Protocol J2A-MC-GZGQ(d)

A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared With Placebo in Adult Participants With Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)

NCT05872620

Approval Date: 31-Oct-2023

Title Page

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Protocol Title:

A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared with Placebo in Adult Participants with Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)

Protocol Number: J2A-MC-GZGQ

Amendment Number: d

Compound: LY3502970

Brief Title:

Efficacy and Safety of LY3502970 Compared with Placebo in Participants with Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)

Study Phase: Phase 3

Acronym: ATTAIN-2

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND: 156143

EU trial number: 2022-502837-24-00

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

Document ID: VV-CLIN-116484

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	**Date**
Protocol Amendment c	*24-Aug-2023*
Protocol Amendment b	*12-May-2023*
Protocol Amendment a	*5-Apr-2023*
Original Protocol	*9-Feb-2023*

Amendment [d]

The amendment is considered to be substantial because it is likely to have a significant impact on the reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to address regulatory feedback and to include CCI These and other changes and a brief rationale are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 3. Objectives, Endpoints, and Estimands	• Heading changed from "Primary Estimands" to "Estimands" • Added "treatment regimen" estimand will be the primary estimand	Clarification
1.3. Schedule of Activities (SoA)	Comments updated for Fundus photography and further ophthalmological assessment (if applicable) to clarify the tolerance window, reference to Section 8.3.3.10 and footnotes removed	Clarification
	Added CCI to Visits 4, 5, 7, and 8 CCI CCI	To allow for more frequent evaluation of CCI CCI
	Removed comments about PK samples. Added reference to Section 8.4 for PK sampling details	To provide clarity
	Abbreviations updated	To maintain editorial consistency
5.2. Exclusion Criteria	Revised Criterion 17 to include cystatin-C equation for eGFR calculation	Clarification
	Removed the language in the exception note of Criterion 25 stating that participants must be anticipated to remain on the same dose of thyroid replacement therapy throughout the trial period	
	Added "intra-articular" preparations to the list of exceptions to systemic glucocorticoid therapy in Criterion 37	

	Revised Criterion 39 to include atypical antipsychotics, tricyclic antidepressants, and mood stabilizers	
5.3.1. Meals and Dietary Restrictions	Revised wording to remove "overnight" from the first sentence to read as "For certain assessments, the participants will be required to come to the site in a fasting state, before taking study intervention, after a period of approximately 8 hours without eating or drinking (except water) as specified in the SoA"	To allow flexibility
6.1. Study Intervention(s) Administered	Text revised to clarify the use of medications that may be CCI	Clarification
6.9. Prior and Concomitant Therapy	Text revised to clarify the use of medications that may be CCI	Clarification
6.9.3. Prohibited or Restricted Use Medications	CCI	Clarification
7.1.1. Liver Chemistry Stopping Criteria	Content deleted and reference to Section 8.2.7.3 included	Alignment with hepatic safety monitoring guidance update
7.1.2. Temporary Study Intervention Interruption	Text updated for study intervention interruption of 2 consecutive doses or less, 3-6 consecutive doses, and 7 or more consecutive doses	To provide clarity
8.2.7. Hepatic Safety Monitoring	Updated as per latest guidance on hepatic safety monitoring	Alignment with hepatic safety monitoring guidance update
8.4. Pharmacokinetics	Removed text on PK sampling at specific visits and included a table on PK sampling relative to study intervention dose	Clarification
9.1.1. Multiplicity Adjustment	• Modified text for additional details on the graphical approach to be used for multiplicity adjustment • Added a figure to illustrate the current graphical testing procedure	Clarification
9.2. Analyses Sets	Removed full participants and updated description for randomized participants	To follow the intent-to-treat principle
9.3.3. Primary Endpoints and Estimand Analyses	• Removed "No multiplicity adjustments is planned between estimands" • Revised text to indicate primary analysis will be using the randomized population rather than full participants population • Imputation procedure details added	• Alignment with multiplicity adjustment approach • To follow the intent-to-treat principle • To provide clarity on imputation procedure

10.4.1. Appendix 4 Definitions	In definition of WNOCBP Removed ī’ īu—(z¯’ “ (xy●w¯≥„ī≥ ”(’ z(hysterectomy Mxxyx(¯y● –ī≥”•(≥”(w’ ”z¯≥“ yx(≥”zy¯ī≥ī– (ī’ (≤u- y(u(w’ ”•y”≥īu–(u”’ “ u—(such as Müllerian agenesis f y“ ’ - yx(Q u“ „,–y●(’ z(“ yī≤’ x● include (u”x(uxxyx(Mwwy„īuv–y(● ¯•≥wu–(– sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy In definition of Postmenopausal state Changed follicle-stimulating hormone J>9(“ Ū 8‘ X(ī’ (>9(“ Ū 8‘ X In foot note a P y–yīyx(≤’ ¯“ ’ ”y●5(gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy ī≤uī(w’ –x(≥”x wy(ī¯u”●≥y”ī(u“ y”’ ¯¯≤yu (Mxxyx(≤’ ¯“ ’ ”y(¯y„–uwy“ y”ī(ī≤y¯u„ ((HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Females on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study y”¯’ —“ y”ī7	Alignment with contraception guidance update
10.4.2. Appendix 4 Contraception Guidance	Added an instruction that participants must not plan a pregnancy during the study In the Highly effective contraception (less than 1% failure rate) P y–yīyx(zy“ u–y(●ī¯y¯≥≥–uī≥ ” Mxxyx(zu—’„≥u”(ī val 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 refer to WNOCBP xyz≥”≥ī≥ ”(uv’ - y7	Alignment with updated contraception guidance

	• Vasectomy updated to read as "vasectomy (for men in clinical trials and for female partner if only sexual partner)" In effective contraception • Added a note that male and female condoms should not be used in combination	
10.8.1. Appendix 8 Excluded/Prohibited or Restricted Use Medications	• CCI • Clarification note added for medications that are used both for weight loss and hyperglycemia	Clarification
CCICCI		Clarification
CCI	Text revised to clarify the use of medications that may be CCI	Clarification
10.10. Appendix 10 Country-specific Requirements 10.10.2. Brazil	The time period that must be followed if a direct benefit is identified from enrolling a participant who has not completed 1 year since participation in another clinical study of an investigational drug or device corrected from 30 days to 90 days	Editorial correction
Throughout	Minor editorial changes have been made throughout	Minor, therefore not detailed

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1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared with Placebo in Adult Participants with Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)

Brief Title: Efficacy and Safety of LY3502970 Compared with Placebo in Participants with Obesity or Overweight and Type 2 Diabetes (ATTAIN-2)

Regulatory Agency Identifier Numbers:

IND: 156143

EU trial number: 2022-502837-24-00

Rationale:

ATTAIN-2 (Study J2A-MC-GZGQ [GZGQ]) is designed to provide evidence of safety and efficacy of LY3502970 in the patient population with obesity or overweight and Type 2 diabetes (T2D). Compared to people without diabetes, patients with T2D and obesity or overweight often respond less favorably to weight management treatments and may face unique safety issues (Wilding et al. 2021; Davies MJ et al. 2021). Therefore, it is important to conduct a dedicated Phase 3, randomized, double-blind, placebo-controlled study in participants with obesity or overweight and T2D to evaluate the safety and efficacy of novel anti-obesity medications. In addition, efficacy in terms of body weight reduction should be demonstrated over the course of at least 1 year before a product can be considered as effective for weight management (FDA 2007; EMA 2016).

ATTAIN-2 (Study GZGQ) is a Phase 3, multicenter, randomized, parallel, placebo-controlled, double-blind, 72-week study. This study will investigate the effect of once daily oral treatment with LY3502970 CCI mg, CCI mg, and CCI mg, compared with placebo, CCI CCI on body weight in individuals with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) and T2D. Additionally, the study will compare the effects of LY3502970 and placebo on glycemic control, blood pressure, lipid parameters, and overall safety profile.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that LY3502970 [redacted]mg, [redacted] mg and/or [redacted]mg is superior to placebo in change from baseline for the following: • Body weight	From baseline to Week 72, • Mean percent change in body weight
Key Secondary (controlled for type 1 error)	
To demonstrate that LY3502970 [redacted] mg is superior to placebo in change from baseline for the following: • Body weight	From baseline to Week 72, • Percentage of participants who achieve a body weight reduction of: ○ ≥5% ○ ≥10%
To demonstrate that LY3502970 [redacted]mg and/or [redacted]mg is superior to placebo in change from baseline for the following: • Body weight	From baseline to Week 72, • Percentage of participants who achieve a body weight reduction of: ○ ≥5% ○ ≥10% ○ ≥15%
To demonstrate that LY3502970 [redacted]mg, [redacted] mg, and/or [redacted]mg is superior to placebo in change from baseline for the following: • Waist circumference • Glycemic control	From baseline to Week 72, • Mean change in waist circumference (cm) • Mean change in HbA1c (%) • Mean change in fasting glucose (mg/dL) • Percentage of participants achieving HbA1c target value of <7.0% • Percentage of participants achieving HbA1c target value of ≤6.5%

To demonstrate that LY3502970 [redacted]mg, [redacted]mg and [redacted]mg pooled doses) is superior to placebo in change from baseline for the following:
• SBP
• Lipid parameters
	From baseline to Week 72,
	• Mean change in SBP (mmHg)
	• Mean percent change in fasting
	  ○ non-HDL cholesterol
	  ○ triglycerides

Additional Secondary	
To demonstrate that LY3502970 [redacted]mg, [redacted]mg, and/or [redacted]mg is superior to placebo in change from baseline for the following: • Body weight • Glycemic control • Fasting insulin	From baseline to Week 72, • Mean change in absolute body weight (kg) • Mean change in BMI (kg/m^2) • Percentage of participants achieving HbA1c target value of <5.7% • Mean percent change in fasting insulin

To demonstrate that LY3502970 ([redacted]mg, [redacted]mg and [redacted]mg pooled doses) is superior to placebo in change from baseline for the following:
• DBP
• Lipid parameters
• Patient-reported outcomes
	From baseline to Week 72,
	• Mean change in DBP (mmHg)
	• Mean percent change in fasting
	  ○ total cholesterol
	  ○ LDL-cholesterol
	  ○ HDL cholesterol
	From baseline to Week 72,
	• Mean change in SF-36v2 acute form domain scores
	• Mean change in EQ-5D-5L health state utilities and VAS
	• Mean change in IWQOL-Lite-CT Physical Function, Physical, and Psychosocial composite scores, and total score
	• Change in PGI-S and PGI-C limitations on physical function due to weight

To describe the safety of LY3502970 as compared to placebo	Frequency of treatment-emergent adverse events

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; DBP = Diastolic Blood Pressure; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL = low-density lipoprotein; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; SBP = Systolic Blood Pressure; SF-36v2 = Short Form 36 Version 2 health survey acute form; VAS = visual analog scale.

Estimands

There will be 2 estimands for the primary objectives planned in the study. The estimands address ICEs using either the treatment policy strategy or the hypothetical strategy.

Treatment regimen estimand

The "treatment regimen" estimand will be the primary estimand.

The clinical question of interest: *What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 CCI mg, CCI mg, and CCI mg and placebo, CCI CCI , in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of prohibited weight management treatments?*

Efficacy estimand

The clinical question of interest: *What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 CCI mg, CCI mg, and CCI mg and placebo, CCI CCI , in individuals who meet the eligibility criteria if they would remain on their randomly assigned treatment for 72 weeks and would not initiate prohibited weight management treatments?*

Overall Design

ATTAIN-2 (Study GZGQ) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 72 week study.

Study details include:

- Screening period: CCI weeks

CCI

Brief Summary:

The study will investigate the safety and efficacy of treatment with daily oral doses of LY3502970 (CCI mg, CCI mg, and CCI mg) compared with placebo, in participants with obesity (BMI 30 kg/m^2 or greater) or overweight (BMI 27 kg/m^2 or greater) who have T2D.

Participants may be treated with up to 3 oral antihyperglycemic medications (AHMs) (excluding dipeptidyl peptidase-4 inhibitors [DPP-4i] and glucagon-like peptide-1 receptor agonists [GLP-1

RA]) or may be treated with diet and exercise alone; regardless of type of treatment (pharmacotherapy or diet and exercise), it must be stable for at least 90 days prior to Visit 1.

The study duration will be approximately CCI weeks including screening and follow-up.

The treatment duration will be approximately 72 weeks.

The visit frequency will be CCI .

Study Population

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

- Are ≥18 years of age inclusive, or the legal age of consent in the jurisdiction in which the study is taking place at screening.
- Have a BMI ≥27.0 kg/m^2 at Visit 1.
- Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.
- Have a diagnosis of T2D according to the World Health Organization (WHO) classification or other locally applicable standards, with HbA1c ≥7% (≥53 mmol/mol) to ≤10% (86 mmol/mol) at Visit 1.
- Are on stable treatment for T2D for at least 90 days prior to Visit 1, consisting of:
  - either diet/exercise alone or
  - up to 3 oral AHMs (excluding DPP-4i or GLP-1 RA).

Number of Participants:

Approximately 1500 participants will be randomly assigned in a CCI ratio to receive daily dose of LY3502970 (CCI mg, CCI mg or CCI mg) or placebo QD.

An upper limit of 70% enrollment of females will be used to ensure a sufficiently large sample of males. In addition, an upper limit of 30% enrollment of participants treated with sulfonylurea will be used to allow sufficient enrollment of participants treated with other oral AHMs.

Intervention Groups and Duration:

This table lists the interventions used in this clinical study

Intervention Name	LY3502970	Placebo
Dosage Level(s)	CCI mg, CCI mg, CCI mg, CCI mg, CCI mg, and CCI mg CCI	CCI of LY3502970-placebo to match
Route of Administration	Oral QD	Oral QD
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized

All participants will initiate treatment with a [redacted] mg QD dose of LY3502970 or matching placebo and [redacted] ([redacted] mg, [redacted] mg or [redacted] mg) is reached as outlined in the below figure.



The maintenance dose ([redacted] mg, [redacted] mg or [redacted] mg) of LY3502970 or placebo will be continued for the remainder of the study, unless study intervention dose modification is necessary.

Duration: The study duration will be approximately [redacted] weeks including screening and follow-up.

Ethical Considerations of Benefit/Risk:

The safety and efficacy profile seen to date for LY3502970 supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 RAs, namely [redacted] These risks are monitorable, usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized AEs from LY3502970 other than those related to GLP-1 receptor agonism. GLP-1 RAs have generally been associated with reduced risk of CV events in people with T2D (Giugliano et al. 2021).

The potential risks based on the knowledge for the GLP-1 RA class are considered acceptable in the context of the potential benefits anticipated from treatment with LY3502970 in adult participants with obesity or overweight and T2D.

Data Monitoring Committee: No

1.2. Schema



1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in ATTAIN-2 (Study GZGQ). However, for those whose participation in this study is affected by exceptional circumstances, such as pandemics or natural disasters, please refer to Section 10.11 for additional guidance.

Screening

All screening activities should take place within the [redacted] week period.

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

Fasting visits

Study participants should be reminded to report for fasting visits before taking study intervention(s) in a fasting condition, after a period of approximately 8 hours without eating or drinking (except water). Study participants should not take any AHMs prior to the office visits.

- If a participant attends these visits in a nonfasting state, body weight measurement and samples for laboratory testing should not be collected and the participant should be asked to return to the site in a fasting state as soon as possible; all other procedures scheduled at the visit may be performed.
- All procedures, especially vital signs, laboratory procedures and ECGs, should be completed prior to the participant taking study intervention on the days of office visits.

Early discontinuation (ED)

Participants who are unable or unwilling to continue the study treatment period for any reason will perform an ED of treatment visit. If the participant is discontinuing during an unscheduled visit or a scheduled visit, that visit should be performed as the ED visit.

Post-treatment follow-up

All participants are required to complete a post-treatment follow-up visit (Visit 801), according to the SoA. Participants discontinuing the study early and performing an ED visit will also be asked to perform the post-treatment follow-up visit.

Telehealth visits

Telehealth visits may be by telephone or other technology. In the event a visit designated as telehealth in the SoA is preferred to be conducted as an office visit (for example, to modify study intervention dose level, AE follow-up), an exception may be granted after consultation with the sponsor-designated medical monitor.

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
Informed consent	X																							The ICF must be signed before any protocol-specific tests or procedures are performed. See Section 10.1.3 for additional details.
Inclusion and exclusion criteria, review and confirm	X	X	X																					Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.
Demographics	X																							Includes ethnicity (where permissible), year of birth, sex and race.
Preexisting conditions and medical history, including relevant surgical history	X																							Medical history includes assessment of preexisting conditions (for example, history of gallbladder disease, cardiovascular disease, and medullary thyroid carcinoma).

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
Prespecified medical history (indication and history of interest)	X																							Includes but not limited to obesity or overweight and T2D medical history.
Prior treatments for indication	X																							Includes prior weight management and AHMs.
Substance use (alcohol, caffeine, tobacco, nicotine replacement use)			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	X	
Assess medication intensity (dyslipidemia, hypertension, hyperglycemia)									X												X	X		
AEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Any events that occur after signing the informed consent are considered AEs as defined in Section 8.3.1. Additional data are

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								collected for certain AEs. See Section 8.3.3.
Physical evaluation																								
Height	X																							See Sections 8.2.1 and 10.9.
Weight	X		X	X	X	X	X	X	X			X			X			X			X	X	X	Weight measurements should be obtained per the detailed protocol guidance in Section 10.9. Body weight must be measured in the 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.
Waist circumference	X		X	X	X	X	X	X	X			X			X			X			X	X	X	See Sections 8.2.1 and 10.9.

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
Vital signs	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 participant has been sitting at least 5 min. See Sections 8.2.2 and 10.9.
Physical examination	X																				X	X		See Section 8.2.1.
Symptom-direct physical assessment			X																				X	Symptom-directed physical assessment may be conducted at the discretion of the PI or qualified personnel as indicated per local regulations based on participant status and standard of care.
12-lead ECG (Central)			X						X						X						X	X	X	Collect CCI ECGs before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. ECG measurements

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						[redacted] wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								should be obtained after at least 5 minutes of rest per the instructions in Section 8.2.3.
Fundus photography and further ophthalmological assessment (if applicable)		X							X												X	X		Week CCI Follow-up fundus photography and additional ophthalmological evaluation will be performed only if retinopathy or DME was present at baseline. Week CCI or within CCI prior to this week: follow-up fundus photography and additional ophthalmological evaluation will be performed for all participants. Repeat at ED visit: if more than CCI weeks

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								have passed since the last examination. See Sections 8.2.9
Participant diary (electronic)																								
Dispense diary (electronic device)		X																						Includes daily study intervention dose, hypoglycemia, weekly FBG from SMBG, and 7-point SMBG. All training should be repeated as needed to encourage participant compliance.
Diary review (electronic)			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	Diary review to include SMBG data, daily dosing, and hypoglycemic events.
Remind participants about 7-point SMBG		X						X												X				Participant is required to collect two 7-point SMBGs on non-consecutive days within 2 weeks prior to the next visit. A 7-point SMBG consists of measurements before

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
	CCI																						
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								and 2 hr after each of 3 main meals within the same day and at bedtime.
Review 7-point SMBG			X						X												X			
Diary return (electronic)																							X	
Patient-reported outcomes (electronic) PROs should be administered as early as possible in the visit but after the assessment of AEs The PROs will be administered if an approved and translated version is available for use.																								
SF-36v2 acute form			X						X												X	X		
EQ-5D-5L			X						X												X	X		
PGIS-Physical Function Weight			X						X												X	X		
PGIC-Physical Function Weight									X												X	X		
IWQOL-Lite CT			X						X												X	X		

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
PHQ-9	X		X			X			X			X			X			X			X	X	X	PHQ-9 is self-administered and should be completed after assessment of AEs. This should be conducted with the safety assessments.
Clinician-administered assessments (paper)																								
C-SSRS screening/ baseline	X																							The C-SSRS should be administered after assessment of AEs. 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.
C-SSRS since last assessed			X	X	X	X	X	X	X			X			X			X			X	X	X	The C-SSRS should be administered after assessment of AEs. For this study, the C-SSRS is adapted for the assessment of the

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
			CCI																				
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						[redacted] wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.
Participant education																								
Diabetes education (includes BG meter dispensing and SMBG training)		X																						See Section 5.3.4.
Lifestyle program instructions			X	X	X	X			X			X			X			X			X	X		The lifestyle program instruction may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window. Beginning at Week [redacted] the consultation may be delivered by telehealth. See Section 5.3.

