

Protocol J2A-MC-GZGP (d)

A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral Orforglipron Compared With Placebo in Adult Participants With Obesity or Overweight With Weight-Related Comorbidities (ATTAIN-1)

NCT05869903

Approval Date: 30 APR 2025

Title Page

Confidential Information

The information contained in this document is confidential and is intended for the use of clinical investigators. It is the property of Eli Lilly and Company or its subsidiaries and should not be copied by or distributed to persons not involved in the clinical investigation of orforglipron (LY3502970) unless such persons are bound by a confidentiality agreement with Eli Lilly and Company or its subsidiaries.

Note to Regulatory Authorities: This document may contain protected personal data and/or commercially confidential information exempt from public disclosure. Eli Lilly and Company requests consultation regarding release/redaction prior to any public release. In the United States, this document is subject to Freedom of Information Act (FOIA) Exemption 4 and may not be reproduced or otherwise disseminated without the written approval of Eli Lilly and Company or its subsidiaries.

Protocol Title:

A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral Orforglipron Compared with Placebo in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Protocol Number: J2A-MC-GZGP

Amendment Number: d

Compound: orforglipron (LY3502970)

Brief Title:

Efficacy and Safety of Orforglipron Compared with Placebo in Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Study Phase: 3

Acronym: ATTAIN-1

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana, USA 46285

Regulatory Agency Identifier Numbers:

IND: 156143

EU trial number: 2022-502839-19-00

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

Document ID: VV-CLIN-116515

Medical monitor name and contact information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Amendment c</i>	<i>23-Oct-2023</i>
<i>Amendment b</i>	<i>11-May-2023</i>
<i>Amendment a</i>	<i>05-Apr-2023</i>
<i>Original Protocol</i>	<i>24-Feb-2023</i>

Amendment [d]

This amendment is considered to be substantial.

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

Overall Rationale for the Amendment:

The main purpose for the current protocol amendment is to extend the timeframe from the final treatment visit (Visit 117) for participants with prediabetes at randomization to the posttreatment follow-up visit (Visit 802) in order to fully assess the effect on HbA1c after the study intervention is washed out and adequate time for red blood cell turnover has occurred. These and other changes and a brief rationale are provided in the table below. Minor editorial or formatting changes are not included in this table.

Section # and Name	Description of Change	Brief Rationale
Synopsis, and 3. Objectives, Endpoints, and Estimands	Added Key Secondary Objective at 190 weeks	An additional key secondary objective was added to better understand the impact of participants being off drug for 14 weeks on the development of T2D
Synopsis, and 4.1. Overall Design	Added Study Details table	To clarify study duration for participants with and without prediabetes at randomization
Synopsis	Increased approximate study duration from 181 weeks to 193 weeks	To extend the timeframe from the final treatment visit (Visit 117) for participants with prediabetes at randomization to the posttreatment follow-up visit (Visit 802)
Schema	Updated schema	To extend the timeframe from the final treatment visit (Visit 117) for participants with prediabetes at randomization

Section # and Name	Description of Change	Brief Rationale
		to the posttreatment follow-up visit (Visit 802)
1.3 Schedule of Activities (SoA), 1.3.2 Prediabetes Additional Treatment Period (Visits 101 to 117), Early Discontinuation, and Posttreatment Follow-up Visit 802, and 4.2 Scientific Rationale for Study Design	Increased posttreatment follow up for Visit 802 from 2 weeks to 14 weeks	To extend the timeframe from the final treatment visit (Visit 117) for participants with prediabetes at randomization to the posttreatment follow-up visit (Visit 802)
1.3.2 Prediabetes Additional Treatment Period (Visits 101 to 117), Early Discontinuation, and Posttreatment Follow-up Visit 80	Updated clinical chemistry comment	To clarify actions required for participants meeting hepatic laboratory criteria at Visit 802
6.4. Blinding	Added unblinding after primary database lock details	To provide clarity for maintaining blinding after the primary database lock
6.9.2. Initiation of Antihyperglycemic Medications	Updated text	To clarify use of antihyperglycemic medicines for indications other than T2D
7.1. Discontinuation of Study Intervention	Deleted “an active or untreated” from fifth bullet point	For clarity
7.1.2. Temporary Study Intervention Interruption	Expanded “then...” text for study interruptions of 7 or more consecutive doses	To allow flexibility for an interruption of 7 or more consecutive doses.
8.4. Pharmacokinetics	Revised language regarding early discontinuation PK samples	For clarity
9. Statistical Considerations	Added “primary outcome”	For clarity
9.1. Statistical Hypotheses	Updated to reflect the changes specified in the key secondary objectives and endpoints in Section 3	For consistency
9.3.1 General Considerations	Revised language within the general descriptions of analyses	For clarity
10.2. Appendix 2: Clinical Laboratory Tests	Deleted “segmented” from “Neutrophils, segmented” Clinical Laboratory Tests	To align the protocol-defined testing and central laboratory result
10.2. Appendix 2: Clinical Laboratory Tests	Updated comment for “Low-density lipoprotein cholesterol (LDL-C)”	To align the protocol-defined testing and central laboratory result

Section # and Name	Description of Change	Brief Rationale
10.6. Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Guidelines	Updated Hepatic Evaluation Testing	Editorial and formatting revisions
Throughout	Replaced compound number with compound name (orforglipron)	LY3502970 is now orforglipron
Throughout	Minor editorial and formatting revisions	Clarification

Table of Contents

1.	Protocol Summary	10
1.1.	Synopsis	10
1.2.	Schema.....	19
1.3.	Schedule of Activities (SoA)	20
1.3.1.	Screening Period I (Visits 1 and 2), Treatment Period II (Visits 3-21), Early Discontinuation and Posttreatment Follow-Up	22
1.3.2.	Prediabetes Additional Treatment Period (Visits 101 to 117), Early Discontinuation, and Posttreatment Follow-up Visit 802	45
2.	Introduction.....	58
2.1.	Study Rationale.....	58
2.2.	Background.....	58
2.3.	Benefit/Risk Assessment	60
2.3.1.	Risk Assessment	60
2.3.2.	Benefit Assessment.....	60
2.3.3.	Overall Benefit Risk Conclusion	60
3.	Objectives, Endpoints, and Estimands	61
4.	Study Design.....	66
4.1.	Overall Design	66
4.2.	Scientific Rationale for Study Design	68
4.3.	Justification for Dose	69
4.4.	End of Study Definition	70
5.	Study Population.....	71
5.1.	Inclusion Criteria	71
5.2.	Exclusion Criteria	72
5.3.	Lifestyle Considerations	76
5.3.1.	Meals and Dietary Restrictions.....	76
5.3.2.	Monitoring Nutritional Needs.....	76
5.3.3.	Healthy Physical Activity	77
5.3.4.	Activity Before Blood Collections.....	77
5.3.5.	Blood Donation.....	77
5.3.6.	Diabetes Education	77
5.4.	Screen Failures.....	77
5.5.	Criteria for Temporarily Delaying Enrollment of a Participant	77
6.	Study Intervention(s) and Concomitant Therapy	78
6.1.	Study Intervention(s) Administered.....	78
6.2.	Preparation, Handling, Storage, and Accountability	79
6.3.	Assignment to Study Intervention	79
6.4.	Blinding	80
6.5.	Study Intervention Compliance	80
6.6.	Dose Modification	81
6.6.1.	Management of Gastrointestinal Symptoms.....	81
6.7.	Continued Access to Study Intervention After the End of the Study	83

6.8.	Treatment of Overdose	83
6.9.	Prior and Concomitant Therapy	83
6.9.1.	Symptomatic Medication for Gastrointestinal Symptoms	84
6.9.2.	Initiation of Antihyperglycemic Medications	85
6.9.3.	Prohibited or Restricted Use Medications	85
6.9.4.	Prohibited or Restricted Surgical Treatments or Procedures	85
7.	Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.....	86
7.1.	Discontinuation of Study Intervention.....	86
7.1.1.	Liver Chemistry Stopping Criteria.....	87
7.1.2.	Temporary Study Intervention Interruption.....	87
7.2.	Participant Discontinuation/Withdrawal from the Study.....	88
7.3.	Lost to Follow-up.....	89
8.	Study Assessments and Procedures.....	90
8.1.	Efficacy Assessments	90
8.1.1.	Primary Efficacy Assessments.....	90
8.1.2.	Secondary Efficacy Assessments.....	90
8.1.3.	Tertiary Efficacy Assessments.....	90
8.1.4.	Patient-Reported Outcomes	90
8.2.	Safety Assessments.....	93
8.2.1.	Physical Examinations	93
8.2.2.	Vital Signs.....	93
8.2.3.	Electrocardiograms	93
8.2.4.	Clinical Safety Laboratory Tests	94
8.2.5.	Pregnancy Testing.....	95
8.2.6.	Suicidal Ideation and Behavior Risk Monitoring	95
8.2.7.	Hepatic Safety Monitoring.....	95
8.2.8.	Hypersensitivity Reactions	99
8.3.	Adverse Events, Serious Adverse Events, and Product Complaints	99
8.3.1.	Timing and Mechanism for Collecting Events	100
8.3.2.	Pregnancy.....	101
8.3.3.	Adverse Events of Special Interest and Other Safety Topics	102
8.4.	Pharmacokinetics	109
8.4.1.	Bioanalysis.....	110
8.5.	Pharmacodynamics	110
8.6.	Genetics	110
8.7.	Biomarkers.....	110
8.8.	Immunogenicity Assessments.....	111
8.9.	Medical Resource Utilization and Health Economics	111
9.	Statistical Considerations.....	112
9.1.	Statistical Hypotheses	112
9.1.1.	Multiplicity Adjustment.....	113
9.2.	Analyses Sets	114
9.3.	Statistical Analyses	115

9.3.1.	General Considerations	115
9.3.2.	Treatment Group Comparability	116
9.3.3.	Primary Endpoint and Estimands Analyses	117
9.3.4.	Secondary Endpoints and Estimands Analyses	117
9.3.5.	Tertiary Endpoints and Estimands Analyses	117
9.3.6.	Pharmacokinetic/Pharmacodynamic Analyses	117
9.3.7.	Safety Analyses.....	118
9.3.8.	Other Analyses.....	118
9.4.	Interim Analysis.....	119
9.5.	Sample Size Determination	119
10.	Supporting Documentation and Operational Considerations	120
10.1.	Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	120
10.1.1.	Regulatory and Ethical Considerations.....	120
10.1.2.	Financial Disclosure.....	121
10.1.3.	Informed Consent Process	121
10.1.4.	Data Protection.....	121
10.1.5.	Committees Structure.....	122
10.1.6.	Dissemination of Clinical Study Data.....	122
10.1.7.	Data Quality Assurance	123
10.1.8.	Source Documents	125
10.1.9.	Study and Site Start and Closure	125
10.1.10.	Publication Policy	126
10.1.11.	Investigator Information	126
10.1.12.	Sample Retention.....	126
10.2.	Appendix 2: Clinical Laboratory Tests.....	127
10.2.1.	Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event.....	130
10.3.	Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow- up, and Reporting.....	131
10.3.1.	Definition of AE	131
10.3.2.	Definition of SAE	132
10.3.3.	Definition of Product Complaints.....	133
10.3.4.	Recording and Follow-Up of AE and/or SAE and Product Complaints	133
10.3.5.	Reporting of SAEs	135
10.3.6.	Regulatory Reporting Requirements.....	135
10.4.	Appendix 4: Contraceptive and Barrier Guidance.....	137
10.4.1.	Definitions.....	137
10.4.2.	Contraception Guidance.....	138
10.5.	Appendix 5: Genetics.....	140
10.6.	Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments and Study Intervention Guidelines	141
10.7.	Appendix 7: Measurement of Height, Weight, Waist Circumference, Vital Signs and OGTT	143

10.8.	Appendix 8: Prohibited Medications or Medications with Special Use Restrictions	146
10.8.1.	Excluded/Prohibited or Restricted Use Medications	146
10.8.2.	Medications with Special Use Restrictions.....	150
10.9.	Appendix 9: Definition and Management of Diabetes	152
10.10.	Appendix 10: Information for Sites that have Access to Whole-Body DXA Scanners with Body Composition Capability	155
10.10.1.	Introduction.....	155
10.10.2.	Objectives, Endpoints, and Estimands.....	156
10.10.3.	Study Population.....	156
10.10.4.	Dual-energy X-ray Absorptiometry Scan	156
10.10.5.	Randomization	157
10.10.6.	Statistical Analyses	157
10.10.7.	Sample Size.....	157
10.10.8.	Data Capture	157
10.11.	Appendix 11: Information for Sites on Scoring the Appetite Visual Analog Scale.....	158
10.12.	Appendix 12: Country-specific Requirements	159
10.12.1.	Brazil.....	159
10.13.	Appendix 13: Provisions for Changes in Study Conduct During Exceptional Circumstances.....	161
10.14.	Appendix 14: Abbreviations and Definitions	165
10.15.	Appendix 15: Protocol Amendment History	169
11.	References	176

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 Orforglipron Compared with Placebo in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Brief Title: Efficacy and Safety of Orforglipron Compared with Placebo in Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Regulatory Agency Identifier Numbers:

IND: 156143

EU trial number: 2022-502837-24-00

Rationale:

ATTAIN-1 (Study J2A-MC-GZGP [GZGP]) is designed to provide evidence of safety and efficacy of orforglipron in the patient population with obesity or overweight and at least 1 weight-related comorbidity (excluding type 2 diabetes). Phase 3 studies of novel chronic weight management medications should demonstrate efficacy in terms of body weight reduction over the course of at least 1 year and be randomized, double-blind, and placebo controlled.

ATTAIN-1 (Study GZGP) is a multicenter, randomized, parallel-arm, double-blind, placebo-controlled, Phase 3 study. The study will investigate the effect of treatment with daily oral orforglipron 6 mg, 12 mg, or 36 mg, compared with placebo for at least 72 weeks, as an adjunct to healthy diet and physical activity, on body weight in participants with either obesity (BMI 30 kg/m² or greater), or overweight (BMI 27 kg/m² or greater) with the presence of at least 1 weight-related comorbidity (for example, hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease). Additionally, the study will compare the effects of orforglipron and placebo on blood pressure, lipid parameters, and overall safety profile. Participants who have prediabetes at randomization will be studied for a total of 176 weeks of treatment to provide sufficient follow-up time to assess the effects of orforglipron on progression to T2D and on long-term body weight changes.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary Objective	
To demonstrate that orforglipron 6 mg, 12 mg, and/or 36 mg QD is superior to placebo for: • Body weight	From baseline to Week 72 • Mean percent change in body weight
Key Secondary Objectives (controlled for type 1 error)	
To demonstrate that orforglipron 6 mg, 12 mg, and/or 36 mg QD is superior to placebo in change from baseline for the following: • Body weight • Waist circumference	From baseline to Week 72 • Percentage of participants who achieve a body weight reduction of ○ $\geq 5\%$ ○ $\geq 10\%$ ○ $\geq 15\%$ ○ $\geq 20\%$ • Mean change in waist circumference (cm)
To demonstrate that orforglipron (6 mg, 12 mg, and 36 mg QD 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
Key Secondary Objective at 176 Weeks for Participants with Prediabetes at Randomization (controlled for type 1 error), pooled dose analysis	
To demonstrate in participants with prediabetes at randomization that orforglipron (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo at 176 weeks: • Body weight	From baseline to Week 176 • Mean percent change in body weight

Objectives	Endpoints
Key Secondary Objectives at 176 or 190 Weeks for Participants with Prediabetes at Randomization (controlled for type 1 error), pooled dose analysis	
To demonstrate in participants with prediabetes at randomization that orforglipron (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo for: • Delayed progression to T2D at 176 weeks • Delayed progression to T2D at 190 weeks	• Time to onset of T2D during 176 week treatment period • Time to onset of T2D during entire study including posttreatment follow-up period
Additional Secondary Objectives	
To demonstrate that orforglipron 6 mg, 12 mg, and/or 36 mg QD 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/m²) • Mean change in HbA1c (%) • Mean change in fasting glucose (mg/dL) • Mean percent change in fasting insulin
To demonstrate that orforglipron (6 mg, 12 mg and 36 mg QD pooled dose) 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 from baseline 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

Objectives	Endpoints
	Change in PGIS and PGIC limitations on physical function due to weight
To describe the safety of orforglipron as compared to placebo	Summary of safety data, including number and incidence of Treatment-emergent adverse events
Additional Secondary Objectives at 72 Weeks in Participants with Prediabetes at Randomization	
To demonstrate orforglipron (6 mg, 12 mg, and/or 36 mg QD) is superior to placebo in change from baseline for: Glycemic control	From baseline to Week 72 Percentage of participants achieving normoglycemia (see Section 10.9)
Additional Secondary Objectives at 176 Weeks in Participants with Prediabetes at Randomization	
To demonstrate in participants with prediabetes at randomization that orforglipron 6 mg, 12 mg, and/or 36 mg QD is superior to placebo for the following at 176 weeks: - Body weight - Glycemic control	From baseline to Week 176 - Percentage of study participants who achieve $\geq 5\%$ body weight reduction - Mean percent change in body weight from baseline - Mean change in HbA1c (%) - Mean change in fasting glucose (mg/dL) - Percentage of participants achieving normoglycemia

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of life-Lite-Clinical Trial; LDL = low-density lipoprotein; PGI-C = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; QD= once-daily; SBP = systolic blood pressure; SF-36v2 = 36-item Short Form Health Survey, version 2; T2D = type 2 diabetes; VAS = visual analogue scale.

