication	Excluded medications
Strong CYP3A4 inhibitors or Strong CYP3A4 inducers	COVID-19 therapy	nirmatrelvir and ritonavir (Paxlovid™)
	Antibiotics	- clarithromycin^a - telithromycin^a - josamycin^a - rifamycins
	Antifungals	- ketoconazole^b - itraconazole^b - posaconazole^b - voriconazole^b Note: 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^d

Abbreviations: AE = adverse events; BCRP = breast cancer-resistance protein; COVID-19 = coronavirus disease 2019; CYP3A4 = cytochrome P450 family 3 subfamily A member 4; HIV = human immunodeficiency virus; HMG-CoA = β -Hydroxy β -methylglutaryl coenzyme A; P-gp = P-glycoprotein.

- 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.
- d For participants taking rosuvastatin, if switched to another statin at least 3 weeks prior to randomization.

10.10. Appendix 10: Clinical Signs Associated with Common Nutritional Deficiencies

The following table displays clinical signs that are associated with common deficiencies of micro- and macronutrients (Parrott et al. 2017; Astrup and Bügel 2019; Wilson et al. 2022; Linus Pauling Institute 2023). This list of nutritional deficiencies is not exhaustive.

Micronutrient	Clinical Signs of Deficiency
A	Vision loss, night blindness, dry, scaly, or itchy skin, frequent respiratory tract infections, infertility, delayed growth and development in children
B1	Peripheral neuropathy, muscle weakness (dry beriberi), tachycardia, heart failure, edema (wet beriberi), ataxia, abnormal eye movements, impaired memory, confusion (cerebral beriberi or Wernicke-Korsakoff syndrome)
B9	Macrocytic anemia, extreme tiredness, shortness of breath, memory problems, irritability, ulcerations in the oral mucosa
B12	Macrocytic anemia, fatigue, shortness of breath, irritability, memory disturbances, depression, disorientation, glossitis, peripheral neuropathy, paresthesia
D	Weak and thinning bones, osteomalacia in adults, rickets in children, muscle weakness and pain
Calcium	Weak and thinning bones, muscle weakness and pain, numbness or tingling in feet and hands, irregular heartbeat
Magnesium	Muscle pain, tremors, cramps, weakness
Phosphorus	Bone pain, fragility, poor development, joint stiffness and pain, weakness, numbness, tingling in limbs, fatigue and loss of appetite, breathing problems, irregular heartbeat
Iron	Microcytic anemia, tiredness, pale skin, shortness of breath, hair loss, brittle nails, cold intolerance
Zinc	Dermatitis, impaired wound healing, impaired taste, decreased immune function
Macronutrient	Clinical Signs of Deficiency
Protein	Muscle wasting, weakness, edema, skin changes, immunosuppression
Fat (essential fatty acid deficiency)	Dry skin, impaired wound healing, susceptibility to infections
Carbohydrate	There is no absolute dietary requirement for carbohydrates, but very low carbohydrate dietary pattern may increase the risk of ketosis, headache, fatigue, halitosis

10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances

Implementation of this appendix

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

In an exceptional circumstance, the sponsor's procedures ensure that relevant parties are kept informed of changes to the design and conduct of the study.

Exceptional circumstances

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

Implementing changes under exceptional circumstances

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

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

Remote visits

Types of remote visits

- **Telemedicine** - Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to,
 - concomitant medications
 - AEs
 - review nutrition goals
 - review of study participant diary, including study intervention compliance
 - contraception, as applicable
 - administration of patient-reported outcomes, and
 - mental health questionnaires, for example, PHQ-9.
- **Mobile healthcare** - Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to,
 - height, weight, and waist measurements
 - vital signs
 - symptom-directed physical assessments
 - ECGs
 - administration of patient-reported outcomes
 - collection of blood and urine samples, and
 - collection of health information.
- **Other alternative locations** - During exceptional circumstances, laboratory samples and ECGs may be collected locally, if needed, outside of mobile healthcare visits.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for Visits 1, 2, 6, 10, 18, ED, and 801. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

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

These requirements must be met before action is taken:

- Alternate delivery of study intervention should be performed in a manner that does not compromise treatment blinding and ensures product integrity. The existing protocol requirements for product accountability remain unchanged, including verification of participant's receipt of study supplies.
- When delivering supplies to a location other than the study site (for example, the participant's home), the investigator, sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
- Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

If study intervention will be administered to the participant during a mobile healthcare visit or at an alternate location, this additional requirements must be met:

- Only authorized study personnel may supply, prepare, or administer the study intervention.