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																				Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
Review diet and physical activity goals			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			All training should be repeated as needed to ensure participant compliance. Study personnel to provide reinforcement and encouragement for lifestyle modifications.
Dispense BG meter/supplies as needed		X	X	X	X	X	X	X	X			X			X			X			X	X		
Laboratory tests and sample collection																								
Hematology	X					X			X												X	X	X	
HbA1c	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	Clinical chemistry labs must be obtained in the 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 labs taken.

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						[redacted] wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								CCI
Lipid panel			X						X												X	X	X	Lipid panels must be obtained in the 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 lipid panels taken.
hsCRP			X						X												X	X	X	
Serum pregnancy	X																							Collect for WOCBP. See Section 10.4.
Urine pregnancy (local)			X			X			X			X			X			X			X	X		The result at Visit 3 must be available before the first dose of study

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
																								intervention for WOCBP. Perform additional pregnancy tests if a menstrual period is missed, if there is clinical suspicion of pregnancy, or as required by local law or regulation. If the urine pregnancy test is inconclusive at any visit, collect an additional serum pregnancy test.
FSH	X																							Perform as needed to confirm postmenopausal status. Definition in Section 10.4.
TSH	X																							
Insulin			X						X												X	X	X	
C-peptide			X						X												X	X	X	
Calcitonin	X					X			X												X	X	X	

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																			Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
Pancreatic amylase	X					X			X												X	X	X	
Lipase	X					X			X												X	X	X	
Free fatty acids			X						X												X	X	X	
ApoB			X						X												X	X	X	
Cystatin-C	X		X			X			X			X			X			X			X	X	X	
Hepatitis C screening	X																							Confirmation by HCV RNA will be performed if positive for HCV antibody.
Hepatitis B screening	X																							Confirmation by HBV DNA will be performed if positive for HBcAb.
PK samples					X		X		X			X			X							X		See Section 8.4 for PK sampling details
eGFR	X		X			X			X			X			X			X			X	X	X	Calculated using CKD-EPI method. See Section 10.2.
UACR			X						X												X	X	X	

ATTAIN-2 (Study GZGQ)	Screening period		Treatment period																				Post Tx follow-up period	Comments
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED	801	
Weeks from randomization	CCI																						wk post end of TxP	
Visit interval tolerance (days)		CCI																					CCI	
Fasting visit	X		X	X	X	X	X	X	X			X			X			X			X	X	X	
Visit details										T	T		T	T		T	T		T	T				T = telehealth visit
Stored samples																								
Genetics sample			X																					Sample can be obtained at or after the specified visit.
Exploratory biomarker samples			X			X			X						X						X	X	X	
Randomization and Dosing																								
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Randomization via IWRS			X																					
Dispense study intervention via IWRS			X	X	X	X	X	X	X			X			X			X						
Dispense study intervention to participant			X	X	X	X	X	X	X			X			X			X						
Participant returns study intervention				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	X	X		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AHMs = antihyperglycemic medications; ApoB = Apolipoprotein B; AST = aspartate aminotransferase; BG = blood glucose; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; C-SSRS= Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; FSH = Follicle Stimulating Hormone; HbA1c= hemoglobin A1c; HBcAb= hepatitis B core antibody; HBV= hepatitis B virus; HCV= hepatitis C virus; hsCRP = High sensitivity C-Reactive Protein; ICF = informed consent form; IWRS = interactive web response system; IWQOL-Lite CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; PHQ-9 = Patient Health Questionnaire-9; PI = principal investigator; PK = pharmacokinetic; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO = patient-reported outcome; SF-36v2 = Short Form-36 version 2 Health Survey Acute Form; SMBG = self-monitoring of blood glucose; T2D = Type 2 diabetes mellitus; TSH = Thyroid Stimulating Hormone; Tx = treatment; TxP = treatment period; UACR = urinary albumin/creatinine ratio; ULN = upper limit of normal; WOCBP = Women of childbearing potential; wk = week.

2. Introduction

GLP-1 receptor agonism is an established therapeutic mechanism for weight management in individuals with obesity or overweight, as well as glycemic control in participants with T2D. Unlike injectable or orally available peptide GLP-1 receptor agonists approved by regulatory authorities to date, LY3502970 is an oral, non-peptide GLP-1 receptor agonist.

LY3502970 is being developed as a daily oral CCI CCI for the treatment of obesity or overweight and T2D.

2.1. Study Rationale

ATTAIN-2 (Study J2A-MC-GZGQ [GZGQ]) is designed to provide evidence of safety and efficacy of LY3502970 in the patient population with obesity or overweight and T2D. Compared to people without diabetes, patients with T2D and obesity or overweight often respond less favorably to weight management treatments and may face unique safety issues (Wilding et al. 2021; Davies et al. 2021). Therefore, it is important to conduct a dedicated Phase 3, randomized, double-blind, placebo-controlled study in participants with obesity or overweight and T2D to evaluate the safety and efficacy of novel anti-obesity medications. In addition, efficacy in terms of body weight reduction should be demonstrated over the course of at least 1 year before a product can be considered as effective for weight management (FDA 2007; EMA 2016).

ATTAIN-2 (Study GZGQ) is a Phase 3, multicenter, randomized, parallel, placebo-controlled, double-blind, 72-week study. This study will investigate the effect of once daily oral treatment with LY3502970 CCI mg, CCI mg, and CCI mg, compared with placebo, CCI CCI , on body weight in individuals with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) and T2D. Additionally, the study will compare the effects of LY3502970 and placebo on glycemic control, blood pressure, lipid parameters, and overall safety profile.

2.2. Background

Obesity or overweight and type 2 diabetes

Obesity is a chronic disease whose increasing prevalence is a public health concern associated with rising incidence of T2D, increased risk for premature death, and increased risk for some cancers (AMA 2013; CSAPH 2013; Lauby-Secretan et al. 2016; Aberle et al. 2021).

For patients with obesity or overweight and who have T2D, efforts targeting weight loss, including lifestyle, medication, and surgical interventions, are recommended (Davies et al. 2018). There is strong and consistent evidence that obesity management is beneficial in the treatment of T2D and weight-related comorbidities (ADA-EASD 2022). Lifestyle changes that result in modest and sustained weight loss produce clinically meaningful reductions in BG, HbA1c, and triglycerides. Greater weight loss produces even greater metabolic benefits, including reductions in blood pressure, improvements in low-density lipoprotein and high-density lipoprotein cholesterol, and reductions in the need for medications to control BG, blood pressure, and lipids, and may even result in achievement of glycemic goals in the absence of glucose-lowering agent use in some patients (UKPDS Group 1990; Pastors et al. 2002; Wing et al. 2011; Rothberg et al. 2017; ADA 2023).

Bariatric surgery is considered as the most potent clinical intervention for weight management, which can also be used in patients with T2D. However, bariatric surgery has risks, including periprocedural complications. For some individuals with obesity or overweight, pharmacological management may be a preferred option.

With the advent of injectable incretin-based therapies, highly efficacious medications, with acceptable safety profile, are increasingly available for people with obesity and T2D (SAXENDA® package insert, 2022; WEGOVY® package insert, 2021). However, there remains a gap in oral formulations of incretin-based therapies for obesity or overweight. Oral formulations would allow for further tailoring of therapy to meet individual patient preferences and needs.

To expand treatment options for people living with obesity or overweight, Lilly is developing LY3502970, an oral non peptide GLP-1 RA that has been shown in Phase 2 studies to reduce body weight in participants with obesity or overweight with and without T2D. Additionally, it improved glycemic control in individuals with T2D.

Epidemiology studies

Overweight and obesity affect almost 60% of adults in the WHO European Region (WHO, 2022). T2D is most strongly associated with obesity. In the majority of European countries, overweight and obesity are responsible for about 80% of cases of T2D (Frühbeck et al. 2013).

Epidemiological studies have shown that 30% to 53% of incident T2D cases in the US are associated with overweight or obesity (Cameron et al. 2021). For the time period 2015–2018, 89.9% of US adults 18 years or older diagnosed with diabetes were also considered to have overweight or obesity (CDC 2022).

The ongoing global obesity epidemic is associated with increases in the incidence of T2D and other comorbidities, including hyperlipidemia and hypertension, resulting in further adverse outcomes in individuals with these conditions. Effective therapies for chronic weight management in people with obesity and T2D, in addition to body weight reduction, may have a potential to improve treatment of T2D, slow its progression, and reduce the risk of chronic complications.

Clinical data for LY3502970

A detailed description of the chemistry, pharmacology, efficacy, and safety of LY3502970 is provided in the IB.

Phase 1

The clinical pharmacology, PK, and PD of LY3502970 were initially studied in 2 completed Phase 1 studies, J2A-MC-GZGA (GZGA) in healthy volunteers and J2A-MC-GZGC (GZGC) in participants with T2D. Results from these studies demonstrated a PK profile appropriate for once daily oral dosing that can be administered without limitations pertaining to food or water intake or time of day. The PK of LY3502970 plasma concentration increase was approximately proportional to the increase of dose across the CCI mg QD to CCI mg QD dose range. Consistent with the GLP-1 RA class, CCI CCI PD results from Study GZGC showed clinically relevant improvements in HbA1c of up to CCI and weight reduction of up to CCI kg after CCI weeks of treatment with LY3502970 CCI mg QD to CCI mg QD in people with T2D.

Phase 2

Two Phase 2 studies have evaluated the safety and efficacy of LY3502970: Study J2A-MC-GZGE (GZGE) in participants with T2D and Study J2A-MC-GZGI (GZGI) in participants with obesity or overweight and at least 1 weight-related comorbidity.

In Study GZGE, LY3502970 treatment for CCI weeks at maintenance doses of CCI mg to CCI mg QD resulted in mean changes from baseline in HbA1c up to CCI (treatment difference of CCI vs placebo) and mean weight change of up to CCI (treatment difference of CCI vs placebo). In people with obesity or overweight (Study GZGI), mean percent weight change of up to CCI from baseline (treatment difference of CCI compared to placebo) was observed with LY3502970 treatment at the primary CCI-week endpoint. The overall safety profile of LY3502970 in both studies was consistent with that established for the GLP-1 RA class, CCI CCI. Data from these Phase 2 studies support the further clinical development of LY3502970.

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of LY3502970 may be found in the IB.

2.3.1. Risk Assessment

Study intervention

The potential risks associated with LY3502970 are similar to those of marketed GLP-1 Ras. The most commonly reported TEAEs observed in the LY3502970 clinical studies, in healthy participants or participants with obesity or T2D are CCI CCI CCI

Rapid improvements in glucose control have been associated with temporary worsening of diabetic retinopathy and is thus another potential risk associated with the study.

Refer to Section 6.2 of the IB for detailed description of potential risks for LY3502970.

Management of risks

Sections 5.1, 5.2, and 8.2 address known potential risks associated with LY3502970.

Study Procedure for Retinopathy assessment

Dilating drops if used for pupil dilation for the eye examination may sting temporarily, and may cause temporary blurred vision, difficulty focusing, and light sensitivity. Pharmacologic dilatation may be contraindicated in some participants with eye conditions, for example, closed angle glaucoma.

2.3.2. Benefit Assessment

The known pharmacology of GLP-1 receptor agonism and Phase 2 studies of LY3502970 support an expectation of such benefits as body weight reduction and improved glycemic control

with LY3502970. Improvements in some cardiometabolic risk factors, including blood pressure and serum lipids, may also be expected.

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

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for LY3502970 supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 RAs, namely CCI . These risks are monitorable, usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized AEs from LY3502970 other than those related to GLP-1 receptor agonism. GLP-1 RAs have generally been associated with reduced risk of CV events in people with T2D (Giugliano et al. 2021).

The potential risks based on the knowledge for the GLP-1 RA class are considered acceptable in the context of the potential benefits anticipated from treatment with LY3502970 in adult participants with obesity or overweight and T2D.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that LY3502970 [redacted] mg, [redacted] mg and/or [redacted] mg is superior to placebo in change from baseline for the following: • Body weight	From baseline to Week 72, • Mean percent change in body weight
Key Secondary (controlled for type 1 error)	
To demonstrate that LY3502970 [redacted] mg is superior to placebo in change from baseline for the following: • Body weight	From baseline to Week 72, • Percentage of participants who achieve a body weight reduction of: ○ ≥5% ○ ≥10%
To demonstrate that LY3502970 [redacted] mg and/or [redacted] mg is superior to placebo in change from baseline for the following: • Body weight	From baseline to Week 72, • Percentage of participants who achieve a body weight reduction of: ○ ≥5% ○ ≥10% ○ ≥15%
To demonstrate that LY3502970 [redacted] mg, [redacted] mg, and/or [redacted] mg is superior to placebo in change from baseline for the following: • Waist circumference • Glycemic control	From baseline to Week 72, • Mean change in waist circumference (cm) • Mean change in HbA1c (%) • Mean change in fasting glucose (mg/dL) • Percentage of participants achieving HbA1c target value of <7.0% • Percentage of participants achieving HbA1c target value of ≤6.5%

To demonstrate that LY3502970 ([redacted] mg, [redacted] mg and [redacted] mg pooled doses) is superior to placebo in change from baseline for the following:
• SBP
• Lipid parameters
	From baseline to Week 72,
	• Mean change in SBP (mmHg)
	• Mean percent change in fasting
	  ○ non-HDL cholesterol
	  ○ triglycerides

Additional Secondary	
To demonstrate that LY3502970 [redacted] mg, [redacted] mg, and/or [redacted] mg is superior to placebo in change from baseline for the following: • Body weight • Glycemic control • Fasting insulin	From baseline to Week 72, • Mean change in absolute body weight (kg) • Mean change in BMI (kg/m^2) • Percentage of participants achieving HbA1c target value of <5.7% • Mean percent change in fasting insulin

To demonstrate that LY3502970 ([redacted] mg, [redacted] mg and [redacted] mg pooled doses) is superior to placebo in change from baseline for the following:
• DBP
• Lipid parameters
• Patient-reported outcomes
	From baseline to Week 72,
	• Mean change in DBP (mmHg)
	• Mean percent change in fasting
	  ○ total cholesterol
	  ○ LDL-cholesterol
	  ○ HDL cholesterol
	From baseline to Week 72,
	• Mean change in SF-36v2 acute form domain scores
	• Mean change in EQ-5D-5L health state utilities and VAS
	• Mean change in IWQOL-Lite-CT Physical Function, Physical, and Psychosocial composite scores, and total score
	• Change in PGIS and PGIC limitations on physical function due to weight

To describe the safety of LY3502970 as compared to placebo	Frequency of treatment-emergent adverse events
Tertiary	
To characterize the population PK of LY3502970 and explore the relationships between LY3502970 concentration and efficacy, safety, and tolerability measures	Population PK and PD parameters

Abbreviations: BMI = body mass index; HbA1c = hemoglobin A1c; DBP = diastolic blood pressure; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials; LDL = low-density lipoprotein; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PD = pharmacodynamics; PK = pharmacokinetics; SBP = systolic blood pressure; SF-36v2 = Short Form 36 Version 2 health survey acute form; VAS = visual analog scale.

Estimands

There will be 2 estimands for the primary objectives planned in the study. The estimands address ICEs using either the treatment policy strategy or the hypothetical strategy.

Treatment policy strategy

The occurrence of the ICE is considered irrelevant in defining the treatment effect of interest; the values for the variable of interest are used regardless of whether the ICE occurs.

Hypothetical strategy

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

Treatment regimen estimand

The "treatment regimen" estimand will be the primary estimand.

The clinical question of interest: *What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 [redacted]mg, [redacted]mg, and [redacted]mg and placebo, [redacted], in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of prohibited weight management treatments?*

The "treatment regimen" estimand is described by the following attributes:

- ***Population:*** Individuals who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- ***Endpoints:*** Percent change from baseline in body weight at 72 weeks.
- ***Treatment condition:*** The randomized treatment with allowance for potential dose interruptions and modifications, regardless of adherence to study intervention or initiation of prohibited weight management treatments.
- ***Intercurrent events:*** No ICEs are defined since treatment adherence and the initiation of prohibited weight management treatments are a part of the treatment condition.

- ***Population-level summary and treatment effect of interest:*** Difference in mean percent changes from baseline in body weight at 72 weeks between LY3502970 and placebo.
- ***Rationale for the estimand:*** The estimand aims to evaluate the efficacy of LY3502970 that reflects the real-life behavior of the target population.

Efficacy estimand

The clinical question of interest: *What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 CCI mg, CCI mg, and CCI mg and placebo, CCI CCI in individuals who meet the eligibility criteria if they would remain on their randomly assigned treatment for 72 weeks and would not initiate prohibited weight management treatments?*

The ”efficacy” estimand is described by the following attributes:

- ***Population:*** Individuals who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- ***Endpoints:*** Percent change in body weight from baseline at 72 weeks.
- ***Treatment condition:*** The randomized treatment with allowance for potential dose interruptions and modifications.
- ***Intercurrent events:*** ICEs include permanent discontinuation of study intervention and initiation of prohibited weight management treatments, which is handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned study intervention for 72 weeks and would not initiate prohibited weight management treatments. Dose modification and interruption will not be considered an ICE since they are part of the treatment condition.
- ***Population-level summary and treatment effect of interest:*** Difference in mean percent changes in body weight from baseline at 72 weeks.
- ***Rationale for the estimand:*** This estimand aims to evaluate the efficacy of LY3502970 under the ideal condition that all participants would adhere to the randomly assigned study intervention without being confounded by the initiation of prohibited weight management treatments.

4. Study Design

4.1. Overall Design

ATTAIN-2 (Study GZGQ) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 72-week study. The study will investigate the safety and efficacy of treatment with daily oral doses of LY3502970 (CCImg, CCI mg, and CCI mg) compared with placebo, in participants with obesity (BMI 30 kg/m^2 or greater) or overweight (BMI 27 kg/m^2 or greater) who have T2D .

Participants may be treated with up to 3 oral AHMs (excluding DPP-4i and GLP-1 RA) or may be treated with diet and exercise alone; regardless of type of treatment (pharmacotherapy or diet and exercise), it must be stable for at least 90 days prior to Visit 1.

Study participants will be randomly assigned in a CCI ratio to receive daily dose of LY3502970 CCImg, CCI mg or CCI mg) or placebo QD. An upper limit of 70% enrollment of females will be used to ensure a sufficiently large sample of males. In addition, an upper limit of 30% enrollment of participants treated with sulfonylurea will be used to allow sufficient enrollment of participants treated with other oral AHMs.

- Screening period: CCI weeks

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See the SoA (Section 1.3) for visit details.

4.2. Scientific Rationale for Study Design

LY3502970 is a chemically synthesized, oral GLP-1 RA. LY3502970 has demonstrated efficacy for weight reduction in pre-clinical and Phase 2 studies. LY3502970 also shows agonist activity for human GLP-1 receptor based on in vitro cellular potency and selectivity data and shows in vivo efficacy in glucose tolerance tests in nondiabetic monkeys, humanized GLP-1 receptor mice, and in clinical studies including participants with T2D.

Choice of primary endpoint

ATTAIN-2 (Study GZGQ) is designed to determine the comparative benefits and risks of LY3502970 CCImg, CCI mg, and CCI mg QD versus placebo in participants with obesity or overweight who have T2D. A double-blind design was selected to minimize participant and investigator bias in assessments for efficacy, safety, and study intervention tolerability.

Choice of comparator

A placebo comparator was selected for this trial in accordance with regulatory guidance (FDA 2007; EMA 2016). In addition, all participants, regardless of treatment assignment, will receive lifestyle modification counseling according to local standard and diabetes education consistent with guidelines for T2D management (ADA-EASD 2022). Specifically, participants will consult with a dietician, or equivalent qualified delegate, throughout the study to focus on CCI CCI .

Study duration

The planned duration of treatment for the primary endpoint at 72 weeks allows for at least a [redacted]-week treatment period at the randomly assigned dose ([redacted]mg, [redacted]mg or [redacted]mg). This duration is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of LY3502970 compared with placebo on body weight and is consistent with regulatory guidelines (FDA 2007; EMA 2016).

