ORIGINAL ARTICLE

Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment

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ABSTRACT

BACKGROUND

Orforglipron, a small-molecule, nonpeptide oral glucagon-like peptide-1 (GLP-1) receptor agonist, is being investigated as a treatment for obesity.

METHODS

In this phase 3, multinational, randomized, double-blind trial, we examined the safety and efficacy of once-daily orforglipron at doses of 6 mg, 12 mg, or 36 mg, as compared with placebo (assigned in a 3:3:3:4 ratio) as an adjunct to healthy diet and physical activity for 72 weeks. All the patients had obesity without diabetes mellitus. The primary end point was the percent change in body weight from baseline to week 72, as assessed according to the treatment-regimen estimand in the intention-to-treat population.

RESULTS

A total of 3127 patients underwent randomization. The mean change in body weight from baseline to week 72 was −7.5% (95% confidence interval [CI], −8.2 to −6.8) with 6 mg of orforglipron, −8.4% (95% CI, −9.1 to −7.7) with 12 mg of orforglipron, and −11.2% (95% CI, −12.0 to −10.4) with 36 mg of orforglipron, as compared with −2.1% (95% CI, −2.8 to −1.4) with placebo ($P<0.001$ for all comparisons with placebo). Among the patients in the orforglipron 36-mg group, 54.6% had a reduction of 10% or more, 36.0% had a reduction of 15% or more, and 18.4% had a reduction of 20% or more, as compared with 12.9%, 5.9%, and 2.8% of the patients, respectively, in the placebo group. Waist circumference, systolic blood pressure, triglyceride levels, and non-HDL cholesterol levels significantly improved with orforglipron treatment as compared with placebo. Adverse events resulted in treatment discontinuation in 5.3 to 10.3% of the patients in the orforglipron groups and in 2.7% of those in the placebo group. The most common adverse events with orforglipron were gastrointestinal effects, which were mostly mild to moderate.

CONCLUSIONS

In adults with obesity, 72-week treatment with orforglipron led to significantly greater reductions in body weight than placebo; the adverse-event profile was consistent with that of other GLP-1 receptor agonists. (Funded by Eli Lilly; ATTAIN-1 ClinicalTrials.gov number, NCT05869903.)

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*The investigators in the ATTAIN-1 trial are listed in the Supplementary Appendix, available at NEJM.org.

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Overweight and obesity affect more than 2.5 billion persons worldwide and increase the risk of multiple health complications.[1] Long-term care for patients with obesity requires a multifaceted approach with safe, durable, and accessible treatment options.[2] Clinical guidelines recommend obesity-management medications for patients with obesity, as well as for those who are overweight with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 27 to less than 30 with coexisting complications.[3,4] The use of incretin-based therapies for obesity, such as glucagon-like peptide-1 (GLP-1) receptor agonists, are reported to result in mean weight reductions of approximately 15 to 20% and have shown additional health benefits, including decreased cardiovascular risk.[5-8] However, most available GLP-1–based medications are administered as a subcutaneous injection, which may limit treatment initiation and adherence.[9,10]

Oral small-molecule GLP-1 receptor agonists may mitigate the limitations of peptide GLP-1 therapies while retaining their biologic properties. These agents may be amenable to easier storage, distribution, and administration. In addition, many patients prefer oral to injectable medications. Such advantages theoretically may increase access to GLP-1–based therapies and to broader health benefits associated with their use and allow patients to select a formulation aligned with their needs.

Orforglipron is a small-molecule, nonpeptide GLP-1 receptor agonist that is designed for once-daily, oral administration without restrictions on food or liquid intake. This drug is in clinical development for obesity as well as for type 2 diabetes, hypertension, osteoarthritis, and obstructive sleep apnea.[11] We performed the ATTAIN-1 trial to evaluate the efficacy and safety of orforglipron at doses of 6 mg, 12 mg, and 36 mg in adults with obesity without diabetes mellitus.

Methods

Trial Design and Oversight

We designed this phase 3, multinational, randomized, placebo-controlled trial to investigate once-daily, orally administered orforglipron, as compared with placebo, as an adjunct to healthy diet and physical activity in patients with obesity who did not have diabetes mellitus. The trial was performed at 137 sites in nine countries.

Local institutional review boards approved the protocol (available with the full text of this article at NEJM.org). The trial was conducted in accordance with the principles of the Declaration of Helsinki and International Council for Harmonisation Good Clinical Practice guidelines. All the patients provided written informed consent.

The trial sponsor, Eli Lilly, designed the trial and oversaw its conduct. Trial investigators were responsible for data collection. The sponsor performed site monitoring, data collation, and data analysis. The investigators and authors worked under confidentiality agreements with the sponsor. The authors, with assistance from sponsor-funded medical writers, wrote the first draft of the manuscript. All the authors had access to the data and analyses, interpreted the data, critically reviewed the manuscript, approved the decision to submit it for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

To be eligible to participate in the trial, adults (≥18 years of age) were required to have a BMI of at least 30 or to have a BMI between 27 and 30 and to have at least one obesity-related complication, including hypertension, dyslipidemia, cardiovascular disease, or obstructive sleep apnea, and a history of at least one patient-reported unsuccessful dietary effort to lose body weight. Key exclusion criteria were a diagnosis of diabetes mellitus and a change in body weight (either gain or loss) of more than 5 kg within 90 days before screening. An upper limit of 70% enrollment of women ensured a sufficient sample of men. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix (available at NEJM.org).

Procedures

Patients were randomly assigned in a 3:3:3:4 ratio to receive once-daily orforglipron at a dose of 6 mg, 12 mg, or 36 mg or placebo. Randomization was stratified according to country, sex, and the presence or absence of prediabetes. Prediabetes was diagnosed according to glycemic thresholds proposed by the American Diabetes Association (with details provided in the Supplementary Appendix). Orforglipron or matching placebo was administered daily by oral capsule. Orforglipron was started at a dose of 1 mg, which was esca-

lated every 4 weeks until the assigned dose was reached (6 mg at 8 weeks, 12 mg at 12 weeks, and 36 mg at 20 weeks) (Fig. S1 in the Supplementary Appendix). Throughout the trial, all the patients received individualized lifestyle counseling focused on a healthy, balanced diet combined with physical activity.

The trial included a 3-week screening period followed by a 72-week treatment period. In patients with normoglycemia at randomization, the treatment period was followed by a 2-week off-drug safety follow-up period, whereas those with baseline prediabetes were scheduled to continue receiving the assigned regimen for 2 additional years. Here, we report the 72-week results for all the patients.

END POINTS

The primary end point was the percent change in body weight from baseline to week 72. Multiplicity-adjusted secondary end points were the percentage of patients who had a reduction in body weight of at least 5%, 10%, 15%, or 20% at week 72, along with the change from baseline to week 72 in waist circumference, systolic blood pressure, non–high-density-lipoprotein (HDL) cholesterol, and triglycerides. Additional secondary end points included changes in glycemic measures, diastolic blood pressure, and other lipid measures. Changes in body composition from baseline to week 72 were assessed for a subgroup of patients by means of dual-energy x-ray absorptiometry (DXA). All prespecified end points are described in the protocol.

STATISTICAL ANALYSIS

We determined that a sample size of 3042 patients would provide the trial with at least 90% power to show the superiority of individual doses of orforglipron over placebo for the primary end point at a familywise two-sided type I error rate of 0.05, assuming that the treatment effect in mean percent body-weight reduction from baseline to week 72, as compared with placebo, would be at least 5 percentage points with a common standard deviation of 10%.

The efficacy analysis included all the patients who had undergone randomization. Two estimands were predefined. The treatment-regimen estimand represents the estimated average treatment effect regardless of treatment discontinuation or the use of prohibited weight-management treatments (consistent with the intention-to-treat analysis). The efficacy estimand represents the treatment effect as if all the randomized patients adhered to the administration of either orforglipron or placebo as intended and did not initiate prohibited weight-management treatment. Thus, the efficacy estimand used a hypothetical strategy to account for intercurrent events; the corresponding potential outcome thus may not be realized. Therefore, the efficacy estimand is likely to lead to a larger treatment effect than the treatment-regimen estimand. All reported results were calculated with the treatment-regimen estimand, unless otherwise noted.

A graphical testing procedure for multiple comparisons was used for testing the primary and multiplicity-adjusted secondary end points[12,13] to control for the overall familywise type I error rate at 0.05 within each estimand. Model-based estimates and confidence intervals are reported. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. Safety analyses were conducted in all the patients who underwent randomization and received at least one dose of orforglipron or placebo. These analyses included data from the treatment and safety follow-up periods.

Statistical analyses for the treatment-regimen estimand were conducted by means of an analysis-of-covariance model for continuous efficacy outcomes and logistic regression for binary outcomes. Missing data at week 72 owing to early discontinuation of orforglipron or placebo were imputed within each trial group with the retrieved-dropouts method. Additional details regarding graphical testing, missing-data imputation, and statistical methods are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From June 5, 2023, to July 25, 2025, a total of 3127 patients underwent randomization in nine countries. At baseline, the demographic and clinical characteristics of the patients were similar in the trial groups (Table 1 and Table S1). The mean age of the patients was 45 years; 64.2% were women; and 56.5% were White, 28.6% were Asian, and 8.6% were Black. At randomization, the mean body weight was 103.2 kg and the mean BMI was 37.0. A total of 46.0% of the patients

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=725)	Orforglipron, 36 mg (N=730)	Placebo (N=949)	Total (N=3127)
Age — yr	44.9±12.1	45.4±12.6	44.9±11.9	45.1±11.9	45.1±12.1
Female sex — no. (%)	469 (64.9)	467 (64.4)	465 (63.7)	608 (64.1)	2009 (64.2)
Race or ethnic group — no. (%)†					
American Indian or Alaska Native	2 (0.3)	3 (0.4)	2 (0.3)	4 (0.4)	11 (0.4)
Asian	202 (28.3)	201 (28.1)	214 (29.6)	267 (28.5)	884 (28.6)
Black	68 (9.5)	60 (8.4)	67 (9.3)	72 (7.7)	267 (8.6)
White	408 (57.1)	405 (56.6)	394 (54.4)	539 (57.5)	1746 (56.5)
Native Hawaiian or other Pacific Islander	0	1 (0.1)	0	2 (0.2)	3 (0.1)
Multiple	35 (4.9)	45 (6.3)	47 (6.5)	54 (5.8)	181 (5.9)
Hispanic or Latino	273 (37.8)	275 (37.9)	258 (35.3)	369 (38.9)	1175 (37.6)
Body weight — kg	103.2±21.7	102.2±21.6	103.1±23.2	103.9±22.0	103.2±22.1
Body-mass index‡					
Mean	37.0±6.5	36.7±6.5	36.9±6.7	37.1±6.3	37.0±6.5
Distribution — no. (%)					
<30	62 (8.6)	72 (9.9)	68 (9.3)	86 (9.1)	288 (9.2)
30 to <35	263 (36.4)	272 (37.5)	285 (39.0)	331 (34.9)	1151 (36.8)
35 to <40	202 (27.9)	198 (27.3)	183 (25.1)	266 (28.0)	849 (27.2)
≥40	196 (27.1)	183 (25.2)	194 (26.6)	266 (28.0)	839 (26.8)
Waist circumference — cm	112.2±14.1	112.0±14.2	112.4±15.3	112.8±14.5	112.4±14.5
Blood pressure — mm Hg					
Systolic	125.4±14.1	125.1±13.7	125.8±15.9	125.8±14.5	125.5±14.6
Diastolic	81.0±9.3	81.2±9.4	80.9±10.1	81.8±9.9	81.3±9.7
Lipid measure — mg/dl					
Total cholesterol	196.2±37.6	195.0±39.0	196.3±39.5	196.5±39.5	196.0±38.9
HDL cholesterol	49.6±12.5	50.1±12.4	48.5±12.6	49.3±12.4	49.4±12.5
LDL cholesterol	119.6±32.2	118.3±34.1	119.4±33.6	119.0±33.6	119.1±33.4
Non-HDL cholesterol	146.4±36.1	144.6±38.0	147.5±38.7	147.0±38.1	146.4±37.7
VLDL cholesterol	26.1±11.8	25.9±11.7	27.3±13.2	27.3±12.9	26.7±12.5
Triglycerides	135.4±72.5	133.5±75.8	142.8±89.1	142.4±91.9	138.8±83.5

* Plus–minus values are means ±SD. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. HDL denotes high-density lipoprotein, LDL low-density lipoprotein, and VLDL very-low-density lipoprotein.

† Race and ethnic group were reported by the patients. The percentages were calculated according to the total number of patients indicating their race or ethnic group. Thus, the denominators in this category were 715 in the 6-mg orforglipron group, 715 in the 12-mg orforglipron group, 724 in the 36-mg orforglipron group, and 938 in the placebo group, for a total of 3092 patients.

‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.

had a BMI of less than 35, and 36.0% of the patients had prediabetes.

The trial was completed by 2662 patients (85.1%), including 625 patients (86.4%) in the orforglipron 6-mg group, 630 patients (86.9%) in the orforglipron 12-mg group, 639 patients (87.5%) in the orforglipron 36-mg group, and 768 patients (80.9%) in the placebo group. Administration of orforglipron or placebo was continued throughout the 72-week trial period in 2344 patients (75.0%), including 565 patients (78.1%) in the orforglipron 6-mg group, 562 patients (77.5%)

Table 2. Primary and Key Secondary End Points.*

End Point	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=725)	Orforglipron, 36 mg (N=730)	Placebo (N=949)
Primary end point				
Percent change in body weight (95% CI)†	−7.5 (−8.2 to −6.8)	−8.4 (−9.1 to −7.7)	−11.2 (−12.0 to −10.4)	−2.1 (−2.8 to −1.4)
Difference vs. placebo (95% CI) — percentage points	−5.5 (−6.5 to −4.5)	−6.3 (−7.3 to −5.4)	−9.1 (−10.1 to −8.1)	—
Key secondary end points				
Category of weight reduction — % of patients (95% CI)‡				
≥5%	60.6 (56.5 to 64.6)	63.5 (59.8 to 67.2)	71.8 (68.1 to 75.4)	26.8 (23.3 to 30.2)
≥10%	33.3 (29.7 to 36.9)	40.0 (36.4 to 43.7)	54.6 (50.7 to 58.4)	12.9 (10.3 to 15.6)
≥15%	15.1 (12.4 to 17.8)	20.3 (17.3 to 23.3)	36.0 (32.4 to 39.5)	5.9 (4.0 to 7.8)
≥20%	6.4 (4.6 to 8.3)§	9.0 (6.9 to 11.1)	18.4 (15.5 to 21.3)	2.8 (1.6 to 4.0)
Change in waist circumference (95% CI) — cm†	−7.1 (−7.7 to −6.5)	−8.2 (−8.9 to −7.5)	−10.0 (−10.7 to −9.3)	−3.1 (−3.7 to −2.4)

* The primary and key secondary end points were tested under a multiplicity-control procedure. P<0.001 for all comparisons with placebo.
† In this category, data are model-based estimates and 95% confidence intervals assessed with the use of analysis of covariance according to the treatment-regimen estimand. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All changes are from baseline to week 72.
‡ Data are presented as model-based estimates and 95% confidence intervals as calculated by logistic regression according to the treatment-regimen estimand. The percentage was calculated by combining the percentages of patients who met the target in imputed datasets with the use of Rubin's rule.
§ This data point was not controlled for multiplicity.

in the orforglipron 12-mg group, 552 patients (75.6%) in the orforglipron 36-mg group, and 665 patients (70.1%) in the placebo group (Fig. S2).

Overall, the percentage of patients who discontinued treatment for any reason was 25.0% (21.9 to 24.4% in the orforglipron groups and 29.9% in the placebo group). The most common reasons were the patient's decision to withdraw from treatment (8.5 to 8.9% of the patients in the orforglipron groups and 13.8% of those in the placebo group), followed by adverse events (in 5.1 to 10.3% of the patients in the orforglipron groups and in 2.6% of those in the placebo group).

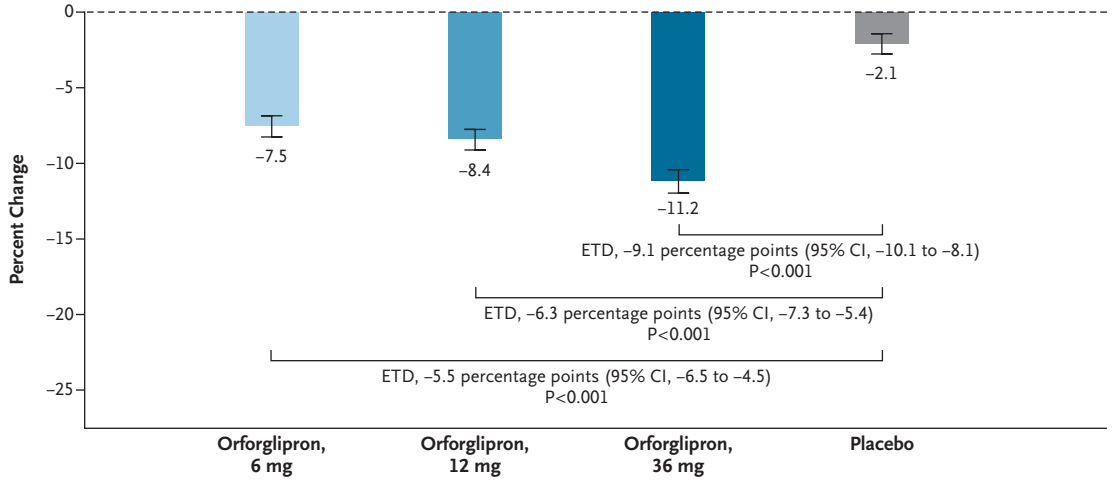
WEIGHT-RELATED END POINTS

The mean change in weight from baseline to week 72 was −7.5% (95% confidence interval [CI], −8.2 to −6.8) in the orforglipron 6-mg group, −8.4% (95% CI, −9.1 to −7.7) in the orforglipron 12-mg group, and −11.2% (95% CI, −12.0 to −10.4) in the orforglipron 36-mg group, as compared with −2.1% (95% CI, −2.8 to −1.4) in the placebo group (Table 2 and Fig. 1A). All orforglipron doses were superior to placebo, with a treatment difference of −5.5 percentage points (95% CI, −6.5 to −4.5) with orforglipron 6 mg, −6.3 percentage points (95% CI, −7.3 to −5.4) with orforglipron 12 mg, and −9.1 percentage points (95% CI, −10.1 to −8.1) with orforglipron 36 mg (P<0.001 for all doses).

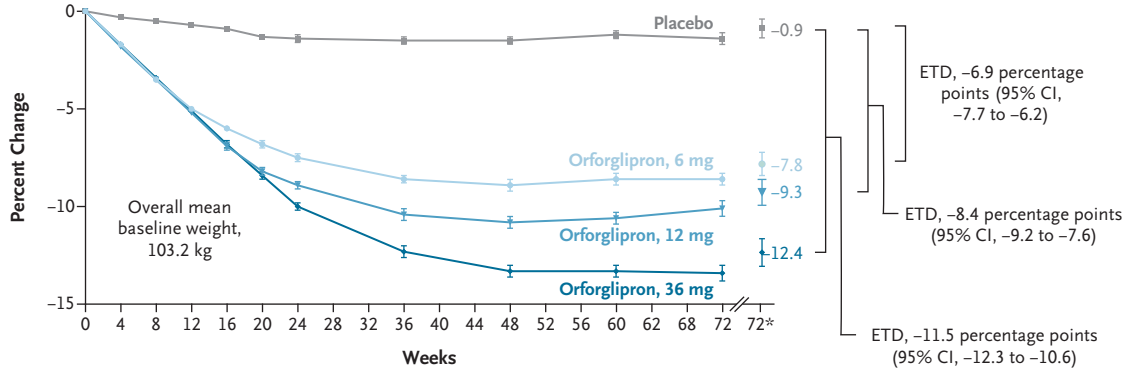
At 72 weeks, significantly more patients in all the orforglipron groups met weight-reduction thresholds of at least 5%, 10%, 15%, and 20% than in the placebo group. Specifically, a body-weight reduction of 10% or more was met in 33.3% of the patients in the orforglipron 6-mg group, in 40.0% of those in the orforglipron 12-mg group, and in 54.6% of those in the orforglipron 36-mg group, as compared with 12.9% of those in the placebo group (P<0.001 for all comparisons with placebo) (Table 2 and Fig. 1C).

Treatment with all orforglipron doses was associated with a greater reduction in absolute body weight and in BMI than with placebo (Figs. S3 and S4). Of the patients in the orforglipron 36-mg group, at week 72, 11.1% had a BMI of less than 25, 18.6% had a BMI of less than 27, and 37.3% had a BMI of less than 30, as compared with 0.9%, 3.5%, and 15.7%, respectively,

A Change in Body Weight from Baseline to Week 72 (treatment-regimen estimand)



B Change in Body Weight from Baseline to Week 72 (efficacy estimand)



No. of Patients

Placebo	949	937	923	910	875	847	817	766	716	688	654	949
Orforglipron, 6 mg	723	713	702	690	675	664	652	630	601	578	559	723
Orforglipron, 12 mg	725	719	695	687	672	652	648	624	602	582	559	725
Orforglipron, 36 mg	730	715	704	689	670	662	644	617	583	573	549	730

C Patients with Weight Reduction According to Logistic-Regression Analysis (treatment-regimen estimand)

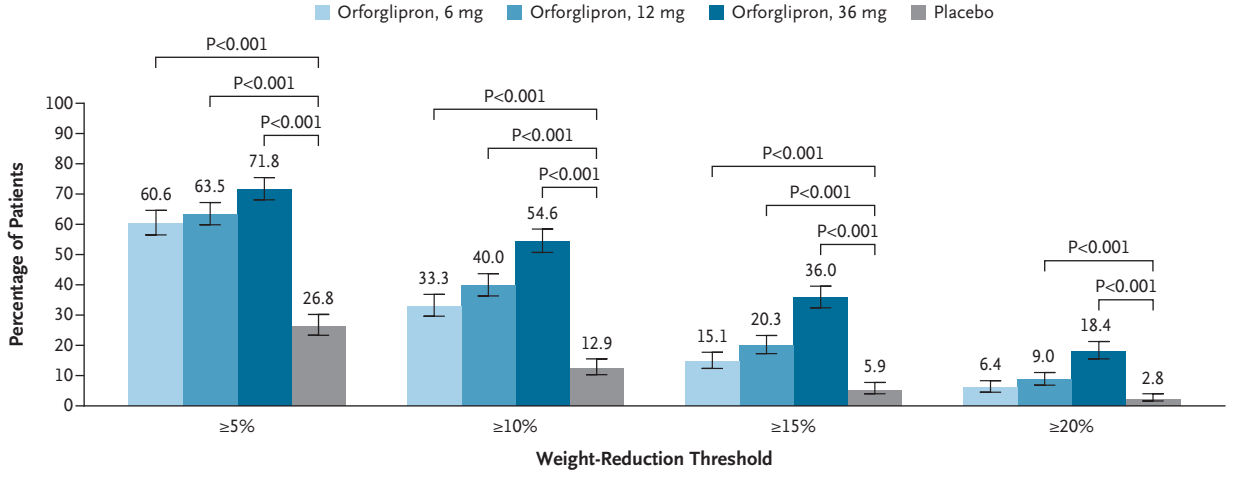


Figure 1 (facing page). Body Weight and Body-Weight Reduction Thresholds.

Panel A shows the model-based estimate with 95% confidence intervals for the percent change in body weight from baseline to week 72 in the orforglipron groups and the placebo group, along with the estimated treatment difference (ETD) between groups, as calculated by means of analysis of covariance (ANCOVA), according to the treatment-regimen estimand. Panel B shows the results of two separate analyses combined into one panel. The curves at the left show changes from week 0 to week 72 based on observed on-treatment means with standard errors according to the efficacy estimand, including all data points obtained during the treatment period and up to the earliest date of discontinuation of orforglipron or placebo or the initiation of prohibited weight-management treatments. The data at the right of the curves at week 72 (marked with an asterisk) show the results of a model-based estimate, with 95% confidence intervals, according to the efficacy estimand — a prespecified analysis for the primary end point of the trial — along with the ETD between the orforglipron groups and the placebo group. Panel C shows the percentage of patients with a weight reduction of at least 5%, 10%, 15%, or 20%, as calculated by logistic-regression analysis (treatment-regimen estimand). The weight-reduction threshold of at least 20% was a key secondary end point for the orforglipron doses of 12 mg and 36 mg only. The percentages were calculated by combining percentages of patients who met targets across imputed datasets with the use of Rubin's rule. I bars indicate 95% confidence intervals. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. For end points that were not controlled for multiplicity, P values are not reported, regardless of statistical significance.

in the placebo group (Fig. S5). Table S3 shows subgroup analyses assessing treatment interaction with important factors that could potentially affect changes in body weight, including baseline BMI, age, and sex. Observed values over time as well as the efficacy estimand for the percent change in body weight are shown in Figure 1B. Additional end points for both estimands are shown in Tables S4 through S6.

ADDITIONAL TREATMENT OUTCOMES

Orforglipron significantly improved cardiometabolic risk factors, which were assessed as key secondary end points controlled for multiplicity, including waist circumference, systolic blood pressure, non-HDL cholesterol, and triglycerides (Table 3, Table S4, and Figs. S4 and S6). Orforglipron was associated with improvements in diastolic blood pressure, other lipid fractions, high-sensitivity C-reactive protein, and waist-to-height ratio (Table S4 and Figs. S6 and S7), as well as levels of glycated hemoglobin, fasting glucose, and fasting insulin (Table S4). In the orforglipron groups, 74.6 to 83.7% of the patients with prediabetes at randomization had normoglycemic levels at week 72, as compared with 44.6% of those in the placebo group.

CHANGES IN BODY COMPOSITION

In the subgroup of 171 patients who underwent DXA, patients in the pooled orforglipron groups had a mean percent change of –13.8% in total body fat mass, –4.5% in lean mass, and –19.0% in visceral fat mass at week 72, as compared with changes of –1.7%, 0.3%, and 7.4%, respectively, with placebo (Fig. S8). In the pooled orforglipron groups, 73.1% of the body-weight reduction was due to a loss in fat mass and 26.9% was due to a loss in lean mass.

SAFETY

The most frequent adverse events with orforglipron were nausea, constipation, diarrhea, vomiting, and dyspepsia (Table S7 and Fig. S9). Gastrointestinal events in the orforglipron groups were mostly mild to moderate in severity and first occurred mainly during dose escalation. Treatment discontinuation because of gastrointestinal adverse events occurred in 3.5 to 7.0% of the patients in the orforglipron groups and in 0.4% of those in the placebo group.

Serious adverse events were reported in 3.8 to 5.5% of the patients in the orforglipron groups and in 4.9% of those in the placebo group (Table 4). During the 72-week trial period, three deaths were reported: one each in the orforglipron 6-mg and 12-mg groups and one in the placebo group (Table 4 and Table S8). Five cases of adjudication-confirmed mild pancreatitis occurred (all in the orforglipron groups), with no complications reported. In four of these patients, confirmation was based solely on symptoms and elevated enzyme levels, with cholelithiasis reported as a contributing factor in one patient. In the fifth patient, obstructive pancreatitis was confirmed on the basis of imaging (Table S9). No cases of medullary thyroid cancer were reported. Aminotransferase levels of at least 10 times the upper limit of the normal range (ULN) were reported in seven patients in the orforglipron groups and in one patient in the

Table 3. Key Secondary and Additional Secondary End Points.*

End Point	Pooled Orforglipron† (N=2178)	Placebo (N=949)	Estimated Treatment Difference vs. Placebo (95% CI)
Key secondary end points‡			
Change in systolic brood pressure (95% CI) — mm Hg	−5.7 (−6.3 to −5.0)	−1.4 (−2.4 to −0.5)	−4.2 (−5.3 to −3.2)
Percent change (95% CI)§			
Triglycerides	−14.8 (−16.3 to −13.3)	−3.8 (−6.8 to −0.7)	−11.5 (−14.5 to −8.3)
Non-HDL cholesterol	−6.7 (−7.6 to −5.8)	−1.9 (−3.6 to −0.2)	−4.9 (−6.7 to −3.1)
Additional secondary end points			
Change in diastolic blood pressure (95% CI) — mm Hg	−2.4 (−2.9 to −2.0)	−1.4 (−2.1 to −0.7)	−1.0 (−1.8 to −0.2)
Percent change (95% CI)§			
Total cholesterol	−4.1 (−4.8 to −3.4)	−2.0 (−3.3 to −0.6)	−2.1 (−3.7 to −0.6)
LDL cholesterol	−4.8 (−5.8 to −3.7)	−1.3 (−3.0 to 0.4)	−3.5 (−5.5 to −1.5)
VLDL cholesterol	−14.6 (−16.1 to −13.1)	−3.5 (−6.3 to −0.6)	−11.5 (−14.5 to −8.5)

* Data are model-based estimates and 95% confidence intervals assessed with the use of analysis of covariance according to the treatment-regimen estimand. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All changes are from baseline to week 72.
† The pooled orforglipron group includes patients in the 6-mg, 12-mg, and 36-mg orforglipron groups.
‡ The key secondary end points were tested under a multiplicity-control procedure. P<0.001 for all comparisons with placebo.
§ Lipid measures were log-transformed before fitting the analysis-of-covariance model, and results were then back-transformed with the delta method from the model-based estimate and standard errors on the natural log scale.

placebo group. For all seven patients in the orforglipron groups, alternative causes were identified (Table S10). In the orforglipron groups, two patients had both a total bilirubin level of more than two times the ULN and an alanine aminotransferase level of more than three times the ULN. Both cases had alternative causes and were not associated with drug-induced liver injury (Table S10). An increase in the mean pulse rate of 4.3 to 5.3 beats per minute occurred in the orforglipron groups, as compared with an increase of 0.8 beats per minute in the placebo group (Table S11). Additional safety information is provided in Table 4 and in Tables S7 and S11.

DISCUSSION

In this phase 3, multinational trial, we compared three once-daily doses of orforglipron (6 mg, 12 mg, and 36 mg) with placebo in 3127 patients who had obesity without diabetes. After 72 weeks of treatment, all the patients in the three orforglipron groups had a significant and clinically meaningful dose-dependent reduction in body weight. The patients who received the highest dose of orforglipron had an average 11.2% weight reduction; more than one third had a reduction of at least 15%, and nearly one fifth had a reduction of at least 20%. All measured cardiometabolic biomarkers improved with orforglipron treatment as compared with placebo.

Weekly injectable incretin-based obesity therapies, such as semaglutide and tirzepatide, have resulted in mean weight reductions of approximately 15% and more than 20%, respectively.[6,7] A weight reduction of 10% or more is a recognized therapeutic threshold, one that has been linked to meaningful cardiometabolic benefits.[14,15] In our current trial, patients who received orforglipron had a mean weight reduction of as much as 11.2%, and such reductions were associated with improvements in systolic and diastolic blood pressure, as well as lipid, glycemic, and high-sensitivity C-reactive protein levels. Although differences in design and population preclude direct cross-trial comparisons, these cardiometabolic improvements were similar to those reported with oral and injectable semaglutide in obesity trials, despite the modestly lower weight loss in the current trial, a finding that

Table 4. Adverse Events.*

Adverse Event	Orforglipron, 6 mg (N=723)	Orforglipron, 12 mg (N=724)	Orforglipron, 36 mg (N=728)	Placebo (N=948)	Total (N=3123)
	number of patients (percent)				
Any adverse event emerging during treatment period	603 (83.4)	627 (86.6)	620 (85.2)	763 (80.5)	2613 (83.7)
Serious adverse event	40 (5.5)	39 (5.4)	28 (3.8)	46 (4.9)	153 (4.9)
Death†	1 (0.1)	1 (0.1)	0	1 (0.1)	3 (0.1)
Event leading to discontinuation of orforglipron or placebo					
Any adverse event	38 (5.3)	57 (7.9)	75 (10.3)	26 (2.7)	196 (6.3)
Gastrointestinal disorder	25 (3.5)	38 (5.2)	51 (7.0)	4 (0.4)	118 (3.8)
Adverse event of special interest and other safety topics					
Hepatic event‡	1 (0.1)	0	2 (0.3)	2 (0.2)	5 (0.2)
Cancer	6 (0.8)	8 (1.1)	6 (0.8)	10 (1.1)	30 (1.0)
Adjudication-confirmed pancreatitis§	1 (0.1)	2 (0.3)	2 (0.3)	0	5 (0.2)
Hypotension or syncope‡	0	0	1 (0.1)	1 (0.1)	2 (0.1)
Adjudication-confirmed MACE	7 (1.0)	0	4 (0.5)	4 (0.4)	15 (0.5)
Any cardiac disorder¶	1 (0.1)	1 (0.1)	0	2 (0.2)	4 (0.1)
Gastrointestinal event‡	10 (1.4)	19 (2.6)	25 (3.4)	6 (0.6)	60 (1.9)
Gallbladder disease‡	3 (0.4)	6 (0.8)	6 (0.8)	4 (0.4)	19 (0.6)
Acute renal event‡	0	0	0	1 (0.1)	1 (<0.1)
Major depressive disorder or suicidal ideation or behavior‡	1 (0.1)	1 (0.1)	2 (0.3)	1 (0.1)	5 (0.2)
Hypersensitivity‡	0	0	0	1 (0.1)	1 (<0.1)
Dysesthesia‖	1 (0.1)	1 (0.1)	9 (1.2)	6 (0.6)	17 (0.5)
Other adverse event emerging during treatment period					
Cholelithiasis	6 (0.8)	11 (1.5)	11 (1.5)	8 (0.8)	36 (1.2)
Acute cholecystitis	1 (0.1)	2 (0.3)	4 (0.5)	1 (0.1)	8 (0.3)
Chronic cholecystitis	2 (0.3)	3 (0.4)	1 (0.1)	1 (0.1)	7 (0.2)

* MACE denotes major adverse cardiovascular event.
† Causes of death were reported as follows: undetermined for the patient in the 6-mg group, metastatic ovarian cancer in the patient in the 12-mg group, and pulmonary embolism for the patient in the placebo group. Deaths were also counted as serious adverse events and discontinuation of the trial regimen owing to adverse events.
‡ This category includes only events that were classified as severe or serious adverse events.
§ Additional information about adjudication-confirmed pancreatitis is provided in Table S10.
¶ Cardiac disorders included events that were classified as severe or serious arrhythmias and cardiac conduction disorders.
‖ Dysesthesia includes the *Medical Dictionary for Regulatory Activities* search terms of allodynia, dysesthesia, burning sensation, hyperesthesia, hyperpathia, pain of skin, paresthesia, sensitive skin, skin discomfort, and skin burning sensation.

reinforces the clinical significance of a weight reduction of 10% or more.[8,16] In the Look AHEAD trial, which included patients with type 2 diabetes, patients who had a weight loss of 10% or more through a lifestyle intervention had a 21% reduction in cardiovascular events. Similarly, in the SELECT study, a cardiovascular outcomes trial involving patients with obesity without diabetes, a 9.4% weight loss with semaglutide over a period of 2 years was associated with a 20% reduction in major adverse cardiovascular events.[7,14] GLP-1 receptor agonists may improve cardiovascular outcomes both by inducing weight reduction and by their direct, weight-

independent actions.[17] Whether orforglipron-induced weight reduction and biomarker changes will translate into a reduction in cardiovascular risk requires dedicated outcome trials.

Clinically, weight-reduction targets are individualized. Treat-to-target approaches that are based on thresholds of BMI or waist-to-height ratio have recently been proposed, although a single defined target remains a matter of debate.[18,19] Results of exploratory analyses in the current trial suggested that patients who received orforglipron had a higher likelihood of having a normal BMI or a near-normal waist-to-height ratio (<0.53) than those who received placebo, particularly among patients who had class I obesity or a BMI of 27 to 30 and associated complications at baseline. As with other obesity-management medications, weight-reduction responses varied substantially; notably, nearly one fifth of patients who received the highest dose had a weight reduction of at least 20%. We speculate that these findings may hold particular clinical relevance for patients with lower BMI values (for example, <35), who constitute the majority of patients with excess adiposity. Furthermore, orforglipron could represent an effective option for many patients, such as those who prefer oral therapy or lack access to injectable peptide-based obesity-management medications, including those in low- and middle-income countries where access is limited owing to low cold-chain availability.

In a phase 2 trial involving patients with obesity, 36-week treatment with 12 mg or 36 mg of orforglipron per day led to a substantial reduction in body weight, a loss that did not appear to plateau.[21] Despite the longer duration of the current trial, weight reduction after 72 weeks was similar to the reduction at 36 weeks in the phase 2 trial. Reasons may include differences in trial design and population, including greater geographic diversity in the current trial than in the phase 2 trial. Also, in the current trial, we enrolled a higher percentage of men than in historical phase 3 obesity trials, a factor that limits cross-trial comparisons, since men are reported to have less weight reduction than women in response to incretin-based treatment.[22] Variability in responses to obesity-management medications is well documented and not fully understood.[20] In this phase 3 study, a healthy, balanced diet, rather than a hypocaloric diet with a 500-kcal deficit, was implemented as part of the recommended lifestyle modifications in line with recent expert recommendations.[10] It remains uncertain whether this regimen influenced the trial results. Changes in body composition were consistent with what is expected after weight reduction with various interventions for weight management, including GLP-1–based therapies.[23]

Although the higher discontinuation rate in the placebo group in the current trial was consistent with earlier clinical trials of GLP-1 receptor agonists in patients with obesity, the increasing availability of efficacious obesity-management medications may have an adverse effect on trial retention.[6,8,24] In this trial, 6.2% of patients in the placebo group discontinued treatment because of a lack of efficacy, as compared with up to 1.0% in the orforglipron groups. Other weight-management interventions were initiated by 2.5% of the patients in the placebo group who continued in the trial.

Small molecules may bind to off-target receptors, which raises the potential for additional adverse effects. No such effects have been detected in the orforglipron development program to date, and the orforglipron safety profile has been consistent with peptide GLP-1 receptor agonists in phase 3 clinical trials.[8,24] The most frequent adverse events were predominantly mild to moderate and gastrointestinal in nature, and the increase in pulse is consistent with findings observed with peptide GLP-1 receptor agonists.[8,24] In clinical practice, following best-practice recommendations for management of gastrointestinal symptoms on incretin-based therapies may further improve the side-effect profile. These practices can include the use of a slower dose-escalation schedule or dietary advice regarding eating schedules and food choices.[25] Liver safety has led to the discontinued clinical development of molecules such as lotiglipron and danuglipron and has been a potential concern with small-molecule oral GLP-1 receptor agonists.[26,27] Consequently, liver safety was thoroughly evaluated in the current trial, and no signal was detected.

Trial limitations include the lack of comparison with currently approved obesity-management medications, the use of cutoffs for BMI inclusion criteria that have been developed in White populations and that exclude patients with lower BMI values who may also have adi-

posity-related risks, and the increasing availability of obesity-management medications, which could have an effect on treatment adherence and efficacy results. The strengths of the trial include a highly diverse, large population from nine countries on four continents (Table S12), including more than 35% enrollment of men.

In patients with obesity, the use of orforglipron resulted in statistically and clinically significant weight reductions and an adverse-event profile that was consistent with that observed with other GLP-1 receptor agonists.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Protocol

Protocol for: Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an oral small-molecule GLP-1 receptor agonist for obesity treatment. N Engl J Med. DOI: 10.1056/NEJMoa2511774

This trial protocol has been provided by the authors to give readers additional information about the work.

This supplement contains the following items:

1. Protocol
    a. Original protocol, dated 24 February 2023
    b. Final protocol including summary of changes and amendment history, dated 30 April 2025
2. Statistical analysis plan
    a. Original statistical analysis plan, dated 24 January 2024
    b. Final statistical analysis plan, including summary of changes, dated 25 June 2025

Title Page

Protocol Title:

A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared with Placebo in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Protocol Number: J2A-MC-GZGP

Amendment Number: This is the initial protocol.

Compound: LY3502970

Brief Title:

Efficacy and Safety of LY3502970 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 Electronically Signed and Approved by Lilly on date provided below.

Document ID: VV-CLIN-075707

Medical monitor name and contact information will be provided separately.

Table of Contents

1. Protocol Summary

1.1. Synopsis

Protocol Title: A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared with Placebo in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Brief Title: Efficacy and Safety of LY3502970 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 LY3502970 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 LY3502970 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/m^2 or greater), or overweight (BMI 27 kg/m^2 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 LY3502970 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 LY3502970 on progression to T2D and on long-term body weight changes.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary Objective	
To demonstrate that LY3502970 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 LY3502970 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 o ≥5% o ≥10% o ≥15% o ≥20% • Mean change in waist circumference (cm)
To demonstrate that LY3502970 (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 o non-HDL cholesterol o 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 baseline that LY3502970 (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo at 176 weeks: • Body weight • Delayed progression to T2D	From baseline to Week 176 • Mean percent change in body weight • Time to onset of T2D

Objectives	Endpoints
Additional Secondary Objectives	
To demonstrate that LY3502970 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/m^2) • Mean change in HbA1c (%) • Mean change in fasting glucose (mg/dL) • Mean change in fasting insulin (pmol/L)
To demonstrate that LY3502970 (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 o total cholesterol o LDL cholesterol o 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 LY3502970 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 LY3502970 (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 baseline that LY3502970 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 ≥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 patients 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-dailySBP = systolic blood pressure; SF-36v2 = 36-item Short Form Health Survey, version 2; T2D = type 2 diabetes; VAS = visual analogue scale

Primary 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 clinical question of interest:

What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 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 LY3502970 that reflects the real-life behavior of the target population.

Efficacy estimand

The clinical question of interest:

What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 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 LY3502970 under the ideal condition that all participants would adhere to the randomly assigned study intervention without being confounded by the initiation of prohibited weight management treatments.

Overall Design

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

Study details include:

- Screening period: 3 weeks
- Treatment period
    - dose escalation period: 20 weeks
    - maintenance dose period (no prediabetes): 52 weeks
    - additional 2-year treatment period (prediabetes): 156 weeks total (including initial 52-week treatment period and 104-week additional prediabetes treatment period)
- Post-treatment follow-up period: 2 weeks

Brief Summary:

The study will investigate the safety and efficacy of treatment with daily oral doses of LY3502970 (6 mg, 12 mg, and 36 mg) compared with placebo, in participants with obesity (BMI 30 kg/m^2 or greater) or overweight (BMI 27 kg/m^2 or greater) with the presence of 1 weight-related comorbidity.

The study duration for participants without prediabetes at baseline will be approximately 77 weeks including screening and follow-up. For participants with prediabetes at baseline, the study duration will be approximately 181 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
  - ≥30.0 kg/m^2, or
  - ≥27.0 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 LY3502970 (702 participants), 12-mg LY3502970 (702 participants), 36-mg LY3502970 (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.

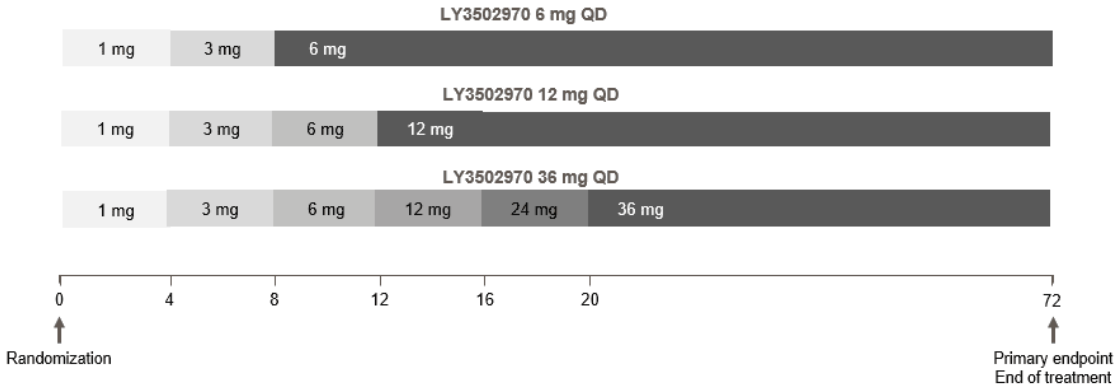
Intervention Groups and Duration:

This table lists the interventions used in this clinical study

Intervention Name	LY3502970	Placebo
Dosage Level(s)	1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg capsules	Capsule of LY3502970-placebo to match

Route of Administration	Oral QD	Oral QD
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized

All participants will initiate treatment with a 1 mg QD dose of LY3502970 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: 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 LY3502970 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 baseline will be approximately 77 weeks including screening and follow-up. For participants with prediabetes at baseline, the study duration will be approximately 181 weeks.

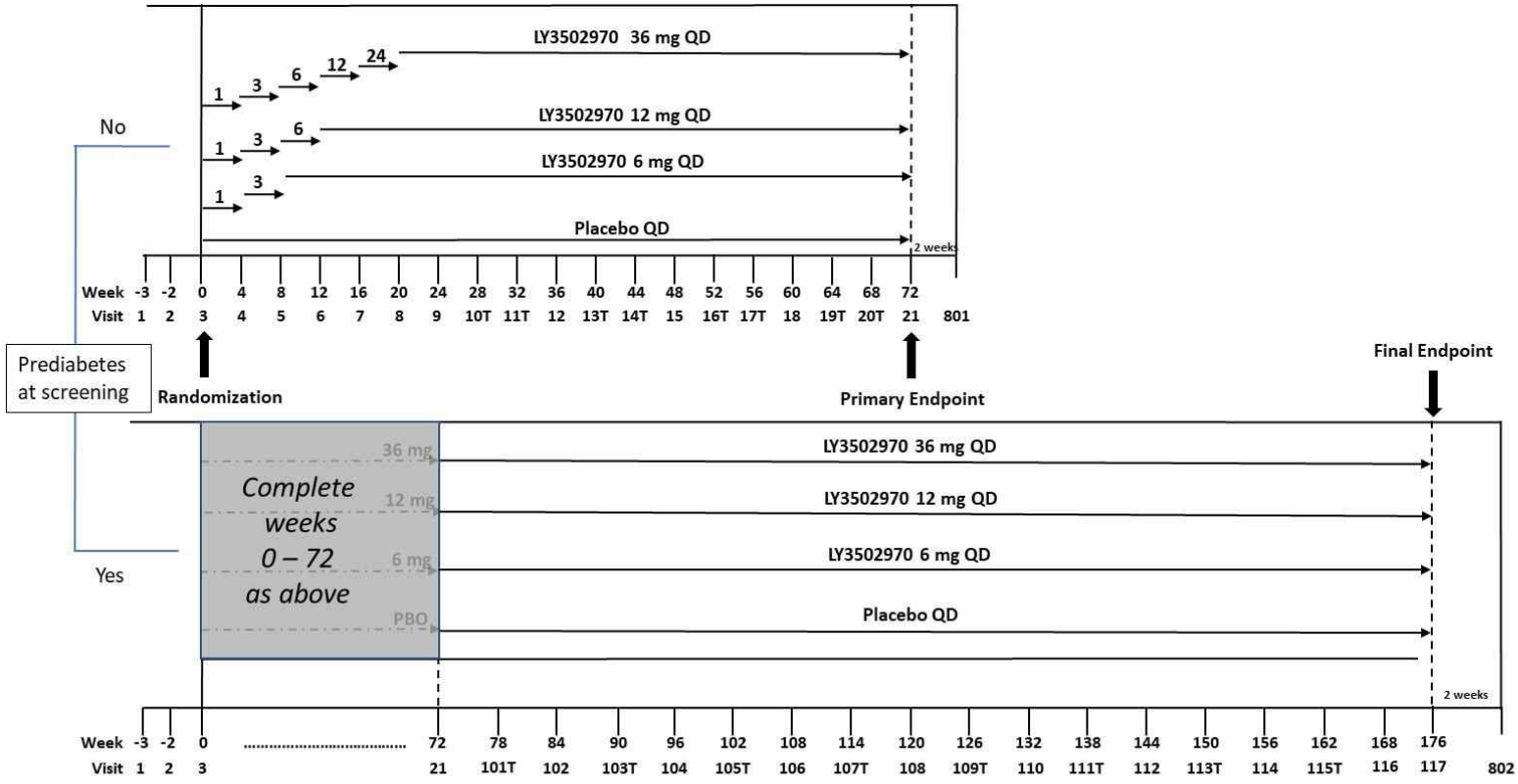
Ethical Considerations of Benefit/Risk:

The safety and efficacy profile seen to date for LY3502970 supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 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 LY3502970 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 LY3502970 in adult participants with obesity or overweight.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: PBO = placebo, 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 10.12 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 and samples for laboratory testing should not be collected and the participant should be asked to return to the site in a fasting state as soon as possible; all other procedures scheduled at the visit may be performed.
- All procedures, especially vital signs, laboratory procedures and ECGs, should be completed prior to the participant taking study intervention on the days of office visits.

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.

Post-treatment 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 2 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 Post-treatment Follow-Up

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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 Screen-ing		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 Screen-ing**		**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 Section

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
																								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 the visit window to have the fasting

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
																								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. ECG measurements

ATTAIN-1 (Study GZGP) Table 1	Period I Screening		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
																								should be obtained per the instructions in Section 8.2.3.
Physical examination	X																				X	X		
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)																								

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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 diary (electronic device)			X																					Includes daily study intervention dose and other data as applicable see Section 6.1. and 8.3.3.4
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	X		Visit 21 diary return applies only to those participants without prediabetes at randomization. All participants with prediabetes at randomization continuing to Visit 101 will retain the electronic diary.

ATTAIN-1 (Study GZGP) Table 1	**Period I Screen-ing**		**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
Patient-reported outcomes (electronic) PROs should be administered as early as possible in the visit but after the assessment of AEs																								
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		
PROMIS Short Form Sleep Disturbance 8b			X						X												X	X		

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
PHQ-9	X		X			X			X			X			X			X			X	X	X	PHQ-9 is self-administered and should be completed after assessment of AEs. This should be conducted with the safety assessments.
Clinician-administered assessments (paper)																								
C-SSRS screening/ baseline	X																							The C-SSRS should be administered after assessment of adverse events. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
																								only. The Intensity of Ideation and Lethality of Behavior sections are removed.
C-SSRS since last assessed			X	X	X	X	X	X	X			X			X			X			X	X	X	The C-SSRS should be administered after assessment of AEs. For this study, the C-SSRS is adapted for the assessment of the ideation and behavior categories only. The Intensity of Ideation and Lethality of Behavior sections are removed.
Participant education																								

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
Lifestyle program instructions			X	X	X	X			X			X			X			X			X	X		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.
Laboratory tests, sample collections and imaging																								
Hematology	X					X			X												X	X	X	
HbA1c	X					X			X			X			X			X			X	X	X	

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
Clinical chemistry	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.
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 Screen-ing		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 Screen-ing		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.
FSH	X																							Perform as needed to confirm postmenopausal status. Definition in Section 10.4.

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		Period II-Treatment Period																				Post-Tx Follow-up	Comments
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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
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	
Apo B			X						X												X	X	X	
Cystatin-C	X		X			X			X			X			X			X			X	X	X	

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		Period II-Treatment Period																				Post-Tx Follow-up	Comments
			Dose Escalation Period						Maintenance Dose Period															
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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
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		PK samples will be collected from participants at these visits: predose (Weeks 8, 24, 48), or post-dose 4 to 12 hr (Week 16) and post-dose 1 to 4 hr (Week 36) and ED, patients may be required to come to site for PK specific

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
																								visits for post-dose samples.
eGFR	X		X			X			X			X			X			X			X	X	X	Calculated using CKD-EPI method See Section 10.2.
UACR			X						X												X	X	X	
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

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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
																								or ED1. See Section 10.10
Stored samples																								
Genetics sample			X																					Sample can be obtained at or after the specified visit.
Exploratory biomarker samples			X			X			X						X						X	X	X	
Randomization and Dosing																								
Register visit with IWRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
Randomization via IWRS			X																					

ATTAIN-1 (Study GZGP) Table 1	Period I Screen-ing		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 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.
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		
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; Apo B= apolipoprotein; 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; PK = pharmacokinetic; 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; wks = weeks; WOCBP = women of child bearing potential

1.3.2. Prediabetes Additional Treatment Period (Visits 101 to 117), Early Discontinuation, and Post-treatment 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		2 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.

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		2 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
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 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

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		2 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
																				has been sitting for at least 5 min. See Section 10.7
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. ECG measurements should be obtained 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 the PI or qualified personnel as indicated per local regulations based on

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		2 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 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	X	
Patient-reported outcomes (electronic) PROs should be administered as early as possible in the visit but after the assessment of AEs																				
SF-36v2 acute form								X									X	X		
IWQOL-Lite CT								X									X	X		
PGIS -Physical Function Weight								X									X	X		
PGIC -Physical Function Weight								X									X	X		
EQ-5D-5L								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		2 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
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.
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 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.

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		2 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 education																				
Lifestyle program instructions		X		X		X		X		X		X		X		X	X	X		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 must be obtained in the fasting state. If the participant is not fasting, the participant should

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		2 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
																				be called in for a new visit within the visit window to have the fasting labs taken.
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) 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

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		2 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 lipid panels taken.
Urine pregnancy (local)		X		X		X		X		X		X		X			X	X		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.
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	

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		2 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
Cystatin-C								X									X	X	X	
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; Apo B= apolipoprotein B; 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; 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, 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, LY3502970 is an oral, non-peptide GLP-1 receptor agonist.

LY3502970 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 LY3502970 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 LY3502970 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/m^2 or greater), or overweight (BMI 27 kg/m^2 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 LY3502970 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 LY3502970 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 patients (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 LY3502970, 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 LY3502970

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

Phase 1

The clinical pharmacology, PK, and PD of LY3502970 were initially studied in 2 completed Phase 1 studies, J2A-MC-GZGA (GZGA) in healthy volunteers and J2A-MC-GZGC (GZGC) in participants with T2D. Results from these studies demonstrated a PK profile appropriate for once daily oral dosing that can be administered without limitations pertaining to food or water intake or time of day. The PK of LY3502970 plasma concentration increase was approximately proportional to the increase of dose across the 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 LY3502970 9 mg QD to 45 mg QD in people with T2D.