Screening period guidance

To ensure the safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 60 days, with the exception of the serum pregnancy test, which is valid for a maximum of 28 days.

The following rules will be applied for active, nonrandomized participants whose participation in the study must be interrupted due to exceptional circumstances.

- If screening is interrupted for less than 60 days from screening, the participant will proceed to the next study visit per the usual SoA, provided that Visit 2 must be conducted within 60 days from the first screening visit.
- The site should conduct the next visit if the participant's eligibility criteria are confirmed, and the site should document the reason for the delay.
- The site should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.

- If screening is interrupted for more than 60 days from screening, the participant must be discontinued because of screening interruption due to an exceptional circumstance. This is documented as a screen failure in the CRF. The participant can re-consent and be rescreened as a new participant. This rescreen is in addition to the one allowed in the study (Section 5.4). The screening procedures per the usual SoA should be followed, starting at the screening visit to ensure participant eligibility by Visit 2.

Adjustments to visit windows

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

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 601, Visit 1	No adjustment to the visit window described in the SoA
Visit 3 to Visit 18	Within 6 days before the intended date or up to 6 days after the intended date
Visit 801	Within 14 days from the intended date or up to 14 days after the intended date

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

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.12. Appendix 12: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AFAB	assigned female at birth
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AMAB	assigned male at birth
anti-HBc	antibody to hepatitis B core antigen
anti-HCV	antibodies to HCV
AST	aspartate aminotransferase
authorized IMP	<i>Applicable to the EU only:</i> a medicinal product authorized in accordance with Regulation (EC) No 726/2004 or in any Member State concerned in accordance with Directive 2001/83/EC, irrespective of changes to the labeling of the medicinal product, which is used as an investigational medicinal product
blinding/masking	A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
BCRP	breast cancer-resistance protein
BG	blood glucose
BMI	body mass index
BP	blood pressure
CEC	clinical event committee
CKD	chronic kidney disease
COA	clinical outcome assessment
complaint	A complaint is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, purity, durability, reliability, safety or effectiveness, or performance of a drug or drug delivery system.
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.

CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
CYP	cytochrome P450
DPS	data point set
DXA	dual-energy X-ray absorptiometry
ECG	electrocardiogram
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.
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulinotropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	glucagon-like peptide-1 receptor agonist
HbA1c	hemoglobin A1c
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HR	heart rate
IAC	internal assessment committee
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee

IMP	Investigational Medicinal Product (see also “investigational product”) A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
INOCBP	individuals not of childbearing potential
IOCBP	individuals of childbearing potential
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also “IMP.”
IRB	institutional review board
IWRS	interactive web-response system
medication error	Errors in the prescribing, dispensing, or administration of a study intervention, regardless of whether or not the medication is administered to the participant or the error leads to an AE. Medication error generally involve a failure to uphold one or more of the five “rights” of medication use: 1. the right participant 2. the right drug 3. the right dose 4. the right route, 5. at the right time.
MEN2	multiple endocrine neoplasia syndrome Type 2
misuse	Use of a study intervention for self-treatment that either is inconsistent with the prescribed dosing regimen, indication, or both, or is obtained without a prescription
MoCA	Montreal cognitive assessment
MRI	magnetic resonance imaging
MTC	medullary thyroid carcinoma
OGTT	oral glucose tolerance test

participant	Equivalent to CDISC term “subject”: an individual who participates in a clinical trial, either as recipient of an investigational medicinal product or as a control
PC	product complaint
P-gp	p-glycoprotein
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetics
QD	once daily
QTc	corrected QT interval
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-36v2	Short-Form 36 Version 2 Health Survey
SMBG	self-monitored blood glucose
SoA	schedule of activities
T2D	type 2 diabetes mellitus
TBL	total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
TUG	Timed Up and Go assessment
ULN	upper limit of normal

10.13. Appendix 13: Protocol Amendment History

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

Amendment GZNI(a): (06-Jun-2025)

This amendment is considered to be substantial.

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

- safety or the rights of the study participants
- reliability and robustness of the data generated in the clinical study,
- the quality or safety of any investigational medicinal product used in the study.