The effects of study intervention cessation will be assessed in the [redacted] post-treatment follow-up period.

Concomitant medications

To minimize the potential confounding effect of changes to 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 intervention (See Sections 6.9 and 10.8).

Collection of race and ethnicity data

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

4.3. Justification for Dose

The LY3502970 doses of [redacted]mg, [redacted]mg and [redacted]mg QD administered orally will be evaluated in this study.

These doses were selected for the chronic weight management program based on assessment of safety, efficacy (weight reduction and glycemic control), and GI tolerability data from Phase 1 and Phase 2 clinical studies. [redacted] for a minimum of [redacted] weeks for the study's primary outcome.

[redacted] Based upon observed body weight reductions following the [redacted] weeks at [redacted] mg and related exposure-response modeling, this dose was selected as the minimally efficacious dose to be assessed in the Phase 3 CWM program.

The [redacted] mg dose was selected as an intermediate dose in this study based upon the placebo-adjusted observed body weight change of [redacted] noted in Study GZGI. Further, in the separate Phase 2 Study GZGE (participants with T2D), LY3502970 maintenance doses of [redacted] resulted in greater placebo-adjusted mean reduction from baseline in HbA1c [redacted] than was observed with the [redacted] mg maintenance dose in this study [redacted]

The [redacted] mg dose was selected as the highest dose based upon the greater placebo-adjusted observed body weight change in Study GZGI of [redacted] compared to the [redacted] mg dose. In Study GZGE, the placebo-adjusted HbA1c reduction for [redacted] mg [redacted]

CCI was also greater than for the CCI mg dose. At the higher maintenance dose of CCI mg, there was no clinically meaningful improvement in weight reduction or HbA1c reduction beyond that observed at CCI mg.

In summary, LY3502970 doses of CCI mg, CCI mg, and CCI mg QD are anticipated to span a dose range producing increasing magnitudes of clinically relevant weight reduction in individuals with obesity or overweight, potentially providing multiple treatment options tailored to individual weight reduction goals and tolerability. Additionally, these doses are anticipated to provide clinically relevant improvements in glycemic control for patients with comorbid T2D.

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4.4. End of Study Definition

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

5. Study Population

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

5.1. Inclusion Criteria

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

Age

1. Participants must be 18 years of age inclusive, or the legal age of consent in the jurisdiction in which the study is taking place at screening.

Type of participant and disease characteristics

2. Tu- y(Na U(; C79(–• 8‘2 at Visit 1.
3. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.
4. Have a diagnosis of T2D according to the WHO classification or other locally applicable standards, with HbA1c 7% 1 A<(“ “ ’ 8‘ ’ 2i’ : 9. (lDB(“ “ ’ 8‘ ’ 2 at Visit 1.
5. Are on stable treatment for T2D for at least 90 days prior to Visit 1, consisting of:

   either diet/exercise alone, or
   up to 3 oral AHMs (excluding DPP-4i or GLP-1 RA).

Sex and contraceptive/barrier requirements

6. Males and females may participate in this trial. Female participants must not be pregnant, intending to be pregnant, breastfeeding, or intending to breastfeed.

   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 for WOCBP, see Section 10.4.

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

Study procedures

7. Are reliable and willing to make themselves available for the duration of the study and are willing and able to follow study procedures for the duration of the study.

Informed consent

8. 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 applies:

Medical conditions

Diabetes related

9. Have T1D, history of ketoacidosis or hyperosmolar state/coma, or any other types of diabetes except T2D.
10. Have had 1 or more episode of severe hypoglycemia and/or 1 or more episode of hypoglycemia unawareness within the 180 days prior to Visit 1.
11. Are currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema (for example, laser photocoagulation or intravitreal injections of anti-vascular endothelial growth factor inhibitors).
    Note: All participants will have a baseline fundus photography assessment. In the presence of any degree of diabetic retinopathy and/or macular edema, further ophthalmologic assessment will be performed to confirm eligibility.
12. Have at least 2 confirmed fasting SMBG values >270 mg/dL (15.0 mmol/L) (on 2 separate days) prior to randomization at Visit 3.

Obesity related

13. Have a self-reported change in body weight >5 kg (11 pounds) within 90 days prior to Visit 1.
14. Have a prior or planned surgical treatment or procedure for obesity.
    Note: The following are allowed if performed >1 year before Visit 1:
    Liposuction
    Abdominoplasty
    Cryolipolysis.
15. Have a prior or planned endoscopic (for example, mucosal ablation or gastric artery embolization) and/or device-based (for example, lap band, intragastric balloon, or duodenal-jejunal endoluminal liner) therapy for obesity.
    Note: Prior device-based therapy is acceptable if device removal was more than 180 days prior to Visit 1.
16. Have obesity induced by other endocrinologic disorders, for example, Cushing syndrome, or diagnosed monogenetic or syndromic forms of obesity, for example, Melanocortin 4 Receptor deficiency or Prader Willi Syndrome.

Renal

17. Have an eGFR <15 mL/min/1.73 m^2, calculated by Chronic Kidney Disease-Epidemiology cystatin-C equation, as determined by central laboratory at Visit 1 or a level of eGFR that would contraindicate the use of the „u¯ī≥w≥„u”ī ●concurrent oral AHM per the label in the respective country.

Gastrointestinal

18. Have a known clinically significant gastric emptying abnormality, for example, severe diabetic gastroparesis or gastric outlet obstruction), or chronically take drugs that directly affect GI motility.

Autoimmune

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

Cardiovascular

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    Acute “ ’ wu¯x≥u–(≥”zu¯wī≥ ” (
    Cerebrovascular accident (stroke)
    Coronary Artery Revascularization
    Unstable u”•≥”u5(’ ¯ (
    Hospitalization due to congestive heart failure.

21. Have New York Heart Association functional classification IV congestive heart failure.

Hepatic

22. Have acute or chronic hepatitis including a history of autoimmune hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of ī≤y(z’ —’ ≥”• 5(u●(xyīy¯“ ≥”yx(v (ī≤y(wy”ī¯u–(–uv’ ¯uī’ ¯ (uī(j ≥●≥ī(: F(

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    Hepatitis B infection, defined as
    - positive HBcAb and positive HBV DNA or
    - positive hepatitis B surface antigen

    Positive Hepatitis C antibody and positive HCV RNA.

    Note: Participants with nonalcoholic fatty liver disease are eligible to participate in this trial if their ALT level is <3.0X the ULN for the reference range.

Endocrine

23. Have family (first-degree relative) or personal history of MTC or MEN2 syndrome.

24. Have a calcitonin level determined by central laboratory uī(j ≥●≥ī(: (’ z(

    ; 9(”• 8X5(≥(yS Rf (B9(“ X8‘ ≥”8 7C<(“², or
    <A(”• 8X5(≥(yS Rf (HB9(“ X8‘ ≥”8 7C<(“ ².

25. Have thyroid stimulating hormone levels outside the normal reference range for the central laboratory at Visit 1.

    Participants with hypothyroidism who are clinically euthyroid and on stable thyroid replacement therapy for at least 60 days prior to Visit 1 are acceptable exceptions to this criterion.

Malignancy

26. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy for less than 5 years.

    Exceptions: basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ or Grade 1 (for example, Gleason 6 or lower) prostate cancer.

Hematologic

27. Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anemias, sickle cell disease).

Psychobehavioral

28. Have a history of active or unstable major depressive disorder or other severe psychiatric disorder, such as schizophrenia, bipolar disorder, or other serious mood or anxiety disorder, within the last 2 years

    OR

    Ư(ī≤y(≥’- y●≥ uī’ ¯ ●(’ „≥”≥on, have any significant mental health disorder that may put the individual at higher risk of study participation.

    Note: Ư(ī≤y(≥’- y●≥ uī’ ¯ ●(’ „≥”≥ ”5(≥’x≥ ≥x u→●(≤’ ●y(x≥●yu●y(●ūuīy(≥●(w’ ”●≥xy¯yx(●ūuv→y(for the past 2 years and expected to remain stable throughout the course of the study may be considered for inclusion if they do not meet exclusion criterion #39 regarding weight gain-promoting concomitant medications.

29. Have a PHQ-9 score of 15 or more at Visit 1 or Visit 3.

30. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide

31. Tu- y(u”● y¯yx(y● (ī’ (y≥ī≤y¯(e y●≥ ”(>(’ ¯(e y●≥ ”(A(’ ”(ī≤y(g ≥w≥xu→(Ux yuī≥ ” (portion of the C-SSRS **and** the ideation occurred within the past month prior to Visit 1 or Visit 3

    OR

Have answered "yes" to any of the suicide-related behaviors on the "Suicidal Behavior" portion of the C-SSRS, **and** the behavior occurred within the past month prior to Visit 1 or Visit 3.

General

32. Have any condition, unwillingness, or inability, not covered by any of the other exclusion criteria, which in the investigator's opinion, might jeopardize the participant's safety (for example, hypersensitivity or contraindication) or compliance with the protocol (for example, recreational drug use or alcohol abuse).
33. At the time of screening have a planned surgery (except for minor surgical procedures) to occur during the course of the study.
34. Had chronic or acute pancreatitis any time prior to Visit 1.
35. Have had a transplanted organ or awaiting an organ transplant.
    Exception: corneal transplants (keratoplasty).

Prior/concomitant therapy

36. Have taken any prohibited glucose-lowering medications (see Section 10.8.1.1) within 90 days of Visit 1, or have a history of insulin therapy within 90 days prior to Visit 1, except for the use of insulin for treatment of gestational diabetes or acute, temporary use of insulin (≤14 days), for example, for acute illness, hospitalization, elective surgery.
37. Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, inhaled preparations or intra-articular) or have received such therapy within 90 days prior to Visit 1, or between Visits 1 and 3.
38. Have used any weight loss drugs or alternative remedies, including herbal or nutritional supplements, within 180 days prior to Visit 1, or between Visit 1 and Visit 3 (See Section 10.8 for more details).
39. Have initiated treatment with, or changed dose of, medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotics, and mood stabilizers (See Section 10.8 for more details), within 12 months prior to Visit 1.
40. Have started implantable or injectable contraceptives within 18 months prior to Visit 1.
    Note: Intrauterine devices are acceptable.
41. 

42. Have known allergies or intolerance to GLP-1 RA.

Prior/concurrent clinical study experience

43. Have previously completed or withdrawn from this study or any other study investigating LY3502970 after receiving at least 1 dose of study intervention.
44. 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.
45. Have participated in a clinical study and received treatment, whether active or placebo within 90 days prior to Visit 1.

Other exclusions

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

5.3. Lifestyle Considerations

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

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5.3.1. Meals and Dietary Restrictions

For certain assessments, the participants will be required to come to the site in a fasting state, before taking study intervention, after a period of approximately 8 hours without eating or drinking (except water) as specified in the SoA.

LY3502970 is a CCI substrate. Participants should refrain from CCI while participating in the study due to the effect on CCI

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At Visit 3 and subsequent visits study participants will receive individualized counseling regarding CCI with the goal of achieving weight reduction. The counseling will be performed by a dietitian or nutritionist, or equivalent qualified designee, according to local standard. The focus of the counseling should facilitate CCI

CCI It should include instruction on CCI

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CCI Consider the following principles in counseling sessions:

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5.3.2. Monitoring Nutritional Needs

Similar to other GLP-1 RAs, LY3502970 acts, in part, by reducing appetite leading to a reduction in food intake. There is potential that a small portion of participants will have significantly reduced caloric intake.

Medical staff should consider clinical monitoring of the participant's nutritional and hydration status if there is report of significantly reduced caloric intake (for example, below 800-1200 kcal). By recognizing early signs of poor intake and dehydration, preventive actions can be taken to reduce the risk of potential complications.

5.3.3. Healthy Physical Activity

At Visit 3 and all subsequent visits, participants will be advised regarding achieving a healthy physical activity level (at least 150 minutes per week, as tolerated).

Counseling in lifestyle modification should be completed according to the SoA and must be documented in the participant's medical record.

Adherence to the CCI will be assessed at each study visit.

To encourage adherence to lifestyle modification, it is recommended that a 3-day CCI CCI log be completed prior to each counseling visit.

5.3.3.1. Activity Before Blood Collections

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

5.3.4. Diabetes Education

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

All participants will be provided with glucometers and related testing supplies for use during the study. Participants will record fasting SMBG values weekly in eDiary. It is recommended that participants measure their fasting glucose on the same day each week. All trainings should be repeated as needed to ensure participant compliance.

Refer to Sections 6.9.1.3 and 8.3.3.5 for management of severe, persistent hyperglycemia and hypoglycemia.

5.3.5. Blood Donation

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

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 CONSORT 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) will not be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

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

6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3502970	Placebo
Dosage Level(s)	CCI mg, CCI mg, CCI mg, CCI mg, CCI mg, and CCI mg CCI	CCI of LY3502970 placebo to match
Route of Administration	Oral QD	Oral QD
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized

Abbreviation: QD = once daily

All participants will initiate treatment with a CCI mg QD dose of LY3502970 or matching placebo and CCI the randomized maintenance dose (CCI mg, CCI mg or CCI mg) CCI as outlined in the below figure.



The maintenance dose (CCI mg, CCI mg or CCI mg) of LY3502970 or placebo will be continued for the remainder of the study. In participants who experience intolerable GI symptoms, the dose can be modified as described in Section 6.6.

Study intervention is administered orally once daily. In general, there are no restrictions on the time of day each dose is taken, but it is recommended to take the dose at approximately the same time each day. For dosing related to PK visits, refer to Sections 1.3 and 8.4. CCI [redacted]

Participants should administer their first dose of study intervention at the end of Visit 3 prior to leaving the study site, after other study procedures and randomization are completed.

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 intervention received and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention. Only authorized study personnel may supply study intervention.

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

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

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

6.3. Assignment to Study Intervention

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

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

Participants will be randomly assigned in a CCI ratio to receive a daily dose of LY3502970 CCI mg, CCI mg, CCI mg or placebo. All doses of study intervention CCI appear the same. Furthermore, placebo CCI look like study intervention CCI to maintain blinding.

The randomization will be stratified by:

- country
- sex (female, male), and

background oral AHMs classified according to potential effect on body weight, see table below.

Stratification based on the use of antihyperglycemic medications

Stratum	Potential Body Weight Effect	Participants to be Included in the Corresponding Stratum
1	Significant weight loss	The use of an SGLT-2 inhibitor alone or in combination with any other AHMs except for an SU or TZD
2	Significant weight gain	The use of an SU alone or in combination with any other AHMs except for an SGLT-2 inhibitor OR The use of a TZD alone or in combination with any other AHMs except for an SGLT-2 inhibitor
3	Weight neutral and others	Lifestyle management only: no background AHMs OR Metformin monotherapy OR The use of an SGLT-2 inhibitor in combination with an SU and/or TZD, with or without other AHMs Note: The body weight effect of SGLT-2 inhibitor may be offset by SU/TZD, and vice-versa, when used in combination. OR All other monotherapy, such as glinides and AGIs or combination therapy which does not fall under stratum 1 or 2

Abbreviations: AGI = alpha-glucosidase inhibitor; AHM = antihyperglycemic medication; SGLT = sodium-glucose cotransporter; SU = sulfonylurea; TZD = thiazolidinedione.

6.4. Blinding

This is a double-blind study. Investigators, site staff, clinical monitors, and participants will remain blinded to study intervention 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.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be permanently discontinued from study intervention, but should be continued in the study to be evaluated for efficacy and safety endpoints and monitored for all visits and testing.

Emergency unblinding

In case of an emergency, the investigator has the sole responsibility for determining if unblinding ’ z(u(„u¯ī≥w≥‚u”ī •(ī¯yuī“ y”ī(u••–”“ y”ī(–•(u¯¯u”īyx(z’ ¯(“ yx≥wu–(“ u”u• y“ y”ī(’ z(ī≤y(y- y”ī7(h≤y(

participant's safety must always be the first consideration in making such a determination. If a participant's treatment assignment is unblinded, Lilly must be notified immediately.

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

Emergency unblinding 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.

6.5. Study Intervention Compliance

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by direct questioning and counting returned CCI and documented in the source documents.

Participants will be instructed to return any unused study intervention CCI at the times specified in the SoA.

Further guidance and information for the final disposition of unused study interventions is provided in the pharmacy manual.

Treatment compliance for each visit interval is defined as taking at least 75% of the required doses of study intervention. Similarly, a participant will be considered significantly noncompliant if he or she is judged by the investigator to have intentionally or repeatedly taken more than the prescribed amount of medication (more than 125%).

In addition to the assessment of a participant's compliance with the study intervention administration, other aspects of compliance with the study will be assessed at each visit based on the participant's adherence to the visit schedule, completion of study diaries, and any other parameters the investigator considers necessary.

Participants considered to be poorly compliant with their medication 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



Study intervention dose reduction during the entire course of the study is only permitted for management of intolerable GI symptoms (see Section 6.6.1).

6.6.1. Management of Gastrointestinal Symptoms

All efforts should be made to prevent permanent discontinuation of study intervention. For participants who report intolerable GI symptoms during the study, the investigator should implement the following steps:

1	Advise participants to eat smaller meals, for example, splitting 3 daily meals into 4 or more smaller meals, and to stop eating when they feel full.
2	Continue #1, and prescribe symptomatic medication, for example, antiemetic or antidiarrheal medication, per local country availability and individual participant needs. Use of symptomatic medication should be captured as concomitant medication in the CRF.
3	Continue #1 and #2 and consider temporarily interrupting study intervention: omit up to 2 consecutive daily doses. Refer to Section 7.1.2 for information on temporary study intervention interruption. After the interruption, the investigator should advise the participant to resume study intervention at the same dose level, with the participant taking medication to alleviate their GI symptoms.





Please note the following



If intolerable GI symptoms persist despite symptomatic treatment, temporary drug interruption, and resumption of study intervention after the CCI , the participant should be permanently discontinued from the study intervention. All participants who permanently discontinue study intervention should be encouraged to continue to attend all scheduled study visits and initiation of another AHM may be considered (Section 6.9.1.4).

CCI
CCI per Section 6.1 are to be recorded in the CRF.

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

LY3502970 will not be made available to participants after conclusion of the study.

6.8. Treatment of Overdose

As any dose of LY3502970 greater than CCI mg within a 24-hour time period will be considered a potential overdose, and considering the maximum dose any participant may receive during the study treatment period is CCI mg, for this blinded study any dose of study intervention ≥3 CCI within a 24-hour time period will be considered a potential overdose and should be reported per criteria described in Section 10.3.1.

In the event of an overdose, the investigator should

- initiate supportive treatment according to the participant's clinical signs and symptoms.
- 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, for example, study intervention no longer has a clinical effect or can no longer be detected systemically (at least 7 days).

6.9. Prior and Concomitant Therapy

Prior therapies of interest including chronic weight management therapies and AHMs will be collected per the SoA (Section 1.3). Prior therapies are only those therapies that were received before enrollment in the study, that is, the stop date is prior to Visit 1.

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

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 in the CRF along with:

- Indication for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency (only for concomitant therapies of special interest)

In this study population, it is likely that many study participants will be taking medications to treat weight-related comorbidities, including hypertension, dyslipidemia, and T2D. Since weight reduction is expected to improve these comorbidities, study participants may require a dose reduction or complete withdrawal of certain concomitant medications. Investigators should closely monitor the need for adjustment of concomitant medications throughout the study, CCI

During the study, a medication (treatment) intensity CRF pertaining to concomitant medications taken for weight-related comorbidities, including T2D, hypertension and dyslipidemia, will be

collected at intervals specified in the SoA to understand the investigator's assessment of changes in treatment intensity for these conditions, for example, changes in dosage or number of medications administered, however, any changes should also be captured in the concomitant medication CRF.

The medical monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Drugs that may be affected CCI CCI Examples (not exhaustive) relevant to the study population include:

CCI

Initial doses of study intervention may delay gastric emptying and have the potential to transiently increase the rate of absorption of concomitantly administered oral medicinal products. In participants receiving oral medicinal products that have rapid GI absorption the dose of study intervention should be separated by 2 to 4 hours.

6.9.1. Antihyperglycemic Medications

6.9.1.1. Background Antihyperglycemic Medications

Use of concomitant glucose-lowering medications are permitted at randomization, except for other GLP-1 RAs (oral or injectable), DPP-4i, or other injectable therapies, for example, GIP/GLP-1 RA or insulin. Examples of prohibited AHMs are provided in Section 10.8.1.1.