Phase 2

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

In Study GZGE, LY3502970 treatment for 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 LY3502970 treatment at the primary 26-week endpoint. The overall safety profile of LY3502970 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 LY3502970.

2.3. Benefit/Risk Assessment

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

2.3.1. Risk Assessment

Study intervention

The potential risks associated with LY3502970 are similar to those of marketed GLP-1 receptor agonists. The most commonly reported TEAEs observed in the LY3502970 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 LY3502970.

Management of risks

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

2.3.2. Benefit Assessment

The known pharmacology of GLP-1 receptor agonism and Phase 2 studies of LY3502970 support an expectation of such benefits as body weight reduction with LY3502970. Improvements in some cardiometabolic risk factors, including blood pressure and serum lipids, may also be expected.

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

2.3.3. Overall Benefit Risk Conclusion

The safety and efficacy profile seen to date for LY3502970 supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 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 LY3502970 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 LY3502970 in adult participants with obesity or overweight.

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary Objective	
To demonstrate that LY3502970 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 LY3502970 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: o ≥5% o ≥10% o ≥15% o ≥20% • Mean change in waist circumference (cm)
To demonstrate that LY3502970 (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 o non-HDL cholesterol o 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 baseline that LY3502970 (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo at 176 weeks: • Body weight • Delayed progression to T2D	From baseline to Week 176 • Mean percent change in body weight • Time to onset of T2D

Objectives	Endpoints
Additional Secondary Objectives	
To demonstrate that LY3502970 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/m^2) • Mean change in HbA1c (%) • Mean change in fasting glucose (mg/dL) • Mean change in fasting insulin (pmol/L)
To demonstrate that LY3502970 (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 o total cholesterol o LDL cholesterol o HDL cholesterol From baseline to Week 72 • Mean change in SF-36v2 acute form domain scores • Mean change in EQ-5D-5L health state utilities and VAS • Mean change in IWQOL-Lite-CT Physical Function, Physical, and Psychosocial composite scores, and total score • Change in PGIS and PGIC limitations on physical function due to weight
To describe the safety of LY3502970 as compared to placebo	Summary of safety data, including number and incidence of • Treatment-emergent adverse events

Objectives	Endpoints
Additional Secondary Objectives at 72 weeks in participants with prediabetes at randomization	
To demonstrate LY3502970 (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 baseline that LY3502970 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 ≥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 patients achieving normoglycemia
Tertiary Objectives	
To characterize the population PK of LY3502970 and explore the relationships between LY3502970 concentration and efficacy, safety, and tolerability measures	• Population PK and PD parameters

Abbreviations: BMI = body mass index; 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

Primary 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 primary clinical question of interest is:

What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 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 LY3502970 and placebo.
- ***Rationale for the estimand:*** This estimand aims to evaluate the efficacy of LY3502970 that reflects the real-life behavior of the target population.

Efficacy estimand

The clinical question of interest:

What is the treatment difference in the percent change in body weight from baseline at 72 weeks between LY3502970 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.

- ***Population-level summary and treatment effect of interest:*** Difference in mean percent changes in body weight from baseline at Week 72 between LY3502970 and placebo.
- ***Rationale for the estimand:*** This estimand aims to evaluate the efficacy of LY3502970 under the ideal condition that all participants would adhere to the randomly assigned study intervention without being confounded by the initiation of prohibited weight management treatments.

4. Study Design

4.1. Overall Design

ATTAIN-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 LY3502970 (6 mg, 12 mg, or 36 mg), compared with placebo in participants without T2D with either obesity (BMI 30 kg/m^2 or greater), or overweight (BMI 27 kg/m^2 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 LY3502970 (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.

The study includes a

- Screening period: 3 weeks
- Treatment period
  - dose escalation period: 20 weeks
  - maintenance dose period (no prediabetes): 52 weeks
  - additional 2-year treatment period (prediabetes): 156 weeks total (including initial 52-week treatment period and 104-week additional prediabetes treatment period)
- Post-treatment follow-up period: 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 ≥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.
HbA1c ≥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

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

Choice of primary endpoint

ATTAIN-1 (Study GZGP) is designed to determine the comparative benefits and risks of LY3502970 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 LY3502970 compared with placebo on body weight and is consistent with regulatory guidelines (FDA 2007; EMA 2016).

The effects of study intervention cessation will be assessed at the 2-week post-treatment follow-up period (Week 74).

Another objective of the study is to evaluate the effect of LY3502970 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 patients 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 LY3502970, 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 LY3502970 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 LY3502970 treatment.

For participants with prediabetes at randomization, the effects of study intervention cessation will be assessed in a 2-week post-treatment follow-up period (Week 178).

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 LY3502970 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), LY3502970 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, LY3502970 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 patients 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/m^2, or
   - ≥27.0 kg/m^2 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 ≥6.5% (≥48 mmol/mol)
   - FSG ≥126 mg/dL (≥7.0 mmol/L)
   - 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 m^2, calculated by Chronic Kidney Disease-Epidemiology, 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 ≥3.0x the ULN for the reference range
    - ALP level ≥1.5x the ULN for the reference range
    - TBL level ≥1.5x 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 <3.0x 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 m^2, or
    - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2.
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 and who are anticipated to remain on this dose throughout the trial period 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 #36 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).

32. Have difficulty swallowing capsules.

Prior/concomitant therapy

33. 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).
34. Are receiving chronic (>14 days) systemic glucocorticoid therapy (excluding topical, intra-ocular, intranasal, or inhaled preparations) or have received such therapy within 90 days prior to Visit 1, or between Visit 1 and Visit 3.
35. 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).
36. Have initiated treatment with or changed dose of medications that may cause significant weight gain (See Section 10.8.1.2 for more details) within 12 months prior to Visit 1.
37. Have started implantable or injectable contraceptives within 18 months prior to Visit 1.

    Note: Intrauterine devices are acceptable.
38. 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.
39. Have known allergies or intolerance to GLP-1 receptor agonist.

Prior/concurrent clinical study experience

40. Have previously completed or withdrawn from this study or any other study investigating LY3502970 after receiving at least 1 dose of study intervention.
41. 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.
42. Have participated in a clinical study and received treatment, whether active or placebo within 90 days prior to Visit 1.

Other exclusions

43. 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.

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

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

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

5.3.3. Healthy Physical Activity

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

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

Adherence to the 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.

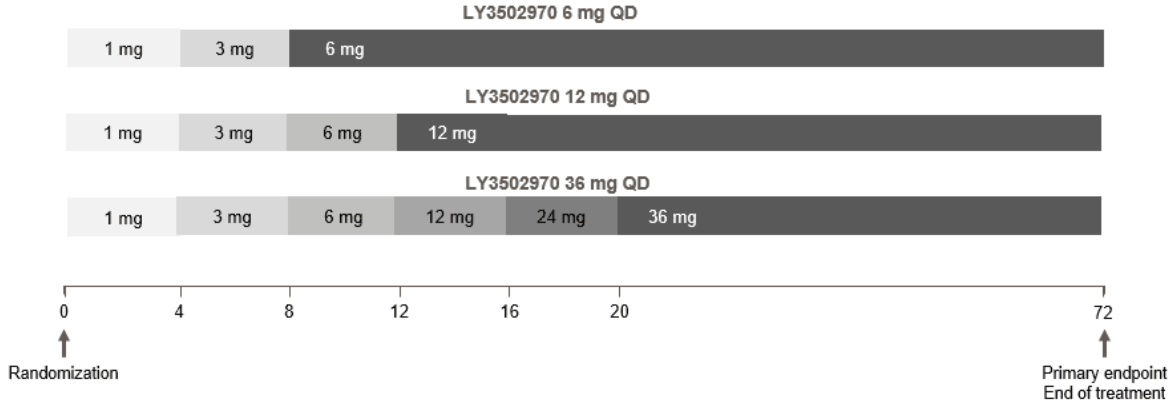
6.1. Study Intervention(s) Administered

This table lists the interventions used in this clinical study.

Intervention Name	LY3502970	Placebo
Dosage Level(s)	1 mg, 3 mg, 6 mg, 12 mg, 24 mg, and 36 mg capsules	Capsule of LY3502970 placebo to match
Route of Administration	Oral QD	Oral QD
Authorized as Defined by EU Clinical Trial Regulation	Not authorized in EU	Not authorized

Abbreviation: QD = once daily

All participants will initiate treatment with a 1 mg QD dose of LY3502970 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: 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 LY3502970 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 to 4 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 LY3502970 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.

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. 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. The data related to temporary interruption of study treatment should be documented in source documents and recorded in the CRF.

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.

However, 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.

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. Only 1 re-escalation attempt will be permitted during the entire course of the study.

If the re-escalation attempt is not tolerated, then depending on which dose level is achieved, the participant should undergo a final dose de-escalation to the next lower dose level or discontinue study intervention.

The below table provides guidance for de-escalating and re-escalating the dose:

If a participant is currently taking…	**Then the dose will be de-escalated for at least 8 weeks to…**	**If subsequent re-escalation attempt was not tolerated, then the dose will be de-escalated for the remainder of the study to…**
1 mg/placebo	Discontinue the study intervention and continue in the study	N/A
3 mg/placebo	1 mg/placebo	Discontinue the study intervention and continue in the study
6 mg/placebo	3 mg/placebo	Discontinue the study intervention and continue in the study
12 mg/placebo	6 mg/placebo	6 mg/placebo
24 mg/placebo	12 mg/placebo	12 mg/placebo
36 mg/placebo	24 mg/placebo	24 mg/placebo

Abbreviations: N/A = not applicable

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.

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.

For temporary study intervention interruption, refer to Section 7.1.2

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

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

6.8. Treatment of Overdose

As any dose of LY3502970 greater than 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 to 4 hours. Examples (not exhaustive) relevant to the study population include:

- simvastatin, levothyroxine, ferrous sulfate, bisphosphonates
- 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). Initiation of metformin or SGLT-2i for the treatment of diabetes is permitted but should not be initiated for the treatment of other conditions during the study, for example, metformin for polycystic ovary syndrome or diabetes prevention; SGLT-2i for heart failure.

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.

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 an active or untreated malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ [for example, Gleason 6 or lower] prostate cancer)
- 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 $\leq$18.5 kg/m^2 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

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

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

Elevation	Exception
ALT or AST >8x ULN	
ALT or AST >5x ULN for more than 2 weeks	
ALT or AST >3x ULN and either TBL >2x ULN or INR >1.5	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for study intervention interruption decisions rather than TBL >2x ULN.
ALT or AST >3x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
ALP >3x ULN, when the source of increased ALP is the liver	
ALP >2.5x ULN and TBL >2x ULN	For participants with Gilbert's syndrome: If baseline direct bilirubin is >0.5 mg/dL, then doubling of direct bilirubin should be used for study intervention interruption decisions rather than TBL >2x ULN.

ALP >2.5x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)	
Source: FDA Guidance for Industry: Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009 and other consensus guidelines, with minor modifications	

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

In study participants with abnormal baseline liver tests (ALT, AST, ALP ≥1.5x ULN), the study intervention should be **interrupted** and close hepatic monitoring initiated (see Section 8.2.7) if 1 or more of these conditions occur:

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

Resuming study intervention after elevated liver tests

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

7.1.2. Temporary Study Intervention Interruption

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

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

If study intervention interruption is…	**then…**
2 consecutive doses or less	participant resumes the study intervention at the previously administered dose level.
3-6 consecutive doses	participant resumes the study intervention at the previously administered dose level unless doing so results in intolerable GI symptoms. See Section 6.6.1 for management of GI symptoms.
7 or more consecutive doses	participant repeats a dose escalation per Section 6.1. from 3 mg/placebo to previously attained dose level unless the interruption occurs within the first 7 weeks, in which case the previously 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 post-treatment follow-up, as shown in the SoA. If the participant has not already discontinued the study intervention, the participant will be permanently discontinued from the study intervention at the time of the decision to discontinue the study.

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

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

7.3. Lost to Follow-up

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

8. Study Assessments and Procedures

Study procedures and their timing are summarized in the SoA.

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

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

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

8.1. Efficacy Assessments

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).

8.2. 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

Single 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. 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

Close hepatic monitoring

Initiating laboratory and clinical monitoring for abnormal liver laboratory test results

Laboratory tests (Section 10.2), including ALT, AST, ALP, TBL, direct bilirubin, gamma-glutamyl transferase, and creatine kinase, should be repeated within 48 to 72 hours to confirm the abnormality and to determine if it is increasing or decreasing, if 1 or more of these conditions occur:

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

What to do if the abnormal condition persists or worsens

If the abnormality persists or worsens, clinical and laboratory monitoring, and 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

- symptoms
- recent illnesses, for example, heart failure, systemic infection, hypotension, or seizures
- recent travel
- history of concomitant medications, including over the counter, herbal and dietary supplements, and
- history of alcohol drinking and other substance abuse.

Frequency of monitoring

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

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

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

Comprehensive hepatic evaluation

When to perform a comprehensive evaluation

A comprehensive evaluation should be performed to search for possible causes of liver injury if 1 or more of these conditions occur:

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

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

What a comprehensive evaluation of liver function should include

At a minimum, this evaluation should include

- physical examination and a thorough medical history, as outlined above
- tests for

- prothrombin time, INR
- viral hepatitis A, B, C, or E, and
- autoimmune hepatitis, and
- an abdominal imaging study, for example, ultrasound or CT scan.

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

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

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

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

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

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

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

8.2.8. 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

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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
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)	Pregnancy paper form	Pregnancy paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hr of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A

Event	Collection Start	Collection Stop	Timing for Reporting to Sponsor or Designee	Mechanism for Reporting	Back-up Method of Reporting
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

LY3502970 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 LY3502970 including nausea, diarrhea, and vomiting. This is consistent with other GLP-1 RA (Aroda and Ratner 2011). The events may lead to dehydration, which could cause a deterioration in renal function, including acute renal failure.

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

8.3.3.7. Pancreatitis

Diagnosis of acute pancreatitis

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

- abdominal pain, characteristic of acute pancreatitis, that is, epigastric pain radiating to the back, often associated with nausea and vomiting
- serum amylase (total, pancreatic, or both) and/or lipase ≥3x ULN
- 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 ≥3x ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

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 LY3502970 to affect thyroid C-cell function, which may indicate development of C-cell hyperplasia and neoplasms.

Calcitonin measurements

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

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

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

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined 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 ≥50% increase from the screening value.* These participants will be requested to repeat the measurement within 1 month. If this repeat value is increasing (≥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 ≥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 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a *serum calcitonin value ≥35 ng/L AND ≥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 LY3502970 will only be determined from blood samples obtained from participants receiving LY3502970 treatment. Blood samples for PK assessment will be collected predose at Week 8, 24, and 48. At Week 16, blood samples for PK assessment will be collected within the sampling window of 4 to 12 hours post-dose, and at Week 36 within the sampling window of 1 to 4 hours post-dose per the SoA or at ED (Section 1.3).

The date and time of the most recent LY3502970 dose 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 LY3502970 will be assayed using a validated liquid chromatography mass spectrometry method.

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

8.4.1. Bioanalysis

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

8.5. Pharmacodynamics

Efficacy measures will be used as indicators of PD response.

8.6. Genetics

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

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

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

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

8.7. Biomarkers

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

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

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

Samples may be used for

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

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

Sample retention is described in Section 10.1.12.

8.8. Immunogenicity Assessments

Immunogenicity parameters are not evaluated in this study.

8.9. Medical Resource Utilization and Health Economics

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

9. Statistical Considerations

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

Unblinding details are specified in the blinding and unblinding plan.

9.1. Statistical Hypotheses

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

- $H_{1,0}$: No difference in 36 mg LY3502970 compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- $H_{2,0}$: No difference in 12 mg LY3502970 compared rior 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 LY3502970 is superior 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H_{170}: No difference in 12 mg LY3502970 compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H_{180}: No difference in 6 mg LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 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 LY3502970 pooled compared to placebo with respect to mean percent change from baseline in body weight at Week 176 in participants with prediabetes at baseline.
- $H_{23,0}$: No difference in 36 mg, 12 mg, and 6 mg LY3502970 pooled compared to placebo with respect to time to onset of T2D at Week 176 in participants with prediabetes at baseline.

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.
Full participants	All randomized participants who meet the eligibility criteria. Participants will be analyzed according to the treatment group to which they were randomly assigned.
Full participants with prediabetes	All randomized participants who meet the eligibility criteria and who have prediabetes at baseline. 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 baseline. 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 after baseline and up to the last visit within the treatment period, regardless of study intervention discontinuation or initiation of prohibited weight management treatments.
Safety data points set	All data points obtained during the intervention period and the follow-up period defined as 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.

Data Points Sets	Description
Efficacy estimand data points set	All data points obtained during the treatment period defined as after baseline and up to the earliest date 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 CSR. Additional exploratory analyses of data will be conducted, as deemed appropriate.

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

General descriptions of analyses

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

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

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

For measures evaluated at multiple 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 with covariates 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 LY3502970 doses with placebo irrespective of adherence to study intervention. Thus, safety analyses will be conducted using the safety participants during the treatment period or during the treatment period plus the post-treatment safety follow-up period.

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

Handling of missing, unused, and spurious data is addressed prospectively in the overall statistical methods described in the protocol and in the SAP, where appropriate. Adjustments to the planned analyses will be described in the final CSR.

9.3.2. Treatment Group Comparability

9.3.2.1. Participant Disposition

A detailed description of participant disposition will be provided.

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

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

All participants who discontinue the study will be identified and the extent of their participation in the study will be reported. If known, a reason for their discontinuation will be given. The primary reasons for discontinuation will be listed and will be summarized by treatment groups. The percentage of participants discontinuing from each LY treatment group will be compared to placebo using the Fisher's exact test. Kaplan-Meier analyses of time from baseline 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). No multiplicity adjustment is planned between estimands.

The primary objective aligned to the “treatment regimen” estimand will be evaluated using the full 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 full participants and the efficacy estimand data points set (Section 9.2).

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

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

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

9.3.4. Secondary Endpoints and Estimands Analyses

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

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

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

9.3.5. Tertiary Endpoints and Estimands Analyses

Details for tertiary analyses will be provided in the SAP.

9.3.6. Pharmacokinetic/Pharmacodynamic Analyses

LY3502970 concentration data will be analyzed using a population PK approach using nonlinear mixed-effects modeling techniques implemented on the NONMEM software. The relationships between LY3502970 doses and/or concentration and selected efficacy, tolerability, and safety

endpoints may be characterized. Additionally, the impact of intrinsic and extrinsic participant factors such as age, weight, sex, and renal function on LY3502970 PK and/or PD parameters may be examined as needed. Further details will be provided in the SAP.

9.3.7. Safety Analyses

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

AEs will be coded from the actual term using the Medical Dictionary for Regulatory Activities and reported by preferred terms within system organ class. Selected notable AEs of interest may be reported using high-level terms or Standardized Medical Dictionary for Regulatory Activities Queries. Summary statistics will be provided for incidence of TEAEs, SAEs, study discontinuation due to AEs, study intervention discontinuation due to AEs, deaths, and other CV endpoints. Counts and percentages of participants experiencing AEs will be reported for each 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 LY3502970 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 *(≤ 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 LY3502970 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 LY3502970 to placebo with regards to mean percent change in body weight from baseline to Week 72. The sample size determination assumes that evaluation of superiority 6 mg, 12 mg, and 36 mg LY3502970 to placebo will be conducted in parallel, each at a 2-sided significance level of 0.016 using a 2-sample t-test for the "treatment regimen" estimand. Additionally, a difference of at least 5% mean body weight reduction from baseline at 72 weeks for 6 mg, 12 mg, and 36 mg LY3502970 compared with placebo, a common SD of 10%, and a dropout rate of 30% for placebo and 20% for the LY3502970 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 LY3502970 or after LY3502970 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, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	Morphology to be performed if abnormalities are detected.
Clinical chemistry	Assayed by Lilly-designated laboratory

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

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

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

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

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

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the 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 • are infertile due to surgical sterilization, or • are postmenopausal. Examples of surgical sterilization include total hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note, or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy[a], who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with 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, hormones, gonadotropin-releasing hormone, anti-estrogens, selective estrogen receptor modulators, or chemotherapy that could induce transient amenorrhea.

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	• 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)	• female sterilization • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • implanted contraceptives • injectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • total abstinence • vasectomy (if only sexual partner) • fallopian tube implants (if confirmed by hysterosalpingogram) • combined contraceptive vaginal ring, or • intrauterine devices

Effective contraception	• male or female condoms with spermicide
	• diaphragms with spermicide or cervical sponges
	• barrier method with use of a spermicide
	  ○ condom with spermicide
	  ○ diaphragm with spermicide, or
	  ○ female condom with spermicide

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

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 LY3502970 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 LY3502970, 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 LY3502970 or study interventions related to this class to understand diabetes, obesity, related traits or complications or related conditions.
- The results of genetic analyses may be reported in the 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 LY3502970 or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases continues but no longer than the sample retention limits described in Section 10.1.12, or other period as per local requirements

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

Hepatic evaluation testing

See Section 8.2.7 for guidance on appropriate test selection.

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

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

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

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

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

Tests assayed ONLY by investigator-designated local laboratory	
Acetaminophen	**Cytomegalovirus (CMV) testing:**
Acetaminophen protein adducts	CMV antibody

Alkaline phosphatase isoenzymes	CMV DNA [b]
Ceruloplasmin	**Herpes simplex virus (HSV) testing:**
Copper	HSV (Type 1 and 2) antibody
Ethyl alcohol (EtOH)	HSV (Type 1 and 2) DNA [b]
Phosphatidylethanol (PEth)	Liver kidney microsomal type 1 (LKM-1) antibody
Urine Chemistry	**Microbiology Culture:**
Ethyl glucuronide (EtG)	Blood
Epstein-Barr virus (EBV) testing:	Urine
EBV DNA [a]	
EBV antibody	

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

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

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

10.7. Appendix 7: 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 (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, allī®

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, 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
- sofobuvir/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

- coumestrol
- daidzein
- genistein
- prazosin
- sulfasalazine

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 to 4 hours. Examples include:

- simvastatin
- levothyroxine
- ferrous sulfate
- bisphosphonates
- other narrow therapeutic index substrates with potential pH-dependent solubility or stability
- tyrosine kinase inhibitors
    - erlotinib
    - dasatinib
    - nilotinib
    - acalabrutinib
    - bosutinib
    - gefitinib
    - lapatinib
    - pazopanib
- antiretrovirals
    - rilpivirine
    - atazanavir
    - nelfinavir
    - ledipasvir/sofosbuvir
    - fosamprenavir
    - delavirdine mesylate
    - emtricitabine+rilpivirine+tenofovir+ disoproxil fumarate (Complera®)
    - ledipasvir+sofosbuvir (Harvoni®)
    - 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 ≥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 ≥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 5µSv 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 135 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 LY3502970 (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 LY3502970 (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 LY3502970 (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

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

Exclusion criteria

46. 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.
47. Have a body weight, height, or width that prohibits the ability to obtain accurate measurements according to the DXA manufacturer's specification.
48. 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. Statistical Analyses

Unless otherwise specified, all analyses for the variables measured or derived from DXA will be conducted using full 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.

10.10.6. Sample Size

A sample size of approximately 156 randomly assigned participants (39 participants per arm) is planned for this appendix to assess the difference between LY3502970 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 LY3502970 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.

10.10.7. 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: Country-specific Requirements

10.11.1. 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 #42 90 days is changed to 1 year.	Resolution No. 251 (Brazil 1997). The National ERB Brazil recommends not having a participant enter a new clinical study if less than 1 year has elapsed since participation in another clinical study of an investigational drug or device unless there is a direct benefit to the research participant.
10.1.12. Sample Retention	Biological samples will be stored for up to 10 years.	Compliance with Brazilian regulation applicable to sample storage, resolution CNS 441 (Brazil 2011).
10.5. Appendix 5: Genetics	Biological samples obtained to evaluate genetic material (DNA/RNA).	Compliance with Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011).
Patient Access to Project Benefits	New section specific to Brazil.	Clarifies the sponsor responsibilities to comply with Resolution CNS 466 (Brazil 2012) and RDC 38 (Brazil 2013).
Section 11. References	Addition of Brazil-specific references	The references are specific to the Brazil-specific requirements.

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

Section 5.2. Exclusion Criteria

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

<u>Are currently enrolled in, discontinued, or completed within a period of 1 year, before inclusion, 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 30 days, as indicated by the protocol, must still be followed if a direct benefit to the research participant is identified.</u>

Section 10.1.12. Sample Retention

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

Section 10.5. Appendix 5: Genetics

In Brazil, the biological samples from this study used to evaluate genetic material (DNA/RNA) will follow the Brazilian laws and regulations (CNS 340/2004 and CNS 441/2011). The sample and any data generated from it can be linked back to the participant only by investigator site personnel. The duration allows the sponsor to respond to regulatory requests related to the study 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 LY3502970, identified through the study (CNS 466/2012 and RDC 38/2013).

10.12. Appendix 12: 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.

10.13. Appendix 13: 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 insulinotropic 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
SGLT-2	sodium-glucose cotransporter-2
SIB	Suicidal Ideation or Behavior
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TBL	Total bilirubin level
TEAE	Treatment-emergent adverse event: An untoward medical occurrence that emerges during a defined treatment period, having been absent pretreatment, or worsens relative to the pretreatment state, and does not necessarily have to have a causal relationship with this treatment.
ULN	Upper limit of normal
WHO	World Health Organization
WOCBP	Women of childbearing potential

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Approval	PPD 22-Feb-2023 13:09:44 GMT+0000

Approval	PPD 24-Feb-2023 03:59:35 GMT+0000

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Title Page

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**
Amendment c	*23-Oct-2023*
Amendment b	*11-May-2023*
Amendment a	*05-Apr-2023*
Original Protocol	*24-Feb-2023*

Amendment [d]

This amendment is considered to be substantial.

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

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/m^2 or greater), or overweight (BMI 27 kg/m^2 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 o ≥5% o ≥10% o ≥15% o ≥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 o non-HDL cholesterol o 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/m^2) • 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 o total cholesterol o LDL cholesterol o 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 ≥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/m^2 or greater) or overweight (BMI 27 kg/m^2 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
  - ≥30.0 kg/m^2, or
  - ≥27.0 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:

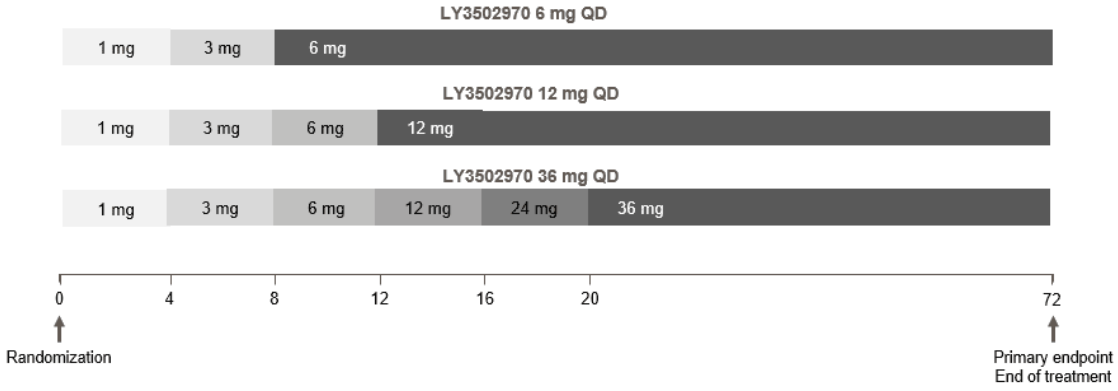
Approximately 3000 participants will be randomized in a 3:3:3:4 ratio to 6-mg orforglipron (702 participants), 12-mg orforglipron (702 participants), 36-mg orforglipron (702 participants), and placebo (936 participants). An upper limit of 70% enrollment of females will be used to ensure a sufficiently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

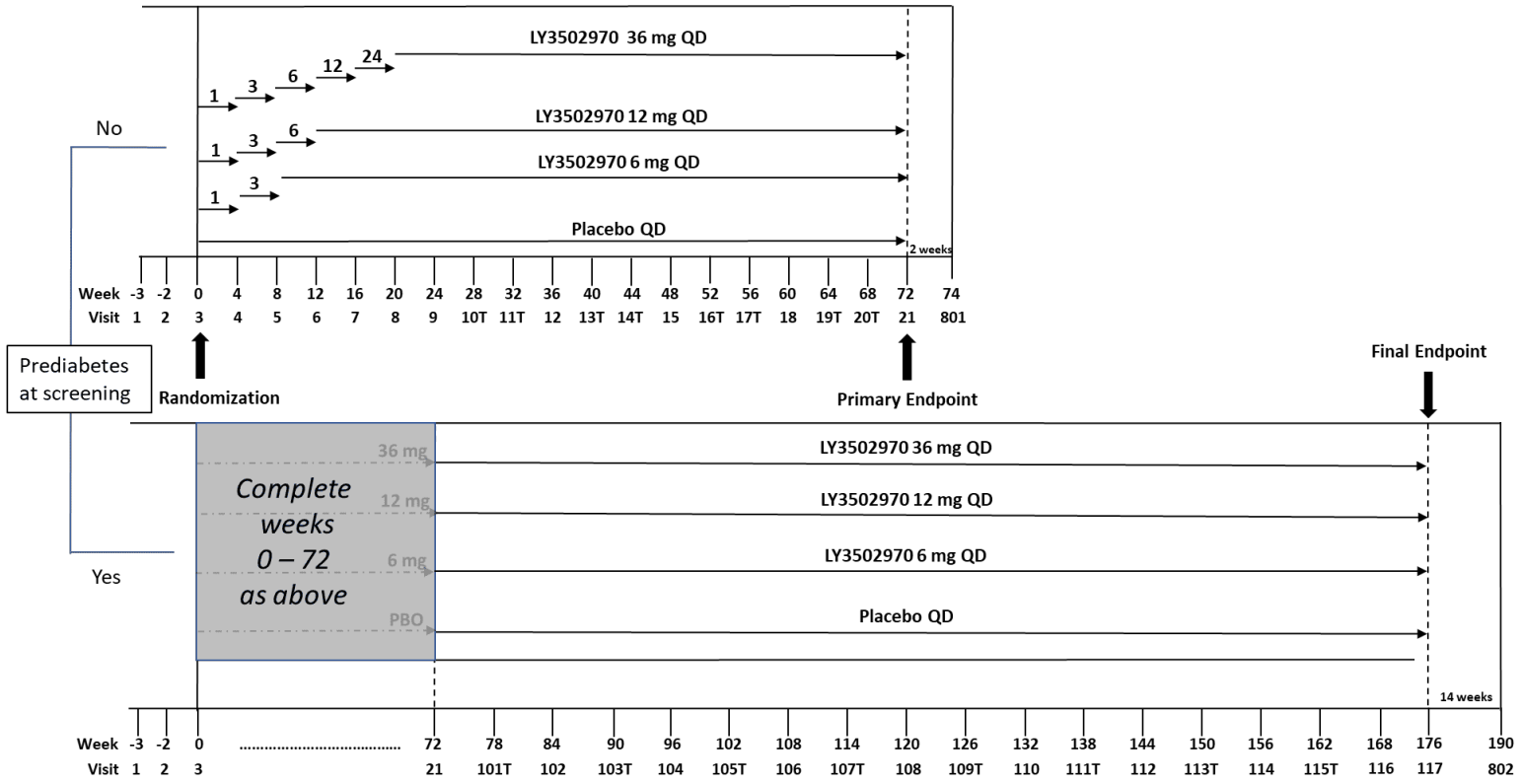
The safety and efficacy profile seen to date for orforglipron supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 receptor agonists, namely gastrointestinal tolerability issues and increased heart rate. 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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening**		**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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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 Screening		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/m^2 or greater), or overweight (BMI 27 kg/m^2 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 o ≥5% o ≥10% o ≥15% o ≥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 o non-HDL cholesterol o 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/m^2) • 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 o total cholesterol o LDL cholesterol o 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 ≥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/m^2 or greater), or overweight (BMI 27 kg/m^2 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 ≥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.

If a participant has…	then the participant…
HbA1c ≥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/m^2, or
   - ≥27.0 kg/m^2 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 ≥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 m^2, 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 ≥3.0x the ULN for the reference range
    - ALP level ≥1.5x the ULN for the reference range
    - TBL level ≥1.5x 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 <3.0x 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 m^2, or
    - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2.
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.

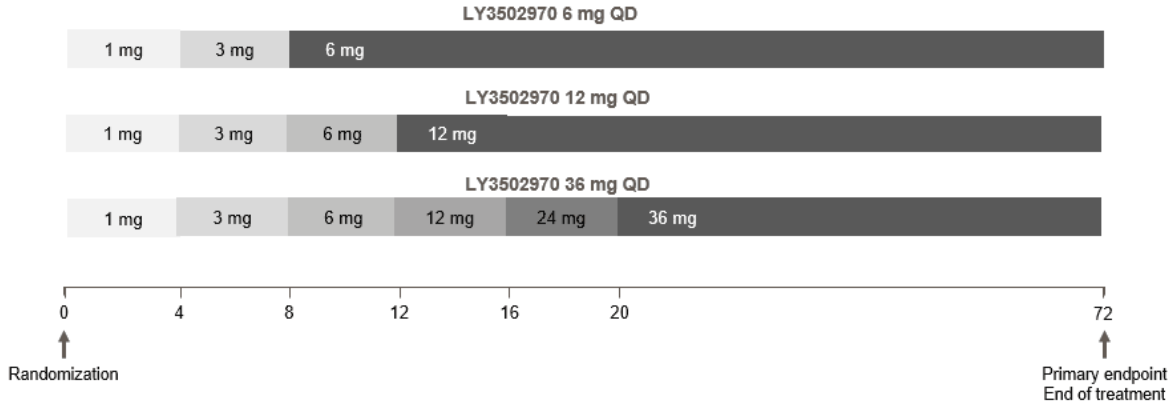
6.1. Study Intervention(s) Administered

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/m^2 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 ≥3x ULN	X		
ALP ≥2x ULN	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥5x ULN	X	X	
ALP ≥2.5x ULN	X	X	
ALT or AST ≥3x ULN with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥5x ULN for more than 2 weeks	X	X	X
ALT or AST ≥8x ULN	X	X	X
ALT or AST ≥3x ULN and TBL ≥2x ULN[b] or INR ≥1.5	X	X	X
ALP ≥3x ULN	X	X	X
ALP ≥2.5x ULN and TBL ≥2x 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 ≥2.5x 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 ≥1.5x 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 ≥2x baseline	X		
ALP ≥2x baseline	X		
TBL ≥2x ULN[b]	X		
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first)	X	X	
ALP ≥2.5x baseline	X	X	
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) with hepatic signs or symptoms[a]	X	X	X
ALT or AST ≥3x baseline or ≥250 U/L (whichever occurs first) for more than 2 weeks	X	X	X
ALT or AST ≥4x baseline or ≥400 U/L (whichever occurs first)	X	X	X
ALT or AST ≥2x baseline or ≥250 U/L (whichever occurs first) and TBL ≥2x ULN[b] or INR≥1.5	X	X	X
ALP ≥3x baseline	X	X	X
ALP ≥2.5x baseline and TBL ≥2x ULN[b]	X	X	X
ALP ≥2.5x 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 ≥3x ULN
- characteristic findings of acute pancreatitis on CT scan or MRI.

If acute pancreatitis is suspected, the investigator should

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

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

  and

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

Discontinuation for acute pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention. 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 ≥3x ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

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 ≥60 mL/min/1.73 m^2

A significant increase in calcitonin for participants with eGFR ≥60 mL/min/1.73 m^2 is defined 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 ≥50% increase from the screening value.* These participants will be requested to repeat the measurement within 1 month. If this repeat value is increasing (≥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 ≥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 m^2

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m^2 is defined as a *serum calcitonin value ≥35 ng/L AND ≥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 *(≤ 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. ***Note:*** The optimal collection time is from 1 to 2 hr after the start of event.	total tryptase

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

What information to record

Record the date and time when the samples are collected.

Allowed additional testing for participant management

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

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

10.3.1. Definition of AE

AE Definition

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

Events Meeting the AE Definition

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

Events <u>NOT</u> Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the 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) • [a]implanted contraceptives • [a]injectable 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, allī®

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 ≥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 ≥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.

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.

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 <u>underlined text</u>.

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.~~

<u>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.</u>

Section 10.1.12. Sample Retention

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

Section 10.5. Appendix 5: Genetics

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

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Title Page

Protocol Title: A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once- Daily Oral LY3502970 Compared with Placebo in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Protocol Number: J2A-MC-GZGP

Compound Number: LY3502970 (orforglipron)

Short Title: GZGP SAP

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

Registry	ID
IND:	156143
EU trial number	2022-502839-19-00

Document ID: VV-CLIN-117409

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Version History

This statistical analysis plan (SAP) for Study J2A-MC-GZGP (GZGP) is based on Protocol GZGP amendment (c), dated 23 October 2023.

SAP Version History Summary

SAP Version	Approval Date	Change	Rationale
1	See date on Page 1	Not Applicable	Original version

1. Introduction

This SAP is intended to describe the analyses of primary and secondary objectives, as well as safety assessments for Study GZGP. Sensitivity and supplementary analyses intended to support the primary and key secondary objectives are also included. Additional exploratory analyses, if needed, may be included in a separate document.

Pharmacokinetic/pharmacodynamic (PK/PD) analyses will be documented in a separate document.

Changes to the protocol-planned analyses are described in Section 4.9.

1.1. 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: o ≥5% o ≥10% o ≥15%, and o ≥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: • systolic blood pressure, and • lipid parameters.	From baseline to Week 72 • mean change in systolic blood pressure (mm Hg) • mean percent change in fasting o non-HDL cholesterol, and o 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 baseline that orforglipron (6 mg, 12 mg, and 36 mg QD pooled doses) is superior to placebo at 176 weeks:	From baseline to Week 176
• body weight, and	• mean percent change in body weight, and
• delayed progression to T2D.	• time to onset of T2D.

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 body mass index (kg/m^2) • 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:
• diastolic blood pressure
• lipid parameters, and
• patient-reported outcomes
	From baseline to Week 72
	• mean change in diastolic blood pressure (mm Hg)
	• mean percent change from baseline in fasting
	  ○ total cholesterol
	  ○ LDL cholesterol, and
	  ○ 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, and
	• change in PGI-S and PGI-C 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.
Additional Secondary objectives at 176 weeks in participants with prediabetes at randomization	
To demonstrate in participants with prediabetes at baseline 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 ≥5% body weight reduction • mean percent change in body weight from baseline • mean change in HbA1c (%) • mean change in fasting glucose (mg/dL), and • percentage of patients achieving normoglycemia
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
Exploratory Objectives	
To determine the effects of orforglipron 6 mg, 12 mg, 36 mg QD, and pooled orforglipron doses (6, 12, and 36 mg) on appetite sensations and desire for specific foods • appetite VAS.	From baseline to Week 24 and 72 • mean item appetite VAS scores, and • mean overall appetite VAS score. From baseline and Week 72 to Week 74 in participants without prediabetes at randomization • mean item appetite VAS scores, and • mean overall appetite VAS score.

	From baseline to Week 176 in participants with prediabetes at randomization • mean item appetite VAS scores, and • mean overall appetite VAS score.
To assess the effects of orforglipron 6 mg, 12 mg, 36 mg QD, and pooled orforglipron doses (6, 12, and 36 mg) on the psychological impact of living in an environment with an abundance of palatable foods • PFS.	From baseline to Week 24 and 72 • mean domain PFS scores, and • mean overall PFS score. From baseline and Week 72 to Week 74 in participants without prediabetes at randomization • mean domain PFS scores, and • mean overall PFS score. From baseline to Week 176 in participants with prediabetes at randomization • mean domain PFS scores, and • mean overall PFS score.

Abbreviations: HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL = low-density lipoprotein; PD = pharmacodynamics; PFS = Power of Food Scale; PGI-C = Patient Global Impression-Change; PGI-S = Patient Global Impression-Severity; PK = pharmacokinetics; QD = once daily; SF-36v2 Acute Form = Short Form 36 Health Survey Acute, version 2; T2D = type 2 diabetes; VAS = visual analog scale.

Estimands

There will be 2 estimands for the primary objectives planned in Study GZGP. These estimands address intercurrent events (ICEs) using either the treatment policy strategy or the hypothetical strategy (ICH 2021), respectively.

Estimands for weight-related, blood pressure, lipid, and patient-reported outcome parameters

The below estimands will be applied to weight-related, blood pressure, lipid, and patient-reported outcome (PRO) parameters, using percent change in body weight at Week 72 visit as an example. For other weight-related, blood pressure, lipid, and PRO parameters, replace percent change in body weight by the endpoints to be analyzed.

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 versus 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?

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.

The treatment regimen estimand is described by the following attributes

- ***Population:*** Individuals who meet the eligibility criteria.
- ***Endpoint:*** Percent change in body weight from baseline to 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 since treatment adherence and the initiation of prohibited weight management treatments are part of the treatment condition.
- ***Population-level summary and treatment effect of interest:*** The difference in mean percent change from baseline in body weight at 72 weeks between orforglipron and placebo.

Rationale for the estimand: The 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 versus 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?

Hypothetical strategy

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

The efficacy estimand is described by the following attributes:

- ***Population:*** Individuals who meet the eligibility criteria.
- ***Endpoint:*** Percent change in body weight from baseline to 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 as ICEs since they are part of the treatment condition.
- ***Population-level summary and treatment effect of interest:*** The difference in mean percent change in body weight from baseline to Week 72 between orforglipron and placebo.

Rationale for the estimand: This estimand aims to study the efficacy of orforglipron under the ideal condition that all participants adhere to their randomly assigned treatment without being confounded by the initiation of other weight management treatments.

Estimands for delayed progression to type 2 diabetes

The below estimands will be applied to time to onset of type 2 diabetes (T2D) for participants with prediabetes at randomization.

Treatment regimen estimand

The treatment regimen estimand will be the primary estimand.

The clinical question of interest: What is the hazard ratio (HR) of time from randomization to onset of T2D up to 176 weeks between pooled orforglipron 36 mg, 12 mg, and 6 mg versus placebo, as an adjunct to healthy diet and physical activity, in individuals with prediabetes who meet the eligibility criteria regardless of adherence to study intervention or initiation of prohibited weight management treatments?

The treatment regimen estimand is described by the following attributes

- ***Population:*** Individuals with prediabetes who meet the eligibility criteria.
- ***Endpoints:*** Time from randomization to onset of T2D.
- ***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 as 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:*** The HR between pooled orforglipron and placebo for the time from randomization to onset of T2D.

Rationale for the estimand: The 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 HR of time from randomization to onset of T2D up to 176 weeks between pooled orforglipron 36 mg, 12 mg, and 6 mg versus placebo, as an adjunct to healthy diet and physical activity, in individuals with prediabetes who meet the eligibility criteria if they would remain on their randomly assigned treatment for 176 weeks and would not initiate prohibited weight management treatments?

The efficacy estimand is described by the following attributes

- ***Population:*** Individuals with prediabetes who meet the eligibility criteria.
- ***Endpoint:*** Time from randomization to onset of T2D.
- ***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 are handled by the hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned study intervention for 176 weeks and would not initiate prohibited weight management treatments. Dose modification and interruption will not be considered as ICEs since they are a part of treatment condition.
- ***Population-level summary and treatment effect of interest:*** The HR between pooled orforglipron and placebo for the time from randomization to onset of T2D.

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.

1.2. Study Design

Study GZGP is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study. Study GZGP 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 (body mass index [BMI] 30 kg/m^2 or greater), or overweight (BMI 27 kg/m^2 or greater) with the presence of at least 1 weight-related comorbidity (for example, hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular [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).

Study GZGP participants will be randomly assigned 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 GZGP includes a

- screening period: 3 weeks
- treatment period:
    - dose escalation period: 20 weeks
    - maintenance dose period (no prediabetes): 52 weeks
    - additional 2-year treatment period (prediabetes): 156 weeks total (including initial 52-week treatment period and 104-week additional prediabetes treatment period), and
- posttreatment follow-up period: 2 weeks.

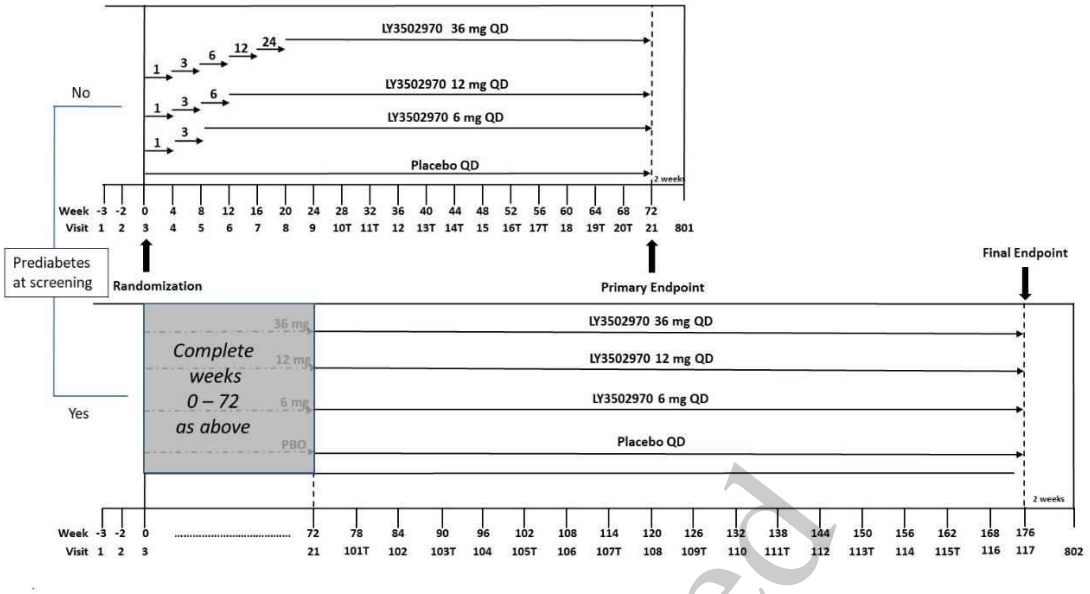
The planned duration of treatment for the primary endpoint at 72 weeks allows for at least a 52 week treatment period at the randomly assigned dose (6 mg, 12 mg, or 36 mg). The effects of study intervention cessation will be assessed at the 2-week posttreatment follow-up period (Week 74).

To obtain additional information regarding the time to new onset of T2D while taking orforglipron, participants with prediabetes diagnosed at the beginning of Study GZGP (who are at increased risk of diabetes), will be treated and observed for an additional 2 years. For participants with prediabetes at randomization, the effects of study intervention cessation will be assessed in a 2-week posttreatment follow-up period (Week 178).

The Study GZGP schema is shown in Figure GZGP.1.1.

The randomization will be stratified by:

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



Abbreviations: PBO = placebo, QD = once daily; T= telehealth visit.

Figure GZGP.1.1. Illustration of study design for Clinical Protocol J2A-MC-GZGP.

2. 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

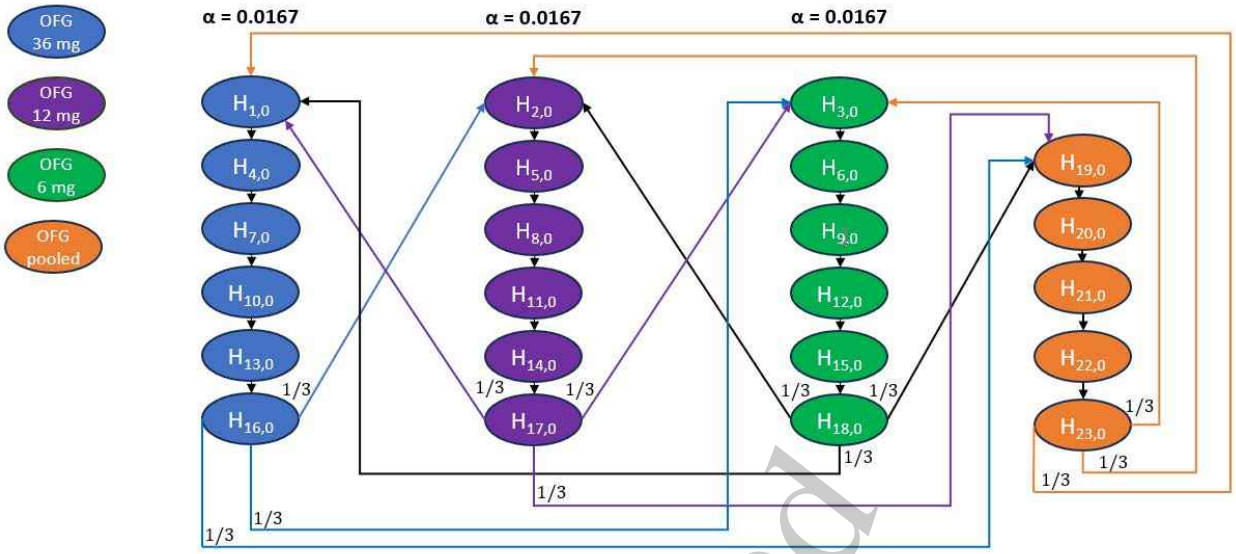
- $H_{4,0}$: No difference in 36 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction from baseline in body weight at Week 72.
- $H_{5,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the percentage 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 systolic blood pressure (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-high-density lipoprotein (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.

2.1. Multiplicity Adjustment

Multiplicity adjusted analyses will be performed on the primary and key secondary objectives to control the overall family-wise Type 1 error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz et al. (2009, 2011) will be used. This approach is a closed testing procedure, hence, it strongly controls the family-wise Type 1 error rate across all hypotheses (Alosh et al. 2014).

Figure GZGP.2.1 illustrates the current graphical testing procedure. Details of the final graphical testing scheme (including testing order, interrelationships, Type 1 error allocation for the primary and key secondary objectives, and the associated propagation) will be pre-specified in a future SAP GZGP version prior to primary database lock. Unless otherwise specified, the treatment regimen estimand is planned to support future product registration; the efficacy estimand will be considered for use in scientific disclosures and other purposes. Since these estimands are intended for distinct purposes, no multiplicity adjustment will be made for conducting separate analyses on the same objectives. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary objectives.



Abbreviations: OFG = orforglipron.

Figure GZGP.2.1. Graphical testing procedure.

3. Analysis Sets

For the purpose of analysis, the following populations are defined in Table GZGP.3.1 along with their attributes.

Table GZGP.3.1. Participant Analysis Sets

Participant Analysis Set	Description
Entered participants	**Definition:** All participants who sign informed consent[a]. **Purpose:** Used for providing summaries for screen failures and reasons associated with screen failures. Treatment Groups: None Inferential Comparisons: None
Randomized participants	**Definition:** All participants who are randomly assigned a study intervention. **Purpose:** Used for listings of disposition and treatment assignment summaries of disposition, demographics, historical illness, preexisting conditions, and analyses of efficacy and health outcomes. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO; OFG pooled vs. PBO No inferential comparisons for summary of disposition, demographics, historical illness, and preexisting conditions.
Safety participants	**Definition:** All participants who are randomly assigned a study intervention and who take at least 1 dose of study intervention. **Purpose:** Used for all safety analyses. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO.
Randomized participants with prediabetes	**Definition:** All participants who are randomly assigned a study intervention and who have prediabetes at randomization[b]. **Purpose:** Used for listings of disposition and treatment assignment summaries of disposition, demographics, historical illness, preexisting conditions, and analyses of efficacy and health outcomes. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO; OFG pooled vs. PBO. No inferential comparisons for summary of disposition, demographics, historical illness, and preexisting conditions.
Safety participants with prediabetes	**Definition:** All participants who are randomly assigned a study intervention and take at least 1 dose of study intervention, and have prediabetes at randomization[b]. **Purpose:** Used for all safety analyses. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO.

Abbreviations: IWRS = interactive web response system; OFG = orforglipron; PBO = placebo.

[a] Refers to the informed consent for the study.

[b] Determined by the IWRS data collected at the time of randomization.

The following data points sets are defined in Table GZGP.3.2 for all parameters:

Table GZGP.3.2. Data Points Sets

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. Baseline is defined in Section 4.1.1.
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 discontinuation of study intervention or initiation of prohibited weight management treatments. Baseline is defined in Section 4.1.1. and the prohibited weight management treatments are specified in Section 6.3 and Table GZGP.6.5.
Safety data points set	All data points obtained during the treatment period defined as at or after baseline and up to the date of study withdrawal or study completion including the follow-up period, regardless of study intervention discontinuation or initiation of prohibited weight management treatments. Baseline is defined in Section 4.1.1.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study 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 SAP GZGP or the clinical study report (CSR). Additional exploratory data analyses may be conducted as deemed appropriate.

Details about the analyses regarding demographic and baseline characteristics, historical illnesses and preexisting conditions, treatment compliance, concomitant medications, and important protocol deviations can be found in Appendices 1 through 5 (Section 6.1 through Section 6.5), respectively.

Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (for example, few events to justify conducting an analysis). Not all analyses described in SAP GZGP will necessarily be included in the CSRs. Any analyses described in this SAP and not provided in the CSR will be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display.

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

The change from baseline will be calculated as the value of interest at the visit minus the baseline value. In general, percent change from baseline will be calculated as the value of change from baseline divided by the baseline value in 100% scale. For some specific predefined parameters, percent change from baseline might be calculated using a log transformation. If the baseline value is missing for a particular variable, then the change from baseline and percent change from baseline will not be calculated.

For stratification factors at baseline, a strata variable is defined for statistical modeling to consist of 4 joint levels. The strata variable includes sex (female, male) and prediabetes status (yes, no). Country is also a stratification factor and will be included in statistical modeling as a separate factor. Countries with fewer than 10 randomized participants will be pooled into 1 category (pooled country).

