

Protocol Amendment J2A-JE-GZPD (b)

A Phase 3, Randomized, Double-Blind Study to Investigate the Efficacy and Safety of Once-Daily Oral LY3502970 Compared with Placebo in Japanese Adult Participants with Obesity Disease (ATTAIN-J)

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Approval Date: 07-Dec-2023

Title Page

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

Protocol Number: J2A-JE-GZPD

Amendment Number: b

Compound: orforglipron (LY3502970)

Brief Title: Efficacy and Safety of LY3502970 versus Placebo in Japanese Participants with Obesity Disease (ATTAIN-J)

Acronym: ATTAIN-J

Study Phase: 3

Sponsor Name: Eli Lilly Japan K.K.

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

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Medical Monitor Name and Contact Information will be provided separately.

Protocol Amendment Summary of Changes Table

DOCUMENT HISTORY	
Document	Date
<i>Amendment (a)</i>	<i>07-Jun-2023</i>
<i>Original Protocol</i>	<i>24-Mar-2023</i>

Amendment [b]

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

Overall Rationale for the Amendment:

The main purpose for the current protocol amendment is to include additional laboratory monitoring during the dose escalation period and change the primary estimand. These and other changes and a brief rationale are provided in the table below.

Amendment Summary for Protocol J2A-JE-GZPD Amendment (b)

Section # and Name	Description of Change	Brief Rationale
1. Synopsis 3. Objectives, Endpoints, and Estimands	Changed the primary estimand from the efficacy estimand to the “treatment regimen” estimand	To align with other orforglipron Phase 3 protocol
1.3. Schedule of Activities	Updated instruction for “Patient-reported outcomes (electronic)” row from “Complete prior to any clinical administered assessments” to “PROs should be administered as early as possible in the visit but after the assessment of AEs”	Clarification
	Added the following text for PROs, “The PROs will be administered if an approved and translated version is available for use”	Clarification
	Added notes that clinical chemistry labs and lipid panels must be obtained in the fasting state	Clarification
	Added chemistry panel to Visits 4, 5, 7, and 8 to allow hepatic evaluation and added a note to repeat chemistry panel 2 weeks later if, at Visit 801, hepatic laboratory values are elevated	To allow for more frequent evaluation of hepatic labs during the escalation period
	Added Diary (electronic) review at Visit 801	To allow reporting of hypoglycemic events during the follow-up period
2.3.1. Risk Assessment	Added risk for diabetic retinopathy and retinopathy assessment	To align with change in monitoring approach for diabetic retinopathy

Section # and Name	Description of Change	Brief Rationale
5.2. Exclusion Criteria	Criterion 9 on diabetic retinopathy has been revised	To align with other orforglipron Phase 3 protocol
	Removed the language in the exception note of Criterion 25 stating that participants must be anticipated to remain on the same dose of thyroid replacement therapy throughout the trial period.	Clarification
	Added “intra-articular” preparations to the list of exceptions to systemic glucocorticoid therapy in Criterion 38	Clarification
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
6.4. Blinding	Updated description for blinding	To align with other orforglipron Phase 3 protocol
6.6.1. Management of Gastrointestinal	Added description for the case that a participant has completed the final dose escalation step	Clarification
6.9.3. Prohibited or Restricted Use Medications	Text added to clarify short-term use of strong CYP3A inhibitors	Clarification
7.1. Discontinuation of Study Intervention	Updated entire section	To align with other orforglipron Phase 3 protocol
7.1.1. Liver Chemistry Stopping Criteria	Content deleted and reference to Section 8.2.5.3 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
8.2.5. Hepatic Safety Monitoring	Updated as per latest guidance on hepatic safety monitoring	Alignment with hepatic safety monitoring guidance update
8.2.6. Pregnancy Testing	Added description on at-home pregnancy testing	Clarification
8.2.9. Diabetic Retinopathy Screening and Evaluation	This section has been added to describe details of retinal photography and other eye assessments.	Added in response to revised diabetic retinopathy monitoring approach to align with other orforglipron Phase 3 protocol
8.3.3.10. Diabetic Retinopathy	This section title has been updated, “Diabetic Retinopathy Complications”	Revised to better reflect AESI topic

Section # and Name	Description of Change	Brief Rationale
	This section has been updated to describe how diabetic retinopathy will be assessed as an AESI.	Clarification: details of the retinal photography and other eye assessments are now included in Section 8.2.9
8.3.3.15. Depression, Suicidal Ideation, and Behavior	The second and third sentences have been revised as “Only report a suicide-related event discovered during collection of the C-SSRS on the AE form if it is an AE that leads to discontinuation or an SAE.”.	To align with C-SSRS protocol language updates
8.4. Pharmacokinetics	Removed text on PK sampling at specific visits and included a table on PK sampling relative to study intervention dose	Clarification
9.3.3. Primary Endpoint(s)/Estimand(s) Analysis	Revised to primary analysis to be conducted using the “treatment regimen” estimand	To align with other orforglipron Phase 3 protocol
	Revised text to indicate that the primary analysis will use the randomized participants population rather than full participants population	To follow ITT principles
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	Alignment with contraception guidance update

Section # and Name	Description of Change	Brief Rationale
	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	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
10.6. Appendix 6 Hepatic Evaluation Testing	Added the following description and updated table footnotes. “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).”	To align with hepatic evaluation testing appendix

Section # and Name	Description of Change	Brief Rationale
10.9.1. Excluded/Prohibited or Restricted Use Medications	- Exception note added for short-term use of strong CYP3A inhibitors - Clarification note added for medications that are used both for weight loss and hyperglycemia	Clarification
10.9.1.4. 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 a narrow therapeutic index shortened to include only prazosin	Clarification
10.9.2.1. Medications Affected by Increase in Gastric pH	Text revised to clarify use of medications that may be affected by increase in gastric pH	Clarification
10.11. Appendix 11 Adjustments to Visit Windows	Visit Number in the visit allowance table were corrected as follows: “Visit 2 through 20” to “Visit 2, 4 through 11, 13, 14, 16, 17, 19, 20” “Visit 21” to “Visit 3, 12, 15, 18 and 21”	Error correction
Throughout	Replaced “LY3502970” with “orforglipron”, except for the title	Per now available generic name
Throughout	Minor editorial changes have been made throughout	These are minor; therefore, they have not been individually summarized

Table of Contents

1.	Protocol Summary	12
1.1.	Synopsis	12
1.2.	Schema.....	20
1.3.	Schedule of Activities	21
2.	Introduction.....	48
2.1.	Study Rationale.....	48
2.2.	Background.....	48
2.3.	Benefit/Risk Assessment	51
2.3.1.	Risk Assessment	51
2.3.2.	Benefit Assessment.....	51
2.3.3.	Overall Benefit Risk Conclusion	52
3.	Objectives, Endpoints, and Estimands	53
4.	Study Design.....	59
4.1.	Overall Design	59
4.2.	Scientific Rationale for Study Design	59
4.3.	Justification for Dose	60
4.4.	End of Study Definition.....	61
5.	Study Population.....	62
5.1.	Inclusion Criteria	62
5.2.	Exclusion Criteria	63
5.3.	Lifestyle Considerations	68
5.3.1.	Meals and Dietary Restrictions.....	68
5.3.2.	Activity	69
5.3.3.	Diabetes Education	69
5.3.4.	Blood Donation.....	69
5.4.	Screen Failures.....	69
5.5.	Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention of a Participant	70
6.	Study Intervention(s) and Concomitant Therapy.....	71
6.1.	Study Intervention(s) Administered.....	71
6.2.	Preparation, Handling, Storage, and Accountability	72
6.3.	Assignment to Study Intervention	72
6.4.	Blinding	73
6.5.	Study Intervention Compliance	73
6.6.	Dose Modification	74
6.6.1.	Management of Gastrointestinal Symptoms.....	74
6.7.	Continued Access to Study Intervention after the End of the Study	76
6.8.	Treatment of Overdose	76
6.9.	Prior and Concomitant Therapy.....	76
6.9.1.	Symptomatic Medication for Gastrointestinal Symptoms	77
6.9.2.	Initiation of Antihyperglycemic Medications.....	77
6.9.3.	Prohibited or Restricted Use Medications	77

6.9.4.	Prohibited Surgical Treatments or Procedures	78
6.9.5.	Rescue Therapy for Severe, Persistent Hyperglycemia	78
6.9.6.	Antihyperglycemic Medications after Permanent Discontinuation of Study Intervention	79
7.	Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal.....	80
7.1.	Discontinuation of Study Intervention.....	80
7.1.1.	Liver Chemistry Stopping Criteria.....	81
7.1.2.	Temporary Study Intervention Interruption.....	81
7.2.	Participant Discontinuation/Withdrawal from the Study.....	82
7.3.	Lost to Follow-up.....	83
8.	Study Assessments and Procedures.....	84
8.1.	Efficacy Assessments	84
8.1.1.	Primary Efficacy Assessments.....	84
8.1.2.	Secondary Efficacy Assessments.....	84
8.2.	Safety Assessments.....	89
8.2.1.	Physical Examinations	89
8.2.2.	Vital Signs.....	89
8.2.3.	Electrocardiograms	89
8.2.4.	Clinical Safety Laboratory Tests	90
8.2.5.	Hepatic Safety Monitoring.....	91
8.2.6.	Pregnancy Testing.....	94
8.2.7.	Suicidal Ideation and Behavior Risk Monitoring	95
8.2.8.	Hypersensitivity Reactions	95
8.2.9.	Diabetic Retinopathy Screening and Evaluation	95
8.3.	Adverse Events, Serious Adverse Events, and Product Complaints.....	96
8.3.1.	Timing and Mechanism for Collecting Events	97
8.3.2.	Pregnancy.....	98
8.3.3.	Adverse Events of Special Interest	99
8.4.	Pharmacokinetics	106
8.4.1.	Bioanalysis	106
8.5.	Pharmacodynamics	106
8.6.	Genetics	106
8.7.	Biomarkers.....	107
8.8.	Immunogenicity Assessments.....	107
8.9.	Medical Resource Utilization and Health Economics	107
9.	Statistical Considerations.....	108
9.1.	Statistical Hypotheses	108
9.1.1.	Multiplicity Adjustment.....	108
9.2.	Analyses Sets	108
9.3.	Statistical Analyses	109
9.3.1.	General Considerations.....	109
9.3.2.	Treatment Group Comparability.....	111
9.3.3.	Primary Endpoint(s)/Estimand(s) Analysis	111