Overall rationale for the amendment

This amendment incorporates a change to the starting dose for Arm 3 from 1 to 2 mg, laboratory values (amylase and lipase) for patient safety, and addresses other minor protocol issues.

Section # and Name	Description of Change	Brief Rationale
Section 1.2, Study Schema	Modified first period description from “Optional Screening” to “Prescreening (optional)”	To align with language in Section 1.3.
		
Section 1.3 Schedule of Activities table	Changed “Diabetes Education” to Hyperglycemia and hypoglycemia education” Removed, “Only applicable for participants with T2D at screening.” Added, “Refer to Section 5.3.5.”	To align with revised heading for Section 5.3.5 and to allow explanation of hyperglycemic and hypoglycemic events for all participants

Section # and Name	Description of Change	Brief Rationale
	For “Explain symptoms of hypoglycemic events” row: Removed, “Only applicable for participants with T2D at screening.” Added, “Refer to Section 5.3.5.”	To allow explanation of hypoglycemic events for all participants
	For “Review SMBG and hypoglycemia events collected in diary” row: Removed note of “Only applicable for participants with T2D at screening.”	To allow the review of SMBG and hypoglycemia events in the diary for all participants in the study.
	For “Lifestyle counseling” row: Added a note “Should occur within 3 days after visit.”	To allow flexibility if the site cannot complete the assessment on the same day
	For “Review nutrition goals” row: Added a note “Should occur within 3 days after visit.”	For sites to complete the assessment within a predefined time window
	Removed MMSE cognitive assessment.	To avoid duplication with MoCA assessment
	For the “24-hour dietary recall” row: Removed the UV 997 visit for the 24-hour dietary recall. Also added a note: “Should occur within 3 days after visit.”	UV 997 visit not required, Predefined time window clarified for sites to complete the assessment
	For “Lipids” row: Added instances at	Additional visits added to coincide with micronutrient

Section # and Name	Description of Change	Brief Rationale
	Visit 6, Visit 10, and Visit 18.	sample collection to provide additional nutritional status information for participants.
	For “Calcitonin” row: Added instances at Visit 10, Visit 18, ED, and Visit 801. Also, added a note: “Refer to Section 8.3.3.8 for Calcitonin Measurements Guidance table.”	Additional timepoints added for calcitonin quantification language. Referral to guidance table added to ensure adequate safety monitoring of thyroid function.
	For Cystatin-C row: Added instances at Visit 6 and Visit 14.	To provide additional monitoring of renal function during the study
	Added entries at Screening and Visit 6, Visit 10, and Visit 18 for: Iron Vitamin B1 Vitamin B12 Vitamin A	To provide additional data on participants’ nutritional status
	For “eGFR” row: Added instances at Visit 6 and Visit 14.	To provide additional monitoring of renal function during the study
	For HBV screening test, removed Note: “Participants who are HBsAg positive are excluded. For participants who have negative HBsAg but are positive for anti-hepatitis B core antibody, confirmation by HBV DNA will be done.” Replaced with Note: “If HBsAg is negative	To provide clarity on screening results from HBsAg and HbcAb, and the need for an HBV DNA test

Section # and Name	Description of Change	Brief Rationale
	and HbcAb is positive, further testing with HBV DNA is required. If the screening HBV DNA is negative, the participant is not excluded. See Section 8.2.9.”	
	For HCV screening tests row, removed Note: “Confirmation by HCV RNA will be performed if positive for HCV antibody.” Replaced with Note: “If HCV antibody test is positive, it must be followed by an HCV RNA test. See Section 8.2.10.”	To provide clarity and clearer instruction on HCV screening
	For serum pregnancy test row, removed Visit 2 instance and added Note: “For IOCBP only.”	Serum pregnancy test will be performed in all females within the study, independent of childbearing potential
	Added “Urine pregnancy test (local)” row with 1 instance at Visit 2. Added Note: “See Section 10.4.”	Urine pregnancy test to be performed at Visit 2;
Section 3. Objectives, Endpoints, and Estimands	From exploratory objective “To characterize the effects of LY3549492 and placebo on cognition,” removed endpoint of “Change from baseline in MMSE scores at Weeks 24 and 48.”	To avoid duplication and potential misrepresentation of cognition by performing both MoCA and MMSE assessments