Data may exist at visits where a variable was not scheduled to be collected, due to, for example, early discontinuation visits. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from the mixed model for repeated measures (MMRM), analysis of covariance (ANCOVA), or logistic regression analysis, unless otherwise specified (Andersen and Millen 2013).

Handling of missing data is addressed in Section 4.1.2 and Table GZGP.4.6. Section 3 provides definitions for the participant analysis set and data points set which includes definitions for

censored data where appropriate. Handling spurious data is addressed in Section 6.5. Section 6.5 also addresses important protocol deviations. Protocol GZGP Section 10.1.7 addresses data quality assurance.

4.1.1. Definition of Baseline

Unless otherwise specified, the baseline for efficacy assessments is defined as the last available non-missing measurement prior to the first dose of study intervention; in most cases, this will be the measurement recorded at Week 0 (Visit 3). If there are no doses of study intervention administered, the baseline will be defined as the last available non-missing measurement on or prior to randomization. In cases where the measurement is taken on the same day (where the time is not collected or not reliable) as the first dose, this measurement will be used as the baseline value for data analysis. For patient-reported outcome measures data obtained at Visit 3, regardless of the timing relative to first dose, will serve as the baseline.

For safety assessments, the definition of baseline and postbaseline are specified in Table GZGP.4.1.

Table GZGP.4.1. Baseline and Postbaseline Definitions for Safety Analyses

Analysis Type	Baseline Period	Postbaseline Period
TEAEs	Starts from informed consent date and ends prior to the first dose (typically at Week 0).	Starts after the first dose of study intervention and ends at the end of the follow-up period, or the date of study withdrawal, or database cut-off date (whichever is earliest)[a].
TE abnormal laboratory values, vital signs, and ECGs	Starts from informed consent date and ends prior to the first dose (typically at Week 0). All scheduled and unscheduled measurements will be included.	Starts after the first dose and ends at the end of the follow-up period or the date of study withdrawal (whichever is earliest). All scheduled and unscheduled measurements will be included.
Change from last baseline to each postbaseline week and to last postbaseline for laboratory values, vital signs, and ECGs	When "last baseline" is used, starts from informed consent date and ends prior to the first dose (typically at Week 0).	Starts after the first dose and ends at the end of the follow-up period or the date of study withdrawal (whichever is earliest). Only scheduled visits will be included. Early termination visits will be considered scheduled visits.

Abbreviations: ECG = electrocardiogram; TE = treatment-emergent; TEAE = treatment-emergent adverse events.

[a] For events occurring on the day of first dose, information collected from the case report form will be used to determine whether the event was pre- versus posttreatment, if available. If the relevant information is not available, then the events will be counted as postbaseline.

4.1.2. Analysis Methods

The analysis methods are consistent with the desired estimands and the FDA guidance on "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products Guidance Document" (FDA 2023).

4.1.2.1. Analysis Methods for Treatment Regimen Estimand

4.1.2.1.1. Method for Continuous Variables

The ANCOVA model will be used to analyze continuous measurements at Week 72 and Week 176 and will be guided by the treatment regimen estimand. The model will include

- treatment group as a factor variable
- country as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)
- interaction between strata variable and treatment group, and
- interaction between baseline value and treatment group.

The estimated treatment group effect and comparison between 6 mg orforglipron, 12 mg orforglipron, and 36 mg orforglipron versus placebo will be reported together, with variability estimated using the robust inference (Ye et al. 2022). The associated 2-sided 95% confidence interval and corresponding p-values will also be reported. If the model fails to converge, all the interaction terms will be removed before the model fitting. The addition of interaction terms is not intended to estimate the heterogeneity effect but to provide robustness and efficiency for the estimate of treatment comparisons on the unconditional effect. The final inference will be derived using Rubin's Rule by combining estimates from multiple imputed datasets.

For some variables, both the baseline and the postbaseline values will be log transformed before fitting the ANCOVA. The treatment group estimates will be the percent change from baseline; the treatment contrasts will be the relative change in orforglipron 6 mg, orforglipron 12 mg, or orforglipron 36 mg compared to the placebo (%). In these cases, least squares (LS) means and 95% CIs for each treatment group and treatment difference will be back-transformed and presented as mean percent change from baseline and relative treatment difference to placebo in percent change.

4.1.2.1.2. Primary Multiple Imputation (PMI) Strategy

Missing data shall be minimized for estimating the treatment regimen estimand. Participants who discontinue the study intervention (that is, discontinue study treatment) will be encouraged to continue in the study for the treatment period/phase and follow-up period/phase (note, the words period and phase are used interchangeably in this SAP; case report forms (CRFs) use the word phase).

If there are occurrences of missing data despite the best precautions, missing data should be imputed in a fashion consistent with what the values would likely have been had they been collected. In general, 5 scenarios are considered regarding the treatment journey of a trial participant relative to primary time point (Week 72 visit) shown in Figure GZGP.4.1.

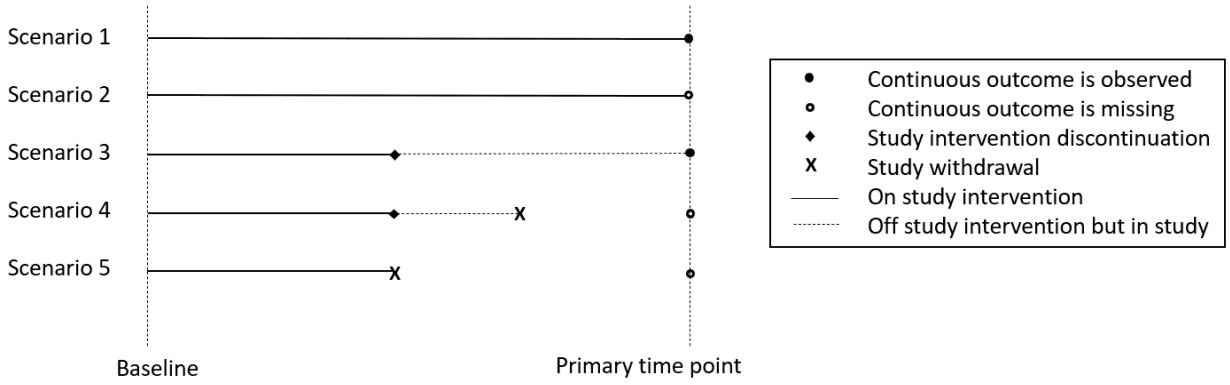


Figure GZGP.4.1. Treatment journey of a trial participant.

In principle, missing data due to permanent discontinuation of study intervention (Scenario 4) will be imputed by treatment group using retrieved dropouts (MI-RD), namely using multiple imputation based on data retrieved from participants who permanently discontinued the study intervention but continued in the study with non-missing measurements from the same treatment group. The overall imputation procedure is provided in Table GZGP.4.2. For scenarios 4 and 5A, if there are not enough retrieved dropouts to provide a reliable imputation model (that is, the model implemented does not converge), an alternative multiple imputation method with reference to the baseline data (a return to baseline approach) will be used. A direct estimation of the treatment regimen estimand theoretically equivalent to the imputation method described in Table GZGP.4.2 may be used instead of actual imputation.

Table GZGP.4.2. Imputation Procedure

Scenario (Study Intervention/Treatment Period Discontinuation; Missingness Status at Endpoint)	**Methods to Handle Missing Values at Endpoint**
1. No study intervention or treatment period discontinuation; no missing value	N/A
2. No study intervention or treatment period discontinuation; with missing value	Use data from Scenario 1 to impute under the MAR assumption by treatment group. There should be very few such cases in a clinical trial.
3. Study intervention discontinuation with no treatment period discontinuation; no missing value	N/A
4. Study intervention discontinuation with treatment period discontinuation at a subsequent visit or completion of treatment period; with missing value	Missing values at endpoint visit for any participants with observed baseline will be imputed under the assumption of multivariate normality for baseline and the endpoint visit through MCMC, based upon data from Scenario 3 (MI-RD) to impute missing values by treatment group.
5. Study discontinuation resulting in study intervention discontinuation; with missing value	5A: If the study discontinuation is possibly related to study intervention (see treatment period discontinuation reasons classified as Category 5A in Table GZGP.4.3), use data from Scenario 3 (MI-RD) to impute by treatment group. In this case, it is assumed that the study intervention discontinuation is related to study intervention. 5B: If the study discontinuation is clearly due to administrative reasons not related to study medication (see treatment period discontinuation reasons classified as Category 5B in Table GZGP.4.3), use data (observed and imputed) in Scenarios 1 to 4, and 5A to impute. The reason for the study intervention discontinuation for this scenario is considered not related to study intervention.

Abbreviations: MAR = missing at random; MCMC = Markov chain Monte Carlo; MI = multiple imputation; RD = retrieved dropouts; N/A = not applicable.

Table GZGP.4.3. Categorization of Treatment Period Discontinuation Reasons

Disposition Reason	Associated Sub-Categories	Category
Adverse Event		5A
Death		5A
Protocol Deviation		5A
Pregnancy		5B
Non-Compliance With Study Drug		5A
Lack of Efficacy	Investigator	5A
	Study subject	5A
Withdrawal by Subject	Concern about study procedures/perceived risks	5A
	Health insurance changes	5B
	Scheduling conflicts	5B
	Subject is moving or has moved	5B
	Personal issue unrelated to trial	5B
	Due to epidemic/pandemic	5B
	Other	5A
Physician Decision	Due to epidemic/pandemic	5B
	Other	5A
Study Terminated by Sponsor		5B
Site Terminated by Sponsor		5B
Study Terminated by IRB/ERB		5B
Lost to Follow-up		5A
Other		5A

Abbreviations: ERB = ethical review board; IRB = institutional review board.

4.1.2.1.3. Modified Multiple Imputation Strategy

A modified multiple imputation (mMI) analysis is planned as a sensitivity analysis to assess the robustness of the primary efficacy results. The imputation method in Scenario 5B of Table GZGP.4.2 assumes that treatment discontinuation that is clearly due to administrative reasons is not related to study intervention. An additional analysis will be conducted to assess the robustness of the primary efficacy results with different missing method of handling missing values in Scenario 5B. Instead of following Table GZGP.4.2, data observed from Scenario 3 will be used to impute Scenario 5B.

4.1.2.1.4. Multiple Imputation Based Tipping-Point Analysis

A multiple imputation-based tipping-point (MI-TP) analysis is planned as a sensitivity analysis to explore how different patterns of body weight change post treatment period discontinuation by different treatment groups could impact the treatment comparisons.

To start with, missing data are imputed according to the primary imputation strategy (PMI) as shown in Section 4.1.2.1.2. A penalty is then added to those imputed values at the Week 72 visit. The MI-TP analysis varies the magnitude of the penalties added for both treatment groups under comparison and evaluates the impact these would have on the Study GZGP conclusion. A 2-dimensional space of penalties will be assessed for orforglipron 36 mg, orforglipron 12 mg, or orforglipron 6 mg and placebo, ranging from -30% to 30%. An MI-TP analysis aims to evaluate

the robustness of the superiority claim to the assumptions of using the observed data to impute the missing body weight in all treatment groups.

4.1.2.1.5. Method for Binary Variables

The binary outcomes will be analyzed with following the procedure:

- Using the same imputation strategy – PMI as in Section 4.1.2.1.2 on the underlying continuous endpoint that determines the binary value. For example, the continuous body weight values at Weeks 72 visit will be imputed first.
- Transform the observed and imputed continuous value to the binary value, for example, convert the continuous body weight values at Weeks 72 visit to whether the corresponding percent change from baseline meets a certain threshold (Ma et al. 2022).
- Fit a logistic regression model to the data with the following terms:
    - treatment group as a factor variable
    - country as a factor variable
    - strata as a factor variable
    - baseline value (of the dependent variable)
- Provide estimates and inferences of unconditional treatment effects defined by the risk difference and/or relative risk based on the delta-method using the formula provided (Ye et al. 2023).
- Derive the final inference using Rubin's rule by combining estimates from multiple imputed datasets.

4.1.2.1.6. Analysis Methods for Time to Event Variables

For time-to-event analysis, a Cox proportional hazards model conditioned on the strata variable and with treatment group as a factor, will be used as the primary analysis to estimate the HR between the treatment groups and the corresponding confidence interval and Wald p-value.

For time-to-event analyses, participants who have not experienced the event of interest will be censored at the participant's end of follow-up. The censoring date will be the earliest of

1. date of death and
2. date of study completion/withdrawal, and
3. the last confirmed visit date before participant was lost-to-follow-up.

The Kaplan-Meier method will be used to estimate the cumulative event curve over time. Counts and proportions of participants who experience an event will be calculated by treatment group.

For time-to-event analysis, if a participant experiences the event of interest, then time-to-event for that specific event of interest will be the number of days between the date of randomization and the onset date of the event plus 1 day. If a participant does not experience the event, then time-to-event for that specific event of interest will be the number of days between the date of randomization and the date of the participant's end of follow-up plus 1 day. If a participant experiences multiple events the date of the first event will be used, unless otherwise specified. In rare cases where randomization occurred prior to the Visit 3 date, the Visit 3 date will be used instead.

4.1.2.2. Analysis Methods for Efficacy Estimand

4.1.2.2.1. Method for Continuous Variables

An MMRM will be used to analyze continuous measurements at each postbaseline visit guided by the efficacy estimand. Missing data should be minimized at the best precaution. The hypothetical strategy will be used to handle ICEs. For MMRM analysis, only data collected before the occurrence of any ICEs will be used in the MMRM analysis. Through the MMRM, the potential efficacy measures (after the ICEs) will be implicitly imputed as if participants did not have ICEs. Participant dose modification and interruption will not disqualify their measurements from being included into the model.

The MMRM model will include the following terms:

- treatment group as a factor variable
- visit as a factor variable
- country as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)
- interaction between treatment group, strata variable and visit, and
- interaction between treatment group, baseline value and visit.

The estimated treatment group effect and comparison between 6 mg orforglipron, 12 mg orforglipron, or 36 mg orforglipron and placebo at the scheduled visits will be reported together with the variability estimated using the robust inference (Wang and Du 2023). The sandwich estimator (Diggle et al. 1994) for the variance-covariance matrix will be used. The addition of 3-way interaction terms is not intended to estimate the heterogeneity effect but to provide robustness and efficiency for the estimate of treatment comparisons on the unconditional effect. The associated 2-sided 95% confidence interval and corresponding p-values will also be reported. An unstructured covariance matrix by each treatment group will be used to model the within-participant errors, assuming heteroscedasticity and the measurements for different participants are independent. If the model fails to converge, the model will be simplified to include the following terms, removing 3-way interactions and the heteroscedasticity assumption:

- treatment group as a factor variable
- visit as a factor variable
- country as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)
- interaction between treatment group and visit
- interaction between strata variable and visit, and
- interaction between baseline value and visit.

If the model still fails to converge, the following covariance structures will be tested in order for the simplified model:

- heterogeneous Toeplitz
- heterogeneous autoregressive
- heterogeneous compound symmetry
- homogeneous Toeplitz
- homogeneous autoregressive, and
- homogeneous compound symmetry.

The first covariance structure that converges will be used.

For some variables, both the postbaseline response variables and baseline variable will be log-transformed before fitting the MMRM. The treatment group estimates will be the percent change from baseline while the treatment contrasts will be the relative change in orforglipron 6 mg, orforglipron 12 mg, or orforglipron 36 mg compared to the placebo (%) over the scheduled visits.

4.1.2.2.2. Method for Binary Variables

The binary outcomes will be analysed with the following procedure:

- Impute the missing continuous-valued measurements at the scheduled visits using the randomized participants with efficacy estimand data points set assuming MAR with multiple imputation.
- At the visit of interest, transform the observed and imputed continuous value to the binary value, for example, convert the continuous body weight value at a visit to whether the corresponding percent change from baseline meets a certain threshold.
- Fit a logistic regression model to the transformed binary data with the following terms:
    - treatment group as a factor variable
    - country as a factor variable
    - strata as a factor variable
    - continuous baseline value (of the dependent variable)
- Provide for the visit of interest the estimates and inferences of unconditional treatment effects defined by the risk difference and/or risk ratio based on the delta-method using the formula provided (Ye et al. 2023).
- Derive the final inference using Rubin's rule by combining estimates from multiple imputed datasets.

4.1.2.2.3. Analysis Methods for Time to Event Variables

Similar methodology will be used as described in Section 4.1.2.1.6, with the exception of the censoring rules.

For time-to-event analyses, participants who have not experienced the event of interest will be censored at the participant's end of follow-up. The censoring date will be the earliest of

1. date of death
2. date of discontinuation of study intervention, and

3. the last confirmed visit date before participant was lost-to-follow-up.

4.1.2.3. Analysis Methods for Safety

In general, 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 based on data observed during treatment period plus the posttreatment follow-up period, that is, the period from first dose of treatment to the end of the follow-up visit or the date of study withdrawal. It is noted that for some safety endpoints, such as treatment discontinuation due to adverse event (AE) and so forth, the analyses will be based on data observed during treatment period only.

Fisher's exact test will be used for treatment comparisons of percentages. The risk differences and 95% confidence intervals will be provided.

An MMRM analysis will be used for selected continuous safety data with multiple postbaseline measurements. The model specifications are as described in Section 4.1.2.2.1. If the data does not warrant an MMRM model, then an ANCOVA model will be conducted as described in Section 4.1.2.1.1. For some variables, both the postbaseline response variables and baseline variable will be log transformed before fitting the MMRM.

The Kaplan–Meier (KM) product limit method will be used to estimate the cumulative event-free survival rates over time for the time-to-event analyses. A Cox proportional hazards regression analysis will be used to compare hazard rates among treatments.

A logistic regression model will be used for hypoglycemia incidence for postbaseline treatment comparisons. The model will include the fixed effects of treatment, country, and strata variable. Where necessary, the rate of events will be analyzed using a generalized linear mixed-effects model, assuming the number of events follow a negative binomial distribution and treatment group as a fixed effect. The logarithm of days during the analysis interval will be adjusted as an offset to account for the possible unequal treatment duration of follow-up between participants.

Some safety analyses may be conducted after excluding data after the initiation of anti-hyperglycemic medications for those who develop T2D.

4.2. Participant Dispositions

The participant dispositions for the screening period, study intervention, the treatment period, and/or the follow-up period will be collected in the CRFs with the corresponding primary reason.

The study completion status is defined as

- at the end of the 72-week treatment period (when the primary endpoint is ascertained and the primary database is locked): for participants without prediabetes at randomization, completers will be considered as those who complete the treatment period (Week 72) and the follow-up visit; for participants with prediabetes at randomization, completers will be considered as those who complete Week 72; otherwise, participants will be considered as non-completers.

- at the end of the 176-week treatment period for participants with prediabetes at randomization, completers will be considered as those who complete the treatment period (Week 176) and the follow-up visit; otherwise, participants will be considered as non-completers.

The planned listings and summary tables for dispositions are provided in Table GZGP.4.4. No inferential analysis will be performed. Additionally, the planned listings and summary tables for dispositions will be provided for participants with prediabetes at randomization for the final lock.

Table GZGP.4.4. Listings and Summary Tables Related to Dispositions

Analysis	Population/Period
Summary of disposition (prior to randomization)	Entered participants
Patient allocation by region, country, and center/site	Entered participants
Summary of study and study intervention disposition	Randomized participants/TP + FP (TP for study treatment disposition)
Kaplan-Meier plot of time to study discontinuation	Randomized participants/TP + FP
Kaplan-Meier plot of time to study intervention discontinuation	Randomized participants/TP
Kaplan-Meier plot of time to study treatment discontinuation due to AEs	Randomized participants/TP
Listing of randomization	Randomized participants
Listing of randomized participants not administering study intervention	Randomized participants
Listing of randomized participants who were discontinued from the study intervention due to inadvertent enrollment	Randomized participants
Listing of study and study intervention disposition	Randomized participants

Abbreviations: FP = follow-up period; TP = treatment period.

4.3. Primary Endpoint/Estimand Analysis

4.3.1. Definition of endpoint(s)

The primary efficacy endpoint is percent change in body weight at 72 weeks. As specified in Table GZGP.4.5, the percent change in body weight is defined as:

(postbaseline body weight [kg] – baseline body weight [kg]) / baseline body weight [kg] × 100%.

4.3.2. Main analytical approach

The analytical approaches are specified in Section 4.1.2.1.1 and Section 4.1.2.1.2 (ANCOVA with PMI) and Section 4.1.2.2.1 (MMRM).

4.3.3. Sensitivity Analyses

The sensitivity analyses are specified in Section 4.1.2.1.3 (mMI) and Section 4.1.2.1.4 (MI-TP).

4.3.4. Supplementary analyses

No supplementary analysis is planned for the primary endpoint.

4.4. Secondary Endpoints/Estimands Analysis

Table GZGP.4.5 includes the description and derivation of all the primary and secondary endpoints for the efficacy measures and PROs.

Table GZGP.4.6 provides the detailed analyses including endpoint, estimand, data points set, method and imputation, population, and time point for the primary and secondary endpoints.

Table GZGP.4.5. Descriptions and Derivation of Primary and Secondary Endpoints for Efficacy Measures and Patient Reported Outcomes

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
Body weight	Per Protocol GZGP Section 10.7: 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 will be measured in fasting state at all visits. 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.	Body weight (kg)	As measured	Single item, missing if missing
		Change from baseline in body weight (kg)	Calculated as: postbaseline body weight (kg) – baseline body weight (kg)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in body weight (%)	Calculated as: (postbaseline body weight [kg] – baseline body weight [kg]) / baseline body weight [kg] × 100 (%)	Missing if baseline or postbaseline value is missing
		≥x% body weight reduction from baseline where, x = 5, 10, 15, 20	Response = yes if at least a x% reduction in body weight from baseline, that is, percent change from baseline in body weight ≤ -x%	Missing if baseline or postbaseline value is missing
BMI	BMI: Round to one decimal point. For example, a BMI of 29.9 kg/m^2 should not be rounded to 30.0 kg/m^2.	BMI (kg/m^2)	BMI will be calculated as: Weight (kg) / (height [m])^2	Missing if weight or height is missing
		Change from baseline in BMI (kg/m^2)	Calculated as: postbaseline BMI (kg/m^2) – baseline BMI (kg/m^2)	Missing if baseline or postbaseline value is missing
		BMI target value of <35 kg/m^2	Response = yes if the postbaseline BMI value <35 kg/m^2	Missing if postbaseline value is missing
		BMI target value of <30 kg/m^2	Response = yes if the postbaseline BMI value <30 kg/m^2	Missing if postbaseline value is missing

		BMI target value of <25 kg/m^2	Response = yes if the postbaseline BMI value <25 kg/m^2	Missing if postbaseline value is missing
Waist circumference	Per Protocol GZGP Section 10.7: 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.	Waist circumference (cm)	The average of 2 measures	If there is at least one measurement, take the average of all non-missing measurements; otherwise, set it to be missing
		Change from baseline in waist circumference (cm)	Calculated as: postbaseline Waist circumference (cm) – baseline Waist circumference (cm)	Missing if baseline or postbaseline value is missing
Blood pressure	Per Protocol GZGP Section 10.7: 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. Blood pressure must be taken with an automated blood pressure instrument	SBP (mm Hg)	The average of 3 measures	If there is at least one measurement, take the average of all non-missing measurements; otherwise, set it to be missing
		Change from baseline in SBP (mm Hg)	Calculated as: postbaseline SBP (mm Hg) – baseline SBP (mm Hg)	Missing if baseline or postbaseline value is missing
		DBP (mm Hg)	The average of 3 measures	If there is at least one measurement, take the average of all non-missing measurements; otherwise, set it to be missing

		Change from baseline in DBP (mm Hg)	Calculated as: postbaseline DBP (mm Hg) – baseline DBP (mm Hg)	Missing if baseline or postbaseline value is missing
Lipid parameter	The tests will be performed by the central laboratory. HDL-C, triglycerides, and total cholesterol will be assayed by Lilly designated laboratory. LDL-cholesterol, non-HDL-cholesterol, and VLDL-C will be calculated by Lilly designated laboratory.	Triglycerides	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in triglycerides (%)	Calculated as: log(postbaseline triglyceride) – log (baseline triglyceride) then will transform back to percent change.	Missing if baseline or postbaseline value is missing
		Total cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in total cholesterol (%)	Calculated as: log(postbaseline total cholesterol) – log(baseline total cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		Non-HDL-cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in non-HDL-cholesterol (%)	Calculated as: log(postbaseline non-HDL-cholesterol) – log(baseline non-HDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		LDL-cholesterol	As provided. If triglycerides are >400 mg/dL, the direct LDL will be directly measured Log transformation before the analysis.	Single item, missing if missing

		Percent change from baseline in LDL-cholesterol (%)	Calculated as: log(postbaseline LDL-cholesterol) – log(baseline LDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		HDL-cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in HDL-cholesterol (%)	Calculated as: log(postbaseline HDL-cholesterol) – log(baseline HDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		VLDL-cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in VLDL-cholesterol (%)	Calculated as: log(postbaseline VLDL-cholesterol – log(baseline VLDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
Glycemic control	Fasting glucose will be performed by the central laboratory and will be assayed by Lilly-designated laboratory.	Fasting glucose (mg/dL and mmol/L)	As provided	Single item, missing if missing
		Change from baseline fasting glucose (mg/dL and mmol/L)	Calculated as: Postbaseline fasting glucose – Baseline fasting glucose	Missing if baseline or postbaseline value is missing
	HbA1c will be performed by the central laboratory and will be assayed by Lilly-designated laboratory.	HbA1c (% and mmol/mol)	As provided	Single item, missing if missing
		Change from baseline HbA1c (% and mmol/mol)	Calculated as: Postbaseline HbA1c – Baseline HbA1c	Missing if baseline or postbaseline value is missing

	Delayed progression to T2D is evaluated by time to onset of T2D (only for participants with prediabetes at randomization).	Time to onset of T2D	Calculated as: (date of onset of CEC adjudicated T2D event – date of first dose of study intervention) + 1 day	Censored if no postbaseline event of T2D was observed
	Percentage of participants with prediabetes at randomization achieving normoglycemia.	Percentage of participants achieving normoglycemia	Response = Yes if FSG < 100 mg/dL (obtained alone or at time = 0 during an OGTT), OGTT 2h SG < 140 mg/dL, and HbA1c < 5.7%.	Missing if postbaseline values of HbA1c, FSG and OGTT are missing
	2-hour OGTT will be performed per Protocol Section 10.7: • participants should attend visits in the fasting state, and • serum samples will be collected at 0, 30, 60, 90, and 120 minutes	Point x OGTT (mg/dL) x= 0, 30, 60, 90, 120 minutes	As provided	Single item, missing if missing
		Change from baseline in point x OGTT (mg/dL)	Calculated as: postbaseline point x OGTT (mg/dL) – baseline point x OGTT(mg/dL)	Missing if baseline or postbaseline value is missing
Insulin sensitivity	Per Protocol GZGP Section 10.2: Fasting insulin will be performed by the central laboratory and will be assayed by Lilly-designated laboratory.	Percent change from baseline in fasting insulin (%)	Calculated as: log(postbaseline fasting insulin) – log(baseline fasting insulin) then will transform back to percent change.	Missing if baseline or postbaseline value is missing
Renal Function	Per Protocol GZGP Section 10.2: UACR and eGFR will be performed by the central laboratory and will be assayed by Lilly-designated laboratory.	UACR	As provided Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in UACR (%)	Calculated as: log(postbaseline UACR) – log(baseline UACR) then will transform back to percent change.	Missing if baseline or postbaseline value is missing
		eGFR CKD-EPI Cystatin C (ml/min/1.73m^2)	As provided as: eGFR (CKD-EPI Cystatin C 2012)	Single item, missing if missing
		Change from baseline in eGFR	Calculated as: postbaseline eGFR CKD-EPI Cystatin C (ml/min/1.73m^2) –	Missing if baseline or postbaseline value is missing

		CKD-EPI Cystatin C (ml/min/1.73m^2)	Baseline eGFR CKD-EPI Cystatin C (ml/min/1.73m^2)	
		eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	As provided as: eGFR (CKD-EPI Creatinine 2021)	Single item, missing if missing
		Change from baseline in eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	Calculated as: postbaseline eGFR CKD-EPI Creatinine (ml/min/1.73m^2) – Baseline eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	Missing if baseline or postbaseline value is missing
Inflammatory biomarker	Per Protocol GZGP Section 10.2: hsCRP will be performed by the central laboratory and will be assayed by Lilly-designated laboratory.	hsCRP (mg/L)	As provided	Single item, missing if missing
		Change from baseline in hsCRP (mg/L)	Calculated as: postbaseline hsCRP (mg/L) – baseline hsCRP (mg/L)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in hsCRP (mg/L)	Calculated as: log(postbaseline hsCRP (mg/L)) – log(baseline hsCRP (mg/L))	Missing if baseline or postbaseline value is missing
FFAs	Per Protocol GZGP Section 10.2: FFAs will be performed by the central laboratory and will be assayed by Lilly-designated laboratory.	FFAs (mmol/L)	As provided	Single item, missing if missing
		Change from baseline in FFAs (mmol/L)	Calculated as: postbaseline FFAs (mmol/L) – baseline FFAs (mmol/L)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in FFAs (mmol/L)	Calculated as: log(postbaseline FFAs (mmol/L)) – log(baseline FFAs (mmol/L))	Missing if baseline or postbaseline value is missing
HOMA	HOMA2 B estimates steady state beta cell function	HOMA2 B (insulin)	Calculated from the link[a] using fasting glucose and insulin laboratory values	Missing if fasting glucose or insulin is missing
		Change from baseline in HOMA2 B (insulin)	Calculated as: postbaseline HOMA2 B (insulin) – baseline HOMA2 B (insulin)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in HOMA2 B (insulin)	Calculated as: [postbaseline HOMA2 B (insulin) – baseline HOMA2 B (insulin)]/	Missing if baseline or postbaseline value is missing

			baseline HOMA2 B (insulin) × 100%	
		HOMA2 B (C-peptide)	Calculated from the link[a] using fasting glucose and C-peptide laboratory values	Missing if fasting glucose or C-peptide is missing
		Change from baseline in HOMA2 B (C-peptide)	Calculated as: postbaseline HOMA2 B (C-peptide) – baseline HOMA2 B (C-peptide)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in HOMA2 B (C-peptide)	Calculated as: [postbaseline HOMA2 B (C-peptide) – baseline HOMA2 B (C-peptide)] / baseline HOMA2 B (C-peptide) × 100%	Missing if baseline or postbaseline value is missing
	HOMA2 IR estimates insulin resistance	HOMA2 IR (insulin)	Calculated from the link[a] using fasting glucose and insulin laboratory values	Missing if fasting glucose or insulin is missing
		Change from baseline in HOMA2 IR (insulin)	Calculated as: postbaseline HOMA2 IR (insulin) – baseline HOMA2 IR (insulin)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in HOMA2 IR (insulin)	Calculated as: [postbaseline HOMA2 IR (insulin) – baseline HOMA2 IR (insulin)] / baseline HOMA2 IR (insulin) × 100%	Missing if baseline or postbaseline value is missing
		HOMA2 IR (C-peptide)	Calculated from the link[a] using fasting glucose and C-peptide laboratory values	Missing if fasting glucose or C-peptide is missing
		Change from baseline in HOMA2 IR (C-peptide)	Calculated as: postbaseline HOMA2 IR (C-peptide) – baseline HOMA2 IR (C-peptide)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in HOMA2 IR (c-peptide)	Calculated as: [postbaseline HOMA2 IR (C-peptide) – baseline HOMA2 IR (C-peptide)] / baseline HOMA2 IR (C-peptide) × 100%	Missing if baseline or postbaseline value is missing

SF-36	SF-36v2 will 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. The Physical functioning domain does not have a recall period 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, a Physical Component Summary, and a 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[b].	SF-36 domain scores and SF-36 component scores	Per copyright owner, the Quality Metric Health Outcomes™ Scoring Software will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will recalibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (T-scores) using the 1-week recall period. This entails exporting the patient data in a CSV or tab-delimited file for import, generation of the SF-36 scores and reports, and export of the calculated scores in a CSV or tab-delimited file.	Missing data handling offered by SF-36 software will be used. "Maximum Data Recovery" will be selected for Missing Score Estimator in the software.
		SF-36 change from baseline for domains and component scores (PCS and MCS)	Calculated as: postbaseline SF-36 score – baseline SF-36 score	Missing if baseline or postbaseline value is missing
PGI-S	The PGI-S Physical Function 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	PGI-S rating	As assessed. The responses are on a 5-point scale ranging from "not at all limited" to "extremely limited."	Single item, missing if missing

	their ability to perform physical activities in the past 7 days.			
PGI-C	The PGI-C Physical Function 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 intervention.	PGI-C rating	As assessed. The responses are based on a 5-point scale ranging from "much better" to "much worse."	Single item, missing if missing
IWQOL-Lite-CT	IWQOL-Lite-CT[c] is a 20-item, obesity-specific, patient-reported outcome instrument developed for use in weight management clinical studies. The IWQOL-Lite-CT assesses 2 primary domains of obesity-and health-related quality of life: Physical (7 items) and Psychosocial (13 items), and a 5-item subset of the Physical domain, the Physical Function composite. 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 2 domain scores, 1 composite score and total score range from 0 to 100 with higher scores indicating greater functioning, derived as below: Raw scores for each subscale are computed if a minimum of 50% of the items for that subscale are non-missing, and for the IWQOL-Lite-CT	Physical domain score and psychosocial domain score	Physical domain includes Items 1-5, 16, 17; Psychosocial domain includes Items 6-8, 9-15, 18, 19, 20	The minimum requirements for non-missing responses: Psychosocial: 7 of 13 items, Physical: 4 of 7 items, otherwise considered missing
		Change from baseline in physical domain score and psychosocial domain score	Calculated as: Postbaseline score – baseline score	Missing if baseline or postbaseline value is missing
		Physical function composite score	Include Items 1-3, 16, 17.	The minimum requirements for non-missing responses: 3 of 5 items, otherwise considered missing
		Change from baseline in physical function composite score	Calculated as: postbaseline score – baseline score	Missing if baseline or postbaseline value is missing
		Total score	Items 1-20	The minimum requirements for

	total score if a minimum of 75% of all items are non-missing. If the minimum number of items is answered for a composite, then • compute the average of the valid non-missing responses corresponding to the items in the total or each domain/composite will be calculated (1 = "never" or "not at all true" and 5 = "always" or "completely true"). • The score will be then calculated by transforming the raw score to the 0 (worst) to 100 (best) metric using the following formula for every participant at each time point: $100(S_{max} - C_{avg})/(S_{max} - S_{min})$ o C_{avg} is the raw average score of all non-missing item responses in the composite; this average must be a number between 1 and 5, inclusive. o S_{max} is the maximum possible raw score value (that is, 5) o S_{min} is the minimum possible raw score value (that is, 1) o Inserting the maximum and minimum possible score values, the formula is reduced to: $100(5 - C_{avg})$			non-missing responses: 15 of 20 items, otherwise considered missing
		Change from baseline in total score	Calculated as: Postbaseline score – baseline score	Missing if baseline or postbaseline value is missing
EQ-5D-5L and VAS	The EQ-5D-5L[d] 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	EQ-5D-5L item scores	Five health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems	Each dimension is a single item, missing if missing. Note: Missing value can be coded as 9.

	population health surveys. The EQ-5D-5L assesses 5 dimensions of health: Item 1: mobility Item 2: self-care Item 3: usual activities Item 4: pain/discomfort Item 5: 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 labeled as "best imaginable health state" (100) and "worst imaginable health state" (0).		5 = extreme problems It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a primary score.	
		EQ-5D-5L UK population-based utility index	EQ-5D-5L health states are converted into a single index "utility" score using a scoring algorithm based on public preferences. Uses the concatenation of the value of each EQ-5D-5L dimension score in the order: item 1; item 2; item 3; item 4; item 5. Derive EQ-5D-5L UK population-based index score according to the link[b] by using the UK algorithm to produce a patient-level index score between -0.59 and 1.0 (continuous variable)[e].	If any of the items is missing or coded as 9, the index score is missing
		Change from baseline in EQ-5D-5L utility index	Calculated as: Postbaseline utility index score – baseline utility index score	Missing if baseline or postbaseline value is missing
		EQ-5D VAS	Range from 0 = "worst imaginable health state" to 100 = "best imaginable health state"	Single item, missing if missing.
		Change from baseline in EQ-5D-5L VAS	Calculated as: postbaseline VAS score – baseline VAS score	Missing if baseline or postbaseline value is missing
PROMIS	The PROMIS Short Form v1.0 Sleep Disturbance 8b assesses self-reported perceptions of sleep quality, sleep depth, and	PROMIS individual and total scores	Raw scores are converted to a T-score, which is standardized with a mean of 50 and a SD of 10[f].	Missing if any of the items are missing

	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.	Change from baseline in individual and total scores	Calculated as: postbaseline score – baseline score	Missing if baseline or postbaseline value is missing
Appetite VAS	The aim of the appetite VAS is to determine the effects of study intervention on appetite sensations and desire for specific foods. 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 10-cm (100 mm) line. The ratings will include the following 8 questions[g]: • 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?	Appetite VAS item scores	For questions 1-4: range from 0 mm = "not at all" to 100 mm = "extremely" For questions 5-8: range from 0 mm = "Yes, very much" to 100 mm = "No, not all"	Single item, missing if missing
		Appetite VAS overall score	Calculated as the mean of the following 4 fasting appetite VAS item scores: • 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?	Missing if any single item is missing
		Change from baseline in appetite	Calculated as: postbaseline VAS score – baseline VAS score	Missing if baseline or postbaseline value is missing

		VAS item and overall scores		
		Change from Week 72 in appetite VAS item and overall scores	Calculated as: postbaseline VAS score – Week 72 VAS score	Missing if baseline or postbaseline value is missing
PFS	The PFS[h] 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: • food available • food present, and • food tasted.	PFS scores item scores	5-point Likert scale ranging from 1 (do not agree at all) to 5 (strongly agree) Higher scores indicate a higher psychological impact of food.	Single item, missing if missing
		PFS domain scores	Calculated as the mean of the item scores within each of the individual 3 domains	Missing if any single item is missing
		PFS overall score	Calculated as the mean of all 15 items	Missing if any single item is missing
		Change from baseline in PFS domain and overall scores	Calculated as: postbaseline PFS score – Baseline PFS score	Missing if baseline or postbaseline value is missing
		Change from Week 72 in PFS domain and overall scores	Calculated as: postbaseline PFS score – Week 72 PFS score	Missing if baseline or postbaseline value is missing

Abbreviations: BMI = body mass index; CRF = case report form; CSV = comma separated values; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FFA = free fatty acids; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; HOMA = homeostasis model assessment; HOMA2 B = homeostasis model assessment 2 B; HOMA2 IR = homeostasis model assessment 2 IR; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MCS = Mental Component Score; OGTT = oral glucose tolerance test; PGI--C = patient global impression of change; PCS = Physical Component Score; PFS = Power of Food Scale; PGI-S = patient global impression of severity; PROMIS = Patient-Reported Outcomes Measurement Information System; SBP = systolic blood pressure; SF-36 = Short Form 36-item Health Survey; SF-36v2 = Short Form 36 Health Survey Version 2; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; VAS = visual analog scale; VLDL = very low-density lipoprotein.

[a] Derive HOMA2 B and HOMA2 IR using the calculator at https://www.rdm.ox.ac.uk/about/our-clinical-facilities-and-mrc-units/DTU/software/homa

[b] Maruish 2011.

[c] Kolotkin et al. 2017, 2019.

[d] EuroQol Research Foundation 2019.

[e] Derive EQ-5D-5L UK population-based index score using the calculator at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

[f] Northwestern 2016.

[g] Flint et al. 2000.

[h] Cappelleri et al. 2009; Lowe et al. 2009.

Note: For EQ-5D VAS and Appetite VAS a higher value indicates better health state.

Table GZGP.4.6. Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Estimand Data Points Set / Population[a]	Analysis Method	Time Point[b]	Analysis Type
Body weight	Percent change from baseline in body weight (%)	Treatment Regimen	ANCOVA with PMI	Week 72 visit	Primary endpoint, main analysis
		Efficacy	MMRM	Week 72 visit	Primary endpoint, main analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176	Exploratory analysis
		Treatment Regimen	ANCOVA with MI-TP	Week 72 visit	Primary endpoint, sensitivity analysis
		Treatment Regimen	ANCOVA with mMI	Week 72 visit	Primary endpoint, sensitivity analysis
		Treatment Regimen	Cumulative distribution function (CDF) plot with PMI	Week 72 visit	Exploratory analysis
		Efficacy	CDF plot with MI	Week 72 visit	Exploratory analysis
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI	Week 176 visit	Key secondary, main analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Key secondary, main analysis
	Percentage of participants with ≥x% body weight reduction from baseline, where x = 5, 10, 15, 20	Treatment Regimen	Logistic regression with PMI	Week 72 visit	Key secondary, main analysis
		Efficacy	Logistic regression with MI	Week 72 visit	Key secondary, main analysis
		Efficacy / Randomized participants with prediabetes	Logistic regression with MI	Week 176	Exploratory analysis
	Percentage of participants with ≥5% body weight reduction from baseline	Treatment Regimen / Randomized participants with prediabetes	Logistic regression with PMI	Week 176 visit	Additional secondary

		Efficacy / Randomized participants with prediabetes	Logistic regression with MI	Week 176 visit	Additional secondary
	Change from baseline in body weight (kg)	Efficacy	MMRM	Week 72 visit	Additional secondary
BMI	Change from baseline in BMI (kg/m^2)	Efficacy	MMRM	Week 72 visit	Additional secondary
	Percentage of participants with BMI target value of <35 kg/m^2	Efficacy	Logistic regression with MI	Week 72 visit	Exploratory analysis
	Percentage of participants with BMI target value of <30 kg/m^2	Efficacy	Logistic regression with MI	Week 72 visit	Exploratory analysis
	Percentage of participants with BMI target value of <25 kg/m^2	Efficacy	Logistic regression with MI	Week 72 visit	Exploratory analysis
Waist circumference	Change from baseline in waist circumference (cm)	Treatment Regimen	ANCOVA with PMI	Week 72 visit	Key secondary, main analysis
		Efficacy	MMRM	Week 72 visit	Key secondary, main analysis
Blood pressure	Change from baseline in SBP (mmHg)	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Key secondary, main analysis
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Key secondary, main analysis
	Change from baseline in DBP (mmHg)	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary
Lipid parameter	Percent change from baseline in triglycerides (%)	Treatment Regimen	ANCOVA with PMI[c] (log transformation; pooled OFG doses)	Week 72 visit	Key secondary, main analysis
		Efficacy	MMRM (log transformation; pooled OFG doses)	Week 72 visit	Key secondary, main analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled OFG doses)	Week 176 visit	Exploratory analysis
	Percent change from baseline in non-HDL-cholesterol (%)	Treatment Regimen	ANCOVA with PMI[c]	Week 72 visit	Key secondary, main analysis

			(log transformation; pooled OFG doses)		
		Efficacy	MMRM (log transformation; pooled OFG doses)	Week 72 visit	Key secondary, main analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled OFG doses)	Week 176 visit	Exploratory analysis
	Percent change from baseline in total cholesterol (%)	Treatment Regimen	ANCOVA with PMI[c] (log transformation; pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (log transformation; pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled OFG doses)	Week 176 visit	Exploratory analysis
	Percent change from baseline in LDL-cholesterol (%)	Treatment Regimen	ANCOVA with PMI[c] (log transformation; pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (log transformation; pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled OFG doses)	Week 176 visit	Exploratory analysis
	Percent change from baseline in HDL-cholesterol (%)	Treatment Regimen	ANCOVA with PMI[c] (log transformation; pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (log transformation; pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled OFG doses)	Week 176 visit	Exploratory analysis

	Percent change from baseline in VLDL-cholesterol (%)	Treatment Regimen	ANCOVA with PMI[c] (log transformation; pooled OFG doses)	Week 72 visit	Exploratory analysis
		Efficacy	MMRM (log transformation; pooled OFG doses)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled OFG doses)	Week 176 visit	Exploratory analysis
Glycemic control	Change from baseline in fasting glucose (mg/dL and mmol/L)	Efficacy	MMRM	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Additional secondary
	Change from baseline in HbA1c (%)	Efficacy	MMRM	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Additional secondary
	Time to onset of T2D	Treatment Regimen / Randomized participants with prediabetes	Cox-proportional hazards (pooled OFG doses)	Up to Week 176 visit	Key secondary, main analysis
		Efficacy / Randomized participants with prediabetes	Cox-proportional hazards model (pooled OFG doses)	Up to Week 176 visit	Key secondary, main analysis
	Percentage of patients achieving normoglycemia	Treatment Regimen / Randomized participants with prediabetes	Logistic regression with PMI	Weeks 72 and 176 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	Logistic regression with MI	Weeks 72 and 176 visit	Additional secondary
	Change from baseline in point x OGTT (mg/dL), where x = 30, 60, 90, and 120 minutes	Efficacy	MMRM	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Weeks 120 and 176 visit	Exploratory analysis
Insulin sensitivity	Percent change baseline in fasting insulin (%)	Efficacy	MMRM (log transformation)	Week 72 visit	Additional secondary

Renal function	Percent change from baseline in UACR (%)	Efficacy	MMRM (log transformation)	Week 72 visit	Exploratory analysis
	Change from baseline in eGFR CKD-EPI Cystatin-C (ml/min/1.73m^2)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Change from baseline in eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
Inflammatory biomarker	Change from baseline in hsCRP (mg/L)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Percent change from baseline in hsCRP (%)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
Free fatty acids	Change from baseline in FFAs (mmol/L)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Percent change from baseline in FFAs (%)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
Homeostasis Model Assessment	Change from baseline in HOMA2 B (insulin)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Percent change from baseline in HOMA2 B (insulin)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Change from baseline in HOMA2 IR (insulin)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Percent change from baseline in HOMA2 IR (insulin)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Change from baseline in HOMA2 B (C-peptide)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Percent change from baseline in HOMA2 B (C-peptide)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Change from baseline in HOMA2 IR (C-peptide)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
	Percent change from baseline in HOMA2 IR (C-peptide)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
SF-36	Change from baseline in SF-36v2 Acute Form Physical Functioning domain score	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary

		Treatment Regimen / Randomized participants with limitations in physical function at baseline[d]	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with limitations in physical function at baseline[d]	MMRM (pooled OFG doses)	Week 72 visit	Exploratory analysis
	Change from baseline in SF-36v2 Acute Form domain scores (all except Physical Functioning), PCS and MCS	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary
PGI-S	PGI-S rating	Treatment Regimen	Shift from baseline (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	Shift from baseline (pooled OFG doses)	Week 72 visit	Additional secondary
PGI-C	PGI-C rating	Treatment Regimen	Descriptive statistics (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	Descriptive statistics (pooled OFG doses)	Week 72 visit	Additional secondary
IWQOL-Lite-CT	Change from baseline in physical function composite score	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary
	Change from baseline in physical domain score	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary
	Change from baseline in psychosocial domain score	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary
	Change from baseline in total score	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Additional secondary
EQ-5D-5L	Change from baseline in EQ-5D-5L utility index and VAS	Treatment Regimen	ANCOVA with PMI (pooled OFG doses)	Week 72 visit	Additional secondary

		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Exploratory analysis
PROMIS	Change from baseline in individual and total scores	Treatment Regimen	ANCOVA with PMI	Week 24 and 72 visits	Exploratory analysis
		Efficacy	MMRM (pooled OFG doses)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (pooled OFG doses)	Week 176	Exploratory analysis
Appetite VAS	Change from baseline in appetite VAS item and overall scores	Treatment Regimen	ANCOVA with PMI (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Treatment Regimen / Randomized participants without prediabetes		Week 74 visit	Exploratory analysis
		Treatment Regimen / Randomized participants with prediabetes		Week 176	Exploratory analysis
		Efficacy	MMRM (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Efficacy / Randomized participants without prediabetes		Week 74 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes		Week 176 visit	Exploratory analysis
	Change from Week 72 in appetite VAS item and overall scores	Treatment Regimen / Randomized participants without prediabetes	ANCOVA with PMI (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 74 visit	Exploratory analysis
		Efficacy / Randomized participants without prediabetes	MMRM (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 74 visit	Exploratory analysis
Power of food scale (PFS)	Change from baseline in PFS domain and overall scores	Treatment Regimen	ANCOVA with PMI (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Treatment Regimen / Randomized participants without prediabetes		Week 74 visit	Exploratory analysis

		Treatment Regimen / Randomized participants with prediabetes		Week 176	Exploratory analysis
		Efficacy	MMRM (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Efficacy / Randomized participants without prediabetes		Week 74 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes		Week 176 visit	Exploratory analysis
	Change from Week 72 in PFS domain and overall scores	Treatment Regimen / Randomized participants without prediabetes	ANCOVA with PMI (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 74 visit	Exploratory analysis
		Efficacy / Randomized participants without prediabetes	MMRM (OFG 6 mg, 12 mg, and 36 mg doses and pooled OFG doses)	Week 74 visit	Exploratory analysis

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CDF = cumulative distribution function; CSV = comma separated values; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FFA = free fatty acids; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; IWQOL-Lite-CT = impact of weight on quality of life-lite clinical trials; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MCS = Mental Component Score; MI = multiple imputation; MMRM = mixed-effects model for repeated measures; OGTT = oral glucose tolerance test; PGI-S = patient global impression of severity; PGI-C= patient global impression of change; PCS = Physical Component Score; PFS = power of food scale; PMI = primary multiple imputation; PROMIS = patient-reported outcomes measurement information system; SBP = systolic blood pressure; SF-36 = Short Form 36-item Health Survey; TP = tipping point; UACR = urine albumin-creatinine ratio; VAS = visual analog scale; VLDL = very low-density lipoprotein.

[a] Population is displayed if different from Randomized Participants.

[b] Assessments collected at multiple postbaseline visits will be analyzed at those scheduled visits using MMRM as supplemental analyses, in addition to the primary time point listed in the table.

[c] PMI strategy will be performed after the log transformation.

[d] The limitation in physical function at baseline is defined as PGI-S response at baseline of “moderately limited,” “very much limited,” or “extremely limited.”

4.4.1. Key Secondary Endpoints

4.4.1.1. Definition of endpoints

The definitions of key secondary endpoints are specified in Table GZGP.4.5.

4.4.1.2. Main analytical approach

The analytical approaches for the key secondary endpoints are specified in Table GZGP.4.6.

4.4.1.3. Sensitivity Analyses

No sensitivity analyses are planned for key secondary endpoints.

4.4.1.4. Supplementary analyses

No supplemental analyses are planned for key secondary endpoints.

4.4.2. Supportive secondary Endpoints

The definitions of additional secondary endpoints are specified in Table GZGP.4.5. Additionally, the analytical approaches are specified in Table GZGP.4.6.

4.5. Exploratory Endpoints/Estimands Analysis

Exploratory endpoints and analyses are specified in Table GZGP.4.5 and Table GZGP.4.6. Additional exploratory analyses will be described in the Exploratory Analyses and Health Technology Analyses Plan.

4.6. Safety Analyses

The planned safety analyses are consistent with compound-level safety standards, which are based on various sources, including company standards, internal and external subject matter experts, publications from cross-industry initiatives (for example, PHUSE 2013, PHUSE 2015, PHUSE 2017, PHUSE 2018, PHUSE 2022), and publications from regulatory agencies (for example, EMA 2014, CDER/BIRRS 2022a, 2022b). Descriptions of the safety analyses are provided in this SAP, but some details are found in compound-level safety standards.

For safety interpretation, p-values will not be used for hypothesis testing. P-values will be considered as a number between 0 and 1 that gives an idea of how strong the evidence is for an imbalance between study intervention arms. The evidence for an imbalance is stronger toward 0 and weaker toward 1. Similarly, confidence intervals will not be used for hypothesis testing. They reflect the uncertainty of an estimate.

Unless otherwise specified, safety analyses will be conducted using the safety participants (Table GZGP.3.1) and the safety data points set (Table GZGP.3.2). It is noted that for some safety endpoints, such as treatment discontinuation due to AE and so forth, the analyses will be based on data observed during treatment period only.

Summary tables with risk difference will be sorted by decreasing order in risk difference.

Additionally, the planned safety analyses will be provided for participants with prediabetes at randomization for the final lock.

4.6.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by treatment group for safety participants. Descriptive statistics for participant weeks (or days) of exposure and total participant years in exposure will be provided. Overall exposure will be summarized in total participant-year (PY) of exposure, derived in the following manner:

total PY of exposure = sum of duration of exposure in days (for all participants in treatment group) / 365.25

The frequency of participants falling into different exposure ranges will be summarized:

- >0; ≥4 weeks; ≥8 weeks; ≥12 weeks; ≥16 weeks; ≥20 weeks; ≥24 weeks; ≥36 weeks; ≥48 weeks, ≥60 weeks, and ≥72 weeks.

For participants with prediabetes at baseline, the following additional exposure ranges will be summarized:

- ≥84 weeks; ≥96 weeks; ≥108 weeks; ≥120 weeks; ≥132 weeks; ≥144 weeks; ≥156 weeks; ≥168 weeks, and ≥176 weeks.

No p-values will be reported.

4.6.2. Adverse Events

The planned summaries for AEs are provided in Table GZGP.4.7 and are described more fully in compound-level safety standards.