9.3.4.	Secondary Endpoint(s)/Estimand(s) Analysis	112
9.3.5.	Pharmacokinetic/Pharmacodynamic Analyses	112
9.3.6.	Safety Analyses.....	112
9.3.7.	Other Analyses.....	112
9.4.	Interim Analysis.....	113
9.5.	Sample Size Determination	113
10.	Supporting Documentation and Operational Considerations	114
10.1.	Appendix 1: Regulatory, Ethical, and Study Oversight Considerations	114
10.1.1.	Regulatory and Ethical Considerations.....	114
10.1.2.	Financial Disclosure.....	115
10.1.3.	Informed Consent Process	115
10.1.4.	Data Protection.....	115
10.1.5.	Committees Structure.....	116
10.1.6.	Dissemination of Clinical Study Data.....	116
10.1.7.	Data Quality Assurance	116
10.1.8.	Source Documents	118
10.1.9.	Study and Site Start and Closure	118
10.1.10.	Publication Policy	119
10.1.11.	Investigator Information	119
10.1.12.	Sample Retention	119
10.2.	Appendix 2: Clinical Laboratory Tests.....	120
10.2.1.	Laboratory Samples to be Obtained at the Time of a Systemic Hypersensitivity Event.....	123
10.3.	Appendix 3: Adverse Events and Serious Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow- up, and Reporting.....	124
10.3.1.	Definition of AE	124
10.3.2.	Definition of SAE	125
10.3.3.	Definition of Product Complaints.....	126
10.3.4.	Recording and Follow-Up of AE and/or SAE and Product Complaints	126
10.3.5.	Reporting of SAEs	128
10.3.6.	Regulatory Reporting Requirements.....	129
10.4.	Appendix 4: Contraceptive and Barrier Guidance.....	130
10.4.1.	Definitions.....	130
10.4.2.	Contraception Guidance.....	131
10.5.	Appendix 5: Genetics.....	133
10.6.	Appendix 6: Liver Safety: Suggested Actions and Follow-up Assessments	134
10.7.	Appendix 7: Measurement of Height, Weight, Waist Circumference, Vital Signs, Electrocardiogram, Computed Tomography.....	136
10.8.	Appendix 8: JASSO Guidelines	139
10.9.	Appendix 9: Prohibited Medications or Medications with Special Use Restrictions	140

10.9.1.	Excluded/Prohibited or Restricted Use Medications	140
10.9.2.	Medications with Special Use Restrictions.....	144
10.10.	Appendix 10: Definition and Management of Diabetes	146
10.11.	Appendix 11: Provisions for Changes in Study Conduct During Exceptional Circumstances.....	149
10.12.	Appendix 12: Abbreviations and Definitions	153
10.13.	Appendix 13: Protocol Amendment History	160
11.	References.....	163

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 Japanese Adult Participants with Obesity Disease (ATTAIN-J)

Brief Title: Efficacy and Safety of LY3502970 versus Placebo in Japanese Participants Who Have Obesity Disease (ATTAIN-J)

Regulatory Agency Identifier Number(s): Not applicable

Rationale:

Orforglipron is an oral non-peptide GLP-1 receptor agonist (GLP-1 RA) that is being developed as a daily oral adjunct therapy to diet and physical activity to improve weight management in adults who are obese or overweight with obesity-related comorbidities. Unlike the peptide GLP-1 receptor agonists approved by regulators to-date, orforglipron is a small molecule being developed for daily oral administration.

Study J2A-JE-GZPD (GZPD) is a multicenter, randomized, parallel-arm, double-blind, placebo controlled, Phase 3 study designed to investigate the effects of once daily oral treatment with 3 dose levels of orforglipron compared with once daily oral treatment with placebo when used in conjunction with a reduced calorie diet and increased physical activity for weight management, in Japanese participants with obesity disease with a body mass index (BMI) ≥ 27 kg/m² and < 35 kg/m² and at least 2 obesity-related health problems or with BMI ≥ 35 kg/m² and at least 1 obesity-related health problem according to the guidelines of the Japan Society for the Study of Obesity (JASSO) (JASSO 2022). At least one obesity-related health problem should be type 2 diabetes (T2D), hypertension, or dyslipidemia. Additionally, the study will compare the effects of orforglipron and placebo on glycemic control, blood pressure and lipid parameters.

The co-primary endpoints are the effect of orforglipron on percent change in body weight and proportion of participants who achieve $\geq 5\%$ body weight reduction.

Objectives, Endpoints, and Estimands:

Objectives	Endpoints
Primary	
To demonstrate that orforglipron 6 mg, 12 mg, and 36 mg QD is superior to placebo in change from baseline for: Body weight	From baseline to Week 72 - Mean percent change in body weight - Percentage of participants who achieve $\geq 5\%$ body weight reduction

Secondary	
To demonstrate that orforglipron 6 mg, 12 mg, and 36 mg QD is superior to placebo in change from baseline for the following: • Body weight • Improvement of comorbidities	From baseline to Week 72 • Percentage of participants who achieve: ○ $\geq 7\%$ body weight reduction ○ $\geq 10\%$ body weight reduction ○ $\geq 15\%$ body weight reduction ○ $\geq 20\%$ body weight reduction • Mean change in: ○ Body weight (kg) ○ BMI (kg/m^2) • Percentage of participants who had improvements in: ○ Hypertension (only for participants with hypertension at baseline) ○ Dyslipidemia (only for participants with dyslipidemia at baseline) ○ T2D ($<6.5\%$ [48 mmol/mol] in HbA1c) (only T2D at baseline) • Percentage of participants who achieve HbA1c target value at Week 72 (only T2D at baseline): ○ $<7.0\%$ (53 mmol/mol) ○ $<5.7\%$ (39 mmol/mol) • Change in anti-hypertensive medication (decrease, no change, increase) (only hypertension at baseline) • Change in lipid-lowering medication (decrease, no change, increase) (only dyslipidemia at baseline) • Change in concomitant oral anti-glycemic medication (decrease, no change, increase) (only T2D at baseline) • Change in glycemic category (normo-glycemia, borderline type-diabetes, T2D) • Proportion of participants who achieved the following number of improvements of obesity-related health problems (hypertension, dyslipidemia, and T2D) at Week 72 from baseline, regardless of BMI at baseline

VAT and SAT in CT subgroups	- Achieved 0, 1, 2 or 3 improvements (only for participants with 3 obesity-related health problems) - Achieved 0, 1 or 2 improvements (only for participants with 2 obesity-related health problems) - Achieved 0 or 1 improvements (only for participants with 1 obesity-related health problems) - Mean change in - VAT (cm²) - SAT (cm²) - VAT/SAT ratio - Percentage of participants who achieve VAT <100 cm² (only for participants with VAT ≥100 cm² at baseline)
To demonstrate that orforglipron 6 mg, 12 mg, and 36 mg QD is superior to placebo in change from baseline for the following: - Waist circumference - Blood pressure in overall and hypertension at baseline - Lipid in overall and dyslipidemia at baseline - Glycemic control in overall and T2D at baseline	From baseline to Week 72 - Mean change in waist circumference at umbilical level (cm) - Mean change in: - Systolic BP (mmHg) - Diastolic BP (mmHg) - Mean change in: - Total cholesterol (mg/dL) - Non-HDL cholesterol (mg/dL) - Triglyceride (mg/dL) - LDL cholesterol (mg/dL) - HDL cholesterol (mg/dL) - VLDL cholesterol (mg/dL) - Free fatty acid (mg/dL, mEq/L) - Mean change in: - Fasting blood glucose (mg/dL) - HbA1c (%, mmol/mol) - Fasting insulin (mg/dL, pmol/L) - Fasting C-peptide (mg/dL) - Mean change in (only T2D at baseline) 7-point SMBG

• Biomarkers • Patient reported outcomes	• Mean change in: ○ High-sensitivity C-reactive protein (hsCRP) (mg/L) ○ Uric acid (mg/dL) ○ UACR (mg/gCre) ○ eGFR (mL/min/1.73 m²) • 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 score • Mean change in PGI-S and PGI-C limitations on physical function due to weight score
To demonstrate orforglipron (6 mg, 12 mg, and 36 mg QD pooled dose) is superior to placebo for the following: • Body weight • Improvement of comorbidities	From baseline to Week 72 • Percentage of participants who achieve: ○ BMI <25 kg/m² ○ BMI <27 kg/m² • Percentage of participants who had improvements in: ○ Hypertension (only for participants with hypertension at baseline) ○ Dyslipidemia (only for participants with dyslipidemia at baseline) ○ T2D (<6.5% [48 mmol/mol] in HbA1c) (only T2D at baseline) • Change in anti-hypertensive medication (decrease, no change, increase) (only hypertension at baseline) • Change in lipid-lowering medication (decrease, no change, increase) (only dyslipidemia at baseline) • Change in concomitant oral anti-glycemic medication (decrease, no change, increase) (only T2D at baseline) • Change in glycemic category (normo-glycemia, borderline type-diabetes, T2D)

	- Proportion of participants who achieved the following number of improvements of obesity-related health problems (hypertension, dyslipidemia, and T2D) at Week 72 from baseline, regardless of BMI at baseline - Achieved 0, 1, 2 or 3 improvements (only for participants with 3 obesity-related health problems) - Achieved 0, 1 or 2 improvements (only for participants with 2 obesity-related health problems) - Achieved 0 or 1 improvements (only for participants with 1 obesity-related health problems)
To demonstrate orforglipron (6 mg, 12 mg, and 36 mg QD pooled dose) is superior to placebo in change from baseline for the following: - Biomarkers - Glycemic control (only T2D at baseline) - Delayed progression to T2D - Patient reported outcomes	From baseline to Week 72 - Mean change in: - Adiponectin ($\mu\text{g/dL}$) (both high molecular weight and total adiponectin) - Leptin (ng/dL) - UACR (mg/gCre) - eGFR (mL/min/1.73 m^2) - Mean change in: - HOMA2-IR - HOMA2-B - Time to onset of T2D (only nonT2D at baseline) - Mean change in SF-36v2 acute form scores: - physical functioning - role-physical score - bodily pain score - general health score - vitality score - social functioning score - role-emotional score - mental health score - physical component summary - mental component summary - Mean change in IWQOL-Lite-CT scores: - physical function score