Estimands

There will be 2 estimands for the primary objective 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 orforglipron 36 mg, 12 mg, and 6 mg and placebo, as an adjunct to healthy diet and physical activity, in individuals who meet eligibility criteria regardless of adherence to study intervention or initiation of prohibited weight management treatments?

Rationale for the estimand: This estimand aims to evaluate the efficacy of orforglipron 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 orforglipron 36 mg, 12 mg, and 6 mg and placebo, as an adjunct to healthy diet and physical activity, 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?

Rationale for the estimand: This estimand aims to evaluate the efficacy of orforglipron 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.

Overall Design

ATTAIN-1 (Study GZGP) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study.

Study details include:

	Without Prediabetes at Randomization	Prediabetes at Randomization
Screening Period	3 weeks	3 weeks
Treatment Period		
Dose escalation period	20 weeks	20 weeks
Maintenance dose period	52 weeks	52 weeks
Additional treatment period for participants with prediabetes at randomization	N/A	104 weeks
Posttreatment Follow-up Period	2 weeks	14 weeks ^a
Total Study Duration	77 weeks	193 weeks

^a If participants with prediabetes at randomization discontinue study intervention during the first 72 weeks, the posttreatment follow-up period will be 2 weeks.

Brief Summary:

The study will investigate the safety and efficacy of treatment with daily oral doses of orforglipron (6 mg, 12 mg, and 36 mg) compared with placebo, in participants with obesity (BMI 30 kg/m² or greater) or overweight (BMI 27 kg/m² or greater) with the presence of 1 weight-related comorbidity.

The study duration for participants without prediabetes at randomization will be approximately 77 weeks including screening and follow-up. For participants with prediabetes at randomization, the study duration will be approximately 193 weeks.

The treatment duration will be approximately 72 weeks or 176 weeks for those without prediabetes or with prediabetes, respectively.

The visit frequency will be every 4 to 6 weeks.

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
 - $\geq 30.0 \text{ kg/m}^2$, or
 - $\geq 27.0 \text{ kg/m}^2$ and presence of at least one of the following weight-related comorbidities (treated or untreated) at Visit 1:
 - Hypertension
 - Dyslipidemia
 - Obstructive sleep apnea
 - Cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association Functional Class I-III heart failure)
- Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight

Number of Participants:

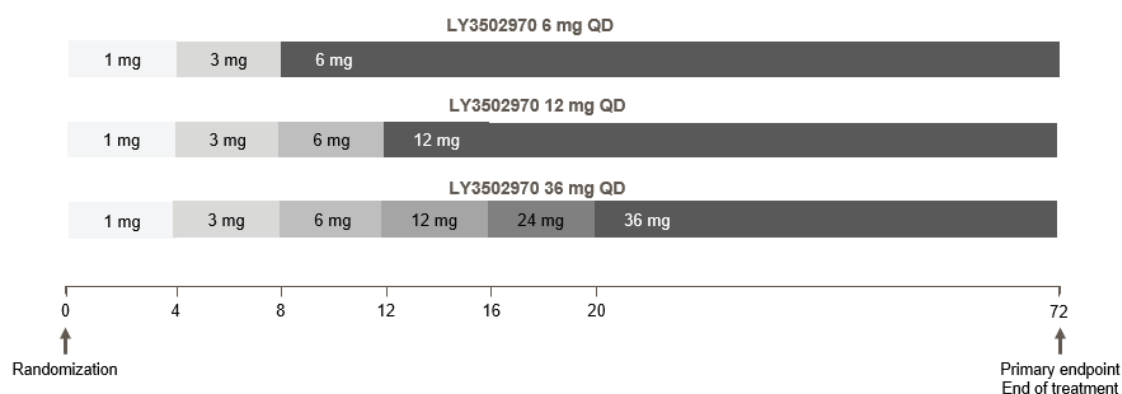
Approximately 3000 participants will be randomized in a 3:3:3:4 ratio to 6-mg orforglipron (702 participants), 12-mg orforglipron (702 participants), 36-mg orforglipron (702 participants), and placebo (936 participants). An upper limit of 70% enrollment of females will be used to ensure a sufficiently large sample of males.

Intervention Groups and Duration:

This table lists the interventions used in this clinical study

Intervention Name	Orforglipron	Placebo
Dosage Level(s)	1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg capsules	Capsule of orforglipron-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 1 mg QD dose of orforglipron or matching placebo and increase dose every 4 weeks until the randomized maintenance dose (6 mg, 12 mg or 36 mg) is reached as outlined in the below figure.



Abbreviation: LY3502970 = orforglipron; QD = once daily.

Note: LY dose increases occur every 4 weeks in a blinded fashion until the randomized maintenance dose (6 mg, 12 mg, or 36 mg) is reached.

The maintenance dose (6 mg, 12 mg or 36 mg) of orforglipron or placebo will be continued for the remainder of the study, unless study intervention dose modification is necessary.

Duration: The study duration for participants without prediabetes at randomization will be approximately 77 weeks including screening and follow-up. For participants with prediabetes at randomization, the study duration will be approximately 193 weeks.

Ethical Considerations of Benefit/Risk:

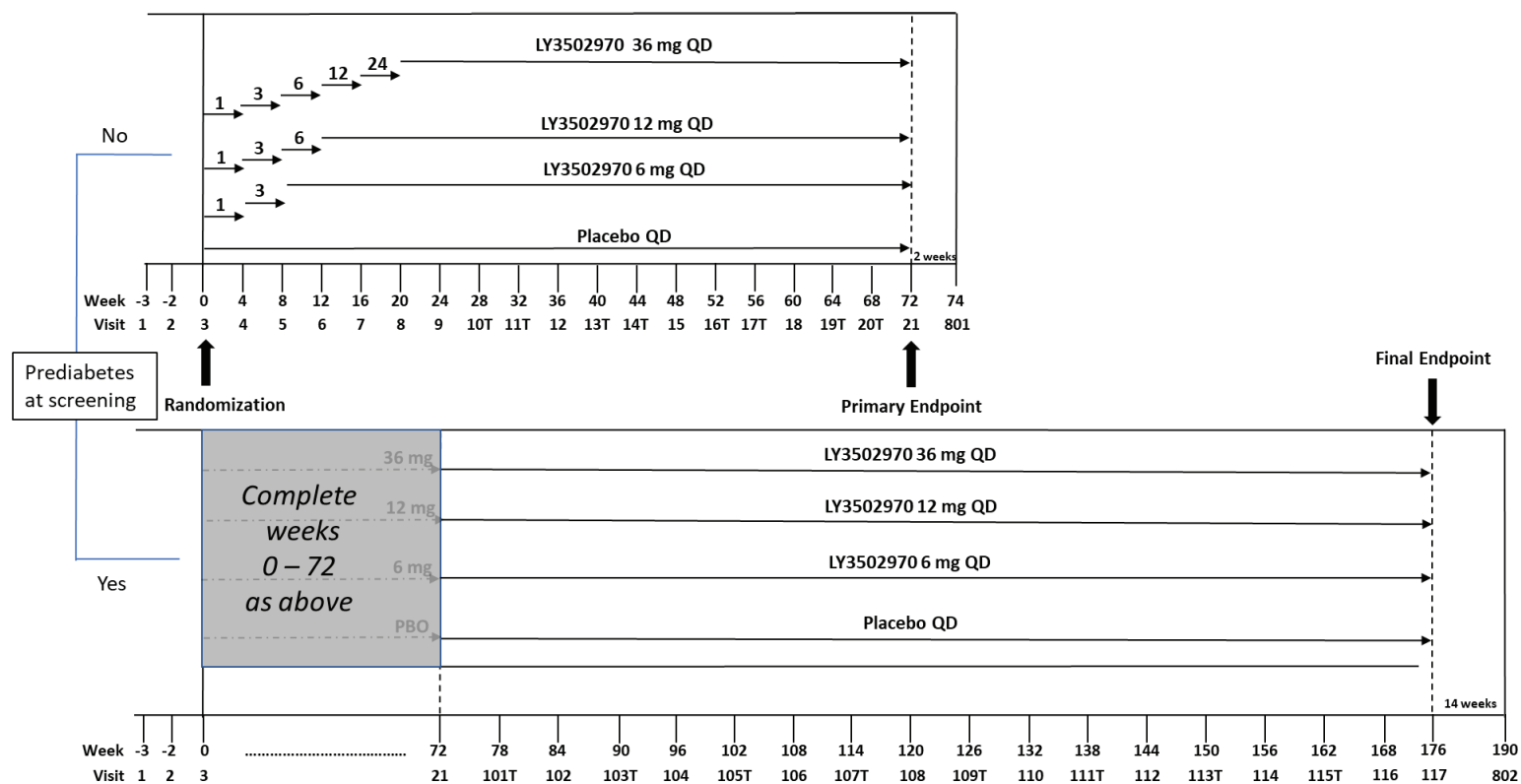
The safety and efficacy profile seen to date for orforglipron supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 receptor agonists, namely gastrointestinal tolerability issues and increased heart rate. These risks are monitorable, usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized AEs from orforglipron other than those related to

GLP-1 receptor agonism. GLP-1 receptor agonists have generally been associated with reduced risk of CV events in people with T2D.

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

Data Monitoring Committee: No

1.2. Schema



Abbreviations: LY3502970 = orforglipron; QD = once daily; T= telehealth visit.

1.3. Schedule of Activities (SoA)

The SoA described below should be followed for all participants enrolled in ATTAIN-1 (Study J2A-MC-GZGP [GZGP]). However, for those participants whose participation in this study is affected by exceptional circumstances, such as pandemics, or natural disasters, please refer to Section 10.13 for additional guidance.

Screening

All screening activities should take place within the 3-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 or Visit 2, 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).

- If a participant attends these visits in a nonfasting state, body weight measurement, samples for laboratory testing, Power of Food Scale, and Appetite Visual Analog Scale (VAS) 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.

Treatment period

Eligible participants will be assigned to either 72 or 176 weeks of treatment based upon prediabetes status at randomization (no prediabetes and prediabetes, respectively). See Section 10.9 for the definition of prediabetes.

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.

Posttreatment follow-up

All participants completing or discontinuing treatment at or before Visit 21 will perform a follow-up (Visit 801) according to the SoA, 2 weeks after the last visit during the 72-week treatment period.

Participants with prediabetes at randomization continuing to Week 78 should not perform Visit 801 but rather a follow-up Visit 802 should be performed 14 weeks after the last visit during the additional 2-year treatment period.

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.

1.3.1. Screening Period I (Visits 1 and 2), Treatment Period II (Visits 3-21), Early Discontinuation and Posttreatment Follow-Up

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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 informed consent form must be signed before any protocol-specific tests or procedures are performed.
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

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								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).
Prespecified medical history (indication and history of interest)	X																							Including, but not limited to, obesity or overweight medical history
Prior treatments for indication	X																							Includes prior weight management medications.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
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 and hypertension)									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

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								Section 10.3.1. Additional data are collected for certain AEs.
Physical evaluation																								
Height	X																							See Section 10.7
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 10.7. 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

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								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 Section 10.7
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 Section 10.7
12-lead ECG (Central)			X						X						X						X	X	X	Collect before blood samples for laboratory testing. ECG may be repeated at the investigator’s discretion at any visit. Triplicate

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								ECG measurements should be obtained after at least 5 minutes of rest per the instructions in Section 8.2.3.
Physical examination	X																				X	X		

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments	
			Dose Escalation Period							Maintenance Dose Period															
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801		
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP		
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3		
Fasting visit	X	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	
Symptom- directed 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.
Participant diary (electronic)																									
Dispense diary (electronic device)			X																					Includes daily study intervention dose and other data as applicable see Section 6.1. and 8.3.3.4	

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
Diary review (electronic)				X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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		
IWQOL-Lite CT			X						X												X	X		
PGIS -Physical Function Weight			X						X												X	X		
PGIC -Physical Function Weight									X												X	X		
EQ-5D-5L			X						X												X	X		

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																			Post- Tx Follow- up	Comments	
			Dose Escalation Period						Maintenance Dose Period															
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
PROMIS Short Form Sleep Disturbance 8b			X						X												X	X		
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.
Patient-reported outcomes (paper) 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. Administration of the PROs below after randomization will only be performed for those participants with a baseline (Visit 3) assessment.																								
Power of Food Scale (15 questions)			X						X												X	X	X	PFS must be obtained each time in the fasting state. If

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								the participant is not fasting, the participant should be called in for a new visit within the visit window to have the fasting PRO completed.
Appetite VAS			X						X												X	X	X	Appetite VAS must be obtained each time 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 PRO completed.
Clinician-administered assessments (paper)																								

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
C-SSRS screening/ baseline	X																							The C-SSRS should be administered after assessment of adverse 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.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
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 ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.
Participant education																								
Lifestyle program instructions			X	X	X	X			X			X			X			X			X	X		Lifestyle counseling may occur on a separate day from the rest of that

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								visit’s study procedures but must occur within the visit window. Beginning at Week 8, counseling may be delivered by telehealth. Refer to Section 5.3
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	X		All training should be repeated as needed to ensure participant compliance. Study personnel to provide reinforcement and encouragement for lifestyle modifications.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
Laboratory tests, sample collections and imaging																								
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. At Visit 801, if hepatic laboratory values

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								are elevated (participants with normal baseline: ALT or AST ≥3x ULN; participants with elevated baseline: ≥2x baseline), then repeat 2 weeks later.
2-hr oral glucose tolerance test (includes glucose, insulin, c-peptide at each time point)		X																			X	X		2-hr OGTT testing should be omitted at visits following a protocol-defined diabetes diagnosis (Section 10.9). OGTT must be obtained in the fasting state. If the participant is not fasting, the participant should

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								be called in for a new visit within the visit window to have the fasting OGTT performed.
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.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
Urine pregnancy (local)			X			X			X			X			X			X			X	X		The result must be available before the first dose of study 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.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
FSH	X																							Perform as needed to confirm postmenopausal status. Definition in Section 10.4.
TSH	X																							
Insulin			X						X												X	X		
C-peptide			X						X												X	X		
Calcitonin	X					X			X												X	X	X	
Pancreatic amylase	X					X			X												X	X	X	
Lipase	X					X			X												X	X	X	
Free fatty acids			X						X												X	X	X	

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
Apo B			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.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																			Post- Tx Follow- up	Comments	
			Dose Escalation Period						Maintenance Dose Period															
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
UACR			X						X												X	X	X	
DXA scan		X																			X	X		Applicable only to a subset of participants. Perform baseline scan between Visits 2 and 3 after all eligibility criteria are confirmed. Post baseline DXA scans may be performed within ±7 days of Visit 21 or ED1. See Section 10.10
Stored samples																								
Genetics sample			X																					Sample can be obtained at or

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
																								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			X			Dispensing at Visit 21 applies only to participants continuing to prediabetes additional treatment period.

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
Dispense study intervention to participant			X	X	X	X	X	X	X			X			X			X			X			Dispensing at Visit 21 applies only to participants continuing to prediabetes additional treatment period.
Participant returns study intervention				X	X	X	X	X	X			X			X			X			X	X		

ATTAIN-1 (Study GZGP) Table 1	Period I Screeni ng		Period II-Treatment Period																				Post- Tx Follow- up	Comments
			Dose Escalation Period							Maintenance Dose Period														
Visit number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	ED 1	801	
Weeks from randomization	-3	-2	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		2 wks post end of TxP	
Visit interval tolerance (days)		±3	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7		±3	
Fasting visit	X	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
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; Apo B= apolipoprotein; AST = aspartate aminotransferase; BCKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; C-SSRS= Columbia-Suicide Severity Rating Scale; DNA= deoxyribonucleic acid; DXA = dual-energy x-ray absorptiometry; ECG = Electrocardiogram; ED = early discontinuation; eGFR= estimated glomerular filtration rate; FSH = Follicle Stimulating Hormone; HbA1c= hemoglobin A1c; HBV= hepatitis B virus; HCV= hepatitis C virus; hsCRP = High sensitivity C-Reactive Protein; hr=hour; IWRS = interactive web response system; IWQOL-Lite CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; OGTT= oral glucose tolerance test; PHQ-9 = Patient Health Questionnaire-9; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PI= principle investigator; PFS = Power of Food Scale; PK = pharmacokinetic; PRO = patient-reported outcome; PROMIS= patient-reported outcomes measurement system; RNA= ribonucleic acid; SF-36v2 = Short Form-36 version 2 Health Survey Acute Form; TSH = Thyroid Stimulating Hormone; TxP = Treatment period; UACR = Urinary albumin/creatinine ratio; ULN = upper limit of normal; wks = weeks; VAS = visual analog scale; WOCBP = women of child bearing potential.