To minimize the risk for hypoglycemia, participants taking CCI CCI should have their dose halved (or stopped if already on the lowest dose) at randomization. All other AHM will be continued at their current dose at randomization.

6.9.1.2. Initiation of new Antihyperglycemic Medications

The introduction of new AHMs other than study intervention is expected during the study ONLY in the following situations:

- As a rescue therapy for the management of severe, persistent hyperglycemia as defined in Section 6.9.1.3
- In those participants who require permanent discontinuation of study intervention but remain in the study as defined in Section 6.9.1.4

GLP-1 RAs, GIP/GLP-1 RA, DPP-4i and amylin analogues/agonists are not allowed at any time during study.

6.9.1.3. Rescue Therapy for Severe, Persistent Hyperglycemia

Criteria for severe, persistent hyperglycemia

Glycemic rescue criteria will be primarily determined from weekly fasting SMBG values recorded in participant eDiaries. Investigators will be trained on how to apply decision criteria

for the timing and method of intervention in participants who do not reach glycemic targets during the treatment period. Participants should continue administering assigned study intervention. An additional therapeutic intervention should be considered in participants who meet the following criteria:

≥2 confirmed values over at least 2 consecutive weeks are:	**Time period in the study**
>270 mg/dL (15.0 mmol/L)	at any time from Week 0 and prior to Week [redacted]
>240 mg/dL (13.3 mmol/L)	at any time from Week [redacted] to Week [redacted]
>200 mg/dL (11.1 mmol/L)	at any time after Week [redacted]
One value	**Time period in the study**
HbA1c ≥8.5% (69 mmol/mol)	on and after Week [redacted]
Note: Investigators should first confirm that the study participant is fully compliant with the assigned study intervention and that he or she does not have an acute condition causing severe hyperglycemia.	

Rescue medication

For participants treated with study intervention who meet criteria for severe persistent hyperglycemia, the investigator will decide, in consultation with the participant, on an appropriate glucose-lowering intervention (rescue therapy) that is not a prohibited medication listed in Sections 6.9.1 and 10.8. Investigators should follow national standards of care for diabetes management in respective participating countries or the guidelines for T2D management (ADA-EASD 2022). If deemed necessary at the discretion of the investigator, insulin rescue therapy can be initiated, if so it should be according to ADA-EASD guidelines.

Participants who receive rescue medicine for hyperglycemia management should also continue administering study intervention for the remaining period in the trial.

Short-term treatment with insulin not as rescue therapy

- Short-term treatment with insulin for less than 14 days is allowed for certain clinical situations such as, elective surgery, during hospitalization, hyperosmolar states, or acute illness.
- This is not considered as rescue therapy, and it must be differentiated from rescue therapy when reported in the CRF.

6.9.1.4. Antihyperglycemic Medications After Permanent Discontinuation of Study Intervention

Following permanent discontinuation of study intervention, participants may require additional diabetes therapy to maintain glycemic control. Addition of diabetes therapeutic agents will be decided upon by the principal investigator in consultation with the participant. Any locally approved diabetes therapy that is not an exception shown below and is not contraindicated for use in the participant may be prescribed in accordance with local prescribing information.

Exceptions: GLP-1 RAs or other incretin-based therapies (for example, tirzepatide), insulin (except as rescue medication for severe, persistent hyperglycemia [Section 6.9.1.3]), pramlintide (amylin analogs), and DPP-4i are prohibited medications.

6.9.2. Symptomatic Medication for Gastrointestinal Symptoms

The investigator may prescribe symptomatic medication for management of GI symptoms as needed during the study; for example, antiemetic or antidiarrheal medication, per local country availability and standard of care (see Section 6.6.1). Record the use of symptomatic medication as concomitant medication in the CRF.

6.9.3. Prohibited or Restricted Use Medications

The following medications are prohibited throughout the study:

- GLP-1 RAs or other incretin-based therapies (for example, tirzepatide), pramlintide (amylin analogs), and DPP-4i (Section 10.8.1.1) and must not be included in the rescue intervention or otherwise used during the study.
- Those intended to promote weight loss, including prescribed, over the counter, or alternative remedies. Examples are provided in Section 10.8.1.2.
- 

The following medications are restricted (strongly discouraged) for initiation during the study, and alternative medications should be considered whenever possible:

- CCI Examples are provided in Section 10.8.2.2.
- Weight gain medications. Examples are provided in Section 10.8.1.3.

6.9.4. Prohibited or Restricted Surgical Treatments or Procedures

Any planned elective major surgery during the study should be discussed with the sponsor's designated medical monitor.

Surgical treatments, endoscopic therapy, and/or device-based therapy for weight management are not permitted during the study.

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

If a participant permanently discontinues study intervention for any reason, except pregnancy (Section 7.2), the participant should be encouraged to remain in the study and adhere to the study schedule until the final visit. If the participant is unwilling or unable to return for all applicable study visits, the site should attempt to collect as much follow-up information as possible, especially data collection pertaining to primary and key secondary efficacy endpoints at the final visit of the treatment period.

A participant must be permanently discontinued from study intervention if

- the participant becomes pregnant during the study
- the participant is diagnosed with acute or chronic pancreatitis confirmed by adjudication. See Section 8.3.3.8
- the participant is diagnosed with MTC or MEN2 syndrome
- the participant develops significant elevation of serum calcitonin. See Section 8.3.3.9
- the participant is diagnosed with an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ [for example, Gleason 6 or lower] prostate cancer)
- a participant is diagnosed with T1D
- the participant requests to discontinue study intervention
- a participant develops any other TEAE, SAE, or clinically significant laboratory value for which the investigator believes that permanent study intervention discontinuation is the appropriate measure to be taken
- the participant initiates any other GLP-1 RA, GIP/GLP-1 RA, amylin analogues/agonists, or DPP-4i, if the participant will not or cannot discontinue them
- if an investigator, site personnel performing assessments, or participant is unblinded

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

- the participant has intolerable GI symptoms despite management as described in Section 6.6.1.
- Na Ų(: DŽA(–• 8‘ 2 is reached at any time during the treatment period
- b ’ īyH(h≤y(≥’- y●≥• uī’ ¯(●≤’ –x(w’ ”īuwī(ī≤y(●,,’ ”●’ ¯ ●(xy●≥• ”uīyx(“ yx≥wu–(“ ’ ”≥ī’ ¯(ī’ (discuss whether it is medically appropriate for the participant to continue study intervention.
- initiation of other weight management medications (Section 10.8.1.2) or if the participant has bariatric surgery or body weight reduction procedures
- systemic hypersensitivity reaction

- 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 study intervention is warranted, the investigator may consult the sponsor.

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

Note: In the event either the PHQ-9 score or C-SSRS conditions above are met, participants should be referred to a mental health professional for consultation. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy (see Section 10.8 for restricted use medications), then the participant, at the discretion of the investigator (in agreement with the mental health professional) may be continued in the study on study intervention.

7.1.1. Liver Chemistry Stopping Criteria

See Section 8.2.7.3 for hepatic criteria for study intervention interruption or discontinuation.

7.1.2. Temporary Study Intervention Interruption

All efforts should be made to keep participants on study intervention at the randomized dose level and with minimal dose interruptions throughout the study.

Due to the short half-life of LY3502970, for any dose interruptions >2 days it is recommended that the investigator consult with the sponsor's medical monitor. Every effort should be made by the investigator to restart study intervention after any temporary interruption as soon as it is safe to do so, according to the guidance provided in the table below. Distribution of study intervention at the correct dose will be per IWRS instructions.

If study intervention interruption is	**then**
2 consecutive doses or less	participant resumes the study intervention at the last administered dose level. If the dose interruption occurred immediately prior to a scheduled CCI [redacted], the participant should proceed with the next CCI [redacted]

If study intervention interruption is	then
3-6 consecutive doses	participant resumes the study intervention at the last administered dose level unless doing so results in intolerable GI symptoms. See Section 6.6.1 for management of GI symptoms. If the dose interruption occurred immediately prior to a scheduled CCI [redacted], the participant should proceed with the next CCI [redacted]
7 or more consecutive doses	participant CCI [redacted] per Section 6.1. CCI [redacted] to previously attained dose level unless the interruption occurs within the first CCI [redacted] in which case the last administered dose level should be resumed
due to an AE (**including recurrent GI symptoms**), a clinically significant laboratory value, or a participant's personal circumstances*	the event is to be documented and followed according to the procedures in Section 8.3
due to intolerable persistent GI AE	participant should be treated as suggested in Section 6.6.1.

* Travel, hospitalizations, or planned or unplanned procedures.

The data related to temporary interruption of study intervention will be documented in source documents and entered on the CRF.

7.2. Participant Discontinuation/Withdrawal from the Study

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

Female participants will be discontinued from the study if the participant becomes pregnant.

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
- 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.

Participants who agree to provide information relevant to any trial endpoint at the end of the study are not considered to have discontinued from the study.

7.3. Lost to Follow-up

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

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. Primary Efficacy Assessments

The primary efficacy endpoint includes percent change in body weight.

Body weight measurements will be collected at specific visits as summarized in the SoA. Methods for measuring body weight are described in Section 10.9.

8.1.2. Secondary Efficacy Assessments

Body weight (kg)
Waist circumference (see Section 10.9)
Glycemic control (see Section 3)
Blood pressure (see Section 3)
Lipid parameters (see Section 3)
Fasting insulin (see Section 3)
Patient-reported outcomes (see Section 8.1.4)

8.1.3. Tertiary Efficacy Assessment

PK and PD

8.1.4. Patient-Reported Outcomes

8.1.4.1. Short Form 36 Version 2 Health Survey, Acute Form, 1-Week Recall Version

The SF-36v2 will be included to assess health-related quality of life. The SF-36v2 acute form, 1-week recall version is a 36-item generic, participant-completed measure designed to assess the following 8 domains.

Physical functioning
Role-physical
Bodily pain
General health
Vitality

Social functioning
Role-emotional, and
Mental health

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8.1.4.2. Impact of Weight on Quality of Life-Lite Clinical Trials Version

The IWQOL-Lite-CT (Kolotkin et al. 2017, 2019) is a 20-item, obesity-specific patient-reported outcomes instrument developed for use in weight management clinical studies.

The IWQOL-Lite-CT assesses 2 primary domains of obesity related health-related quality of life: Physical (7 items) and Psychosocial (13 items). A 5-item subset of the Physical domain the Physical Function composite is also supported. Items in the Physical Function composite describe physical impacts related to general and specific physical activities.

All items are rated on either a 5-„,’≥”ī(z¯yı y”w (1 ”y-y¯ (ī’ (u—u ● 2(●wu-y(’¯(u(A-point truth 1 ”’ī(uī(u—(ī¯ y (ī’ (w’“ „,-y-iy—(ī¯ y 2(●wu-y7 The three domain scores and total score range from 0 to 100 with higher scores indicating greater functioning.

8.1.4.3. EQ-5D-5L

The EQ-5D-5L (EuroQol Research Foundation 2019) is a standardized 5-item, self-administered instrument for use as a measure of health outcome. It provides a simple descriptive profile and a single index value for health status that can be used in the clinical and economic evaluation of health care as well as population health surveys. The EQ-5D-5L assesses 5 dimensions of health:

mobility
self-care
usual activities
pain/discomfort, and
anxiety/depression.

Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems.

h≤y(j Mg(¯yw’¯x●(ī≤y(¯y●„’ ”xy”ī ●(●y-z-rated health on a vertical VAS where the endpoints are -uvy-yx(u●(vy●ī(≥“ u•≥”uv-y(≤yu-ī≤(●īuīy (l: 992(u”x(’¯●ī(≥“ u•≥”uv-y(≤yu-ī≤(●īuīy (1927

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

The PGIS-Physical Function due to k y≥•≤ī(●wu-y(≥●(xy●≥•”yx(ī’ (u●●y●●(ī≤y(„,u¯ī≥w≥„u”ī●(’ - y¯u—(— perception of their condition. This is a single global item that asks participants to rate how their

weight limited their ability to perform physical activities in the past 7 days on a 5-point scale ranging from “not at all limited” to “extremely limited”.

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

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

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the CV, respiratory, gastrointestinal, and neurological systems.
- Height, weight, and waist circumference will also be measured and recorded. See Section 10.9 for further details on physical examinations.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and following the study-specific recommendations included in Section 10.9.

Any clinically significant findings from vital signs measurement that result in a diagnosis and occur during the study should be reported as an AE via the CRF.

8.2.3. Electrocardiograms

CCI 12-lead ECGs will be obtained as outlined in the SoA (see Section 1.3). Participants should be supine for approximately 5 to 10 minutes before ECG collections and remain supine but awake during the ECG collection. CCI [redacted] CCI [redacted]
Collect ECG before blood samples for laboratory testing.

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

All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated 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 heart rate may be used for data analysis and report-writing purposes, unless a cardiologist overreading of the ECGs is conducted prior to completion of the final study report (in which case, the overread data would be used).

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

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. O ”wu (”wu”ī(uv”’ “ u (uv’ uī’ (z”x”• (u y(ī’ y(w(u y(”’ ī(u wuīyx(ī(ī≤y(”xy ”• (x yu y(” y (. . x• yx(v (ī≤y(”- y uī’ (ī’ (vy(“ ’ y(y- y y(ī≤u”(y ,,ywīyx(z’ (ī≤y(,,u ī wu”ī (w’ ”x ī ”7

All laboratory tests with values considered clinically significantly abnormal during participation in the study should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

> If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified, and the sponsor notified.
>
> All protocol-required laboratory assessments, as defined in 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

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

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

Participants who become pregnant during the study should be permanently discontinued from study intervention (Section 7.1) and from the study (Section 7.2).

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

8.2.6. Suicidal Ideation and Behavior Risk Monitoring

Baseline assessment of SIB will be monitored during the study using the C-SSRS. See Section 8.3.3.15 for more details.

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

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

8.2.7. Hepatic Safety Monitoring

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)

..))))			
	Initiate or continue close hepatic monitoring (see Section 8.2.7.1)	**Initiate comprehensive evaluation (see Section 8.2.7.2)**	**Interrupt or discontinue study drug (see Section 8.2.7.3)**
MXh(’¯(Mgh(< (i Xb	X		
MXd(; (i Xb(	X		
hNX(; (i Xb[b]	X		
MXh(’¯(Mgh(A (i Xb	X	X	
MXd(; 7A (i Xb	X	X	
MXh(’¯(Mgh(< (i Xb(≥ī≤(≤y„uī≥w(●≥”●(’¯(● “ „ī’“ ●	X	X	X
MXh(’¯(Mgh(A (i Xb (z’¯(“ ’¯y(ī≤u”(; (yy–●	X	X	X
MXh(’¯(Mgh(D (i Xb	X	X	X
ALT or Mgh(< (i Xb (u”x(hNX(; (i Xb[b]’¯(Ub f (: 7A	X	X	X
MXd(< (i Xb(	X	X	X
MXd(; 7A (i Xb (u”x(hNX(; (i Xb[b]	X	X	X
MXd(; 7A (i Xb(≥ī≤(≤y„uī≥w(●≥”●(’¯(● “ „ī’“ ●	X	X	X

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

[b] U”(„u¯ī≥w≥„u”ī●(≥ī≤(S≥vy¯ī ●(● ”x¯’“ y5(ī≤y(ī≤¯y●≤’ –x(z’¯(hNX(“ u (vy(≤● ≤y¯7

))))Gs Ns Ns)s)aSe) I

..)))))			
	Initiate or continue close hepatic monitoring	**Initiate comprehensive evaluation**	**Interrupt or discontinue study drug**
MXh(’ ¯(Mgh(; (vu•y–≥”y(	X		
MXd(; (vu•y–≥”y(	X		
hNX(; (i Xb[b]	X		
MXh(’ ¯(Mgh(< (vu•y–≥”y(’ ¯(; A9(i 8X (whichever occurs first)	X	X	
ALP ; 7A (vu•y–≥”y	X	X	
MXh(’ ¯(Mgh(; (vu•y–≥”y(’ ¯(; A9(i 8X (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
MXh(’ ¯(Mgh(< (vu•y–≥”y(’ ¯(; A9(i 8X (whichever occurs first) for more than 2 weeks	X	X	X
MXh(’ ¯(Mgh(> (vu•y–≥”y(’ ¯(>99(i 8X(whichever occurs first)	X	X	X
MXh(’ ¯(Mgh(; (vu•y–≥”y(’ ¯(; A9(i 8X 1 ≤w≤y-y¯(’ ww ¯•(z≥•2(u”x(hNX(; (i Xb[b] ’ ¯(Ub f : 7A	X	X	X
MXd(< (vu•y–≥”y(	X	X	X
MXd(; 7A (vu•y–≥”y(u”x(hNX(; (i Xb[b]	X	X	X
MXd(; 7A (vu•y–≥”y(≥1≤(≤y,,uī≥w(•≥ ”•(’ ¯(• “ „ī’ “ •	X	X	X

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

[b] U”(„,u¯ī≥w≥„u”ī•(≥1≤(S≥vy¯ī •(• ”x¯’ “ y(ī≤y(ī≤¯y•≤’ –x(z’ ¯(hNX(“ u (vy(≤•≤y¯

8.2.7.1. Close Hepatic Monitoring

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Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	**Participants with elevated baseline (ALT, AST, or ALP)aSe) I**
MXh(’ ¯(Mgh(< (i Xb (or	MXh(’ ¯(Mgh(; (vu•y–≥”y(
MXd(; (i Xb (or	MXd(; (vu•y–≥”y(
hNX(; (i Xb[b]	hNX(; (i Xb[b]

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8.2.7.2. Comprehensive Hepatic Evaluation

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Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	Participants with elevated baseline (ALT, AST, or ALP aSe) I
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[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] U’(„u¯ī≥w≥„u”ī●(≥≥≤(S≥≥vy¯ī ●(●”x¯’“ y5ī≤y(ī≤¯y●≤’ –x(z’¯(h NX(“u (vy(≤•≤y¯7

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8.2.7.3. Study Drug Interruption or Discontinuation

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Participants with normal or near normal baseline (ALT, AST, or ALP <1.5x ULN)	))))(S Ns N))s) **1.5x ULN)**
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MXh(’ ¯(Mgh(D (i Xb(**or**	MXh(’ ¯(Mgh(> (vu●y-≥’y(’ ¯(>99(i 8X(1 ≤w≤y- y¯(’ ww ¯●(first) **or**
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MXd(; 7A (i Xb(u”x(h NX(; (i Xb[b] **or**	MXd(; 7A (vu●y-≥’y(u”x(h NX(; (i Xb[b] **or**
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[a] Examples of hepatic signs or symptoms: severe fatigue, nausea, vomiting, right upper quadrant abdominal pain, fever, rash, and/or eosinophilia >5%.

[b] U”(„,u¯ī≥w≥,,u”ī●(≥ī≤(S ≥vy¯ī ●(● ”x¯’ “ y5ī≤y(ī≤¯y●≤’ x(z’ ¯(h NX(“ u (vy(≤• ≤y¯7(

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8.2.8. Hypersensitivity Reactions

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

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

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

8.2.9. Diabetic Retinopathy Screening and Evaluation

Baseline fundus photography should be performed on participants who remain eligible based on screening activities performed at Visit 1 (including laboratory results). The overall ophthalmological evaluation of the baseline fundus photographs must be completed prior to randomization to confirm eligibility. Participants with any degree of diabetic retinopathy or macular edema on the baseline assessment that warrants treatment based on the clinical judgement of the ophthalmologist will be excluded (See exclusion criterion #11).

All participants will have follow-up fundus photography performed according to the SoA (Section 1.3). Fundus photography may be performed more frequently if warranted based on the severity of retinopathy or macular edema at baseline or during the study consistent with screening guidelines for diabetic retinopathy (Solomon et al. 2017; Flaxel et al. 2020).

Fundus photography should be performed in both eyes (unless precluded due to severe cataract, prosthesis, or other conditions) using the broadest field of view available to the site or associated qualified eye care professional, including 7-standard views, 4-wide field views, or at a minimum 2-field views with at least 60-degree field of view. Photographs may be performed at the study site if equipment and staff trained in collecting the required views are available; otherwise, they should be referred to an ophthalmologist or other suitable qualified health care provider.