	○ physical score ○ psychosocial score ○ total score • Mean change in PGI-C and PGI-S scores: ○ Shift of the ordinal response category • Mean change in PROMIS Short Form Sleep Disturbance 8b score from baseline
To characterize the population PK of orforglipron	• Population PK parameters
Exploratory	
To explore the relationships between orforglipron concentration and efficacy, safety, and tolerability measures	• Population PD parameters

Abbreviations: BMI = body mass index; BP = blood pressure; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CT = computerized tomography; eGFR = estimated glomerular filtration rate (calculated by Japanese Society of Nephrology coefficient-modified CKD-EPI equation); EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; HbA1c = hemoglobin A1c; HDL = high density lipoprotein cholesterol; HOMA2-B = homeostasis model assessment estimates steady state beta cell function; HOMA2-IR = homeostasis model assessment estimates insulin resistance beta cell function; hsCRP = high-sensitivity C-reactive protein IWQOL-Lite-CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; LDL = low density lipoprotein; PD = pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Status; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily; SF 36v2 = Short-Form 36-item Health Survey Version 2; SMBG = self-monitoring of blood glucose SAT = subcutaneous adipose tissue; T2D = type 2 diabetes; UACR = urine albumin/creatinine ratio; VAT = visceral adipose tissue; VAS = visual analogue scale; VLDL = very low density lipoprotein.

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 and percentage of participants who achieve 5% or more body weight reduction from baseline at 72 weeks between orforglipron 6 mg, 12 mg, 36 mg and placebo, as an adjunct to healthy diet and physical activity, in participants who meet the eligibility criteria regardless of adherence to study intervention or initiation of prohibited weight management treatments?

Overall Design:

ATTAIN-J (study GZPD) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled study. The study will investigate the efficacy and safety of treatment with daily oral doses of orforglipron (6 mg, 12 mg, and 36 mg) compared with placebo when used in conjunction with a reduced calorie diet and increased physical activity for weight management, in Japanese participants with a BMI ≥ 27 kg/m² and < 35 kg/m² and at least 2 obesity-related health problems (treated or untreated), OR a BMI ≥ 35 kg/m² and at least 1 obesity-related health

problem (treated or untreated). At least 1 obesity-related health problem should be hypertension, dyslipidemia or T2D (approximately 25% of participants).

The study population will be enriched for participants who do not have T2D so that approximately 75% of the total study population will consist of participants without T2D.

Study participants will be randomized in a 1:1:1:1 ratio to once daily oral treatment with 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.

Brief Summary:

The purpose of this study is to measure the change in body weight with oral daily doses of orforglipron compared with placebo in participants with obesity disease.

Study details include:

- All participants will undergo a 3-week screening period.
- The treatment duration will be up to 72 weeks (including 20 weeks of dose escalation).
- The safety follow-up period will be 2 weeks.
- The visit frequency will be every 4 weeks (including telephone visits).

Study Population:

The study will include Japanese participants who have a BMI ≥ 27 kg/m² and less than 35 kg/m², and at least 2 obesity-related health problems (treated or untreated), OR a BMI ≥ 35 kg/m² and at least 1 obesity-related health problem (treated or untreated). At least one obesity-related health problem should be hypertension, dyslipidemia or T2D (approximately 25% of participants).

Number of Participants:

Approximately 236 participants (59 per treatment group) will be randomized to provide more than 80% power to demonstrate superiority of 6 mg, 12 mg, and/or 36 mg orforglipron compared to placebo in percentage of participants achieving at least 5% body weight reduction from baseline to Week 72. An upper limit of 70% enrollment of females will be used to ensure a sufficiently large sample of males.

Intervention Groups and Duration:

The study interventions are orforglipron at 6 mg, 12 mg, or 36 mg, or placebo administered orally once daily. Study participants will be randomized in a 1:1:1:1 ratio to once daily oral treatment with orforglipron 6 mg, 12 mg, or 36 mg or placebo.

Ethical Considerations of Benefit/Risk:

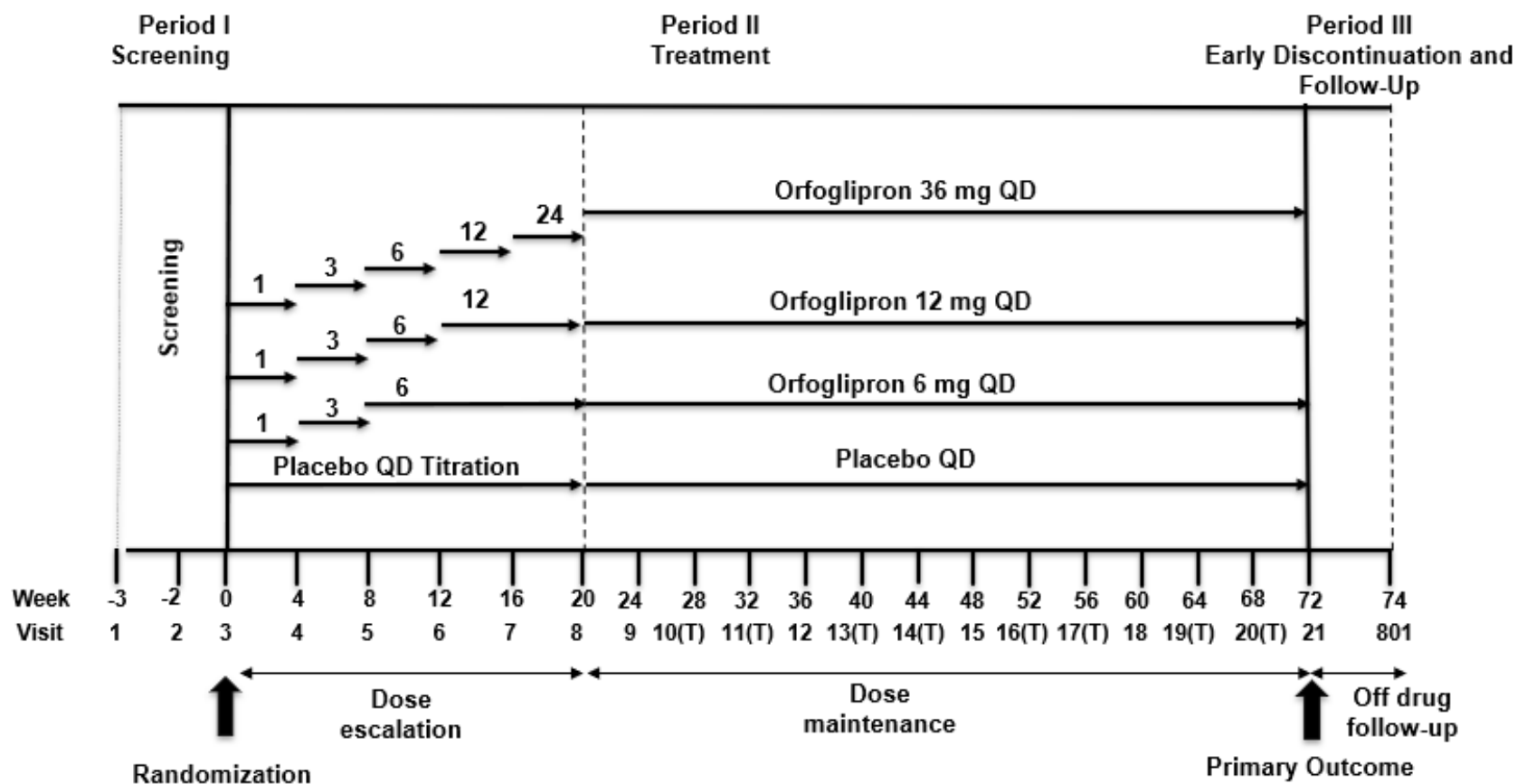
The safety and efficacy profile seen to date for orforglipron supports the overall benefit risk for participants in this study. The anticipated risks are those associated with known pharmacologic effects of GLP-1 receptor agonists, namely gastrointestinal tolerability issues and increased heart rate.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

those related to GLP-1 receptor agonism. GLP-1 receptor agonists have generally been associated with reduced risk of cardiovascular (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 disease.

Data Monitoring Committee: No

1.2. Schema



Abbreviations: QD= once daily; T= telephone visit.

1.3. Schedule of Activities

The Schedule of Activities (SoA) described below should be followed for all participants enrolled in ATTAJN-J (Study J2A-JE-GZPD). However, for those participants whose participation in this study is affected by exceptional circumstances, such as pandemics, or natural disasters, please refer to Section 10.11 for additional guidance.

Screening

All screening activities must 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, participants must return on another day in the fasted state, to complete all procedures that require fasting.

Fasting Visits

On all office visits, study participants should be reminded to report to the site before taking study intervention (s) in a fasting condition, after a period of approximately 8 hours without eating or drinking (except water). Study participants with T2D should not take any antihyperglycemic medications (AHMs) prior to the office visits.

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

Treatment Period

Eligible participants will be assigned to 72 weeks of treatment at randomization.

Early Discontinuation (ED)

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

Post-Treatment Follow-up

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

Telehealth visits

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

Table 1. Period I - Screening Period

	Period I – Screening Period		Comments
Visit Number	1	2	
Weeks from randomization	-3	-2	
Visit interval tolerance (days)		±3	
Fasting Visit	X	X	
Visit Details			
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	Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention. Review and confirm if T2D or non-T2D (borderline and normoglycemia).
Demographics	X		Includes year of birth and sex
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		
Prior treatments for indication	X		Includes prior weight management medications.
Concomitant medications	X	X	
Obesity disease assessment	X		Eleven of obesity-related health problems defined by JASSO will be utilized (Appendix 8, Section 10.8).
Adverse events (AEs)	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.