1.3.2. Prediabetes Additional Treatment Period (Visits 101 to 117), Early Discontinuation, and Posttreatment Follow-up Visit 802

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Assess medication intensity (dyslipidemia, hypertension)				X				X				X					X	X		
AEs	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 10.3.1. Additional data are collected for certain AEs.
Physical evaluation																				
Weight		X		X		X		X		X		X		X		X	X	X	X	Weight measurements should be obtained per the detailed protocol guidance in

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				Section 10.7. 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	
Vital signs		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 for at least 5 min. See Section 10.7

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
12-lead ECG (Central)				X				X				X					X	X	X	Collect ECG before blood samples for laboratory testing. ECG may be repeated at the investigator's discretion at any visit. Triplicate ECG measurements should be obtained after at least 5 minutes of rest per the instructions in Section 8.2.3.
Physical examination																	X	X		
Symptom- directed physical assessment	X																		X	Symptom- directed physical assessment may be conducted at the discretion of

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				the PI or qualified personnel as indicated per local regulations based on participant status and standard of care.
Participant diary (electronic)																				
Diary review (electronic)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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		
IWQOL-Lite CT								X									X	X		
PGIS -Physical Function Weight								X									X	X		

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
PGIC -Physical Function Weight								X									X	X		
EQ-5D-5L								X									X	X		
PROMIS Short Form Sleep Disturbance 8b								X									X	X		
PHQ-9		X		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.
Patient-reported outcomes (paper) 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. Administration of the PROs below after randomization will only be performed for those participants with a baseline (Visit 3) assessment.																				
Power of Food Scale (15 questions)																	X	X		PFS must be obtained each time in the fasting state. If the participant is not fasting, the

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				participant should be called in for a new visit within the visit window to have the fasting PRO completed.
Appetite VAS																	X	X		Appetite VAS must be obtained each time 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 PRO completed.
Clinician- Administered Assessments (Paper)																				
C-SSRS since last assessed		X		X		X		X		X		X		X		X	X	X	X	The C-SSRS should be administered

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				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.
Participant education																				
Lifestyle program instructions		X		X		X		X		X		X		X		X	X	X		Lifestyle counseling may occur on a separate day from the rest of that visit's study procedures but must occur within the visit window.

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				Beginning at Week 8, counseling may be delivered by telehealth. Refer to Section 5.3
Review diet and physical activity goals	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.
Laboratory tests and sample collections																				
Hematology								X								X	X	X	X	
HbA1c		X		X		X		X		X		X		X		X	X	X	X	
Clinical chemistry		X		X		X		X		X		X		X		X	X	X	X	Clinical Chemistry labs

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				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. If at Visit 802, hepatic laboratory criteria are met, follow the actions outlined in Section 8.2.7.
2-hr oral glucose tolerance test (includes glucose, insulin, c-peptide at each time point)								X									X	X	X	2-hr OGTT testing (Section 10.7) should be omitted at visits following a protocol-defined diabetes diagnosis (Section 10.9)

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				OGTT 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 OGTT performed.
Lipid panel								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.
Urine pregnancy (local)		X		X		X		X		X		X		X			X	X		Perform additional

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
																				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.
hsCRP								X									X	X	X	
Calcitonin								X									X	X	X	
Pancreatic amylase								X									X	X	X	
Lipase								X									X	X	X	
Free fatty acids								X									X	X	X	
Apo B								X									X	X	X	
Cystatin-C		X		X		X		X		X		X		X			X	X	X	

ATTAIN-1 (Study GZGP) Table 2	Period III – Additional Prediabetes Maintenance Period																		Post-Tx Follow- up	Comments
Visit number	101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	ED 2	802	
Weeks from randomization	78	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168	176		14 wks post end of TxP	
Visit interval tolerance (days)	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7	±7		±3	
Fasting visit		X		X		X		X		X		X		X		X	X	X	X	
Visit details	T		T		T		T		T		T		T		T					T = telehealth visit
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	
Stored Samples																				
Exploratory biomarker samples		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	
Dispense study intervention via IWRS		X		X		X		X		X		X		X		X				
Dispense study intervention to participant		X		X		X		X		X		X		X		X				
Participant returns study intervention		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		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; Apo B= apolipoprotein B; AST = aspartate aminotransferase; CKD-EPI = Chronic Kidney Disease-Epidemiology Collaboration; C-SSRS= Columbia-Suicide Severity Rating Scale; ECG = Electrocardiogram; ED = early discontinuation; eGFR= estimated glomerular filtration rate; HbA1c= hemoglobin A1c; hsCRP = High sensitivity C-Reactive Protein; IWRS = interactive web response system; IWQOL-Lite CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; OGTT= oral glucose tolerance test; PFS = Power of Food Scale; PHQ-9 = Patient Health Questionnaire-9; PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PRO= patient-reported outcome; PROMIS= patient-reported outcomes measurement system; SF-36v2 = Short Form-36 version 2 Health Survey Acute Form; TxP= treatment period; UACR = Urinary albumin/creatinine ratio; ULN = upper limit of normal; VAS = visual analog scale; wks = weeks; WOCBP= women of child bearing potential.

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 T2D. Unlike injectable or orally available peptide GLP-1 receptor agonists approved by regulatory authorities to date, orforglipron is an oral, non-peptide GLP-1 receptor agonist.

Orforglipron is being developed as a daily oral adjunct therapy to a healthy diet and physical activity for the treatment of obesity or overweight and as an adjunct to diet and exercise to improve glycemic control in adults with T2D.

2.1. Study Rationale

ATTAIN-1 (Study GZGP) is designed to provide evidence of safety and efficacy of orforglipron in the patient population with obesity or overweight and at least 1 weight-related comorbidity (excluding T2D). Phase 3 studies of novel chronic weight management medications should demonstrate efficacy in terms of body weight reduction over the course of at least 1 year and be randomized, double-blind, and placebo-controlled (FDA 2007; EMA 2016).

ATTAIN-1 (Study GZGP) is a multicenter, randomized, parallel-arm, double-blind, placebo-controlled, Phase 3 study. The study will investigate the effects of treatment with daily oral orforglipron 6 mg, 12 mg, or 36 mg, compared with placebo for at least 72 weeks, as an adjunct to healthy diet and physical activity, on body weight in participants without T2D with either obesity (BMI 30 kg/m² or greater), or overweight (BMI 27 kg/m² or greater) with the presence of at least 1 weight-related comorbidity (for example, hypertension, dyslipidemia, obstructive sleep apnea, or CV disease). Additionally, the study will compare the effects of orforglipron and placebo on blood pressure, lipid parameters, and overall safety profile. Participants who have prediabetes at randomization will be studied for a total of 176 weeks of treatment to provide sufficient follow-up time to assess the effects of orforglipron on progression to T2D and on long-term body weight changes.

2.2. Background

Obesity or overweight

Obesity is a chronic disease associated with a number of comorbidities such as, T2D, CV disease, obstructive sleep apnea, osteoarthritis, increased risk for some cancers and increased risk for premature death (Allison et al. 2008; AMA 2013; CSAPH 2013). 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 reduction 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 participants (UKPDS Group 1990; Pastors et al. 2002; Wing et al. 2011; Rothberg et al. 2017; ADA 2023).

Glucagon like peptide-1 is secreted after meal ingestion and mediates the incretin effect, beta-cell neogenesis and proliferation, and protects beta cells from apoptosis. It also exerts actions on alpha cells, modifying glucagon secretion (Skow et al. 2016). Based on these properties, several GLP-1 receptor agonists have been approved for pharmacological treatment of T2D (Tomlinson et al. 2016).

In addition to its pancreatic effects, GLP-1 receptor activation decreases gut motility, slows gastric emptying, and promotes satiety (presumably through a combination of GLP-1 receptor activation in the central and peripheral nervous system), thereby regulating food intake and body weight (Baggio and Drucker 2007). With the advent of injectable incretin-based therapies, safe, highly efficacious, and well-tolerated medications are increasingly available. Incretin-based therapies have been able to overcome the efficacy and safety issues that have challenged this therapeutic space for decades. Specifically, semaglutide and liraglutide (WEGOVY® package insert 2021 and patient leaflet 2022; SAXENDA® package insert and patient leaflet 2022), both injectable peptide GLP-1 receptor agonists, have been shown to be safe and effective for the treatment of obesity and overweight and have established CV safety.

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 and overweight, Lilly is developing orforglipron, an oral non peptide GLP-1 receptor agonist that has been shown in Phase 2 studies to reduce body weight in participants with obesity or overweight with and without T2D. Additionally, it demonstrated improved glycemic control in individuals with T2D.

Clinical data for Orforglipron

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

Phase 1

The clinical pharmacology, PK, and PD of orforglipron 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 orforglipron plasma concentration increase was approximately proportional to the increase of dose across the 9 mg QD to 45 mg QD dose range. Consistent with the GLP-1 receptor agonist class, GI AEs of nausea, vomiting, and constipation were the most reported AEs. PD results from Study GZGC showed clinically relevant improvements in HbA1c of up to -1.4%, and weight change of up to -5.8 kg after 12 weeks of treatment with orforglipron 9 mg QD to 45 mg QD in people with T2D.

Phase 2

Two Phase 2 studies have evaluated the safety and efficacy of orforglipron: 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, orforglipron treatment for 26 weeks at maintenance doses of 3 mg to 45 mg QD resulted in mean changes from baseline in HbA1c up to -2.1% (treatment difference of -1.7% vs

placebo) and mean weight change of up to -9.6% (treatment difference of -7.4% vs placebo). In people with obesity or overweight (Study GZGI), mean percent weight change of up to -12.6% from baseline (treatment difference of -10.6% compared to placebo) was observed with orforglipron treatment at the primary 26-week endpoint. The overall safety profile of orforglipron in both studies was consistent with that established for the GLP-1 receptor agonist class, with most common TEAEs being GI related (nausea, vomiting, diarrhea and constipation). Data from these Phase 2 studies support the further clinical development of orforglipron.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Study intervention

The potential risks associated with orforglipron are similar to those of marketed GLP-1 receptor agonists. The most commonly reported TEAEs observed in the orforglipron clinical studies, in healthy participants or participants with obesity or T2D are GI effects, including nausea, vomiting, diarrhea, and constipation. Most were mild to moderate in severity and tended to occur during the dose escalation period.

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

Management of risks

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

2.3.2. Benefit Assessment

The known pharmacology of GLP-1 receptor agonism and Phase 2 studies of orforglipron support an expectation of such benefits as body weight reduction with orforglipron. 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 orforglipron supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 receptor agonists, namely GI tolerability issues and increased heart rate. These risks are monitorable, usually mild to moderate in severity, reversible, and readily manageable. To date there are no recognized AEs from orforglipron other than those related to GLP-1 receptor agonism.

The potential risks based on the knowledge for the GLP-1 receptor agonist class are considered being acceptable in the context of the potential benefits anticipated from treatment with orforglipron in adult participants with obesity or overweight.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary Objective	
To demonstrate that orforglipron 6 mg, 12 mg, and/or 36 mg QD is superior to placebo for: • Body weight	From baseline to Week 72 • Mean percent change in body weight
Key Secondary Objectives (controlled for type 1 error)	
To demonstrate that orforglipron 6 mg, 12 mg, and/or 36 mg QD is superior to placebo in change from baseline for the following: • Body weight • Waist circumference	From baseline to Week 72 • Percentage of participants who achieve a body weight reduction of ○ $\geq 5\%$ ○ $\geq 10\%$ ○ $\geq 15\%$ ○ $\geq 20\%$ • Mean change in waist circumference (cm)
To demonstrate that orforglipron (6 mg, 12 mg, and 36 mg QD 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
Key Secondary Objectives at 176 Weeks for Participants with Prediabetes at Randomization (controlled for type 1 error), pooled dose analysis	
To demonstrate in participants with prediabetes at randomization that orforglipron (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo at 176 weeks: • Body weight	From baseline to Week 176 • Mean percent change in body weight

Objectives	Endpoints
Key Secondary Objectives at 176 or 190 Weeks for Participants with Prediabetes at Randomization (controlled for type 1 error), pooled dose analysis	
To demonstrate in participants with prediabetes at randomization that orforglipron (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo for: • Delayed progression to T2D at 176 weeks • Delayed progression to T2D at 190 weeks	• Time to onset of T2D during 176 week treatment period • Time to onset of T2D during entire study including posttreatment follow-up period
Additional Secondary Objectives	
To demonstrate that orforglipron 6 mg, 12 mg, and/or 36 mg QD 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/m²) • Mean change in HbA1c (%) • Mean change in fasting glucose (mg/dL) • Mean percent change in fasting insulin
To demonstrate that orforglipron (6 mg, 12 mg and 36 mg QD pooled dose) 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 from baseline 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

Objectives	Endpoints
	Change in PGIS and PGIC limitations on physical function due to weight
To describe the safety of orforglipron as compared to placebo	Summary of safety data, including number and incidence of Treatment-emergent adverse events
Additional Secondary Objectives at 72 Weeks in Participants with Prediabetes at Randomization	
To demonstrate orforglipron (6 mg, 12 mg, and/or 36 mg QD) is superior to placebo in change from baseline for: Glycemic control	From baseline to Week 72 Percentage of participants achieving normoglycemia (see Section 10.9)
Additional Secondary Objectives at 176 Weeks in Participants with Prediabetes at Randomization	
To demonstrate in participants with prediabetes at randomization that orforglipron 6 mg, 12 mg, and/or 36 mg QD is superior to placebo for the following at 176 weeks: - Body weight - Glycemic control	From baseline to Week 176 - Percentage of study participants who achieve $\geq 5\%$ body weight reduction - Mean percent change in body weight from baseline - Mean change in HbA1c (%) - Mean change in fasting glucose (mg/dL) - Percentage of participants achieving normoglycemia

Objectives	Endpoints
Tertiary Objectives	
To characterize the population PK of orforglipron and explore the relationships between orforglipron concentration and efficacy, safety, and tolerability measures	Population PK and PD parameters

Abbreviations: BMI = body mass index; DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL = high density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of life-Lite-Clinical Trial; LDL = low-density lipoprotein; PD = pharmacodynamic(s); PGIC = Patient Global Impression of Change; PGIS = Patient Global Impression of Severity; PK = pharmacokinetic(s); QD= once-daily; SBP = systolic blood pressure; SF-36v2 = 36-item Short Form Health Survey, version 2; T2D = type 2 diabetes; VAS = visual analogue scale.

Estimands

There will be 2 estimands for the primary objective 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 primary clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at 72 weeks between orforglipron 36 mg, 12 mg, 6 mg and placebo, as an adjunct to healthy diet and physical activity, 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:** Participants who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- **Endpoint:** 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 change from baseline in body weight at 72 weeks between orforglipron and placebo.

- **Rationale for the estimand:** This estimand aims to evaluate the efficacy of orforglipron 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 orforglipron 36 mg, 12 mg, 6 mg and placebo, as an adjunct to healthy diet and physical activity, 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.
 - **Endpoint:** 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 treatment 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.
33. **Population-level summary and treatment effect of interest:** Difference in mean percent changes in body weight from baseline at Week 72 between orforglipron and placebo.
- **Rationale for the estimand:** This estimand aims to evaluate the efficacy of orforglipron 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-1 (Study GZGP) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study. The study will investigate the safety and efficacy of treatment with daily oral doses of orforglipron (6 mg, 12 mg, or 36 mg), compared with placebo in participants without T2D with either obesity (BMI 30 kg/m² or greater), or overweight (BMI 27 kg/m² or greater) with the presence of at least 1 weight-related comorbidity (for example, hypertension, dyslipidemia, obstructive sleep apnea, or CV disease). Eligible participants will be assigned to either 72 or 176 weeks of treatment based upon baseline prediabetes status (no prediabetes and prediabetes, respectively). See Section 10.9 for the definition of prediabetes.

Study participants will be randomized in a 3:3:3:4 ratio to receive a daily dose of orforglipron (6 mg, 12 mg, or 36 mg) or placebo. An upper limit of 70% enrollment of females will be used to ensure a sufficiently large sample of males.

Study details include:

	Without Prediabetes at Randomization	Prediabetes at Randomization
Screening Period	3 weeks	3 weeks
Treatment Period		
Dose escalation period	20 weeks	20 weeks
Maintenance dose period	52 weeks	52 weeks
Additional treatment period for participants with prediabetes at randomization	N/A	104 weeks
Posttreatment Follow-up Period	2 weeks	14 weeks ^a
Total Study Duration	77 weeks	193 weeks

^a If participants with prediabetes at randomization discontinue study intervention during the first 72 weeks, the posttreatment follow-up period will be 2 weeks.

See the SoA (Section 1.3) for visit details.

During the screening period, participants will undergo laboratory assessments at Visits 1 and 2 to determine prediabetes status as follows:

Screening Visit 1

All participants will have a fasting glucose and HbA1c test. Results of these tests determine eligibility to proceed to Screening Visit 2. Exclusionary results suggest diabetes mellitus.

If a participant has...	then the participant...
FSG $\geq$ 126 mg/dL ($\geq$ 7.0 mmol/L)	is excluded from the study and should be referred to their primary care physician for further work-up to confirm the diagnosis.

If a participant has...	then the participant...
HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol)	is excluded from the study and should be referred to their primary care physician for further work-up to confirm the diagnosis.
FSG < 126 mg/dL (< 7.0 mmol/L) and HbA1c $< 6.5\%$ (< 48 mmol/mol) and participant is otherwise eligible	will proceed to Visit 2.