Table GZGP.4.7. Summary Tables Related to Adverse Events

Analysis	Method	Population/Period
Overview of AEs, including • TEAE • SAE • death, and • permanent discontinuation from study intervention due to an AE.	Fisher's exact	Safety/TP + FP (TP for study treatment discontinuation due to an AE)
TEAEs by PT within SOC	Fisher's exact	Safety/TP + FP
TEAEs by PT	Fisher's exact	Safety/TP + FP
Maximum Severity TEAEs by PT within SOC	Fisher's exact	Safety/TP + FP
TEAEs with incidence ≥5% by PT	Fisher's exact	Safety/TP + FP
SAEs by PT within SOC	Fisher's exact	Safety/TP + FP
Primary AEs leading to permanent discontinuation of study intervention by PT within SOC	Fisher's exact	Safety/TP
Primary AEs leading to permanent discontinuation of study by PT within SOC	Fisher's exact	Safety/TP
AEs leading to study intervention interruption by PT within SOC	Fisher's exact	Safety/TP
AEs leading to study intervention modifications by PT within SOC	Fisher's exact	Safety/TP
Listing of SAEs		Safety/TP + FP

Analysis	Method	Population/Period
Listing of primary AEs leading to permanent discontinuation of study intervention		Safety/TP
Listing of primary AEs leading to permanent discontinuation of study		Safety/TP + FP
Listing of deaths		Safety/TP + FP
Listing AEs related to suspected overdosing[a]		Safety/TP
Narratives for participants with at least 1 notable event		Randomized/TP + FP

Abbreviations: AE =Adverse Event; FP = follow-up period; TP = treatment period; TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event; PT = Preferred Term; SOC = System Organ Class.

[a] Any dose of orforglipron greater than 100 mg within a 24-hour time period will be considered a potential overdose. Considering the maximum dose any participant may receive during the study treatment period is 36 mg of orforglipron, any dose of study intervention ≥3 capsules within a 24-hour time period will be considered a potential overdose. Such cases are supposed to be entered as an AE in the eCRF.

4.6.3. Clinical Laboratory Evaluation

The planned summaries for clinical laboratory evaluations are provided in Table GZGP.4.8 and are described more fully in compound-level safety standards.

Table GZGP.4.8. Summary Tables Related to Clinical Laboratory Evaluations

Analysis	Method	Population/Period
Box plots and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plots and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Summary for participants with elevated or low values meeting specified levels	Descriptive statistics	Safety/TP + FP
Listing of abnormal laboratory findings		Safety/TP + FP

Abbreviations: CI = confidence intervals; FP = follow-up period; SD = standard deviation; TP = treatment period.

4.6.4. Vital Signs and Physical Characteristics

Triplicate vital signs will be collected at the same visit, thus the mean of these measurements will be used for the vital signs analyses. The planned summaries for vital signs (SBP, diastolic blood pressure, and pulse rate) are provided in Table GZGP.4.9, and are described more fully in the compound-level safety standards.

Table GZGP.4.9. Summary Tables Related to Vital Signs

Analysis	Method	Population/Period
Box plots and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plots and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Analysis of pulse rate and change from baseline	MMRM	Safety/TP + FP
Summary for participants meeting specific blood pressure and pulse rate levels	Descriptive statistics	Safety/TP + FP
Shift of maximum-to-maximum for pulse rate	Descriptive statistics	Safety/TP + FP

Abbreviations: CI = confidence intervals; FP = follow-up period; MMRM = mixed model repeated measures; SD = standard deviation; TP = treatment period.

4.6.5. Electrocardiograms

Triplicate electrocardiograms (ECGs) will be collected at the same visit; thus the mean of these measurements will be used for the analysis. The planned summaries for ECG parameters are provided in Table GZGP.4.10 and are described more fully in the compound-level safety standards.

Table GZGP.4.10. Summary Tables Related to ECG Parameters

Analysis	Method	Population/Period
Box plot and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plot and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Heart rate and PR interval in specified categories	Descriptive statistics	Safety/TP + FP
Analysis for change from baseline in ECG parameters (heart rate, PR interval)	MMRM	Safety/TP + FP

Abbreviations: CI = confidence intervals; FP = follow-up period; MMRM = mixed model repeated measures; SD = standard deviation; TP = treatment period.

4.6.6. Safety Topics of Interest

This section includes safety topics of interest whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, safety topics of interest will be identified by one or more standardized Medical Dictionary for Regulatory Activities (MedDRA) query(ies) (SMQs), system organ class (SOC), high level terms (HLT), FDA medical query(ies) (FMQ), or by a Lilly-defined MedDRA preferred term (PT) listing based upon the review of the most current MedDRA Version, or by relevant laboratory changes. Search criteria are detailed in the compound-level safety standards.

The planned analyses for safety topics of interest are provided in Table GZGP.4.11 and are described more fully in compound-level safety standards.

Table GZGP.4.11. Description and Analyses of Safety of Interest

Special Safety Topic	Short Description	Analysis	Method	Population/Period
Major Adverse Cardiovascular Events	Death and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise: Clinical Endpoint Committee (CEC).	Positively adjudicated MACE by category/subcategory and PT	Fisher's exact	Safety/TP + FP
		Listing of MACE reported by investigator (whether or not positively adjudicated)		Safety/TP + FP
Arrhythmias and Cardiac Conduction Disorders	The treatment-emergent (TE) arrhythmias and cardiac conduction disorders events will be derived using the MedDRA PTs contained in certain SMQs.	TE arrhythmias and cardiac conduction disorders by PT nested within SMQ and HLT[a]	Fisher's exact	Safety/TP + FP
Hypotension, Orthostatic Hypotension, and Syncope	The TE hypotension, orthostatic hypotension, and syncope events will be derived using MedDRA PTs.	TE hypotension, orthostatic hypotension, and syncope by PT[a]	Fisher's exact	Safety/TP + FP
Hypoglycemia	The 2023 American Diabetes Association position statement on glycemic targets (El Sayad et al. 2023) will be used to define: • Level 1 hypoglycemia • Level 2 hypoglycemia • Level 3 hypoglycemia (severe/serious hypoglycemia) Nocturnal hypoglycemia events (including severe hypoglycemia) **occur at night** and presumably during sleep.	Incidence (percent of patients experiencing 1 or more episode) of level 2 or level 3 hypoglycemia	Logistic regression	Safety/TP + FP excluding events after initiation of new antihyperglycemic therapy as defined in Section 6.3 and Section 6.4. Supportive analysis: Safety/TP + FP regardless of initiation of new antihyperglycemic therapy
		Incidence of level 3 (severe/serious) hypoglycemia		
		Incidence of level 1 hypoglycemia (if warranted by data) [a]		
		Rate (episodes/patient/year) of level 2 or level 3 hypoglycemia	Negative binomial regression (the logarithm of days during the analysis interval will be adjusted as an offset)	
		Rate of level 3 (severe/serious) hypoglycemia		
		Rate of level 1 hypoglycemia (if warranted by data)		
		Listing of level 2 or level 3 hypoglycemia events		
		Listing of level 2 or level 3 nocturnal hypoglycemia events		
		Severe or serious TE gastrointestinal events by PT	Fisher's exact	Safety/TP + FP

Severe Gastrointestinal (GI) Adverse Events[b]	GI AEs using Gastrointestinal disorders SOC will be captured.	Study intervention discontinuation due to TE gastrointestinal events	Fisher's exact	Safety/TP + FP
		TE nausea, vomiting, diarrhea, constipation, and NVD by maximum severity	Fisher's exact	Safety/TP + FP
		Prevalence and incidence over time for TE nausea, vomiting, diarrhea, constipation, and NVD		Safety/TP + FP
		Plot of time to the onset of TE nausea, vomiting, diarrhea, constipation, and NVD	KM	Safety/TP + FP
		Plot of prevalence and incidence over time for TE nausea, vomiting, diarrhea, constipation, and NVD by maximum severity		Safety/TP + FP
Renal Safety	Laboratory measures related to renal safety will be analyzed. Renal events including acute renal failure and chronic renal failure exacerbation will be captured using SMQs. Dehydration events will be captured using SMQ.	Shift of min-to-min for eGFR estimated by the CKD-EPI equation		Safety/TP + FP
		Shift of max-to-max for UACR		Safety/TP + FP
		MMRM analyses for eGFR	MMRM	Safety/TP + FP
		MMRM analyses for UACR (log transformation)	MMRM	Safety/TP + FP
		TE renal events by PT nested within SMQ [a]	Fisher's exact	Safety/TP + FP
		TE dehydration events by PT [a]	Fisher's exact	Safety/TP + FP
Pancreatitis	The pancreatic enzyme data (p-amylase and lipase) will be observed through laboratory testing. All suspected cases of acute or chronic pancreatitis and AEs of severe or serious abdominal pain of unknown etiology will be sent for adjudication by an independent clinical endpoint committee.	Summary of maximum postbaseline pancreatic enzyme value exceeding the thresholds by maximum baseline		Safety/TP + FP
		MMRM analysis for pancreatic enzymes (p-amylase and lipase) with a log transformation (postbaseline/baseline)	MMRM	Safety/TP + FP
		Pancreatitis events by SMQ and PT for both investigator-reported events and subsequently confirmed adjudicated events	Fisher's exact	Safety/TP + FP
		Listing of adjudicated and investigator-reported pancreatitis		Safety/TP + FP
Thyroid Malignancies and C-Cell Hyperplasia	TE thyroid malignancies and C-cell hyperplasia will be identified using MedDRA HLT and PT.	TE thyroid C-cell hyperplasia and malignancies by PT	Fisher's exact	Safety/TP + FP
		Summary of maximum postbaseline calcitonin value in the thresholds		Safety/TP + FP

	The purpose of calcitonin measurements is to assess the potential effect of orforglipron on thyroid C-cell function.	Summary of participants with eGFR < 60 mL/min/1.73 m^2, serum calcitonin value ≥35 ng/L AND ≥50% increase from the baseline value[a]		Safety/TP + FP
		Summary of participants with eGFR ≥ 60 mL/min/1.73 m^2, serum calcitonin value ≥20 and <35 ng/L AND ≥50% increase from the baseline value[a]		Safety/TP + FP
		Summary of participants with eGFR ≥ 60 mL/min/1.73 m^2, serum calcitonin value ≥35 ng/L AND ≥50% increase from the baseline value[a]		Safety/TP + FP
		MMRM analysis for calcitonin (log transformation)	MMRM	Safety/TP + FP
Malignancies	The malignancy events will be derived using the MedDRA PTs contained certain SMQs.	TE malignancy by PT nested within SMQ[a]	Fisher's exact	Safety/TP + FP
Hepatic Safety	Hepatic labs include ALT, AST, ALP, TBL, DBL, and GGT. When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety eCRFs.	Abnormal postbaseline categories for hepatic safety parameters: ALT, AST, ALP, TBL, DBL, and GGT		Safety/TP + FP
		Hepatocellular drug-induced liver injury screening plot (TBL vs ALT or AST)		Safety/TP + FP
		Hepatocellular drug-induced liver injury screening table		Safety/TP + FP
		Cholestatic drug-induced liver injury screening table		Safety/TP + FP
		Cholestatic drug-induced liver injury screening plot (TBL vs ALP)		Safety/TP + FP
		Listing of potential hepatocellular drug-induced liver injury		Safety/TP + FP
		Listing of potential cholestatic drug-induced liver injury		Safety/TP + FP
		Participant profiles for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol).		Safety/TP + FP
Gallbladder and Biliary Tract Disorders	All events of TE gallbladder and biliary tract disorders will be identified by using certain SMQs.	TE gallbladder and biliary tract disorders by PT nested within SMQ[a]	Fisher's exact	Safety/TP + FP

Hypersensitivity Reactions	All events of TE allergic reaction and hypersensitivities will be identified by using certain SMQs.	TE allergic reaction and hypersensitivities by PT nested within SMQ [a]	Fisher's exact	Safety/TP + FP
Depression, Suicidal Ideation, and Behavior	AEs will be searched using MedDRA PTs from certain SMQs.	TE major depressive disorder, suicidal ideation, or behavior events by PT nested within SMQ [a]	Fisher's exact	Safety/TP + FP
	Suicide-related thoughts and behaviors will be collected based on the C-SSRS.	Summary of C-SSRS categories and composite measures		Safety/TP + FP
		Summary of C-SSRS Treatment Emergent Events		Safety/TP + FP
	Patient health questionnaire-9 (PHQ-9) will be collected to assesses the specific diagnostic symptoms that determine the presence of a clinical depressive disorder. The PHQ-9 total scores will be categorized as none (not depressed), mild, moderate, moderately severe, and severe	Shift of each baseline category (maximum value) versus each postbaseline category (maximum value)		Safety/TP + FP
		Shift of categories based on the maximum values during baseline and postbaseline: • any increase in depression category (that is, worsening of depression) • increase from No or Mild Depression to Moderate, Moderately Severe, or Severe Depression • increase from Mild or Moderate Depression to Moderately Severe or Severe Depression		Safety/TP + FP
Abuse Potential	AEs will be searched using a modified abuse potential FMQ.	TE abuse potential events by PT [a]	Fisher's exact	Safety/TP + FP

Abbreviations: AE = adverse event; ALP = serum alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CEC = clinical endpoint committee; CKD-EPI = Chronic Kidney Disease Epidemiology; C-SSRS = Columbia-Suicide Severity rating scale; CV = cardiovascular; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; DBL = direct bilirubin; FDA = United States Food and Drug Administration; FMQ = FDA Medical Query; FP = follow-up period; GGT = gamma glutamyl transferase; GI = gastrointestinal; HLT = high-level term; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; MMRM = mixed model repeated measure; PT = Preferred Term; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event; TBL = total bilirubin; TP = treatment period; UACR = urinary albumin-to-creatinine ratio; vs = versus.

[a] For these tables, if the number of events is less than 10, a listing will be provided instead.

[b] Additionally, all GI events will be analyzed.

Note: Listings and participant profiles may be provided through interactive display tools instead of a static display.

4.7. Other Analyses

4.7.1. Subgroup analyses

Subgroup analyses will be conducted for the primary endpoint with the treatment regimen estimand:

- percent change in body weight from baseline at Week 72 visit.

The variables for subgroup analysis are specified in Table GZGP.6.1.

The ANCOVA model specified in Section 4.1.2.1.1, will be fitted separately within each subgroup. The least squares (LS) mean, LS mean difference, standard error (SE), and 95% confidence interval will be presented. The LS means and variance-covariance estimates from these separate models will be used to test the treatment-by-subgroup interaction at a significance level of 0.10.

If the subgroup factor is part of the strata variable, a new strata variable that excludes the subgroup categories will be used.

If the number of participants is too small (<10%) within a subgroup, then the subgroup categories may be redefined prior to unblinding the study. If any category within the subgroup is <5% of the total population, only descriptive statistics will be provided for that category (that is, there will be no inferential testing within the subgroup category).

A forest plot including the treatment difference and 95% confidence interval estimated for each subgroup level will be presented.

A Bayesian shrinkage method will be used to provide adjusted estimates and inferences from subgroup analyses to potentially account for multiplicity. Following regulatory guidance (FDA 2019; Rothmann 2021), for a given baseline characteristic with k subgroups, let Y_i $(i = 1, \ldots, k)$ be the observed sample estimate of the treatment effect in subgroup i. The following hierarchical model will be used:

$$Y_i \sim N(\mu_i, \sigma_i^2),$$

$$\mu_i \sim N(\mu, \tau^2),$$

$$\mu \sim N(0, 4^2),$$

$$\frac{1}{\tau^2} \sim \Gamma(0.0001, 0.0001)$$

Additional subgroup evaluations may be conducted as exploratory analyses.

4.8. Interim Analyses

No interim analyses are planned for Study GZGP. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, Protocol GZGP must be amended.

4.8.1. Data Monitoring Committee

A data monitoring committee (DMC) is not planned for this study.

An independent DMC will be established for interim safety monitoring of Study J2A-MC-GZGS (ACHIEVE-4) (GZGS), "A Phase 3, Open Label, Study of Once-Daily orforglipron Compared with Insulin Glargine in Adult Participants with Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk", a study within the orforglipron Phase 3 program for chronic weight management (CWM) and T2D. The DMC will have the responsibility to review unblinded interim safety analysis results from Study GZGS. The DMC may be asked to review unblinded safety data from Study GZGP if a need arises following the blinded trial-level safety reviews (TLSRs) conducted by the sponsor. If needed, permanent data transfers will occur for the purposes of supporting the DMC. Only the statisticians from the statistical analysis center (SAC) will have access to the unblinded data that are presented to the DMC. The SAC and members of the DMC will abide by the principles and responsibilities described in the Study GZGS DMC charter, which includes keeping all unblinded information confidential until the planned unblinding of the trial.

4.9. Changes to Protocol-Planned Analyses

There are no changes to the analyses described in the protocol.

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 standard deviation (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.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for randomly assigned participants. The listing of basic demographic characteristics (that is, age, sex, ethnicity, race, country, baseline body weight, and so forth.) for randomly assigned participants will be provided. Additionally, demographics and baseline characteristics will be provided for participants with prediabetes at randomization for the final lock.

The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages. No inferential analysis for the comparability of baseline demographics and characteristics across treatment groups will be performed.

Table GZGP.6.1 describes the specific variables and how they will be summarized. The last column specifies variables used for the subgroup analysis described in Section 4.7.1.

Table GZGP.6.1. Demographics and Baseline Characteristics with Variables for Subgroup Analysis

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]
Demographics			
Age[b]	Yes	<65, ≥65 years	X
		<75, ≥75 years	
		<65, ≥65 and <75, ≥75 and <85, ≥85 years	
Sex	No	Male, Female	X
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino	X
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X
Country	No	By each country	X
Geographic region	No	North America, Europe, Other	
		North America, Europe, Asia, Australia, or Central/South America	
Height (cm)	Yes		
Baseline waist circumference (cm)	Yes		
Baseline body weight (kg)	Yes		
Baseline BMI	Yes	(≥27 to <30, ≥30 to <35, ≥35 to <40, ≥40 kg/m^2	
		≤ median, < median	X

Caffeine use	No	Never, Current, Former	
Alcohol use	No	Never, Current, Former	
Tobacco use	No	Never, Current, Former	
Nicotine Replacement use	No	Never, Current, Former	
Recreational drug use - methamphetamine	No	Never, Current, Former	
Recreational drug use - cocaine	No	Never, Current, Former	
Baseline Disease Characteristics			
Baseline systolic blood pressure (mmHg)	Yes		
Baseline diastolic blood pressure (mmHg)	Yes		
Baseline pulse rate (beats/min)	Yes		
Baseline eGFR CKD-EPI Cystatin-C (mL/min/1.73m^2)	Yes	<60, ≥60 mL/min/1.73m^2	
Baseline eGFR CKD-EPI Creatinine (mL/min/1.73m^2)	Yes	<60, ≥60 mL/min/1.73m^2	
Baseline UACR (g/kg)	Yes	<30, ≥30 and ≤300, >300 g/kg	
Baseline triglycerides (mg/dL)	Yes		
Baseline total cholesterol (mg/dL)	Yes		
Baseline VLDL-cholesterol (mg/dL)	Yes		
Baseline non-HDL-cholesterol (mg/dL)	Yes		
Baseline LDL-cholesterol (mg/dL)	Yes		
Baseline HDL-cholesterol (mg/dL)	Yes		
Baseline fasting insulin (pmol/L)	Yes		
Baseline HbA1c (%)	Yes		
Baseline HbA1c (mmol/mol)	Yes		
Baseline fasting glucose (mg/dL)	Yes		
Baseline fasting glucose (mmol/L)	Yes		
Duration of obesity (years)	Yes		
Prediabetes[c]	No	Yes, No	X
Baseline Medical History			
Impaired glucose intolerance	No	Yes, No	X
Hypertension	No	Yes, No	X
Dyslipidemia	No	Yes, No	X
Hyperuricemia and Gout	No	Yes, No	X
Cardiovascular disease, myocardial infarction, and angina	No	Yes, No	X
Cerebral infarction and TIA	No	Yes, No	X
Menstrual disorder and infertility	No	Yes, No	X
OSAS and obesity-hypoventilation syndrome	No	Yes, No	X
Motor dysfunction: arthritis/osteoarthritis	No	Yes, No	X

NAFLD / MAFLD	No	Yes, No	X
Obesity-related renal disease	No	Yes, No	X
Comorbidity number category	No	None, 1, 2, 3, 4, ≥5	

Abbreviations: eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAFLD = metabolic associated fatty liver disease; NAFLD = nonalcoholic fatty liver disease; OSAS = obstructive sleep apnea syndrome; TIA = transient ischemic attack; UACR = urine albumin-to-creatinine ratio; VLDL = very low-density lipoprotein.

[a] Subgroup analyses are defined in Section 4.7.1 with more details.

[b] Age in years will be calculated as length of the time interval from the imputed date of birth (July 1st in the year of birth collected in the eCRF) to the informed consent date.

[c] Prediabetes status at baseline is determined from the laboratory data in CLRM.

6.2. Appendix 2: Historical Illnesses and Preexisting Conditions

Historical illness is defined as a condition/event with an end date prior to the date of informed consent.

A preexisting condition is defined as a condition/event with a start date prior to the first dose of the study intervention and stop date that is at or after the informed consent date or has no stop date (that is, ongoing). Randomization date will be used if a participant has not been dosed.

The planned summaries for historical illness and preexisting conditions are provided in Table GZGP.6.2. No inferential analysis will be performed. Additionally, analyses for historical illnesses and preexisting conditions will be provided for participants with prediabetes at randomization for the final lock.

Table GZGP.6.2. Summary Tables Related to Historical Illness and Preexisting Conditions

Analysis	Population/Period
Historical illness by PT within SOC	Randomized
Preexisting conditions by PT within SOC	Randomized

Abbreviations: PT = preferred term; SOC = system organ class.

6.3. Appendix 3: Concomitant Medications

Medications that start before or at the last date of treatment period or follow-up period and are ongoing or ended during the treatment period or follow-up period will be classified as concomitant medication. Medications that start and end before the first dose date of the study intervention will be classified as prior therapy.

Baseline is defined as the corresponding medication taken on the day of the first dose of study intervention.

If there are no doses of study intervention, randomization date will be used instead of the first dose date.

The planned summaries for concomitant medications are provided in Table GZGP.6.3. Additionally, analyses for concomitant medications will be provided for participants with prediabetes at randomization for the final lock.

Table GZGP.6.3. Summary Tables Related to Concomitant Medications

Analysis	Method	Population/Period
CMs by PN	Fisher's exact	Randomized/TP + FP
Antihypertensive CMs at baseline by PN within ATC code		Randomized
Lipid lowering CMs at baseline by PN within ATC code		Randomized
Status change of antihypertensive, lipid lowering, and antihyperglycemic CMs		Randomized/TP
Antihyperglycemic CM initiated after baseline by PN	Fisher's exact	Randomized/TP
Antiemetic CM initiated after baseline by PN	Fisher's exact	Randomized/TP
Antidiarrheal CM initiated after baseline by PN	Fisher's exact	Randomized/TP
Prohibited concomitant medication and surgical procedure on weight management treatment by PN		Randomized Participants/TP
Prohibited concomitant medication on glycemic therapy by PN		Randomized Participants/TP

Abbreviations: ATC = Anatomical Therapeutic Chemical; CM = concomitant medication; PN = preferred name; FP = follow-up period; TP = treatment period.

Table GZGP.6.4 provides the protocol-specified concomitant medications of interest.

Table GZGP.6.4. Protocol-Specified Concomitant Medication

Category	Preferred Name / ATC Code
Antihypertensive Medication	All medications with ATC code containing 'C01', 'C03', 'C07', 'C08', or 'C09'
Lipid Lowering Medication	All medications with ATC code containing 'C10'
Antihyperglycemic Medication	All medications with ATC code containing 'A10', except for 'A10XA'

Abbreviations: ATC = Anatomical Therapeutic Chemical.

Table GZGP.6.5 provides the protocol-specified prohibited concomitant medication and surgical procedure rules.

Table GZGP.6.5. Prohibited Concomitant Medication Rules

Timing	Preferred Name / ATC Code	ATC Classification	Rule
Prohibited Concomitant Medication on Weight Management Treatment[a]			
Post baseline	All medications with ATC code of A08AA	Centrally acting antiobesity products	Any initiation is prohibited during treatment period
	All medications with ATC code of A08AB	Peripherally acting antiobesity products	Any initiation is prohibited during treatment period
	All medications with ATC code of A08AX	Other antiobesity drugs	Any initiation is prohibited during treatment period
	LIRAGLUTIDE		Any initiation is prohibited during treatment period
	SEMAGLUTIDE		Any initiation is prohibited during treatment period
	TIRZEPATIDE		Any initiation is prohibited during treatment period
	ORLISTAT		Any initiation is prohibited during treatment period
	SIBUTRAMINE		Any initiation is prohibited during treatment period
	PHENYLPROPANOLAMINE		Any initiation is prohibited during treatment period
	MAZINDOL		Any initiation is prohibited during treatment period
	PHENTERMINE		Any initiation is prohibited during treatment period
	LORCASERIN		Any initiation is prohibited during treatment period
	TOPIRAMATE		Any initiation is prohibited during treatment period if taken with PHENTERMINE
	BUPROPION		Any initiation is prohibited during treatment period if taken with NALTREXONE
Prohibited Surgical Procedure on Weight Management Treatment[a]			
Post-baseline	ABDOMINOPLASTY		Any initiation is prohibited during treatment period
	GASTRIC BANDING		Any initiation is prohibited during treatment period
	GASTRIC BYPASS		Any initiation is prohibited during treatment period
	LIPOSUCTION		Any initiation is prohibited during treatment period
	SLEEVE GASTRECTOMY		Any initiation is prohibited during treatment period
	CRYOLIPOLYSIS		Any initiation is prohibited during treatment period

Timing	Preferred Name / ATC Code	ATC Classification	Rule
	MUCOSAL ABLATION		Any initiation is prohibited during treatment period
	GASTRIC ARTERY EMBOLIZATION		Any initiation is prohibited during treatment period
	INTRAGASTRIC BALLOON		Any initiation is prohibited during treatment period
	DUODENAL-JEJUNAL ENDOLUMINAL LINER		Any initiation is prohibited during treatment period
Prohibited Concomitant Medication on Glycemic Therapy[a]			
Post-baseline	All medications with ATC code of A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Any initiation is prohibited during treatment period
	All medications with ATC code of A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	Any initiation is prohibited during treatment period
	DULAGLUTIDE		Any initiation is prohibited during treatment period
	LIRAGLUTIDE		Any initiation is prohibited during treatment period
	SEMAGLUTIDE		Any initiation is prohibited during treatment period
	EXENATIDE		Any initiation is prohibited during treatment period
	TIRZEPATIDE		Any initiation is prohibited during treatment period
	PRAMLINTIDE		Any initiation is prohibited during treatment period
	SITAGLIPTIN		Any initiation is prohibited during treatment period
	SAXAGLIPTIN		Any initiation is prohibited during treatment period
	LINAGLIPTIN		Any initiation is prohibited during treatment period
	ALOGLIPTIN		Any initiation is prohibited during treatment period

Abbreviations: ATC = Anatomical Therapeutic Chemical; T2D = Type 2 diabetes; ICE = intercurrent event.

[a] Use of these medications will be reviewed by the study team (blinded to study treatment) on a case-by-case basis to assess the clinical significance of the change in medication. After review, if deemed to be non-clinically significant, the case won't be considered as an ICE.

6.4. Appendix 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. Compliance will be calculated by

([total number of doses dispensed – total number of doses returned]/total number of doses expected to be administered) × 100%.

Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment group using the safety participants during treatment period. No inferential analysis will be performed.

Additionally, analyses for treatment compliance will be provided for participants with prediabetes at randomization for the final lock.

Participants with dose interruptions/modifications will be summarized with reasons. Interruptions will be summarized if the duration of the interruption is 7 days or longer for all reasons other than an AE.

6.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan. A listing and summary of important protocol deviations by treatment group will be provided for all randomly assigned participants. No inferential analysis will be performed. Additionally, analyses for important protocol deviations will be provided for participants with prediabetes at randomization for the final lock.

6.6. Appendix 6: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following

Summary of AEs, provided as a dataset which will be converted to an XML file. Both serious AEs (SAEs) and "Other" Non-Serious Adverse Events are summarized by treatment group and MedDRA PT.

- An AE is considered "Serious" whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each SAE and "Other" AE, for each term and treatment group, the following are provided
    - the number of participants at risk of an event
    - the number of participants who experienced each event term, and
    - the number of events experienced.
- For each SAE, these additional terms are provided for EudraCT:
    - the total number of occurrences causally related to treatment
    - the total number of deaths, and
    - the total number of deaths causally related to treatment.
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of participants in every treatment group may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4% and 5%.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

Demographic table including the following age ranges required by EudraCT: ≥18 to <65 years, ≥65 to <85 years, and ≥85 years.

6.7. Appendix 7: Body Composition Assessments via Dual-Energy X-ray Absorptiometry (DXA)

This section is applicable to the participants who are enrolled in the Dual Energy X-ray Absorptiometry (DXA) appendix.

The primary objective of DXA addendum is to demonstrate that orforglipron (6 mg, 12 mg, and 36 mg pooled doses) once daily (QD) is superior to placebo in percent change in total body fat mass loss from baseline to 72 weeks.

Percent change of total body fat mass will be calculated as

[(Total body fat mass at 72 weeks - Total body fat mass at baseline) / Total body fat mass at baseline] ×100

The secondary objectives include:

- To demonstrate that orforglipron (6 mg, 12 mg, and 36 mg pooled doses) QD is superior to placebo with regards to change in total body fat mass (kg) from baseline to 72 weeks, and
- To assess, for orforglipron (6 mg, 12 mg, and 36 mg pooled doses) QD, the following parameters, from baseline to 72 weeks:
    - percent change in total body lean mass, and
    - change in total body lean mass (kg).

Percent change of total body lean mass will be calculated as

[(Total body lean mass at 72 weeks - Total body lean mass at baseline) / Total body lean mass at baseline] × 100

DXA will be performed at the baseline and at the end of 72-week treatment (Visit 21), or at the early discontinuation visit (ED).

In addition to the endpoints listed above, the following parameters may also be analyzed:

- total body mass (kg)
- total body fat mass (kg)
- total body lean mass (kg)
- percent body fat mass = total body fat mass / total body mass × 100
- percent body lean mass = total body lean mass / total body mass × 100
- fat lean mass ratio = total body fat mass / total body lean mass
- fat lean mass loss ratio = total body fat mass change / total body lean mass change, and
- fat lean mass percent loss ratio = percent change of total body fat mass / percent change of total body lean mass.

Unless otherwise specified, all analyses for the variables measured or derived from DXA will be conducted on all randomized participants who are enrolled in the DXA addendum (as indicated in the interactive web response system [IWRS]). Baseline is defined as the last non-missing data collected at randomization (prior to first dosing of study drug).

Descriptive summary statistics (for example, sample size, mean, SD, minimum, maximum, and median) of all the parameters listed above (but not limited to) will be provided by treatment group (placebo, orforglipron 6 mg, orforglipron 12 mg, orforglipron 36 mg, and all orforglipron pooled doses) at baseline and postbaseline visits (for both the actual value and change from baseline value).

In addition, a summary of demographics and baseline characteristics for participants in the DXA addendum will be provided.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided. There will be no multiplicity adjustment.

The analysis of covariance (ANCOVA) model described in Section 4.1.2.1.1 will be used to analyze the continuous outcomes with treatment regimen estimand data points set. Missing data will be imputed as described in Section 4.1.2.1.2.

A sample size of approximately 156 randomly assigned participants (approximately 39 participants per arm) was 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.

6.8. Appendix 8: Sample Size Determinations for Patient-Reported Outcomes of Cravings and Psychological Impact of Food

A sample size of 94 participants (22 participants per orforglipron treatment group and 28 participants in the placebo group) will provide more than 70% power to demonstrate superiority of 6 mg, 12mg, 36 mg, and/or pooled doses of orforglipron to placebo with regards to mean change from baseline in overall appetite visual analog scale (VAS) score 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 each at a 2-sided significance level of 0.05 using a 2-sample t-test. Additionally, a difference of at least 15 mm in mean change from baseline in overall appetite VAS score at Week 72 for 6 mg, 12 mg, 36 mg, and pooled doses of orforglipron compared with placebo, and a common SD of 20 mm (Sadoul 2014).

Additionally, the sample size provides greater than 90% power to demonstrate superiority of 6 mg, 12mg, 36 mg, and/or pooled doses of orforglipron to placebo with regards to mean change from baseline in Power of Food Scale (PFS) score 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 each at a 2-sided significance level of 0.05 using a 2-sample t-test. Additionally, a difference of at least 0.7 in mean change from baseline in PFS overall score at Week 72 for 6 mg, 12 mg, 36 mg, and pooled doses of orforglipron compared with placebo, and a common SD of 0.66 (Ullrich 2013).

6.9. Appendix 9: Statistical Analysis for China

Multiplicity adjustments

Co-primary endpoints of mean percent change in body weight from baseline and percentage of participants who achieve ≥5% body weight reduction will be adopted as the co-primary endpoints in the China submission. The details of the family-wise type 1 error rate control strategy and methods for the hypotheses of co-primary endpoints and key secondary endpoints will be illustrated in a future version of SAP GZGP before primary database lock and unblinding.

General Considerations

Analyses will be performed for the following subpopulations

- participants enrolled in mainland China
- participants enrolled in East Asian Countries/regions (mainland China, Japan, Taiwan, and Korea).

The analysis methods for the above-mentioned subgroups will be similar to those described for the main part of SAP GZGP. If there is not sufficient number of participants in the subpopulation, summary statistics will be provided.

The analyses to be included will be documented in a separate list of analyses which should include disposition, demographics, and selected efficacy and safety endpoints.

6.10. Appendix 10: Statistical Analysis for Japan

The statistical analysis method for subpopulation analysis used for publication is described below.

The primary endpoint, mean percent change in body weight from baseline, percentage of participants who achieve ≥ 5% body weight reduction, key secondary endpoints and safety will be analyzed by the JASSO subpopulation analysis. The JASSO subpopulation analysis will be performed according to the criteria of both BMI and obesity related health problems according to the treatment flow of obesity disease in the obesity disease treatment guideline (JASSO 2022). The JASSO guideline states patients with either a BMI ≥ 27 and at least 2 obesity-related health problems or a BMI ≥ 35 and at least one obesity-related health problem will be treated with weight loss medications. There are 11 obesity-related health problems, including T2D, as shown in Table GZGP.6.6. All participants and participants with obesity disease according to the JASSO guideline will be compared.

Eleven obesity-related health problems

The JASSO guideline (JASSO 2022) defines 11 health problems for the diagnosis of "obesity disease" in participants who need weight reduction for medical reasons.

Table GZGP.6.6. The 11 Obesity-Related Health Problems

Obesity-related health problems	Medical History Term
1) Glucose intolerance disorder (T2D, IGT)	Glucose tolerance impaired (IGT, etc.)
2) Dyslipidemia	Dyslipidemia
3) Hypertension	Hypertension
4) Hyperuricemia and Gout	Hyperuricaemia Gout
5) Cardiovascular disease, myocardial infarction, and angina	Coronary artery disease
6) Cerebral infarction and TIA	Cerebral infarction
7) NAFLD	Nonalcoholic fatty liver disease
8) Menstruation disorder and infertility	Dysmenorrhoea Infertility Menstrual cycle abnormal
9) OSAS and obesity-hypoventilation syndrome	Obstructive sleep apnoea
10) Motor dysfunction: arthritis/osteoarthritis	Motor dysfunction Osteoarthritis
11) Obesity-related renal disease	Renal disease

Abbreviations: IGT = impaired glucose tolerance; NAFLD = non-alcoholic fatty liver disease; OSAS = obstructive sleep apnea; T2D = Type 2 diabetes; TIA = transient ischemic attack.

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Signature Page for VV-CLIN-117409 v1.0

Title Page

Protocol Title: A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared with Placebo in Adult Participants with Obesity or Overweight with Weight-Related Comorbidities (ATTAIN-1)

Protocol Number: J2A-MC-GZGP

Compound Number: LY3502970 (orforglipron)

Short Title: GZGP SAP

Sponsor Name: Eli Lilly and Company

Legal Registered Address: Indianapolis, Indiana USA 46285

Regulatory Agency Identifier Number(s)

Registry	ID
IND:	156143
EU trial number	2022-502839-19-00

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Version History

The statistical analysis plan (SAP) Version 1 for Study J2A-MC-GZGP (GZGP) was based on Protocol GZGP amendment (c), dated 23 October 2023.

GZGP SAP Version 2 included updates based on regulatory feedback. The major updates in the Version 2 amendment are listed in the table below.

GZGP SAP Version 3 was updated based on Protocol GZGP amendment (d), dated 30 April 2025, and regulatory feedback. The major updates in this amendment are listed in the table below.

SAP Version History Summary

SAP Version	Approval Date	Section	Change	Rationale
1	January 24, 2024		Not Applicable	Original version
2	November 6, 2024	1.1	Added prohibited glycemic therapy to Week 176 estimands	Clarification
		3	Removed note regarding no inferential comparisons for the summary of disposition, demographics, historical illness, and preexisting conditions	Clarification
		4.1.2.1.2	Further clarified the definition of Scenario 5 Removed the direct imputation method Updated the imputation method for Scenario 5B Added footnote in Table GZGP.4.4 for protocol deviation, inadvertent enrolment, and emergency unblinding	The direct imputation method is not fully aligned with the primary imputation strategy. Used a different method to handle Scenario 5B, based on simulation results from Liu et al. (2024) Clarified the distinction of imputing discontinuation due to

SAP Version	Approval Date	Section	Change	Rationale
				protocol deviation, inadvertent enrolment
		4.1.2.1.4	Updated the penalty range for the MI-TP analysis to -15% to 15%	Updated due to magnitude of projected weight loss
		4.1.2.2.3	Added a censoring condition for date of initiation of prohibited medications	To align with the defined estimand
		4.1.2.3	Updated MMRM model for safety analysis Clarified the definition of start time for different analyses	To be consistent with the PSAP
		4.4	Updated the derivation for the appetite VAS item and overall scores	To align with CRFs and the literature
		4.4	Added PRO analyses for the extension	Clarification
		4.6.6	Modified Table GZGP.4.11	To be consistent with the PSAP
		4.7.1	Updated the testing of subgroup effects. Added details for the Bayesian shrinkage method	Clarification
		Table GZGP.6.1	Updated subgroup analyses	Clarification
		Table GZGP.6.5	Added anti-hyperglycemic prohibited meds	To align with protocol
		6.9	Updated the statistical analysis for China	Clarification

SAP Version	Approval Date	Section	Change	Rationale
		6.10	Updated the statistical analysis for Japan	Clarification
3	See date on Page 1	1.1	Moved 6 mg endpoint "percentage of participants who achieve a body weight reduction of ≥20%" from key secondary list to additional secondary list, and updated hypotheses list accordingly	Limited clinical meaningfulness in anticipated percentage of participants achieving ≥20% weight reduction from 6 mg.
		1.1	Added Key secondary objective "Delayed progression to T2D at 190 weeks"	To align with protocol (d)
		1.1	Updated language for PGI endpoints	Clarification
		1.1	Added exploratory objectives for participants with prediabetes at randomization at 176 and 190 weeks	Clarification
		1.1	Remove prohibited glycemic therapy as an intercurrent event for the delayed progression to T2D endpoint	Due to rare use and minimal impact given the non-T2D study population
		1.1	Added safety estimand for the newly added key 2nd objective "Delayed progression to T2D at 190 weeks"	To align with protocol (d)

SAP Version	Approval Date	Section	Change	Rationale
		1.2	Added description for primary and final database lock	Clarification
		2.1	Updated the graphical testing scheme with the final version	Clarification
		3	Minor updates on data points sets	Clarification
		4	Replaced country with region in the statistical analysis models	To improve model convergence
		4.1.2.1.1	For method for continuous variables, added description for obtaining estimates of the pooled dose vs. placebo	Clarification
		4.1.2.1.2	Clarified the imputation strategy for all scenarios Updated study discontinuation reason categories for imputation purpose	Clarification
		4.1.2.1.5	For the method for binary variables, added interaction terms in logistic regression, and clarified the statistical testing for risk difference is the primary approach for treatment comparisons	Consistency with other analyses Clarification
		4.1.2.3	Replaced negative binomial model with empirical method for	The approach aligns with the limited events.

SAP Version	Approval Date	Section	Change	Rationale
			analysis of rate of hypoglycemia	
		4.4	In Table GZGP.4.5, modified and added variables	Clarification and to align with study endpoints
		4.4	In Table GZGP.4.6, modified and added additional analyses	Clarification and to align with study objectives
		4.6.6	Modified Table GZGP.4.11	To be consistent with the PSAP
		4.7.1	Added details for the Bayesian shrinkage method for subgroup analysis	Clarification
		6.7 (Appendix 7)	Modified parameter list and provide additional details on analyses method	Clarification
		Throughout SAP	Minor changes and reorganization	For clarity, no change to analysis methodologies, so not detailed

Abbreviations: MI-TP = multiple imputation tipping point; MMRM = mixed model for repeated measures; PGI = Patient Global Impression; PRO = Patient-Reported Outcome; PSAP = program safety analysis plan; SAP = statistical analysis plan; T2D = type 2 diabetes; vs = versus.

1. Introduction

This SAP is intended to describe the analyses of primary and secondary objectives, as well as safety assessments for Study GZGP. Sensitivity and supplementary analyses intended to support the primary and key secondary objectives are also included. Additional exploratory analyses, if needed, may be included in a separate document.

Pharmacokinetic/pharmacodynamic (PK/PD) analyses will be described in a separate document.

Changes to the protocol-planned analyses, if any, are described in Section 4.9.

1.1. 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 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: o ≥5% o ≥10% o ≥15%, and o ≥20% mean change in waist circumference (cm)
To demonstrate that orforglipron 6 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: o ≥5% o ≥10%, and o ≥15% 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: • systolic blood pressure, and • lipid parameters.	From baseline to Week 72 • mean change in systolic blood pressure (mmHg) • mean percent change in fasting o non-HDL cholesterol, and

	○ 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:	From baseline to Week 176
• body weight.	• mean percent change in body weight
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 post-treatment 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	From baseline to Week 72
• body weight	• mean change in absolute body weight (kg) • mean change in body mass index (kg/m^2)
• glycemic control	• mean change in HbA1c (%) • mean change in fasting glucose (mg/dL)
• fasting insulin.	• mean percent change in fasting insulin.
To demonstrate that orforglipron 6 mg QD is superior to placebo in change from baseline for the following:	From baseline to Week 72

• body weight	• percentage of participants who achieve a body weight reduction of: o ≥20%
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: • diastolic blood presssure • lipid parameters, and • patient-reported outcomes	From baseline to Week 72 • mean change in diastolic blood pressure (mmHg) • mean percent change from baseline in fasting o total cholesterol o LDL cholesterol, and o HDL cholesterol • 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 • proportion of participants with improved categorical shift in PGI-S physical function due to weight, and • proportion of participants with improvement in PGI-C 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 in participants with prediabetes at randomization that 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
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 ≥5% body weight reduction • mean percent change in body weight • mean change in HbA1c (%) • mean change in fasting glucose (mg/dL), and • percentage of participants achieving normoglycemia
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
Exploratory Objectives	
To determine the effects of orforglipron 6 mg, 12 mg, 36 mg QD, and pooled orforglipron doses (6, 12, and 36 mg) on appetite sensations and desire for specific foods • appetite VAS.	From baseline to Week 24 and 72 • mean change in item appetite VAS scores, and • mean change in overall appetite VAS score. From baseline and Week 72 to Week 74 in participants without prediabetes at randomization • mean change in item appetite VAS scores, and • mean change in overall appetite VAS score. From baseline to Week 176 in participants with prediabetes at randomization • mean change in item appetite VAS

	scores, and • mean change in overall appetite VAS score.
To assess the effects of orforglipron 6 mg, 12 mg, 36 mg QD, and pooled orforglipron doses (6, 12, and 36 mg) on the psychological impact of living in an environment with an abundance of palatable foods • PFS.	From baseline to Week 24 and 72 • mean change in domain PFS scores, and • mean change in overall PFS score. From baseline and Week 72 to Week 74 in participants without prediabetes at randomization • mean change in domain PFS scores, and • mean change in overall PFS score. From baseline to Week 176 in participants with prediabetes at randomization • mean change in domain PFS scores, and • mean change in overall PFS score.
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 • waist circumference • fasting insulin	From baseline to Week 176 • percentage of participants who achieve a body weight reduction of: o ≥10% o ≥15%, and o ≥20% • mean change in absolute body weight (kg) • mean change in BMI (kg/m^2) • mean change in waist circumference (cm) • mean percent change in fasting insulin
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:	From baseline to Week 176

• blood pressure • lipid parameters	• mean change in SBP (mm Hg) • mean change in DBP (mm Hg) • mean percent change in fasting o non-HDL cholesterol o triglycerides o total cholesterol o LDL cholesterol o HDL cholesterol
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 190 weeks: • body weight • waist circumference • glycemic control	From baseline to Week 190 • mean percent change in body weight • mean change in absolute body weight (kg) • mean change in waist circumference (cm) • mean change in HbA1c (%) • mean change in fasting glucose (mg/dL), and • percentage of participants achieving normoglycemia
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 190 weeks: • blood pressure • lipid parameters	From baseline to Week 190 • mean change in SBP (mmHg) • mean change in DBP (mmHg) • mean percent change in fasting o non-HDL cholesterol o triglycerides o total cholesterol o LDL cholesterol o HDL cholesterol

Abbreviations: DBP = diastolic blood pressure; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; LDL = low-density lipoprotein; PD = pharmacodynamics; PFS = Power of Food Scale; PGI-C = Patient Global Impression-Change; PGI-S = Patient Global Impression-Severity; PK = pharmacokinetics; QD = once daily; SBP = systolic blood pressure; SF-36v2 Acute Form = Short Form 36 Health Survey Acute, version 2; T2D = type 2 diabetes; VAS = visual analog scale.

Estimands

There will be 2 estimands for the primary objective planned in Study GZGP. These estimands address intercurrent events (ICEs) using either the treatment policy strategy or the hypothetical strategy (ICH 2021), respectively.

Estimands for weight-related, blood pressure, and lipid parameters

The below estimands will be applied to weight-related, blood pressure, and lipid parameters, using percent change in body weight at Week 72 visit as an example. For other weight-related, blood pressure, and lipid parameters, replace percent change in body weight by the endpoints to be analyzed. For endpoints at other time points, replace Week 72 with the appropriate timepoint.

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 to 72 weeks between orforglipron 6 mg, 12 mg, and 36 mg versus 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?

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.

The treatment regimen estimand is described by the following attributes

1) ***Population:*** Individuals who meet the eligibility criteria. This represents the target population identified through study inclusion/exclusion criteria (ICH E9). For the analysis, intent-to-treatment principle will be applied. Details are defined in Section 3.
2) ***Endpoint:*** Percent change in body weight from baseline to 72 weeks.
3) ***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.
4) ***Intercurrent events:*** No ICEs since treatment adherence and the initiation of prohibited weight management treatments are part of the treatment condition.

5) ***Population-level summary and treatment effect of interest:*** The difference in mean percent change from baseline in body weight to Week 72 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 to 72 weeks between orforglipron 6 mg, 12 mg, and 36 mg versus 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?

Hypothetical strategy

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

The efficacy estimand is described by the following attributes:

6) ***Population:*** Individuals who meet the eligibility criteria. This represents the target population identified through study inclusion/exclusion criteria (ICH E9). For the analysis, intent-to-treatment principle will be applied. Details are defined in Section 3.
7) ***Endpoint:*** Percent change in body weight from baseline to 72 weeks.
8) ***Treatment condition:*** The randomized treatment with allowance for potential dose interruptions and modifications.
9) ***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 as ICEs since they are part of the treatment condition.
10) ***Population-level summary and treatment effect of interest:*** The difference in mean percent change in body weight from baseline to 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 adhere to their randomly assigned treatment without being confounded by the initiation of other weight management treatments.

Estimands for delayed progression to type 2 diabetes

The below estimands will be applied to time to onset of type 2 diabetes (T2D) for participants with prediabetes at randomization.

Treatment regimen estimand

The treatment regimen estimand will be the primary estimand.

The clinical question of interest: What is the hazard ratio (HR) of developing T2D from randomization up to 176 weeks between pooled orforglipron 6 mg, 12 mg, and 36 mg versus placebo, as an adjunct to healthy diet and physical activity, in individuals with prediabetes who meet the 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

11) ***Population:*** Individuals with prediabetes who meet the eligibility criteria. This represents the target population identified through study inclusion/exclusion criteria (ICH E9). For the analysis, intent-to-treatment principle will be applied. Details are defined in Section 3.
12) ***Endpoints:*** Time from randomization to onset of T2D up to 176 weeks.
13) ***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.
14) ***Intercurrent events:*** No ICEs are defined as treatment adherence and the initiation of prohibited weight management treatments are a part of the treatment condition.
15) ***Population-level summary and treatment effect of interest:*** The HR between pooled orforglipron and placebo for the time from randomization to onset of T2D.

Rationale for the estimand: The 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 HR of developing T2D from randomization up to 176 weeks between pooled orforglipron 6 mg, 12 mg, and 36 mg versus placebo, as an adjunct to healthy diet and physical activity, in individuals with prediabetes who meet the eligibility criteria if they would remain on their randomly assigned treatment for 176 weeks and would not initiate prohibited weight management treatments?

The efficacy estimand is described by the following attributes

16) ***Population:*** Individuals with prediabetes who meet the eligibility criteria. This represents the target population identified through study inclusion/exclusion criteria (ICH E9). For the analysis, intent-to-treatment principle will be applied. Details are defined in Section 3.
17) ***Endpoint:*** Time from randomization to onset of T2D up to 176 weeks.
18) ***Treatment condition:*** The randomized treatment with allowance for potential dose interruptions and modifications.
19) ***Intercurrent events:*** ICEs include permanent discontinuation of study intervention and initiation of prohibited weight management treatments, which are handled by the

hypothetical strategy. The potential outcome of interest is the response in the efficacy measurement if participants would remain on their randomly assigned study intervention for 176 weeks and would not initiate prohibited weight management treatments. Dose modification and interruption will not be considered as ICEs since they are a part of treatment condition.

20) ***Population-level summary and treatment effect of interest:*** The HR between pooled orforglipron and placebo for the time from randomization to onset of T2D.

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.

Safety estimand

The clinical question of interest: What is the hazard ratio (HR) of developing T2D from randomization up to 190 weeks (including a 14-week post-treatment follow-up period) between pooled orforglipron 6 mg, 12 mg, and 36 mg versus placebo, as an adjunct to healthy diet and physical activity, in individuals with prediabetes who meet the eligibility criteria regardless of adherence to study intervention or initiation of prohibited weight management treatments?

The safety estimand is described by the following attributes

21) ***Population:*** Individuals with prediabetes who meet the eligibility criteria. This represents the target population identified through study inclusion/exclusion criteria (ICH E9). For the analysis, intent-to-treatment principle will be applied. Details are defined in Section 3.
22) ***Endpoints:*** Time from randomization to onset of T2D up to 190 weeks.
23) ***Treatment condition:*** The randomized treatment including a 14-week posttreatment follow-up period with allowance for potential dose interruptions and modifications regardless of adherence to study intervention or initiation of prohibited weight management treatments.
24) ***Intercurrent events:*** No ICEs are defined as treatment adherence and the initiation of prohibited weight management treatments are a part of the treatment condition.
25) ***Population-level summary and treatment effect of interest:*** The HR between pooled orforglipron and placebo for the time from randomization to onset of T2D.

Rationale for the estimand: The estimand aims to evaluate the efficacy of orforglipron that reflects the real-life behavior of the target population including both the treatment and the posttreatment follow-up period.

1.2. Study Design

Study GZGP is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study. Study GZGP 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 have obesity (body mass index [BMI] 30 kg/m^2 or greater), or overweight (BMI 27 kg/m^2 or greater) with the presence of at least 1 weight-related comorbidity

(for example, hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular [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).

Study GZGP participants will be randomly assigned 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 GZGP includes a

- screening period: 3 weeks
- treatment period:
  - dose escalation period: 20 weeks
  - maintenance dose period
    - no prediabetes: 52 weeks
    - prediabetes: 156 weeks total (including initial 52-week treatment period and 104-week additional prediabetes treatment period), and
- posttreatment follow-up period:
  - no prediabetes, or participants discontinuing study intervention during the first 72 weeks: 2 weeks
  - prediabetes: 14 weeks

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). The effects of study intervention cessation will be assessed at the 2-week posttreatment follow-up visit (Week 74).

Primary database lock will occur after:

- all randomized participants with normoglycemia at baseline either complete Visit 801 or discontinue prior to Visit 801.
- all randomized participants with prediabetes at baseline either complete the 72-Week visit or discontinue the study prior to the 72-week visit.

The primary objective of Study GZGP will be assessed following the primary database lock.

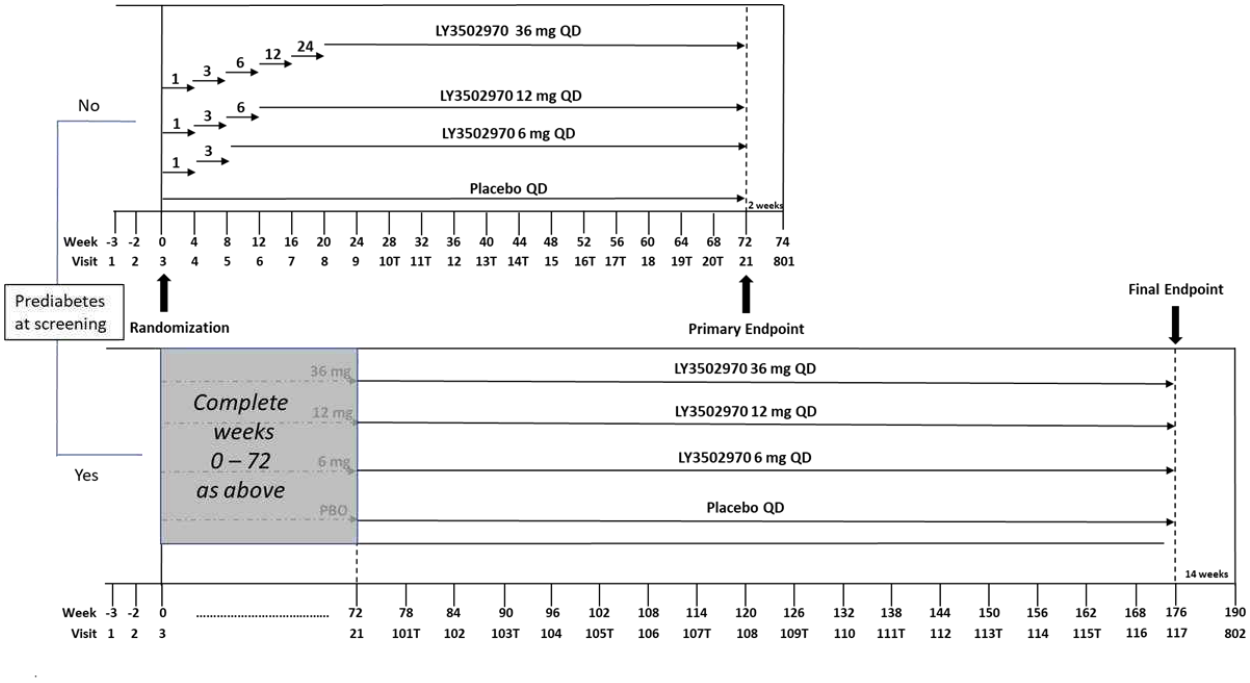
To obtain additional information regarding the time to new onset of T2D while taking orforglipron, participants with prediabetes diagnosed at the beginning of Study GZGP (who are at increased risk of diabetes), will be treated and observed for an additional 2 years. For participants with prediabetes at randomization, the effects of study intervention cessation will be assessed at a 14-week posttreatment follow-up visit (Week 190).