	Period I – Screening Period		Comments
Visit Number	1	2	
Weeks from randomization	-3	-2	
Visit interval tolerance (days)		±3	
Fasting Visit	X	X	
Visit Details			
Physical Evaluation			
Height	X		
Weight	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.
Vital signs	X	X	Includes pulse rate and blood pressure. Measured in triplicate after participant has been sitting at least 5 min. See protocol Sections 8.2.2 and 10.7.
Dilated Fundoscopic Examination		X	Perform for T2D participants at baseline who have not had an evaluable dilated fundoscopic examination performed by an ophthalmologist or optometrist within 90 days of Visit 1. See exclusion criterion 9 (Section 5.2). The screening period can be extended for the diagnosis of T2D. Follow-up dilated fundoscopic examination will be performed per the study schedule, or when clinically indicated by any AE suspected of worsening retinopathy. See Section 8.2.9.
Physical examination	X		A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems, as well as a thyroid exam.
Symptom-direct physical assessment		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.

	Period I – Screening Period		Comments
Visit Number	1	2	
Weeks from randomization	-3	-2	
Visit interval tolerance (days)		±3	
Fasting Visit	X	X	
Visit Details			
Participant Diary (Electronic)			
Dispense Diary (electronic device)		X	Includes hypoglycemia, daily study intervention dose, BG, and 7-point SMBG. All training should be repeated as needed to encourage participant compliance.
Remind participants about 7-point SMBG		X	Participant with T2D at baseline is required to collect two 7-point SMBGs on non-consecutive days within 2 weeks prior to Visit 3. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime.
Patient-Reported Outcomes (Electronic) <i>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.</i>			
PHQ-9	X		PHQ-9 is self-administered and should be completed <u>after</u> assessment of adverse events. This should be conducted with the safety assessments.
Clinician-Administered Assessments (Paper)			
C-SSRS Screening/Baseline	X		The C-SSRS should be administered <u>after</u> 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.
Participant Education			
Diabetes Education (includes BG meter dispensing and SMBG training)		X	For participants with T2D at baseline, diabetes education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, and diabetes management. Participants are

	Period I – Screening Period		Comments
Visit Number	1	2	
Weeks from randomization	-3	-2	
Visit interval tolerance (days)		±3	
Fasting Visit	X	X	
Visit Details			
			required to measure fasting SMBG values weekly and record them in the study diary. It is recommended that participants measure their fasting glucose on the same day each week. All trainings should be repeated as needed to ensure participant compliance. Non-T2D participants at baseline who develop diabetes during the study will be followed (see Section 10.10).
CT			
Visceral and subcutaneous adipose tissue imaging		X	CT will be done in about 40% of total participants. Image analysis to be conducted centrally.
Laboratory Tests and Sample Collections			
Hematology	X		
Hemoglobin A1c (HbA1c)	X	X	
Clinical Chemistry (include Cr for eGFR calculation and glucose)	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.
Lipid panel	X		Lipid panels must be obtained in the fasting state.
Serum pregnancy	X		Collect for WOCBP. See Section 10.40.

	Period I – Screening Period		Comments
Visit Number	1	2	
Weeks from randomization	-3	-2	
Visit interval tolerance (days)		±3	
Fasting Visit	X	X	
Visit Details			
Follicle Stimulating Hormone (FSH)	X		Perform as needed to confirm postmenopausal status. Definition in Section 10.4.
Thyroid Stimulating Hormone (TSH)	X		
Calcitonin	X		
Pancreatic amylase	X		
Lipase	X		
Cystatin-C	X		
Hepatitis C Screening	X		For participants who are positive for HCV antibody, a follow-up test for HCV RNA will be performed automatically. Participants who are positive for HCV antibody and negative for HCV RNA may be enrolled.
Hepatitis B Screening	X		For participants who are positive for HBcAb, testing for HBV DNA will be performed automatically. Participants who are positive for HBcAb and negative for HBV DNA may be enrolled.
Estimated glomerular filtration rate (eGFR)	X		Calculated by Japanese Society of Nephrology coefficient-modified Chronic Kidney Disease - Epidemiology equation.

	Period I – Screening Period		Comments
Visit Number	1	2	
Weeks from randomization	-3	-2	
Visit interval tolerance (days)		±3	
Fasting Visit	X	X	
Visit Details			
Randomization and Dosing			
Urinary albumin/creatinine ratio (UACR)	X		
Register visit with IWRS	X	X	

Abbreviations: BG = blood glucose; Cr = creatinine; C-SSRS = Columbia-Suicide Severity Rating Scale; ECG = electrocardiogram; ED = early discontinuation; eGFR = estimated glomerular filtration rate; HbA1c = glycated hemoglobin; HBcAB = hepatitis B core antibody; HBV = hepatitis B virus; HCV = hepatitis C virus; IWRS = interactive web response system; PHQ-9 = Patient Health Questionnaire; PI = principal investigator; PK = pharmacokinetics; PR = pulse rate; SMBG = self-monitoring of blood glucose; T2D = type 2 diabetes; wks = weeks; WOCBP = women of childbearing potential.

Table 2. Period II - Treatment Period

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
Inclusion and exclusion criteria, review and confirm	X																			Confirm inclusion and exclusion criteria prior to randomization and administration of first dose of study intervention.	
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		
Assess medication intensity (dyslipidemia, hypertension, hyperglycemia)				X			X			X			X			X			X		
Adverse events (AEs)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	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.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	See Sections 8.2.1 and 10.7.	
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 at least 5 min. See protocol Sections 8.2.2 and 10.7.	
Dilated Fundoscopic Examination																			X	Perform for T2D participants at baseline. Follow-up dilated fundoscopic examination will be performed per the study schedule, or when clinically indicated by any AE suspected of worsening retinopathy. See Section 8.2.9.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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 examination																			X		
12-lead ECG (Central)	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 10.7.	
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		
Remind participants about 7-point SMBG						X												X		Participant with T2D at baseline is required to collect two 7-point SMBGs on non-consecutive days within 2 weeks prior to the next visit. A 7-point SMBG consists of measurements before and 2 hours after each of 3 main meals within the same day and at bedtime.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
Record 7-point SMBG	X						X												X	Only for participants with T2D at baseline. Participants without T2D at baseline who develop diabetes during the study will follow “Management of Incident Diabetes” (see Section 10.10).	
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		
Patient Global Impression of Status-Physical Function Weight (PGI-S)	X						X												X		
Patient Global Impression of Change-Physical Function Weight (PGI-C)							X												X		

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
EQ-5D-5L	X						X												X		
PROMIS Short Form Sleep Disturbance 8b	X						X												X		
PHQ-9	X			X			X			X			X			X			X	PHQ-9 is self-administered and should be completed after assessment of adverse events. 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 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.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	Counselling on diet and exercise, to be performed by a dietitian or equivalent qualified delegate, to include dietary composition and amount of physical activity. The Lifestyle Program instruction may be delivered on a separate day from the rest of that visit’s study procedures but must occur within the visit window. Beginning at Week 8, the consultation may be delivered by telehealth. Refer to Section 5.3.	
Review diet and exercise goals	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	All training should be repeated as needed to ensure participant compliance. Study personnel to provide reinforcement and encouragement for lifestyle modifications.	
Dispense BG meter/supplies as needed	X	X	X	X	X	X	X			X			X			X			X	Only for participants with T2D at baseline. If participants without T2D at baseline who develop diabetes during the study will follow “Management of Incident Diabetes” in Section 10.10.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
CT																					
Visceral and subcutaneous adipose tissue imaging																			X	CT will be done in about 40% of total participants. Image analysis to be conducted centrally.	
Laboratory Tests and Sample Collections																					
Hematology				X			X												X		
Hemoglobin A1c (HbA1c)	X			X			X			X			X			X			X		
Clinical Chemistry (include Cr for eGFR calculation and glucose)	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.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
Lipid panel	X						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.	
High sensitivity C-Reactive Protein (hsCRP)	X						X						X						X		
Urine pregnancy (local)	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	
Insulin	X						X			X			X			X			X		
C-peptide	X						X			X			X			X			X		

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
Calcitonin				X			X												X		
Pancreatic Amylase				X			X												X		
Lipase				X			X												X		
Free Fatty Acids	X						X			X			X			X			X		
Cystatin-C	X			X			X			X			X			X			X		
Adiponectin (high molecular weight and total) and Leptin	X						X						X						X		
PK Samples			X		X		X			X			X							PK samples will be collected from participants at these visits: pre-dose (Weeks 8, 24, 48), post-dose 4 to 12 hours (Week 16) and post-dose 1 to 4 hours (Week 36). Participants may be required to come to site for PK specific visits for post-dose samples.	

	Period II - Treatment Period																				Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72		
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).	
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	
Estimated glomerular filtration rate (eGFR)	X			X			X			X			X			X			X	Calculated by Japanese Society of Nephrology coefficient-modified Chronic Kidney Disease - Epidemiology equation	
Urinary albumin/creatinine ratio (UACR)	X			X			X			X			X			X			X		
Stored Samples																					
Genetics sample	X																			Sample can be obtained at or after the specified visit.	
Exploratory biomarker samples	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		

	Period II - Treatment Period																			Comments
Visit Number	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	
Weeks from randomization	0	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	
Visit interval tolerance (days)	±7	±3	±3	±3	±3	±3	±3	±3	±3	±7	±3	±3	±7	±3	±3	±7	±3	±3	±7	The visit date after randomization visit (except for Visit 801) is determined in relation to the date of the randomization visit (± the allowed visit window).
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
Randomization via IWRS	X																			
Dispense Study Intervention via IWRS	X	X	X	X	X	X	X			X			X			X				
Dispense study intervention to participant	X	X	X	X	X	X	X			X			X			X				
Participant returns study intervention		X	X	X	X	X	X			X			X			X			X	
Assess study intervention compliance		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

Abbreviations: BG = blood glucose; BP = blood pressure; Cr = creatinine; C-SSRS = Columbia-Suicide Severity Rating Scale; CT = computerized tomography; ECG = electrocardiogram; ED = early discontinuation; IWRS = interactive web response system; PHQ-9 = Patient Health Questionnaire; PI = principal investigator; PK = pharmacokinetics; PR = pulse rate; SMBG = self-monitoring of blood glucose; wks = weeks.