All fundus photographs will be evaluated by an ophthalmologist or other qualified health care provider experienced in the assessment of diabetic retinopathy and macular edema. The evaluation will include whether diabetic retinopathy and/or macular edema are present and whether treatment is recommended. Fundus photographs deemed unevaluable for any reason will be repeated as recommended by the ophthalmological evaluator. Whenever possible, the same qualified evaluator should review all photographs for an individual participant throughout the study. Any evidence of diabetic retinopathy, macular edema, or other clinically significant findings on the fundus photographs will require additional ophthalmological follow-up per local standards of care. The use of optical coherence tomography should be encouraged to confirm cases of macular edema.

Results from the overall ophthalmological evaluation, including final diagnoses of nonproliferative retinopathy, proliferative retinopathy, or diabetic macular edema, will be provided to the investigator and recorded on a specific retinopathy CRF. Any interventions initiated for diabetic retinopathy or macular edema during the study will be captured on the concomitant medication CRF.

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 study (see Section 7).

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

After the initial report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs and AEs of special interest and other safety topics 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 and/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 „u¯ı≥≥,u”ī ◄(study participation has ended **and** the investigator becomes aware	After „u¯ı≥≥,u”ī ◄(study participation has ended	N/A	Promptly	SAE paper form	N/A
Pregnancy					
Pregnancy in female participants and female partners of male participants	After the start of study intervention	At least 30 days after the last dose	Within 24 hours (see Section 8.3.2)	Pregnancy CRF	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	N/A

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

8.3.2. Pregnancy

Collection of pregnancy information

Male participants with partners who become pregnant

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

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

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

Female participants who become pregnant

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

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

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

A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring uī(; 9(yy—•(y•ūuī≥ ”u (u• y2(≥•(u—u •(ẇ ”•≥xy¯yx(ī’ (vy(u”(gMQ(u”x(≥ (vyreported as such.

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

Any female participant who becomes pregnant while participating in the study will be discontinued from the study. The follow-up on the pregnancy outcome should continue independent of study discontinuation.

8.3.3. Adverse Events of Special Interest and Other Safety Topics

8.3.3.1. Major Adverse Cardiovascular Events

CV safety will be assessed in this study. Nonfatal CV AEs and all deaths will be adjudicated. The nonfatal CV AEs to be adjudicated include

myocardial infarction

hospitalization for unstable angina

hospitalization for heart failure

coronary interventions (such as coronary artery bypass graft or percutaneous coronary intervention), and

cerebrovascular events, including cerebrovascular accident (stroke) and transient ischemic attack.

Case adjudication and data entry

An independent CEC with cardiology expertise will adjudicate all suspected cases of major adverse cardiovascular events. The investigator must first report these events as an AE as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5). Clinical event reporting begins after randomization. The CEC will be blinded to treatment assignment.

8.3.3.2. Arrhythmias and Cardiac Conduction Disorders

Treatment-emergent cardiac arrhythmias and conduction disorders will be further evaluated. Participants who develop any event from these groups of disorders should undergo an ECG, which should be electronically transmitted to the designated central ECG laboratory. 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 10.3.2 must be reported as SAEs.

8.3.3.3. Hypotension, Orthostatic hypotension, and Syncope

All events of hypotension/orthostatic hypotension/syncope should be evaluated, and additional diagnostic tests performed as needed.

8.3.3.4. Hypoglycemia

Participants will be trained by authorized study personnel about signs and symptoms of hypoglycemia, how to treat hypoglycemia, and instructed to record relevant information for each episode of hypoglycemia in the study eDiary.

Participants will collect information on episodes of hypoglycemia starting from Visit 2 until the last study visit (follow-up visit or ED visit).

All hypoglycemic episodes will be collected in the study eDiary. Because all hypoglycemic episodes will be collected in the study eDiary, they should not be recorded on the AE CRF unless the event meets criteria of severe hypoglycemia which should then be recorded as serious on the AE CRF and reported to Lilly as an SAE.

To avoid duplicate reporting, all consecutive BG values <70 mg/dL (3.9 mmol/L) occurring within a 1-hour period may be considered a single hypoglycemic event (Weinberg et al. 2010; Danne et al. 2013). Participants who develop recurrent unexplained hypoglycemia during the treatment period will be asked to reduce the dose or discontinue any concomitant glucose-lowering agents other than study intervention. Study intervention discontinuation for recurrent hypoglycemia should be considered only if these events continue despite complete discontinuation of concomitant medications.

Investigators should use the following classification of hypoglycemia. The plasma glucose values in this section refer to values determined by a laboratory or International Federation of Clinical Chemistry and Laboratory Medicine plasma-equivalent glucose meters and strips.

Hypoglycemia definitions and categories

Level 1 hypoglycemia)t l a) R)6eIa) R 7)) hg) R)6eIa) R 7

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

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

Level 2 hypoglycemia is a glucose value of <54 mg/dL (3.0 mmol/L). This glucose threshold is clinically relevant regardless of the presence or absence of symptoms of hypoglycemia.

Level 3 hypoglycemia Severe hypoglycemia (in adults)

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

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

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

Nocturnal hypoglycemia

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

8.3.3.5. Severe Persistent Hyperglycemia

Criteria for severe, persistent hyperglycemia are provided in Section 6.9.1.3.

Occurrences of severe, persistent hyperglycemia that meet these criteria for rescue therapy should be reported as an AE on the CRF.

8.3.3.6. Severe Gastrointestinal Adverse Events

LY3502970 may cause CCI . Information about GI AEs as well as antiemetic or antidiarrheal use will be collected in the AE and concomitant medications CRFs, respectively. For detailed information concerning the management of GI AEs, please refer to Sections 6.6.1 and 6.9.2.

8.3.3.7. 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 LY3502970 including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 RA (Aroda and Ratner 2011). The 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, diarrhea, frequent vomiting, or symptoms of dehydration.

8.3.3.8. Pancreatitis

Diagnosis of acute pancreatitis

Acute pancreatitis is an AE of interest in all studies with LY3502970, including this study. The diagnosis of acute pancreatitis requires 2 of the following 3 features (Banks and Freeman 2006; Koizumi 2006)

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

If acute pancreatitis is suspected, the investigator should

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

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

  And

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

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention. In this case, the participant needs to receive an appropriate alternative glucose-lowering regimen. Afterwards, if pancreatitis is confirmed by the adjudication committee, the study intervention must be permanently discontinued, and the participant needs to be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart the study intervention if the investigator deems as clinically appropriate as described in Section 6.6.

Case adjudication and data entry

An independent CEC will adjudicate all suspected cases of acute pancreatitis and all AEs of severe or serious abdominal pain of unknown etiology. The investigator must first report these events as an AE as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5). Clinical event reporting begins after randomization. The CEC will be blinded to treatment assignment.

Asymptomatic elevation of serum amylase and/or lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or pancreatic amylase < (i Xb 2(≥●(”’ ī(“ u”xuīyx(v ī(“ u (vy(,,y¯z’ ¯“ yx vu●yx(’ ”(ī≤y(≥’- y●i≥• uī’ ¯ ●(w≥”≥wu (.. x• “ y”ī(u”x(u●●y●●“ y”ī(’ z(ī≤y(,,u¯ī≥w≥,u”ī ●(’ - y¯u (w≥”≥wu (condition.

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

8.3.3.9. Thyroid Malignancies and C-Cell Hyperplasia

Participants who are diagnosed with MTC and/or MEN2 syndrome during the study will have study intervention discontinued and should continue follow-up with an endocrinologist.

The assessment of thyroid safety during the trial will include reporting of any case of thyroid neoplasms (including MTC, papillary carcinoma, and others) and measurements of calcitonin. The purpose of calcitonin measurements is to assess the potential of LY3502970 to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Calcitonin measurements

If an increased calcitonin value (see definitions below) is observed in a participant who has been administered a medication that is known to increase serum calcitonin, then this medication should be stopped, and calcitonin levels should be measured after an appropriate washout period.

For participants who require additional endocrine assessment because of increased calcitonin concentration as defined in this section, data from the follow-up assessment will be collected in the specific section of the CRF.

Calcitonin measurements in participa))) i a) R RIIe) [2]

A significant increase in calcitonin for participants with eGFR 60 mL/min/1.73 m^2 is defined below. If a participant ●(–uv’ ¯uī’ ¯ (¯y● –ī●(“ yyī(ī≤y●y(w¯≥ī¯y¯≥u5(ī≤y●y(w≥’≥wu—(●≥ ”≥≥wu”ī(laboratory results should be recorded as an AE.

. . . *hf* . *e* . .*v i m e* . . *mf 5* . . . . .

value. These participants will be requested to repeat the measurement within 1 month. If ī≤≥●(¯y,,yuī(- u—y(≥●(≥’wīyu●≥’•(1 : 9. (≥’wīyu●y25(ī≤y(●ī x (intervention should be discontinued, and the participant should undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude adverse effects on the thyroid gland.

. . . *i m e* . . *mf 5* . . . . . In these participants, study intervention should be discontinued, and the participant should be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude adverse effects on the thyroid gland.

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

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a . . . *i m e* . . *mf 5* . . . . *d*If a participant ●(laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

In these participants, study intervention should be discontinued if the increased concentration of calcitonin is confirmed. The participant must be recommended to immediately undergo additional endocrine assessments and longer-term follow-up by an endocrinologist to exclude adverse effects on the thyroid gland.

8.3.3.10. Diabetic Retinopathy

Diabetic retinopathy and macular edema will be monitored using retinal fundus photography and additional ophthalmological follow-up as warranted throughout the study (Section 8.2.9). Diabetic retinopathy will be assessed as nonproliferative (mild, moderate, or severe), proliferative, and diabetic macular edema as present or absent. All TEAEs of new or worsening diabetic retinopathy, macular edema, and other related complications will also be assessed.

8.3.3.11. Malignancies

All events of malignancy or other suspected events related to malignancy should be evaluated and additional diagnostic tests performed as needed.

8.3.3.12. Hepatic Disorders

All events of hepatic disorders or other suspected events related to hepatic disorders should be evaluated and additional diagnostic tests performed as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.7.

8.3.3.13. Gallbladder and Biliary Tract Disorders

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

8.3.3.14. Hypersensitivity Reactions

Refer to Section 8.2.8.

8.3.3.15. Depression, Suicidal Ideation, and Behavior

Participants will be monitored for depression and suicidal ideation or behavior through AE collection and by using the C-SSRS (Section 8.2.6) and the PHQ-9 questionnaires. Scores of the questionnaires are reviewed by the investigator at the time of each assessment, and appropriate actions as described below should be taken.

Suicide monitoring

Columbia-Suicide Severity Rating Scale (C-SSRS)

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

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

Timing of collection and AE monitoring

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

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

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

Depression monitoring

Monitor participants receiving study intervention for depression or any other unusual changes in behavior.

Patient Health Questionnaire-9 (PHQ-9)

The PHQ-9 (Spitzer, et al. 1999; Moriarty, et al. 2015) is a validated, participant-reported instrument that assesses the specific diagnostic symptoms that determine the presence of a

clinical depressive disorder per the Diagnosis and Statistical Manual for Mental Disorders, 5th Edition (DSM-5).

The questionnaire assesses the previous 2 weeks.

The PHQ-9 assesses 9 diagnostic symptoms:

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

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

This table describes the interpretation of results.

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

8.3.3.16. Abuse Potential

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

8.4. Pharmacokinetics

Pharmacokinetic samples will be collected from all randomized participants.

Plasma concentrations of LY3502970 will only be determined from blood samples obtained from participants receiving LY3502970 treatment. Blood samples for PK assessment will be collected at timepoints as indicated in the table below.

Visit	PK Sample Relative to Study Intervention Dose
Visit 5 (Week [redacted])	Pre-dose[a]
Visit 7 (Week [redacted])	4 to 12 hours post-dose
Visit 9 (Week [redacted])	Pre-dose[a]
Visit 12 (Week [redacted])	1 to 4 hours post-dose
Visit 15 (Week [redacted])	Pre-dose[a]
Early Discontinuation (ED)[b]	At any time relative to dosing

[a] If 3 or more prior doses of study intervention are missed prior to PK sample collection, study participant should be requested to return at a later date after having resumed at least 7 doses in order to have pre-dose samples drawn. Participants should take study intervention only after PK samples are taken on the pre-dose PK sample visits.

[b] Early discontinuation PK samples should be collected regardless of study week at which the discontinuation occurs (even if after Week 48).

The date and time of the most recent LY3502970 doses prior to collecting the PK sample must be recorded on the CRF from the eDiary. The date and time at which each sample was drawn must be recorded on the laboratory accession page.

Concentrations of LY3502970 will be assayed using a validated liquid chromatography mass spectrometry method.

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

8.4.1. Bioanalysis

Bioanalytical samples collected to measure LY3502970 concentration will be retained for a maximum of 1 year following last participant visit for the study (See Section 10.1.12). During this time, samples remaining after the bioanalyses may be used for exploratory analyses such as metabolism work, protein binding, and/or bioanalytical method cross-validation.

8.5. Pharmacodynamics

Efficacy measures will be used as indicators of PD response.

8.6. Genetics

A whole blood sample will be collected from participants to enable DNA isolation for exploratory pharmacogenetics analysis as specified in the SoA, where local regulations allow.

Samples will not be used to conduct unspecified disease or population genetic research either now or in the future.

Samples may be used to investigate variable exposure or response to LY3502970 and to investigate genetic variants thought to play a role in obesity, diabetes mellitus, and related clinical traits or complications, including nonalcoholic steatohepatitis. Assessment of variable response may include evaluation of AEs or differences in PD, mechanistic, safety, or efficacy measures.

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

8.7. Biomarkers

Plasma and serum samples will be collected to enable exploratory nonpharmacogenetic biomarker research.

Biomarker research is performed on stored samples to address questions of relevance to

drug disposition

target engagement
PD
mechanism of action
variability of participant response, including safety, and
clinical outcomes.

Samples may be used for

research on the drug target
disease process
variable response to LY3502970
pathways associated with diabetes mellitus, obesity, and related clinical traits or complications, including nonalcoholic steatohepatitis
mechanism of action of LY3502970, and
research method or validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, or related clinical traits or complications.

Samples will be collected according to the schedule described in the SoA.

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity parameters 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 study 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.

Unblinding details are specified in the blinding and unblinding plan.

9.1. Statistical Hypotheses

The null hypotheses corresponding to the primary objective are as follows:

- $H_{1,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- $H_{2,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- $H_{3,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.

The null hypotheses corresponding to the key secondary objectives are as follows:

- $H_{4,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction in body weight at Week 72.
- H_{50}: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction in body weight at Week 72.
- $H_{6,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the occurrence of participants who achieve 5% or more body weight reduction at Week 72.
- $H_{7,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 10% or more body weight reduction in body weight at Week 72.
- $H_{8,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 10% or more body weight reduction in body weight at Week 72.
- $H_{9,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 10% or more body weight reduction in body weight at Week 72.
- $H_{10,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 15% or more body weight reduction in body weight at Week 72.
- $H_{11,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants who achieve 15% or more body weight reduction in body weight at Week 72.
- $H_{12,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in waist circumference at Week 72.

- $H_{13,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- $H_{14,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- $H_{15,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in HbA1c at Week 72.
- $H_{16,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in HbA1c at Week 72.
- $H_{17,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in HbA1c at Week 72.
- $H_{18,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in fasting glucose at Week 72.
- $H_{19,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in fasting glucose at Week 72.
- $H_{20,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to mean change from baseline in fasting glucose at Week 72.
- $H_{21,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants achieving HbA1c target of <7.0% at Week 72.
- $H_{22,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants achieving HbA1c target of <7.0% at Week 72.
- $H_{23,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants achieving HbA1c target of <7.0% at Week 72.
- $H_{24,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants achieving HbA1c target of ≤6.5% at Week 72.
- $H_{25,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants achieving HbA1c target of ≤6.5% at Week 72.
- $H_{26,0}$: No difference in [redacted] mg LY3502970 compared to placebo with respect to the percentage of participants achieving HbA1c target of ≤6.5% at Week 72.
- $H_{27,0}$: No difference in [redacted] mg, [redacted] mg, and [redacted] mg LY3502970 pooled compared to placebo with respect to mean change from baseline in SBP at Week 72.
- $H_{28,0}$: No difference in [redacted] mg, [redacted] mg, and [redacted] mg LY3502970 pooled compared to placebo with respect to mean percent change from baseline in non-high-density lipoprotein cholesterol at Week 72.
- $H_{29,0}$: No difference in [redacted] mg, [redacted] mg, and [redacted] mg LY3502970 pooled compared to placebo with respect to mean percent change from baseline in triglycerides at Week 72.

9.1.1. Multiplicity Adjustment

Multiplicity adjusted analyses will be performed on the primary and key secondary objectives in order to control the overall family-wise Type I error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009, 2011) will be used. This approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all hypotheses (Alosh et al. 2014).

The following figure illustrates the current graphical testing procedure. Details of the final graphical testing scheme (including testing order, interrelationships, Type I error allocation for the primary and key secondary objectives, and the associated propagation) will be pre-specified in the SAP prior to primary database lock. Unless otherwise specified, the "treatment regimen" estimand is planned to support future product registration and the "efficacy estimand" will be considered for use in scientific disclosures and other purposes. Since these 2 types of estimands are intended for distinct purposes, no multiplicity adjustment will be made for conducting separate analyses on the same objectives. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary objectives.



9.2. Analyses Sets

The following participant analysis sets are defined:

Participant Analysis Set	Description
Entered participants	All participants who sign informed consent.
Randomized participants	All participants who are randomly assigned a study intervention. Participants will be analyzed according to the treatment group to which they were randomly assigned.

Participant Analysis Set	Description
Safety participants	All participants who are randomly assigned a study intervention and who take at least 1 dose of study intervention. Participants will be analyzed according to the treatment group to which they were randomly assigned.

The following data points sets are defined for all parameters except for the glycemic-related parameters:

Data Points Sets	Description
Treatment regimen estimand data points set	All data points obtained during the treatment period defined as at or after baseline and up to the last visit within the treatment period, regardless of study intervention discontinuation or initiation of prohibited weight management treatments.
Safety data points set	All data points obtained during the intervention period and the follow-up period defined as at or after baseline and up to the date of study withdrawal including the follow-up period and regardless of study intervention discontinuation or initiation of prohibited weight management treatments.
Efficacy estimand data points set	All data points obtained during the treatment period defined as at or after baseline and up to the earliest date of study intervention discontinuation or initiation of prohibited weight management treatments.

The following data points sets are defined for all glycemic-related parameters:

Data Points Sets	Description
Treatment regimen estimand data points set	All data points obtained during the treatment period defined as at or after baseline and up to the last visit within the treatment period, regardless of study intervention discontinuation or initiation of prohibited weight management treatments or glycemic rescue therapy.
Safety data points set	All data points obtained during the treatment period and the follow-up period defined as at or after baseline and up to the date of study withdrawal including the follow-up period and regardless of study intervention discontinuation or initiation of prohibited weight management treatments or glycemic rescue therapy.
Efficacy estimand data points set	All data points obtained during the treatment period defined as at or after baseline and up to the earliest date of study intervention discontinuation or initiation of prohibited weight management treatments or glycemic rescue therapy.

9.3. Statistical Analyses

9.3.1. General Considerations

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

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

Baseline is defined as the last available non-missing measurement prior to the first dosing of study intervention, unless otherwise specified.

General descriptions of analyses

Unless otherwise noted, all tests for superiority will be conducted at the 2-sided alpha level of 0.05. CIs will be calculated as 2-sided, 95% CIs.

For continuous measures, summary statistics will include sample size, mean, SD, median, minimum, and maximum for both the actual and the change from baseline measurements. LS means and standard errors derived from the analysis models will also be displayed for the change from baseline measurements. Treatment comparisons will be displayed showing the treatment difference LS means and the 95% CIs for the treatment differences, along with the p-values for the treatment comparisons.

The analysis model to make comparisons between treatment groups relative to continuous efficacy measurements will be an ANCOVA with robust inference (Ye et al. 2022).

For measures evaluated at multiple postbaseline visits, the analysis model to make comparisons between treatment groups relative to continuous measurements assessed over time will include a mixed model for repeated measures, with fixed effects of visit, and treatment, stratification factors, and baseline measurement all nested within visits.