The final database lock will occur after participants with prediabetes at randomization have completed a 176-week treatment period and a 14-week follow-up period or discontinued the study early.

The Study GZGP schema is shown in Figure GZGP.1.1.

The randomization will be stratified by:

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



Abbreviations: PBO = placebo, QD = once daily; T= telehealth visit.

Figure GZGP.1.1. Illustration of study design for Clinical Protocol J2A-MC-GZGP.

2. 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

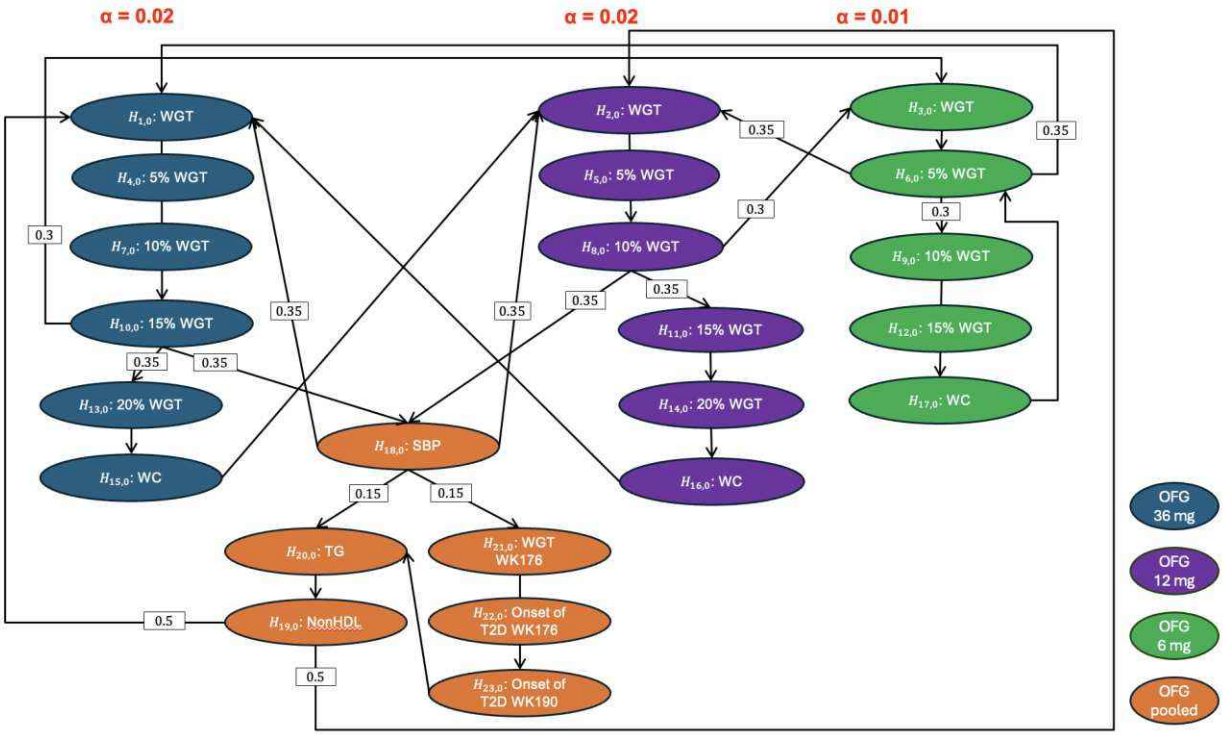
- $H_{4,0}$: No difference in 36 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction from baseline at Week 72.
- $H_{5,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the percentage of participants who achieve 5% or more body weight reduction from baseline 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 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 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 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 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 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 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 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 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 at Week 72.
- $H_{15,0}$: No difference in 36 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- $H_{16,0}$: No difference in 12 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- $H_{17,0}$: No difference in 6 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, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to mean change from baseline in systolic blood pressure (SBP) at Week 72.
- $H_{19,0}$: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in non-high-density lipoprotein (HDL) cholesterol at Week 72.
- $H_{20,0}$: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in triglycerides at Week 72.
- $H_{21,0}$: No difference in 6 mg, 12 mg, and 36 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.
- $H_{22,0}$: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to time to onset of T2D up to Week 176 in participants with prediabetes at randomization.
- $H_{23,0}$: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to time to onset of T2D up to Week 190 in participants with prediabetes at randomization.

2.1. Multiplicity Adjustment

Multiplicity adjusted analyses will be performed on the primary and key secondary objectives to control the overall family-wise Type 1 error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described in Bretz and colleagues (2009, 2011) will be used. This approach is a closed testing procedure, hence, it strongly controls the family-wise Type 1 error rate across all hypotheses (Alosh et al. 2014).

Figure GZGP.2.1 illustrates the final graphical testing scheme, including testing order, interrelationships, Type 1 error allocation for the primary and key secondary objectives, and the associated propagation. The treatment regimen estimand will be the primary estimand, with the efficacy estimand considered supportive. Since these estimands are intended for distinct purposes, no multiplicity adjustment will be made for conducting separate analyses on the same objectives. Unless otherwise specified, there will be no adjustment for multiple comparisons for any other analyses outside the primary and key secondary objectives.



Abbreviations: OFG = orforglipron.

Figure GZGP.2.1. Graphical testing procedure.

3. Analysis Sets

For the purpose of analysis, the analysis populations are defined in Table GZGP.3.1 along with their attributes.

Table GZGP.3.1. Participant Analysis Sets

Participant Analysis Set	Description
Entered participants	**Definition:** All participants who sign informed consent[a]. **Purpose:** Used for providing summaries for screen failures and reasons associated with screen failures. Treatment Groups: None Inferential Comparisons: None
Randomized participants	**Definition:** All participants who are randomly assigned a study intervention. **Purpose:** Used for listings of disposition and treatment assignment summaries of disposition, demographics, historical illness, preexisting conditions, and analyses of efficacy and health outcomes. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO; OFG pooled vs. PBO.
Safety participants	**Definition:** All participants who are randomly assigned a study intervention and who take at least 1 dose of study intervention. **Purpose:** Used for all safety analyses. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO.
Randomized participants with prediabetes	**Definition:** All participants who are randomly assigned a study intervention and who have prediabetes at randomization[b]. **Purpose:** Used for listings of disposition and treatment assignment summaries of disposition, demographics, historical illness, preexisting conditions, and analyses of efficacy and health outcomes. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO; OFG pooled vs. PBO.
Safety participants with prediabetes	**Definition:** All participants who are randomly assigned a study intervention and take at least 1 dose of study intervention and have prediabetes at randomization[b]. **Purpose:** Used for all safety analyses. **Treatment Groups:** OFG 6 mg, OFG 12 mg, OFG 36 mg, PBO **Inferential Comparisons:** OFG 6 mg vs. PBO; OFG 12 mg vs. PBO; OFG 36 mg vs. PBO.

Abbreviations: IWRS = interactive web response system; OFG = orforglipron; PBO = placebo.

[a] Refers to the informed consent for the study.

[b] Determined by confirmed IWRS data .

The following data points sets are defined in Table GZGP.3.2 for all parameters:

Table GZGP.3.2. Data Points Sets

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. Baseline is defined in Section 4.1.1.
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 discontinuation of study intervention or initiation of prohibited weight management treatments. Baseline is defined in Section 4.1.1. and the prohibited weight management treatments are specified in Section 6.3 and Table GZGP.6.5.
Safety data points set	All data points obtained during the treatment period and follow-up period defined as at or after baseline and up to the date of study withdrawal or study completion including the follow-up period, regardless of intercurrent events. Baseline is defined in Section 4.1.1.

Note: at the time of the primary database lock, the treatment period is defined from Week 0 visit to Week 72 visit; for safety analyses, the additional 2-year treatment period and the corresponding follow-up period for prediabetes participants will not be included.

For the analysis of change from baseline to Week 190 for selected efficacy endpoints in randomized participants with prediabetes, the analyses will be conducted using a modified efficacy estimand data points set and the safety data points set. The modified efficacy estimand data points set includes all data points obtained during the 176-week treatment period and the follow-up visit at Week 190 defined as at or after baseline and up to the earliest date of discontinuation of study intervention or initiation of prohibited weight management treatments.

4. Statistical Analyses

4.1. General Considerations

Statistical analysis of this study 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 SAP GZGP or the clinical study report (CSR). Additional exploratory data analyses may be conducted as deemed appropriate.

Details about the analyses regarding demographic and baseline characteristics, historical illnesses and preexisting conditions, treatment compliance, concomitant medications, and important protocol deviations can be found in Appendices 1 through 5 (Section 6.1 through Section 6.5), respectively.

Some analyses and summaries described in this analysis plan may not be conducted if not warranted by data (for example, few events to justify conducting an analysis). Not all analyses described in SAP GZGP will necessarily be included in the CSRs. Any analyses described in this SAP and not provided in the CSR will be available upon request. Not all displays will necessarily be created as a "static" display. Some may be incorporated into interactive display tools instead of, or in addition to, a static display.

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

The change from baseline will be calculated as the value of interest at the visit minus the baseline value. In general, percent change from baseline will be calculated as the value of change from baseline divided by the baseline value in 100% scale. For some specific predefined parameters, percent change from baseline might be calculated using a log transformation. If the baseline value is missing for a particular variable, then the change from baseline and percent change from baseline will not be calculated when deriving the summary statistics.

For stratification factors at baseline, a strata variable is defined for statistical modeling to consist of 4 joint levels. The strata variable includes sex (female, male) and prediabetes status (yes, no). For analyses for participants with prediabetes at randomization, the strata variable will only include sex. Although country is also a stratification factor, geographic region (North America, Europe, Asia, or Central/South America) will be included in statistical modeling as a separate factor to improve model convergence.

Data may exist at visits where a variable was not scheduled to be collected, due to, for example, discontinuation visits. In these situations, data from the early discontinuation visit that does not correspond to the planned collection schedule will be excluded from the mixed model for repeated measures (MMRM), analysis of covariance (ANCOVA), or logistic regression analysis, unless otherwise specified (Andersen and Millen 2013).

Handling of missing data is addressed in Section 4.1.2 and Table GZGP.4.6. Section 3 provides definitions for the participant analysis set and data points set which includes definitions for censored data where appropriate. Handling spurious data is addressed in Section 6.5. Section 6.5 also addresses important protocol deviations. Protocol GZGP Section 10.1.7 addresses data quality assurance.

4.1.1. Definition of Baseline

Unless otherwise specified, the baseline for efficacy assessments is defined as the last available non-missing measurement prior to the first dose of study intervention; in most cases, this will be the measurement recorded at Week 0 (Visit 3). If there are no doses of study intervention administered, the baseline will be defined as the last available non-missing measurement on or prior to randomization. In cases where the measurement is taken on the same day (where the time is not collected or not reliable) as the first dose, this measurement will be used as the baseline value for data analysis. For patient-reported outcome measures data obtained at Visit 3, regardless of the timing relative to first dose, will serve as the baseline.

For safety assessments, the definition of baseline and postbaseline are specified in Table GZGP.4.1.

Table GZGP.4.1. Baseline and Postbaseline Definitions for Safety Analyses

Analysis Type	Baseline Period	Postbaseline Period
TEAEs	Starts from informed consent date and ends prior to the first dose (typically at Week 0).	Starts after the first dose of study intervention[a] and ends at the end of the follow-up period[b], or the date of study withdrawal.
TE abnormal laboratory values, vital signs, and ECGs	Starts from informed consent date and ends prior to the first dose (typically at Week 0). All scheduled and unscheduled measurements will be included.	Starts after the first dose and ends at the end of the follow-up period[b] or the date of study withdrawal. All scheduled and unscheduled measurements will be included.
Change from last baseline to each postbaseline week and to last postbaseline for laboratory values, vital signs, and ECGs	When "last baseline" is used, starts from informed consent date and ends prior to the first dose (typically at Week 0).	Starts after the first dose and ends at the end of the follow-up period[b] or the date of study withdrawal. Only scheduled visits and early termination visits that fall on the scheduled visits will be included.

Abbreviations: ECG = electrocardiogram; TE = treatment-emergent; TEAE = treatment-emergent adverse events.

[a] For events occurring on the day of first dose, information collected from the case report form will be used to determine whether the event was pre- versus posttreatment, if available. If the relevant information is not available, then the events will be counted as postbaseline.

[b] At Week 74 visit for participants without prediabetes or Week 72 visit if continuing in the trial for prediabetes participants at the primary database lock; and at Week 190 for prediabetes participants at final database lock.

4.1.2. Analysis Methods

The analysis methods are consistent with the desired estimands and the FDA guidance on "Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biological Products Guidance Document" (FDA 2023).

4.1.2.1. Analysis Methods for Treatment Regimen Estimand

4.1.2.1.1. Method for Continuous Variables

The ANCOVA model will be used to analyze continuous measurements at Week 72 and Week 176 and will be guided by the treatment regimen estimand. The model will include

- treatment group as a factor variable
- region as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)
- interaction between strata variable and treatment group, and
- interaction between baseline value and treatment group.

The estimated treatment group effect and comparison between 6 mg orforglipron, 12 mg orforglipron, and 36 mg orforglipron versus placebo will be reported together, with variability estimated using the robust inference (Ye et al. 2022; FDA 2023). The associated 2-sided 95% confidence interval and corresponding p-values will also be reported. If the model fails to

converge, all the interaction terms will be removed before the model fitting. The addition of interaction terms is not intended to estimate the heterogeneity effect but to provide robustness and efficiency for the estimate of treatment comparisons on the unconditional effect. The final inference will be derived using Rubin's Rule which combines estimates from multiple imputed datasets. The imputation procedure for creating a single imputed dataset is detailed in Table GZGP.4.2.

For some variables, both the baseline and the postbaseline values will be log transformed before fitting the ANCOVA. The treatment group estimates will be the percent change from baseline; the treatment contrasts will be the relative change in orforglipron 6 mg, orforglipron 12 mg, or orforglipron 36 mg compared to the placebo (%). In these cases, least squares (LS) means and 95% confidence intervals for each treatment group and treatment difference will be back-transformed and presented as mean percent change from baseline and relative treatment difference to placebo in percent change.

A linear contrast, averaging estimates from the individual doses, will be used to estimate the treatment effect of the pooled doses compared with placebo as needed.

4.1.2.1.2. Primary Multiple Imputation (PMI) Strategy

Participants who discontinue study intervention (that is, discontinue study treatment) will be encouraged to continue in the study for the treatment period and follow-up period (note, the case report forms [CRFs] use "phase", which is interchangeable with the "period" in SAP). In this section, study discontinuation refers to treatment phase discontinuation captured in CRF.

If there are occurrences of missing data despite the best precautions, missing data should be imputed in a fashion consistent with what the values would likely have been had they been collected. In general, 5 scenarios are considered regarding the treatment journey of a trial participant relative to primary time point (Week 72 visit) shown in Figure GZGP.4.1.The same scenarios are considered for other relevant time points (e.g. Week 176).

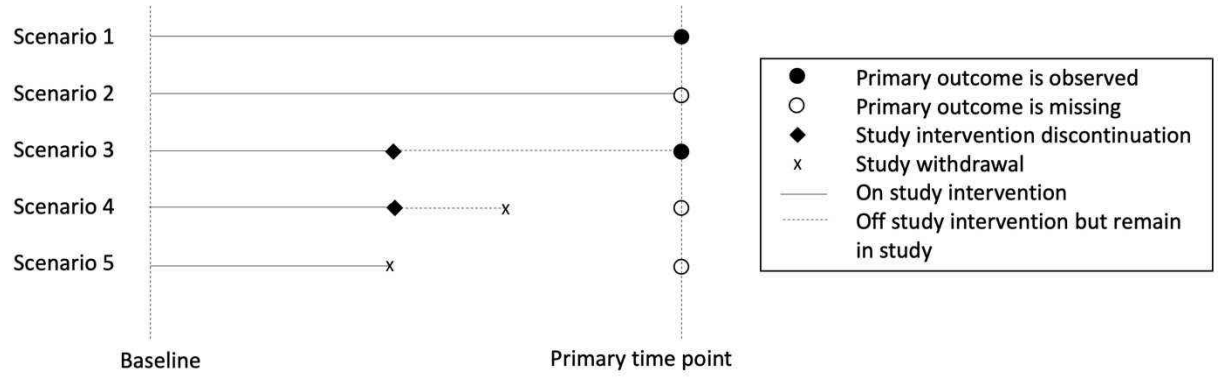


Figure GZGP.4.1. Treatment journey of a trial participant.

Scenario 5 covers the situations where a participant discontinues from the study intervention and then comes back for a study discontinuation visit for the same discontinuation reason on or prior to a scheduled visit. Additional details on scenario 5 are provided in Table GZGP.4.3.

In principle, missing data due to permanent discontinuation of study intervention (Scenario 4 and Scenario 5A) will be imputed by treatment group using retrieved dropouts (MI-RD), namely using multiple imputation based on data retrieved from participants who permanently discontinued the study intervention but continued in the study with non-missing measurements from the same treatment group. For scenarios 4 and 5A, if there are not enough retrieved dropouts to provide a reliable imputation model (that is, the model implemented does not converge), an alternative multiple imputation method (placebo-washout method) (Wang 2023) will be used. Any missing values at baseline will be imputed in the same model when imputing the endpoint.

Table GZGP.4.2. Imputation Procedure

Scenario (Study Intervention/Treatment Period Discontinuation; Missingness Status at Endpoint)	**Methods to Handle Missing Values at Endpoint**
1. No study intervention discontinuation; no missing value	N/A
2. No study intervention discontinuation; with missing value	Use observed data, including baseline and all postbaseline visits, across all time points from Scenario 1 and 2 to impute under the MAR assumption by treatment group. There should be very few such cases in a clinical trial. No additional covariates will be included in the imputation model.
3. Study intervention discontinuation; no missing value	N/A
4. Study intervention discontinuation with treatment period discontinuation at a subsequent visit or completion of treatment period; with missing value	Missing values at the endpoint visit will be imputed through MCMC (predictive mean matching method), using baseline and the endpoint visit data from Scenario 3 (MI-RD) by treatment group. No additional covariates will be included in the imputation model.
5. Study discontinuation resulting in study intervention discontinuation; with missing value	5A: If the study discontinuation is possibly related to study intervention (see treatment period discontinuation reasons classified as Category 5A in Table GZGP.4.3), missing values at the endpoint visit will be imputed in the same way as Scenario 4. 5B: If the study discontinuation is clearly due to administrative reasons not related to study intervention (see treatment period discontinuation reasons classified as Category 5B in Table GZGP.4.3), missing values at the endpoint visit will be imputed in the same way as Scenario 2.

Abbreviations: MAR = missing at random; MCMC = Markov chain Monte Carlo; MI = multiple imputation; RD = retrieved dropouts; N/A = not applicable.

Table GZGP.4.3. Categorization of Treatment Period Discontinuation Reasons

Disposition Reason	Associated Sub-Categories	Category
Adverse Event		5A
Death		5A
Protocol Deviation		5A
Pregnancy		5A
Non-Compliance With Study Drug		5A
Lack of Efficacy	Investigator	5A
	Study subject	5A
Withdrawal by Subject	Concern about study procedures/perceived risks	5A
	Health insurance changes	5A
	Scheduling conflicts	5A
	Subject is moving or has moved	5A
	Personal issue unrelated to trial	5A
	Due to epidemic/pandemic	5B
	Other	5A
Physician Decision	Due to epidemic/pandemic	5B
	Other	5A
Study Terminated by Sponsor		5B
Site Terminated by Sponsor		5B
Study Terminated by IRB/ERB		5B
Lost to Follow-up		5A
Other		5A

Abbreviations: ERB = ethical review board; IRB = institutional review board.

Note: For participants that discontinued the study due to emergency unblinding, the study disposition will be classified based upon the reason leading to emergency unblinding (for example, Adverse Event [5A]).

4.1.2.1.3. Modified Multiple Imputation Strategy

A modified multiple imputation (mMI) analysis is planned as a sensitivity analysis to assess the robustness of the primary efficacy results. An additional analysis will be conducted and data observed from Scenario 3 will be used to impute Scenario 5B.

4.1.2.1.4. Multiple Imputation Based Tipping-Point Analysis

A multiple imputation-based tipping-point (MI-TP) analysis is planned as a sensitivity analysis to explore how different patterns of body weight change post treatment period discontinuation by different treatment groups could impact the treatment comparisons.

To start with, missing data are imputed according to the primary imputation strategy (PMI) as shown in Section 4.1.2.1.2. A penalty is then added to those imputed values at the Week 72 visit. The MI-TP analysis varies the magnitude of the penalties added for both treatment groups under comparison and evaluates the impact these would have on the Study GZGP conclusion. A 2-dimensional space of penalties will be assessed for orforglipron 6 mg, orforglipron 12 mg, or orforglipron 36 mg and placebo. An MI-TP analysis aims to evaluate the robustness of the superiority claim to the assumptions of using the observed data to impute the missing body weight in all treatment groups.

4.1.2.1.5. Method for Binary Variables

The binary outcomes will be analyzed with the following procedure:

- Using the same imputation strategy – PMI as in Section 4.1.2.1.2 on the underlying continuous endpoint that determines the binary value. For example, the continuous body weight values at Week 72 visit will be imputed first.
- Transform the observed and imputed continuous value to the binary value, for example, convert the continuous body weight values at Week 72 visit to whether the corresponding percent change from baseline meets a certain threshold (Ma et al. 2022).
- Fit a logistic regression model to the data with the following terms:
    - treatment group as a factor variable
    - region as a factor variable
    - strata as a factor variable
    - baseline value (of the dependent variable)
    - interaction between treatment group and strata, and
    - interaction between treatment group and baseline value.
- Provide estimates and inferences of unconditional treatment effects defined by the risk difference and/or relative risk based on the delta-method using the formula provided (Ye et al. 2023).
- Derive the final inference using Rubin's rule which combines estimates from multiple imputed datasets. The imputation procedure for creating a single imputed dataset is detailed in Table GZGP.4.2.

The statistical testing for risk difference will be used as the primary approach for treatment comparisons.

4.1.2.1.6. Analysis Methods for Time to Event Variables

For time-to-event analysis, the log-rank test stratified on the strata variable will be conducted for the comparison between treatment groups. A Cox proportional hazards model stratified by the strata variable with treatment group as a factor, will be used as the primary analysis to estimate the HR between the treatment groups and the corresponding confidence interval.

For time-to-event analyses, participants who have not experienced the event of interest will be censored at the participant's end of follow-up. The censoring date will be the earliest of

- date of death
- date of the end of the analysis period/withdrawal, and
- the last confirmed visit date before participant was lost-to-follow-up.

The Kaplan-Meier method will be used to estimate the cumulative event curve over time. Counts and proportions of participants who experience an event will be calculated by treatment group.

For time-to-event analysis, if a participant experiences the event of interest, then time-to-event for that specific event of interest will be the number of days between the date of randomization and the onset date of the event plus 1 day. If a participant does not experience the event, then time-to-event for that specific event of interest will be the number of days between the date of randomization and the date of the participant's end of follow-up plus 1 day. If a participant

experiences multiple events the date of the first event will be used, unless otherwise specified. In rare cases where randomization occurred prior to the Visit 3 date, the Visit 3 date will be used instead.

4.1.2.2. Analysis Methods for Efficacy Estimand

4.1.2.2.1. Method for Continuous Variables

A maximum likelihood-based MMRM will be used to analyze continuous measurements at each postbaseline visit guided by the efficacy estimand. Missing data should be minimized at the best precaution. The hypothetical strategy will be used to handle ICEs. For MMRM analysis, only data collected before the occurrence of any ICEs will be used in the MMRM analysis. Through the MMRM, the potential efficacy measures (after the ICEs) will be implicitly imputed as if participants did not have ICEs. Participant dose modification and interruption will not disqualify their measurements from being included into the model.

The MMRM model will include the following terms:

- treatment group as a factor variable
- visit as a factor variable
- region as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)
- interaction between treatment group, strata variable and visit, and
- interaction between treatment group, baseline value and visit.

The estimated treatment group effect and comparison between 6 mg orforglipron, 12 mg orforglipron, or 36 mg orforglipron and placebo at the scheduled visits will be reported together with the variability estimated using the robust inference (Wang and Du 2023). The sandwich estimator (Diggle et al. 1994) for the variance-covariance matrix will be used. The addition of 3-way interaction terms is not intended to estimate the heterogeneity effect but to provide robustness and efficiency for the estimate of treatment comparisons on the unconditional effect. The associated 2-sided 95% confidence interval and corresponding p-values will also be reported. An unstructured covariance matrix by each treatment group will be used to model the within-participant errors, assuming heteroscedasticity and the measurements for different participants are independent. If the model fails to converge, the model will be simplified to include the following terms, removing 3-way interactions and the heteroscedasticity assumption:

- treatment group as a factor variable
- visit as a factor variable
- region as a factor variable
- strata as a factor variable
- baseline value (of the dependent variable)
- interaction between treatment group and visit
- interaction between strata variable and visit, and
- interaction between baseline value and visit.

If the model still fails to converge, the following covariance structures will be tested in order for the simplified model:

- heterogeneous Toeplitz
- heterogeneous autoregressive
- heterogeneous compound symmetry
- homogeneous Toeplitz
- homogeneous autoregressive, and
- homogeneous compound symmetry.

The first covariance structure that converges will be used.

For some variables, both the postbaseline response variables and baseline variable will be log-transformed before fitting the MMRM. The treatment group estimates will be the percent change from baseline while the treatment contrasts will be the relative change in orforglipron 6 mg, orforglipron 12 mg, or orforglipron 36 mg compared to the placebo (%) over the scheduled visits.

If the data does not warrant the use of an MMRM model, then an ANCOVA model will be conducted, as described in Section 4.1.2.1.1. Missing values at the visit of interest will be imputed through multiple imputation using all non-missing data (excluding data collected after ICEs) from the same treatment group under the missing at random (MAR) assumption.

A linear contrast, averaging estimates from the individual doses, will be used to estimate the treatment effect of the pooled doses compared with placebo as needed.

4.1.2.2.2. Method for Binary Variables

The binary outcomes will be analysed with the following procedure:

- Impute the missing continuous-valued measurements at the scheduled visits using the randomized participants with efficacy estimand data points set assuming MAR with multiple imputation.
- At the visit of interest, transform the observed and imputed continuous value to the binary value, for example, convert the continuous body weight value at a visit to whether the corresponding percent change from baseline meets a certain threshold.
- Fit a logistic regression model to the transformed binary data with the following terms:
    - treatment group as a factor variable-
    - region as a factor variable
    - strata as a factor variable
    - continuous baseline value (of the dependent variable)
    - interaction between treatment group and strata, and
    - interaction between treatment group and baseline value.
- Provide for the visit of interest the estimates and inferences of unconditional treatment effects defined by the risk difference and/or risk ratio based on the delta-method using the formula provided (Ye et al. 2023).

- Derive the final inference using Rubin's rule by combining estimates from multiple imputed datasets.

The statistical testing for risk difference will be considered the primary method for treatment comparisons.

4.1.2.2.3. Analysis Methods for Time to Event Variables

Similar methodology will be used as described in Section 4.1.2.1.6, with the exception of the censoring rules.

For time-to-event analyses, participants who have not experienced the event of interest will be censored at the participant's end of follow-up. The censoring date will be the earliest of

- date of death
- date of initiation of prohibited weight management treatments
- date of discontinuation of study intervention, and
- the last confirmed visit date before participant was lost-to-follow-up.

4.1.2.3. Analysis Methods for Safety

In general, safety assessments will be guided by an estimand comparing safety of orforglipron doses with placebo regardless of intercurrent events. Thus, safety analyses will be conducted using the safety participants based on data observed during treatment period plus the posttreatment follow-up period, that is, the period from first dose of treatment to the end of the follow-up visit or the date of study withdrawal. It is noted that for some safety endpoints, such as study intervention discontinuation due to adverse event (AE) and so forth, the analyses will be based on data observed during treatment period only.

Fisher's exact test will be used for treatment comparisons of percentages. The risk differences and 95% confidence intervals will be provided.

For selected continuous safety measures, unless otherwise specified, treatment group differences of mean change or percent mean change from baseline at all scheduled visits will be assessed via an MMRM using maximum likelihood, which will include the following terms:

- treatment group as a factor variable
- visit as a factor variable
- baseline value (of the dependent variable)
- interaction between visit and treatment group

If the data does not warrant the MMRM model, then an ANCOVA model with treatment group as a fixed effect and the continuous baseline value as a covariate will be used.

No explicit imputation will be conducted for safety measures. Some parameters (such as urinary albumin to creatinine ratio [UACR], p-amylase, and lipase) may be log-transformed before fitting the MMRM as specified in Section 4.1.2.1.1. In these cases, least squares (LS) means and 95% confidence intervals for each treatment group and treatment difference will be back-transformed and presented as mean percent change from baseline and as relative treatment difference of orforglipron treatment groups compared to placebo in percent change.

The Kaplan–Meier (KM) product limit method will be used to estimate the cumulative event-free survival rates over time for the time-to-event analyses. An unstratified Cox proportional hazards regression analysis will be used to compare hazard rates among treatments. An unstratified log-rank test will be used to calculate p-values. Time-to-event for the specific safety event of interest will be calculated from the date of first dose.

A logistic regression model will be used for hypoglycemia incidence for treatment comparisons for the overall postbaseline period. The model will include the fixed effects of treatment. Given the expected small number of hypoglycemic events in the study population, the rate of events will be analyzed using an empirical method for the overall postbaseline period.

Some safety analyses may be conducted after excluding data after the initiation of anti-hyperglycemic medications for those who develop T2D.

4.2. Participant Dispositions

The participant dispositions for the screening period, study intervention, the treatment period, and/or the follow-up period will be collected in the CRFs with the corresponding primary reason.

The study completion status is defined as

- at the end of the 72-week treatment period (when the primary endpoint is ascertained and the primary database is locked): for participants without prediabetes at randomization, completers will be considered as those who complete the treatment period (Week 72) and the follow-up visit; for participants with prediabetes at randomization, completers will be considered as those who complete Week 72; otherwise, participants will be considered as non-completers.
- at the end of the 176-week treatment period for participants with prediabetes at randomization, completers will be considered as those who complete the treatment period (Week 176) and the follow-up visit; otherwise, participants will be considered as non-completers.

The planned listings and summary tables for dispositions are provided in Table GZGP.4.4. No inferential analysis will be performed. Additionally, the planned listings and summary tables for dispositions will be provided for participants with prediabetes at randomization for the final lock.

Table GZGP.4.4. Listings and Summary Tables Related to Dispositions

Analysis	Population/Period
Summary of disposition (prior to randomization)	Entered participants
Patient allocation by region, country, and center/site	Entered participants
Summary of study and study intervention disposition	Randomized participants/TP + FP (TP for study treatment disposition)
Kaplan-Meier plot of time to study discontinuation	Randomized participants/TP + FP
Kaplan-Meier plot of time to study intervention discontinuation	Safety participants/TP
Kaplan-Meier plot of time to study intervention discontinuation due to AEs	Safety participants/TP
Listing of randomization	Randomized participants
Listing of randomized participants who were discontinued from the study intervention due to inadvertent enrollment	Randomized participants
Listing of study and study intervention disposition	Randomized participants

Abbreviations: FP = follow-up period; TP = treatment period.

Time-to-study intervention discontinuation will be calculated from the date of first dose. Time-to-study discontinuation will be calculated from the date of randomization.

4.3. Primary Endpoint/Estimand Analysis

4.3.1. Definition of endpoint(s)

The primary efficacy endpoint is percent change in body weight at 72 weeks. As specified in Table GZGP.4.5, the percent change in body weight is defined as:

(postbaseline body weight [kg] – baseline body weight [kg]) / baseline body weight [kg] × 100%.

4.3.2. Main analytical approach

The analytical approaches are specified in Section 4.1.2.1.1 and Section 4.1.2.1.2 (ANCOVA with PMI) and Section 4.1.2.2.1 (MMRM).

4.3.3. Sensitivity Analysis

The sensitivity analysis are specified in Section 4.1.2.1.3 (MI-TP).

4.3.4. Supplementary analyses

No supplementary analysis is planned for the primary endpoint.

4.4. Secondary Endpoints/Estimands Analysis

Table GZGP.4.5 includes the description and derivation of the primary and secondary endpoints for the efficacy measures and PROs.

Table GZGP.4.6 provides the detailed analyses including endpoint, estimand, data points set, method and imputation, population, and time point for the primary and secondary endpoints.

Table GZGP.4.5. Descriptions and Derivation of Efficacy Measures and Patient Reported Outcomes

Measure	Description	Variable	Derivation/Comment	Handling Missing Components
Body weight	Per Protocol GZGP Section 10.7: 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 will be measured in fasting state at all visits. 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.	Body weight (kg)	As measured	Single item, missing if missing
		Change from baseline in body weight (kg)	Calculated as: postbaseline body weight (kg) – baseline body weight (kg)	Missing if baseline or postbaseline value is missing
		Percent change from baseline in body weight (%)	Calculated as: (postbaseline body weight [kg] – baseline body weight [kg]) / baseline body weight [kg] × 100 (%)	Missing if baseline or postbaseline value is missing
		≥x% body weight reduction from baseline where, x = 5, 10, 15, 20	Response = yes if at least a x% reduction in body weight from baseline, that is, percent change from baseline in body weight ≤ -x%	Missing if baseline or postbaseline value is missing
BMI	BMI: Round to one decimal point. For example, a BMI of 29.9 kg/m^2 should not be rounded to 30.0 kg/m^2.	BMI (kg/m^2)	BMI will be calculated as: Weight (kg) / (height [m])^2	Missing if weight or height is missing
		Change from baseline in BMI (kg/m^2)	Calculated as: postbaseline BMI (kg/m^2) – baseline BMI (kg/m^2)	Missing if baseline or postbaseline value is missing
		BMI threshold value of <x kg/m^2 Where, x = 25, 27, 30, 35	Response = yes if the postbaseline BMI value <x kg/m^2	Missing if postbaseline value is missing
Waist circumference	Per Protocol GZGP Section 10.7: 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.	Waist circumference (cm)	The average of 2 measures	If there is at least one measurement, take the average of all non-missing measurements; otherwise, set it to be missing

	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.	Change from baseline in waist circumference (cm)	Calculated as: postbaseline Waist circumference (cm) – baseline Waist circumference (cm)	Missing if baseline or postbaseline value is missing
Blood pressure	Per Protocol GZGP Section 10.7: 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. Blood pressure must be taken with an automated blood pressure instrument	SBP (mmHg)	The average of 3 measures	If there is at least one measurement, take the average of all non-missing measurements; otherwise, set it to be missing
		Change from baseline in SBP (mmHg)	Calculated as: postbaseline SBP (mmHg) – baseline SBP (mmHg)	Missing if baseline or postbaseline value is missing
		DBP (mmHg)	The average of 3 measures	If there is at least one measurement, take the average of all non-missing measurements; otherwise, set it to be missing
		Change from baseline in DBP (mmHg)	Calculated as: postbaseline DBP (mmHg) – baseline DBP (mmHg)	Missing if baseline or postbaseline value is missing
Lipid parameter	HDL-C, triglycerides, and total cholesterol will be assayed by Lilly designated laboratory. LDL-cholesterol, non-HDL-cholesterol, and VLDL-C will be calculated by Lilly designated laboratory.	Triglycerides	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in triglycerides (%)	Calculated as: log(postbaseline triglycerides) – log (baseline triglycerides)	Missing if baseline or postbaseline value is missing

			then will transform back to percent change.	
		Total cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in total cholesterol (%)	Calculated as: log(postbaseline total cholesterol) – log(baseline total cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		Non-HDL-cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in non-HDL-cholesterol (%)	Calculated as: log(postbaseline non-HDL-cholesterol) – log(baseline non-HDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		LDL-cholesterol	As provided. If triglycerides are >400 mg/dL, the direct LDL will be directly measured Log transformation before the analysis.	Single item, missing if missing
		Percent change from baseline in LDL-cholesterol (%)	Calculated as: log(postbaseline LDL-cholesterol) – log(baseline LDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		HDL-cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing

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		Percent change from baseline in HDL-cholesterol (%)	Calculated as: log(postbaseline HDL-cholesterol) – log(baseline HDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
		VLDL-cholesterol	As provided. Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in VLDL-cholesterol (%)	Calculated as: log(postbaseline VLDL-cholesterol – log(baseline VLDL-cholesterol) then will transform back to percent change	Missing if baseline or postbaseline value is missing
Glycemic control	Fasting glucose will be assayed by Lilly-designated laboratory.	Fasting glucose (mg/dL and mmol/L)	As provided	Single item, missing if missing
		Change from baseline fasting glucose (mg/dL and mmol/L)	Calculated as: Postbaseline fasting glucose – Baseline fasting glucose	Missing if baseline or postbaseline value is missing
	HbA1c will be assayed by Lilly-designated laboratory.	HbA1c (% and mmol/mol)	As provided	Single item, missing if missing
		Change from baseline HbA1c (% and mmol/mol)	Calculated as: Postbaseline HbA1c – Baseline HbA1c	Missing if baseline or postbaseline value is missing
	Delayed progression to T2D is evaluated by time to onset of T2D (only for participants with prediabetes at randomization).	Time to onset of T2D	Calculated as: (date of onset of CEC adjudicated T2D event – date of randomization) + 1 day	Censored if no postbaseline event of T2D was observed
	Percentage of participants with prediabetes at randomization achieving normoglycemia.	Percentage of participants achieving normoglycemia	Response = Yes if FSG <100 mg/dL (obtained alone or at time = 0 during an OGTT), OGTT 2h SG <140 mg/dL, and HbA1c <5.7%.	Missing if postbaseline values of HbA1c, FSG and OGTT are missing

	2-hour OGTT will be performed per Protocol Section 10.7: • participants should attend visits in the fasting state, and • serum samples will be collected at 0, 30, 60, 90, and 120 minutes	Point x OGTT (mg/dL) x= 0, 30, 60, 90, 120 minutes	As provided	Single item, missing if missing
		Change from baseline in point x OGTT (mg/dL)	Calculated as: postbaseline point x OGTT (mg/dL) – baseline point x OGTT (mg/dL)	Missing if baseline or postbaseline value is missing
Insulin Sensitivity	Matsuda index will be derived from 2-hour OGTT results.	Matsuda index	Calculated as: $\frac{10000}{\sqrt{(FSG \times FPI) \times (\bar{G} \times \bar{I})}}$, where FSG is the fasting glucose, FPI is the fasting insulin, $\bar{G}$ denotes the mean glucose during OGTT, and $\bar{I}$ denotes the mean insulin during OGTT.	Missing if any values in the derivation formula is missing
		Change from baseline in Matsuda index	Calculated as: postbaseline Matsuda index – baseline Matsuda index	Missing if baseline or postbaseline value is missing
Fasting Insulin	Per Protocol GZGP Section 10.2: Fasting insulin will be assayed by Lilly-designated laboratory.	Fasting insulin	As provided Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in fasting insulin (%)	Calculated as: log(postbaseline fasting insulin) – log(baseline fasting insulin) then will transform back to percent change.	Missing if baseline or postbaseline value is missing
Renal Function	Per Protocol GZGP Section 10.2: UACR and eGFR will be assayed by Lilly-designated laboratory.	UACR	As provided Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in UACR (%)	Calculated as: log(postbaseline UACR) – log(baseline UACR) then will transform back to percent change.	Missing if baseline or postbaseline value is missing

		eGFR CKD-EPI Cystatin C (ml/min/1.73m^2)	As provided as: eGFR (CKD-EPI Cystatin C 2012)	Single item, missing if missing
		Change from baseline in eGFR CKD-EPI Cystatin C (ml/min/1.73m^2)	Calculated as: postbaseline eGFR CKD-EPI Cystatin C (ml/min/1.73m^2) – Baseline eGFR CKD-EPI Cystatin C (ml/min/1.73m^2)	Missing if baseline or postbaseline value is missing
		eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	As provided as: eGFR (CKD-EPI Creatinine 2021)	Single item, missing if missing
		Change from baseline in eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	Calculated as: postbaseline eGFR CKD-EPI Creatinine (ml/min/1.73m^2) – Baseline eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	Missing if baseline or postbaseline value is missing
Inflammatory biomarker	Per Protocol GZGP Section 10.2: hsCRP will be assayed by Lilly-designated laboratory.	hsCRP (mg/L)	As provided Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in hsCRP (%)	Calculated as: log(postbaseline hsCRP) – log(baseline hsCRP)	Missing if baseline or postbaseline value is missing
FFAs	Per Protocol GZGP Section 10.2: FFAs will be assayed by Lilly-designated laboratory.	FFAs (mmol/L)	As provided Log transformation before the analysis	Single item, missing if missing
		Percent change from baseline in FFAs (%)	Calculated as: log(postbaseline FFAs) – log(baseline FFAs)	Missing if baseline or postbaseline value is missing
HOMA	HOMA2 B estimates steady state beta cell function	HOMA2 B (insulin)	Calculated from the link[a] using fasting glucose and insulin laboratory values	Missing if fasting glucose or insulin is missing
		Percent change from baseline in HOMA2 B (insulin) (%)	Calculated as: log[postbaseline HOMA2 B (insulin)] – log[baseline HOMA2 B (insulin)]	Missing if baseline or postbaseline value is missing

		HOMA2 B (C-peptide)	Calculated from the link[a] using fasting glucose and C-peptide laboratory values	Missing if fasting glucose or C-peptide is missing
		Percent change from baseline in HOMA2 B (C-peptide) (%)	Calculated as: log [postbaseline HOMA2 B (C-peptide)] – log [baseline HOMA2 B (C-peptide)]	Missing if baseline or postbaseline value is missing
	HOMA2 IR estimates insulin resistance	HOMA2 IR (insulin)	Calculated from the link[a] using fasting glucose and insulin laboratory values	Missing if fasting glucose or insulin is missing
		Percent change from baseline in HOMA2 IR (insulin) (%)	Calculated as: log[postbaseline HOMA2 IR (insulin)] – log[baseline HOMA2 IR (insulin)]	Missing if baseline or postbaseline value is missing
		HOMA2 IR (C-peptide)	Calculated from the link[a] using fasting glucose and C-peptide laboratory values	Missing if fasting glucose or C-peptide is missing
		Percent change from baseline in HOMA2 IR (C-peptide) (%)	Calculated as: log[postbaseline HOMA2 IR (C-peptide)] – log[baseline HOMA2 IR (C-peptide)]	Missing if baseline or postbaseline value is missing
SF-36	SF-36v2 will 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.	SF-36 domain scores and SF-36 component scores	Per copyright owner, the Quality Metric Health Outcomes™ Scoring Software will be used to derive SF-36 domain and component scores. After data quality-controls, the SF-36 software will recalibrate the item-level responses for calculation of the domain and component scores. These raw scores will be transformed into the domain scores (T-scores) using the 1-week recall period. This entails exporting the patient data in a CSV or tab-	Missing data handling offered by SF-36 software will be used. "Maximum Data Recovery" will be selected for Missing Score Estimator in the software.

	The Physical Functioning domain assesses limitations due to health now. The Physical functioning domain does not have a recall period 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, a Physical Component Summary, and a 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[b].		delimited file for import, generation of the SF-36 scores and reports, and export of the calculated scores in a CSV or tab-delimited file.	
		SF-36 change from baseline for domains and component scores (PCS and MCS)	Calculated as: postbaseline SF-36 score – baseline SF-36 score	Missing if baseline or postbaseline value is missing
PGI-S	The PGI-S Physical Function 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.	PGI-S rating	As assessed. The responses are on a 5-point scale ranging from "not at all limited" to "extremely limited."	Single item, missing if missing
PGI-C	The PGI-C Physical Function 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 intervention.	PGI-C rating	As assessed. The responses are based on a 5-point scale ranging from "much better" to "much worse."	Single item, missing if missing

IWQOL-Lite-CT	IWQOL-Lite-CT[c] is a 20-item, obesity-specific, patient-reported outcome instrument developed for use in weight management clinical studies. The IWQOL-Lite-CT assesses 2 primary domains of obesity-and health-related quality of life: Physical (7 items) and Psychosocial (13 items), and a 5-item subset of the Physical domain, the Physical Function composite. 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 2 domain scores, 1 composite score and total score range from 0 to 100 with higher scores indicating greater functioning, derived as below: Raw scores for each subscale are computed if a minimum of 50% of the items for that subscale are non-missing, and for the IWQOL-Lite-CT total score if a minimum of 75% of all items are non-missing. If the minimum number of items is answered for a composite, then • compute the average of the valid non-missing responses corresponding to the items in the total or each domain/composite will be calculated (1 = "never" or "not at all true" and 5 = "always" or "completely true"). • The score will be then calculated by transforming the raw score to the 0 (worst) to 100 (best) metric using the following	Physical domain score and psychosocial domain score	Physical domain includes Items 1-5, 16, 17; Psychosocial domain includes Items 6-8, 9-15, 18, 19, 20	The minimum requirements for non-missing responses: Psychosocial: 7 of 13 items, Physical: 4 of 7 items, otherwise considered missing
		Change from baseline in physical domain score and psychosocial domain score	Calculated as: Postbaseline score – baseline score	Missing if baseline or postbaseline value is missing
		Physical function composite score	Include Items 1-3, 16, 17.	The minimum requirements for non-missing responses: 3 of 5 items, otherwise considered missing
		Change from baseline in physical function composite score	Calculated as: postbaseline score – baseline score	Missing if baseline or postbaseline value is missing
		Total score	Items 1-20	The minimum requirements for non-missing responses: 15 of 20 items, otherwise considered missing
		Change from baseline in total score	Calculated as: Postbaseline score – baseline score	Missing if baseline or postbaseline value is missing

	formula for every participant at each time point: $100(S_{max} - C_{avg})/(S_{max} - S_{min})$ ○ C_{avg} is the raw average score of all non-missing item responses in the composite; this average must be a number between 1 and 5, inclusive. ○ S_{max} is the maximum possible raw score value (that is, 5) ○ S_{min} is the minimum possible raw score value (that is, 1) ○ Inserting the maximum and minimum possible score values, the formula is reduced to: $100(5 - C_{avg}) / 4$			
EQ-5D-5L and VAS	The EQ-5D-5L[d] 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: Item 1: mobility Item 2: self-care Item 3: usual activities Item 4: pain/discomfort Item 5: 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	EQ-5D-5L item scores	Five health profile dimensions, each dimension has 5 levels: 1 = no problems 2 = slight problems 3 = moderate problems 4 = severe problems 5 = extreme problems It should be noted that the numerals 1-5 have no arithmetic properties and should not be used as a primary score.	Each dimension is a single item, missing if missing. Note: Missing value can be coded as 9.
		EQ-5D-5L UK population-based utility index	EQ-5D-5L health states are converted into a single index "utility" score using a scoring algorithm based on public preferences. Uses the concatenation of the value of each EQ-5D-5L dimension score	If any of the items is missing or coded as 9, the index score is missing

	are labeled as “best imaginable health state” (100) and “worst imaginable health state” (0).		in the order: item 1; item 2; item 3; item 4; item 5. Derive EQ-5D-5L UK population-based index score according to the link[b] by using the UK algorithm to produce a patient-level index score between -0.59 and 1.0 (continuous variable)[e].	
		Change from baseline in EQ-5D-5L utility index	Calculated as: Postbaseline utility index score – baseline utility index score	Missing if baseline or postbaseline value is missing
		EQ-5D VAS	Range from 0 = “worst imaginable health state” to 100 = “best imaginable health state” Note: Higher value indicates better health state.	Single item, missing if missing.
		Change from baseline in EQ-5D-5L VAS	Calculated as: postbaseline VAS score – baseline VAS score	Missing if baseline or postbaseline value is missing
PROMIS SD	The 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.” Higher T-scores indicate more sleep disturbance.	PROMIS SD T-scores	T-scores are generated using response pattern scoring with a mean of 50 and a SD of 10[f].	Missing if all of the items are missing
		Change from baseline in PROMIS SD T-scores	Calculated as: postbaseline score – baseline score	Missing if baseline or postbaseline value is missing

Appetite VAS	The aim of the appetite VAS is to determine the effects of study intervention on appetite sensations and desire for specific foods. 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 10-cm (100 mm) line. The ratings will include the following 8 questions[g]: • 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?	Appetite VAS item scores	For questions 1-4: range from 0 mm = "not at all" to 100 mm = "extremely" For questions 5-8: range from 0 mm = " No, not all " to 100 mm = "Yes, very much"	Single item, missing if missing
		Appetite VAS overall score	Calculated as the mean of the following 4 fasting appetite VAS item scores: • 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? (van Can et al. 2014) A higher value means feeling hungry or strong desire to eat.	Missing if any single item is missing
		Change from baseline in appetite VAS item and overall scores	Calculated as: postbaseline VAS score – baseline VAS score	Missing if baseline or postbaseline value is missing
		Change from Week 72 in appetite VAS item and overall scores	Calculated as: postbaseline VAS score – Week 72 VAS score	Missing if Week 72 or postbaseline value is missing
PFS	The PFS[h] 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	PFS item scores	5-point Likert scale ranging from 1 (do not agree at all) to 5 (strongly agree) Higher scores indicate a higher psychological impact of food.	Single item, missing if missing

	appetite for food based on 3 levels of food proximity: • food available • food present, and • food tasted.	PFS domain scores	Calculated as the mean of the item scores within each of the individual 3 domains	Missing if any single item is missing
		PFS overall score	Calculated as the mean of all 15 items	Missing if any single item is missing
		Change from baseline in PFS domain and overall scores	Calculated as: postbaseline PFS score – Baseline PFS score	Missing if baseline or postbaseline value is missing
		Change from Week 72 in PFS domain and overall scores	Calculated as: postbaseline PFS score – Week 72 PFS score	Missing if baseline or postbaseline value is missing

Abbreviations: BMI = body mass index; CRF = case report form; CSV = comma separated values; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FFA = free fatty acids; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials Version; HOMA = homeostasis model assessment; HOMA2 B = homeostasis model assessment 2 B; HOMA2 IR = homeostasis model assessment 2 IR; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MCS = Mental Component Score; OGTT = oral glucose tolerance test; PGI--C = patient global impression of change; PCS = Physical Component Score; PFS = Power of Food Scale; PGI-S = patient global impression of severity; PROMIS SD = Patient-Reported Outcomes Measurement Information System Sleep Disturbance; SBP = systolic blood pressure; SF-36 = Short Form 36-item Health Survey; SF-36v2 = Short Form 36 Health Survey Version 2; T2D = type 2 diabetes; UACR = urine albumin-creatinine ratio; VAS = visual analog scale; VLDL = very low-density lipoprotein.

[a] Derive HOMA2 B and HOMA2 IR using the calculator at https://www.rdm.ox.ac.uk/about/our-clinical-facilities-and-mrc-units/DTU/software/homa

[b] Maruish 2011.

[c] Kolotkin et al. 2017, 2019.

[d] EuroQol Research Foundation 2019.

[e] Derive EQ-5D-5L UK population-based index score using the calculator at https://euroqol.org/eq-5d-instruments/eq-5d-5l-about/valuation-standard-value-sets/crosswalk-index-value-calculator/

[f] Scoring algorithm obtained from the developer, Northwestern University (Chapman 2022).

[g] Flint et al. 2000.

[h] Cappelleri et al. 2009; Lowe et al. 2009.