Table 3. Period III - Early Discontinuation and Follow-Up Period

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Concomitant medications	X	X	
Assess medication intensity (dyslipidemia, hypertension, hyperglycemia)	X		
Adverse events (AEs)	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	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	

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Vital signs	X	X	Includes pulse rate and blood pressure. Measured in triplicate after participant has been sitting at least 5 min. See protocol Sections 8.2.2 and 10.7.
Dilated Fundoscopic Examination	X		Perform for T2D participants at baseline. Follow-up dilated fundoscopic examination will be performed per the study schedule, or when clinically indicated by any AE suspected of worsening retinopathy. See Protocol Section 8.2.9.
Physical examination	X		
Symptom-direct physical assessment		X	Symptom-directed physical assessment may be conducted at the discretion of the PI or qualified personnel as indicated per local regulations based on participant status and standard of care.
12-lead ECG (Central)	X	X	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 10.7.

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Participant Diary (Electronic)			
Diary Review (electronic)	X	X	
Diary return (electronic)		X	
Patient-Reported Outcomes (Electronic) <i>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.</i>			
SF-36v2 acute form	X		
IWQOL-Lite CT	X		
Patient Global Impression of Status-Physical Function Weight (PGI-S)	X		

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Patient Global Impression of Change-Physical Function Weight (PGI-C)	X		
EQ-5D-5L	X		
PROMIS Short Form Sleep Disturbance 8b	X		
PHQ-9	X	X	PHQ-9 is self-administered and should be completed after assessment of adverse events. This should be conducted with the safety assessments.
Clinician-Administered Assessments (Paper)			
C-SSRS Since Last Assessed	X	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.

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Participant Education			
Lifestyle Program instructions	X		Counselling on diet and exercise, to be performed by a dietitian or equivalent qualified delegate, to include dietary composition and amount of physical activity. The Lifestyle Program instruction may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window. Beginning at Week 8, the consultation may be delivered by telehealth. Refer to Section 5.3.
Review diet and exercise goals	X		All training should be repeated as needed to ensure participant compliance. Study personnel to provide reinforcement and encouragement for lifestyle modifications.
Dispense BG meter/supplies as needed	X		Only for participants with T2D at baseline. If participants without T2D at baseline who develop diabetes during the study will follow "Management of incident diabetes" in Section 10.10.
CT			
Visceral and subcutaneous adipose tissue imaging	X		CT will be done in about 40% of total participants. Image analysis to be conducted centrally. At ED visit, CT should only be performed on participants who have had at least 9 months (36 weeks) study intervention exposure; for those participants, the procedures should be done within 2 weeks (+2 weeks) as much as possible of the last dose of study intervention.

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Laboratory Tests and Sample Collections			
Hematology	X	X	
Hemoglobin A1c (HbA1c)	X	X	
Clinical Chemistry (include Cr for eGFR calculation and glucose)	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 are elevated (participants with normal baseline: ALT or AST ≥ 3 x ULN; participants with elevated baseline: ≥ 2 x baseline), then repeat 2 weeks later.

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Lipid panel	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.
High sensitivity C-Reactive Protein (hsCRP)	X		
Insulin	X		
C-peptide	X		
Calcitonin	X	X	
Pancreatic Amylase	X	X	
Lipase	X	X	

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Free Fatty Acids	X	X	
Cystatin-C	X	X	
Adiponectin (high molecular weight and total) and Leptin	X		
PK Samples	X		PK samples will be collected from participants at an ED visit.
Estimated glomerular filtration rate (eGFR)	X	X	Calculated by Japanese Society of Nephrology coefficient-modified Chronic Kidney Disease-Epidemiology equation
Urinary albumin/creatinine ratio (UACR)	X	X	
Stored Samples			
Exploratory biomarker samples	X	X	

	Period III - Early Discontinuation and Follow-Up Period		Comments
Visit Number	ED	801	
Weeks from randomization		2 wks post end of TxP	For participants who discontinue the study within 72 weeks, Visit 801 (safety follow-up visit) should be performed 2 weeks after ED visit. For participants who complete the study including study treatment discontinuation, Visit 801 (safety follow-up visit) should be performed 2 weeks after Visit 21.
Visit interval tolerance (days)		± 3	The visit date of visit 801 is determined in relation to the date of the ED visit or Visit 21 ($\pm$ the allowed visit window).
Fasting Visit	X	X	
Visit Details			
Randomization and Dosing			
Register visit with IWRS	X	X	
Participant returns study intervention	X		
Assess study intervention compliance	X		

Abbreviations: BG = blood glucose; BP = blood pressure; Cr = creatinine; C-SSRS = Columbia-Suicide Severity Rating Scale; CT = computerized tomography; ECG = electrocardiogram; ED = early discontinuation; WOCBP = women of childbearing potential; IWRS = interactive web response system; PHQ-9 = Patient Health Questionnaire; PI = principal investigator; PK = pharmacokinetics; PR = pulse rate; SMBG = self-monitoring of blood glucose; T2D = Type 2 Diabetes; Tx = treatment; TxP = treatment period; wks = weeks.

2. Introduction

Glucagon-like peptide 1 (GLP-1) receptor agonism is an established therapeutic mechanism for weight management in individuals with obesity or overweight, as well as glycemic control in type 2 diabetes (T2D). Unlike injectable or orally available peptide GLP-1 receptor agonists (GLP-1 RA) approved by regulatory authorities to date, orforglipron is an oral, small molecule GLP-1 RA.

Orforglipron is being developed both 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.

Thus, orforglipron has potential to achieve to the objective required for medical therapy on obesity disease in the guidelines by the Japan Society for the Study of Obesity (JASSO), which suggests accelerating weight loss safely, leading to improvement in complications of obesity, and to suppress the combined use of multiple drugs in patients who have difficulty achieving weight loss goals by individual efforts alone.

2.1. Study Rationale

ATTAIN-J (Study GZPD) is designed to provide substantial evidence of safety and efficacy of orforglipron for the obesity disease indication.

In Japan, body mass index (BMI) ≥ 25 kg/m² is defined as obesity, and “obesity disease” is defined as obesity-related health problems medically requiring weight loss (Matsuzawa 2011). Drug treatment of obesity disease is required in participants with a BMI ≥ 25 kg/m² and < 35 kg/m² and at least 2 obesity-related health problems, or a BMI ≥ 35 kg/m² and at least 1 obesity-related health problem according to the JASSO guideline. The guideline defined 11 obesity-related health problems. In particular, 3 metabolic disorders in the obesity-related health problems (glucose tolerance disorders, hypertension, and dyslipidemia) are located upstream of the metabolic syndrome (Ito 2003) and promote the onset and progression of complications.

ATTAIN-J (Study GZPD) is a multicenter, randomized, parallel-arm, double-blind, placebo controlled, Phase 3 study designed to investigate the effects of once daily oral treatment with 6 mg, 12 mg, and 36 mg of orforglipron compared with once daily oral treatment with placebo when used in conjunction with a reduced calorie diet and increased physical activity for weight management, in Japanese participants who have obesity (BMI ≥ 27 kg/m²) with obesity-related health problems (either T2D, hypertension or dyslipidemia). Additionally, the study will compare the effects of orforglipron and placebo on glycemic control, blood pressure, and lipid parameters.

The co-primary endpoints will be the effect of orforglipron on percent change in body weight and proportion of participants who achieve $\geq 5\%$ body weight reduction.

2.2. Background

Obesity Disease

Obesity is a chronic disease, and its increasing prevalence is a public health concern associated with rising incidence of T2D, increased risk for premature death, and increased risk for some

cancers (AMA 2013; CSAPH 2013; Lauby-Secretan et al. 2016).

In Japan, if obesity disease is diagnosed, the patients try lifestyle intervention including diet, exercise, and behavioral therapy for 3 to 6 months to improve body weight and obesity-related health problems. If improvement of the health problems is achieved by lifestyle modification therapy, the therapy is continued. If not, and any of following criteria are met: 1) BMI ≥ 25 kg/m², visceral fat area ≥ 100 cm² and/or 2 or more health problems, 2) BMI ≥ 35 kg/m² with 1 or more health problems, medical therapy is indicated. There remains an unmet need in the pharmacologic treatment of obesity disease for drugs that are safe, efficacious, and well tolerated. At present in Japan, Sanorex[®] (mazindol) is covered only for patients with severe obesity disease by national health insurance with a prescription limit of 3 months or less. Chinese herbal medicines are also available and Alli[®] (orlistat) will be launched in 2023 as a non-prescription over-the-counter medicine.

Bariatric surgery is also approved for patients with severe obesity disease, but only laparoscopic sleeve gastrectomy is covered by national health insurance and some facilities implement laparoscopic sleeve gastrectomy with duodenojejunal bypass as an advanced medical treatment (JSTO 2013). Weight loss induced by GLP-1 RAs appears to be mediated through a combination of hormonal inputs to satiety centers (van Bloemendaal et al. 2014) and has not been consistently associated with changes in mental health or with potential for addiction in long term studies conducted to establish cardiovascular (CV) safety in patients with diabetes (Marso et al. 2016a; Marso et al. 2016b; Gerstein et al. 2019).

GLP-1 RA Therapy

The GLP-1 RAs have demonstrated beneficial effects on weight management (Frias et al. 2018; Newsome et al. 2019). Furthermore, liraglutide and semaglutide (SAXENDA[®] package insert, 2022; WEGOVY[®] package insert, 2021 [in the US]), both injectable peptide GLP-1 RAs, have been shown to be safe and effective for weight management and have established cardiovascular safety.

Although the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) approved the GLP-1 RA liraglutide for the treatment of individuals who are overweight or obese (SAXENDA[®] package insert, 2014; SAXENDA[®] SmPc, 2015), this drug is not approved in Japan. Moreover, the FDA approved semaglutide injection (2.4 mg once weekly) for chronic weight management in adults with obesity or overweight with at least one weight-related condition (such as hypertension, T2D, or dyslipidemia), for use in addition to a reduced calorie diet and increased physical activity (WEGOVY[®] package insert, 2021) and it has been submitted to the Japanese authorities and expected to be approved in Japan in 2023.

To expand treatment options for obesity disease, Lilly is developing orforglipron, an oral non-peptide GLP-1 RA that has been shown in Phase 2 studies to reduce body weight in addition to improved glycemic control, blood pressure, and lipid parameters for participants with obesity or overweight with and without T2D.