For categorical measures, summary statistics will include sample size, frequency, and percentages. A logistic regression model with treatment and stratification factors as fixed effects and the continuous baseline value as a covariate will be used to examine the treatment difference ≥”(v≥”u¯ (yzz≥wuw (’ īẇ “ y●7R≥●≤y¯ ●(y uw̄(īy●ī(’ ¯(dyu¯●’ ” ●(w◇≥square test will be used for treatment comparisons in other categorical outcomes.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of LY3502970 doses with placebo irrespective of adherence to study intervention. Thus, safety analyses will be conducted using the safety participants during the treatment period or during the treatment period plus the posttreatment safety follow-up period.

Other statistical methods may be used, as appropriate, and details will be described 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. Treatment Group Comparability

9.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided.

Frequency counts and percentages of all safety participants will be presented by treatment groups.

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

All participants who discontinue the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment groups. The percentage of participants discontinuing from each LY treatment group will be compared to „ uwyv' (•' • (ī≤y(R•≤y¯ •(y uwī(īy•7Wu,, u"-Meier analyses of time from randomization to premature discontinuation from study and premature discontinuation from study intervention by treatment group will be provided.

9.3.2.2. Participant Characteristics

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

9.3.2.3. Concomitant Therapy

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

9.3.2.4. Treatment Compliance

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

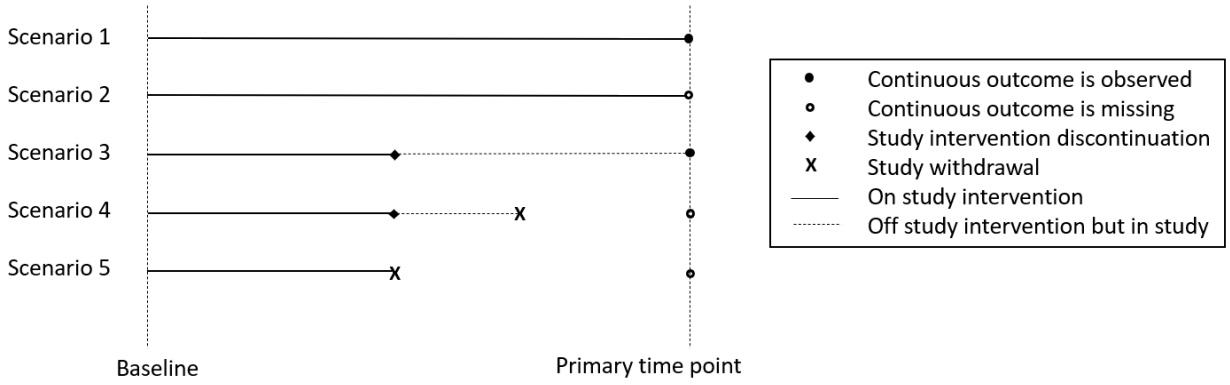
9.3.3. Primary Endpoints and Estimand Analyses

The null hypotheses corresponding to the primary objective is specified in Section 9.1.

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d¯≥" u¯ (' v.yw≥ y•(u≥•"yx(ī' (ī≤y(ī¯yuī" y"ī(¯y•≥" y" (y•≥" u"x(≥ (vy(y- u uīyx(•' • (ī≤y(randomized participants and the treatment regimen estimand data points sets as described in Section 9.2.

Missing data should be minimized for estimating the treatment regimen estimand. If there are occurrences of missing data despite the best precautions, missing data should be imputed in a manner consistent with what the values would likely have been had they been collected. In general, 5 scenarios are considered regarding the treatment journey of a trial participant relative to the primary time point (Week 72 visit) as shown in the below figure.



In principle, missing data due to permanent discontinuation of study intervention (Scenario 4) will be imputed using retrieved dropouts (MI-RD), namely using multiple imputation based on data retrieved from participants who permanently discontinued study intervention but continued in the study with non-missing measurements from the same treatment group. The overall imputation procedure is provided in the below table.

Scenario (Treatment/Treatment Period Discontinuation; Missingness Status at Endpoint)	**Methods to Handle Missing Values at Endpoint**
1. No study intervention or treatment period discontinuation; no missing value	N/A
2. No study intervention or treatment period discontinuation; with missing value	Use data from Scenario 1 to impute under the MAR assumption. There should be very few such cases in a clinical trial.
3. Study intervention discontinuation with no treatment period discontinuation; no missing value	N/A
4. Study intervention discontinuation with treatment period discontinuation at a subsequent visit or completion of treatment period; with missing value	Use data from Scenario 3 (MI-RD) to impute missing values by treatment group.
5. Treatment period discontinuation resulting in study intervention discontinuation; with missing value	5A: If the treatment period discontinuation is possibly related to study intervention, use data from Scenario 3 (MI-RD) to impute. In this case, it is assumed that the treatment discontinuation is related to study intervention. 5B: If the treatment period discontinuation is clearly due to administrative reasons not related to study medication, use data (observed and imputed) in Scenarios 1 to 4, and 5A to impute. The reason for the study intervention discontinuation for this scenario is considered not related to study intervention.

Abbreviations: MAR = missing at random; N/A = not applicable.

Additional details regarding the imputation for missing values will be described in the SAP.

For percent change in body weight at Week 72, missing data will be imputed and then will be analyzed using an ANCOVA model with adjustment for baseline body weight and stratification factors (Ye et al. 2022).

d¯≥“ u¯ (’ v.yw≥ y•(u→”yx(ī’ (ī≤y(yzz≥wuw (y•≥“ u”x(≥→(∨y(y- u—uīyx(•≥”• (ī≤y(randomized participants and the efficacy estimand data points set (Section 9.2).

Details regarding the imputation for missing values will be described in the SAP.

Percent change in body weight will be analyzed using a mixed model for repeated measures model characterizing percent change in body weight over time.

Additional details of the statistical modeling will be provided in the SAP.

9.3.4. Secondary Endpoints and Estimands Analyses

The null hypotheses corresponding to the key secondary objectives can be found in Section 9.1. Key secondary objectives aligned with both estimands described in Section 9.3.3 will be evaluated.

Key secondary endpoint analyses will be controlled for type 1 error.

Details for additional secondary analyses will be provided in the SAP.

9.3.5. Tertiary Endpoints and Estimands Analyses

Details for tertiary analyses will be provided in the SAP.

9.3.6. Pharmacokinetic/Pharmacodynamic Analyses

LY3502970 concentration data will be analyzed using a population PK approach using nonlinear mixed-effects modeling techniques implemented on the NONMEM software. The relationships between LY3502970 doses and/or concentration and selected efficacy, tolerability, and safety endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic participant factors such as age, weight, sex, and renal function on LY3502970 PK and/or PD parameters may be examined as needed. Further details will be provided in the SAP.

9.3.7. Safety Analyses

Safety analyses will be conducted using the safety participants and the safety data points set.

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported by preferred terms within system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized Medical Dictionary for Regulatory Activities Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study intervention discontinuation due to AEs, deaths, and other CV endpoints. Counts and percentages of participants experiencing AEs will be reported for each ī¯yuī“ y”ī(•¯’ „ʃu”x(R≥•≤y¯ •(y uwī(īy•ī(≥→(∨y(•yx(ī’ (ẇ“ „u¯y(ī≤y(ī¯yuī“ y”ī(•¯’ „•7

9.3.7.1. Adverse Events of Special Interest and Other Safety Topics

The analysis details for the AEs of special interest and other safety topics (as defined in Section 8.3.3) will be provided in the SAP.

9.3.7.2. Gastrointestinal Events

Summaries and analyses for incidence, prevalence, and severity of nausea, vomiting, constipation, and diarrhea will be provided by treatment group.

9.3.7.3. Central Laboratory Measures, Vital Signs, and Electrocardiograms

Actual and change from baseline to postbaseline values of central laboratory measures, vital signs, and selected ECG parameters will be summarized at each scheduled visit. Continuous variables, as well as the change from baseline for these variables, will be analyzed by MMRM models as described in Section 9.3.1. The percentages of participants with treatment-emergent abnormal, high, or low measures (including laboratory, vital, and ECG parameters) will be ● “ “ u¯≥yx(u”x(w’“ „u¯yx(vyī yy”(ī¯yuī“ y”ī(•¯’ „●(●≥’•(R≥●≤y¯ ●(y uwī(īy●ī(’¯(dyu¯●’” ●(O≤≥ square test.

9.3.8. Other Analyses

Subgroup analyses

Subgroup analyses to assess consistency of the effect of LY3502970 across subgroups for the primary endpoints will be detailed in the SAP. The following subgroups will be considered (but not limited to):

M• y(•¯’ „(lHBA5(BA(yu¯●2
Sex (female, male)
Baseline background oral AHMs (according to potential effect on body weight change)
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Race
Ethnicity
Country/Region

The interaction of subgroup and treatment will be evaluated to assess the treatment by subgroup interaction. A forest plot including the treatment difference and 95% CI estimated for each subgroup level will be presented. Subgroup analyses will be performed vu●yx(’”(ī≤y(ī¯yuī“ y”ī(¯y•≥“ y” (y●ī≥“ u”x7(Additional subgroup analyses may also be performed.

If the number of participants is too small (less than [10%]) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. Further details on the statistical analysis will be provided in the SAP.

Analysis of C-SSRS data

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

9.4. Interim Analysis

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

9.5. Sample Size Determination

A sample size of 1,500 participants (CCI participants per LY3502970 treatment group and CCI placebo participants) provides more than 90% power to demonstrate superiority of CCI mg, CCI mg, and/or CCI mg LY3502970 to placebo with regards to mean percent change in body weight from baseline to Week 72. The sample size determination assumes that evaluation of superiority of CCI mg, CCI mg, and CCI mg LY3502970 to placebo will be conducted in parallel, each at a 2-sided significance level of 0.016 using a 2-sample t-test for the "treatment regimen" estimand. Additionally, a difference of at least 5% mean body weight reduction at 72 weeks for CCI mg, CCI mg, and CCI mg LY3502970 compared with placebo, a common SD of 10%, and a dropout rate of 30% in the placebo group and 20% in the LY3502970 groups are assumed for statistical power calculations.

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
- Applicable laws and regulations

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

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

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

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of study conduct for participants under their responsibility and adherence to requirements of 21 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 completion of the study.

10.1.3. Informed Consent Process

The investigator or ī≤y(≥”- y●ī≥• uī’ ¯ ●representative will explain the nature of the study, including the risks and benefits, to the potential participant (or the potential „u¯ī≥w≥„u”ī ● legally authorized representative) and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants (or their legally authorized representatives) 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.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant (’ ¯(ī≤y(„u¯ī≥w≥„u”ī ●(–y• u—(authorized representative) and is kept on file.

10.1.4. Data Protection

Participants will be assigned a unique identifier by the sponsor ī’ („¯’ īywī(ī≤y(„u¯ī≥w≥„u”ī ●(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.

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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, including data transfer, 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 u”x(„¯’ wy●●y●7h≤y(●„’ ”●’ ¯ ●(„¯’ wy●●y●(u¯y(w’ “ „→a”ī(≥ī≤(—’ w—u—(„¯≥ uw (—u— ●(u”x relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

10.1.5.1. Clinical Endpoint Committee

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

Prospective adjudication of major adverse CV events and pancreatic AEs will be performed for this study. Sections 8.3.3.1 and 8.3.3.8 outline additional information on CV and pancreatic adjudication committees.

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 PK or genetic data.

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

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

Data and documents, including the study protocol, SAP, 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

Investigator responsibilities

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.

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

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

Data monitoring and management

Quality tolerance limits will be pre-defined to identify systematic issues that can impact participant safety and/or reliability of study results. These pre-defined parameters will be monitored during the study and important excursions from the 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 retention and audits

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, 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 sponsor or its representatives, and/or regulatory agencies at any time. Investigators will be given notice before an audit occurs.

Data capture system

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

Electronic data capture system

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

Clinical outcome assessments

The COA data (participant-focused outcome instrument) and other data will be collected by the authorized study personnel via a paper source document and will be transcribed by the authorized study personnel into the EDC system.

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

Data storage and access

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

Data managed by a central vendor, such as laboratory test data, will be stored electronically in ī≤y(wy”ī¯u-(–y”x’¯ •(xuīuvu•y(• •ī‘“ (u”x(reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. g’ ¯wy(x’ w “ y”ī•(u¯y(z≥yx(uī(ī≤y(≥”- y•ī≥• uī’¯ •(•ī≥y7

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 10.1.7.

10.1.9. Study and Site Start and Closure

First act of recruitment

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

Study or site termination

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

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

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

For study termination:

Discontinuation of further study intervention development

For site termination:

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

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

Ư(uww¯xu”wy(≥ī≤(ī≤y(●„’ ”●’ ¯ ●(„ v–≥wuī≥’ ”(„’ –≥w , 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 use of new technologies, response to regulatory questions, and investigation oz(- u¯≥uv–y(¯y●„’ ”●y(ī≤uī(“ u (”’ ī(vy(’ v●y¯- yx(”ī≥(–uīy¯(≥”(ī≤y(xy- y¯–„“ y”ī(’ z LY3502970 ’ ¯(uzīy¯ LY3502970 vyw’ “ y1●2(w’ “ “ y¯w≥u——(u- u≥uv–y.

Sample Type	Custodian	Retention Period After Last Participant Visit[a]
Exploratory biomarkers	Sponsor or Designee	7 years
Pharmacokinetic	Sponsor or Designee	1 year
Genetics/PD	Sponsor or Designee	7 years

[a] Retention periods may differ locally.

10.2. Appendix 2: Clinical Laboratory Tests

The tests detailed in the table below will be performed by 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/analyte 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 - Red Blood Cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - White Blood Cells)	
Differential	
Absolutes count of:	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	To be performed if abnormalities are detected
Clinical chemistry	Assayed by Lilly-designated laboratory
Sodium	

Potassium	
Chloride	
Bicarbonate	
Total bilirubin	
Direct bilirubin	
Alkaline phosphatase (ALP)	
Alanine aminotransferase (ALT)	
Aspartate aminotransferase (AST)	
Gamma-glutamyl transferase (GGT)	
Blood urea nitrogen (BUN)	
Creatinine	
Creatine kinase (CK)	
Uric acid	
Total protein	
Albumin	
Calcium	
Phosphorus	
Glucose	
Lipid panel	Assayed by Lilly-designated laboratory
Total Cholesterol	
Triglycerides	
Low-density lipoprotein cholesterol (LDL-C)	Generated by Lilly-designated laboratory. If triglycerides are >400 mg/dL, the direct LDL will be directly measured.
Very Low-density lipoprotein cholesterol (VLDL-C)	Generated by Lilly-designated laboratory
High-density lipoprotein cholesterol (HDL-C)	Generated by Lilly-designated laboratory
Non-High density lipoprotein cholesterol (non-HDL)	Generated by Lilly-designated laboratory
Hepatitis serology	Assayed by Lilly-designated laboratory.
Hepatitis C Virus (HCV) testing:	
HCV antibody	
HCV RNA	Performed only for participants who test positive for anti-HCV
Hepatitis B Virus (HBV) testing:	
HBV DNA	Performed only for participants who test positive for anti-HBc.
Hepatitis B core antibody (HBc-Ab)	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B surface antibody (anti-HBs)	
Hormones (female)	Assayed by Lilly-designated laboratory unless stated otherwise.
Serum pregnancy	

Urine pregnancy	Assayed and evaluated locally
Follicle stimulating hormone (FSH)	
Urine chemistry	Assayed by Lilly-designated laboratory.
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	CKD-EPI Creatinine equation (2021), Results will not be provided to the investigative sites.
eGFR (CKD-EPI)	CKD-EPI Cystatin-C equation (2012) Results will be used for eligibility criteria.
Urinary albumin/creatinine ratio (UACR)	
Other testing	Assayed by Lilly-designated laboratory.
Apolipoprotein B	Results will not be provided to investigative sites.
HbA1c	
Calcitonin	
Pancreatic Amylase	
Lipase	
Thyroid stimulation hormone (TSH)	
Insulin	Results will not be provided to investigative sites.
C-peptide	Results will not be provided to investigative sites.
C-reactive protein, high-sensitivity (hsCRP)	Results will not be provided to investigative sites.
Free fatty acids	Results will not be provided to investigative sites.
Cystatin-C	Results will not be provided to investigative sites.
Pharmacokinetic samples LY3502970 concentration	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Genetics sample	DNA isolation and assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Whole blood (EDTA)	
Exploratory biomarker storage samples	Assayed by Lilly-designated laboratory. Results will not be provided to the investigative sites.
Serum	
Plasma (EDTA)	

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

Timing	Laboratory Test [a]
Collect from 30 min to 4 hr after the start of the event. Note: The optimal collection time is from 1 to 2 hr after the start of event.	total tryptase

[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.

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

10.3.1. Definition of AE

AE definition

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

Events meeting the AE definition

Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (for example, ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (that is, not related to progression of underlying disease).
Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition.
New 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 <u>NOT</u> meeting the AE definition

Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the
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The disease/disorder being studied or expected progression, signs, or symptoms of the x≥●yu●y&x≥●’ ¯xy¯(vy≥”• (●ī x≥yx5(”–y●●(“ ’ ¯y(●y- y¯y(ī≤u”(y „ywīyx(z’ ¯(ī≤y(„u¯ī≥w≥„u”ī •(
condition.
Medical or surgical procedure (for example, endoscopy and appendectomy): the condition that leads to the procedure is the AE.
Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

An SAE is defined as any untoward medical occurrence that, at any dose, meets 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 „≤ •≥wzu" •(' zz≥wy(' ¯(' ī„uī≥y"ī(•yīī≥'• 7(O' " „–≥wuī≥' "•(ī≤uī(' ww ¯(x ¯≥'•(hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious.
- Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

Results in persistent disability/incapacity

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- 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.

PCs related to study interventions used in clinical trials are collected to ensure the safety of participants, monitor quality, and to facilitate process and product improvements. Investigators will instruct participants to contact the site as soon as possible if he or she has a PC or problem with the study intervention 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.

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 ≥”z’ ¯“ uī≥ ”(≥’(ī≤y(„u¯ī≥w≥„u”ī •(medical records, in accordance with ī≤y(≥’- y•ī≥• uī’ ¯ •(”’ ¯“ u–(w≥”≥wu–(„¯uwī≥wy7(ME/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** uwwy„īuv–y(z’ ¯(ī≤y(≥’- y•ī≥• uī’ ¯(ī’ (•y”x(„≤’ ī’ w’ „≥y•(’ z(ī≤y(„u¯ī≥w≥„u”ī •(“ yx≥wu–(– records to 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 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 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 1 of the pre-defined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship.
M(¯yu● ’ ”uv–y(„ ’ ●●>v≥≥I (’ z(u(¯y–ui≥ ’ ”●<>„(w ’ ”- y ●(ī≤uī(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.
For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to sponsor or designee. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to sponsor or designee.
The investigator may change their opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
The causality assessment is 1 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 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 should make every effort to provide sponsor or designee with a copy of any postmortem findings including histopathology.

10.3.5. Reporting of SAEs

SAE reporting via an electronic data collection tool

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

SAE reporting via paper form

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

10.3.6. Regulatory Reporting Requirements

SAE regulatory reporting

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

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. 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
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they have a congenital anomaly such as Müllerian agenesis 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	The postmenopausal state is defined as a woman: at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note or aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle stimulating hormone 4s0 mIU/mL or 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. [a] Women **should not** be taking medications during amenorrhea such as oral contraceptives, hormonal replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea. Females on HRT and those whose menopausal status cannot be confirmed will be required to comply with protocol contraception requirements if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Females
WOCBP who are completely abstinent as their preferred and usual lifestyle, or in a same sex relationship as their preferred and usual lifestyle:

	)
agree to either remain abstinent or stay in a same sex relationship without sexual relationships with males and not plan a pregnancy during the study	use periodic abstinence methods o calendar o ovulation o symptothermal, or o post-ovulation declare abstinence just for the duration of a trial, or use the withdrawal method

WOCBP who are NOT completely abstinent as their preferred and usual lifestyle, or NOT in a same-sex relationship as their preferred and usual lifestyle, must do the following:

Topic	Condition
Pregnancy testing	Have a negative serum test result at screening followed by a negative urine result within 24 hours prior to treatment exposure. See the protocol SoA for subsequent pregnancy testing requirements.
Contraception	Agree to use 2 forms of effective contraception, where at least 1 form must be highly effective. These forms of contraception must be used during the study and after the study for at least 30 days after the last dose of the study intervention.