Abbreviations: FSG= fasting serum glucose; HbA1c= hemoglobin A1c

Screening Visit 2

All participants attending Screening Visit 2 will undergo a 2-hour OGTT test. These results, in combination with those obtained from Screening Visit 1, will be used to determine study eligibility and randomization glycemic status. Exclusionary results suggest diabetes mellitus.

If...	then the participant...
0-hr OGTT ≥ 126 mg/dL (≥ 7.0 mmol/L)	is excluded from the study and should be referred to their primary care physician for further work-up to confirm the diagnosis.
2-hr OGTT ≥ 200 mg/dL (≥ 11.1 mmol/L)	is excluded from the study and should be referred to their primary care physician for further work-up to confirm the diagnosis.
0-hr OGTT < 126 mg/dL (< 7.0 mmol/L) and 2-hr OGTT < 200 mg/dL (< 11.1 mmol/L) and participant is otherwise eligible	will proceed to Visit 3.

Abbreviations: OGTT= oral glucose tolerance test

Glycemic classification

All participants without laboratory tests suggestive of diabetes will be classified as having either normoglycemia or prediabetes.

See Section 10.9 for further details on definitions for normoglycemia, prediabetes, and classification of participants at randomization.

Incident diabetes during the treatment period

Participants will be monitored throughout the study for incident diabetes. For the definition of incident diabetes, confirmation of diabetes diagnosis, recording of incident diabetes events, and management of incident diabetes, refer to Section 10.9. All reported or suspected cases of incident diabetes will be adjudicated by an independent CEC (adjudication committee) with endocrinology expertise that will be blinded to treatment assignment. 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 to the CEC for adjudication (see Section 10.1.5). Decisions of the CEC regarding diabetes diagnosis and the onset date will be recorded in a dedicated adjudication CRF. Participants with incident diabetes during the study will continue participation in the study with study intervention unless discontinuation criteria are met (Section 7).

See the SoA (Section 1.3) for visit details.

4.2. Scientific Rationale for Study Design

Orforglipron is a chemically synthesized, oral GLP-1 receptor agonist. Orforglipron has demonstrated efficacy for weight reduction in preclinical and Phase 2 studies. Orforglipron 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-1 (Study GZGP) is designed to determine the comparative benefits and risks of orforglipron 6 mg, 12 mg, and 36 mg QD versus placebo in participants with obesity or overweight and at least 1 weight-related comorbidity. A double-blind design was selected to minimize participant and investigator bias in assessments for efficacy, safety, and study intervention tolerability. Participants who have prediabetes at randomization (Section 10.9) will be studied for a total of 176 weeks of treatment to provide sufficient follow-up time to detect potential differences in progression to T2D.

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 standards. Specifically, participants will consult with a dietician, or equivalent qualified delegate, throughout the study to focus on a healthy diet and physical activity.

Study duration

The planned duration of treatment for the primary endpoint at 72 weeks allows for at least a 52-week treatment period at the randomly assigned dose (6 mg, 12 mg, or 36 mg). This duration is considered appropriate to assess the full effects and benefit/risk of each maintenance dose of orforglipron 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 at the 2-week posttreatment follow-up period (Week 74).

Another objective of the study is to evaluate the effect of orforglipron on the risk of new onset diabetes. Obesity is associated with an increased risk of developing T2D, and diabetes prevention is of a great importance in participants with obesity to protect them from complications of the disease. Several studies have shown that interventions leading to weight reduction may help prevent diabetes (Adams et al. 2017, le Roux et al. 2017).

To obtain additional information regarding the time to new onset of T2D while taking orforglipron, participants with prediabetes diagnosed at the beginning of the study (being at increased risk of diabetes), will be treated and observed for an additional 2 years. Based on available literature, the 3 years of treatment with orforglipron should be sufficient to demonstrate the risk reduction of developing T2D compared to placebo. This additional treatment period

would also permit collecting data on the durability of weight reduction and safety of long-term orforglipron treatment.

For participants with prediabetes at randomization, the effects of study intervention cessation will be assessed in a 14-week posttreatment follow-up period (Week 190).

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 Section 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 orforglipron doses of 6 mg, 12 mg and 36 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. The Phase 2 CWM Study GZGI included starting doses of 2 mg and 3 mg with dose escalation steps occurring at 1 to 3 week intervals. The maintenance doses studied were 12 mg, 24 mg, 36 mg, and 45 mg for a minimum of 16 weeks for the study's primary outcome.

While the 6 mg dose was not assessed as a maintenance dose in Study GZGI, study participants randomized to the 12 mg maintenance dose received the 6 mg dose for 8 weeks as part of the dose escalation scheme. Based upon observed body weight reductions following the 8 weeks at 6 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 12 mg dose was selected as an intermediate dose in this study based upon the placebo-adjusted observed body weight change of -6.5% (95% CI -8.9% to -4.2%) noted in Study GZGI. Further, in the separate Phase 2 Study GZGE (participants with T2D), orforglipron maintenance doses of 12 mg and higher resulted in greater placebo-adjusted mean improvement from baseline in HbA1c (-1.49% [95% CI -1.85% to -1.12%]) than was observed with the 3 mg maintenance dose in this study (-0.77% [95% CI -1.13% to -0.40%]).

The 36 mg dose was selected as the highest dose based upon the greater placebo-adjusted observed body weight change in Study GZGI of -10.2% (95% CI -12.4% to -8.0%) compared to the 12 mg dose. In Study GZGE, the placebo adjusted HbA1c improvement for the 36 mg dose (-1.60% [95% CI -1.96% to -1.25%]) was also greater than for the 12 mg dose. At the higher maintenance dose of 45 mg, there was no clinically meaningful improvement in weight reduction or HbA1c reduction beyond that observed at 36 mg.

In summary, orforglipron doses of 6 mg, 12 mg, and 36 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 participants with comorbid T2D.

The dose escalation method was selected to optimize GI tolerability based on assessment of different starting doses and escalation intervals used in the Phase 1 and 2 studies. The totality of these results suggested a lower starting dose of 1 mg for 4 weeks prior to escalating to 3 mg, followed by no more than a doubling of dose at 4-week intervals thereafter until the target dose is attained (Section 6.1). This dose regimen would permit adequate time for development of tolerance to GI events and is predicted to improve GI tolerability in the Phase 3 studies.

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 (Section 1.3) 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. Participant 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. Have a BMI
 - ≥ 30.0 kg/m², or
 - ≥ 27.0 kg/m² and presence of at least 1 of the following weight-related comorbidities (treated or untreated) at Visit 1:
 - Hypertension
 - Dyslipidemia
 - Obstructive sleep apnea
 - Cardiovascular disease (for example, ischemic cardiovascular disease, New York Heart Association Functional Class I-III heart failure).
3. Have a history of at least 1 self-reported unsuccessful dietary effort to lose body weight.

Sex and contraceptive/barrier requirements

4. 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

5. 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

6. Capable of giving signed informed consent as described in Appendix 10.1.3, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.2. Exclusion Criteria

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

Medical conditions

Diabetes related

7. Have T1D, T2D, or any other types of diabetes, history of ketoacidosis, or hyperosmolar state/coma

Note: Participants with a history of gestational diabetes are eligible to participate in this trial.

8. Have central laboratory evidence diagnostic of diabetes at Visit 1 or Visit 2, including 1 or more of:
 - HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol)
 - FSG ≥ 126 mg/dL (≥ 7.0 mmol/L), including 0-hour OGTT (see Section 4.1)
 - 2-hour glucose measurement from a 2-hour OGTT ≥ 200 mg/dL (≥ 11.1 mmol/L)

Obesity related

9. Have a self-reported change in body weight >5 kg (11 pounds) within 90 days prior to Visit 1.

10. 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, or
- Cryolipolysis.

11. 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.

12. 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

13. Have an eGFR <15 mL/min/1.73 m², calculated by Chronic Kidney Disease-Epidemiology cystatin-C equation, as determined by central laboratory at Visit 1.

Gastrointestinal

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

Autoimmune

15. 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

16. Have had any of the following CV conditions within 90 days prior to Visit 1
- acute myocardial infarction
 - cerebrovascular accident (stroke)
 - coronary artery revascularization
 - unstable angina or
 - hospitalization due to congestive heart failure.
17. Have New York Heart Association Functional Classification IV congestive heart failure.

Hepatic

18. 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 the following, as determined by the central laboratory at Visit 1:
- ALT or AST level ≥ 3.0 x the ULN for the reference range
 - ALP level ≥ 1.5 x the ULN for the reference range
 - TBL level ≥ 1.5 x the ULN for the reference range, except for cases of known Gilbert's Syndrome
 - 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 < 3.0 x the ULN for the reference range.

Endocrine

19. Have family (first-degree relative) or personal history of MTC or MEN2 syndrome.
20. Have a calcitonin level determined by the central laboratory at Visit 1 of
- ≥ 20 ng/L, if eGFR ≥ 60 mL/min/1.73 m², or
 - ≥ 35 ng/L, if eGFR < 60 mL/min/1.73 m².
21. 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

22. 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.

Hematology

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

Psychobehavioral

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

or

In the investigator's opinion, have any significant mental health disorder that may put the individual at higher risk of study participation.

Note: In the investigator's opinion, individuals whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study may be considered for inclusion if they do not meet exclusion criterion #35 regarding weight gain-promoting concomitant medications.

25. Have a PHQ-9 score of 15 or more at Visit 1 or Visit 3
26. Are, in the judgment of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide
27. Have answered "yes" to either Question 4 or Question 5 on the "Suicidal Ideation" portion of the C-SSRS **and** the ideation occurred within the past month 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

28. 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).
29. At the time of screening have a planned surgery (except for minor surgical procedures) to occur during the course of the study.
30. Had chronic or acute pancreatitis any time prior to Visit 1.
31. Have had a transplanted organ or awaiting an organ transplant.

Exception: corneal transplants (keratoplasty).

Prior/concomitant therapy

32. Are receiving metformin or any other glucose-lowering medication, regardless of the indication for use, within 90 days prior to Visit 1, or between Visit 1 and Visit 3 (see Section 10.8.1.3 for more details).
33. Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, inhaled, or intra-articular preparations) or have received such therapy within 90 days prior to Visit 1, or between Visit 1 and Visit 3.
34. 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 10.8.1.1 for more details).
35. 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 10.8.1.2 for more details), within 12 months prior to Visit 1.
36. Have started implantable or injectable contraceptives within 18 months prior to Visit 1.
Note: Intrauterine devices are acceptable.
37. Are receiving strong CYP3A inhibitors or CYP3A inducers, strong OATP inhibitors, or drugs that are sensitive P-gp/BCRP substrates with narrow therapeutic index (see Section 10.8.1.4 for more details).
Note: To be eligible for screening into this study, these 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 Visit 3.
38. Have known allergies or intolerance to GLP-1 receptor agonist.

Prior/concurrent clinical study experience

39. Have previously completed or withdrawn from this study or any other study investigating orforglipron after receiving at least 1 dose of study intervention.
40. 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.
41. Have participated in a clinical study and received treatment, whether active or placebo within 90 days prior to Visit 1.

Other exclusions

42. 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.
43. 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. Participants in the additional 2-year treatment period for participants with prediabetes (Section 10.9) at randomization will continue to receive lifestyle management counseling at 3-month intervals as defined in the SoA (Section 1.3).

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

5.3.1. Meals and Dietary Restrictions

For certain assessments, study 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.

Orforglipron is a CYP3A4 substrate. Participants should refrain from consuming grapefruit juice while participating in the study due to the effect on CYP3A4.

Healthy diet

At Visit 3 and subsequent visits study participants will receive individualized counseling regarding a healthy diet with the goal of achieving weight reduction. The counseling will be performed by a dietitian/nutritionist, or equivalent qualified designee, according to local standard. The focus of the counseling should facilitate healthier food choices and promote portion control through mindful eating. It should include instruction on customized nutrient-dense food and beverage choices to reflect personal preferences, cultural traditions, and budgetary considerations.

Consider the following principles in counseling sessions:

- eating smaller more frequent (every 3-4 hours) meal/snacks and avoid skipping meals
- for a given meal, consider including approximately ½ plate from fruits/vegetables, ¼ plate from whole grains, and ¼ plate from protein
- including fiber rich foods, and
- limiting foods high in solid fats, added sugar, and salt.

5.3.2. Monitoring Nutritional Needs

Similar to other GLP-1 receptor agonists, orforglipron 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 healthy diet and physical activity will be assessed at each study visit.

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

5.3.4. Activity Before Blood Collections

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

5.3.5. Blood Donation

Study participants should be instructed not to donate blood or blood products during the study and for 2 weeks following the study.

5.3.6. Diabetes Education

Diabetes education, as well as a glucometer, will be provided to study participants who develop T2D (Refer to Section 10.9) during the study. 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.

Refer to Section 8.3.3.4 for management of hypoglycemia risk

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.

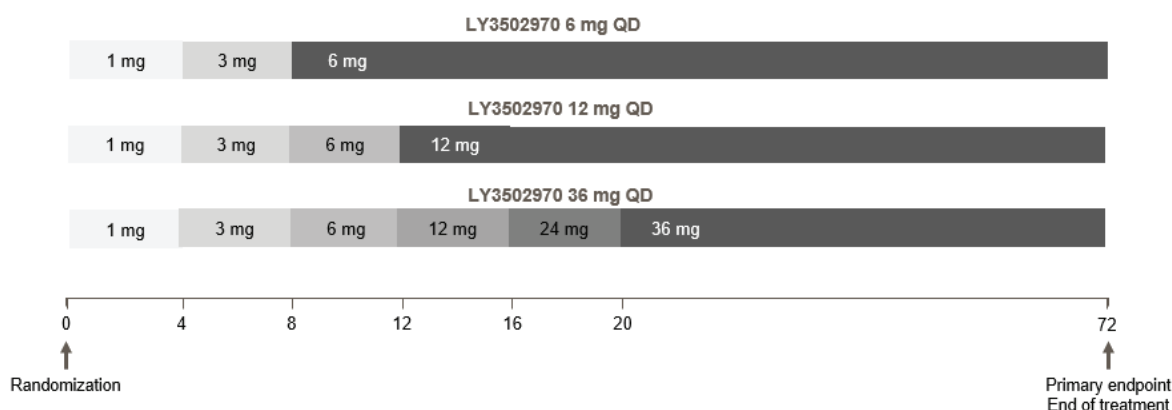
6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	Orforglipron	Placebo
Dosage Level(s)	1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg capsules	Capsule of orforglipron 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 1 mg QD dose of orforglipron or matching placebo and increase dose every 4 weeks until the randomized maintenance dose (6 mg, 12 mg, or 36 mg) is reached as outlined in the below figure.



Abbreviation: LY3502970 = orforglipron; QD = once daily.

Note: LY dose increases occur every 4 weeks in a blinded fashion until the randomized maintenance dose (6 mg, 12 mg, or 36 mg) is reached.

The maintenance dose (6 mg, 12 mg, 36 mg) of orforglipron or placebo will be continued for the remainder of the study (72 weeks for participants without prediabetes at randomization or 176 weeks for participants with prediabetes at randomization). 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. Medications that may be affected by an increase in gastric pH should be separated from study intervention administration by at least 2 hours (Sections 6.9 and 10.8.2.1). The participant will record the actual date and time of all dose administrations in an eDiary.

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 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 3:3:3:4 ratio to receive a daily dose of orforglipron 6 mg, 12 mg, 36 mg, or placebo. All doses of study intervention capsules appear the same. Furthermore, placebo capsules look like study intervention capsules to maintain blinding.

The randomization will be stratified by:

- prediabetes status (yes, no) (Section 10.9)
- sex (female, male), and
- country.

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.

Unblinding after primary database lock

The primary database lock will occur after all randomized participants complete the 72-week treatment period (and the 2-week posttreatment follow-up [Visit 801] for those without prediabetes at randomization) or discontinue the study early. The primary objective of the study will be assessed following the primary database lock. The final database lock will occur after participants classified with prediabetes at randomization have completed a 176-week treatment period and the posttreatment follow-up visit (Visit 802) or discontinued the study early.

To ensure that blinding is maintained after the primary database lock, a subset of the study team members, assigned to work on preparation of the clinical study report and regulatory submissions using unblinded data, will be replaced by new, blinded team members. The blinded team members will not have access to the unblinded treatment assignments until the final database lock. The unblinded team members must not share the unblinded participant-level data with blinded team members and must not have any direct contact with the sites after they become unblinded. Additional details are in the Blinding and Unblinding Plan for the study.

Emergency unblinding

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

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

Emergency unblinding 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 capsules and documented in the source documents.

Participants will be instructed to return any unused study intervention capsules 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

The dose escalation period of the study occurs over the first 20 weeks to allow escalation to the maximum dose of 36 mg for those randomized to this treatment arm. All participants will undergo each dose escalation step regardless of randomized treatment assignment. These dose escalations steps will be handled in a blinded fashion using the IWRS. During the dose escalation period, the investigator should make every effort to proceed through each dose escalation step per the study schedule in order for participants to achieve their randomized dose. Participants should continue on this dose for the duration of the treatment period.

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.

If GI symptoms become tolerable or resolve with the above measures, the participant should continue study intervention at the same dose level until the next scheduled dose escalation step (if during the dose escalation period) or continue for the duration of the study if the participant has completed the final dose escalation step.