Section # and Name	Description of Change	Brief Rationale
Section 4.3 Justification for Dose	CCI [REDACTED] [REDACTED] [REDACTED] [REDACTED]	Textual change to align with change in dosing titration for Arm 3.
Section 5.2 Exclusion Criteria	Added new Gastroenterological criteria #10 and #11: #10: Have a known clinically significant gastric emptying abnormality, e.g., severe gastroparesis or gastric outlet obstruction, or chronically take drugs that directly affect GI motility. #11: Have a significant history (within the past 6 months) of or current comorbidities capable of altering the absorption of nutrients.	Additional details to ensure participants do not have prior medical history that could prevent LY2549492 absorption or impede absorption of nutrients
	Added new Nutrition Status criterion #12: Have clinical or biochemical evidence of significant nutritional deficiency that, in the investigator's judgment, poses a safety risk to the individual.	To provide detail for participant exclusion based on nutritional status
	Modified Neurological criterion #13: Removed "MMSE" from the assessments. Also, removed "The enrollment of any	To avoid duplication and potential misrepresentation of cognition by performing both MoCA and MMSE assessments.

Section # and Name	Description of Change	Brief Rationale
	participant with MoCA or MMSE scores of 17 or below will require a discussion between the investigator and sponsor medical regarding the potential eligibility.	
	Modified Hepatic criterion #24 to specify ALT or AST level >2.0x ULN.	To provide more stringent criteria for exclusion of participants based on ALT and AST levels as a measure of liver function
	Modified Hepatic criterion #26 to clarify wording about HBV infection.	Updated text for clarity around exclusion criteria for HBV infection
	Modified criterion #27 to clarify wording about HCV infection.	Updated text for clarity around exclusion criteria for HCV infection
Section 5.3.5	Renamed section title from “Diabetes Education” to “Hyperglycemia and Hypoglycemia Education”	Textual change as this section applies to all participants and not only to participants with diabetes
	Removed the terms “diabetes” and “for participants with T2D at screening” from this section	Textual change as this section applies to all participants and not only to participants with diabetes
Section 6.3 Assignment to Study Intervention		To align with study design.
	For Stratification, changed wording from “each age group	To allow flexibility around enrollment.

Section # and Name	Description of Change	Brief Rationale
	should constitute a maximum of 60%..." to "each age group should constitute approximately no more than 60%..."	
Section 6.6 Dose Modification	Removed the term "intolerable" for describing GI symptoms throughout this section.	GI symptoms are assigned severity in Section 10.3.4; "intolerable" is not a defined classification
Section 6.6.1 Management of Participants with GI Symptoms	Added reference for the GI symptom grading scale in Section 10.3.4.	Definition of GI symptoms cross referenced for clarity
	Removed "if the participant has taken the last 2 weeks of dosing" from instruction #3.	Modified so that interruption of study treatment can be carried out following dietary measures, medication, or both, as outlined in Section 6.6.1, irrespective of a need for participants to have completed 2 weeks of dosing prior to interruption
	From "Temporary dose de-escalation" subsection, removed "contact the sponsor to" regarding temporary de-escalation of study intervention.	To define the temporary de-escalation as being performed by the site investigator and not in consultation with the sponsor
Section 6.6.2 Management of Study Intervention in Participants with BMI ≤ 20 kg/m ²	For all table rows, removed "contact the sponsor" regarding dose reduction or discontinuation of study intervention.	To define the management of study intervention in participants with BMI ≤ 20 kg/m ² is performed by the site investigator and not together in consultation with the sponsor
	Removed row for "body weight	To ensure the clarity of management of participants