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WNOCBP definition above combination oral contraceptive pill progestin-only contraceptive pill (mini-pill) implanted contraceptives[a] injectable contraceptives[a] contraceptive patch (only women <198 pounds or 90 kg) total abstinence vasectomy (for men in clinical trials and for female partner if only sexual partner) fallopian tube implants (if confirmed by hysterosalpingogram) combined contraceptive vaginal ring, or

	intrauterine devices
Effective contraception	male or female condoms with spermicide diaphragms with spermicide or cervical sponges barrier method with use of a spermicide o condom with spermicide o diaphragm with spermicide, or o female condom with spermicide Note: Male and female condoms should not be used in combination.
Ineffective forms 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]Participants that have started implantable or injectable contraceptives within 18 months prior to Visit 1 will be excluded from the study.

Males

Males may participate in this trial.

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

10.5. Appendix 5: Genetics

Use/Analysis of DNA

Genetic - u¯≥ūī≥’ ”(“ u (≥“ „uwī(u(„u¯ī≥w≥„u”ī •(¯y•„’ ”•y(ī’ (•ī x (≥”ī¯- y”ī≥’ ”5(• •wy„ī≥v≥≥ī (
to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a blood sample will be collected for DNA analysis from consenting participants.

DNA samples may be used for research related to LY3502970 or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases. They may also be used to develop tests/assays including diagnostic tests related to LY3502970, study interventions related to this drug class, or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases. Genetic research may consist of the analysis of 1 or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome as appropriate.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to LY3502970 or study interventions related to this class to understand diabetes, obesity, related traits or complications or related conditions.

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

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

The samples will be retained while research on LY3502970 or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases continues but no longer than the sample retention limits described in Section 10.1.12, or other period as per local requirements.

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

Hepatic evaluation testing

See Section 8.2.7 for guidance on appropriate test selection.

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

In circumstances where required in accordance with local regulations, local laboratory testing may be performed in lieu of Lilly-designated central laboratory testing (in the table below).

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

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

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

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

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

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

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

10.7. Appendix 7: World Health Organization Classification of Diabetes and Diagnostic Criteria

Type 1 diabetes

T1D is judged to be present when the classical symptoms of diabetes (thirst, polyuria, wasting and stupor, or coma) are associated with readily detectable concentrations of glucose and ketone bodies in the blood and urine. Insulin treatment is necessary not only to control hyperglycemia but also to prevent spontaneous ketosis and death.

Type 2 diabetes

T2D, although often asymptomatic, may also present with classical hyperglycemic symptoms (thirst, polyuria, weight loss), but despite hyperglycemia, ketone bodies are present in only low concentrations in the blood and urine. Coma is rare in T2D but may result from extreme hyperglycemia and hyperosmolarity; lactic acidosis or ketoacidosis can also occur in fulminating illness (for example, severe infection or mesenteric artery thrombosis) due to an acute increase in insulin requirements, but spontaneous ketosis does not occur. Some patients with T2D later progress to a state of absolute insulin deficiency (Alberti and Zimmet 1998).

10.8. Appendix 8: Prohibited Medications or Medications with Special Use Restrictions

10.8.1. Excluded/Prohibited or Restricted Use Medications

Medications within the following categories are strictly prohibited during the study, except CCI , as outlined in Section 6.9.3. The lists below provide examples of each category of medication, but the examples are not exhaustive.

In addition, please note that while some GLP-1 medications (e.g., semaglutide, liraglutide) are listed under both weight loss and antihyperglycemic medications, the duration for eligibility depends on the indication for which the medication was being used. If for weight loss, then the duration must be >180 days.

10.8.1.1. Antihyperglycemic Medications

The following glucose-lowering medications within 90 days of Visit 1 or any time during the study are prohibited.

- dulaglutide
- liraglutide
- semaglutide
- exenatide
- tirzepatide
- pramlintide
- sitagliptin
- saxagliptin
- linagliptin
- alogliptin

10.8.1.2. Weight Loss Medications

Weight loss medications within 180 days of Visit 1 or any time during the study are prohibited.

- liraglutide
- semaglutide
- orlistat
- sibutramine
- phenylpropanolamine
- mazindol
- phentermine
- lorcaserin
- phentermine/topiramate
- naltrexone/bupropion

- ingested material that transiently occupies space in the stomach, for example, Plenity®
- over-the-counter medications, for example, alli®

10.8.1.3. Weight Gain Medications

Participants are excluded if they have initiated or changed dose for the following medications, which may cause weight gain, within 12 months prior to Visit 1. Common examples of these medications are the following:

- imipramine
- amitriptyline
- mirtazapine
- paroxetine
- phenelzine
- chlorpromazine
- thioridazine
- clozapine
- olanzapine
- quetiapine
- valproic acid (and its derivatives)
- lithium
- paroxetine

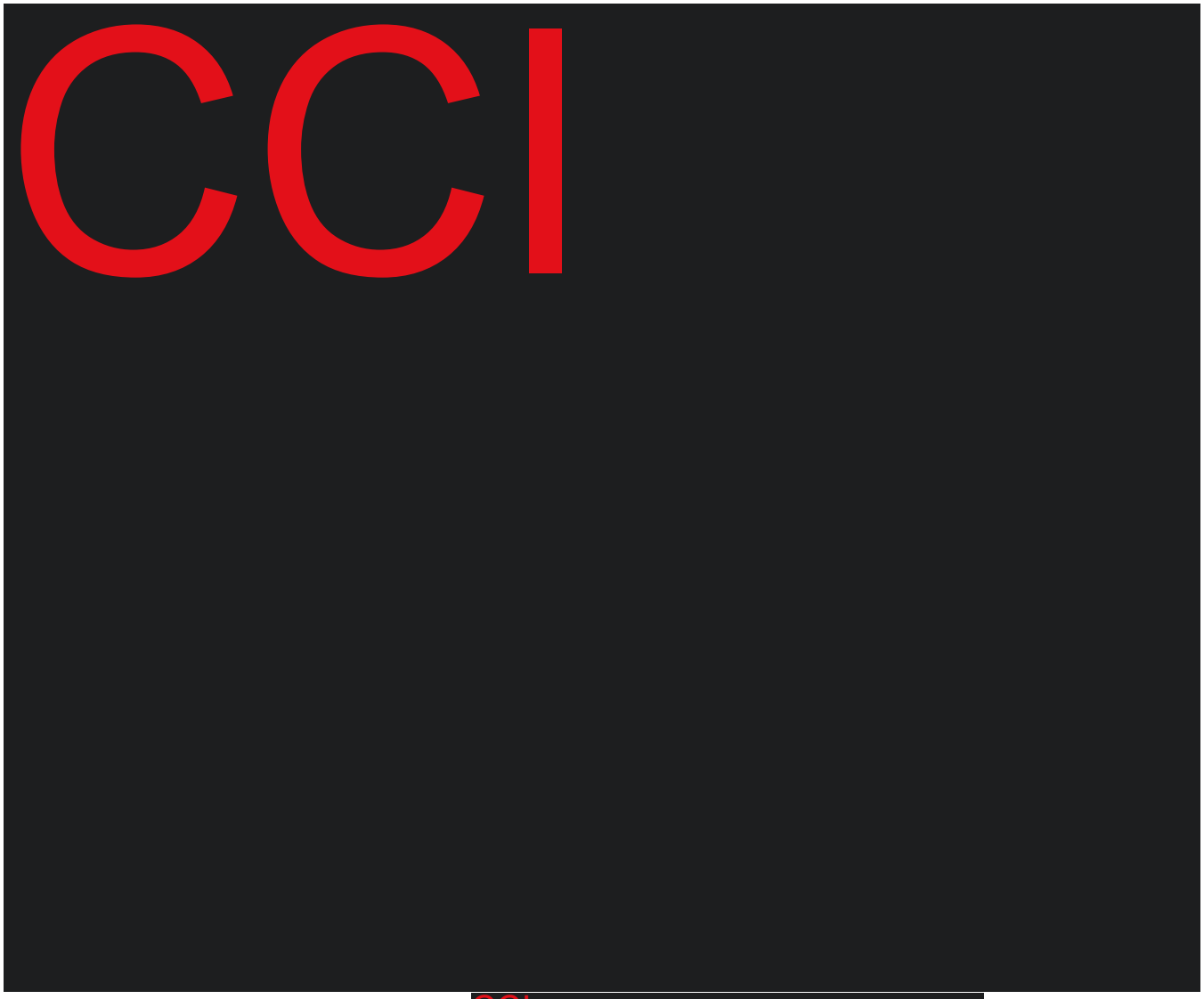
Initiation of these medications during the study is strongly discouraged, and alternative therapies which do not lead to weight gain should be considered instead.

CCI

Participants cannot be taking strong CCI CCI CCI within 2 weeks prior to randomization at Visit 3 or at any time while taking study intervention. To be eligible for randomization into this study, those drugs need to be washed out for at least 2 weeks prior to Visit 3 and the participant should be on a stable dose of alternative medications for at least 2 weeks prior to randomization at Visit 3.

Non-exhaustive lists of examples of these medications are provided below:

CCI



[a] Participants taking these medications CCI CCI should, if appropriate, switch to at least 2 weeks prior to randomization at Visit 3:



[b] For participants taking CCI may be substituted at least 2 weeks prior to randomization at Visit 3.





10.8.2. Medications with Special Use Restrictions





Approved on 31 Oct 2023 GMT

10.9. Appendix 9: Standardized Protocols for the Measurement of Height, Weight, Waist Circumference and Vital Signs

The following information has been adapted from standardized physical measurement protocols z’ ¯(ī≤y(k Tc •(ghQd ≥•y(u,,,,¯’ uw≤(ī’ (g ¯- y≥—u”wy(lghQdg2(lk Tc (; 9: C27

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. M•—(ī≤y(,,u¯ı≥w≥,,u”ī(ī’ (v¯yuī≤y(≥’(u”x(•īu”x(īu—7(a yu• ¯y(u”x(¯yw’ ¯x(ī≤y(,,u¯ı≥w≥,,u”ī •(height in centimeters 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 to 1 decimal place.

All weights for a given participant should be measured using the same scale, whenever possible, at approximately the same time in the morning after evacuation of bladder contents.

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

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

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

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

Measuring waist circumference

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

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

Step 1*:* Ask the participant to wear little clothing (if available, patient gowns 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*:* M●–(ī≤y(„u¯ī≥w≥„u”ī(ī’ (¯y–u– (u”x(“ yu● ¯y(ī≤y(„u¯ī≥w≥„u”ī ●(u≥●ī(w≥w “ zy¯y”wy7

Vital sign measurements (blood pressure and heart rate)

Measure vital signs before obtaining an ECG tracing and before collection of blood samples for laboratory testing

Have the participant sit quietly for about 5 minutes before vital signs measurements are taken

For each parameter, take 3 measurements from the same arm, preferably the nondominant arm

Measure the recordings at least 1 minute apart

BP must be taken with an automated BP instrument

Heart rate is measured by pulse

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

If BP and pulse measurements are taken separately, pulse should be taken prior to BP.

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

10.10. Appendix 10: Country-specific Requirements

10.10.1. Germany

This section describes protocol changes applicable for adult participants in study sites in Germany.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
5.2. Exclusion Criteria	Added an exclusion criterion for individuals who are committed to an institution	Per Article 34 of EU Regulation No. 536/2014 in conjunction with Section 40(a) S. 1 No. 2 of the AMG.
7.2. Participant Discontinuation/Withdrawal from the Study 8.3. Adverse Events, Serious Adverse Events, and Product Complaints 10.1.3. Informed Consent Process 10.12. Appendix 12: Abbreviations and Definitions	P y ~~yī~~yx(¯yzy¯y”wy●(ī’ (~~ y•~~ u—(u ī≤’ ¯≥ yx(¯y,,¯y●y”īuī≥ y5 (~~ y•~~ u ~~(•~~ u¯x≥u”5 (,,u¯y”ī● (	The German Drug Law (Arzneimittelgesetz AMG) with reference to EU Regulation 536/2014 requires that adult participants act on their own behalf and provide their own written informed consent. If written consent is not possible, verbal consent with a witness is acceptable. No legal representative consent is accepted.
10.1.9. Study and Site Start and Closure	Updated the criteria for study closure	Per Annex I Section D Number 17 letter p) of EU Regulation No. 536/2014 and Article 77 of the Regulation (EU) Number 536/2014 i.c.w. Section 42 Paragraph 6 AMG. 5.4.19.
10.11. Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances	Revision in temporary measures	In Germany, the temporary measures described in the Section 10.12 are applicable only to the COVID-19 pandemic.

The revised text in the following sections show the changes applicable for adult participants at study sites in Germany. Deletions are identified by ~~strikethrough format~~.

5.2. Exclusion Criteria

48. Are committed to an institution.

7.2. Participant Discontinuation/Withdrawal from the Study

A participant may withdraw from the study:

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at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons

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.

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

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

AEs
SAEs, and
PCs

These events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, ~~’ ¯(ī≤y(„u¯ī≥w≥„u”ī •(y• u (u ī≤’ ¯≥ yx(¯y„ ¯y•y”īuī≥ y2~~.

10.1.3. Informed Consent Process

h≤y(≥”- y•ī≥• uī’ ¯(’ ¯(ī≤y(≥”- y•ī≥• uī’ ¯ •(¯y„ ¯y•y”īuī≥ y(≥ (y „ ~~u≥~~”(ī≤y(”uī ¯y(’ z(ī≤y(•ī x 5(≥”w x≥”• (ī≤y(¯≥• •(u”x(vy”yz≥ī•5(ī’ (ī≤y(„’ īy”ī≥u („u¯ī≥w≥„u”ī(l’ ¯(ī≤y(„’ īy”ī≥u („u¯ī≥w≥„u”ī •(legally authorized representative) and answer all questions regarding the study.

Potential participants must be informed that their participation is voluntary. Participants ~~(or their legally authorized representatives)~~ 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.

Participants must be reconsented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the participant ~~l’ ¯(ī≤y(„u¯ī≥w≥„u”ī •(y• u (~~ ~~authorized representative)~~ and is kept on file.

10.1.9. Study and Site Start and Closure

Study or site termination

For study termination:

Discontinuation of further study intervention development

<u>If the approval of the responsible National Competent Authority has been revoked.</u>

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

In Germany, the temporary measures described in the Section 10.11 are applicable only to the COVID-19 pandemic.

Section 10.12. Appendix 12: Abbreviations and Definitions

enter	Participants entered into a study are those who sign the informed consent form directly ~~or through their legally acceptable representatives.~~

10.10.2. Brazil

This section describes protocol changes applicable to adult participants at study sites in Brazil.

This table describes the changes and provides a rationale for the changes.

Protocol Section Number and Name	Description of the Change	Brief Rationale
5.2. Exclusion Criteria	Exclusion criterion #45 90 days is changed to 1 year.	Resolution No. 251 (Brazil 1997). The National ERB Brazil recommends not having a participant enter a new clinical study if less than 1 year has elapsed since participation in another clinical study of an investigational drug or device unless there is a direct benefit to the research participant.
10.1.12. Sample Retention	Biological samples will be stored for up to 10 years.	Compliance with Brazilian regulation applicable to sample storage, resolution CNS 441 (Brazil 2011).
10.5. Appendix 5: Genetics	Biological samples obtained to evaluate genetic material (DNA/RNA).	Compliance with Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011).
Patient Access to Project Benefits	New section specific to Brazil.	Clarifies the sponsor responsibilities to comply with Resolution CNS 466 (Brazil 2012) and RDC 38 (Brazil 2013).
Section 11. References	Addition of Brazil-specific references	The references are specific to the Brazil-specific requirements.

The revised text described below shows the changes applicable to adult participants at study sites in Brazil. Deletions are identified by ~~strikethrough format~~ and additions by <u>underlined text</u>.

Section 5.2. Exclusion Criteria

45. ~~Have participated in a clinical study and received treatment, whether active or placebo within 90 days prior to Visit 1.~~

    <u>Are currently enrolled in, discontinued, or completed within a period of 1 year, before inclusion, a clinical study involving an investigational intervention or nonapproved use of a drug or device, or concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study unless there is direct benefit to the research subject. A time period of 90 ~~30~~ days, as indicated by the protocol, must still be followed if a direct benefit to the research participant is identified.</u>

Section 10.1.12. Sample Retention

In Brazil, the biological samples obtained within this study will be stored for up to 10 years, with possibility of renewal under request, followed by appropriate justification and a report with all activities developed with the biological samples (CNS 441/2011). The sample and any data generated from it can be linked back to the participant only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study intervention.

Section 10.5. Appendix 5: Genetics

In Brazil, the biological samples from this study used to evaluate genetic material (DNA/RNA) will follow the Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011). The sample and any data generated from it can be linked back to the participant only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study drug.

Patient Access to the Project Benefits

In Brazil, at the end of their participation in the study, all participants must have assured access to the best proven prophylactic, diagnostic, and therapeutic methods, which may include LY3502970, identified through the study (CNS 466/2012 and RDC 38/2013).

Section 11. References

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 251/1997 do Conselho Nacional de Saúde/MS: Normas de Pesquisa com Novos Fármacos, Medicamentos, Vacinas e Testes Diagnósticos Envolvendo Seres Humanos.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 466/2012 do Conselho Nacional da Saúde / MS: Diretrizes e Normas Regulamentadoras de Pesquisas Envolvendo Seres Humanos. Publicado no Diário Oficial da União em 13 de junho, 2013.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 340/2004 do Conselho Nacional da Saúde/MS: Diretrizes para Análise Ética e Tramitação dos Projetos de Pesquisa da Área Temática Especial de Genética Humana.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução 441/2011 do Conselho Nacional da Saúde / MS: Diretrizes para análise ética de projetos de pesquisas que envolvam armazenamento de material biológico humano ou uso de material armazenado em pesquisas anteriores.

BRASIL, MINISTÉRIO DA SAÚDE. Resolução-RDC 38/2013 da Agência Nacional deVigilância Sanitária/MS: Aprova o regulamento para os programas de acesso expandido, usocompassivo e fornecimento de medicamento pós-estudo.

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.

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

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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 f y“ ’ īy(j ≥•≥ī•5
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

Telehealth: 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

collection of AEs
administer C-SSRS since last assessed
review ediary
review diet and physical activity goals
review SMBG values and
concomitant medications.

Mobile healthcare or other alternative locations: 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,

concomitant medications
vital signs (BP and PR)
body weight
patient-reported outcomes
collection of blood samples
physical assessments, and
collection of health information.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local laboratory testing option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: Visits 1, 3, 21, ED, and Visit 801. The local laboratory must be qualified in accordance with applicable local regulations.

Study intervention and ancillary supplies (including participant diaries)

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

asking the participant to go to the site and receive study supplies from site staff without completion of a full study visit
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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
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When delivering supplies to a location other than the study site (for example, „u¯ı≥w≥„u”ī ●(≤’“ y2(ī≤y(≥’-y●ı≥•utor or sponsor, or both should ensure oversight of the shipping process to ensure accountability and product quality (that is, storage conditions maintained and intact packaging upon receipt).
Instructions may be provided to the participant or designee on the final disposition of any unused or completed study supplies.

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at screening visit are valid for a maximum of 30 days. The following rules will be applied for active, nonrandomized participants whose participation in the study must be paused due to exceptional circumstances:

If screening is paused for less than 30 days from screening visit to randomization visit: the participant will proceed to the next study visit per the usual SoA, provided that randomization visit must be conducted within 30 days from first screening visit.
- The site should conduct the next visiī(≥z(ī≤y(„u¯ı≥w≥„u”ī ●(y–≥•≥v≥–ī (w¯ıy¯≥u(u¯y(confirmed, and the site should document the reason for delay.
- Due to the pause in screening, sites should also reconfirm the impacted „u¯ı≥w≥„u”ī ●(w’”●y”ī(u”x(x’w“ y”ī(ī≤–●(w’”z≥“ uī≥”(≥’(ī≤y(●’ ¯wy(documentation.