Table GZGP.4.6. Description of Efficacy/Health Outcomes Analyses

Measure	Variable	Estimand Data Points Set / Population[a]	Analysis Method	Time Point[b]	Analysis Type
Body weight	Percent change from baseline in body weight (%)	Treatment Regimen	ANCOVA with PMI	Week 72 visit	Primary endpoint, main analysis
		Efficacy	MMRM	Week 72 visit	Primary endpoint, main analysis
		Treatment Regimen	ANCOVA with MI-TP	Week 72 visit	Primary endpoint, sensitivity analysis
		Treatment Regimen	Cumulative distribution function (CDF) plot with PMI	Week 72 visit	Exploratory analysis
		Efficacy	CDF plot with MI	Week 72 visit	Exploratory analysis
		Treatment Regimen	Waterfall Plot with observed data	Week 72 visit	Exploratory analysis
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI	Week 176 visit	Key secondary, main analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Key secondary, main analysis
		Modified efficacy/Randomized participants with prediabetes	MMRM	Week 190 visit	Exploratory analysis
		Safety /Randomized participants with prediabetes	MMRM	Week 190 visit	Exploratory analysis
	Percentage of participants with ≥x% body weight reduction from baseline, where x = 5, 10, 15, 20	Treatment Regimen	Logistic regression with PMI	Week 72 visit	Key secondary, main analysis
		Efficacy	Logistic regression with MI	Week 72 visit	Key secondary, main analysis

		Treatment Regimen / Randomized participants with prediabetes	Logistic regression with PMI	Week 176	Additional secondary (x = 5); Exploratory analysis (x = 10, 15, 20)
		Efficacy / Randomized participants with prediabetes	Logistic regression with MI	Week 176	Additional secondary (x = 5); Exploratory analysis (x = 10, 15, 20)
	Change from baseline in body weight (kg)	Efficacy	MMRM	Week 72 visit	Additional secondary
		Treatment Regimen	ANCOVA with PMI	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Exploratory analysis
		Modified efficacy/Randomized participants with prediabetes	MMRM	Week 190	Exploratory analysis
		Safety /Randomized participants with prediabetes	MMRM	Week 190 visit	Exploratory analysis
BMI	Change from baseline in BMI (kg/m^2)	Efficacy	MMRM	Week 72 visit	Additional secondary

		Treatment Regimen	ANCOVA with PMI	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Exploratory analysis
	Percentage of participants with BMI threshold value of <x kg/m^2, where x = 25, 27, 30, 35	Efficacy	Logistic regression with MI	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	Logistic regression with MI	Week 176 visit	Exploratory analysis
		Treatment Regimen	Logistic regression with PMI	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	Logistic regression with PMI	Week 176 visit	Exploratory analysis
Waist circumference	Change from baseline in waist circumference (cm)	Treatment Regimen	ANCOVA with PMI	Week 72 visit	Key secondary, main analysis
		Efficacy	MMRM	Week 72 visit	Key secondary,

					main analysis
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI	Week 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Exploratory analysis
		Modified efficacy/Randomized participants with prediabetes	MMRM	Week 190	Exploratory analysis
		Safety /Randomized participants with prediabetes	MMRM	Week 190 visit	Exploratory analysis
Blood pressure	Change from baseline in SBP (mm Hg) Change from baseline in DBP (mm Hg)	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 72 visit	Key secondary, main analysis; exploratory analysis
		Efficacy	MMRM (pooled and individual OFG doses)	Week 72 visit	Key secondary, main analysis; exploratory analysis

		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Modified efficacy/Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 190	Exploratory analysis
		Safety /Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 190 visit	Exploratory analysis
Lipid parameter	Percent (%) change from baseline in • triglycerides • non-HDL-cholesterol • total cholesterol • LDL-cholesterol • HDL-cholesterol • VLDL-cholesterol	Treatment Regimen	ANCOVA with PMI[c] (log transformation; pooled and individual OFG doses)	Week 72 visit	Key secondary, main analysis; exploratory analyses
		Efficacy	MMRM (log transformation; pooled and individual OFG doses)	Week 72 visit	Key secondary, main analysis; exploratory analyses

		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI[c] (log transformation; pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation; pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Modified efficacy/Randomized participants with prediabetes	MMRM (log transformation; pooled and individual OFG doses)	Week 190	Exploratory analysis
		Safety /Randomized participants with prediabetes	MMRM (log transformation; pooled and individual OFG doses)	Week 190 visit	Exploratory analysis
Glycemic control	Change from baseline in fasting glucose (mg/dL and mmol/L)	Efficacy	MMRM	Week 72 visit	Additional secondary
		Treatment Regimen	ANCOVA with PMI	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Additional secondary
		Modified efficacy/Randomized participants with prediabetes	MMRM	Week 190	Exploratory analysis

		Safety /Randomized participants with prediabetes	MMRM	Week 190 visit	Exploratory analysis
	Change from baseline in HbA1c (%)	Efficacy	MMRM	Week 72 visit	Additional secondary
		Treatment Regimen	ANCOVA with PMI	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Additional secondary
		Modified efficacy/Randomized participants with prediabetes	MMRM	Week 190	Exploratory analysis
		Safety /Randomized participants with prediabetes	MMRM	Week 190 visit	Exploratory analysis
	Time to onset of T2D	Treatment Regimen / Randomized participants with prediabetes	Stratified Log-Rank / Cox-proportional hazards (pooled and individual OFG doses)	Up to Week 176 visit	Key secondary, main analysis; exploratory analysis
		Efficacy / Randomized participants with prediabetes	Stratified Log-Rank / Cox-proportional hazards model (pooled and individual OFG doses)	Up to Week 176 visit	Key secondary, main analysis; exploratory analysis
		Safety / Randomized participants with prediabetes	Stratified Log-Rank / Cox-proportional hazards model (pooled and individual OFG doses)	Up to Week 190 visit	Key secondary, main analysis; exploratory analysis

	Percentage of participants achieving normoglycemia	Treatment Regimen / Randomized participants with prediabetes	Logistic regression with PMI	Weeks 72,176, and 190 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	Logistic regression with MI	Weeks 72, 176, and 190 visit	Additional secondary
	Change from baseline in point x OGTT (mg/dL and nmol/L), where x = 30, 60, 90, and 120 minutes	Efficacy	ANCOVA with MI	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Weeks 120 and 176 visit	Exploratory analysis
Insulin sensitivity	Change from baseline in Matsuda Index	Efficacy	ANCOVA with MI	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Weeks 72 and 176 visit	Exploratory analysis
Fasting insulin	Percent change from baseline in fasting insulin (%)[e]	Efficacy	MMRM (log transformation)	Week 72 visit	Additional secondary
		Treatment Regimen	ANCOVA with PMI (log transformation)	Week 72 visit	Additional secondary
		Efficacy / Randomized participants with prediabetes	MMRM	Week 176 visit	Exploratory analysis
Renal function	Percent change from baseline in UACR (%)	Efficacy	MMRM (log transformation)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation)	Weeks 176 visit	Exploratory analysis

	Change from baseline in eGFR CKD-EPI Cystatin-C (ml/min/1.73m^2)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Weeks 176 visit	Exploratory analysis
	Change from baseline in eGFR CKD-EPI Creatinine (ml/min/1.73m^2)	Efficacy	MMRM	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM	Weeks 176 visit	Exploratory analysis
	Percent change from baseline in hsCRP (%)	Efficacy	MMRM (log transformation)	Week 72 visit	Exploratory analysis
		Treatment Regimen	ANCOVA with PMI (log transformation)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation)	Weeks 176 visit	Exploratory analysis
		Treatment Regimen/ Randomized participants with prediabetes	ANCOVA with PMI (log transformation)		
	Percent change from baseline in FFAs (%)	Efficacy	MMRM (log transformation)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation)	Weeks 176 visit	Exploratory analysis
Homeostasis Model Assessment	Percent change from baseline in • HOMA2 B (insulin[e]) • HOMA2 IR (insulin[e])	Efficacy	MMRM (log transformation)	Week 72 visit	Exploratory analysis

	• HOMA2 B (C-peptide) • HOMA2 IR (C-peptide)				
		Efficacy / Randomized participants with prediabetes	MMRM (log transformation)	Weeks 176 visit	Exploratory analysis
	Change from baseline in SF-36v2 Acute Form Physical Functioning domain score	Treatment Regimen / Randomized participants with limitations in physical function at baseline[d]	ANCOVA with PMI (pooled and individual OFG doses)	Week 72 visit	Exploratory analysis
		Efficacy / Randomized participants with limitations in physical function at baseline[d]	MMRM (pooled and individual OFG doses)	Week 72 visit	Exploratory analysis
	Change from baseline in SF-36v2 Acute Form domain scores, PCS and MCS	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled and individual OFG doses)	Week 72 visit	Additional secondary
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
PGI-S	PGI-S rating	Treatment Regimen	Shift from baseline (pooled and individual OFG doses)	Week 24 and 72 visits	Additional secondary

		Efficacy	Shift from baseline (pooled and individual OFG doses)	Week 24 and 72 visits	Additional secondary
		Treatment Regimen / Randomized participants with prediabetes	Shift from baseline (pooled and individual OFG doses)	Week 120 and 176 visits	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	Shift from baseline (pooled and individual OFG doses)	Week 120 and 176 visits	Exploratory analysis
PGI-C	PGI-C rating	Treatment Regimen	Descriptive statistics (pooled and individual OFG doses)	Week 24 and 72 visits	Additional secondary
		Efficacy	Descriptive statistics (pooled and individual OFG doses)	Week 24 and 72 visits	Additional secondary
		Treatment Regimen / Randomized participants with prediabetes	Descriptive statistics (pooled and individual OFG doses)	Week 120 and 176 visits	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	Descriptive statistics (pooled and individual OFG doses)	Week 120 and 176 visits	Exploratory analysis
IWQOL-Lite-CT	Change from baseline in: • physical function composite score • physical domain score • psychosocial domain score • total score	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled and individual OFG doses)	Week 72 visit	Additional secondary
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis

EQ-5D-5L	Change from baseline in EQ-5D-5L utility index and VAS	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 72 visit	Additional secondary
		Efficacy	MMRM (pooled and individual OFG doses)	Week 72 visit	Additional secondary
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 176 visit	Exploratory analysis
PROMIS SD	Individual items	Treatment Regimen	Descriptive statistics	Week 24 and 72 visits	Exploratory analysis
		Efficacy	Descriptive statistics	Week 24 and 72 visit	Exploratory analysis
		Treatment Regimen / Randomized participants with prediabetes	Descriptive statistics	Week 120 and 176 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	Descriptive statistics	Week 120 and 176 visit	Exploratory analysis
	Change from baseline in PROMIS SD T-scores	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Efficacy	MMRM (pooled and individual OFG doses)	Week 72 visit	Exploratory analysis
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 120 and 176 visits	Exploratory analysis
		Efficacy / Randomized participants with prediabetes	MMRM (pooled and individual OFG doses)	Week 176	Exploratory analysis
Appetite VAS	Change from baseline in appetite VAS item and overall scores	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 24 and 72 visits	Exploratory analysis

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		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 176	Exploratory analysis
		Efficacy	MMRM (pooled and individual OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Safety / Randomized participants without prediabetes		Week 74 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes		Week 176 visit	Exploratory analysis
	Change from Week 72 in appetite VAS item and overall scores	Safety / Randomized participants without prediabetes	ANCOVA with MI (pooled and individual OFG doses)	Week 74 visit	Exploratory analysis
Power of food scale (PFS)	Change from baseline in PFS domain and overall scores	Treatment Regimen	ANCOVA with PMI (pooled and individual OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Treatment Regimen / Randomized participants with prediabetes	ANCOVA with PMI (pooled and individual OFG doses)	Week 176	Exploratory analysis
		Efficacy	MMRM (pooled and individual OFG doses)	Week 24 and 72 visits	Exploratory analysis
		Safety / Randomized participants without prediabetes		Week 74 visit	Exploratory analysis
		Efficacy / Randomized participants with prediabetes		Week 176 visit	Exploratory analysis
	Change from Week 72 in appetite VAS item and overall scores	Safety / Randomized participants without prediabetes	ANCOVA with MI (pooled and individual OFG doses)	Week 74 visit	Exploratory analysis

Abbreviations: ANCOVA = analysis of covariance; BMI = body mass index; CDF = cumulative distribution function; CSV = comma separated values; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FFA = free fatty acids; HDL = high-density lipoprotein; HOMA = homeostasis model assessment; IWQOL-Lite-CT = impact of weight on quality of life-lite clinical trials; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; MCS = Mental Component Score; MI = multiple imputation; MMRM = mixed-effects model for repeated measures; OFG = orforglipron; OGTT = oral glucose tolerance test; PGI-S = patient global impression of severity; PGI-C= patient global impression of change; PCS = Physical Component Score; PFS = power of food scale; PMI = primary multiple imputation; PROMIS SD = patient-reported outcomes measurement information system sleep disturbance;
SBP = systolic blood pressure; SF-36 = Short Form 36-item Health Survey; TP = tipping point; UACR = urine albumin-creatinine ratio; VAS = visual analog scale; VLDL = very low-density lipoprotein.

[a] Population is displayed if different from Randomized Participants.

[b] Assessments collected at multiple postbaseline visits will be analyzed at those scheduled visits using MMRM as supplemental analyses, in addition to the primary time point listed in the table.

[c] PMI strategy will be performed after the log transformation.

[d] The limitation in physical function at baseline is defined as PGI-S response at baseline of “moderately limited,” “very much limited,” or “extremely limited.”

[e] Fasting insulin is collected at the 0 minute OGTT timepoint for the Week 176 analysis.

4.4.1. Key Secondary Endpoints

4.4.1.1. Definition of endpoints

The definitions of key secondary endpoints are specified in Table GZGP.4.5.

4.4.1.2. Main analytical approach

The analytical approaches for the key secondary endpoints are specified in Table GZGP.4.6.

4.4.1.3. Sensitivity Analyses

No sensitivity analyses are planned for key secondary endpoints.

4.4.1.4. Supplementary analyses

No supplemental analyses are planned for key secondary endpoints.

4.4.2. Supportive secondary Endpoints

The definitions of additional secondary endpoints are specified in Table GZGP.4.5. Additionally, the analytical approaches are specified in Table GZGP.4.6.

4.5. Exploratory Endpoints/Estimands Analysis

Exploratory endpoints and analyses are specified in Table GZGP.4.5 and Table GZGP.4.6. Additional exploratory analyses will be described in the Exploratory/Supplemental Analyses Plan and Health Technology Analyses Plan.

4.6. Safety Analyses

The planned safety analyses are consistent with compound-level safety standards, which are based on various sources, including company standards, internal and external subject matter experts, publications from cross-industry initiatives (for example, PHUSE 2013, PHUSE 2015, PHUSE 2017, PHUSE 2018, PHUSE 2022), and publications from regulatory agencies (for example, EMA 2014, CDER/BIRRS 2022a, 2022b). Descriptions of the safety analyses are provided in this SAP, but some details are found in compound-level safety standards.

For safety interpretation, p-values will not be used for hypothesis testing. P-values will be considered as a number between 0 and 1 that gives an idea of how strong the evidence is for an imbalance between study intervention arms. The evidence for an imbalance is stronger toward 0 and weaker toward 1. Similarly, confidence intervals will not be used for hypothesis testing. They reflect the uncertainty of an estimate.

Unless otherwise specified, safety analyses will be conducted using the safety participants (Table GZGP.3.1) and the safety data points set (Table GZGP.3.2). It is noted that for some safety endpoints, such as treatment discontinuation due to AE and so forth, the analyses will be based on data observed during treatment period only.

Summary tables with risk difference will be sorted by decreasing risk difference.

Additionally, the planned safety analyses will be provided for participants with prediabetes at randomization for the final lock.

4.6.1. Extent of Exposure

Duration of exposure to study treatment will be summarized by treatment group for safety participants. Descriptive statistics for participant weeks (or days) of exposure and total participant years in exposure will be provided. Overall exposure will be summarized in total participant-year (PY) of exposure, derived in the following manner:

total PY of exposure = sum of duration of exposure in days (for all participants in treatment group) / 365.25

The frequency of participants falling into different exposure ranges will be summarized:

- >0; ≥4 weeks; ≥8 weeks; ≥12 weeks; ≥16 weeks; ≥20 weeks; ≥24 weeks; ≥36 weeks; ≥48 weeks, ≥60 weeks, and ≥72 weeks.

For participants with prediabetes at baseline, the following additional exposure ranges will be summarized:

- ≥84 weeks; ≥96 weeks; ≥108 weeks; ≥120 weeks; ≥132 weeks; ≥144 weeks; ≥156 weeks; ≥168 weeks, and ≥176 weeks.

No p-values will be reported.

4.6.2. Adverse Events

The planned summaries for AEs are provided in Table GZGP.4.7 and are described more fully in compound-level safety standards.

Table GZGP.4.7. Summary Tables Related to Adverse Events

Analysis	Method	Population/Period
Overview of AEs, including • TEAE • SAE • death, and • permanent discontinuation from study intervention due to an AE.	Fisher's exact	Safety/TP + FP (TP for study treatment discontinuation due to an AE)
TEAEs by PT within SOC	Fisher's exact	Safety/TP + FP
TEAEs by PT	Fisher's exact	Safety/TP + FP
Maximum Severity TEAEs by PT within SOC		Safety/TP + FP
TEAEs with incidence ≥2% by PT	Fisher's exact	Safety/TP + FP
SAEs by PT within SOC	Fisher's exact	Safety/TP + FP
Primary AEs leading to permanent discontinuation of study intervention by PT within SOC	Fisher's exact	Safety/TP
Primary AEs leading to permanent discontinuation of study by PT within SOC	Fisher's exact	Safety/TP + FP
AEs leading to study intervention interruption by PT within SOC	Fisher's exact	Safety/TP
AEs leading to study intervention reduction by PT within SOC	Fisher's exact	Safety/TP
Listing of SAEs		Safety/TP + FP

Analysis	Method	Population/Period
Listing of primary AEs leading to permanent discontinuation of study intervention		Safety/TP
Listing of primary AEs leading to permanent discontinuation of study		Safety/TP + FP
Listing of deaths		Safety/TP + FP
Listing AEs related to suspected overdosing		Safety/TP
Listing of participants with at least 1 notable event		Randomized/TP + FP

Abbreviations: AE =Adverse Event; FP = follow-up period; TP = treatment period; TEAE = Treatment Emergent Adverse Event; SAE = Serious Adverse Event; PT = Preferred Term; SOC = System Organ Class.

4.6.3. Clinical Laboratory Evaluation

The planned summaries for clinical laboratory evaluations are provided in Table GZGP.4.8 and are described more fully in compound-level safety standards.

Table GZGP.4.8. Summary Tables Related to Clinical Laboratory Evaluations

Analysis	Method	Population/Period
Box plots and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plots and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Summary for participants with elevated or low values meeting specified levels	Descriptive statistics	Safety/TP + FP
Listing of abnormal laboratory findings		Safety/TP + FP

Abbreviations: CI = confidence intervals; FP = follow-up period; SD = standard deviation; TP = treatment period.

4.6.4. Vital Signs and Physical Characteristics

Triplicate vital signs will be collected at each visit, thus the mean of these measurements will be used for the vital signs analyses. The planned summaries for vital signs (SBP, diastolic blood pressure, and pulse rate) are provided in Table GZGP.4.9, and are described more fully in the compound-level safety standards.

Table GZGP.4.9. Summary Tables Related to Vital Signs

Analysis	Method	Population/Period
Box plots and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plots and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Analysis of blood pressure and pulse rate for change from baseline	MMRM	Safety/TP + FP
Summary for participants meeting specific blood pressure and pulse rate levels	Descriptive statistics	Safety/TP + FP
Shift of maximum-to-maximum for pulse rate	Descriptive statistics	Safety/TP + FP

Abbreviations: CI = confidence intervals; FP = follow-up period; MMRM = mixed model repeated measures; SD = standard deviation; TP = treatment period.

4.6.5. Electrocardiograms

Triplicate electrocardiograms (ECGs) will be collected at the same visit; thus the mean of these measurements will be used for the analysis. The planned summaries for ECG parameters are

provided in Table GZGP.4.10 and are described more fully in the compound-level safety standards.

Table GZGP.4.10. Summary Tables Related to ECG Parameters

Analysis	Method	Population/Period
Box plot and mean/SD (or 95% CI) for observed values by visit	Descriptive statistics	Safety/TP + FP
Box plot and mean/SD (or 95% CI) for change from baseline values by visit	Descriptive statistics	Safety/TP + FP
Heart rate and PR interval in specified categories	Descriptive statistics	Safety/TP + FP
Analysis for change from baseline in ECG parameters (heart rate, PR interval)	MMRM	Safety/TP + FP

Abbreviations: CI = confidence intervals; FP = follow-up period; MMRM = mixed model repeated measures; SD = standard deviation; TP = treatment period.

4.6.6. Safety Topics of Interest

This section includes safety topics of interest whether due to observed safety findings, potential findings based on drug class, or safety topics anticipated to be requested by a regulatory agency for any reason. In general, safety topics of interest will be identified by one or more standardized Medical Dictionary for Regulatory Activities (MedDRA) query(ies) (SMQs), system organ class (SOC), high level terms (HLT), FDA medical query(ies) (FMQ), or by a Lilly-defined MedDRA preferred term (PT) listing based upon the review of the most current MedDRA Version, or by relevant laboratory changes. Search criteria are detailed in the compound-level safety standards.

The planned analyses for safety topics of interest are provided in Table GZGP.4.11 and are described more fully in compound-level safety standards.

Table GZGP.4.11. Description and Analyses of Safety of Interest

Special Safety Topic	Short Description	Analysis	Method	Population/Period
Major Adverse Cardiovascular Events	Death and nonfatal CV AEs will be adjudicated by a committee of physicians external to Lilly with cardiology expertise: Clinical Endpoint Committee (CEC).	Positively adjudicated MACE by category/subcategory MACE reported by investigators may be summarized		Safety/TP + FP
		Listing of all MACE reported by investigator (whether or not positively adjudicated)		Safety/TP + FP
Arrhythmias and Cardiac Conduction Disorders	The treatment-emergent (TE) arrhythmias and cardiac conduction disorders events will be derived using the MedDRA PTs contained in certain SMQs and HLT.	TE arrhythmias and cardiac conduction disorders by PT nested within SMQ and HLT[a]	Fisher's exact	Safety/TP + FP
Hypotension, Orthostatic Hypotension, and Syncope	The TE hypotension, orthostatic hypotension, and syncope events will be derived using MedDRA PTs and FMQs.	TE hypotension, orthostatic hypotension, and syncope by PT[a]	Fisher's exact	Safety/TP + FP
		Hypotension by baseline antihypertensive medication use using hypotension narrow FMQ		
Hypoglycemia[a,b]	The American Diabetes Association position statement on glycemic targets (ADA 2025) will be used to define: • Level 1 hypoglycemia • Level 2 hypoglycemia • Level 3 hypoglycemia (severe/serious hypoglycemia) Nocturnal hypoglycemia events (including severe hypoglycemia) **occur at night** and presumably during sleep.	Incidence (percent of patients experiencing 1 or more episode) of level 2 or level 3 hypoglycemia	Logistic regression for the overall postbaseline period	Safety/TP + FP excluding events after initiation of new antihyperglycemic therapy as defined in Section 6.3. Supportive analysis: Safety/TP + FP regardless of initiation of new antihyperglycemic therapy
		Incidence of level 3 (severe/serious) hypoglycemia		
		Incidence of level 1 hypoglycemia (if warranted by data) [a]		
		Rate (episodes/patient/year) of level 2 or level 3 hypoglycemia	Empirical method for the overall postbaseline period	
		Rate of level 3 (severe/serious) hypoglycemia		
		Rate of level 1 hypoglycemia (if warranted by data)		
		Listing of level 2 or level 3 hypoglycemia events		
		Listing of level 2 or level 3 nocturnal hypoglycemia events		Safety/TP + FP
		Severe or serious TE gastrointestinal events by PT	Fisher's exact	Safety/TP + FP

Gastrointestinal (GI) Safety[c]	GI AEs using Gastrointestinal disorders SOC and FMQ will be captured.	Study intervention discontinuation due to TE gastrointestinal events	Fisher's exact	Safety/TP + FP
		TE abdominal pain by FMQ narrow PT	Fisher's exact	Safety/TP + FP
		Prevalence and incidence over time for TE nausea, vomiting, diarrhoea, constipation, and NVD		Safety/TP + FP
		Plot of time to the onset of TE nausea, vomiting, diarrhoea, constipation, and NVD	KM	Safety/TP + FP
		Plot of prevalence and incidence over time for TE nausea, vomiting, diarrhoea, constipation, and NVD by maximum severity		Safety/TP + FP
Renal Safety	Laboratory measures related to renal safety will be analyzed. Renal events including acute renal failure and chronic renal failure exacerbation will be captured using SMQs. Dehydration events will be captured using SMQ.	Shift of minimum-to-minimum for eGFR as estimated by the CKD-EPI Cystatin C equation		Safety/TP + FP
		Shift of maximum-to-maximum for UACR		Safety/TP + FP
		Summary of eGFR decrease from baseline		Safety/TP + FP
		MMRM analyses for eGFR estimated by the CKD-EPI Cystatin C equation	MMRM	Safety/TP + FP
		MMRM analyses for UACR (log transformation)	MMRM	Safety/TP + FP
		TE renal events by PT nested within SMQ [a]	Fisher's exact	Safety/TP + FP
		Listing of TE dehydration events by PT [a]		Safety/TP + FP
Pancreatic Safety	The pancreatic enzyme data (p-amylase and lipase) will be observed through laboratory testing. All suspected cases of acute or chronic pancreatitis and AEs of severe or serious abdominal pain of unknown etiology will be sent for adjudication by an independent clinical endpoint committee.	Shift of maximum-to-maximum for pancreatic enzyme		Safety/TP + FP
		MMRM analysis for pancreatic enzymes (p-amylase and lipase) with a log transformation (postbaseline/baseline)	MMRM	Safety/TP + FP
		Investigator-reported events and subsequently confirmed adjudicated events, respectively	Fisher's exact	Safety/TP + FP
		TE Pancreatic events by "Acute pancreatitis" SMQ (narrow scope) and "Chronic pancreatitis" PT		Safety/TP + FP
		Listing of adjudicated and investigator-reported pancreatic events		Safety/TP + FP
Thyroid Safety		TE thyroid C-cell hyperplasia and malignancies by PT within Event Category	Fisher's exact	Safety/TP + FP

	TE thyroid malignancies and C-cell hyperplasia will be identified using MedDRA HLT and PT. The purpose of calcitonin measurements is to assess the potential effect of orforglipron on thyroid C-cell function.	Shift of maximum-to-maximum for calcitonin value in the thresholds		Safety/TP + FP
		Listing of participants who meet protocol defined discontinuation criteria based on calcitonin: • with eGFR <60 mL/min/1.73 m2 at baseline, serum calcitonin value ≥35 ng/L AND ≥50% increase from the baseline value[a] • with eGFR ≥60 mL/min/1.73 m^2 at baseline, serum calcitonin value ≥20 and <35 ng/L AND ≥50% increase from the baseline value and ≥10% increase on retest[a] • with eGFR ≥60 mL/min/1.73 m^2 at baseline, serum calcitonin value ≥35 ng/L AND ≥50% increase from the baseline value[a]		Safety/TP + FP
		MMRM analysis for calcitonin (log transformation)	MMRM	Safety/TP + FP
Malignancies	The malignancy events will be derived using the MedDRA PTs contained certain SMQs.	TE malignancy by PT nested within SMQ[a]	Fisher's exact	Safety/TP + FP
Hepatic Safety	Hepatic labs include ALT, AST, ALP, TBL, DBL, and GGT. When criteria are met for hepatic evaluations, investigators will conduct close monitoring of hepatic symptoms and liver tests, perform a comprehensive evaluation for alternative causes of abnormal liver tests, and complete follow-up hepatic safety eCRFs. Potentially drug-related hepatic disorders will be identified using SMQs.	Abnormal postbaseline categories for hepatic safety parameters: ALT, AST, ALP, TBL, DBL, and GGT		Safety/TP + FP
		Treatment-emergent potentially drug-related hepatic disorders by PT nested within SMQ	Fisher's exact	Safety/TP + FP
		Hepatocellular drug-induced liver injury screening plot (maximum TBL vs maximum ALT or AST)		Safety/TP + FP
		Hepatocellular drug-induced liver injury screening table		Safety/TP + FP
		Cholestatic drug-induced liver injury screening table		Safety/TP + FP
		Cholestatic drug-induced liver injury screening plot (maximum TBL vs maximum ALP)		Safety/TP + FP
		Hepatic Laboratory Parameters (ALT, AST, ALP, TBL, DBL, and GGT) with a log transformation (postbaseline/baseline)	MMRM	Safety/TP + FP

		Listing of participants with ALT or AST ≥3X ULN		Safety/TP + FP
		Listing of participants with ALP or TBL ≥2X ULN		Safety/TP + FP
		Shift of maximum-to-maximum for ALT, AST, ALP, TBL		Safety/TP + FP
		Participant profiles for participants meeting criteria for a comprehensive hepatic evaluation (as defined in the protocol).		Safety/TP + FP
Gallbladder and Biliary Tract Disorders	All events of TE gallbladder and biliary tract disorders will be identified by using certain SMQs.	TE gallbladder and biliary tract disorders by PT nested within SMQ [a]	Fisher's exact	Safety/TP + FP
Hypersensitivity Reactions	All events of TE allergic reaction and hypersensitivities will be identified by using certain SMQs.	TE allergic reaction and hypersensitivities by PT nested within SMQ [a]	Fisher's exact	Safety/TP + FP
Depression, Suicidal Ideation, and Behavior	AEs will be searched using MedDRA PTs that satisfy the search criteria.	TE major depressive disorder, suicidal ideation, or behavior events by PT nested within applicable FMQ or SMQ [a]	Fisher's exact	Safety/TP + FP
	Suicide-related thoughts and behaviors will be collected based on the C-SSRS.	Summary of C-SSRS categories and composite measures		Safety/TP + FP
		Listing of C-SSRS categories and composite measures		Safety/TP + FP
	Patient health questionnaire-9 (PHQ-9) will be collected to assess the specific diagnostic symptoms that determine the presence of a clinical depressive disorder. The PHQ-9 total scores will be categorized as minimal to none, mild, moderate, moderately severe, and severe	Shift of each baseline category (maximum value) versus each postbaseline category (maximum value)		Safety/TP + FP
		Summary of categories based on the maximum values during baseline and postbaseline: • any increase in depression category (that is, worsening of depression) • increase from Minimal to none or Mild depression to Moderate, Moderately severe, or Severe depression • increase from Mild or Moderate depression to Moderately severe or Severe depression		Safety/TP + FP
Abuse Potential	AEs will be searched using a modified study agent abuse potential FMQ.	TE abuse potential events by PT [a]	Fisher's exact	Safety/TP + FP

AEs possibly related to loss of lean muscle mass	AEs will be identified using MedDRA HLTs and PTs	TEAEs possibly related to loss of lean muscle mass by PT within Event Category	Fisher's exact	Safety/TP + FP
Malnutrition	AEs will be identified using MedDRA HLTs and PTs	TE malnutrition by PT within Event Category	Fisher's exact	Safety/TP + FP
Excessive weight loss	AEs will be identified using MedDRA PTs BMI <18.5 kg/m2 will be analyzed	Severe or serious TE excessive weight loss by PT or BMI <18.5kg/m^2	Fisher's exact	Safety/TP + FP
		Listing of participants with BMI <18.5 kg/m^2		

Abbreviations: AE = adverse event; ALP = serum alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CEC = clinical endpoint committee; CKD-EPI = Chronic Kidney Disease Epidemiology; C-SSRS = Columbia-Suicide Severity rating scale; CV = cardiovascular; eCRF = electronic case report form; eGFR = estimated glomerular filtration rate; DBL = direct bilirubin; FMQ = FDA Medical Query; FP = follow-up period; GGT = gamma glutamyl transferase; GI = gastrointestinal; HLT = high-level term; MACE = major adverse cardiovascular event; MedDRA = Medical Dictionary for Regulatory Activities; MMRM = mixed model repeated measure; PT = Preferred Term; SMQ = standardized MedDRA query; SOC = system organ class; TEAE = treatment-emergent adverse event; TBL = total bilirubin; TP = treatment period; UACR = urinary albumin-to-creatinine ratio; vs = versus.

[a] For these tables, if the number of events is low, a listing might be provided instead.

[b] Glucose values collected on the same date as an OGTT assessment are not included

[c] Additionally, all GI events will be analyzed.

Note: Listings and participant profiles may be provided through interactive display tools instead of a static display.

4.7. Other Analyses

4.7.1. Subgroup analyses

Subgroup analyses will be conducted for the primary endpoint with the treatment regimen estimand:

- percent change in body weight from baseline at Week 72 visit.

The variables for subgroup analysis are specified in Table GZGP.6.1.

The ANCOVA model specified in Section 4.1.2.1.1, will be fitted separately within each subgroup. The least squares (LS) mean, LS mean difference, standard error (SE), and 95% confidence interval will be presented. The LS means and variance-covariance estimates from these separate models will be used to test the treatment-by-subgroup interaction at a significance level of 0.10.

If the subgroup factor is part of the strata variable, a new strata variable that excludes the subgroup categories will be used.

If any category within the subgroup is <5% of the total population, only descriptive statistics will be provided for that category (that is, there will be no inferential testing within the subgroup category).

A forest plot including the treatment difference and 95% confidence interval estimated for each subgroup level will be presented.

A Bayesian shrinkage method will be used to provide adjusted estimates and improve estimation precision. Following the paper by Wang et. al. (2024), for a given baseline characteristic with k subgroups, let Y_i $(i = 1, \ldots, k)$ be the observed sample estimate of the treatment effect difference in subgroup i. The following hierarchical model will be used:

$$Y_i \sim N(\mu_i, \sigma_i^2),$$

$$\mu_i \sim N(\mu, \tau^2),$$

$$\mu \sim N(0, 30^2),$$

$$\tau \sim N^+(10),$$

where σ_i^2 is set to the observed variance for sample estimate, $N^+(10)$ is the half-normal distribution with a scaled parameter of 10. A weakly informative prior, as suggested by Röver et al. (2021) and specified above, will be applied to μ and τ. Of note, the unit information standard deviation (UISD) is assumed to be 15% based on historical weight management studies, and a standard deviation of 30% is chosen for the centrality parameter μ , so that it is approximately twice the unit information standard deviation (UISD). A scale parameter of 10 is chosen for the half-normal distribution such that the median heterogeneity in percent body weight reduction is approximately 6.7%, which is a reasonably large difference.

Additional subgroup evaluations may be conducted as exploratory analyses.

4.7.2. Supplementary Analyses

A sensitivity supplementary analysis will be conducted for all primary and key secondary efficacy endpoints based on the population specified in Section 3, excluding participants randomized at sites closed due to Good Clinical Practice (GCP) non-compliance issues. Each endpoint will be evaluated based on the approaches described in Sections 4.3.2 and 4.4.1.2. For safety analyses, overview of adverse events and summary of treatment-emergent adverse events will be conducted, also excluding participants randomized at sites closed due to GCP non-compliance issues.

4.8. Interim Analyses

No interim analyses are planned for Study GZGP. If an unplanned interim analysis is deemed necessary for reasons other than a safety concern, Protocol GZGP must be amended.

4.8.1. Data Monitoring Committee

A data monitoring committee (DMC) is not planned for this study.

An independent DMC will be established for interim safety monitoring of Study J2A-MC-GZGS (ACHIEVE-4) (GZGS), "A Phase 3, Open Label, Study of Once-Daily orforglipron Compared with Insulin Glargine in Adult Participants with Type 2 Diabetes and Obesity or Overweight at Increased Cardiovascular Risk", a study within the orforglipron Phase 3 program for chronic weight management (CWM) and T2D. The DMC will have the responsibility to review unblinded interim safety analysis results from Study GZGS. The DMC may be asked to review unblinded safety data from Study GZGP if a need arises following the blinded trial-level safety reviews (TLSRs) conducted by the sponsor. If needed, permanent data transfers will occur for the purposes of supporting the DMC. Only the statisticians from the statistical analysis center (SAC) will have access to the unblinded data that are presented to the DMC. The SAC and members of the DMC will abide by the principles and responsibilities described in the Study GZGS DMC charter, which includes keeping all unblinded information confidential until the planned unblinding of the trial.

4.9. Changes to Protocol-Planned Analyses

There are changes to the analyses described in the protocol:

1. orforglipron 6 mg endpoint "percentage of participants who achieve a body weight reduction of ≥20%" was removed from the key secondary objectives, and added to additional secondary objectives.
2. treatment compliance is defined as taking at least 75% of required study intervention during the treatment period.

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 of 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 standard deviation (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.

6. Supporting Documentation

6.1. Appendix 1: Demographic and Baseline Characteristics

Demographics and baseline characteristics will be summarized by treatment group for randomly assigned participants. The listing of basic demographic characteristics (that is, age, sex, ethnicity, race, country, baseline body weight, and so forth.) for randomly assigned participants will be provided. Additionally, demographics and baseline characteristics will be provided for participants with prediabetes at randomization for the final lock.

The continuous variables will be summarized using descriptive statistics and the categorical variables will be summarized using frequency counts and percentages.

Table GZGP.6.1 describes the specific variables and how they will be summarized. The last column specifies variables used for the subgroup analysis described in Section 4.7.1.

Table GZGP.6.1. Demographics and Baseline Characteristics with Variables for Subgroup Analysis

Variable	Quantitative Summary	Categorical Summary	Subgroup Analysis[a]
Demographics			
Age[b]	Yes	<65, ≥65 years	X
		<75, ≥75 years	X
		<65, ≥65 and <75, ≥75 and <85, ≥85 years	
Sex	No	Male, Female	X
Ethnicity	No	Hispanic/Latino, Non-Hispanic/Non-Latino	X
Race	No	American Indian/Alaska Native, Asian, Black/African American, Native Hawaiian or other Pacific Islander, White, or Multiple	X
Country	No	By each country	X
Geographic region	No	North America, Europe, Asia, or Central/South America	X
Height (cm)	Yes		
Baseline waist circumference (cm)	Yes		
Baseline body weight (kg)	Yes		
Baseline BMI	Yes	≥27 to <30, ≥30 to <35, ≥35 to <40, ≥40 kg/m^2	X
		≤ median, > median	
Caffeine use	No	Never, Current, Former	
Alcohol use	No	Never, Current, Former	
Tobacco use	No	Never, Current, Former	

Nicotine Replacement use	No	Never, Current, Former	
Recreational drug use - methamphetamine	No	Never, Current, Former	
Recreational drug use - cocaine	No	Never, Current, Former	
Baseline Disease Characteristics			
Baseline systolic blood pressure (mmHg)	Yes		
Baseline diastolic blood pressure (mmHg)	Yes		
Baseline pulse rate (beats/min)	Yes		
Baseline eGFR CKD-EPI Cystatin-C (mL/min/1.73m^2)	Yes	<60, ≥60 mL/min/1.73m^2	
Baseline eGFR CKD-EPI Creatinine (mL/min/1.73m^2)	Yes	<60, ≥60 mL/min/1.73m^2	
Baseline UACR (g/kg)	Yes	<30, ≥30 and ≤300, >300 g/kg	
Baseline triglycerides (mg/dL)	Yes		
Baseline total cholesterol (mg/dL)	Yes		
Baseline VLDL-cholesterol (mg/dL)	Yes		
Baseline non-HDL-cholesterol (mg/dL)	Yes		
Baseline LDL-cholesterol (mg/dL)	Yes		
Baseline HDL-cholesterol (mg/dL)	Yes		
Baseline fasting insulin (pmol/L)	Yes		
Baseline HbA1c (%)	Yes		
Baseline HbA1c (mmol/mol)	Yes		
Baseline fasting glucose (mg/dL)	Yes		
Baseline fasting glucose (mmol/L)	Yes		
Duration of obesity (years)	Yes		
Prediabetes[c]	No	Yes, No	X

Abbreviations: eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; UACR = urine albumin-to-creatinine ratio; VLDL = very low-density lipoprotein.

[a] Subgroup analyses are defined in Section 4.7.1 with more details.

[b] Age in years will be calculated as length of the time interval from the imputed date of birth (July 1 in the year of birth collected in the eCRF) to the informed consent date.

[c] Prediabetes status at baseline is determined from the laboratory data in LabsConnect.

6.2. Appendix 2: Historical Illnesses and Preexisting Conditions

Historical illness is defined as a condition/event with an end date prior to the date of informed consent.

A preexisting condition is defined as a condition/event with a start date prior to the first dose of the study intervention and stop date that is at or after the informed consent date or has no stop date (that is, ongoing). Randomization date will be used if a participant has not been dosed.

The planned summaries for historical illness and preexisting conditions are provided in Table GZGP.6.2. Additionally, analyses for historical illnesses and preexisting conditions will be provided for participants with prediabetes at randomization for the final lock.

Table GZGP.6.2. Summary Tables Related to Historical Illness and Preexisting Conditions

Analysis	Population/Period
Historical illness by PT within SOC	Randomized
Preexisting conditions by PT within SOC	Randomized
Obesity related health disorders[a]	Randomized
Comorbidities at baseline[b]	Randomized

Abbreviations: PT = preferred term; SOC = system organ class.

[a] Include the 11 Obesity-Related Health Disorders defined in Table GZGP.6.6.

[b] Include hypertension, dyslipidemia, coronary artery disease, cerebrovascular disease, obstructive sleep apnea, osteoarthritis, anxiety/depression, metabolic dysfunction-associated steatotic liver disease, asthma or chronic obstructive pulmonary disease, gout or hyperuricemia, renal disease, and female reproductive disorders.

6.3. Appendix 3: Prior/Concomitant Medications

Medications that start before or at the last date of treatment period or follow-up period and are ongoing or ended during the treatment period or follow-up period will be classified as concomitant medication. Medications that start and end before the first dose date of the study intervention will be classified as prior therapy.

Baseline is defined as the corresponding medication taken on the day before the date of the first dose of study intervention.

If there are no doses of study intervention, randomization date will be used instead of the first dose date.

The planned summaries for concomitant medications are provided in Table GZGP.6.3. Additionally, analyses for concomitant medications will be provided for participants with prediabetes at randomization for the final lock.

Table GZGP.6.3. Summary Tables Related to Concomitant Medications

Analysis		Population/Period
CMs by PN		Randomized/TP + FP
CMs by PN within ATC code		Randomized/TP + FP
Antihypertensive CMs at baseline by PN within ATC code		Randomized
Lipid lowering CMs at baseline by PN within ATC code		Randomized
Status change of antihypertensive and lipid lowering CMs		Randomized/TP
Antihyperglycemic CM initiated after baseline by PN within ATC code		Randomized/TP
Antidiarrheal, Antiemetic, and Constipation CMs at baseline by PN within ATC code		
Antidiarrheal, Antiemetic, and Constipation CMs initiated after baseline by PN within ATC code		Randomized/TP
Prohibited concomitant medication and surgical procedure on weight management treatment by PN within ATC code		Randomized Participants/TP
Prohibited concomitant medication on anti-hyperglycemic therapy by PN within ATC code		Randomized Participants/TP
Obesity management medications 1 year prior to screening by PN within ATC code		Randomized

Abbreviations: ATC = Anatomical Therapeutic Chemical; CM = concomitant medication; PN = preferred name; FP = follow-up period; TP = treatment period.

Table GZGP.6.4 provides the protocol-specified concomitant medications of interest.

Table GZGP.6.4. Protocol-Specified Concomitant Medication

Category	Preferred Name / ATC Code
Antihypertensive Medication	All medications with ATC code containing ‘C01’, ‘C03’, ‘C07’, ‘C08’, or ‘C09’
Lipid Lowering Medication	All medications with ATC code containing ‘C10’
Antihyperglycemic Medication[a]	All medications with ATC code containing ‘A10', except for ‘A10XA'

Abbreviations: ATC = Anatomical Therapeutic Chemical; T2D = type 2 diabetes.

[a] For participants who develop T2D during the conduct of the study.

Table GZGP.6.5 provides the protocol-specified prohibited concomitant medication and surgical procedure rules.

Table GZGP.6.5. Prohibited Concomitant Medication Rules

Timing	Preferred Name / ATC Code	ATC Classification	Rule
Prohibited Concomitant Medication on Weight Management Treatment[a]			
Post baseline	All medications with ATC code of A08AA	Centrally acting antiobesity products	Any initiation is prohibited during treatment period
	All medications with ATC code of A08AB	Peripherally acting antiobesity products	Any initiation is prohibited during treatment period
	All medications with ATC code of A08AX	Other antiobesity drugs	Any initiation is prohibited during treatment period
	All medications with ATC code A08AW	Herbal antiobesity preparations	Any initiation is prohibited during treatment period
	All medications that contain phenylpropanolamine, tirzepatide, semaglutide, or liraglutide in the preferred term		Any initiation is prohibited during treatment period
Prohibited Surgical Procedure on Weight Management Treatment[a]			
Post-baseline	ABDOMINOPLASTY		Any initiation is prohibited during treatment period
	GASTRIC BANDING		Any initiation is prohibited during treatment period
	GASTRIC BYPASS		Any initiation is prohibited during treatment period
	LIPOSUCTION		Any initiation is prohibited during treatment period
	SLEEVE GASTRECTOMY		Any initiation is prohibited during treatment period
	CRYOLIPOLYSIS		Any initiation is prohibited during treatment period
	MUCOSAL ABLATION		Any initiation is prohibited during treatment period
	GASTRIC ARTERY EMBOLIZATION		Any initiation is prohibited during treatment period
	INTRAGASTRIC BALLOON		Any initiation is prohibited during treatment period
	DUODENAL-JEJUNAL ENDOLUMINAL LINER		Any initiation is prohibited during treatment period
Prohibited Concomitant Medication on Anti-hyperglycemic Therapy			
Post-baseline	All medications with ATC code of A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	Any initiation is prohibited during treatment period

Timing	Preferred Name / ATC Code	ATC Classification	Rule
	All medications with ATC code of A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	Any initiation is prohibited during treatment period
	All medications with ATC code of A10BX	Other blood glucose lowering drugs, excluding insulins	Any initiation is prohibited during treatment period
	All medications that contain tirzepatide, semaglutide, or liraglutide in the preferred term		Any initiation is prohibited during treatment period
	All medications with ATC code A10BD and preferred term containing any of the following: 'liptin' 'tide'	Combinations of oral blood glucose lowering drugs	Any initiation is prohibited during treatment period
	All medications containing the following in the preferred term: Empagliflozin, Dapagliflozin, Canagliflozin, Tofogliflozin	Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Any initiation prior to the diagnosis of T2D during treatment period
	All medications with ATC code A10BA	Biguanides	Any initiation prior to the diagnosis of T2D during treatment period
	All medications with ATC code A10BD and preferred term containing any of the following: 'Metformin' 'gliflozin'	Combinations of oral blood glucose lowering drugs	Any initiation prior to the diagnosis of T2D during treatment period

Abbreviations: ATC = Anatomical Therapeutic Chemical; T2D = type 2 diabetes; ICE = intercurrent event.

[a] Use of these medications will be reviewed by the study team (blinded to study treatment) on a case-by-case basis to assess the clinical significance of the change in medication. After review, if deemed to be non-clinically significant, the case won't be considered as an ICE.

6.4. Appendix 4: Treatment Compliance

Treatment compliance is defined as taking at least 75% of required study intervention during the treatment period. Compliance will be calculated by

([total number of doses dispensed – total number of doses returned]/total number of doses expected to be administered) × 100%.

Frequency counts and percentages of participants compliant to study intervention will be summarized by treatment group using the safety participants during treatment period. No inferential analysis will be performed.

Additionally, analyses for treatment compliance will be provided for participants with prediabetes at randomization for the final lock.

Participants with dose interruptions/modifications will be summarized with reasons. Interruptions will be summarized if the duration of the interruption is 7 days or longer for all reasons other than an AE.

6.5. Appendix 5: Important Protocol Deviations

Important protocol deviations are identified in the Trial Issues Management Plan. A listing and summary of important protocol deviations by treatment group will be provided for all randomly assigned participants. No inferential analysis will be performed. Additionally, analyses for important protocol deviations will be provided for participants with prediabetes at randomization for the final lock.

6.6. Appendix 6: Clinical Trial Registry Analyses

Additional analyses will be performed for the purpose of fulfilling the Clinical Trial Registry (CTR) requirements.

Analyses provided for the CTR requirements include the following

Summary of AEs, provided as a dataset which will be converted to an XML file. Both serious AEs (SAEs) and "Other" Non-Serious Adverse Events are summarized by treatment group and MedDRA PT.

- An AE is considered "Serious" whether or not it is a TEAE.
- An AE is considered in the "Other" category if it is both a TEAE and is not serious. For each SAE and "Other" AE, for each term and treatment group, the following are provided
    - the number of participants at risk of an event
    - the number of participants who experienced each event term, and
    - the number of events experienced.
- For each SAE, these additional terms are provided for EudraCT:
    - the total number of occurrences causally related to treatment
    - the total number of deaths, and
    - the total number of deaths causally related to treatment.
- Consistent with www.ClinicalTrials.gov requirements, "Other" AEs that occur in fewer than 5% of participants in every treatment group may be excluded if a 5% threshold is chosen. Allowable thresholds include 0% (all events), 1%, 2%, 3%, 4% and 5%.
- AE reporting is consistent with other document disclosures for example, the CSR, manuscripts, and so forth.

Demographic table including the following age ranges required by EudraCT: ≥18 to <65 years, ≥65 to <85 years, and ≥85 years.

6.7. Appendix 7: Body Composition Assessments via Dual-Energy X-ray Absorptiometry (DXA)

This section is applicable to the participants who are enrolled in the Dual Energy X-ray Absorptiometry (DXA) appendix.

The primary objective of DXA addendum is to demonstrate that orforglipron (6 mg, 12 mg, and 36 mg pooled doses) once daily (QD) is superior to placebo in percent change in total body fat mass loss from baseline to 72 weeks.

Percent change of total body fat mass will be calculated as

[(Total body fat mass at 72 weeks - Total body fat mass at baseline) / Total body fat mass at baseline] ×100

The secondary objectives include:

- To demonstrate that orforglipron (6 mg, 12 mg, and 36 mg pooled doses) QD is superior to placebo with regards to change in total body fat mass (kg) from baseline to 72 weeks, and
- To assess, for orforglipron (6 mg, 12 mg, and 36 mg pooled doses) QD, the following parameters, from baseline to 72 weeks:
    - percent change in total body lean mass, and
    - change in total body lean mass (kg).

Percent change of total body lean mass will be calculated as

[(Total body lean mass at 72 weeks - Total body lean mass at baseline) / Total body lean mass at baseline] × 100

DXA will be performed at the baseline and at the end of 72-week treatment (Visit 21), or at the early discontinuation visit (ED).

In addition to the endpoints listed above, the following parameters may also be analyzed:

- total body mass (kg)
- total body fat mass (kg)
- total body lean mass (kg)
- percent body fat mass = total body fat mass / total body mass × 100
- percent body lean mass = total body lean mass / total body mass × 100
- fat lean mass ratio = total body fat mass / total body lean mass
- visceral fat mass in android region (kg)
- percent visceral fat mass = visceral fat mass in android region / (body fat mass in android region + body lean mass in android region) × 100
- fat loss index (FLI) = total body fat mass change / (total body fat mass change + total body lean mass change) × 100

Unless otherwise specified, all analyses for the variables measured or derived from DXA will be conducted on all randomized participants who have a baseline DXA scan. Baseline is defined as the last non-missing data collected at randomization (prior to first dosing of study drug).

Descriptive summary statistics (for example, sample size, mean, SD, minimum, maximum, and median) of all the parameters listed above (but not limited to) will be provided by treatment group (placebo, orforglipron 6 mg, orforglipron 12 mg, orforglipron 36 mg, and all orforglipron pooled doses) at baseline and postbaseline visits (for both the actual value and change from baseline value).

In addition, a summary of demographics and baseline characteristics for participants in the DXA addendum will be provided.

Unless otherwise noted, all tests of treatment effects will be conducted at a 2-sided alpha level of 0.05, and the confidence interval will be calculated at 95%, 2-sided. There will be no multiplicity adjustment.

The analysis of covariance (ANCOVA) model described in Section 4.1.2.1.1 will be used to analyze the continuous outcomes with treatment regimen estimand data points set. Missing data will be imputed as described in Section 4.1.2.1.2. DXA total body endpoints will be analyzed including and excluding head.

For the FLI metric, least square means (LSMs) from ANCOVA models for total body fat mass change and total body lean mass change will be used to estimate mean FLI in each treatment group. We propose to use LSMs instead of fitting regression models on subject-level data because FLI is subject to wide fluctuations when the denominator is small, and subject-level FLI can have large variability if the body weight reduction is small. Treatment comparison in mean FLI may be performed by using delta method. Median and interquartile range of subject-level FLI in each treatment group may be reported.

A sample size of approximately 156 randomly assigned participants (approximately 39 participants per arm) was 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.

6.8. Appendix 8: Sample Size Determinations for Patient-Reported Outcomes of Cravings and Psychological Impact of Food

A sample size of 94 participants (22 participants per orforglipron treatment group and 28 participants in the placebo group) will provide more than 70% power to demonstrate superiority of 6 mg, 12mg, 36 mg, and/or pooled doses of orforglipron to placebo with regards to mean change from baseline in overall appetite visual analog scale (VAS) score 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 each at a 2-sided significance level of 0.05 using a

2-sample t-test. Additionally, a difference of at least 15 mm in mean change from baseline in overall appetite VAS score at Week 72 for 6 mg, 12 mg, 36 mg, and pooled doses of orforglipron compared with placebo, and a common SD of 20 mm (Sadoul 2014).

Additionally, the sample size provides greater than 90% power to demonstrate superiority of 6 mg, 12mg, 36 mg, and/or pooled doses of orforglipron to placebo with regards to mean change from baseline in Power of Food Scale (PFS) score 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 each at a 2-sided significance level of 0.05 using a 2-sample t-test. Additionally, a difference of at least 0.7 in mean change from baseline in PFS overall score at Week 72 for 6 mg, 12 mg, 36 mg, and pooled doses of orforglipron compared with placebo, and a common SD of 0.66 (Ullrich 2013).

6.9. Appendix 9: Statistical Analysis for China

General Considerations

Analyses will be performed for the following subpopulations

- participants enrolled in China
- participants enrolled in East Asian Countries/regions (mainland China, Japan, Taiwan, and Korea).

The analysis methods for the above-mentioned subgroups will be similar to those described for the main part of SAP GZGP. If there is not sufficient number of participants in the subpopulation, summary statistics will be provided.

The analyses to be included will be documented in a separate list of analyses which should include disposition, demographics, and selected efficacy and safety endpoints.

6.10. Appendix 10: Statistical Analysis for Japan

Analyses will be performed for the following subpopulations

- participants enrolled in Japan
- participants who meet the Japan Society for the Study of Obesity (JASSO) subpopulation criteria.

The subpopulation analyses are subsets of the analyses described in the main part of SAP GZGP. The analyses to be included will be documented in a list of analyses which should include disposition, demographics, and selected efficacy and safety endpoints. If there is not a sufficient number of participants in this subpopulation, summary statistics will be provided.