If intolerable GI symptoms persist, despite the above measures, the investigator should contact the sponsor to consider de-escalating to the next lower dose level for 8 weeks in a blinded fashion. De-escalation may be performed during an unscheduled dispensing visit.

The below table provides guidance for de-escalating the dose.

If a participant is currently taking...	Then de-escalate the dose for at least 8 weeks to...
1 mg/placebo	discontinue the study intervention and continue in the study
3 mg/placebo	discontinue the study intervention and continue in the study
6 mg/placebo	3 mg/placebo
12 mg/placebo	6 mg/placebo
24 mg/placebo	12 mg/placebo
36 mg/placebo	24 mg/placebo

If GI symptoms become tolerable or resolve with dose de-escalation, the investigator should initiate re-escalation after at least 8 weeks have passed and only at a scheduled visit. For this purpose, if necessary, a telehealth visit may be performed as an office visit.

If the re-escalation attempt is tolerated, then the participant should continue to complete the remaining dose escalation steps to achieve the randomized maintenance dose per Section 6.1.

If the re-escalation attempt is not tolerated or if intolerable GI symptoms recur at any subsequent time point following the re-escalation, then depending on which dose level is achieved, the participant should undergo a final dose de-escalation to the next lower dose level, discontinue study intervention, or receive placebo in a blinded fashion.

The below table provides guidance if the re-escalation attempt was not tolerated.

If the re-escalation attempt is not tolerated with this dose...	then the dose will be de-escalated for the remainder of the study to...
6 mg/placebo	discontinue the study intervention and continue in the study or placebo ^a
12 mg/placebo	6 mg/placebo
24 mg/placebo	12 mg/placebo
36 mg/placebo	24 mg/placebo

^a If a participant is assigned to the 6 mg dose arm and successfully achieves their assigned dose, but subsequently develops intolerable GI symptoms and the minimum dose of 6 mg is not tolerated, the IWRS will dispense placebo in a blinded fashion.

Please note the following

- only 1 re-escalation attempt is permitted during the entire course of the study, and
- only 1 de-escalation is permitted after re-escalation.

If intolerable GI symptoms persist despite symptomatic treatment, temporary drug interruption, and resumption of study intervention after the final dose de-escalation, 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.

All dose adjustments, for example, dose de-escalation or re-escalation, aside from planned dose escalation steps per Section 6.1 are to be recorded in the CRF.

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

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

6.8. Treatment of Overdose

As any dose of orforglipron greater than 100 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 36 mg, for this blinded study, any dose of study intervention ≥ 3 capsules 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, 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 and dyslipidemia. Since weight reduction is expected to improve these comorbidities, study participants may require a dose reduction or complete withdrawal of certain concomitant medications. Investigators should closely monitor the need for adjustment of concomitant medications throughout the study, especially anti-hypertensives, as incretin-based therapies and weight reduction are commonly associated with a reduction in blood pressure.

During the study, a medication (treatment) intensity CRF pertaining to concomitant medications taken for weight-related comorbidities, including 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 by an increase in gastric pH should be separated from study intervention administration by at least 2 hours. Examples (not exhaustive) relevant to the study population include

- simvastatin, levothyroxine, ferrous sulfate, bisphosphonates, and
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability (further examples provided in Section 10.8.2.1).

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. 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.

6.9.2. Initiation of Antihyperglycemic Medications

Participants who develop diabetes (Section 10.9) during the study may initiate medication for glucose control, with the exception of DPP-4 inhibitors or GLP-1 receptor agonists or other incretin-based therapies, for example, tirzepatide (Section 10.8.1.3).

During the study, metformin and sodium-glucose cotransporter-2 inhibitors should not be initiated for the treatment of conditions other than T2D. Metformin should not be initiated for the treatment of other conditions (for example, prediabetes or polycystic ovary syndrome) at any time in the study. In addition, for other comorbid conditions, such as heart failure or chronic kidney disease, investigators are encouraged to prescribe medications that do not have antihyperglycemic effects. However, if no other effective and tolerable medication is medically appropriate, the use of an sodium-glucose cotransporter-2 inhibitor will not be considered a protocol deviation.

6.9.3. Prohibited or Restricted Use Medications

The following medications are prohibited throughout the study:

- GLP-1 receptor agonists or other incretin-based therapies (for example, tirzepatide), and DPP-4 inhibitors (Section 10.8.1.3).
- Those intended to promote weight loss, including prescribed, over the counter, or alternative remedies. Examples are provided in Section 10.8.1.1.
- Strong CYP3A inducers or inhibitors, drugs that are sensitive P-gp/BCRP substrates with a narrow therapeutic index, or strong inhibitors of OATPs. Examples of these classifications of medications are provided in Section 10.8.1.4. Note that in some circumstances a strong CYP3A inhibitor may be used for a short duration of time (e.g., for the treatment of a viral infection), if necessary. If this need arises, participants should undergo a temporary study intervention interruption and not re-initiate study intervention until at least 14 days after the end date of the strong CYP3A inhibitor. Refer to Section 7.1.2 for guidance.

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

- Moderate CYP3A inducers or inhibitors. Examples are provided in Section 10.8.2.2.
- Weight gain medications. Examples are provided in Section 10.8.1.2.

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 8.3.3.13
- the participant is diagnosed with MTC or MEN2 syndrome
- the participant develops significant elevation of serum calcitonin. See Section 8.3.3.1
- the participant is diagnosed with 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)
- the participant is diagnosed with T1D
- the participant requests to discontinue study intervention
- the 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 receptor agonist, GIP/GLP-1 receptor agonist, or DPP-4 inhibitor, 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.
- BMI ≤ 18.5 kg/m² is reached at any time during the treatment period
Note: The investigator should contact the sponsor's designated medical monitor to discuss whether it is medically appropriate for the participant to continue study intervention.
- initiation of other weight management medications (Section 10.8.1.1) or if the participant has bariatric surgery or body weight reduction procedures
- systemic hypersensitivity reaction (Section 8.2.8)

- 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 10.8.1.2 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 orforglipron, 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 dose escalation visit, the participant should proceed with the next escalation.
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

If study intervention interruption is...	then...
	scheduled dose escalation visit, the participant should proceed with the next escalation.
7 or more consecutive doses	participant may resume the study intervention at the last administered dose level or repeat a dose escalation per Section 6.1. from 3 mg/placebo to previously attained dose level at the discretion of the investigator. If the interruption occurs within the first 7 weeks, 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 ^a	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.

^a 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 posttreatment follow-up, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

Participants 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

See Section 3 for specific efficacy endpoints.

Patient-reported outcome measures are described in Section 8.1.4.

Safety-related measures are described in Section 8.2 and 8.3.

The independent CEC adjudicating events is described in Section 10.1.5

8.1.1. Primary Efficacy Assessments

The primary efficacy endpoint is percent change in body weight.

Body weight measurements will be collected at specific clinic visits as summarized in the SoA. Methods for measuring body weight are described in Section 10.7

8.1.2. Secondary Efficacy Assessments

- Body weight (kg) (see Section 10.7)
- Waist circumference (see Section 10.7)
- Glycemic control (see Section 3)
- Blood pressure (see Section 3)
- Lipid parameters (see Section 3)
- Patient-reported outcomes (see Section 8.1.4)

8.1.3. Tertiary Efficacy Assessments

- 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.

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

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-point frequency (“never” to “always”) scale or a 5-point truth (“not at all true” to “completely true”) scale. The 3 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.

The VAS records the respondent’s self-rated health on a vertical VAS where the endpoints are labelled as “best imaginable health state” (100) and “worst imaginable health state” (0).

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

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

8.1.4.5. 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".

8.1.4.6. PROMIS Short Form v1.0 Sleep Disturbance 8b

The Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form v1.0 Sleep Disturbance 8b assesses self-reported perceptions of sleep quality, sleep depth, and restoration associated with sleep, including perceived difficulties and concerns with getting to sleep or staying asleep, as well as perceptions of the adequacy of and satisfaction with sleep. The PROMIS Short Form v1.0 Sleep Disturbance 8b has a recall period of 7 days and each of its 8 items are rated on a 5-point scale ranging from "not at all" to "very much", "never" to "always," or "very poor" to "very good." Individual item scores are totaled to obtain a raw score, with higher scores indicating more sleep disturbance. Raw scores can be converted to a T-score, which is standardized with a mean of 50 and a SD of 10 (Northwestern, 2016).

8.1.4.7. Appetite Visual Analog Scale

The aim of the appetite VAS is to determine the effects of study intervention on appetite sensations and desire for specific foods. Administration of the appetite VAS after randomization will only be performed for those participants with a baseline (Visit 3) assessment.

Participants will be asked to rate their feelings of hunger, satiety, fullness, prospective food consumption, and desire for specific foods by making a vertical mark on a 100-mm line, represented on a piece of paper anchored by verbal descriptors such as "not at all" and "extremely." The appetite VAS will include the following 8 questions (Flint et al. 2000):

- How hungry do you feel right now?
- How satisfied do you feel right now?
- How full do you feel right now?
- How much food do you think you could eat right now?
- Would you like to eat something sweet?
- Would you like to eat something salty?
- Would you like to eat something savory?
- Would you like to eat something fatty?

Pen-and-paper VAS will be used and each of the 8 questions will have a fixed 100-mm length line for response. Each end of the line represents the extreme limits of the parameter (e.g., not at all hungry, extremely hungry). Participants will mark each respective line to indicate their rating for each question.

Refer to Section 10.11 for information on scoring the VAS.

Only the study-provided ruler along with the provided paper VAS can be used, as photocopying alters the line length.

8.1.4.8. Power of Food Scale

The Power of Food Scale (Cappelleri et al. 2009; Lowe et al. 2009) is a 15-item, self-administered instrument that assesses the psychological impact of living in an environment with an abundance of palatable foods. It measures the appetite for food based on 3 levels of food proximity, namely, food available, food present, and food tasted.

Respondents indicate their agreement with each of the 15 items on a 5-point Likert scale, ranging from 1 (do not agree at all) to 5 (strongly agree). Total scores can be generated for the individual 3 domains, and there is also an aggregate total score. Higher scores indicate a higher psychological impact of food.

Administration of the Power of Food Scale after randomization will only be performed for those participants with a baseline (Visit 3) assessment.

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, GI, and neurological systems.
- Height, weight, waist circumference and vital signs will also be measured and recorded. See Section 10.7 for further details.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital sign measurements should be conducted according to the SoA and Section 10.7.

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

8.2.3. Electrocardiograms

Triplicate 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. The recording of each ECG should occur at approximately

1-minute intervals. The collection of all replicates at a time point should not exceed 5 minutes. 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. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study 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 (C-SSRS 2013). See Section 8.3.3.13 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)

If this laboratory value is observed...	Then...		
	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)
ALT or AST ≥ 3 x ULN	X		
ALP ≥ 2 x ULN	X		
TBL ≥ 2 x ULN ^b	X		
ALT or AST ≥ 5 x ULN	X	X	
ALP ≥ 2.5 x ULN	X	X	
ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^a	X	X	X
ALT or AST ≥ 5 x ULN for more than 2 weeks	X	X	X
ALT or AST ≥ 8 x ULN	X	X	X
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5	X	X	X
ALP ≥ 3 x ULN	X	X	X
ALP ≥ 2.5 x ULN and TBL ≥ 2 x ULN ^b	X	X	X

If this laboratory value is observed...	Then...		
	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)
ALP ≥ 2.5 x ULN with hepatic signs or symptoms ^a	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 In participants with Gilbert's syndrome, the threshold for TBL may be higher.

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

If this laboratory value is observed...	Then...		
	Initiate or continue close hepatic monitoring	Initiate comprehensive hepatic evaluation	Interrupt or discontinue study drug
ALT or AST ≥ 2 x baseline	X		
ALP ≥ 2 x baseline	X		
TBL ≥ 2 x ULN ^b	X		
ALT or AST ≥ 3 x baseline or ≥ 250 U/L (whichever occurs first)	X	X	
ALP ≥ 2.5 x baseline	X	X	
ALT or AST ≥ 2 x baseline or ≥ 250 U/L (whichever occurs first) with hepatic signs or symptoms ^a	X	X	X
ALT or AST ≥ 3 x baseline or ≥ 250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥ 4 x baseline or ≥ 400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥ 2 x baseline or ≥ 250 U/L (whichever occurs first) and TBL ≥ 2 x ULN ^b or INR ≥ 1.5	X	X	X
ALP ≥ 3 x baseline	X	X	X
ALP ≥ 2.5 x baseline and TBL ≥ 2 x ULN ^b	X	X	X
ALP ≥ 2.5 x baseline with hepatic signs or symptoms ^a	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 In participants with Gilbert's syndrome, the threshold for TBL may be higher

8.2.7.1. Close Hepatic Monitoring

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

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

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

Close hepatic monitoring should include these actions:

- Laboratory tests ([Appendix 6](#)), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, creatine kinase, and complete blood count with differential, should be checked within 48 to 72 hours of the detection of elevated liver tests to confirm the abnormality and to determine if it is increasing or decreasing.
- If the abnormality persists, clinical and laboratory monitoring should continue at a frequency of 2 to 3 times weekly until levels normalize or return to approximate baseline values.
- In addition to lab tests, basic evaluation for possible causes of abnormal liver tests should be initiated by the investigator in consultation with the Lilly-designated medical monitor. At a minimum, this evaluation should include physical examination and a thorough medical history, including current symptoms, recent illnesses (for example, heart failure, systemic infection, hypotension, or seizures), recent travel, concomitant medications (including over-the-counter), herbal and dietary supplements, and history of alcohol drinking and other substance abuse.

8.2.7.2. Comprehensive Hepatic Evaluation

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

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

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

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

Comprehensive hepatic evaluation should include these actions:

- At a minimum, comprehensive hepatic evaluation should include physical examination and a thorough medical history, as outlined above, as well as tests for Prothrombin time, INR; tests for viral hepatitis A, B, C, and E; tests for autoimmune hepatitis; and an abdominal imaging study (for example, ultrasound or CT scan).
- Based on the participant's history and initial results, further testing should be considered in consultation with the Lilly-designated medical monitor, including tests for hepatitis D virus, cytomegalovirus, Epstein-Barr virus, acetaminophen levels, acetaminophen protein adducts, urine toxicology screen, Wilson's disease, blood alcohol levels, urinary ethyl glucuronide, and blood phosphatidylethanol.
- Based on the circumstances and the investigator's assessment of the participant's clinical condition, the investigator should consider referring the participant for a hepatologist or gastroenterologist consultation, and additional tests including magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, cardiac echocardiogram, or a liver biopsy.
- Clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until levels normalize or return to approximate baseline values.
- All the medical information and tests results related to the hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.

8.2.7.3. Study Drug Interruption or Discontinuation

If a participant develops any one of the following laboratory or clinical changes, interrupt the study-drug and continue close monitoring and comprehensive hepatic evaluation as described in Sections 8.2.7.1 and 8.2.7.2.

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

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

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

Interruption or discontinuation of study drug should include these actions:

- While the participant is not receiving the study drug, clinical and laboratory monitoring should continue at a frequency of 1 to 2 times weekly until liver tests normalize or return to approximate baseline values.
- If the hepatic event continues past the anticipated end of the study (that is, data lock), the investigator should consult with the Lilly-designated medical monitor to determine the need for further data collection beyond the end date of the study (that is, data lock date).
- All the medical information and tests results related to the close hepatic monitoring and comprehensive hepatic evaluation should be collected and recorded in a hepatic safety CRF.
- Resumption of the study drug after interruption for a hepatic reason can be considered only in consultation with the Lilly-designated medical monitor and only if the liver test results returned to near baseline and if a self-limited non-study-drug etiology is identified. Otherwise, the study drug should be permanently discontinued.

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.

8.3. 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 7.1).

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 informed consent form ICF	Participation in study has ended	As soon as possible upon site awareness	AE CRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE and SAE updates – after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hr of awareness	SAE CRF	SAE paper form
SAE ^a – after participant's study participation has ended and the investigator becomes aware	After participant's study participation has ended	N/A	Promptly	SAE paper form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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 hr (see Section 8.3.2)	e-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 hr of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

^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

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

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

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

Female participants who become pregnant

- The investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. The initial information will be recorded on the appropriate form and submitted to the sponsor within 24 hours of learning of a participant's pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The investigator will collect follow-up information on the participant and the neonate and the information will be forwarded to the sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of gestational age, fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE.
- A spontaneous abortion (occurring at <20 weeks gestational age) or still birth (occurring at ≥20 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be discontinued from the study. 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

Cardiovascular 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 CV 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

Distribution of glucometers and study diaries

All participants who develop T2D during the study will be provided with glucometers.

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

All participants, regardless of diabetes status during the study, will receive an eDiary. Participants will be trained about the signs and symptoms of hypoglycemia and its treatment and instructed to record relevant information about hypoglycemic events in their eDiary.

Responding to recurrent hypoglycemia in participants taking concomitant antihyperglycemic medication

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

sulfonylurea. Study intervention discontinuation for recurrent hypoglycemia should be considered only if these events continue despite complete discontinuation of concomitant medications.

Recording hypoglycemic episodes

Participants will be trained to record all hypoglycemic episodes in the 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 below, which should then be recorded as serious on the AE CRF and reported to Lilly as an SAE.