Section # and Name	Description of Change	Brief Rationale
	continues to decline despite a dose reduction in the previous titration step”	based on changes in body weight
Section 6.6.3 Management of Participants with Perceived Excessive Weight Loss	Removed “contact the sponsor to” regarding dose reduction.	To ensure management of participants based on changes in body weight is performed by the site investigator only
Section 6.6.4 Temporary Discontinuation	Removed, “1 to 3” regarding doses to be omitted; Added “until acute symptoms have subsided,” and removed “in consultation with the sponsor medical” regarding temporary discontinuation of study intervention.	To allow temporary discontinuation irrespective of number of doses omitted. To allow temporary discontinuation by the study investigator independent of the sponsor.
Section 7.1 Discontinuation of Study Intervention	Added conditions for discontinuation related to hypoglycemia, CKD, MACE, and HBV or HCV positivity.	To provide additional details on discontinuation based on hypoglycemia, CKD, MACE, and HBV or HCV positivity
Section 7.1.2 Cardiac Arrhythmia and QTc Stopping Criteria	Modified third bulleted criterion regarding arrhythmia to “including but not limited to atrial fibrillation.”	To widen the criteria to include other arrhythmias other than atrial fibrillation alone
Section 8.1.3.2 Mini Mental State Examination (MMSE)	Deleted this section.	To avoid duplication with MoCA assessment
Section 8.2.5 Pregnancy Testing	Modified that serum pregnancy test will be performed at screening instead of at Visit 2.	The serum pregnancy test is a definitive pregnancy test. Screening is performed up to a maximum of 5 weeks allowing inclusion of female participants into the study,

Section # and Name	Description of Change	Brief Rationale
		with an additional urine test to ensure female participants are not pregnant prior to dosing.
Section 8.2.8 Hepatic Safety Monitoring, Evaluation, and Criteria for Study Intervention Interruption or Discontinuation	Added the following from the table titled “Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)”: For “ALP $\geq$2.5x ULN” row, added an instance for “Interrupt or discontinue study intervention.” Removed the following rows from the table: • ALP $\geq$3x ULN • ALP $\geq$2.5x ULN and TBL $\geq$2x ULN • ALP $\geq$2.5x ULN with hepatic signs or symptoms	To provide more stringent criteria for intervention, interruption, or discontinuation of study intervention based on ALT, ALP, and AST levels as a measure of liver function
	Added the following from the table titled “Participants with elevated baseline (ALT, AST, or ALP $\geq$1.5x ULN)”: For “ALP $\geq$2.5x baseline” row, added an instance for “Interrupt or discontinue study intervention.” Removed the following rows from	To provide more stringent criteria for intervention, interruption or discontinuation of study intervention based on ALT, ALP, and AST levels as a measure of liver function

Section # and Name	Description of Change	Brief Rationale
	the table titled “Participants with elevated baseline (ALT, AST, or ALP $\geq 1.5\times$ ULN)”: • ALP $\geq 3\times$ baseline • ALP $\geq 2.5\times$ baseline and TBL $\geq 2\times$ ULN • ALP $\geq 2.5\times$ baseline with hepatic signs or symptoms	
Section 8.2.8.3 Study Intervention Interruption or Discontinuation	Modified table entry in column titled “Participants with normal or near normal baseline (ALT, AST, or ALP $< 1.5\times$ ULN)” from “ALP $\geq 3\times$ ULN or” to “ALP $\geq 2.5\times$ ULN” Removed the following entries: • ALP $\geq 2.5\times$ ULN and TBL $\geq 2\times$ ULN or • ALP $\geq 2.5\times$ ULN with hepatic signs or symptoms	To provide more stringent criteria for intervention, interruption, or discontinuation of study intervention based on ALT, ALP, and AST levels as a measure of liver function
	Modified table entry in column titled “Participants with elevated baseline (ALT, AST, or ALP $\geq 1.5\times$ ULN) from “ALP $\geq 3\times$ baseline or” to “ALP $\geq 2.5\times$ baseline”	To provide more stringent criteria for intervention, interruption or discontinuation of study intervention based on ALT, ALP, and AST levels as a measure of liver function

Section # and Name	Description of Change	Brief Rationale
	Removed the following entries: • ALP ≥ 2.5x baseline and TBL ≥ 2x ULN or • ALP ≥ 2.5x baseline with hepatic signs or symptoms	
Section 8.2.9 Hepatitis B Testing and Monitoring	Revised to specify exclusion and study intervention rules based on HbsAg, HbcAg, and HBV DNA testing.	To provide clarity on screening results from HBsAg and HbcAb, and the need for an HBV DNA test as per exclusion criterion #26
Section 8.2.10 Hepatitis C Testing	Revised to specify exclusion and intervention rules based on anti-HCV and HCV RNA testing.	To provide clarity on screening results for Hepatitis C testing as per exclusion criterion #27
Section 8.2.11 Malnutrition	Added clarification of guidances for discontinuing and for temporary interruption of study intervention based on nutritional status.	Additional measurements of micronutrients are being carried out as part of the modified SoA. Additional language has been added to Section 8.2.11 to provide guidance to the investigator on the course of action following suspected malnutrition in study participants.
Section 8.3.3.7 Hypoglycemia	For Level 1 hypoglycemia, added, "Participants should be advised to recheck their glucose 15 minutes after ingesting carbohydrates and to repeat carbohydrate ingestion for ongoing hypoglycemia."	To provide additional information around the treatment of Level 1 hypoglycemia