JASSO subpopulation criteria

The JASSO subpopulation analysis will be performed according to the criteria of both BMI- and obesity-related health disorders according to the obesity disease label in Japan.

The target population is defined as participants who are diagnosed as having either hypertension, or dyslipidemia with:

1) baseline BMI between 27 to <35 kg/m^2, with at least 2 obesity-related health disorders, and
2) baseline BMI between ≥35 kg/m^2,

where the obesity-related health disorders are defined according to obesity disease treatment guideline (JASSO 2022). There are 11 obesity-related health disorders below Table GZGP.6.6. All participants and participants with obesity disease according to the JASSO treatment guideline will be compared.

Eleven obesity-related health disorders

The JASSO treatment guideline (JASSO 2022) defines 11 health disorders for the diagnosis of "obesity disease" in participants who need weight reduction for medical reasons.

Table GZGP.6.6. The 11 Obesity-Related Health Disorders

Obesity-related health disorders	Medical History Term
1) Glucose intolerance (including T2D, IGT)	Glucose tolerance impaired (IGT, etc.)
2) Dyslipidemia	Dyslipidemia
3) Hypertension	Hypertension
4) Hyperuricemia or Gout	Hyperuricaemia Gout
5) Cardiovascular disease, myocardial infarction, and angina	Coronary artery disease
6) Cerebral infarction and TIA	Cerebral infarction Transient ischemic attack
7) MASLD	Metabolic dysfunction-associated steatotic liver disease
8) Menstruation abnormalities and female infertility	Dysmenorrhoea Infertility Menstrual cycle abnormal
9) OSA and obesity-hypoventilation syndrome	Obstructive sleep apnoea
10) Motor dysfunction / Osteoarthritis	Motor dysfunction Osteoarthritis
11) Obesity-related renal disease	Renal disease

Abbreviations: IGT = impaired glucose tolerance; MASLD = Metabolic dysfunction-associated steatotic liver disease; OSA = obstructive sleep apnea; T2D = Type 2 diabetes; TIA = transient ischemic attack.

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Supplementary Appendix

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This appendix has been provided by the authors to give readers additional information about the work.

ATTAIN-1

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SUPPLEMENTAL METHODS

STUDY PROTOCOL INCLUSION AND EXCLUSION CRITERIA

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/m^2, or
   - ≥27.0 kg/m^2 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 who are women of child-bearing potential should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

   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, which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

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 ≥6.5% (≥48 mmol/mol)
   - FSG ≥126 mg/dL (≥7.0 mmol/L), including 0-hour OGTT
   - 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 m^2, 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 ≥3.0x the ULN for the reference range
    - ALP level ≥1.5x the ULN for the reference range
    - TBL level ≥1.5x 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 <3.0x 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 m^2, or
    - ≥35 ng/L, if eGFR <60 mL/min/1.73 m^2.
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.
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.
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 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.
    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 LY3502970 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.

STUDY PROTOCOL CRITERIA FOR DIAGNOSIS OF PREDIABETES

The duration of treatment in ATTAIN-1 was determined by glycemic status at randomization. Participants were categorized as those with prediabetes or normoglycemia at Visit 3/randomization (participants with T2D were excluded), as defined by the 2023 American Diabetes Association Standards of Medical Care in Diabetes (ADA 2023).[1] At least 2 abnormal tests were required to diagnose prediabetes. The following ranges for normoglycemia, prediabetes, and diabetes were used:

	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.

STATISTICAL ANALYSIS METHODS

Randomization

Participants were randomized in a 3:3:3:4 ratio to receive orforglipron 6 mg, 12 mg, 36 mg, or placebo. Assignments to treatment groups were determined by a computer-generated random sequence using an interactive web response system (IWRS) stratified by country, sex and the presence or absence of prediabetes, as defined by the 2023 American Diabetes Association Standards of Medical Care in Diabetes.[1]

Estimands

In this study, two estimands were prespecified in the protocol and both intended to estimate the treatment effect for all randomized participants. The 2 estimands, treatment regimen estimand and efficacy estimand, address intercurrent events (ICEs) using the treatment policy strategy and the hypothetical strategy[2], respectively. The detailed analysis with respect to the two estimands are provided below.

Treatment-Regimen Estimand The assessments guided by the treatment regimen estimand were conducted using the treatment regimen estimand data points set, including all data points from randomized participants obtained during the treatment period, regardless of study treatment discontinuation or initiation of prohibited weight management treatments.

Randomized participants with observed values at baseline and Week 72 for our primary and key secondary endpoints under the treatment regimen estimand are shown below to assess the extent of missingness.

Parameter	Orforglipron 6 mg N=723				Orforglipron 12 mg N=725				Orforglipron 36 mg N=730				Placebo N=949			
	Baseline		Week 72		Baseline		Week 72		Baseline		Week 72		Baseline		Week 72	
	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)
Weight	723	0	609	114 (15.8)	725	0	625	100 (13.8)	730	0	622	108 (14.8)	949	0	722	227 (23.9)
WC	723	0	609	114 (15.8)	725	0	625	100 (13.8)	730	0	622	108 (14.8)	949	0	722	227 (23.9)
SBP	723	0	609	114 (15.8)	725	0	625	100 (13.8)	730	0	622	108 (14.8)	949	0	722	227 (23.9)
Non-HDL cholesterol	716	7(1.0)	603	120 (16.6)	714	11 (1.5)	616	109 (15.0)	716	14 (1.9)	615	115 (15.8)	936	13 (1.4)	712	237 (25.0)
Triglycerides	714	9 (1.2)	604	119 (16.5)	713	12 (1.7)	614	111 (15.3)	715	15 (2.1)	615	115 (15.8)	936	13 (1.4)	712	237 (25.0)

*WC=waist circumference

Participants who discontinued study treatment were encouraged to continue in the study for the treatment and follow-up periods. Occurrences of missing data at Week 72 were imputed in a fashion consistent with what the values would likely have been had they been collected. In principle, missing data due to permanent discontinuation of study treatment were imputed by treatment group using retrieved dropouts, namely using multiple imputation based on data retrieved from participants who permanently discontinued the study treatment but continued in the study with non-missing measurements from the same treatment group. The baseline value was included in the imputation model. Any missing values at baseline were imputed in the same model when imputing the endpoint. In few cases where participants completed the study while on study treatment or discontinued study clearly due to administrative reasons, missing endpoint values were imputed under the missing at random (MAR) assumption using all observed on-treatment data from the same treatment arm. For each variable, multiple imputations were conducted (50 times) using fully conditional specification with mice package in R, and Rubin's rule was used to synthesize results across multiple imputations for statistical inference.[3] If there were not enough retrieved dropouts (less than 8) to provide a reliable imputation model, the placebo-washout method was used under the assumption that data were missing at random for participants assigned to placebo and missing not at random for participants assigned to orforglipron. All observed values from the placebo arm were used for multiple imputation.[4] In addition, a multiple imputation-based tipping point analysis was performed as a sensitivity

analysis for the primary endpoint. The Week 72 missing values were first obtained through the multiple imputation as described, then values with varying magnitudes were added to the imputed values for all treatment groups under comparison to evaluate the robustness of the superiority claim for the primary analysis. More details can be found in the statistical analysis plan.

For the assessment of continuous efficacy measures guided by the treatment regimen estimand, data for participants with missing values at Week 72 were imputed as above, and then an ANCOVA model was used with a variance estimator that is robust to model misspecification and heteroscedasticity.[5,6] The ANCOVA model included variables of treatment group (each dose of orforglipron and placebo), region, strata (defined by joint levels of sex and prediabetes status [Yes or No]), baseline value of the dependent variable, treatment-by-strata interaction, and treatment-by-baseline interaction.

Lipid parameters were log-transformed before fitting the ANCOVA with the associated log-transformed baseline value as a covariate. In these cases, model-based estimates (MBE) and 95% CIs for each treatment group and treatment difference were back-transformed using the delta method from the model-based estimates and standard errors on the natural log-scale and presented as mean percent change from baseline and as relative treatment difference to placebo in percent change.

A linear contrast, averaging estimates from the individual doses of orforglipron, was used to estimate the treatment effect of pooled orforglipron compared with placebo.

For binary efficacy measures derived from a continuous variable and guided by the treatment regimen estimand, the missing value in the underlying continuous variable were imputed first and then the corresponding binary variable was derived. For the assessment of binary efficacy measures, a logistic regression model was used to examine the treatment difference, which included treatment group (each dose of orforglipron and placebo), region, strata (sex, and prediabetes status [Yes or No]), the continuous baseline value, treatment-by-strata interaction, and treatment-by-baseline interaction. The unconditional treatment group effect was assessed by risk difference and relative risk based on the delta-method using the formula provided.[7] Number and % are reported from imputed data, which were calculated by combining proportion of participants achieving target in imputed datasets using Rubin's rule.

Efficacy Estimand The assessments guided by the efficacy estimand were conducted using the efficacy estimand data points set, including all data points from randomized participants obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments.

Parameter	Orforglipron 6 mg N=723				Orforglipron 12 mg N=725				Orforglipron 36 mg N=730				Placebo N=949			
	Baseline		Week 72		Baseline		Week 72		Baseline		Week 72		Baseline		Week 72	
	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)	n	Missing n (%)
Weight	723	0	559	164 (22.7)	725	0	559	166 (22.9)	730	0	549	181 (24.8)	949	0	654	295 (31.1)
WC	723	0	559	164 (22.7)	725	0	559	166 (22.9)	730	0	549	181 (24.8)	949	0	654	295 (31.1)
SBP	723	0	559	164 (22.7)	725	0	559	166 (22.9)	730	0	549	181 (24.8)	949	0	654	**295 (31.1)**
Non-HDL cholesterol	716	7 (1.0)	550	173 (23.9)	714	11 (1.5)	539	186 (25.7)	716	14 (1.9)	533	197 (27.0)	936	13 (1.4)	637	312 (32.9)
Triglycerides	714	9 (1.2)	549	174 (24.1)1	713	12 (1.7)	536	189 (26.1)	715	15 (2.1)	532	198 (27.1)	936	13 (1.4)	637	312 (32.9)

For the assessment of continuous efficacy measures guided by the efficacy estimand, a maximum likelihood-based mixed-model for repeated measures (MMRM)[8] analysis was used. All the longitudinal observations at each scheduled postbaseline visit were included in the analysis. Missing values (discarded after the initiation of prohibited weight management treatments and/or study treatment discontinuation, or unobserved) were implicitly handled by the MMRM under

the assumption of MAR. The MMRM model included variables of region, strata, baseline value of the dependent variable, treatment-by-visit interaction, baseline-by-treatment-by-visit interaction, and strata-by-treatment-by-visit interaction. The estimated treatment group effect and comparison between each of the orforglipron treatment groups and placebo at the scheduled visits were reported together with the variability estimated using the robust inference.[8] The sandwich estimator for the variance-covariance matrix was used.[9] An unstructured covariance matrix by treatment groups was used to model the within-participant errors, assuming heteroscedasticity (variant covariance structure across treatment groups) and the measurements for different participants are independent.

For binary efficacy measures derived from a continuous variable and guided by the efficacy estimand, the missing value in the underlying continuous variable was imputed first under the assumption of missing at random by treatment group. The logistic regression model as described above for the treatment regimen estimand was used after imputation and model-based estimation of treatment group specific risk, risk difference, relative risk, p-value, and 95% CI were presented.

Multiplicity Control Strategy for Primary and Key Secondary Efficacy Analysis
Multiplicity adjusted analyses were performed on the primary and key secondary objectives at 72 weeks listed in the graphical testing approach figure to control the overall family-wise Type 1 error rate at a 2-sided alpha level of 0.05. The graphical multiple testing procedure described by Bretz et al. was used.[10,11] This approach is a closed testing procedure; hence, it strongly controls the family-wise Type 1 error rate across all hypotheses.[12]

The treatment regimen estimand was the primary estimand, with the efficacy estimand considered supportive. There was no adjustment for multiple comparisons between estimands, nor for any other analyses beyond the primary and key secondary objectives.

The null hypotheses corresponding to the primary objectives are:

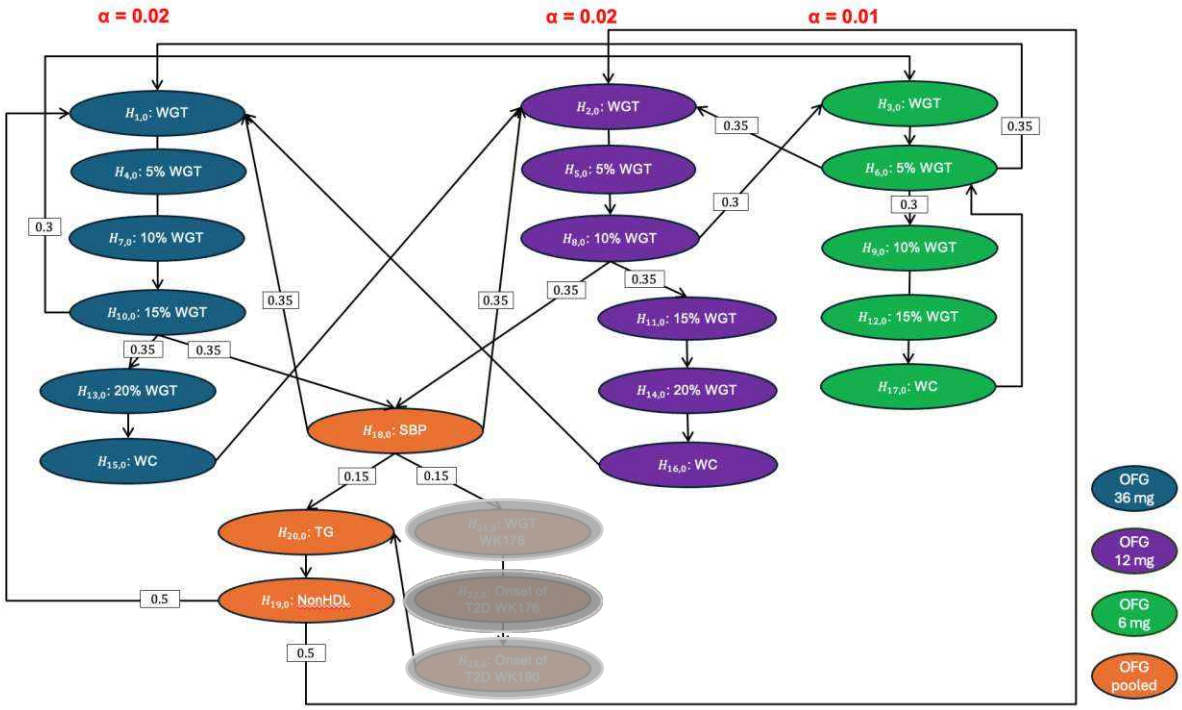
- H1,0: No difference in 36 mg orforglipron compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- H2,0: No difference in 12 mg orforglipron compared to placebo with respect to the mean percent change from baseline in body weight at Week 72.
- H3,0: No 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 72-week key secondary objectives are:

- H4,0: 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 at Week 72.
- H5,0: 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 at Week 72.
- H6,0: 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 at Week 72.
- H7,0: 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 at Week 72.
- H8,0: 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 at Week 72.

- H9,0: 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 at Week 72.
- H10,0: 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 at Week 72.
- H11,0: 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 at Week 72.
- H12,0: 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 at Week 72.
- H13,0: 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 at Week 72.
- H14,0: 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 at Week 72.
- H15,0: No difference in 36 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H16,0: No difference in 12 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H17,0: No difference in 6 mg orforglipron compared to placebo with respect to mean change from baseline in waist circumference at Week 72.
- H18,0: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to mean change from baseline in systolic blood pressure (SBP) at Week 72.
- H19,0: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in non-high-density lipoprotein (HDL) cholesterol at Week 72.
- H20,0: No difference in 6 mg, 12 mg, and 36 mg orforglipron pooled compared to placebo with respect to mean percent change from baseline in triglycerides at Week 72.

R version 4.3.2 and SAS version 8.2 were used for statistical calculations.



nonHDL = Non-HDL cholesterol; OFG = orforglipron; SBP = systolic blood pressure; TG = triglycerides; WC = waist circumference; WGT = weight.

SUPPLEMENTAL FIGURES

Figure S1. Study design

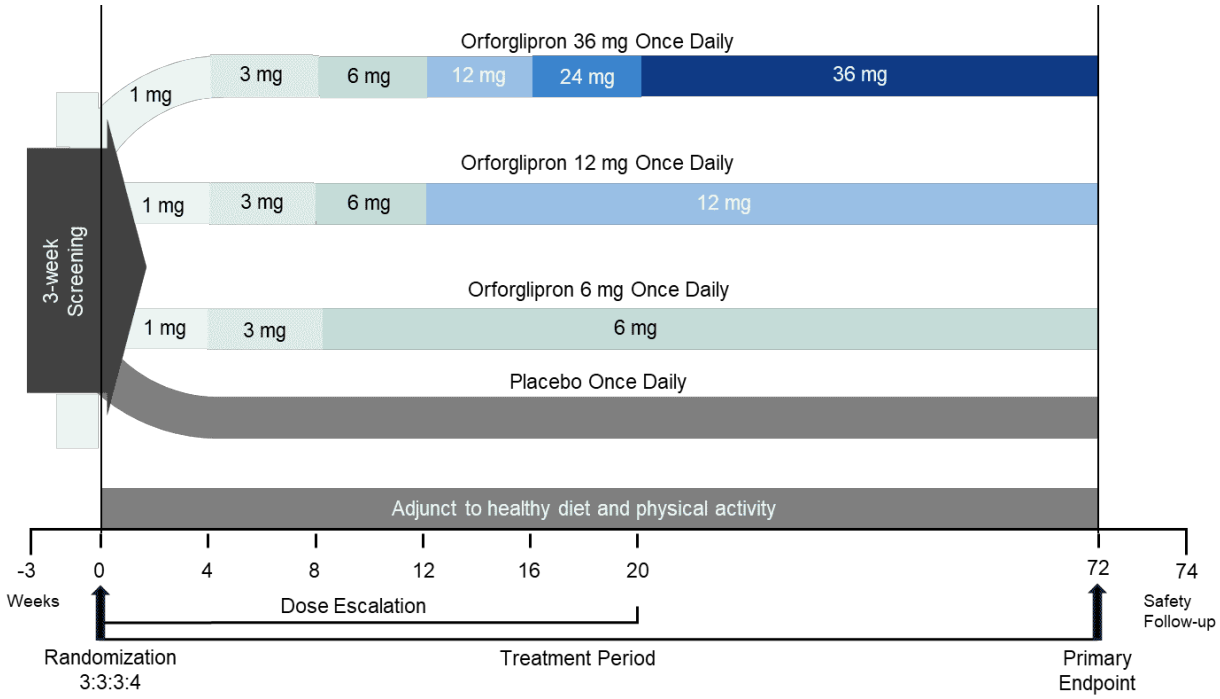
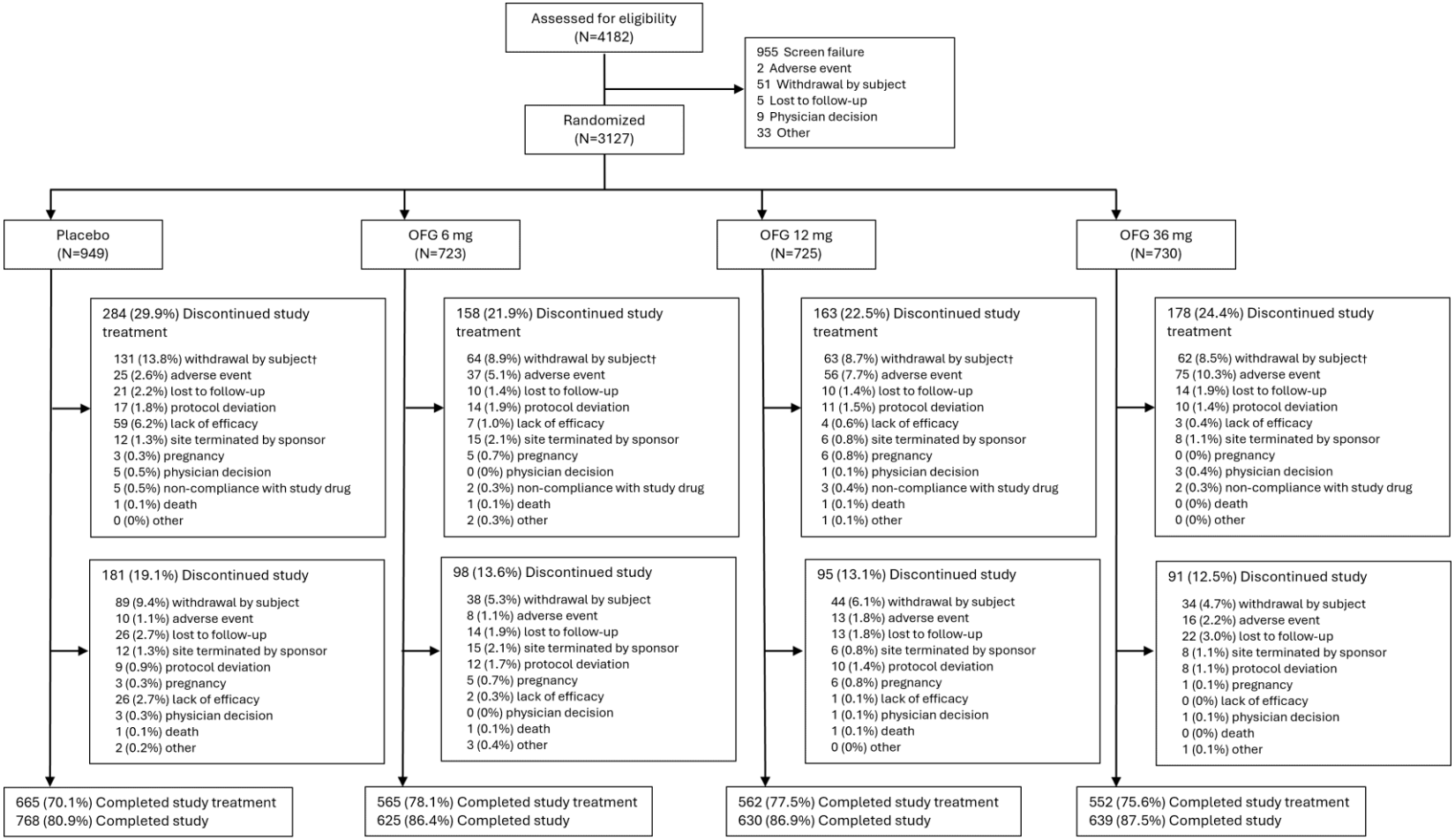


Figure S2. Participant disposition



† The most frequently reported reasons were scheduling conflicts and personal issues unrelated to the trial.

Study completion is defined as completing both the 72-week treatment period and the safety follow-up period (V801) for participants without prediabetes at randomization. For participants with prediabetes at randomization, study completion is defined as completing the 72-week treatment period. Four participants were randomized and not treated.

Figure S3. Change in body weight (kg) over time

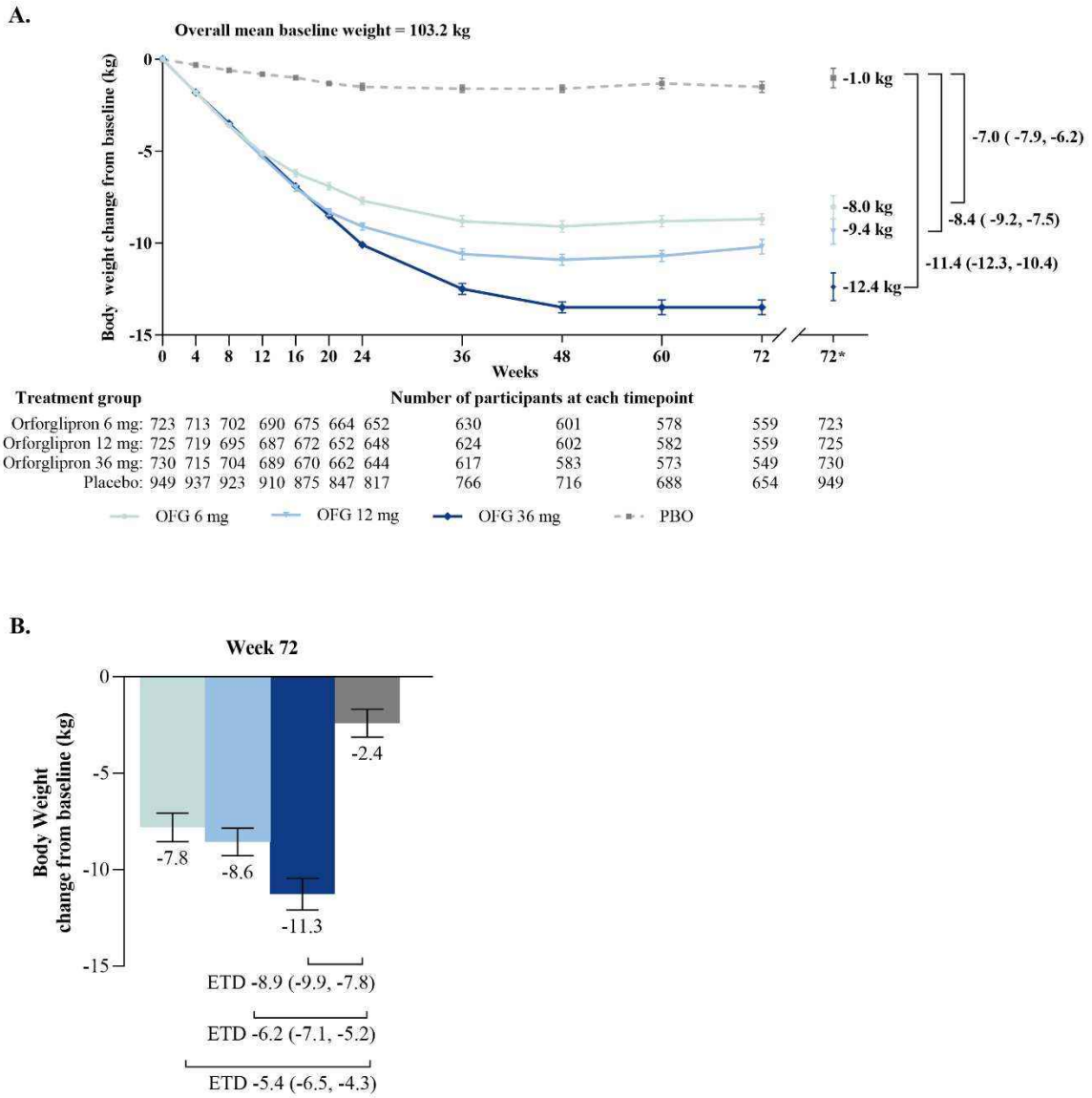


Figure S3. (A) * MBE (95% CI) for change from baseline in body weight and ETD (95% CI) between orforglipron groups and placebo based on MMRM analysis (efficacy estimand). The curves shown from week 0 to week 72 are based on observed on treatment mean (standard error) using efficacy estimand data points set, including all data points obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments. (B) MBE with 95% CI for change from baseline to week 72 in body weight and ETD (95% CI) between orforglipron groups and placebo based on ANCOVA analysis (treatment regimen estimand). The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. ANCOVA=analysis of covariance; ETD=estimated treatment difference; MBE=model based estimate; MMRM=mixed model repeated measures.

Figure S4. Change in waist circumference and body mass index

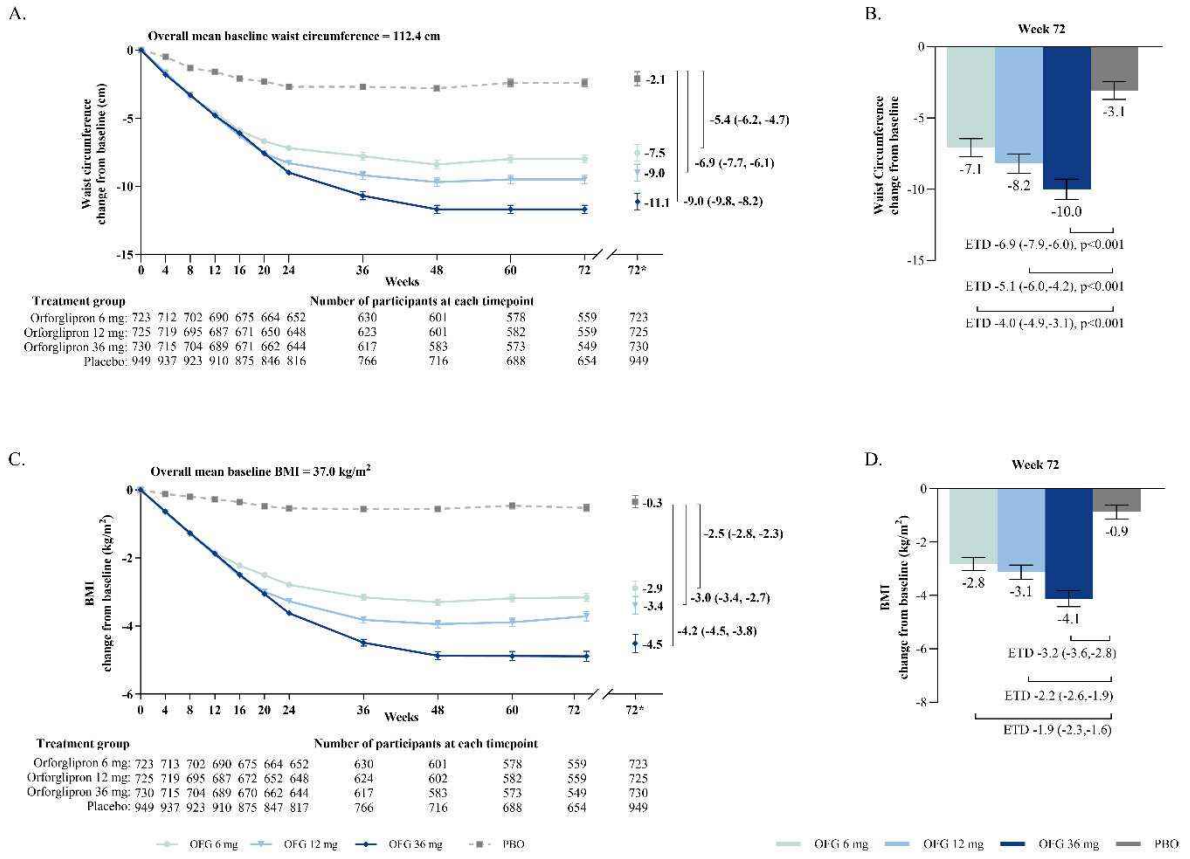


Figure S4. For endpoints not controlled for multiplicity, p-values are not reported, regardless of statistical significance. (A) * MBE (95% CI) for change from baseline in waist circumference and ETD (95% CI) between orforglipron groups and placebo based on MMRM analysis (efficacy estimand). The curves shown from week 0 to week 72 are based on observed on treatment mean (standard error) using efficacy estimand data points set, including all data points obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments. (B) MBE (95% CI) for change from baseline to week 72 in waist circumference and ETD (95% CI) between orforglipron groups and placebo based on ANCOVA analysis (treatment regimen estimand). (C) * MBE (95% CI) for change from baseline in BMI and ETD (95% CI) between orforglipron groups and placebo based on MMRM analysis (efficacy estimand). The curves shown from week 0 to week 72 are based on observed on treatment mean (standard error) using efficacy estimand data points set, including all data points obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments. (D) MBE (95% CI) for change from baseline to week 72 in BMI and ETD (95% CI) between orforglipron groups and placebo based on ANCOVA analysis (treatment regimen estimand). . ANCOVA=analysis of covariance; BMI=Body Mass Index; ETD = estimated treatment difference; MBE=model based estimate; MMRM=mixed model repeated measures.

Figure S5. Percentages of participants who achieved Body Mass Index thresholds at week 72

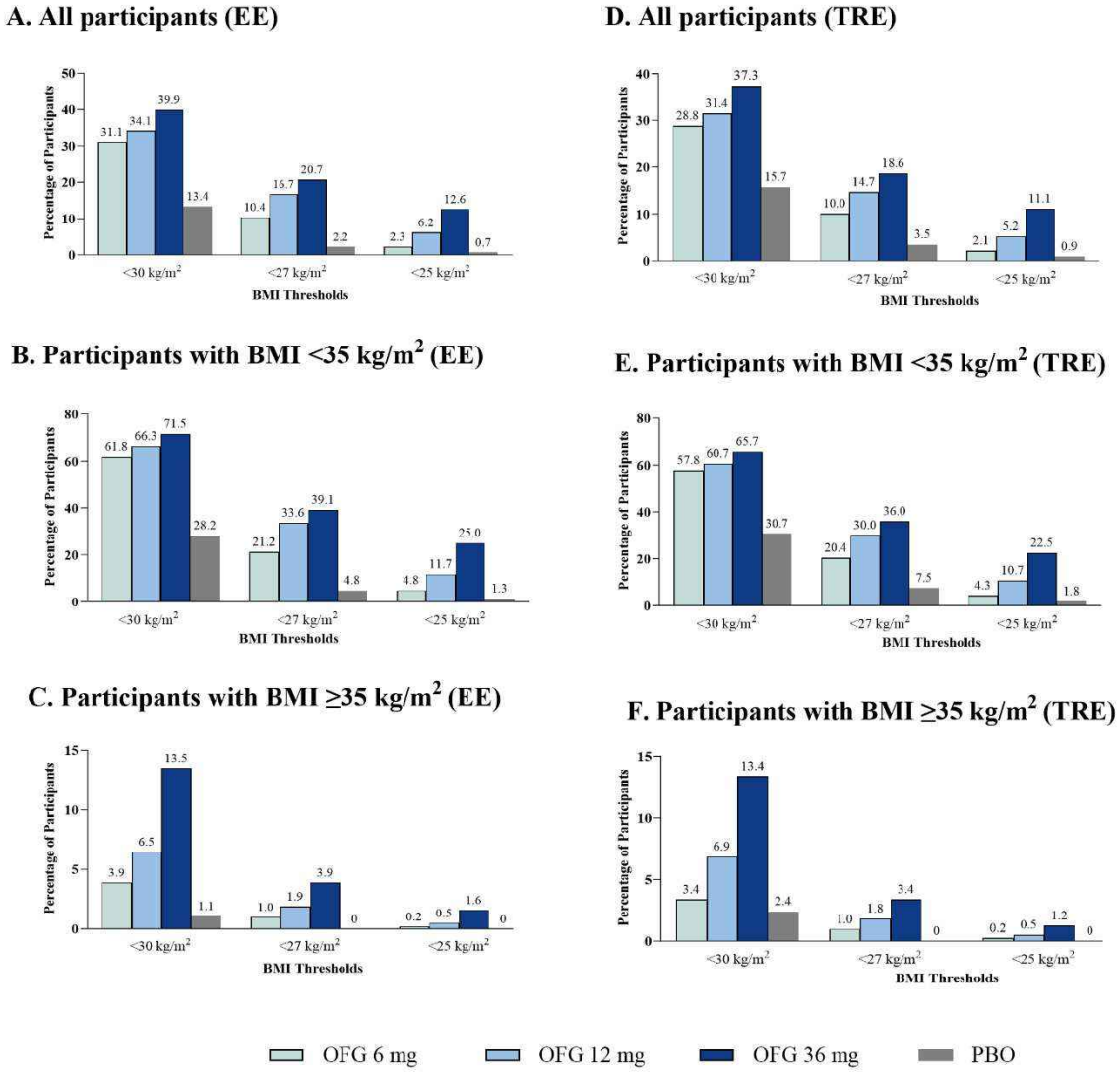


Figure S5. Percentages of participants who achieved BMI thresholds <30 kg/m^2, <27 kg/m^2 and <25 kg/m^2 at week 72 (Efficacy Estimand) for: all participants (Panel A), participants with BMI <35 kg/m^2 at baseline (Panel B), and participants with BMI ≥35 kg/m2 at baseline (Panel C). Percentages of participants who achieved BMI thresholds <30 kg/m^2, <27 kg/m^2 and <25 kg/m^2 at week 72 (Treatment Regimen Estimand) for: all participants (Panel D), participants with BMI <35 kg/m^2 at baseline (Panel E), and participants with BMI ≥35 kg/m2 at baseline (Panel F). EE=efficacy estimand; TRE=treatment regimen estimand.

Figure S6. Change in systolic and diastolic blood pressure over time

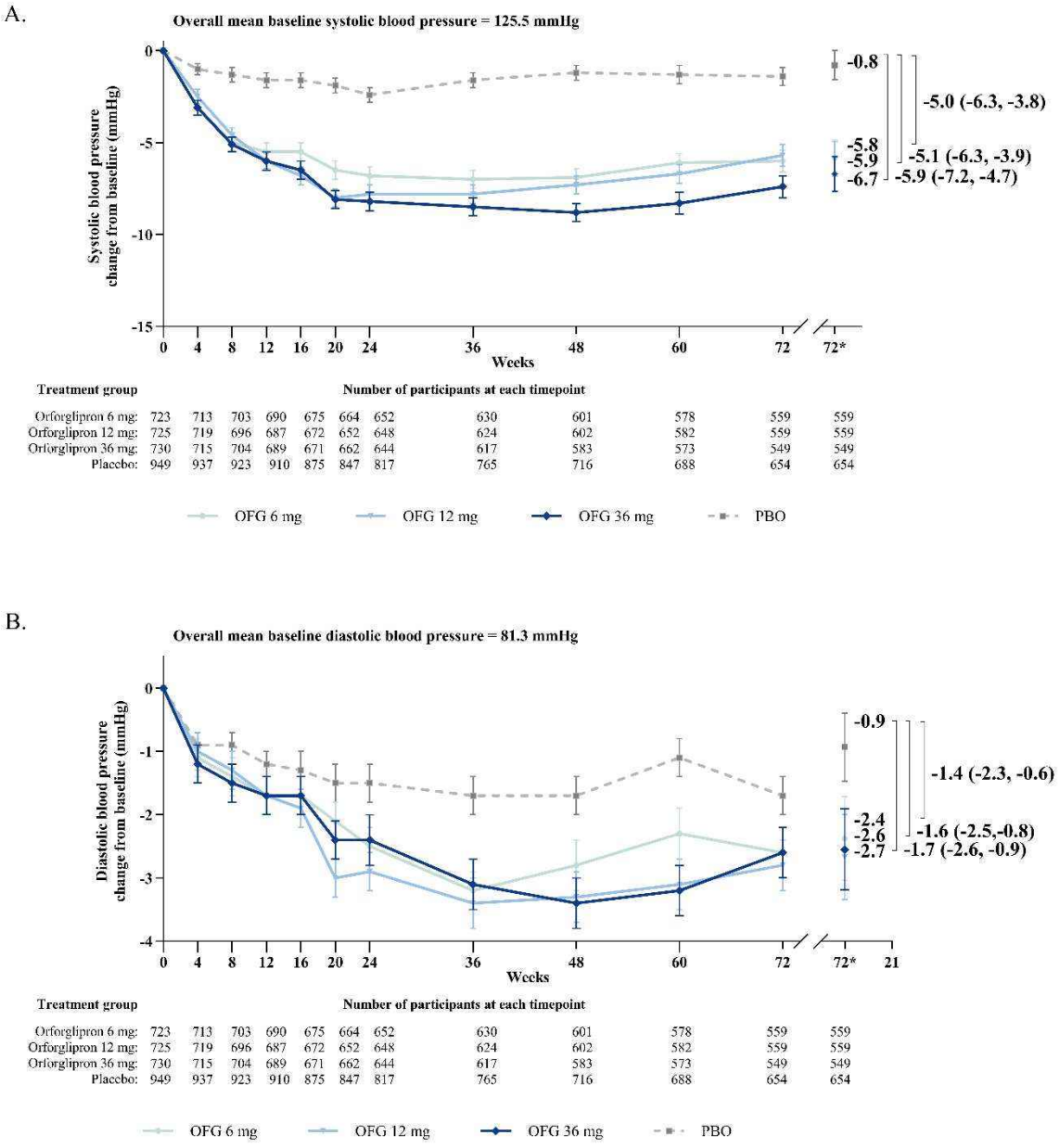


Figure S6. * MBE (95% CI) of change from baseline in systolic blood pressure (A), and diastolic blood pressure (B) and ETD (95% CI) between orforglipron groups and placebo based on MMRM analysis (efficacy estimand). The curves shown from week 0 to week 72 are based on observed on treatment mean (standard error) using efficacy estimand data points set, including all data points obtained during the treatment period and up to the earliest date of discontinuation of study treatment or initiation of prohibited weight management treatments. The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. ETD=estimated treatment difference; MBE = model-based estimate; MMRM=mixed model repeated measures.

Figure S7. Percentages of participants achieving Waist-to-Height Ratio <0.53 at week 72

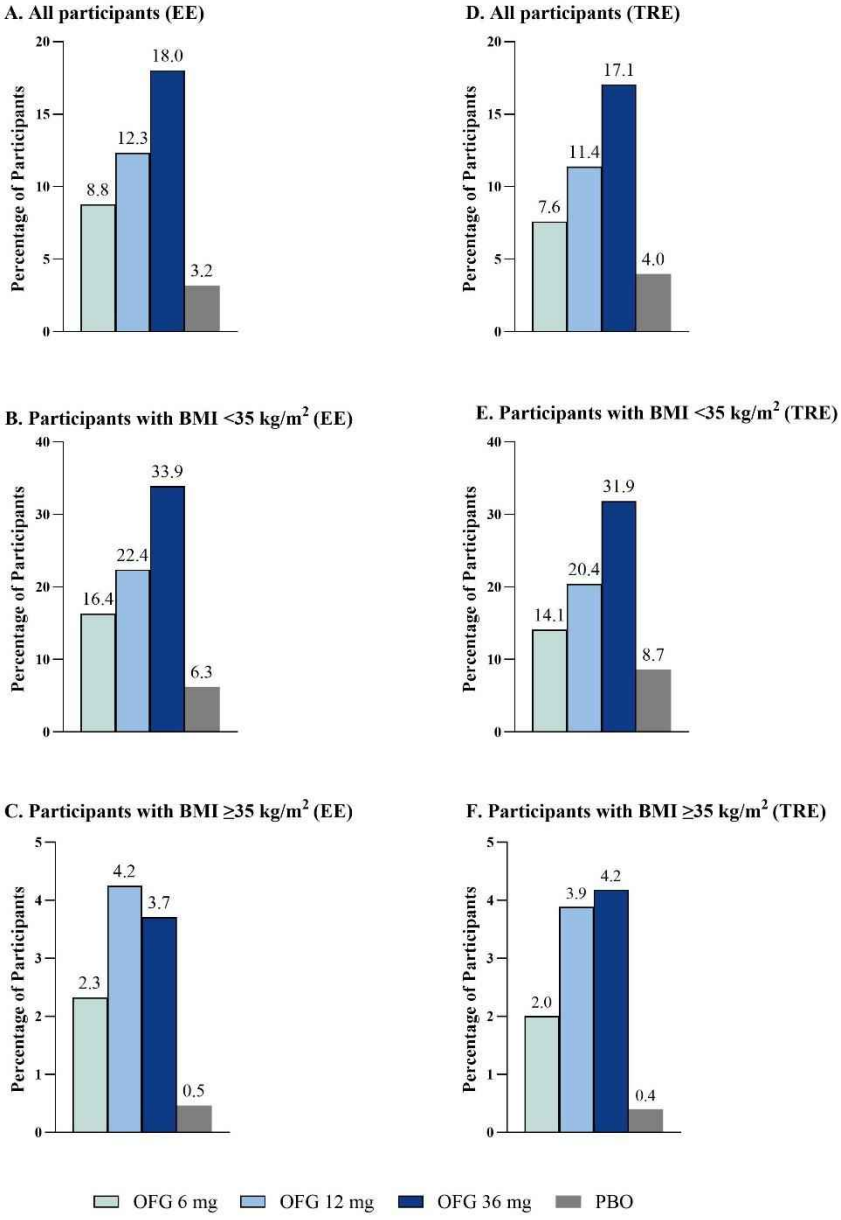


Figure S7. Percentages of participants who achieved Waist-to-Height Ratio <0.53 at week 72 (Efficacy Estimand) for: all participants (Panel A), participants with BMI <35 kg/m^2 at baseline (Panel B), and participants with BMI ≥35 kg/m^2 at baseline (Panel C). Percentages of participants who achieved Waist-to-Height Ratio <0.53 at week 72 (Treatment Regimen Estimand) for: all participants (Panel D), participants with BMI <35 kg/m^2 at baseline (Panel E), and participants with BMI ≥35 kg/m^2 at baseline (Panel F). The proportions are calculated by combining percentages of participants achieving targets across imputed data sets using Rubin's rule. EE=efficacy estimand; TRE=treatment regimen estimand.

Figure S8. Change in body composition

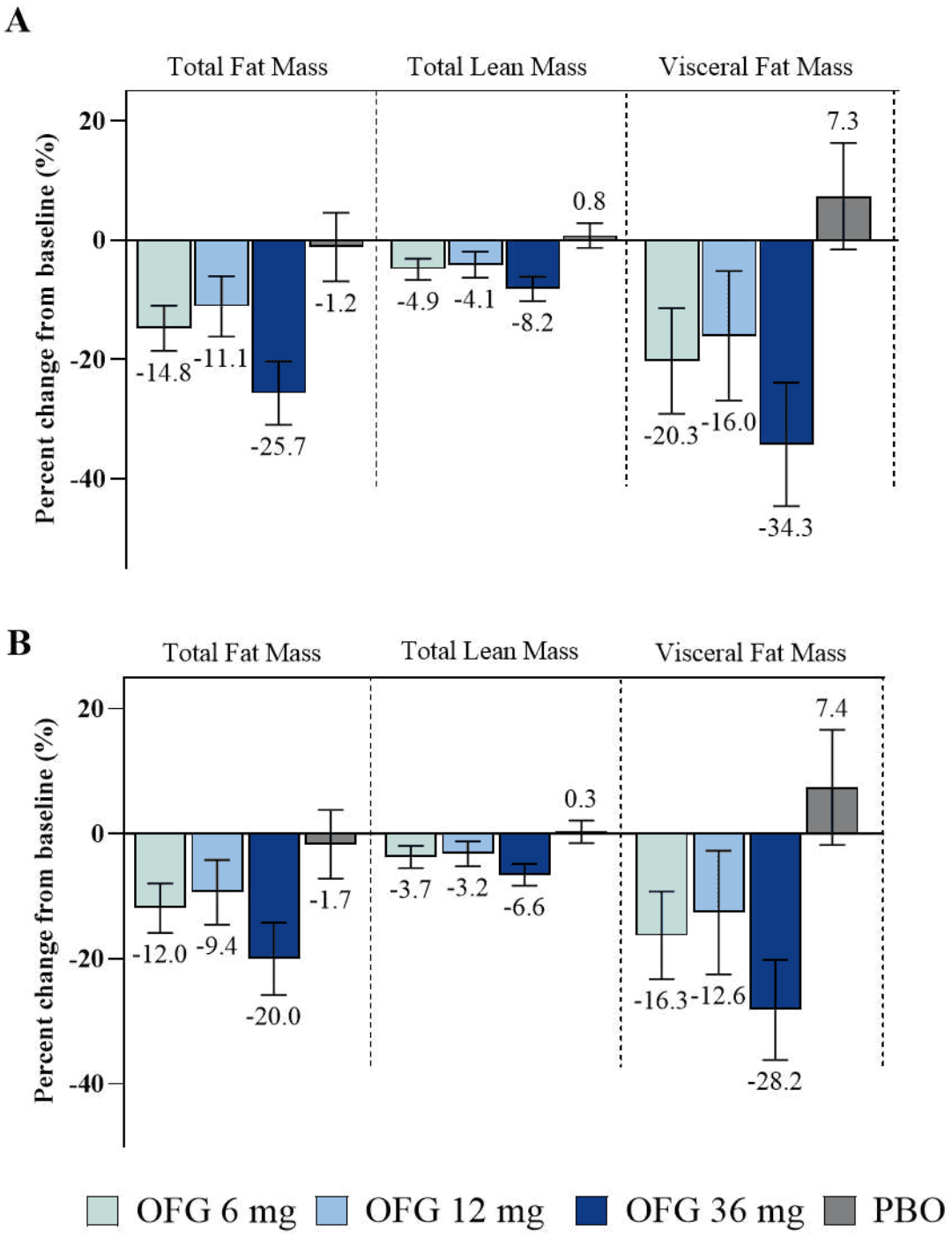


Figure S8. Change in body composition (A) Efficacy Estimand and (B) Treatment Regimen Estimand. Data are model-based estimates (MBE) and 95% confidence interval. The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. Enrolled n=171; completers with both baseline and week 72 DXA n=140. MBE=model-based estimate.

Figure S9. Incidence of nausea, vomiting, and diarrhea

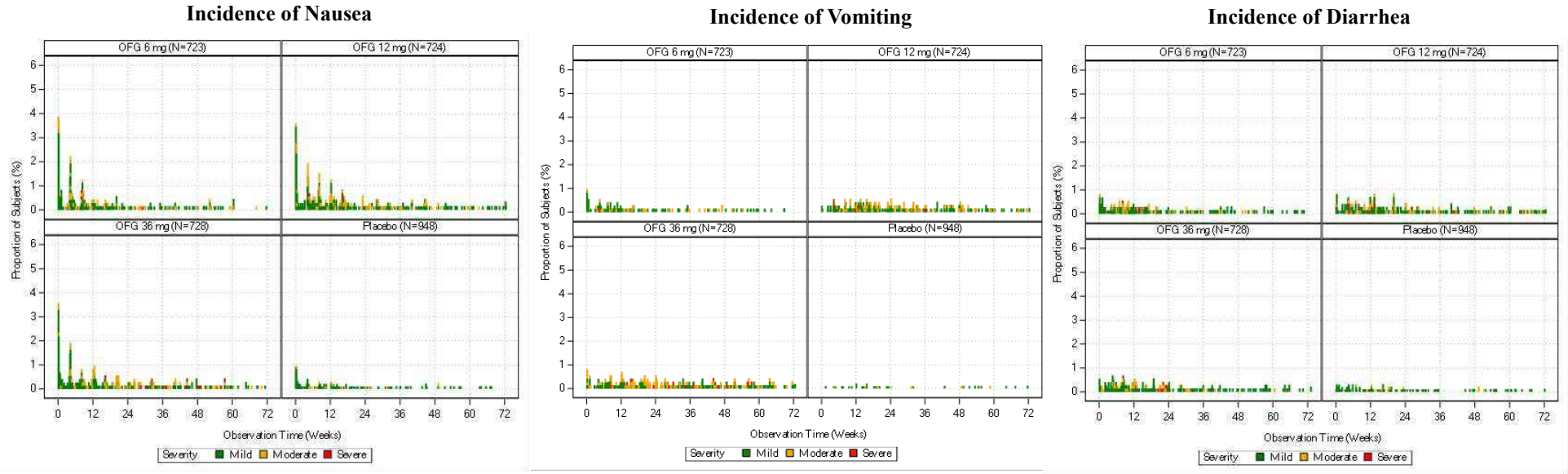


Figure S9. Incidence of nausea, vomiting, and diarrhea over time. The percentage of participants receiving orforglipron or placebo who reported nausea (Panel A), vomiting (Panel B), or diarrhea (Panel C) are presented. OFG, Orforglipron. Percentages are based on number of participants at risk at specific observation time. Events were classed as mild (shown in green), moderate (shown in orange), or severe (shown in red).

Figure S10. Cumulative distribution plot of percent change in body weight at week 72

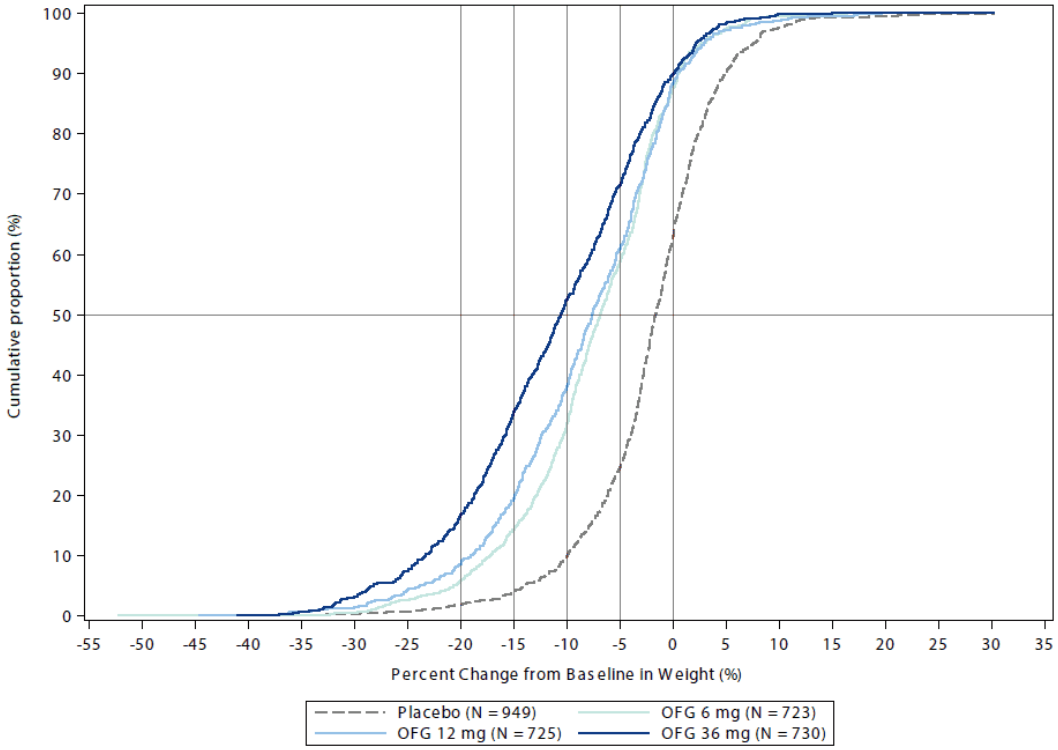


Figure S10. Cumulative distribution plot of percent change in body weight over time from baseline from all randomized participants in the treatment regimen estimand data points set (including data obtained during treatment period regardless of treatment discontinuation or the use of prohibited weight management treatments). Reference values for percent changes (-20%, -15%, -10%, -5%, 0%) are marked with gray, solid lines on the x-axis; 50% percentile is marked with a gray, solid line on the y-axis.