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

Hypoglycemia definitions and categories

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.

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

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 Gastrointestinal Adverse Events

Orforglipron may cause severe GI AEs, such as nausea, vomiting, and diarrhea. 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 6.9.1.

8.3.3.6. 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 orforglipron 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.

8.3.3.7. Pancreatitis

Diagnosis of acute pancreatitis

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

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting
- serum amylase (total, pancreatic, or both) and/or lipase $\geq 3\times$ ULN
- 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. 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 7.1.2.

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 $\geq 3 \times$ ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

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

8.3.3.8. 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 orforglipron 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 participants with $eGFR \geq 60$ mL/min/1.73 m²

A significant increase in calcitonin for participants with $eGFR \geq 60$ mL/min/1.73 m² is defined below. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

- *Serum calcitonin value ≥ 20 ng/L and < 35 ng/L AND $\geq 50\%$ increase from the screening value.* These participants will be requested to repeat the measurement within 1 month. If this repeat value is increasing ($\geq 10\%$ increase), the study intervention should be discontinued, and the participant should undergo additional endocrine assessment and longer-term follow-up by an endocrinologist to exclude adverse events on the thyroid gland.
- *Serum calcitonin value ≥ 35 ng/L AND $\geq 50\%$ over the screening value.* 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 events on the thyroid gland.

Calcitonin measurement in participants with eGFR < 60 mL/min/1.73 m²

A significant increase in calcitonin for participants with eGFR < 60 mL/min/1.73 m² is defined as a *serum calcitonin value ≥ 35 ng/L AND $\geq 50\%$ over the screening value.* If a participant's 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 AEs on the thyroid gland.

8.3.3.9. Malignancies

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

8.3.3.10. 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](#)

8.3.3.11. 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.

8.3.3.12. Hypersensitivity Reactions

Refer to Section [8.2.8](#)

8.3.3.13. 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 and the PHQ-9 questionnaires (see Section [8.2.6](#)). 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

8.3.3.14. 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 orforglipron will only be determined from blood samples obtained from participants receiving orforglipron treatment. Blood samples for PK assessment will be collected at time points as indicated in the table below.

Visit	PK Sample Relative to Study Intervention Dose
Visit 5 (Week 8)	Pre-dose ^a
Visit 7 (Week 16)	4 to 12 hours post-dose
Visit 9 (Week 24)	Pre-dose ^a
Visit 12 (Week 36)	1 to 4 hours post-dose
Visit 15 (Week 48)	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 (ED1) PK samples should be collected regardless of study week at which the discontinuation occurs (even after Week 48 but before Week 72).

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

Concentrations of orforglipron 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 orforglipron 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 orforglipron 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 orforglipron
- pathways associated with obesity, diabetes, and related clinical traits or complications, including nonalcoholic steatohepatitis
- mechanism of action of orforglipron, and
- research method or validating diagnostic tools or assay(s) related to obesity, diabetes, 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 primary outcome 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 36 mg orforglipron compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- $H_{2,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- $H_{3,0}$: No difference in 6 mg orforglipron 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 36 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction from baseline in body weight at Week 72.
- $H_{5,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction from baseline in body weight at Week 72.
- $H_{6,0}$: No difference in 6 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction from baseline in body weight at Week 72.
- $H_{7,0}$: No difference in 36 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 10% or more body weight reduction from baseline in body weight at Week 72.
- $H_{8,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 10% or more body weight reduction from baseline in body weight at Week 72.
- $H_{9,0}$: No difference in 6 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 10% or more body weight reduction from baseline in body weight at Week 72.
- $H_{10,0}$: No difference in 36 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 15% or more body weight reduction from baseline in body weight at Week 72.
- $H_{11,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 15% or more body weight reduction from baseline in body weight at Week 72.

- H_{12,0}: No difference in 6 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 15% or more body weight reduction from baseline in body weight at Week 72.
- H_{13,0}: No difference in 36 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 20% or more body weight reduction from baseline in body weight at Week 72.
- H_{14,0}: No difference in 12 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 20% or more body weight reduction from baseline in body weight at Week 72.
- H_{15,0}: No difference in 6 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 20% or more body weight reduction from baseline in body weight at Week 72.
- H_{16,0}: No difference in 36 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H_{17,0}: No difference in 12 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H_{18,0}: No difference in 6 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H_{19,0}: No difference in 36 mg, 12 mg, and 6 mg orforglipron pooled compared to placebo with respect to mean change from baseline in SBP at Week 72.
- H_{20,0}: No difference in 36 mg, 12 mg, and 6 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in non-HDL cholesterol at Week 72.
- H_{21,0}: No difference in 36 mg, 12 mg, and 6 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in triglycerides at Week 72.
- H_{22,0}: No difference in 36 mg, 12 mg, and 6 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in body weight at Week 176 in participants with prediabetes at randomization.
- H_{23,0}: No difference in 36 mg, 12 mg, and 6 mg orforglipron pooled compared to placebo with respect to time to onset of T2D at Week 176 in participants with prediabetes at randomization.
- H_{24,0}: No difference in 36 mg, 12 mg, and 6 mg orforglipron pooled compared to placebo with respect to time to onset of T2D at Week 190 in participants with prediabetes at randomization.

9.1.1. Multiplicity Adjustment

A prespecified graphical scheme (Bretz et al. 2009, 2011) will be implemented to control the family-wise error rate at a 2-sided alpha level of 0.05 for testing the hypotheses stated in Section 9.1. More specifically, multiple testing adjusted p-values described by Bretz et al. (2009) will be calculated, and any hypothesis tests with a multiple testing adjusted 2-sided p-value of less than 0.05 will be considered statistically significant. This graphical approach is a closed testing procedure; hence, it strongly controls the family-wise error rate across all endpoints (Bretz et al. 2009, 2011; Alosh et al. 2014).

The testing scheme will be fully detailed in the SAP. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary endpoints.

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.
Randomized participants with prediabetes	All participants who are randomly assigned a study intervention and who have prediabetes at randomization. Participants will be analyzed according to the treatment group to which they were randomly assigned.
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.
Safety participants with prediabetes	All participants who are randomly assigned a study intervention, who take at least 1 dose of study intervention, and who have prediabetes at randomization. Participants will be analyzed according to the treatment group to which they were randomly assigned.

The following data points sets are defined:

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.
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.

Data Points Sets	Description
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.

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 clinical study report. 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 post baseline 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 in binary efficacy outcomes. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons in other categorical outcomes.

The Kaplan-Meier method will be used for estimation of time-to-event endpoints, and Cox proportional hazards regression analysis conditioned for stratification factors will be used to compare hazard rates among treatments. The hazard ratio, CI, and p-value will be provided.

Time-to-event for a specific event of interest

If a participant ...	then the time-to-event for a specific event of interest will be...
experiences the event	the number of days between baseline and the onset date of the event plus 1 day.
does not experience the event	the number of days between baseline and the date of the participant's end of follow-up plus a 1 day.
experiences multiple events	the date of the first event will be used, unless otherwise specified.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of orforglipron 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 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 clinical study report.

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 orforglipron treatment group will be compared to placebo using the Fisher's exact test. Kaplan-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 Endpoint and Estimands Analyses

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

The primary objective will be evaluated relative to 2 estimands, “treatment regimen” and “efficacy” (see Section 3).

The primary objective aligned to the “treatment regimen” estimand will be evaluated using the 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. 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).

The primary objective aligned to the “efficacy” estimand will be evaluated using the 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

Orforglipron concentration data will be analyzed using a population PK approach using nonlinear mixed-effects modeling techniques implemented on the NONMEM software. The

relationships between orforglipron 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 orforglipron 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 treatment group, and Fisher's exact test will be used to compare the treatment groups.

9.3.7.1. Adverse Events of Special Interest and Other Safety Topics

The analysis details for the adverse events 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 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 mixed model for repeated measures 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 summarized and compared between treatment groups using Fisher's exact test or Pearson's Chi-square test.

9.3.8. Other Analyses

Subgroup analyses

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

- Age group (< 65 , ≥ 65 years)
- Sex (female, male)
- Baseline prediabetes status (yes, no)
- Baseline BMI ($\leq$ median, $>$ median)
- 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 based on the “treatment regimen” estimand. 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 reasons other than a safety concern, the protocol must be amended.

9.5. Sample Size Determination

A sample size of 3,042 participants (702 participants per orforglipron treatment group and 936 participants in the placebo group) provides more than 90% power to demonstrate superiority of 6 mg, 12 mg, and/or 36 mg orforglipron 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 6 mg, 12 mg, and 36 mg orforglipron 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 from baseline at 72 weeks for 6 mg, 12 mg, and 36 mg orforglipron compared with placebo, a common SD of 10%, and a dropout rate of 30% for placebo and 20% for the orforglipron treatment groups are assumed for the statistical power calculation

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 the investigator's representative will explain the nature of the study, including the risks and benefits, to the potential participant (or the potential participant's 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 (or the participant's legally authorized representative) and is kept on file.

10.1.4. Data Protection

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

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

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

The sponsor has processes in place to ensure information security, data integrity, and data protection, 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 and processes. The sponsor's processes are compliant with local privacy laws and relevant legislations including the General Data Protection Regulation (GDPR).

10.1.5. Committees Structure

10.1.5.1. 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 8.3.3.7 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, clinical study report, 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 clinical study report.
- 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 the central vendor's database system and reports will be provided to the investigator for review and retention. Data will subsequently be transferred from the central vendor to the sponsor data warehouse.

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
- Data reported on or entered in the CRF and are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in [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 or sponsor's designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

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

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

For study termination:

- 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

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

10.1.11. Investigator Information

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

10.1.12. Sample Retention

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

Sample Type	Custodian	Retention Period After Last Patient 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	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	Morphology to be performed if abnormalities are detected.

Clinical Laboratory Tests	Comments
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. Direct measurement will be performed if triglycerides exceed maximum value for calculation.
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 (HBcAb)	
Hepatitis B surface antigen (HBsAg)	
Hepatitis B surface antibody (anti-HBs)	

Clinical Laboratory Tests	Comments
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 – Orforglipron 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 predose samples at the next regularly scheduled laboratory sample collection (ideally prior to the next dose after the event) to assess post-event return to baseline values.

Timing	Laboratory Test ^a
Collect from 30 min to 4 hr after the start of the event. <i>Note:</i> 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 NOT Meeting the AE Definition

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

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

10.3.2. Definition of SAE

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

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

- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Definition of Product Complaints

Product complaint

- A 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 information in the participant's medical records, in accordance with the investigator's normal clinical practice. AE/SAE information is reported on the appropriate CRF page and PC information is reported on the Product Complaint Form.
- Note: An event may meet the definition of both a PC and an AE/SAE. In such cases, it should be reported as both a PC and as an AE/SAE.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to 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.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the IB in their assessment.
- 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 ≥ 40 mIU/mL, or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. ^a Women should not be taking medications during amenorrhea such as oral contraceptives, hormonal replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, SERMs, 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 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:

Must...	Must not...
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 ○ calendar ○ ovulation ○ symptothermal, or ○ 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) • ^aimplanted contraceptives • ^ainjectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg)

Methods	Examples
	• 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 ○ condom with spermicide ○ diaphragm with spermicide, or ○ 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 variation may impact a participant's response to study intervention, susceptibility to, and severity and progression of disease. Variable response to study intervention may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the 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 orforglipron or obesity, diabetes, 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 orforglipron, study interventions related to this drug class, or obesity, diabetes, 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 orforglipron 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 clinical study report 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 orforglipron 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 from the table below. Note that testing for some analytes may not be available from the central lab or local lab in certain regions due to local availability of assay or regulatory requirements. If testing is not available, this will not be considered a protocol deviation.

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

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

TESTS TO BE PERFORMED BY INVESTIGATOR-DESIGNATED LABORATORY, AS NEEDED	
Acetaminophen	Hepatitis D virus (HDV) testing ^c
Acetaminophen protein adducts	HDV total antibody ^a
Alkaline phosphatase isoenzymes	HDV IgM antibody
Ceruloplasmin	HDV RNA ^b
Copper	Herpes simplex virus (HSV) testing:
Cytomegalovirus (CMV) testing:	HSV (Type 1 and 2) antibody
CMV antibody	HSV (Type 1 and 2) DNA ^b
CMV DNA ^b	Liver kidney microsomal type 1 (LKM-1) antibody

Ethyl alcohol (ethanol, EtOH)	Phosphatidylethanol (PEth)
Ethyl glucuronide (EtG)	Microbiology Culture:
Epstein Barr virus (EBV) testing:	Blood
EBV antibody	Urine
EBV DNA ^b	

Abbreviations: Ig = immunoglobulin; INR = international normalized ratio; RBC = red blood cells; WBC = white blood cells.

- ^a If lab does not offer total antibody testing, IgG and/ or IgM are acceptable substitutes
- ^b Reflex/confirmation dependent on regulatory requirements, testing availability, or both.
- ^c If HDV testing is not available, HBV testing may be sufficient. If HBV testing is positive, consult with the Lilly-designated medical monitor.

10.7. Appendix 7: Measurement of Height, Weight, Waist Circumference, Vital Signs and OGTT

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

Height

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

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

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

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

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.

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 garments could also be used).

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

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

Vital sign measurements (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.

2-hour oral glucose tolerance test

Participants should attend visits requiring a 2-hour OGTT in the fasting state. Samples will be collected at 0, 30, 60, 90, and 120 minutes during the 2-hour OGTT, unless the OGTT is repeated to confirm the diagnosis of diabetes. For glycemic classification, the values at time = 0 min (FSG) and 120 minutes (2-hour OGTT) will be used. If a 2-hour OGTT is repeated to confirm the diagnosis of diabetes, only samples at 0 and 120 minutes for glucose measurement will be collected.

2-hour OGTTs should be performed per the SoA (Section 1.3) until such time as a protocol-defined diagnosis of diabetes is confirmed. 2-hour OGTT testing should be omitted at visits following a protocol-defined diabetes diagnosis

- Participants should maintain adequate carbohydrate intake for 3 days prior to the scheduled 2-hour OGTT.
- In the 24 hours preceding the test, participants should refrain from drinking any alcohol or performing any extreme physical activity.

- Participants should fast for approximately 8 hours before the administration of the test and should not eat until the test is complete.
- Placement of a venous cannula, preferably in an antecubital vein, is recommended to simplify collection of multiple blood samples for glucose, insulin, and C-peptide at time 0, 30, 60, 90, and 120 minutes.

Note: Placement of a venous cannula may not be required when a 2-hour OGTT is repeated to confirm the diagnosis of diabetes (see Section 10.9), and only samples at 0 and 120 minutes for glucose measurement will be collected.

- Immediately after collection of the time 0 sample, a 75-gram glucose dose will be given orally, using a commercial product approved for this use (and in a total volume of not more than 350 mL).
- The participant should consume the glucose load within 5 minutes.
- The participant should remain minimally active for the duration of the test.

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 short-term use of strong CYP3A inhibitors, as outlined in Section 6.9.3. The lists below provide examples of each category of medication, but the examples are not exhaustive.

10.8.1.1. 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[®]

10.8.1.2. 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.

10.8.1.3. Glucose-Lowering Medications

Participants are excluded if taking glucose-lowering medications within 90 days prior to Visit 1, or between Visit 1 and Visit 3, regardless of indication for use. Examples of exclusionary medications are the following:

- metformin
- canagliflozin
- dapagliflozin
- empagliflozin
- dulaglutide
- liraglutide
- semaglutide
- exenatide
- tirzepatide
- sitagliptin
- saxagliptin
- linagliptin
- alogliptin

For participants with a confirmed diagnosis of T2D during the study, GLP-1 receptor agonists, GIP/GLP-1 receptor agonists and DPP-4 inhibitor are prohibited throughout the study. The following medications are examples:

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

10.8.1.4. Strong CYP3A Inhibitors or Inducers, Sensitive P-gp/BCRP Substrates, and OATP Inhibitors

Participants cannot be taking strong CYP3A inhibitors or inducers (exception: topical or inhaled formulations), drugs that are sensitive P-gp/BCRP substrates with a narrow therapeutic index, or strong OATP inhibitors 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:

Strong CYP3A4 inhibitors or inducers (FDA classification)

- boceprevir
- cobicistat
- danoprevir and ritonavir
- elvitegravir and ritonavir
- grapefruit juice
- indinavir and ritonavir
- itraconazole^a
- ketoconazole^a
- lopinavir and ritonavir
- paritaprevir and ritonavir and ombitasvir and/or dasabuvir
- posaconazole^a
- ritonavir
- saquinavir and ritonavir
- telaprevir
- tipranavir and ritonavir
- telithromycin^b
- troleandomycin
- voriconazole^a
- clarithromycin^b
- nefazodone
- nelfinavir
- apalutamide
- carbamazepine
- enzalutamide
- mitotane
- phenytoin
- rifampin

- St. John's wort

^a Participants taking these medications (ketoconazole, itraconazole, voriconazole, or posaconazole) should, if appropriate, switch to at least 2 weeks prior to randomization at Visit 3:

- miconazole, or
- clotrimazole.

^b For participants taking clarithromycin or telithromycin, azithromycin may be substituted at least 2 weeks prior to randomization at Visit 3.