If screening is paused for more than 30 days from screening visit to randomization visit: 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 reconsent and be rescreened as a new participant. The screening procedures per the usual SoA should be followed, starting at screening visit to ensure participant eligibility by randomization visit.

Adjustments to visit windows

Whenever „’ ●●≥v–y(u”x(●uzy(ī’(x’(●’ 5(u●(xyīy¯“ ≥”yx(v (ī≤y(≥’-y●ı≥•uī’¯ ●(x≥●wyī≥”5(„u¯ı≥w≥„u”ī●(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
In-person site Visit 3 through Visit 9	within 6 days before or after the intended date per the SoA
In-person site Visit 12 to 21	within 14 days before or after the intended date per the SoA
Telehealth Visit 10 to 20	within 6 days before or after the intended date per the SoA
Visit 801	up to 28 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 ≥”- y◐≥ uī’ ¯ ●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
ADA-EASD	The American Diabetes Association and the European Association for the Study of Diabetes
AE	adverse event
AHM	antihyperglycemic medication
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CCI	
BG	blood glucose
BMI	body mass index
blinding/masking	A single-blind study is one in which the investigator and/or the investigator's staff are aware of the treatment but the participant is not, or vice-versa, or when the sponsor is aware of the treatment but the investigator and/the investigator's staff and the participant are not. A double-blind study is one in which neither the participant nor any of the investigator or sponsor staff who are involved in the treatment or clinical evaluation of the subjects are aware of the treatment received.
CEC	clinical endpoint committee
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease-Epidemiology
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.
CONSORT	Consolidated Standards of Reporting Trials
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
CV	Cardiovascular
CCI	

DMC	data monitoring committee. A data monitoring committee is a group of independent scientists who are appointed to monitor the safety and scientific integrity of a human research intervention, and to make recommendations to the sponsor regarding the stopping of a study for efficacy, or for harm, or for futility. The composition of the committee is dependent upon the scientific skills and knowledge required for monitoring the particular study.
DPP-4i	Dipeptidyl peptidase-4 inhibitor
ECG	Electrocardiogram
ED	Early discontinuation
EDC	Electronic data capture
eGFR	estimated glomerular filtration rate
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
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IB	Ư- y●≥• uī≥’ ”u-(a yx≥w≥”u-(d¯’ x wī(l•yy(u-●’ (≥’- y●≥• uī≥’ ”u-(,,¯’ x wī 2 A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
ICE	Intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Ư- y●≥• uī≥’ ”u-(a yx≥w≥”u-(d¯’ x wī(l•yy(u-●’ (≥’- y●≥• uī≥’ ”u-(,,¯’ x wī 2 A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
INR	International normalized ratio
IRB	Institutional Review Board
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 ¯y-y- u”ī(ī’ (ī≤y(,,u¯ī≥w≥,u”ī •(xyw≥≥on to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.

investigational product	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including products already on the market when used or assembled (formulated or packaged) in a way different from the authorized form, or marketed products used for an unauthorized indication, or marketed products used to gain further information about the authorized form. See also "IMP."
IWQOL-Lite-CT	Impact of Weight on Quality of Life-Lite Clinical Trial
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: the right participant, the right drug, the right dose, right route, at the right time. In addition to the core five rights, the following may also represent medication errors: • dose omission associated with an AE or a product complaint • dispensing or use of expired medication • use of medication past the recommended in-use date • dispensing or use of an improperly stored medication • use of an adulterated dosage form or administration technique inconsistent with the medication's labeling (for example, Summary of Product Characteristics, IB, local label, protocol), or • shared use of cartridges, prefilled pens, or both.
MEN2	Multiple endocrine neoplasia 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
MMRM	Mixed Model for Repeated Measures
MRI	Magnetic Resonance Imaging
MTC	Medullary thyroid cancer
CCI	
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
PGIC	Patient Global Impression of Change
PGIS	Patient Global Impression of Severity
PHQ-9	Patient Health Questionnaire-9
CCI	
PK/PD	pharmacokinetics/pharmacodynamics
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
PT	prothrombin time
QD	once daily
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.
SD	standard deviation
SF-36v2	Short Form-36 version 2 Health Survey Acute Form
SGLT-2	sodium-glucose cotransporter-2
SIB	Suicidal Ideation or Behavior
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	Upper limit of normal
WHO	World Health Organization

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 (TOC).

Amendment [c]: 24-Aug-2023

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The primary rationale for this amendment is to address regulatory feedback. Changes and rationale are summarized in the table below.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.1 Germany	Updated the table to indicate which sections of the protocol were updated per German regulations.	Per German regulations.
	Added the following (the underscore indicates additions to the initial protocol text):	
	Section 5.2. Exclusion Criteria 48. Are committed to an institution.	
	Section 10.1.9. Study and Site Start and Closure For study termination: • Discontinuation of further study intervention development • If the approval of the responsible National Competent Authority has been revoked.	

Amendment [b]: 12-May-2023

This amendment is considered to be nonsubstantial.

Overall Rationale for the Amendment:

The main purpose for the current protocol amendment is to clarify the dose modification language in Section 6.6.1.

Section # and Name	Description of Change	Brief Rationale
Section 6.6.1. Management of Gastrointestinal Symptoms	Made updates throughout this section to clarify when dose modifications should occur and the guidance for the dose modifications. • Added a reference to Section 7.1.2. and removed repetitive reference to documentation in the CRF in the table of steps for intolerable GI symptoms. • CCI [redacted] into 2 tables and positioned them with associated text.	Clarifications

Section # and Name	Description of Change	Brief Rationale
	 • Moved some text within Section 6.6.1.	
Section 8.1.1. Primary Efficacy Assessments	Removed “achieving ≥5% body weight reduction”	Correction
Throughout	Minor editorial changes have been made throughout	These are minor; therefore, they have not been individually summarized

Amendment [a]: 05 Apr 2023

This amendment is considered to be nonsubstantial.

This amendment has occurred before any study participant was consented or dosed at any study site.

Overall Rationale for the Amendment:

The main purpose of this protocol amendment is to have the body weight primary endpoint for the percentage of participants who achieve ≥5% body weight reduction as a secondary endpoint CCI

Additional changes including the above, and a brief rationale are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis and 3 Objectives, Endpoints, and Estimands	Moved "Percentage of participants who achieve ≥5% body weight reduction" endpoint from Primary to Key Secondary Endpoint	CCI
1.1 Synopsis and 3 Objectives, Endpoints, and Estimands	Added "[redacted]mg" dose to the primary objective	
1.1 Synopsis and 3 Objectives, Endpoints, and Estimands	For fasting insulin "mean change" was changed to "mean percent change" and deleted units	
1.1 Synopsis and 3 Objectives, Endpoints, and Estimands	Estimands information has been updated	
1.3. Schedule of Activities	CCI	
1.3. Schedule of Activities	Updated "Dilated fundoscopic examination" row to "Fundus photography and further ophthalmological assessment (if applicable)" with updated comment and added footnotes	
1.3. Schedule of Activities	Updated instruction for "Patient-reported outcomes (electronic)" row from "Complete prior to any clinical administered assessments" row to "PROs should be administered as early as possible in the visit but after the assessment of AEs"	
1.3. Schedule of Activities	Added the following text for PROs, "The PROs will be administered if an approved and translated version is available for use"	

Section # and Name	Description of Change	Brief Rationale
2.3.1. Risk Assessment	Added risk for diabetic retinopathy and retinopathy assessment	CCI
5.2. Exclusion Criteria	EC#11: The criterion on diabetic retinopathy has been revised	
5.2. Exclusion Criteria	The criterion (previously EC#36) on difficulty swallowing CCI has been removed	
6.3. Assignment to Study Intervention	Updated "gender" to "sex" stratification factor	
8.2.3. Electrocardiograms	CCI	
8.2.3. Electrocardiograms	Removed "initially" from ECG being interpreted by the investigator or qualified designee at the site	
8.2.9. Diabetic Retinopathy Screening and Evaluation	This section has been added to describe details of retinal photography and other eye assessments.	
8.3.1. Timing and Mechanism for Collecting Events	Mechanism of reporting pregnancy has been changed from "paper form" to "pregnancy CRF"	
8.3.3.3. Hypotension, Orthostatic hypotension, and Syncope	This section has been added as a new AESI topic	
8.3.3.10. Diabetic Retinopathy	This section title has been updated, "Diabetic Retinopathy ~~Complications~~"	
8.3.3.10. Diabetic Retinopathy	This section has been updated to describe how diabetic retinopathy will be assessed as an AESI.	
9.1. Statistical Hypotheses	Updated "alternative" hypotheses to "null" hypotheses	
9.1. Statistical Hypotheses	The hypotheses have been updated to align with changes made to the objectives	
9.1. Statistical Hypotheses	Text change from "is superior" to "compared"	

Section # and Name	Description of Change	Brief Rationale
9.2. Analyses Sets	The description of the data points set were changed to add the text "at or" after baseline…	CCI
9.3.2.1. Participant Disposition	Replaced "baseline" with "randomization"	
9.3.3. Primary Endpoints and Estimand Analyses	Updated " alternative" hypotheses to "null" hypotheses	
9.3.3. Primary Endpoints and Estimand Analyses	The analyses have been updated to align with changes made to the objectives	
9.3.4. Secondary Endpoints and Estimands Analyses	Updated "alternative" hypotheses to "null" hypotheses	
9.3.6. Pharmacokinetic/ Pharmacodynamic Analyses	Updated "gender" to "sex"	
9.3.8. Other Analyses	Updated "gender" to "sex"	
9.5. Sample Size Determination	Section updated with [redacted] mg dose and 2-sided significance level	
10.1.12. Sample Retention	Updated with the correct LY number	
10.4.2 Contraceptive Guidance	A footnote was added stating "Participants that have started implantable or injectable contraceptives within 18 months prior to Visit 1 will be excluded from the study."	
11. References	Added or updated references	
Throughout	Minor editorial changes have been made throughout	

11. References

Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med*. 1998; 15(7):539-53. https://doi.org/10.1002/(SICI)1096-9136(199807)15:7<539::AID-DIA668>3.0.CO;2-S

Aberle J, Lautenbach A, Meyhöfer S, et al. Obesity and diabetes. *Exp Clin Endocrinol Diabetes*. 2021;129(S 01):S44-S51. https://doi.org/10.1055/a-1284-6050

[ADA-EASD] American Diabetes Association. Management of hyperglycemia in Type 2 Diabetes: ADA-EASD Consensus Report 2022. Presented at the 58th EASD Annual Meeting on September 23, 2022. Accessed January 18, 2023. https://professional.diabetes.org/content-page/management-hyperglycemia-type-2-diabetes-ada-easd-consensus-report-2022

[ADA] American Diabetes Association. Introduction and methodology: *Standards of Care in Diabetes*. *Diab Care*. 2023;46(1):S1-S4. https://doi.org/10.2337/dc23-Sint

Alosh, M, Bretz, F, Huque M. Advanced multiplicity adjustment methods in clinical trials. *Stat Med.* 2014;33(4):693-713. https://doi.org/10.1002/sim.5974

[AMA] American Medical Association House of Delegates: Recognition of obesity as a disease. Resolution: 420 (A-13). 2013. Available at: https://media.npr.org/documents/2013/jun/ama-resolution-obesity.pdf. Accessed February 3, 2023.

Aroda VR, Ratner R. The safety and tolerability of GLP-1 receptor agonists in the treatment of type 2 diabetes: a review. *Diabetes Metab Res Rev.* 2011;27(6):528-542. https://doi.org/10.1002/dmrr.1202

Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400. https://doi.org/10.1111/j.1572-0241.2006.00856.x

Bretz F, Maurer W, Brannath W, et al. A graphical approach to sequentially rejective multiple test procedures. *Stat Med*. 2009;28(4):586-604. https://doi.org/10.1002/sim.3495

Bretz, F, Posch M, Glimm E, et al. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. *Biom J*. 2011;53(6):894-913. https://doi.org/10.1002/bimj.201000239

Cameron NA, Petito LC, McCabe M, et al. Quantifying the Sex-Race/Ethnicity-Specific Burden of Obesity on Incident Diabetes Mellitus in the United States, 2001 to 2016: MESA and NHANES. *J Am Heart Assoc*. 2021;10(4):e018799. https://doi.org/10.1161/JAHA.120.018799

[CDC] Centers for Disease Control and Prevention. National and state diabetes trends. Diabetes incidence and prevalence. Updated May 17, 2022. Accessed February 2, 2023. https://www.cdc.gov/diabetes/library/reports/reportcard/national-state-diabetes-trends.html

[CSAPH] Council on Science and Public Health. Report of the Council on Science and Public Health: is obesity a disease? (Resolution 115-A-12). Report number: 3-A-13. 2013. Council on Science and Public Health. Accessed February 3, 2023. https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/aboutama/councils/Council%20Reports/council-on-science-public-health/a13csaph3.pdf.

Danne T, Philotheou A, Goldman D, et al. A randomized trial comparing the rate of hypoglycemia assessed using continuous glucose monitoring in 125 preschool children with type 1 diabetes treated with insulin glargine or NPH insulin (the PRESCHOOL study). *Pediatr Diabetes.* 2013;14(8):593-601. https://doi/10.1111/pedi.12051

Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. *Lancet*. 2021;397(10278):971-984. https://doi.org/10.1016/S0140-6736(21)00213-0

Davies MJ, D'Alessio DA, Fradkin J, et al. Management of Hyperglycemia in Type 2 Diabetes, 2018. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care*. 2018;41(12):2669-2701. https://doi.org/10.2337/dci18-0033

[EMA] European Medicines Agency. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical evaluation of medicinal products used in weight management. June 23, 2016. EMA/CHMP/311805/2014 June 23, 2016.

EuroQol Research Foundation. EQ-5D-5L user guide, version 3.0. Updated September 2019. Accessed July 29, 2022. https://euroqol.org/publications/user-guides.

[FDA] Food and Drug Administration. Guidance for industry: developing products for weight management. Published February 2007. Accessed January 31, 2023. https://www.fda.gov/media/71252/download.

Flaxel CJ, Adelman RA, Bailey ST et al. Diabetic Retinopathy Preferred Practice Pattern®. *Ophthalmology*. 2020;127(1):P66-P145. https://doi.org/10.1016/j.ophtha.2019.09.025. Erratum in: *Ophthalmology*. 2020;127(9):1279. https://doi.org/10.1016/j.ophtha.2020.06.047

Frühbeck G, Toplak H, Woodward E, et al. Obesity: the gateway to ill health - an EASO position statement on a rising public health, clinical and scientific challenge in Europe. *Obes Facts*. 2013;6(2):117-120. https://doi.org/10.1159/000350627

Giugliano D, Scappaticcio L, Longo M, et al. GLP-1 receptor agonists and cardiorenal outcomes in type 2 diabetes: an updated meta-analysis of eight CVOTs. *Cardiovasc Diabetol*. 2021;20(1):189. https://doi.org/10.1186/s12933-021-01366-8

Koizumi M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Hirota M, Kimura Y, Takeda K, Isaji S, Otsuki M, Matsuno S. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13(1):25-32

Kolotkin RL, Ervin CM, Meincke HH, et al. Development of a clinical trials version of the impact of weight on quality of life-lite questionnaire (IWQOL-Lite clinical trials version): results from two qualitative studies. *Clin Obes.* 2017;7(5):290-299. https://doi.org/10.1111/cob.12197

Kolotkin RL, Williams VSL, Ervin CM, et al. Validation of a new measure of quality of life in obesity trials: impact of weight on quality of life-lite clinical trials version. *Clin Obes.* 2019;9(3):e12310. https://doi.org/10.1111/cob.12310

Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer -viewpoint of the IARC Working Group. *N Engl J Med*. 2016;375(8):794-798. https://doi.org/10.1056/NEJMsr1606602

a u¯ ≥●≤(a Q∑yx≥ī’ ¯7(i ●y¯ ●(a u” u–(ź’ ¯(ī≤y(gR-36v2 Health Survey. 3rd ed. Lincoln, RI: Quality Metric Incorporated; 2011

Moriarty AS, Gilbody S, McMillan D, Manea L. Screening and case finding for major depressive disorder using the Patient Health Questionnaire. *Gen Hosp Psychiatry*. 2015;37(6):567-576. https://doi.org/10.1016/j.genhosppsych.2015.06.012

Nauck MA, Meier JJ, Schmidt WE. Incretin-based glucose-lowering medications and the risk of acute pancreatitis and/or pancreatic cancer: reassuring data from cardio-vascular outcome trials. *Diabetes Obes Metab.* 2017;19(9):1327-1328. https://doi.org/10.1111/dom.12981

Pastors JG, Warshaw H, Daly A, et al. The evidence for the effectiveness of medical nutrition therapy in diabetes management. *Diabetes Care.* 2002;25(3):608-613. https://doi.org/10.2337/diacare.25.3.608

Rothberg AE, McEwen LN, Kraftson AT, et al. Impact of weight loss on waist circumference and the components of the metabolic syndrome. *BMJ Open Diabetes Res Care*. 2017;5(1):e000341. https://doi.org/10.1136/bmjdrc-2016-000341

Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2022.

Solomon SD, Chew E, Duh EJ et al. Diabetic retinopathy: a position statement by the American Diabetes Association. *Diabetes Care*. 2017;40(3):412-418. https://doi.org/10.2337/dc16-2641. Erratum in: *Diabetes Care*. 2017;40(6):809. https://doi.org/10.2337/dc17-er06e

Spitzer RL, Kroeke K, Williams JB. Validation and utility of a self-report version of PRIME-MMD: The PHQ primary care stud. *JAMA*. 1999; 282(18):1737-1744. https://doi.org/10.1001/jama.282.18.1737

Steinberg WM, Buse JB, Ghorbani MLM, et al. Amylase, lipase, and acute pancreatitis in people with type 2 diabetes treated with liraglutide: results from the LEADER randomized trial. *Diabetes Care.* 2017a;40(7):966-972. https://doi.org/10.2337/dc16-2747 [Erratum in: *Diabetes Care*. 2018;41(7):1538.]

Steinberg WM, Rosenstock J, Wadden TA, et al. Impact of liraglutide on amylase, lipase, and acute pancreatitis in participants with overweight/obesity and normoglycemia, prediabetes, or type 2 diabetes: secondary analyses of pooled data from the SCALE clinical development program. *Diabetes Care*. 2017b;40(7):839-848. https://doi.org/10.2337/dc16-2684

UKPDS Group. UK Prospective Diabetes Study 7: response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients. *Metabolism.* 1990;39(9):905 912. https://doi.org/10.1016/0026-0495(90)90299-R

WEGOVY [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2021.

Weinberg ME, Bacchetti P, Rushakoff RJ. Frequently repeated glucose measurements overestimate the incidence of inpatient hypoglycemia and severe hyperglycemia. *J Diabetes Sci Technol.* 2010;4(3):577-582. https://doi.org/10.1177/193229681000400311

Wilding J PH, Batterham RL, Calanna S, et al. Once-Weekly Semaglutide in Adults with Overweight or Obesity. *N Engl J Med*. 2021;384(11):989-1002. https://doi.org/ 10.1056/NEJMoa2032183

Wing RR, Lang W, Wadden TA, et al. Look AHEAD Research Group. Benefits of modest weight loss in improving cardiovascular risk factors in overweight and obese individuals with type 2 diabetes. *Diabetes Care*7(; 9: : G<>lC2F: >D: >DB7https://doi.org/10.2337/dc10-2415

[WHO] World Health Organization. WHO STEPS surveillance manual: the WHO STEPwise approach to noncommunicable disease risk factor surveillance. Updated January 26, 2017. Accessed January 05, 2022. https: //cdn.who.int/media/docs/default-source/ncds/ncd-surveillance/steps/steps-manual.pdf?sfvrsn=c281673d_7

[WHO] World Health Organization. Regional Office for Europe. (2022). WHO European Regional Obesity Report 2022. World Health Organization. Regional Office for Europe. https://apps.who.int/iris/handle/10665/353747.

Ye T, Shao J, Yi Y, et al. Toward better practice of covariate adjustment in analyzing randomized clinical trials. *J Am Stat Assoc*. 2022;00(0):1-13. https://doi.org/10.1080/01621459.2022.2049278

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Approval	PPD Statistician 30-Oct-2023 13:28:50 GMT+0000

Approval	PPD Medical Director 31-Oct-2023 11:03:57 GMT+0000

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