Section # and Name	Description of Change	Brief Rationale
	For Level 2 hypoglycemia, removed: “Participants should be treated with fast-acting carbohydrates.” Added: Level 2 hypoglycemia can alert a person to take action, such as treatment with fast-acting carbohydrates. Participants should be advised to recheck their glucose 15 minutes after ingesting carbohydrates and to repeat carbohydrate ingestion for ongoing hypoglycemia.”	To provide additional information around the treatment of Level 2 hypoglycemia
Section 8.3.3.8 Thyroid Malignancies and C-Cell Hyperplasia	Revised text and added a table for calcitonin measurements to assess the potential of LY3549492 to affect thyroid C-cell function.	To provide criteria and cause of action based on calcitonin results
Section 8.3.3.9 Acute Renal Events	Added, “If the investigator determines that an acute renal event has occurred, the participant may be permanently discontinued from the study intervention, and the sponsor’s designated medical monitor should be notified (Section 7.1).”	To allow the site investigator to discontinue a participant based on an acute renal event

Section # and Name	Description of Change	Brief Rationale
Section 8.3.3.10 Hypersensitivity Reactions	Removed reference to national and international guidelines. Added guidance on participant discontinuation following systemic hypersensitivity reaction related to study intervention administration.	To remove reference to guidelines that are not available and provide clarity on discontinuation criteria for hypersensitivity reactions
Section 9.4 Interim Analysis	Removed “An interim analysis may be conducted when approximately 50% to 80% of participants complete the primary outcome visit.” Added, “At least 1 interim analysis may be conducted after at least 50% of participants enter treatment to support planning activities associated with the clinical development program and to aid in the development of PK/PD models. The SAP will describe any interim analysis. At the discretion of the sponsor, the prespecified interim analysis may not be conducted.”	To allow flexibility of timing for earlier interim analysis
Section 10.2, Appendix 2: Clinical Laboratory Tests	Added pancreatic amylase and lipase to	Consistent testing of amylase and lipase is necessary for safety monitoring and

Section # and Name	Description of Change	Brief Rationale
	Clinical Laboratory Tests table.	diagnosis of acute pancreatitis
	Removed Hepatitis B surface antibody (anti-HBs)	Hepatitis B surface antibody (anti-HBs) is not a required test.
	Removed urinary albumin/creatinine ratio (UACR) from Calculations in the Clinical Laboratory Tests table.	Removed UACR to align with SoA as it is not a required procedure
Section 10.3.4 Recording and Follow-Up of AE and/or SAE and Product Complaints	Added new table of Grading Scale for Assessment of Gastrointestinal-associated Adverse Events.	To provide details of the grading scale to objectively define gastrointestinal-associated adverse events
Section 10.5 Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments	From table titled, “Tests available from Lilly-designated central laboratory”, removed, “Hepatitis B surface antibody (anti-HBs)”	Hepatitis B surface antibody (anti-HBs) is not a required test
Section 10.7, Appendix 7: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference, and Vital Signs	In Measuring height, Step 4, removed, “measured in triplicate” and added “and record to 1 decimal place.”	Clarification
Section 10.10, Appendix 10: Clinical Signs Associated with Common Nutritional Deficiencies	Added “This list of nutritional deficiencies is not exhaustive.”	Added additional language for clarity as the table in Section 10.10 does not cover all known nutrient deficiencies
Section 10.11, Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances	Changed central laboratory testing visits from Visits 1, 2, 12, 24, 48, ED and 801 to Visits 1, 2, 6, 10, 18, ED, and 801.	Corrected earlier error that used Week number instead of Visit number.

Section # and Name	Description of Change	Brief Rationale
Global	Minor corrections, e.g., typographical errors, formatting changes.	Minor; therefore, have not been summarized

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Approval	PPD Statistician 26-Jun-2025 16:04:35 GMT+0000
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