Epidemiology Studies

The proportion of obesity (BMI ≥ 25 kg/m²) among Japanese aged 20 years and older is estimated to be 33.0% for male and 22.3% for female, whereas the proportion with BMI ≥ 30 kg/m² is estimated to be 5.3% for male and 3.6% for female. Since 2013, there has

been a significant increase in male, and no significant change in female (MHLW 2015). Although Japan is characterized by a low rate of severe obesity, it has been reported that even mild obesity is more likely to lead to health problems in Japanese than in Westerners (Gill 2001, Kanazawa et al. 2005, Azuma et al. 2009).

The ongoing global obesity epidemic increases the incidence of obesity-related health problems such as T2D, hyperlipidaemia and hypertension, resulting in an increased risk of microvascular and macrovascular complications in individuals with these conditions.

Clinical Data for Orforglipron

A detailed description of the chemistry, pharmacology, efficacy, and safety of orforglipron is provided in the Investigator's Brochure (IB).

Phase 1

The clinical pharmacology, pharmacokinetics (PK), and pharmacodynamics (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 RA class, gastrointestinal (GI) adverse events (AEs) of nausea, vomiting, and constipation were the most reported AEs. PD results from Study GZGC showed clinically relevant improvements in glycated hemoglobin (HbA1c) of up to -1.4%, and weight change of up to -5.8 kg after 12 weeks of treatment with an orforglipron dose of 9 mg once daily (QD) to 45 mg QD in people with T2D.

Japan Phase 1

In the ongoing single-dose and 12-week multiple-dose Study J2A-JE-GZGB (GZGB), a total of 62 Japanese participants with T2D have received either orforglipron (up to 45 mg) or placebo. No serious adverse events (SAEs) were reported. All tested orforglipron doses were tolerated in this study. GI AEs (nausea, vomiting, and constipation) and decreased appetite were the most frequently reported events. These AEs were mostly mild in severity and the majority resolved without treatment. Also, most of the GI AEs occurred during the first week of dosing or early stage of dose escalation. There have been no reports of severe hypoglycemia in this study. There were statistically significant reductions in fasting glucose, HbA1c, and body weight with orforglipron compared to placebo in Study GZGB.

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 obesity-related comorbidity.

In Study GZGE, orforglipron treatment for 26 weeks at 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 RA class, with most common treatment-emergent adverse events (TEAEs) being GI-related (nausea, vomiting, diarrhea and constipation). Data from these Phase 2 studies supported 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 RAs. 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.

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

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

Management of Risks

Sections [5.1](#), [5.2](#), and [8.2](#) address mitigation, management, and monitoring of the known potential risks associated with orforglipron.

Study Procedure for Retinopathy Assessment

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

2.3.2. Benefit Assessment

The known pharmacology of GLP-1 receptor agonism and Phase 2 studies of orforglipron support an expectation of such benefits as body weight reduction and improved glycemic control 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 RAs, 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. GLP-1 RAs have generally been associated with reduced risk of CV events in people with T2D (Giugliano et al. 2021).

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

3. Objectives, Endpoints, and Estimands

Objectives	Endpoints
Primary	
To demonstrate that orforglipron 6 mg, 12 mg, and 36 mg QD is superior to placebo in change from baseline for: • Body weight	From baseline to Week 72 • Mean percent change in body weight • Percentage of participants who achieve $\geq 5\%$ body weight reduction
Secondary	
To demonstrate that orforglipron 6 mg, 12 mg, and 36 mg QD is superior to placebo in change from baseline for the following: • Body weight • Improvement of comorbidities	From baseline to Week 72 • Percentage of participants who achieve weight reduction of: ○ $\geq 7\%$ body weight reduction ○ $\geq 10\%$ body weight reduction ○ $\geq 15\%$ body weight reduction ○ $\geq 20\%$ body weight reduction • Mean change in: ○ Body weight (kg) ○ BMI (kg/m^2) • Percentage of participants who had improvements in: ○ Hypertension (only for participants with hypertension at baseline) ○ Dyslipidemia (only for participants with dyslipidemia at baseline) ○ T2D ($<6.5\%$ [48 mmol/mol]) in HbA1c (only T2D at baseline) • Percentage of participants who achieve HbA1c target value at Week 72 (only T2D at baseline): ○ $<7.0\%$ (53 mmol/mol) ○ $<5.7\%$ (39 mmol/mol) • Change in anti-hypertensive medication (decrease, no change, increase) (only hypertension at baseline)

• VAT and SAT in CT subgroups	• Change in lipid-lowering medication (decrease, no change, increase) (only dyslipidemia at baseline) • Change in concomitant oral anti-glycemic medication (decrease, no change, increase) (only T2D at baseline) • Change in glycemic category (normo-glycemia, borderline type-diabetes, T2D) • Proportion of participants who achieved the following number of improvements of obesity-related health problems (hypertension, dyslipidemia, and T2D) at Week 72 from baseline, regardless of BMI at baseline ○ Achieved 0, 1, 2 or 3 improvements (only for participants with 3 obesity-related health problems) ○ Achieved 0, 1 or 2 improvements (only for participants with 2 obesity-related health problems) ○ Achieved 0 or 1 improvements (only for participants with 1 obesity-related health problem) • Mean change in ○ VAT (cm²) ○ SAT (cm²) ○ VAT/SAT ratio • Percentage of participants who achieve VAT <100 cm² (only for participants with VAT ≥100 cm² at baseline)
To demonstrate that orforglipron 6 mg, 12 mg, and 36 mg QD is superior to placebo in change from baseline for the following: • Waist circumference • Blood pressure in overall and hypertension at baseline • Lipid in overall and dyslipidemia at baseline	From baseline to Week 72 • Mean change in waist circumference at umbilical level (cm) • Mean change in: ○ Systolic BP (mmHg) ○ Diastolic BP (mmHg) • Mean change in: ○ Total cholesterol (mg/dL) ○ Non-HDL cholesterol (mg/dL)

• Glycemic control in overall and T2D at baseline • Biomarkers • Patient reported outcomes	○ Triglyceride (mg/dL) ○ LDL cholesterol (mg/dL) ○ HDL cholesterol (mg/dL) ○ VLDL cholesterol (mg/dL) ○ Free fatty acid (mg/dL, mEq/L) • Mean change in: ○ Fasting plasma glucose (mg/dL) ○ HbA1c (% , mmol/mol) ○ Fasting insulin (mg/dL, pmol/L) ○ Fasting C-peptide (mg/dL) • Mean change in (only T2D at baseline) ○ 7-point SMBG • Mean change in: ○ High-sensitivity C-reactive protein (hsCRP) (mg/L) ○ Uric acid (mg/dL) ○ UACR (mg/gCre) ○ eGFR (mL/min/1.73 m²) • 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 score • Mean change in PGI-S and PGI-C limitations on physical function due to weight score
To demonstrate orforglipron (6 mg, 12 mg, and 36 mg QD pooled dose) is superior to placebo in change from baseline for the following: • Body weight • Improvement of comorbidities	From baseline to Week 72 • Percentage of participants who achieve: ○ BMI <25 kg/m² ○ BMI <27 kg/m² • Percentage of participants who had improvements in: ○ Hypertension (only for participants with hypertension at baseline) ○ Dyslipidemia (only for participants with dyslipidemia at baseline)

	○ T2D (<6.5% [48 mmol/mol]) in HbA1c (only T2D at baseline) ● Change in anti-hypertensive medication (decrease, no change, increase) (only hypertension at baseline) ● Change in lipid-lowering medication (decrease, no change, increase) (only dyslipidemia at baseline) ● Change in concomitant oral anti-glycemic medication (decrease, no change, increase) (only T2D at baseline) ● Change in glycemic category (normo-glycaemia, borderline type-diabetes, T2D) ● Proportion of participants who achieved the following number of improvements of obesity-related health problems (hypertension, dyslipidemia, and T2D) at Week 72 from baseline, regardless of BMI at baseline ○ Achieved 0, 1, 2 or 3 improvements (only for participants with 3 obesity-related health problems) ○ Achieved 0, 1 or 2 improvements (only for participants with 2 obesity-related health problems) ○ Achieved 0 or 1 improvements (only for participants with 1 obesity-related health problem)
To demonstrate orforglipron (6 mg, 12 mg, and 36 mg QD pooled dose) is superior to placebo in change from baseline for the following: ● Biomarkers ● Glycemic control (only T2D at baseline)	From baseline to Week 72 ● Mean change in: ○ Adiponectin (µg/dL) (both high molecular weight and total adiponectin) ○ Leptin (ng/dL) ○ UACR (mg/gCre) ○ eGFR (mL/min/1.73 m²) ● Mean change in: ○ HOMA2-IR ○ HOMA2-B

• Delayed progression to T2D • Patient reported outcomes	• Time to onset of T2D (only nonT2D at baseline) • Mean change in SF-36v2 acute scores: ○ physical functioning ○ role-physical score ○ bodily pain score ○ general health score ○ vitality score ○ social functioning score ○ role-emotional score ○ mental health score ○ physical component summary ○ mental component summary • Mean change in IWQOL-Lite-CT scores from baseline: ○ physical function score ○ physical score ○ psychosocial score ○ total score • Mean change in PGI-C and PGI-S scores from baseline: ○ Shift of the ordinal response category • Mean change in PROMIS Short Form Sleep Disturbance 8b score from baseline
To characterize the population PK of orforglipron	• Population PK parameters
Exploratory	
To explore the relationships between orforglipron concentration and efficacy, safety, and tolerability measures	• Population PD parameters

Abbreviations: BMI = body mass index; BP = blood pressure; CT = computerized tomography; eGFR = estimated glomerular filtration rate (calculated by Japanese Society of Nephrology coefficient-modified CKD-EPI equation); EQ-5D-5L = European Quality of Life 5 Dimensions 5 Level; HbA1c = hemoglobin A1c; HDL = high density lipoprotein cholesterol; HOMA2-B = homeostasis model assessment estimates steady state beta cell function; HOMA2-IR = homeostasis model assessment estimates insulin resistance beta cell function; IWQOL-Lite CT = Impact of Weight on Quality of Life-Lite Clinical Trials version; LDL = low density lipoprotein; PD = pharmacodynamics; PGI-C = Patient Global Impression of Change; PGI-S = Patient Global Impression of Status; PK = pharmacokinetics; PROMIS = Patient-Reported Outcomes Measurement Information System; QD = once daily; SF 36v2 = Short-Form 36-item Health Survey Version 2; T2D = type 2 diabetes; SAT = subcutaneous adipose tissue; UACR = urine albumin/creatinine ratio; VAT = visceral adipose tissue; VAS = visual analogue scale; VLDL = very low density lipoprotein.