Figure S11. Waterfall plots of percent change in body weight at week 72

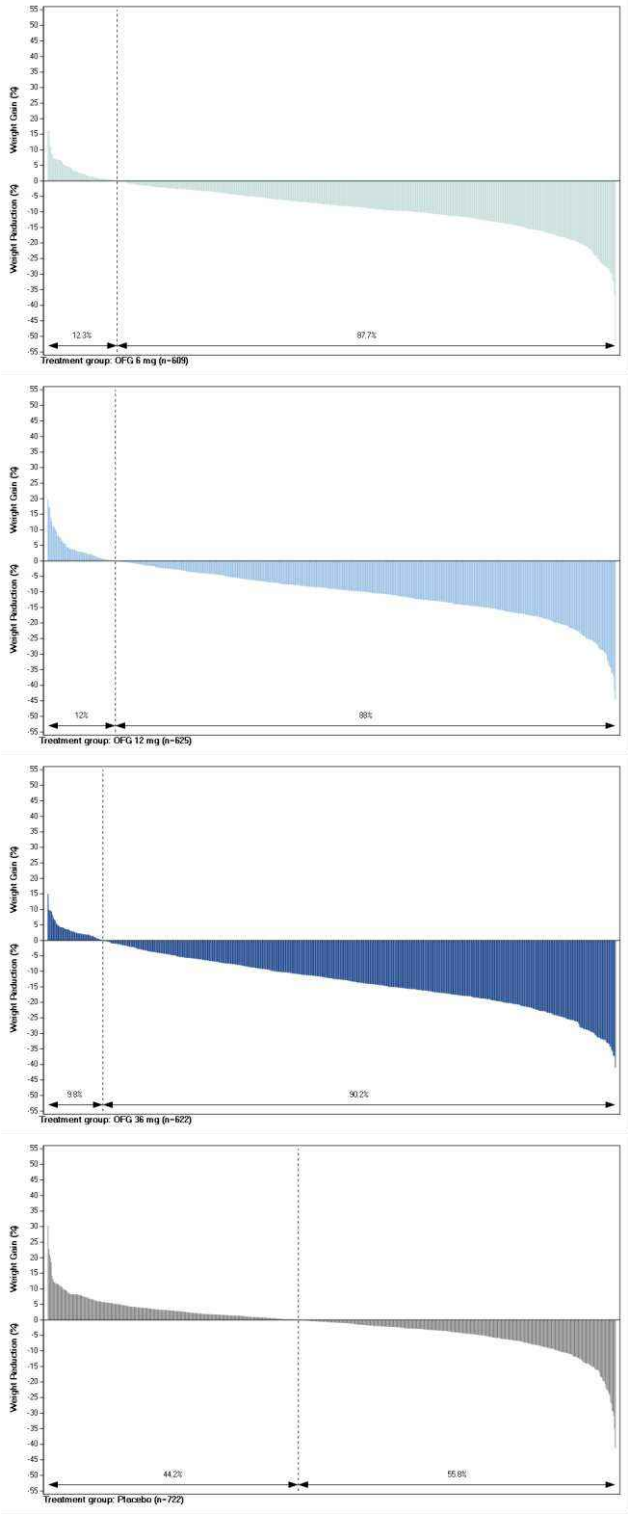


Figure S11. Waterfall plots of percent change in body weight at week 72 in the orforglipron 6 mg, 12 mg, and 36 mg groups and placebo from all randomized participants in the treatment regimen estimand data points set. Body weight reduction was observed in 87.7%, 88%, and 90.2% of participants randomized in orforglipron 6 mg, 12 mg and 36 mg doses, respectively, compared to 55.8% of participants in the placebo group.

Figure S12. Two-way tipping point analysis

Two-way tipping point analysis for orforglipron versus placebo in body weight percent change from baseline

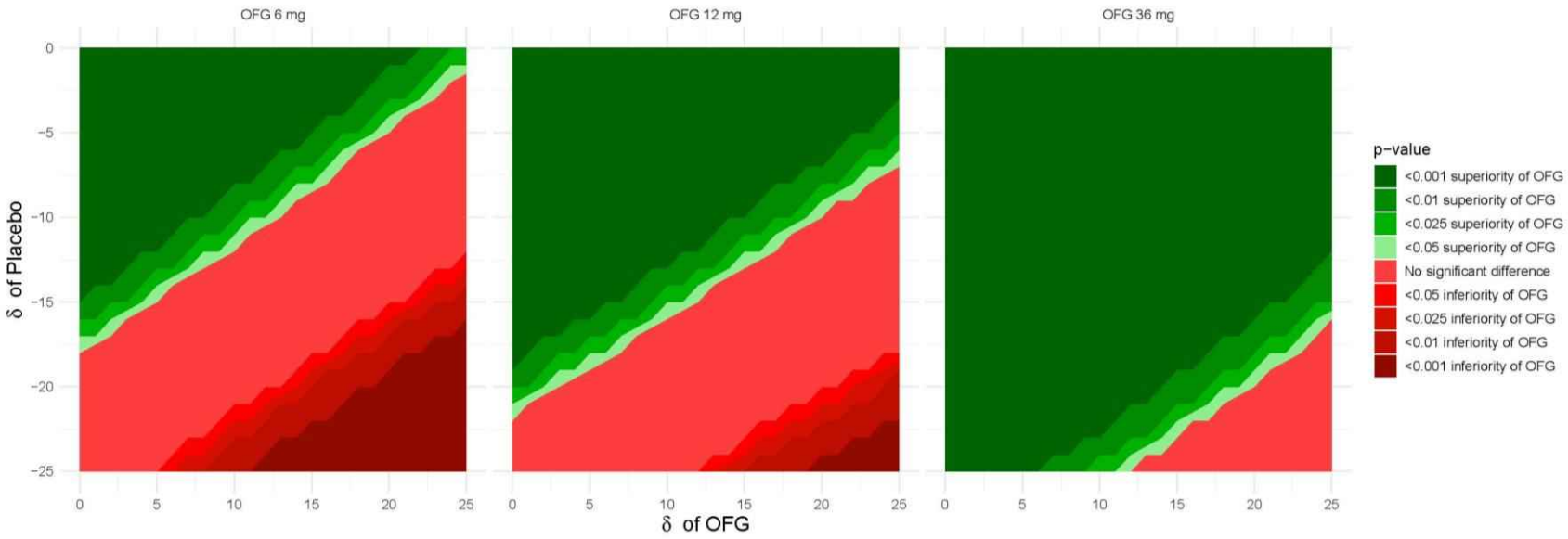


Figure S12. A 2-way tipping point analysis is used to assess the robustness of the superiority claim to the assumptions of using the observed data to impute the missing body weight in all treatment groups. The analysis demonstrated that no plausible level of imputed data could alter the direction or statistical significance of the findings. The x and y axes represent the values added to the imputed data for percent change in body weight at week 72 for orforglipron and placebo groups. The figure illustrates that, to lose statistical significance ($p < 0.05$), the imputed percent change in body weight from baseline at week 72 would need to be increased by more than 25% in the orforglipron 6 mg, 12 mg, and 36 mg groups—assuming no penalty is applied to the placebo group. Conversely, if no penalty is applied to the orforglipron treatment groups, the imputed percent change in body weight from baseline at week 72 in the placebo arm would need to be reduced by at least 19% for the comparison with any orforglipron group to lose statistical significance ($p < 0.05$). Note 1: Statistical inference for endpoint uses Rubin's Rule to combine analyses of imputed datasets. Note 2: Positive δ indicates additive penalty and negative δ indicates additive benefit. OFG = orforglipron.

SUPPLEMENTARY TABLES

Table S1. Additional baseline demographics and clinical characteristics

	Orforglipron 6 mg (N=723)	Orforglipron 12 mg (N=725)	Orforglipron 36 mg (N=730)	Placebo (N=949)	Total (N=3127)
Country, n (%)					
Brazil	203 (28.1)	203 (28.0)	205 (28.1)	273 (28.8)	884 (28.3)
United States*	200 (27.7)	198 (27.3)	198 (27.1)	250 (26.3)	846 (27.1)
Japan	75 (10.4)	74 (10.2)	77 (10.5)	96 (10.1)	322 (10.3)
Spain	69 (9.5)	72 (9.9)	69 (9.5)	95 (10.0)	305 (9.8)
China	69 (9.5)	69 (9.5)	69 (9.5)	89 (9.4)	296 (9.5)
Slovakia	56 (7.7)	58 (8.0)	58 (7.9)	74 (7.8)	246 (7.9)
Republic of Korea	21 (2.9)	20 (2.8)	18 (2.5)	27 (2.8)	86 (2.8)
Taiwan	17 (2.4)	18 (2.5)	20 (2.7)	25 (2.6)	80 (2.6)
India	13 (1.8)	13 (1.8)	16 (2.2)	20 (2.1)	62 (2.0)
Clinical Characteristics					
eGFR[#], mL/min/1.73 m^2	93.1 ± 18.7	92.5 ± 18.7	92.8 ± 18.4	92.4 ± 18.5	92.7 ± 18.6
Prediabetes, n (%)	258 (35.7)	260 (35.9)	265 (36.3)	344 (36.2)	1127 (36.0)
HbA1c, %	5.6 ± 0.4	5.6 ± 0.3	5.6 ± 0.3	5.6 ± 0.3	5.6 ± 0.3
Fasting glucose, mg/dL	92.6 ±10.0	92.1 ± 10.0	93.0 ± 10.5	92.4 ± 10.0	92.5 ± 10.1
Fasting insulin, mIU/L	19.1 ± 13.9	18.5 ± 12.4	19.0 ± 12.3	19.0 ± 13.6	18.9 ± 13.1
hsCRP, mg/L	5.6 ± 6.9	5.7 ± 7.6	5.5 ± 7.1	5.9 ±7.9	5.7 ± 7.4
Duration of obesity, years	13.5 ± 11.1	13.7 ± 10.6	13.4 ± 11.1	13.6 ± 10.9	13.5 ± 10.9
Pulse, beats/min	73.0 ± 10.3	73.0 ± 9.9	73.5 ± 10.8	73.7 ± 10.1	73.4 ± 10.3
Comorbidities, n (%)[†]					
Hypertension	294 (40.7)	276 (38.1)	288 (39.5)	378 (39.8)	1236 (39.5)
Dyslipidemia	278 (38.5)	282 (38.9)	284 (38.9)	386 (40.7)	1230 (39.3)
Coronary artery disease	11 (1.5)	13 (1.8)	11 (1.5)	9 (0.9)	44 (1.4)
Cerebrovascular disease	7 (1.0)	15 (2.1)	13 (1.8)	12 (1.3)	47 (1.5)
Renal disease	25 (3.5)	23 (3.2)	20 (2.7)	24 (2.5)	92 (2.9)
Female reproductive disorders[‡]	64 (13.6)	65 (13.9)	70 (15.1)	82 (13.5)	281 (14.0)
Dysmenorrhea/ Menstrual Cycle Abnormal/ Infertility	59 (12.6)	54 (11.6)	63 (13.5)	71 (11.7)	247 (12.3)
PCOS	12 (2.6)	22 (4.7)	18 (3.9)	21 (3.5)	73 (3.6)
Obstructive sleep apnea	76 (10.5)	67 (9.2)	92 (12.6)	109 (11.5)	344 (11.0)
Osteoarthritis	89 (12.3)	85 (11.7)	78 (10.7)	112 (11.8)	364 (11.6)
Anxiety/Depression	117 (16.2)	104 (14.3)	111 (15.2)	161 (17.0)	493 (15.8)
MASLD	142 (19.6)	154 (21.2)	147 (20.1)	195 (20.5)	638 (20.4)
Asthma or COPD	54 (7.5)	57 (7.9)	63 (8.6)	68 (7.2)	242 (7.7)
Gout or hyperuricemia	77 (10.7)	79 (10.9)	83 (11.4)	90 (9.5)	281 (14.0)
Number of comorbidities, n (%)					
None	154 (21.3)	176 (24.3)	167 (22.9)	207 (21.8)	704 (22.5)
1-2	366 (50.6)	364 (50.2)	358 (49.0)	493 (51.9)	1581 (50.6)
3-4	176 (24.3)	146 (20.1)	180 (24.7)	206 (21.7)	708 (22.6)
≥5	27 (3.7)	39 (5.4)	25 (3.4)	43 (4.5)	134 (4.3)

Abbreviations include eGFR, estimated glomerular filtration rate; hsCRP, high sensitivity C-reactive protein; COPD, chronic obstructive pulmonary disease; MASLD, metabolic dysfunction-associated steatotic liver disease; PCOS, polycystic ovary syndrome.

*Including Puerto Rico.

The value of the eGFR was calculated according to the serum cystatin C-based Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.

†Comorbidities were assessed through a review of medical history.

‡ Percentage is based on total number of female participants in the respective treatment group.

Table S2. Demographics of the United States study population

	Orforglipron 6 mg (N=200)	Orforglipron 12 mg (N=198)	Orforglipron 36 mg (N=198)	Placebo (N=250)	Total (N=845)
Age, years	48.4 ± 13.0	49.6 ± 13.7	48.5 ± 13.0	48.3 ± 12.7	48.7 ± 13.1
Female, n (%)	139 (69.5)	139 (70.2)	137 (69.2)	173 (69.2)	588 (69.5)
Race†, n (%)					
American Indian or Alaska Native	2 (1.0)	3 (1.5)	1 (0.5)	3 (1.2)	9 (1.1)
Asian	5 (2.6)	6 (3.1)	14 (7.2)	8 (3.3)	33 (4.0)
Black or African American	42 (21.4)	38 (19.5)	40 (20.6)	43 (17.5)	163 (19.6)
White	141 (71.9)	140 (71.8)	131 (67.5)	183 (74.4)	595 (71.6)
Native Hawaiian or other Pacific Islander	0	1 (0.5)	0	2 (0.8)	3 (0.4)
Multiple	6 (3.1)	7 (3.6)	8 (4.1)	7 (2.8)	28 (3.4)
Missing	4 (2.0)	3 (1.5)	4 (2.0)	4 (1.6)	15 (1.8)
Hispanic or Latino†, n (%)	54 (27.0)	54 (27.3)	36 (18.2)	62 (24.8)	206 (24.3)

†Race and ethnic group were reported by the participants.
In the U.S., where obesity disproportionately affects Black and Hispanic or Latino people, the study population was representative of U.S. demographics, with 19.6% Black and 24.3% Hispanic or Latino participants.

Table S3. Percent change in body weight by subgroup

Subgroups	Treatment group	n	MBE (95% CI) at Week 72
Age group, n (%)			
<65 years, 2931 (93.7%)	OFG 6 mg	683	-7.6 (-8.3, -6.8)
	OFG 12 mg	674	-8.4 (-9.1, -7.7)
	OFG 36 mg	684	-11.2 (-12.0, -10.4)
	Placebo	890	-2.1 (-2.8, -1.4)
≥65 years, 196 (6.3%)	OFG 6 mg	40	-7.5 (-9.8, -5.1)
	OFG 12 mg	51	-9.3 (-11.6, -6.9)
	OFG 36 mg	46	-11.4 (-14.5, -8.3)
	Placebo	59	-1.7 (-3.6, 0.2)
Sex, n (%)			
Female, 2009 (64.2%)	OFG 6 mg	469	-8.1 (-9.0, -7.3)
	OFG 12 mg	467	-9.4 (-10.2, -8.5)
	OFG 36 mg	465	-12.3 (-13.3, -11.3)
	Placebo	608	-1.9 (-2.7, -1.2)
Male, 1118 (35.8%)	OFG 6 mg	254	-6.5 (-7.5, -5.5)
	OFG 12 mg	258	-6.8 (-7.9, -5.8)
	OFG 36 mg	265	-9.2 (-10.3, -8.1)
	Placebo	341	-2.3 (-3.3, -1.4)
BMI at baseline, n (%)			
<30 kg/m^2, 288 (9.2%)	OFG 6 mg	62	-6.3 (-7.9, -4.8)
	OFG 12 mg	72	-8.9 (-11.0, -6.8)
	OFG 36 mg	68	-12.5 (-14.7, -10.2)
	Placebo	86	-0.5 (-2.2, 1.1)
≥30 to < 35 kg/m^2, 1151 (36.8%)	OFG 6 mg	263	-7.6 (-8.8, -6.5)
	OFG 12 mg	272	-8.4 (-9.5, -7.3)
	OFG 36 mg	285	-11.1(-12.3, -9.9)
	Placebo	331	-1.6 (-2.6, -0.6)
≥35 to < 40 kg/m^2, 849 (27.2%)	OFG 6 mg	202	-7.6 (-8.9, -6.3)
	OFG 12 mg	198	-8.4 (-9.6, -7.1)
	OFG 36 mg	183	-11.5 (-13.0, -10.0)
	Placebo	266	-2.1 (-3.3, -1.0)
≥40 kg/m^2, 839 (26.8%)	OFG 6 mg	196	-7.8 (-9.1, -6.5)
	OFG 12 mg	183	-8.5 (-9.9, -7.0)
	OFG 36 mg	194	-10.7 (-12.3, -9.1)
	Placebo	266	-3.3 (-4.5, -2.1)
Race, n (%)			
White, 1746 (56.5%)	OFG 6 mg	408	-7.5 (-8.5, -6.6)
	OFG 12 mg	405	-8.8 (-9.7, -7.9)
	OFG 36	394	-11.3 (-12.4, -10.3)
	Placebo	539	-2.4 (-3.4, -1.5)
Black or African American, 267 (8.6%)	OFG 6 mg	68	-8.1 (-9.8, -6.4)
	OFG 12 mg	60	-7.3 (-9.9, -4.6)
	OFG 36 mg	67	-9.2 (-11.6, -6.7)

	Placebo	72	-2.4 (-4.2, -0.5)
Asian, 884 (28.6%)	OFG 6 mg	202	-7.6 (-8.8, -6.5)
	OFG 12 mg	201	-8.3 (-9.6, -7.0)
	OFG 36 mg	214	-11.4 (-12.7, -10.0)
	Placebo	267	-1.0 (-1.8, -0.1)
Multiple, 181 (5.9%)	OFG 6 mg	35	-6.0 (-9.0, -2.9)
	OFG 12 mg	45	-8.2 (-10.5, -6.0)
	OFG 36 mg	47	-12.7 (-15.5, -9.9)
	Placebo	54	-3.4 (-5.7, -1.0)
Ethnicity, n (%)			
Hispanic or Latino, 1175 (37.6%)	OFG 6 mg	273	-6.6 (-7.6, -5.5)
	OFG 12 mg	275	-8.1 (-9.2, -7.0)
	OFG 36 mg	258	-10.3 (-11.6, -9.0)
	Placebo	369	-2.6 (-3.6, -1.5)
Not Hispanic or Latino, 1923 (61.5%)	OFG 6 mg	443	-8.1 (-9.0, -7.3)
	OFG 12 mg	441	-8.5 (-9.4, -7.6)
	OFG 36 mg	467	-11.7 (-12.7, -10.8)
	Placebo	572	-1.8 (-2.5, -1.0)
Prediabetes at Randomization, n (%)			
No, 2000 (64.0%)	OFG 6 mg	465	-7.3 (-8.1, -6.4)
	OFG 12 mg	465	-8.3 (-9.2, -7.4)
	OFG 36 mg	465	-11.1 (-12.1, -10.1)
	Placebo	605	-2.0 (-2.8, -1.1)
Yes, 1127 (36.0%)	OFG 6 mg	258	-8.0 (-9.1, -7.0)
	OFG 12 mg	260	-8.6 (-9.8, -7.5)
	OFG 36 mg	265	-11.3 (-12.5, -10.2)
	Placebo	344	-2.2 (-3.1, -1.4)

Data are MBE (95% confidence interval) from analysis of covariance (ANCOVA) model according to the treatment-regimen estimand. N is the number of participants in the subgroups. The race of American Indian/Alaska Native and Native Hawaiian or other Pacific Islander are not included in the subgroup analyses because participants are <5% of the total population. The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.

Table S4. Additional efficacy findings (treatment regimen estimand)

	Orforglipron 6 mg (N=723)	Orforglipron 12 mg (N=725)	Orforglipron 36 mg (N=730)	Placebo (N=949)
Change in:				
SBP, mmHg	-5.7 (-6.8, -4.6)	-5.1 (-6.1, -4.0)	-6.3 (-7.3, -5.3)	-1.4 (-2.4, -0.50)
DBP, mmHg	-2.4 (-3.1, -1.7)	-2.2 (-2.9, -1.5)	-2.7 (-3.4, -2.1)	-1.4 (-2.1, -0.7)
HbA1c, %	-0.27 (-0.30, -0.25)	-0.27 (-0.29, -0.24)	-0.33 (-0.35, -0.31)	-0.05 (-0.09, -0.02)
Fasting glucose, mg/dL	-6.6 (-7.4, -5.8)	-7.2 (-8.0, -6.4)	-7.6 (-8.6, -6.6)	-0.8 (-1.8, 0.1)
Percent change in: ‡				
Fasting insulin	-18.8 (-22.7, -14.6)	-21.8 (-26.0, -17.4)	-26.6 (-30.4, -22.6)	-11.5 (-16.3, -6.4)
Triglycerides	-10.4 (-13.1, -7.6)	-13.5 (-16.0, -11.0)	-20.2 (-22.6, -17.7)	-3.8 (-6.8, -0.7)
Non-HDL cholesterol	-5.4 (-7.0, -3.8)	-7.0 (-8.4, -5.5)	-7.7 (-9.3, -6.1)	-1.9 (-3.6, -0.2)
HDL cholesterol	2.2 (0.9, 3.6)	2.9 (1.6, 4.2)	4.4 (3.1, 5.8)	-0.9 (-2.3, 0.5)
Total cholesterol	-3.4 (-4.6, -2.1)	-4.5 (-5.6, -3.4)	-4.4 (-5.5, -3.2)	-2.0 (-3.3, -0.6)
LDL cholesterol	-3.9 (-5.8, -2.0)	-5.5 (-7.2, -3.8)	-4.9 (-6.7, -3.0)	-1.3 (-3.0, 0.4)
VLDL cholesterol	-10.2 (-12.8, -7.5)	-13.6 (-16.1, -11.1)	-19.7 (-22.1, -17.3)	-3.5 (-6.3, -0.6)
hsCRP	-33.3 (-37.5, -28.8)	-38.6 (-43.0, -34.0)	-43.6 (-47.8, -39.2)	-14.7 (-20.5, -8.4)

Data are model based estimates and 95% confidence interval from ANCOVA (treatment regimen estimand). The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. Note: All changes are from baseline to week 72. DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; VLDL, very-low-density lipoprotein; hsCRP, high sensitivity C-reactive protein.

‡ Lipid parameters, fasting insulin, and hsCRP were analyzed using log-transformation.

Table S5. Additional efficacy findings (efficacy estimand)

	Orforglipron 6 mg (N=723)	Orforglipron 12 mg (N=725)	Orforglipron 36 mg (N=730)	Placebo (N=949)
Change in:				
SBP, mmHg	-5.8 (-6.8, -4.8)	-5.9 (-6.8, -5.0)	-6.7 (-7.7, -5.7)	-0.8 (-1.6, 0.0)
DBP, mmHg	-2.4 (-3.0, -1.7)	-2.7 (-3.3, -2.0)	-2.6 (-3.2, -1.9)	-0.9 (-1.5, -0.4)
HbA1c, %	-0.31 (-0.33, -0.29)	-0.31 (-0.33, -0.29)	-0.38 (-0.40, -0.36)	-0.03 (-0.05, -0.01)
Fasting glucose, mg/dL	-7.7 (-8.3, -7.0)	-8.7 (-9.4, -8.0)	-9.2 (-10.0, -8.5)	0.3 (-0.5, 1.1)
Percent change in: ‡				
Fasting insulin	-20.6 (-24.4, -16.7)	-23.9 (-27.8, -19.8)	-32.8 (-36.4, -29.0)	-7.3 (-11.5, -2.9)
Triglycerides	-12.1 (-14.7, -9.4)	-15.2 (-17.8, -12.4)	-21.6 (-23.7, -19.3)	-4.8 (-7.1, -2.4)
Non-HDL cholesterol	-5.9 (-7.4, -4.3)	-8.3 (-9.9, -6.8)	-8.5 (-10.0, -7.0)	-1.4 (-2.8, 0.0)
HDL cholesterol	2.3 (1.0, 3.7)	3.7 (2.3, 5.0)	5.2 (3.9, 6.6)	0.1 (-1.1, 1.3)
Total cholesterol	-3.5 (-4.7, -2.3)	-5.1 (-6.2, -3.9)	-5.0 (-6.1, -3.8)	-1.1 (-2.1, 0.0)
LDL cholesterol	-4.6 (-6.5, -2.8)	-6.7 (-8.4, -4.9)	-5.3 (-7.0, -3.6)	-0.5 (-2.1, 1.2)
VLDL cholesterol	-12.6 (-15.0, -10.0)	-15.1 (-17.6, -12.5)	-21.7 (-23.9, -19.5)	-4.4 (-6.7, -2.0)
hsCRP	-36.8 (-40.8, -32.6)	-41.1 (-45.0, 37.0)	-47.7 (-51.3, -43.7)	-12.7 (-17.2, -7.9)

Data are model based estimates and 95% confidence interval from MMRM (efficacy estimand). The confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. Note: All changes are from baseline to week 72. DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein; SBP, systolic blood pressure; VLDL, very-low-density lipoprotein; hsCRP, high sensitivity C-reactive protein.

‡ Lipid parameters, fasting insulin, and hsCRP were analyzed using log-transformation.

Table S6. Primary and secondary endpoints by treatment group (efficacy estimand)

	Orforglipron 6 mg (N=723)	**Orforglipron 12 mg (N=725)**	**Orforglipron 36 mg (N=730)**	**Placebo (N=949)**
Primary endpoint				
Percent change in weight, %	-7.8 (-8.4, -7.2)	-9.3 (-9.9, -8.6)	-12.4 (-13.1, -11.6)	-0.9 (-1.4, -0.4)
Difference versus placebo of percent change in weight, %	-6.9 (-7.7, -6.2)	-8.4 (-9.3, -7.6)	-11.5 (-12.3, -10.6)	--
Key secondary endpoints				
Participants with weight reduction ≥5%, % ‡	63.8 (60.0, 67.6)	69.3 (65.5, 73.0)	77.1 (73.8, 80.5)	22.1 (19.2, 25.0)
Participants with weight reduction ≥10%, % ‡	35.9 (32.2, 39.6)	45.1 (41.3, 48.9)	59.6 (55.8, 63.4)	8.6 (6.7, 10.5)
Participants with weight reduction ≥15%, % ‡	16.5 (13.6, 19.5)	24.0 (20.7, 27.3)	39.6 (35.9, 43.4)	3.6 (2.3, 4.8)
Participants with weight reduction ≥20%, % ‡	7.2 (5.2, 9.3)	11.4 (8.9, 13.8)	20.1 (17.1, 23.1)	1.6 (0.8, 2.5)
Change in waist circumference, cm	-7.5 (-8.1, -6.9)	-9.0 (-9.6, -8.4)	-11.1 (-11.8, -10.5)	-2.1 (-2.6, -1.6)

Data are model-based estimates (95% confidence interval) from MMRM (efficacy estimand). The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. Note: All changes are from baseline to week 72.
‡ Data presented as model-based estimate (95% confidence interval) from logistic regression (efficacy estimand). The percentage was calculated by combining the percentages of participants who met the target in imputed data sets with the use of Rubin's rules.

Table S7. Adverse events that emerged during treatment and occurred in ≥5% of participants in any treatment group.

	Orforglipron 6 mg N=723	**Orforglipron 12 mg N=724**	**Orforglipron 36 mg N=728**	**Placebo N=948**	**Overall N=3123**
Nausea	209 (28.9)	260 (35.9)	245 (33.7)	99 (10.4)	813 (26.0)
Constipation	157 (21.7)	216 (29.8)	185 (25.4)	88 (9.3)	646 (20.7)
Diarrhoea	152 (21.0)	165 (22.8)	168 (23.1)	91 (9.6)	576 (18.4)
Vomiting	94 (13.0)	155 (21.4)	175 (24.0)	33 (3.5)	457 (14.6)
Dyspepsia	95 (13.1)	117 (16.2)	103 (14.1)	47 (5.0)	362 (11.6)
Upper respiratory tract infection	75 (10.4)	75 (10.4)	64 (8.8)	103 (10.9)	317 (10.2)
Headache	62 (8.6)	75 (10.4)	71 (9.8)	71 (7.5)	279 (8.9)
Influenza	68 (9.4)	58 (8.0)	44 (6.0)	73 (7.7)	243 (7.8)
Nasopharyngitis	55 (7.6)	61 (8.4)	47 (6.5)	74 (7.8)	237 (7.6)
Abdominal distension	52 (7.2)	68 (9.4)	62 (8.5)	32 (3.4)	214 (6.9)
COVID-19	44 (6.1)	52 (7.2)	54 (7.4)	50 (5.3)	200 (6.4)
Decreased appetite	42 (5.8)	61 (8.4)	53 (7.3)	30 (3.2)	186 (6.0)
Abdominal pain upper	44 (6.1)	45 (6.2)	57 (7.8)	33 (3.5)	179 (5.7)
Gastroenteritis	45 (6.2)	42 (5.8)	50 (6.9)	36 (3.8)	173 (5.5)
Back pain	34 (4.7)	39 (5.4)	45 (6.2)	54 (5.7)	172 (5.5)
Arthralgia	34 (4.7)	37 (5.1)	35 (4.8)	60 (6.3)	166 (5.3)
Abdominal pain	38 (5.3)	50 (6.9)	44 (6.0)	25 (2.6)	157 (5.0)
Anxiety	37 (5.1)	29 (4.0)	27 (3.7)	64 (6.8)	157 (5.0)
Eructation	44 (6.1)	43 (5.9)	55 (7.6)	10 (1.1)	152 (4.9)
Gastroesophageal reflux disease	40 (5.5)	42 (5.8)	46 (6.3)	21 (2.2)	149 (4.8)
Flatulence	31 (4.3)	40 (5.5)	41 (5.6)	17 (1.8)	129 (4.1)
Alopecia	30 (4.1)	36 (5.0)	39 (5.4)	23 (2.4)	128 (4.1)
Fatigue	26 (3.6)	25 (3.5)	37 (5.1)	15 (1.6)	103 (3.3)

Data are shown as number of participants (%).

Table S8. Reported deaths during the study

Participant (age, sex)	Treatment Group	MedDRA PT	Days from Randomization	Days since Last Dose of Study Treatment	Adjudicated Cause of Death (Cardiovascular: Yes or No)	Study Treatment Related per PI: Yes or No
60, M	OFG 6 mg	Death (cause undetermined)[†]	424	1	Yes	No
70, F	OFG 12 mg	Ovarian cancer metastatic	531	51	No	No
45, F	Placebo	Pulmonary embolism	79	1	Yes	No

[†]Participant had a medical history of hypertensive heart disease, dyslipidemia, obstructive sleep apnea, hypertension, and impaired glucose tolerance.

Table S9. Adjudication-confirmed cases of pancreatitis

Participant (age, sex)	Treatment group	Event Preferred Term	Adjudicated Event Severity[†]	Adjudication Diagnostic Criteria			
				Symptoms	Elevated Enzymes	Imaging	Contributing Factors
65, M	OFG 36 mg	Pancreatitis acute	Mild, hospitalized (unknown duration)	Yes	Yes	Negative	Alcohol abuse
50, M	OFG 36 mg	Lipase increased	Mild, no hospitalization	Yes	Yes	Negative	None
36, F	OFG 12 mg	Obstructive pancreatitis	Mild, hospitalized 10 days	Yes	Yes	Negative	Cholelithiasis
34, F	OFG 12 mg	Obstructive pancreatitis	Mild, hospitalized 8 days	Yes	No	Positive	Cholelithiasis
55, F	OFG 6 mg	Pancreatitis acute	Mild, no hospitalization	Yes	Yes	Not Done	None

Acute pancreatitis was adjudication-confirmed based on at least 2 of 3 features: 1) Abdominal pain, characteristic of acute pancreatitis, often associated with nausea and vomiting, 2) Serum amylase and/or lipase ≥ 3 times the upper limit of normal, 3) Characteristic findings on computed tomography scan or magnetic resonance imaging.

[†]Severity was assessed by the external Clinical Evaluation Committee as follows: Mild acute pancreatitis is characterized by absence of both (peri) pancreatic necrosis and organ failure; Moderate acute pancreatitis is characterized by the presence of sterile (peri) pancreatic necrosis and/or transient organ failure; Severe acute pancreatitis is characterized by the presence of either infected (peri) pancreatic necrosis or persistent organ failure; Critical acute pancreatitis: characterized by presence of infected (peri) pancreatic necrosis and organ failure.

F=female; M=male; mg=milligrams; OFG=orforglipron.

Table S10. Summary of participants with maximum post-baseline ALT or AST ≥3X, ≥5X, and ≥10X upper limit of normal

Category	Orforglipron 6 mg N=714	Orforglipron 12 mg N=714	Orforglipron 36 mg N=711	Placebo N=929
ALT				
≥3X ULN	21 (2.9%)	11 (1.5%)	22 (3.1%)	21 (2.3%)
≥5X ULN	6 (0.8%)	5 (0.7%)	9 (1.3%)	8 (0.9%)
≥10X ULN	0 (0.0%)	2 (0.3%)	4 (0.6%)	1 (0.1%)
AST				
≥3X ULN	8 (1.1%)	4 (0.6%)	9 (1.3%)	9 (1.0%)
≥5X ULN	4 (0.6%)	1 (0.1%)	4 (0.6%)	3 (0.3%)
≥10X ULN	1 (0.1%)	0 (0.0%)	1 (0.1%)	0 (0.0%)

Data presented as number of participants, n (%). N = number of participants with at least one post-baseline measurement for the specified parameters including results obtained from both central and local labs.

Note:

- For the 3X and 5X ULN elevations, there was no imbalance.
- A total of 8 participants (1 placebo, 7 orforglipron) experienced ≥10X ULN elevations of transaminases (1 participant had both ALT and AST elevations ≥10X ULN).
- For all orforglipron-treated participants with ≥10X ULN elevations of transaminases, an alternative cause was identified (gallbladder disease, pancreatic adenocarcinoma, and viral hepatitis).
- There were two participants with total bilirubin ≥2X ULN and ALT ≥3X ULN:
    - One of the cases of elevated liver enzymes, in a participant assigned to 36-mg orforglipron, was due to hepatitis A. This participant had ALT 80X ULN, AST 28X ULN, and total bilirubin 4.6X ULN.
    - In the other case, a participant receiving orforglipron 6-mg, bilirubin (2.1X ULN), ALT (8.7X ULN), and AST (17.3X ULN) elevations were accompanied by alkaline phosphatase increase (5.1X ULN) and abdominal pain, with concurrent complicated biliary colic and cholelithiasis. The study treatment was interrupted following the initial elevations. Following cholecystectomy, the abnormalities resolved. Treatment was resumed without further elevations.

Table S11. Additional safety measures

	Normal range	Orforglipron 6 mg N=723	Orforglipron 12 mg N=724	Orforglipron 36 mg N=728	Placebo N=948
Pulse, bpm	60-100 bpm				
Baseline		73.0 ±0.4	73.0 ± 0.4	73.5 ± 0.4	73.7 ± 0.3
Week 72		77.6 ± 0.3	77.9 ± 0.3	78.7 ±0.3	74.1 ± 0.3
Change at week 72		4.3 ± 0.3	4.5 ± 0.3	5.3 ± 0.3	0.8 ± 0.3
Alanine aminotransferase, U/L	Female: 4 – 43 U/L; Male: 5 – 48 U/L				
Baseline		22.9 ± 0.5	22.7 ± 0.5	22.8 ± 0.5	22.7 ± 0.4
Week 72		19.4 ± 0.3	18.9 ± 0.3	18.4 ± 0.4	21.7 ± 0.3
% change at week 72		-15.1 ± 1.5	-17.2 ± 1.4	-19.5 ± 1.6	-5.2 ± 1.4
Aspartate aminotransferase, U/L	8 – 40 U/L				
Baseline		20.1 ± 0.3	20.3 ± 0.3	20.1 ± 0.3	20.4 ± 0.2
Week 72		19.1 ± 0.2	19.1 ± 0.2	18.7 ± 0.3	20.4 ± 0.2
% change at week 72		-5.8 ± 1.1	-5.8 ± 1.0	-7.6 ± 1.2	0.4 ± 1.2
Pancreatic-amylase, U/L	3 – 46 U/L				
Baseline		23.2 ± 0.3	23.4 ± 0.3	23.2 ± 0.3	23.5 ± 0.3
Week 72		26.7 ± 0.3	26.8 ± 0.3	26.7 ± 0.3	23.6 ± 0.2
% change at week 72		14.1 ± 1.3	14.4 ± 1.3	14.2 ± 1.1	1.1 ± 0.8
Lipase, U/L	0 – 100 U/L				
Baseline		28.0 ± 0.4	29.9 ± 0.4	28.7 ± 0.4	28.7 ± 0.3
Week 72		36.9 ± 0.5	37.9 ± 0.6	37.1 ± 0.5	29.9 ± 0.3
% change at week 72		28.1 ± 1.9	31.7 ± 2.0	28.8 ± 1.8	4.0 ± 1.1
Calcitonin, ng/L	Female: < 5.0 ng/L (<1.46 pmol/L); Male: < 8.4 ng/L (<2.46 pmol/L)				
Baseline		1.2 ± 0.04	1.1 ± 0.04	1.2 ± 0.04	1.2 ± 0.04
Week 72		1.2 ± 0.02	1.2 ± 0.02	1.2 ± 0.02	1.1 ± 0.01
% change at week 72		4.0 ± 1.5	5.3 ± 1.6	4.0 ± 1.4	-4.9 ± 1.1
Urine	0 – 30 g/kg				

Albumin-to-Creatinine Ratio, g/kg				
Baseline	7.3 ± 0.3	7.5 ± 0.3	7.6 ± 0.3	7.5 ± 0.2
Week 72	6.6 ± 0.2	6.6 ± 0.2	6.3 ± 0.2	7.5 ± 0.2
% change at week 72	-11.5 ± 2.7	-10.7 ± 2.9	-14.8 ± 2.6	0.8 ± 3.4

Data presented are model based estimate ± standard error. Note: except for pulse, all other measures were analyzed with log-transformation

Table S12. Representativeness of study

Category	Details
Disease under investigation	Obesity (BMI≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2)
Special considerations related to	
Sex and gender	In 2022, 43% of men and 44% of women worldwide had overweight[13] and obesity rates in females reached 18.5% and 14.0% in males.[14]
Age	Worldwide, obesity and overweight affect all adult age groups. Worldwide, the prevalence of overweight and obesity increases with age, up to the age range of 50 to 65 years, before declining slightly after the age of 65.[15]
Race or ethnic group	In the United States, the prevalence of obesity is highest in Black adults (49.9%), followed by Hispanic adults (45.6%), White adults (41.4%) and Asian adults (16.1%).[16]
Geography	Obesity is most prevalent in China, India, the USA, Brazil, Russia, Mexico, Indonesia, and Egypt. Over half of the global population is affected by overweight and obesity. The highest rates are found in Oceania, North Africa, and the Middle East. Rates are lowest in low- to middle-income countries.[17]
Other considerations	
Overall representativeness of this trial	The ATTAIN-1 trial was conducted in adults ≥18 years of age in nine countries across four continents: North America, South America, Asia, and Europe. The United States, which has a higher prevalence of obesity than most countries that participated in the trial, represented 27.1% of the study population. In the ATTAIN-1 trial, to ensure adequate representation of male participants, female enrollment was capped at 70% by country. Sex was captured by asking "What is the sex of the subject?", with the instruction to the site as follows: For transgender individuals, record the sex as their original, genetic sex. Women represented approximately 64.2% of the trial population and men 35.8%. The average age (calculated based upon the reported year of birth) was 45.1 years (range 18 to 88 years), with 6.3% of participants aged ≥65 years. This is in line with the higher prevalence of obesity in the 40 to 59 year age group. All demographic measures (including race and ethnicity) were self-reported. In the ATTAIN-1 trial, the US population was approximately 19.6% African-Americans and 24.3% Latin-Americans. This is representative of the prevailing demographics in the United States. Overall, the trial was representative of the global prevalence of obesity by age and geography.

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Nadia Ahmad

Discloser Identifier: 1079631

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Employment	Self
Title: Associate Vice President **Position Description:** Combined Management and Subject Matter Expert role, leading late phase development programs (Phase 3 trials) for obesity medications. **Additional Information:**		
Eli Lilly and Company	Stock	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Orforglipron, an Oral Small Molecule GLP-1R Agonist for Obesity Treatment

3. **Are you the corresponding author?**

   No.

Certification

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Nasreen Alfaris

Discloser Identifier: 1262348

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli LIlly	Consultant	Self

Category: Consultant
Description: consulting
Additional Information: for educational activity and talks

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

   No.

Certification

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Sheryl Allen

Discloser Identifier: 1262357

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Employment	Self

Title: Executive Director
Position Description: Medical Director for Attain 1
Additional Information: Employee and Stock Holder

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

   No.

Certification

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Louis Aronne

Discloser Identifier: 468237

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Altimmune	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Consultant and investigator		
Amgen Inc.	Consultant	Self
Category: Consultant **Description:** consultant **Additional Information:**		
AstraZeneca	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Research Funding		
Boehringer Ingelheim	Consultant	Self
Category: Consultant **Description:** consulting **Additional Information:**		
Clic Bio	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Eli Lilly and Company	Consultant	Self
Category: Consultant **Description:** Consultant and investigator **Additional Information:** Consultant and investigator		
ERX pharmaceuticals	Other	Self
Category: Other **Description:** **Additional Information:** Equity Interests, board member		
Intellihealth	Fiduciary Officer	Self

Entity	Type	Interest Held By
Official Title: Chief Scientific Advisor **Additional Information:** Equity Interests, Board of Directors' Member	**Position Description:** consultant	
Jamieson Wellness	Fiduciary Officer	Self
Official Title: Board of Directors **Additional Information:**	**Position Description:** Director of company	
Jamieson Wellness	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Consultant / Advisory Board Member, Equity Interests, Board of Directors' Member		
Janssen Biotech	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Consultant/Advisory Board Member, Research Funding		
Jazz Pharmaceuticals Inc.	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Consultant/Advisory Board Member		
Metsera	Stock Option	Self
Additional Information:		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Consultant / Advisory Board Member, Research Funding		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Pfizer	Consultant	Self
Category: Consultant **Description:** **Additional Information:** Consultant / Advisory Board Member		
Pfizer	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Senda biosciences	Consultant	Self

Entity	Type	Interest Held By
Category: Consultant **Description:** **Additional Information:**		
Skye bioscience	Stock Option	Self
Additional Information:		
Syntis	Stock Option	Self
Additional Information:		
Verdiva Bio	Stock Option	Self
Additional Information:		
Versanis	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Veru Inc	Consultant	Self
Category: Consultant **Description:** Scientic advisory board **Additional Information:** equity option compensation		
Weill Cornell Medical College	Employment	Self
Title: MD, FACP, FTOS, DABOM **Additional Information:**	**Position Description:** Sanford I. Weill Professor of Metabolic Research Director, Comprehensive Weight Control Center, Weill Center for Metabolic Health	
Zealand Pharma A/S	Travel	Self
Location(s): London **Purpose:** consulting **Additional Information:**		

Additional Questions

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2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

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ANDREEA Ciudin

Discloser Identifier: 1262354

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Boehringer Ingelheim	Data And Safety Monitoring	Self
Category: Data And Safety Monitoring **Description:** Member of the DMC for the SYCRONIZE clinical trials programe_survodutide **Additional Information:**		
Eli Lilly and Company	Grant / Contract	Self
Recipient Name: Vall Hebron Research Institute-VHIR **Grant / Contract Description:** OBEX educational programe in obesity **Additional Information:** Approved by supervisor, 2 working days/person. A total of 6 persons attending in 2025.	**Recipient Type:** Institution **Grant / Contract Purpose:** Other - Educational programe for starting obesity clinic	
Eli Lilly and Company	Consultant	Self
Category: Consultant **Description:** Co-design for clinical trials **Additional Information:** 8 full hours for an advisory board for co-design for clinical trials.		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** OUTSTEP programe **Additional Information:** Member of the OUTSTEP clinical trials programe.		
Novo Nordisk	Other	Self
Category: Other **Description:** OPEN educational programe **Additional Information:** 4 sessions of 2 hours for education in obesity for health care providers.		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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2. **What is the manuscript title?**

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Bruno Halpern

Discloser Identifier: 787220

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Boehringer Ingelheim	Other	Self
Category: Other **Description:** Talks **Additional Information:**		
Currax Pharmaceuticals LLC	Consultant	Self
Category: Consultant **Description:** Advisory Board **Additional Information:**		
Eli LIlly	Consultant	Self
Category: Consultant **Description:** Advisory Board **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** Advisory Board **Additional Information:**		

Additional Questions

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Aug 22, 2025 07:05:03 EDT
New England Journal of Medicine

Courtney Khouli

Discloser Identifier: 1262305

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Employment	Self
Title: Manager - Scientific Communication - Publications **Position Description:** Provide support with global communications **Additional Information:**		
Eli Lilly and Company	Stock	Self
Additional Information:		

Additional Questions

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2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

   No.

Certification

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Suzanne Klise

Discloser Identifier: 1262358

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Employment	Self
Title: Executive Director - Clinical Research Scientist **Position Description:** Serve as medical lead for Phase 3 clinical research **Additional Information:**		
Eli Lilly and Company	Stock	Self
Additional Information: Stock granted as part of employee compensation		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

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Lisa Macpherson

Discloser Identifier: 1262356

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Employment	Self
Title: Director of Statistics **Additional Information:**	**Position Description:** Serve as the statistical lead for this study	
Eli Lilly and Company	Stock	Self
Additional Information:		
Eli Lilly and Company	Stock Option	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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3. **Are you the corresponding author?**

   No.

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Alpana Shukla

Discloser Identifier: 693658

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Other	Self
Category: Other **Description:** Clinical Trial-Site Principal Investigator (signed FDA form 1572) **Additional Information:** Site Principal Investigator for Weill Cornell Medicine		
Novo Nordisk	Other	Self
Category: Other **Description:** Clinical Trial Site Principal Investigator, signed FDA form 1572 **Additional Information:** Site Principal Investigator for Weill Cornell Medicine		
Sun Pharmaceuticals	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Sun Pharmaceuticals	Other	Self
Category: Other **Description:** Member of Scientific Advisory Board **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

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Adam Stefanski

Discloser Identifier: 1079633

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli Lilly and Company	Employment	Self
Title: Associate VP-Research & Development-Clinical Research – Cardiometabolic Health **Additional Information:** Full-time employment	**Position Description:** Medical role to provide scientific and clinical support during late phase drug development	
Eli Lilly and Company	Stock	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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3. **Are you the corresponding author?**

   No.

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sean wharton

Discloser Identifier: 1053775

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
AbbVie	Other	Self
Category: Other **Description:** Scientific Advisory Board **Additional Information:**		
Amgen Canada	Other	Self
Category: Other **Description:** Speaking engagement **Additional Information:** Advisory Board Involvement		
AstraZeneca	Other	Self
Category: Other **Description:** Academic speaking engagement **Additional Information:** Advisory Boards involvement		
Bausch and Lomb	Other	Self
Category: Other **Description:** Scientific Advisory Board, Academic speaking engagements **Additional Information:** Honoraria for academic speaking engagements		
Biohaven Pharmaceuticals, Inc.	Other	Self
Category: Other **Description:** Scientific Advisory Board **Additional Information:** Academic advisory board		
Boehringer Ingelheim	Other	Self
Category: Other **Description:** Scientific Advisory Board **Additional Information:**		
Eli Lilly and Company	Other	Self
Category: Other **Description:** Speaking Engagement, Advisory Board **Additional Information:**		
Merck	Other	Self
Category: Other **Description:** Scientific Advisory Board		

Entity	Type	Interest Held By
Additional Information:		
Novo Nordisk	Other	Self
Category: Other **Description:** Scientific Advisory Board, Academic Speaking Engagement **Additional Information:** Academic Advisory Board		
Regeneron Pharmaceuticals	Other	Self
Category: Other **Description:** Work on Advisory Board **Additional Information:**		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Orforglipron, an Oral Small Molecule GLP-1 Receptor Agonist for the Treatment of Obesity

3. **Are you the corresponding author?**

   Yes.

   a. **Please list the other authors' names here.**

      Louis J. Aronne, MD, Adam Stefanski, MD, PhD, Nasreen F. Alfaris, MD, MPH, Andreea Ciudin, MD, PhD, Koutaro Yokote, MD, PhD, MBA, Bruno Halpern, MD, PhD7, Alpana Shukla, MD2, Chunmei Zhou, M.S.3, Lisa Macpherson, MSPH, Sheryl E. Allen, MD, MS, Nadia N. Ahmad, MD, MPH, Suzanne R. Klise, B.S.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Koutaro Yokote

Discloser Identifier: 747945

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Astellas Pharma	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Bayer yakuhin	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Daiichi Sankyo Company LTD	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Eli Lilly Japan	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Eli Lilly Japan	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
KOWA COMPANY, LTD.	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
KOWA COMPANY, LTD.	Consultant	Self
Category: Consultant **Description:** advisory board **Additional Information:**		
Mitsubishi Tanabe Pharma Corporation	Grant / Contract	Self
Recipient Name: Koutaro Yokote **Grant / Contract Description:** Research Grant Donation	**Recipient Type:** **Grant / Contract Purpose:**	

Entity	Type	Interest Held By
Additional Information:		
Mitsubishi Tanabe Pharma Corporation	Consultant	Self
Category: Consultant **Description:** Advisor **Additional Information:**		
Mitsubishi Tanabe Pharma Corporation	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Nippon Boehringer Ingelheim Co., Ltd.	Grant / Contract	Self
Recipient Name: Koutaro Yokote **Grant / Contract Description:** Research Grant Donation **Additional Information:**	**Recipient Type:** **Grant / Contract Purpose:** Research	
Nippon Boehringer Ingelheim Co., Ltd.	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Nippon Boehringer Ingelheim Co., Ltd.	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Novartis Pharma	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Novo Nordisk	Consultant	Self
Category: Consultant **Description:** advisory board **Additional Information:**		
Novo Nordisk	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Pfizer	Consultant	Self
Category: Consultant **Description:** **Additional Information:**		
Sanofi	Other	Self

Entity	Type	Interest Held By
Category: Other **Description:** speaking engagement **Additional Information:**		
Sumitomo Dainippon Pharma Co., Ltd.	Grant / Contract	Self
Recipient Name: Koutaro Yokote **Grant / Contract Description:** Research Grant Donation **Additional Information:**	**Recipient Type:** **Grant / Contract Purpose:** Research	
Sumitomo Dainippon Pharma Co., Ltd.	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Taisho	Other	Self
Category: Other **Description:** speaking engagement **Additional Information:**		
Taisho Toyama Pharmaceutical Company	Consultant	Self
Category: Consultant **Description:** Advisor **Additional Information:**		
Takeda Pharmaceutical Company, Limited	Grant / Contract	Self
Recipient Name: **Grant / Contract Description:** Research Grant Donation **Additional Information:**	**Recipient Type:** **Grant / Contract Purpose:** Research	

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

   No.

2. **What is the manuscript title?**

   Orforglipron, an Oral Small Molecule GLP-1 Receptor Agonist for the Treatment of Obesity

3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Chunmei Zhou

Discloser Identifier: 689359

Disclosure Purpose: 25-11774

Summary of Interests

Company or Organization

Entity	Type	Interest Held By
Eli LIlly	Employment	Self
Title: Director **Additional Information:**	**Position Description:** Project statistician	
Eli LIlly	Stock	Self
Additional Information:		

Additional Questions

1. **Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?**

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2. **What is the manuscript title?**

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3. **Are you the corresponding author?**

   No.

Certification

I certify that the information provided in this disclosure is complete and accurate.

Data Sharing Statement

Wharton S, Aronne LJ, Stefanski A, et al. Orforglipron, an Oral Small-Molecule GLP-1 Receptor Agonist for Obesity Treatment. N Engl J Med. DOI: 10.1056/NEJMoa2511774.

Question	Authors' Response
Will the data collected for your study be made available to others?	Yes
Would you like to offer context for your decision?	—
Which data?	Complete de-identified patient data set
Additional information about data	—
How or where can the data be obtained?	Lilly provides access to all individual participant data collected during the trial, after anonymization, with the exception of pharmacokinetic or genetic data. Data are available to request 6 months after the indication studied has been approved in the U.S. and E.U. and after primary publication acceptance, whichever is later. No expiration date of data requests is currently set once data are made available. Access is provided after a proposal has been approved by an independent review committee identified for this purpose and after receipt of a signed data sharing agreement. Data and documents, including the study protocol, statistical analysis plan, clinical study report, blank or annotated case report forms, will be provided in a secure data sharing environment. For details on submitting a request, see the instructions provided at www.vivli.org.
When will data availability begin?	Beginning Date: 6 months after approval (U.S. and E.U.) and after primary publication acceptance
When will data availability end?	—
Will any supporting documents be available?	—
Which supporting documents?	—
Additional information about supporting documents	—
How or where can supporting documents be obtained?	—

When will supporting documents availability begin?	—
When will supporting documents availability end?	—
To whom will data be available?	—
For what type of analysis or purpose?	—
By what mechanism?	—
Any other restrictions?	—
Additional information	—

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