Strong OATP inhibitors

- rifampin
- cyclosporine
- faldaprevir
- tipranavir/ritonavir
- glecaprevir/pibrentasvir
- telaprevir
- sofosbuvir/velpatasvir/voxilaprevir
- lopinavir/ritonavir
- darunavir/ritonavir
- elvitegravir/cobicistat/emtricitabine/tenofovir DF

Sensitive P-gp substrates with narrow therapeutic index

- colchicine
- cyclosporine
- dabigatran etexilate
- digoxin
- everolimus
- pimozide
- quinidine
- quinine
- sirolimus
- tacrolimus

Sensitive BCRP substrates with narrow therapeutic index

- prazosin

10.8.2. Medications with Special Use Restrictions

10.8.2.1. Medications Affected by Increase in Gastric pH

Drugs that may be affected by an increase in gastric pH should be separated from study intervention administration by at least 2 hours. Examples include:

- simvastatin
- levothyroxine
- ferrous sulfate
- bisphosphonates
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability
- tyrosine kinase inhibitors
 - i. erlotinib
 - ii. dasatinib
 - iii. nilotinib
 - iv. acalabrutinib
 - v. bosutinib
 - vi. gefitinib
 - vii. lapatinib
 - viii. pazopanib
- antiretrovirals
 - ix. rilpivirine
 - x. atazanavir
 - xi. nelfinavir
 - xii. ledipasvir/sofosbuvir
 - xiii. fosamprenavir
 - xiv. delavirdine mesylate
 - xv. emtricitabine+rilpivirine+tenofovir+ disoproxil fumarate (Complera[®])
 - xvi. ledipasvir+sofosbuvir (Harvoni[®])
 - xvii. raltegravir, sofosbuvir+velpatasvir (Epclusa[®])

10.8.2.2. Moderate CYP3A Inhibitors or Inducers

If participants are taking moderate CYP3A inhibitors or inducers, investigators should consider alternative medications whenever possible. Examples of these medications include:

- cimetidine
- ciprofloxacin
- clotrimazole
- diltiazem
- erythromycin

- fluconazole
- verapamil

10.9. Appendix 9: Definition and Management of Diabetes

Criteria for diagnosis of prediabetes and diabetes

The duration of treatment in ATTAIn-1 (Study GZGP) is determined by glycemic status at randomization. Participants are categorized as those with prediabetes or normoglycemia at Visit 3/randomization (participants with T2D are excluded), as defined by the 2023 American Diabetes Association Standards of Medical Care in Diabetes (ADA 2023). The following populations are defined:

	Normoglycemia	Prediabetes	Diabetes
Fasting glucose Obtained alone or at time = 0 during an OGTT	<100 mg/dL (<5.6 mmol/L)	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (≥7.0 mmol/L)
2-Hr glucose Obtained at time = 120 min during an OGTT	<140 mg/dL (<7.8 mmol/L)	140-199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (≥11.1 mmol/L)
HbA1c	<5.7% (<39 mmol/mol)	5.7%-6.4% (39-47 mmol/mol)	≥6.5% (≥48 mmol/mol)

Abbreviations: HbA1c = hemoglobin A1c; OGTT = oral glucose tolerance test.

Glycemic classification at randomization

All participants without laboratory tests suggestive of diabetes will be classified as having either normoglycemia or prediabetes. In keeping with American Diabetes Association guidelines (ADA 2023), at least 2 abnormal tests are required to diagnose prediabetes. For example:

- Both 0 AND 2-hour values during the 2-hour OGTT values are in the prediabetes range.
- FSG at Screening Visit 1 AND 0-hour OGTT values at Visit 2 are in the prediabetes range.
- FSG at Screening Visit 1 AND 2-hour values during 2-hour OGTT are in the prediabetes range.
- HbA1c AND 1 of either the FSG or 2-hour OGTT values are in the prediabetes range.

Definition and management of incident diabetes

Definition of incident diabetes

Incident diabetes is defined when any 1 of the following occur after randomization (ADA 2023):

- unequivocal hyperglycemia (random glucose ≥200 mg/dL) with signs or symptoms of hyperglycemia
- any 2 of the following criteria are observed at the same visit, or 1 abnormal value is observed and subsequently confirmed:
 - HbA1c ≥6.5% (≥48 mmol/mol)
 - FSG or 0-hour serum glucose from 2-hour OGTT ≥126 mg/dL (≥7.0 mmol/L)

- 2-hour glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) by a 2-hour OGTT
- initiation of any medication for the treatment of diabetes

Confirmation of diabetes diagnosis

In the event 1 abnormal value is observed (HbA1c $\geq 6.5\%$ [48 mmol/mol]) OR FSG (or 0-hour serum glucose from 2-hour OGTT) ≥ 126 mg/dL (7.0 mmol/L) OR 2-hour glucose from 2-hour OGTT ≥ 200 mg/dL (11.1 mmol/L)^a after randomization, the abnormal test should be repeated within 4 weeks to confirm diagnosis of diabetes and to ensure that diabetes management is initiated without delay.

^a If the abnormal value observed is 2-hour glucose from the OGTT ≥ 200 mg/dL (11.1 mmol/L), the 2-hour OGTT should be repeated within 4 weeks (only samples at 0 and 120 minutes for glucose measurement will be collected).

The diagnosis of diabetes is confirmed if any of the following occur:

- HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol) is observed at 2 measurements any time during the study.
- 2-hour glucose ≥ 200 mg/dL (≥ 11.1 mmol/L) during an OGTT is observed at 2 measurements any time during the study.
- FSG value ≥ 126 mg/dL (≥ 7.0 mmol/L) is observed at a consecutive FSG measurement (either at a scheduled or an unscheduled visit) following an isolated FSG (or 0-hour serum glucose from 2-hour OGTT) value ≥ 126 mg/dL (≥ 7.0 mmol/L).
 - If diabetes diagnosis has not been confirmed at the consecutive FSG measurement, another FSG (or 0-hour serum glucose result from 2-hour OGTT) result ≥ 126 mg/dL (≥ 7.0 mmol/L) observed during the study will be considered as a new finding requiring confirmation.

Note: Once diabetes has been confirmed, repeating any future abnormal test within 4 weeks is no longer required.

Recording of incident diabetes events

- Diabetes diagnosis and the onset date as assessed by investigator will be recorded in the AE CRF and the dedicated endpoint CRF.
- If the diagnosis of diabetes is based on laboratory results, the date of the first abnormal HbA1c or glucose value within the diabetes range should be indicated as the date of diagnosis, unless, in the investigator's opinion, a different date is more appropriate. If the diagnosis is based on initiation of any medication for the treatment of diabetes, the investigator should indicate the most probable date of diagnosis in the CRFs.
- All reported or suspected cases of incident diabetes will be adjudicated by an independent CEC (adjudication committee).
- Decisions of the adjudication committee regarding diabetes diagnosis and the onset date will be recorded in the dedicated adjudication CRF.

Management of incident diabetes

Participants who develop diabetes during the study will be

- provided and trained to use a glucometer
- educated on the signs and symptoms of hypoglycemia and its treatment, and
- instructed to record hypoglycemic episodes in the eDiary

Participants will be referred to their usual care provider and provided with a letter showing the study results indicative of diabetes. The decision to further evaluate, to initiate antihyperglycemic therapy, and the choice of antihyperglycemic medication will be at the discretion of the participant's usual care provider, with the exception of use of DPP-4 inhibitors and GLP-1 receptor agonists or other incretin-based therapies (for example, tirzepatide), which are prohibited during the study. Monitoring for hypoglycemia includes capture of events as defined in Section [8.3.3.4](#).

10.10. Appendix 10: Information for Sites that have Access to Whole-Body DXA Scanners with Body Composition Capability

This appendix is only applicable for sites that have access to either Hologic® or Lunar™ whole-body DXA scanners with body composition capability.

10.10.1. Introduction

Although 5% to 10% body weight reduction has been shown to reduce complications related to obesity and improve quality of life (Knowler et al. 2002; Jenson et al. 2014; Li et al. 2014; Warkentin et al. 2014), both fat and lean body mass are lost (Wadström et al. 2000; Jendle et al. 2009; Cava et al. 2017).

Weight-loss-associated loss of lean body mass (including muscle) could then increase the risk of sarcopenia (defined as low muscle mass and impaired muscle function), affecting individuals' mobility, increasing the risk of falls, and reducing the ability to perform daily living activities (Cava et al. 2017; Barazzoni et al. 2018).

Therefore, decreasing fat body mass while preserving sufficient lean body mass is important in any population where large decreases in body weight occur in a short period of time (Kulovitz et al. 2014).

Regulatory guidance

The Food and Drug Administration Draft Guidance for Industry, Developing Products for Weight Management (2007) and the European Medicines Agency (EMA) Guideline on clinical evaluation of medicinal products used in weight management (2016) recommend that a representative sample of study participants should have an assessment of body composition by dual-energy x-ray absorptiometry, or a suitable alternative, to ensure that weight loss, drug or biologic induced, is caused primarily by a reduction in fat content.

DXA total body composition

Dual-energy x-ray absorptiometry total body composition with regional analysis provides a measure of physiological response to obesity interventions superior to simple anthropometrics, such as BMI. It is safe and widely available in clinical practice (Kendler et al. 2013), making it a useful method to detect changes in fat and lean body mass in weight management studies (Dordevic et al. 2018).

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

Total body composition assessments for this study

In this study, a subset of approximately 156 study participants will undergo a body composition assessment via DXA scans, measured at baseline and Week 72 (Visit 21) or at the time of ED (if at least 1 month after the baseline scan was performed), with the intent of evaluating changes in body composition associated with weight reduction, including both fat and lean mass compartments.

10.10.2. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary Objective	
To demonstrate orforglipron (6 mg, 12 mg and 36 mg pooled doses) is superior to placebo in Change in total body fat mass	From baseline to Week 72: Percent change in total body fat mass
Secondary Objectives	
To demonstrate that orforglipron (6 mg, 12 mg and 36 mg pooled doses) is superior to placebo in Change in total body fat mass	From baseline to Week 72: Change in total body fat mass (kg)
To assess, for orforglipron (6 mg, 12 mg and 36 mg pooled doses) Change in body lean mass	From baseline to Week 72: - Percent change in total body lean mass - Change in total body lean mass (kg)

Abbreviations: QD= once daily

10.10.3. Study Population**Inclusion criteria**

44. All participants meeting all the inclusion and exclusion criteria in Section 5 will have the option to consent to the DXA procedure until the required number of participants is met.

Exclusion criteria

45. Have had a procedure within 10 days of screening (Visit 1) where oral contrast or radionuclides were administered, for example, CT with contrast or nuclear medicine.
46. Have a body weight, height, or width that prohibits the ability to obtain accurate measurements according to the DXA manufacturer's specification.
47. Have implants, hardware, devices, or other foreign materials in the measurement area that may interfere with the scan, according to the DXA manufacturer's specification.

10.10.4. Dual-energy X-ray Absorptiometry Scan

Participants who give consent and meet all eligibility requirements should have a DXA scan performed at the visits described in the SoA Section 1.3.1.

DXA instrument

Investigative sites will perform the body composition DXA scans on either Hologic® or Lunar™ DXA scanners with total body composition capabilities according to the imaging guidelines.

A DXA scan should be performed within 1 week of ED visit, at least 1 month after the baseline scan. Participants who stop study treatment but agree to return for Visit 21 will have an additional scan performed within ± 7 days of Visit 21.

Guidance for conducting DXA scans

To obtain consistent and acceptable quality data, investigators will receive detailed instructions on the DXA scan protocol to be used.

The scans will be read and evaluated by a central reader.

Recommendations

Perform all scans for a given participant using the same DXA scanner and software.

Perform all scans for a given participant under similar circumstances, for example, using consistent scan status and performing the scan at the same time of day.

10.10.5. Randomization

Participants will be randomized in a 1:1:1:1 ratio to receive orforglipron 6 mg, orforglipron 12 mg, orforglipron 36 mg, or placebo. The randomization will be stratified by prediabetes status, country, and sex.

10.10.6. Statistical Analyses

Unless otherwise specified, all analyses for the variables measured or derived from DXA will be conducted using randomized participants with efficacy estimand data points set.

Missing data at the 72-week visit will be imputed, and analysis will be conducted with multiple imputations (see details in the SAP).

The statistical assessment will analyze the measurement obtained at the 72-week visit using ANCOVA with adjustment for baseline response and stratification factors (Ye et al. 2022). There will be no multiplicity adjustment for this addendum.

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

10.10.7. Sample Size

A sample size of approximately 156 randomly assigned participants (approximately 39 participants per arm) is planned for this appendix to assess the difference between orforglipron 6 mg, 12 mg, and 36 mg pooled and placebo in the percent change of total fat mass from baseline at 72 weeks. Assuming the SD of the percent change from baseline in total fat mass is 12.4% and a dropout of 30%, a total of 108 participants completing 72 weeks (27 participants in each orforglipron dose group and the placebo group) will provide at least 90% power to detect a statistically significant difference of 9% using a 2-sided t-test and an alpha level of 0.05.

10.10.8. Data Capture

Any diagnostic data collected from a contracted vendor will be stored electronically in that central vendor's database system. Data will subsequently be transferred from the central vendor according to the contract.

10.11. Appendix 11: Information for Sites on Scoring the Appetite Visual Analog Scale

The VAS tool will be given as a pen-and-paper tool. Each of the 8 questions will have a fixed, 100-mm length line. The ends are the extreme limits of the parameter (e.g., not at all hungry, extremely hungry). Only provided paper VAS can be used, as photocopying alters the line length.

Scoring instructions

Using the study-provided ruler, the score is determined by measuring the distance in millimeters on the 100-mm line between “not at all” anchor point and the participant’s mark. A higher score indicates greater hunger, appetite, or fullness.

For Questions 1 to 4, place the “zero” mm of the ruler at “not at all hungry”, as indicated by the arrow in the below figure, and measure to the participant’s mark to obtain a score.

1. How hungry do you feel right now?

Not at all hungry  Extremely hungry

Questions 5 to 8 have “not at all” at the **opposite end** of the line. To score these questions, the ruler must be flipped to have the “zero” mm of the ruler at the correct position as indicated by the arrow in the below figure.

5. Would you like to eat something sweet?

Yes, very much  No, not at all

10.12. Appendix 12: Country-specific Requirements

10.12.1. 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 #41 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 underlined text.

Section 5.2. Exclusion Criteria

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

Are currently enrolled in, discontinued, or completed within a period of 1 year, before inclusion, from 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.

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 intervention.

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 orforglipron, identified through the study (CNS 466/2012 and RDC 38/2013).

10.13. Appendix 13: 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

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

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

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

Considerations for making a change

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

Informed consent

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

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

Changes in study conduct during exceptional circumstances

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

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

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

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 Pulse Rate)
- 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
- asking the participant's designee to go to the site and receive study supplies on a participant's behalf, and
- arranging delivery of study supplies

These requirements must be met before action is taken:

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

Screening period guidance

To ensure safety of study participants, laboratory values and other eligibility assessments taken at 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 visit if the participant's eligibility criteria are confirmed, and the site should document the reason for delay.
 - Due to the pause in screening, sites should also reconfirm the impacted participant's consent and document this confirmation in the source documentation.
- If screening is paused for more than 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 possible and safe to do so, as determined by the investigator's discretion, participants should complete the usual SoA. To maximize the possibility that these visits can be conducted as on-site visits, the windows for visits may be adjusted, upon further guidance from the sponsor. This minimizes missing data and preserves the intended conduct of the study.

This table describes the allowed adjustments to visit windows.

Visit Number	Tolerance
Visit 3 through Visit 21	within 10 days before or after the intended date per the SoA
Visit 801	up to 28 days after the intended date per the SoA
Prediabetes Additional Treatment Period	within 10 days before or after the intended date per the SoA
Visit 802	up to 28 days after the intended date per the SoA

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

Documentation***Changes to study conduct will be documented***

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

Source documents at alternate locations

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

10.14. Appendix 14: 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
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCRP	breast cancer resistance protein
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.
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	Computed tomography
CV	Cardiovascular
CYP3A	cytochrome P450 3A
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-4	Dipeptidyl peptidase-4
DXA	dual-energy x-ray absorptiometry
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.
FSG	Fasting serum glucose
GCP	good clinical practice
GI	Gastrointestinal
GIP	glucose-dependent insulintropic polypeptide
GLP-1	Glucagon-Like Peptide-1
HbA1c	hemoglobin A1c
HBcAb	Hepatitis B core antibody
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
IB	Investigator's Brochure
ICE	Intercurrent event
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product (see also "investigational product") A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
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 relevant to the participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
interim analysis	An interim analysis is an analysis of clinical study data, separated into treatment groups, that is conducted before the final reporting database is created/locked.
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
MRI	Magnetic Resonance Imaging
MTC	Medullary thyroid cancer
OATP	organic anion transporting polypeptide
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
P-gp	P-glycoprotein
PK/PD	pharmacokinetics/pharmacodynamics
PRO/ePRO	patient-reported outcomes/electronic patient-reported outcomes
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
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
WOCBP	Women of childbearing potential

10.15. Appendix 15: 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]: 23-Oct-2023

The amendment is considered to be substantial because it is likely to have a significant impact on the [select appropriate rationale(s) from the list below and delete any that are not applicable]reliability and robustness of the data generated in the clinical study.