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 and percentage of participants who achieve 5% or more body weight reduction from baseline at 72 weeks between orforglipron 6 mg, 12 mg, 36 mg and placebo, as an adjunct to healthy diet and physical activity, in participants 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:** Participants who meet the eligibility criteria. Further details can be found in Sections 5 and 9.
- **Primary endpoint:** Percent change from baseline in body weight and percentage of participants who achieve 5% or more of body weight reduction from baseline 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 percent change from baseline in body weight and percentage of participants who achieve 5% or more body weight reduction from baseline at 72 weeks of the treatment period (details can be found in Section 9.2) between orforglipron 6 mg, 12 mg, and 36 mg 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.

Additional Secondary Estimands

The “efficacy” estimand described in Section 9.2 will be used as secondary estimand. Further details will be provided in the SAP.

4. Study Design

4.1. Overall Design

ATTAIN-J (Study GZPD) is a Phase 3, multicenter, randomized, parallel-arm, double-blind, placebo-controlled, 72-weeks study. The study will investigate the efficacy and safety of treatment with daily oral doses of orforglipron (6 mg, 12 mg, or 36 mg) compared with placebo when used in conjunction with a reduced calorie diet and increased physical activity for weight management, in Japanese participants with obesity disease with BMI ≥ 27 kg/m² and < 35 kg/m² and at least 2 obesity-related health problems (treated or untreated), or a BMI ≥ 35 kg/m² and at least 1 obesity-related health problem (treated or untreated) according to the guidelines of the Japan Society for the Study of Obesity (JASSO) (JASSO 2022). At least 1 obesity-related health problem should be hypertension, dyslipidemia or T2D (approximately 25% of participants).

The study population will be enriched for participants who do not have T2D so that approximately 75% of the total study population will consist of participants without T2D.

Study participants will be randomized in a 1:1:1:1 ratio to once daily oral treatment with 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.

4.2. Scientific Rationale for Study Design

This study is designed to determine the comparative benefits and risks of once daily oral treatment with orforglipron 6 mg, 12 mg, or 36 mg QD versus placebo in participants with obesity disease who have obesity-related health problems (see [Table 4](#) below).

Table 4. Scientific Rationale for Study Design

Study Design Element	Scientific Rationale
Double blinded parallel-group study	It is appropriate to minimize participant and investigator bias in assessments for efficacy, safety, and study intervention tolerability.
Placebo-controlled study	It was chosen to determine the comparative benefits and risks of once daily oral treatment with orforglipron 6 mg, 12 mg, or 36 mg versus placebo in participants who have obesity disease with obesity-related health problems.
Conjunction with a reduced calorie diet and increased physical activity for weight management	It follows the JASSO guideline that obesity disease patients may initiate medical therapy if, despite adequate lifestyle interventions including diet, exercise, and behavioral therapy for 3 to 6 months, body weight and associated health problems are not improved.
Primary and secondary endpoints	This study is based on the guidance (JASSO Guideline for the management of obesity disease [JASSO 2022]) which emphasizes the importance of improving obesity-related health problems as a secondary endpoint, although reducing body weight loss is set as the primary endpoint.
Study duration	The planned duration of treatment for the primary endpoint at 72 weeks includes a 20-week dose escalation period to either 6 mg, 12 mg, or 36 mg and at least 52-week treatment period with the assigned dose. 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 improvement of associated obesity-related health problems. It is consistent with regulatory guidelines (FDA 2007; EMA 2016) and agreed by PMDA.
Concomitant medications	Participants will be permitted to use concomitant medications that they require during the study, except certain medications that may interfere with the assessment of efficacy and safety characteristics of the study treatment. (Section 6.9).

Abbreviations: EMA = European Medicines Agency; FDA = U.S. Food and Drug Administration; JASSO = Japan Society for the Study of Obesity; PMDA = Pharmaceuticals and Medical Devices Agency.

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 (CWM) 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% confidence interval [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.

Based on the ongoing single-dose and 12-week multiple-dose study GZGB, there were no clinically meaningful differences in the PK, PD, and safety profile between Japanese patients and non-Japanese patients. Hence, the doses and associated escalation schemes chosen for this Phase 3 study GZPD are the same as that chosen for global studies.

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 disease, 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 6.6.1). 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.

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. Japanese participant must be ≥ 18 years of age 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. Participants with a BMI ≥ 27 kg/m² and < 35 kg/m² and at least 2 obesity-related health problems (treated or untreated), OR a BMI ≥ 35 kg/m² and at least 1 obesity-related health problem (treated or untreated) according to the JASSO guidelines (see Appendix 8, Section 10.8). At least one obesity-related health problem should be hypertension, dyslipidemia or T2D (approximately 25% of participants).

Obesity-related health problems:

- Hypertension: treated or with systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 80 mmHg at Visit 1
- Dyslipidemia: treated or with low-density lipoprotein (LDL) ≥ 160 mg/dL (4.1 mmol/L) or triglycerides ≥ 150 mg/dL (1.7 mmol/L), or high-density lipoprotein (HDL) < 40 mg/dL (1.0 mmol/L) at Visit 1
- T2D:
 - followed by Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020)
 - with HbA1C $\geq 7.0\%$ (53 mmol/mol) to $\leq 10.0\%$ (86 mmol/mol) at Visit 1.
 - are on stable treatment of T2D for at least 90 days prior to Visit 1, consisting of:
 - either diet/exercise alone, or
 - up to 3 oral diabetes therapies (excluding dipeptidyl peptidase 4 [DPP-4] inhibitors or GLP-1 RA).
- 3. Have a history of at least one 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 1 (Section 10.1), which includes compliance with the requirements and restrictions listed in the informed consent form (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

For Participants with T2D

7. Have T1D, history of ketoacidosis or hyperosmolar state/coma, or any other types of diabetes except T2D.
8. Have had 1 or more episode of severe hypoglycemia and/or 1 or more episode of hypoglycemia unawareness within the 180 days prior to Visit 1.
9. Are currently receiving or planning to receive treatment for diabetic retinopathy and/or macular edema (for example, laser photocoagulation or intravitreal injections of anti-vascular endothelial growth factor inhibitors).

Note: For participants with a contraindication to pharmacological pupil dilation (for example, closed angle glaucoma), a non-dilated fundoscopic examination performed by an ophthalmologist or optometrist is allowed.

10. Have at least 2 confirmed fasting self-monitored blood glucose (SMBG) values >270 mg/dL (15.0 mmol/L) (on nonconsecutive days) prior to Visit 3.

For Participants without T2D (Borderline type and normoglycemia)

11. Have T1D, T2D, or any other types of diabetes, history of ketoacidosis, or hyperosmolar state/coma.
12. Have central laboratory evidence diagnostic of diabetes at Visit 1 or Visit 2, including 1 or more of: HbA1c $\geq 6.5\%$ (≥ 48 mmol/mol), fasting glucose (FG) ≥ 126 mg/dL (≥ 7.0 mmol/L), or random glucose ≥ 200 mg/dL (≥ 11.1 mmol/L).

Medical Conditions: Obesity-Related

13. Have a self-reported change in body weight >5 kg (11 pounds) within 90 days prior to Visit 1.
14. Have a prior or planned surgical treatment/procedure for obesity.

Note: The following are allowed if performed >1 year before Visit 1:

- Liposuction

- Abdominoplasty
 - Cryolipolysis
15. Have a prior or planned endoscopic and/or device-based therapy for obesity or have had device removal within 180 days prior to Visit 1 (for example, mucosal ablation, lap band, gastric artery embolization, intragastric balloon, or duodenal-jejunal endoluminal liner).
16. Have obesity induced by other endocrinologic disorders (for example Cushing's syndrome) or diagnosed monogenetic or syndromic forms of obesity (for example, melanocortin 4 receptor deficiency or Prader-Willi syndrome).

Medical conditions***Renal***

17. Have an estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m², calculated by Japanese Society of Nephrology coefficient-modified Chronic Kidney Disease – Epidemiology (CKD-EPI) equation as determined by central laboratory at Visit 1.

Gastrointestinal

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

Autoimmune

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

Cardiovascular

20. Have had any of the following CV conditions within 90 days prior to Visit 1:
- acute myocardial infarction
 - cerebrovascular accident (stroke)
 - unstable angina, or
 - hospitalization due to congestive heart failure (CHF)

21. Have New York Heart Association Functional Classification IV CHF.

Hepatic

22. Have acute or chronic hepatitis including a history of autoimmune hepatitis, signs and symptoms of any other liver disease other than nonalcoholic fatty liver disease, or any of the following, as determined by the central laboratory at Visit 1:
- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level $\geq 3.0 \times$ the upper limit of normal (ULN) for the reference range
 - alkaline phosphatase (ALP) level $\geq 1.5 \times$ the ULN for the reference range

- total bilirubin (TBL) level $\geq 1.5 \times$ the ULN for the reference range (except for cases of known Gilbert's syndrome)
- hepatitis B infection, defined as:
 - Positive hepatitis B core antibody (HBcAb) and positive for hepatitis B virus (HBV) DNA or
 - Positive hepatitis B surface antigen (HBsAg)
- positive hepatitis C antibody and positive hepatitis C virus (HCV) RNA

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

Endocrine

- 23. Have family (first-degree relative) or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome type 2 (MEN2)
- 24. Have a calcitonin level determined by the central lab at Visit 1 of:
 - ≥ 20 ng/L, if eGFR ≥ 60 mL/min/1.73 m², or
 - ≥ 35 ng/L, if eGFR < 60 mL/min/1.73 m²
- 25. Have thyroid stimulating hormone (TSH) level outside the normal reference range for the central laboratory at Visit 1.
 - Participants with hypothyroidism who are clinically euthyroid and on stable thyroid replacement therapy for at least 60 days prior to Visit 1 are acceptable exceptions to this criterion.

Malignancy

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

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

Hematologic

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

Psychobehavioral

- 28. Have a history of active or unstable major depressive disorder or other severe psychiatric disorder, such as schizophrenia, bipolar disorder, or other serious mood/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 are not on excluded medications #40 regarding weight gain-promoting concomitant medications.