Overall Rationale for the Amendment:

The main purpose for the current protocol amendment is to include additional laboratory monitoring during the dose escalation period, as well as new patient-reported outcomes. These and other changes and a brief rationale are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
1. Synopsis	Heading changed from “Primary Estimands” to “Estimands” Added new sentence: The “treatment regimen” estimand will be the primary estimand	Clarification
1.3. Schedule of Activities (SoA)	Included Power of Food Scale and Appetite Visual Analog Scale as additional procedures which should not be administered in a nonfasting state	Addition
1.3.1. Screening Period I (Visits 1 and 2), Treatment Period II (Visits 3-21), Early Discontinuation and Posttreatment Follow-Up	Added Diary (electronic) review and return at Visit 801	To allow reporting of hypoglycemic events during the follow-up period
	Removed Diary return (electronic) from Visit 21, ED1 and associated comments	To allow reporting of hypoglycemic events between Visit 21 or ED1 and Visit 801
	Added a note to lifestyle program instructions that “Lifestyle counseling may occur on a separate day from the rest of that visit’s study procedures but must occur within the visit window. Beginning at Week 8 counseling may be delivered by telehealth”.	To allow flexibility
	Removed comments about PK samples. Added reference to Section 8.4 for PK sampling details.	To provide clarity
	Added chemistry panel to Visits 4, 5, 7, and 8 with a note about hepatic evaluation	To allow for more frequent evaluation of hepatic labs during the escalation period
	Added patient-reported outcomes with associated comments	To permit evaluation of cravings and psychological

	Appetite VAS to be administered at Visits 3, 9, 21, ED1, and 801 Power of Food scale to be administered at Visits 3, 9, 21, ED1, and 801	impact of food replete environments at these visits.
	Updated Abbreviations	To maintain editorial consistency
1.3.2. Prediabetes Additional Treatment Period (Visits 101 to 117), Early Discontinuation, and Posttreatment Follow-up Visit 802	Added a note to lifestyle program instructions that “Lifestyle counseling may occur on a separate day from the rest of that visit’s study procedures but must occur within the visit window. Beginning at Week 8 counseling may be delivered by telehealth”.	To allow flexibility
	Added a note about hepatic evaluation in clinical chemistry	Clarification
	Removed Diary return (electronic) from Visit ED2	To allow reporting of hypoglycemic events after the final treatment visit
	Cystatin C assessment added to additional prediabetes maintenance period at Visits 102, 104, 106, 110, 112, and 114	To permit the evaluation of eGFR at these visits
	Added patient-reported outcomes and associated comments Appetite VAS to be administered at Visits 117 and ED2 Power of Food scale to be administered at Visits 117 and ED2	To permit evaluation of cravings and psychological impact of food replete environments at these visits.
	Updated Abbreviations	To maintain editorial consistency
3. Objectives, Endpoints, and Estimands	Heading changed from “Primary Estimands” to “Estimands” Added new sentence: The “treatment regimen” estimand will be the primary estimand	Clarification
5.2. Exclusion Criteria	Revised Criterion 8 second bullet to read “FSG ≥ 126 mg/dL (≥ 7.0 mmol/L), including 0-hour OGTT” and referenced Section 4.1	Clarification
	Revised Criterion 13 to include “cystatin-C equation” for eGFR calculation	
	Removed the language in the exception note of Criterion 21 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 33	
	Revised Criterion 35 to include atypical antipsychotics, tricyclic antidepressants, and mood stabilizers.	
5.3.1. Meals and Dietary Restrictions	Removed “overnight” from the first sentence and revised to read as “For certain assessments, study 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 use of medications that may be affected by an increase in gastric pH	Clarification
6.9. Prior and Concomitant Therapy	Text revised to clarify use of medications that may be affected by an increase in gastric pH	Clarification
6.9.3. Prohibited or Restricted Use Medications	Text added to clarify short-term use of strong CYP3A inhibitors	Clarification
7.1.1. Liver Chemistry Stopping Criteria	Content deleted and reference to Section 8.2.7.3 added	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, 7 or more consecutive doses	To provide clarity
8.1.4. Patient-Reported Outcomes	Added 8.1.4.7. Appetite Visual Analog Scale 8.1.4.8. Power of Food Scale	To allow the evaluation of cravings and psychological impact of food replete environments.
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
9.2 Analyses Sets	Removed full participants and full participants with prediabetes analysis sets, updated description for randomized participants analysis set, and added randomized participants with prediabetes analysis set.	To follow ITT principles
9.3.3. Primary Endpoint and Estimands Analyses	Revised text to indicate that the primary analysis will use the randomized participants population rather than full participants population	Clarification

	Deleted the statement “No multiplicity adjustment is planned between estimands.”	
10.4.1 Appendix 4 Definitions	In definition of WNOCBP Removed “total” from description of hysterectomy. Added “resulting in confirmed infertility” to have a congenital anomaly such as Müllerian agenesis. Removed “Examples of methods include” and added “Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy”. In definition of Postmenopausal state Changed follicle-stimulating hormone >40 mIU/mL to ≥ 40 mIU/mL In foot note a Deleted “hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.” Added “hormonal replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, SERMs, 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 their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.”	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) Deleted “female sterilization” Added “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.” 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.	Alignment with updated contraception guidance

10.8.1. Excluded/Prohibited or Restricted Use Medications	Exception note added for short-term use of strong CYP3A inhibitors	Clarification
10.8.1.4. Strong CYP3A Inhibitors or Inducers, Sensitive P-gp/BCRP Substrates, and OATP Inhibitors	Exception note added for strong CYP3A inhibitors or inducers List of sensitive BCRP substrates with narrow therapeutic index shortened to include only prazosin	Clarification
10.8.2.1. Medications affected by increase in gastric pH	Text revised to clarify use of medications that may be affected by increase in gastric pH	Clarification
10.10.6. Statistical Analyses	Changed full participants to randomized participants.	To follow ITT principles.
10.11. Appendix 11 Information for sites on scoring Appetite Visual Analog Scale	Appendix “Information for sites on scoring the Appetite Visual Analog Scale” added	Guidance for sites for scoring
10.12. Appendix 12 Country-specific Requirements 10.12.1. Brazil	Exclusion criterion number corrected from 42 to 41. 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 is corrected from 30 days to 90 days	Editorial correction
11. References	Added citations for Appetite VAS and Power of Food Scale	To support the newly added text in section 8.1.4.7 and 8.1.4.8
Throughout	Minor editorial changes have been made throughout	Minor, therefore not detailed

Amendment [b]: 11 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
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.	Clarifications

Section # and Name	Description of Change	Brief Rationale
	- Divided the de-escalation and re-escalation table into 2 tables and positioned them with associated text. - Updated the de-escalation for participants currently taking 3 mg to indicate that these participants will be discontinued from study intervention. - Provided clarifications if re-escalation attempts are not tolerated. - Provided further clarification for participants assigned to the 6 mg arm. Moved some text within Section 6.6.1.	

Amendment [a]: 05 April 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 for the current protocol amendment is to change the number of ECGs from single to triplicate in response to Food and Drug Administration feedback.

These and other changes and a brief rationale are provided in the table below.

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis	In the Objectives table for fasting insulin “mean change” was changed to “mean percent change” and deleted units	Fasting insulin will be transformed for analysis purposes
1.3.1 and 1.3.2 Schedule of Activities	12-lead ECG (Central): Added text “Triplicate” and “after at least 5 min of rest” to the ECG comment	To align with regulatory feedback
	Patient-reported outcomes (electronic): Added the following text “The PROs will be administered if an approved and translated version is available for use” in both SoA tables.	Text was inadvertently deleted
1.3.1 Schedule of Activities	DXA: Corrected visits for the DXA scan. Added the activity for the ED1 visit and deleted it from the 801 Visit	Correction
3. Objectives, endpoints, and Estimands	In the Objectives table for fasting insulin “mean change” was changed to “mean percent change” and deleted units	Fasting insulin will be transformed for analysis purposes
5.2 Exclusion Criteria	Removed Exclusion Criterion #32	Criterion was removed to make eligibility criteria less restrictive

Section # and Name	Description of Change	Brief Rationale
8.2.3 Electrocardiograms	“Single” was changed to “Triplicate” 12-lead ECGs A sentence was added stating “The recording of each ECG should occur at approximately 1-minute intervals. The collection of all replicates at a time point should not exceed 5 minutes.”	To align with regulatory feedback
8.3.1 Timing and Mechanism for Collecting Events	Collection of pregnancy mechanism for reporting was changed from “Pregnancy Paper Form” to “e-Pregnancy CRF”	Guidance update for Pregnancy exposure CRF
9.1 Statistical Hypotheses	H _{3,0} : text change from “is superior” to “compared”	Correction
9.2 Analyses sets	The description of the data points set were changed to add the text “ <u>at or</u> after baseline...”	Correction
9.3.2.1 Participant Disposition	Changed the word “baseline” to randomization	Clarification
10.4.2 Contraceptive Guidance	A footnote was added stating “aParticipants that have started implantable or injectable contraceptives within 18 months prior to Visit 1 will be excluded from the study.”	Clarification
10.10 Appendix 10: Information for Sites that have Access to Whole-Body DXA Scanners with Body Composition Capability	10.10.1 Introduction Total body composition assessments for this study: the number of study participants was changed to 156 10.10.3 Study Population Inclusion criteria: # 44 The word “receive” was changed to “consent to”	Correction Clarification
10.10.5 Randomization	Subsection added	This subsection, which was not in the original version, was added for clarification.
Throughout	Minor editorial changes have been made throughout	These are minor; therefore, they have not been individually summarized

11. References

- [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>
- Adams TD, Davidson LE, Litwin SE, et al. Weight and Metabolic Outcomes 12 Years after Gastric Bypass. *N Engl J Med*. 2017;377(12):1143-1155. <https://doi.org/10.1056/NEJMoal700459>
- 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>
- Allison DB, Downey M, Atkinson RL, et al. Obesity as a disease: a white paper on evidence and arguments commissioned by the Council of the Obesity Society. *Obesity (Silver Spring)*. 2008;16(6):1161-1177. <https://doi.org/10.1038/oby.2008.231>
- [AMA] American Medical Association House of Delegates: Recognition of obesity as a disease. Resolution: 420 (A-13). 2013. Accessed February 3, 2023. <https://media.npr.org/documents/2013/jun/ama-resolution-obesity.pdf>.
- 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>
- Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. *Gastroenterol*. 2007;132(6):2131-2157. <https://doi.org/10.1053/j.gastro.2007.03.054>
- 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>
- Barazzoni R, Bischoff S, Boirie Y, et al. Sarcopenic obesity: time to meet the challenge. *Obes Facts*. 2018;11(4):294-305. <https://doi.org/10.1159/000490361>
- 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 de Vigilância Sanitária/MS: Aprova o regulamento para os programas de acesso expandido, uso compassivo e fornecimento de medicamento pós-estudo.
- 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>
- Cava E, Yeat, NC, Mittendorfer B. Preserving healthy muscle during weight loss. *Adv Nutr*. 2017;8(3):511-519. <https://doi.org/10.3945/an.116.014506>
- Cappelleri JC, Bushmakina AG, Gerber RA, et al. Evaluating the Power of Food Scale in obese subjects and a general sample of individuals: development and measurement properties. *Int J Obes*. 2009;33:913-922. <https://doi.org/10.1038/ijo.2009.107>
- [CSAPH] Council on Science and Public Health. Report of the Council on Science and Public Health. Is obesity a disease? (Resolution 115-A-12). Council on Science and Public Health. Report number: 3-A-13, 2013. Accessed January 31, 2023. <https://www.ama-assn.org/sites/ama-assn.org/files/corp/media-browser/public/about-ama/councils/Council%20Reports/council-on-science-public-health/a13csaph3.pdf>
- [C-SSRS] The Columbia Lighthouse Project. Columbia-suicide severity rating scale scoring and data analysis guide. Published February 2013. Accessed February 2, 2023. <https://cssrs.columbia.edu/wp-content/uploads/ScoringandDataAnalysisGuide-for-Clinical-Trials-1.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.org/10.1111/pedi.12051>
- Dordevic AL, Bonham M, Ghasem-Zadeh A, et al. Reliability of compartmental body composition measures in weight-stable adults using GE iDXA: implications for research and practice. *Nutrients*. 2018;10(10):1484. <https://doi.org/10.3390/nu10101484>
- [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>.
- Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. *Int J Obes Relat Metab Disord*. 2000;24:38-48. <https://doi.org/10.1038/sj.ijo.0801083>.

- Jendle J, Nauck MA, Matthews DR, et al. LEAD-2 and LEAD-3 Study Groups. Weight loss with liraglutide, a once-daily human glucagon-like peptide-1 analogue for type 2 diabetes treatment as monotherapy or added to metformin, is primarily as a result of a reduction in fat tissue. *Diabetes Obes Metab*. 2009;11(12):1163-1172. <https://doi.org/10.1111/j.1463-1326.2009.01158.x>
- Knowler WC, Barrett-Connor E, Fowler, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403. <https://doi.org/10.1056/NEJMoa012512>
- Koizumi M, Takada T, Kawarada Y, et al. JPN guidelines for the management of acute pancreatitis: diagnostic criteria for acute pancreatitis. *J Hepatobiliary Pancreat Surg*. 2006;13(1):25-32. <https://doi.org/10.1007/s00534-005-1048-2>
- 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>
- Kulovitz MG, Kolkmeier D, Conn CA, et al. Medical weight loss versus bariatric surgery: does method affect body composition and weight maintenance after 15% reduction in body weight?. *Nutrition*. 2014;30(1):49-54. <https://doi.org/10.1016/j.nut.2013.06.008>
- le Roux CW, Astrup A, Fujioka K, et al. SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. *Lancet*. 2017;389(10077):1399-1409. [https://doi.org/10.1016/S0140-6736\(17\)30069-7](https://doi.org/10.1016/S0140-6736(17)30069-7). Epub 2017 Feb 23. Erratum in: *Lancet*. 2017 Apr 8;389(10077):1398.
- Lewiecki EM, Binkley N, Morgan SL, et al. International Society for Clinical Densitometry. Best practices for dual-energy x-ray absorptiometry measurement and reporting: International Society for Clinical Densitometry Guidance. *J Clin Densitom*. 2016;19(2):127-140. <https://doi.org/10.1016/j.jocd.2016.03.003>
- Li G, Zhang P, Wang J, An Y, et al. Cardiovascular mortality, all-cause mortality, and diabetes incidence after lifestyle intervention for people with impaired glucose tolerance in the Da Qing Diabetes Prevention Study: a 23-year follow-up study. *Lancet Diabetes Endocrinol*. 2014;2(6):474-480. [https://doi.org/10.1016/S2213-8587\(14\)70057-9](https://doi.org/10.1016/S2213-8587(14)70057-9)
- Lowe MR, Butryn ML, Didie ER, et al. The Power of Food Scale. A new measure of the psychological influence of the food environment. *Appetite* 2009;53(1):114-118. <https://doi.org/10.1016/j.appet.2009.05.016>
- Maruish ME, editor. User's Manual for the SF-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>
- [Northwestern]. Northwestern University. PROMIS Short Form v1.0 – Sleep Disturbance 8b. Published May 03, 2016b. Accessed December 01, 2021. https://www.healthmeasures.net/index.php?option=com_instruments&view=measure&id=184&Itemid=992
- 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/bmjdr-2016-000341>
- Saxenda [package insert]. Plainsboro, NJ: Novo Nordisk, Inc.; 2022.
- Skow MA, Bergmann, NC, Knop FK. Diabetes and obesity treatment based on dual incretin receptor activation: “twincretins”. *Diabetes Obes Metab*. 2016;18(9):847-854. <https://doi.org/10.1111/dom.12685>
- Spitzer RL, Kroeke K, Williams JB. Validation and utility of a self-report version of PRIME-MD: The PHQ primary care study. Primary Care Evaluation of Mental Disorders. Patient Health Questionnaire *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>
- Tomlinson B, Hu M, Zhang Y, et al. An overview of new GLP-1 receptor agonists for type 2 diabetes. *Expert Opin Investig Drugs*. 2016;25(2):145-158. <https://doi.org/10.1517/13543784.2016.1123249>
- 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](https://doi.org/10.1016/0026-0495(90)90299-R)
- Wadström C, Backman L, Forsberg AM, et al. Body composition and muscle constituents during weight loss: studies in obese patients following gastroplasty. *Obes Surg*. 2000;10(3):203-213. <https://doi.org/10.1381/096089200321643313>

- Warkentin LM, Das D, Majumdar SR, et al. The effect of weight loss on health-related quality of life: systematic review and meta-analysis of randomized trials. *Obes Rev*. 2014;15(3):169-182. <https://doi.org/10.1111/obr.12113>
- 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>
- 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*. 2011;34(7):1481-1486. <https://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
- 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>

Signature Page for VV-CLIN-116515 v3.0

Approval	PPD 28-Apr-2025 19:53:01 GMT+0000
----------	---

Approval	PPD 30-Apr-2025 16:47:14 GMT+0000
----------	---

Signature Page for VV-CLIN-116515 v3.0