29. Have a Patient Health Questionnaire 9 (PHQ-9) score of 15 or more on or before Visit 3.
30. Are, in the judgement of the investigator, actively suicidal and therefore deemed to be at significant risk for suicide.
31. Have answered “yes” to either Question 4 or Question 5 on the “Suicidal Ideation” portion of the Columbia Suicide Severity Rating Scale (C-SSRS) **and** the ideation occurred within the past month prior to Visit 1 or Visit 3,
OR
Have answered “yes” to any of the suicide-related behaviors on the “Suicidal Behavior” portion of the C-SSRS, **and** the behavior occurred within the past month prior to Visit 1 or Visit 3.

General

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

Prior/concomitant therapy

37. Have taken any prohibited glucose-lowering medications (see Section 10.9.1.1) within 90 days of Visit 1, or have a history of insulin therapy within 90 days prior to Visit 1, except for the use of insulin for treatment of gestational diabetes or acute, temporary use of insulin (less than 14 days), for example, for acute illness, hospitalization, elective surgery
38. 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 3.
39. Have used any weight loss drugs or alternative remedies, including herbal or nutritional supplements, within 180 days prior to Visit 1. Examples include, but are not limited to:
 - Sanorex[®] (mazindol)
 - Bofu tsusho san[®] (Chinese herbal medicine)
 - Saxenda[®] (liraglutide 3.0 mg)
 - Wegovy[®] (semaglutide 2.4 mg)
 - Xenical[®] (orlistat)

- Meridia[®] (sibutramine)
 - Acutrim[®] (phenylpropanolamine)
 - Adipex[®] (phentermine)
 - Belviq[®] (lorcaserin)
 - Qsymia[®] (phentermine/topiramate combination)
 - Contrave[®] (naltrexone/bupropion)
 - ingested material that transiently occupies space in the stomach, for example, Plenity[®]
 - over-the-counter medications, for example, alli[®]
40. Have current or history of (within 12 months prior to Visit 1) treatment with medications that may cause significant weight gain, including but not limited to: tricyclic antidepressants, atypical antipsychotic and mood stabilizers, for example:
- imipramine
 - amitriptyline
 - mirtazapine
 - paroxetine
 - phenelzine
 - chlorpromazine
 - thioridazine
 - clozapine
 - olanzapine
 - valproic acid and its derivatives
 - lithium
- Note:** Selective serotonin reuptake inhibitors other than paroxetine are permitted.
41. Have started implantable or injectable contraceptives within 18 months prior to Visit 1
- Note:** Intrauterine devices are acceptable.
42. Are receiving strong cytochrome P450 3A (CYP3A) inhibitors or CYP3A inducers, strong organic anion transporting polypeptide (OATP) inhibitors, or drugs that are sensitive P-glycoprotein (P-gp)/ breast cancer resistance protein (BCRP) substrates with narrow therapeutic index (see Section 10.9.1.4 for examples).
- 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
43. In non-T2D participants, are receiving metformin or any other glucose-lowering medication, regardless of the indication for use, at Visits 1 through 3.

44. Have known allergies or intolerance to GLP-1 or glucose-dependent insulintropic polypeptide (GIP)/GLP-1 RA.

Prior/concurrent clinical study experience

45. Have previously completed or withdrawn from this study or any other study investigating orforglipron after receiving at least 1 dose of study intervention.
46. 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.
47. Have participated in a clinical study and received treatment, whether active or placebo within 90 days prior to Visit 1.

Other exclusions

48. 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.
49. 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 with a dietitian, or equivalent qualified delegate, according to local standards, to receive counseling on diet and exercise (including dietary composition and amount of physical activity) at all visits during the treatment period (from 0 to 72 weeks after randomization). The Lifestyle Program instructions may be delivered on a separate day from the rest of that visit's study procedures but must occur within the visit window. Beginning at Week 8, the consultation may be delivered by telehealth.

Diet and exercise goals (based on JASSO guidelines) established during the lifestyle management counseling and the importance of adherence to the lifestyle component of the trial will be reinforced at each trial contact 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.

Per the SoA (Section 1.3), study participants will receive diet counselling by a dietitian/nutritionist, or equivalent qualified delegate, according to JASSO guidelines. Dietary counseling will consist of advice on healthy food choices and focus on calorie restriction using a hypocaloric diet with macronutrient composition of:

- approximately 50% to 60% of energy from carbohydrate
- approximately 15% to 20% of energy from protein

- approximately 20% to 25% of energy from fat, and
- daily energy intake up to $25 \text{ kcal/kg} \times \text{standard body weight}$ (as determined by $\text{BMI} = 22 \text{ kg/m}^2$) for the participant whose BMI is $\geq 27 \text{ kg/m}^2$ and $20 \text{ to } 25 \text{ kcal/kg} \times \text{standard body weight}$ for the participant whose BMI is $\geq 35 \text{ kg/m}^2$.

To encourage adherence, it is recommended that a 3-day diet and exercise diary be completed prior to each counseling visit. During each visit, the participant's diet is reviewed and advice to maximize adherence is provided if needed.

The recommended diet is continued after randomization and throughout the treatment period.

If a BMI $\leq 22 \text{ kg/m}^2$ is reached and if needed by investigators decision, the recommended energy intake should be recalculated with an appropriate reference, such as Dietary Reference Intakes for Japanese (MHLW 2015), based on the standard BMI (22 kg/m^2) to maintain a balance between energy intake and consumption with basal metabolic reference value and physical activity level.

5.3.2. Activity

Participants will abstain from strenuous exercise for 24 hours before each blood collection for clinical laboratory tests. Participants may participate in light recreational activities during onsite study procedures (for example, watching television, reading).

At Visit 3 and all subsequent visits, participants will be advised to increase their physical activity to at least 150 minutes per week. Please see Appendix 8 (Section 10.8) for detailed guidance on physical activity.

5.3.3. Diabetes Education

For participants with T2D at baseline, diabetes education will be performed by personnel who are qualified to educate participants on symptoms and management of hyperglycemia and hypoglycemia, SMBG, and diabetes management according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020). Participants will be trained on how to utilize BG meters and how to collect SMBG, including 7-point measurements as appropriate. Blood glucose meters/supplies will be provided to measure SMBG values and participants will be required to record these values in the study diary.

Participants who do not have T2D at baseline and develop diabetes during the study will be followed per the guidelines on Management of Incident Diabetes (Section 10.10).

5.3.4. Blood Donation

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

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to the study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to

respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs.

Individuals who do not meet the criteria for participation in this study (screen failure), will have an opportunity to have 1 additional screening visit with repeat screening laboratory tests at the discretion of the investigator. Before rescreening is performed, the patient must sign a new ICF and receive a new identification number. If, in the opinion of the investigator, an ineligible laboratory test result is the result of an error or extenuating circumstance, then that parameter can be retested once without the patient having to be rescreened.

5.5. Criteria for Temporarily Delaying Enrollment, Randomization, or Administration of Study Intervention of a Participant

Not applicable.

6. Study Intervention(s) and Concomitant Therapy

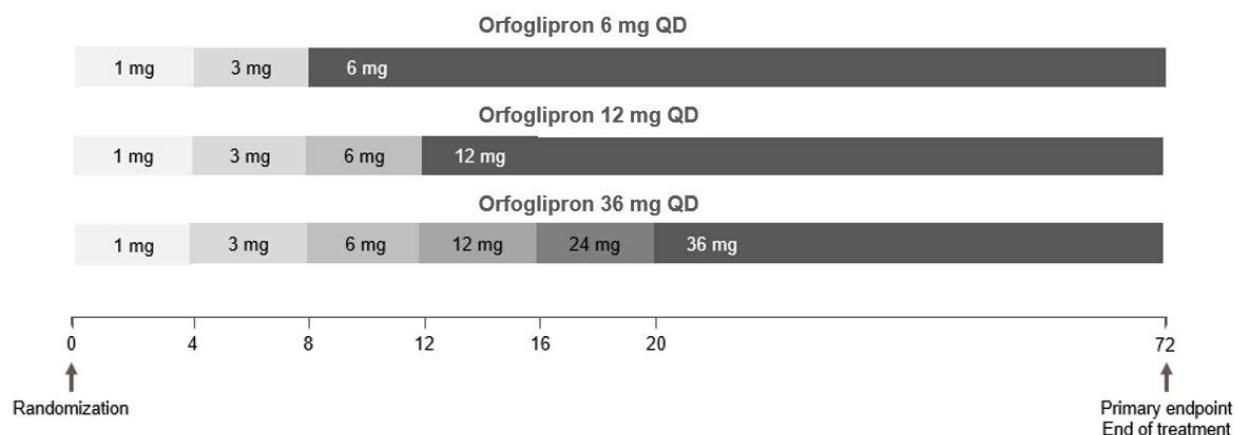
Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to/used by a study participant according to the study protocol.

6.1. Study Intervention(s) Administered

The following 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 treatment dose (6 mg, 12 mg or 36 mg) is reached as outlined in the figure below.



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 of orforglipron (6 mg, 12 mg, or 36 mg) or placebo will be continued for the remainder of the study. In participants who experience intolerable GI symptoms, the dose can be modified as described in Section 6.6.1.

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. Medications that may be affected by an increase in gastric pH should be separated from study intervention administration by at least 2 hours (Section 6.9). The participant will record the actual date and time of all dose administrations in an electronic diary.

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.

Background Diabetes Therapy After End of Treatment Period

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

Exceptions: GLP-1 RAs or other incretin-based therapies (for example, tirzepatide), insulin (except as rescue medication for severe, persistent hyperglycemia [Section 6.9.5]), pramlintide (amylin analogs), and DPP-4 inhibitors are prohibited medications.

Packaging and Labeling

Study interventions will be supplied by the sponsor 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 documents.

6.3. Assignment to Study Intervention

Participants who meet all criteria for enrollment will be randomly assigned to study intervention using a central interactive web response system (IWRS). Study intervention will be dispensed at the study visits summarized in the SoA (Section 1.3). Returned study intervention should not be re-dispensed to the participants.

Participants will be randomized in a 1:1:1:1 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. An upper limit of 70% enrollment of females will be used to ensure a sufficiently large sample of males.

The randomization will be stratified by:

- baseline hypertension (yes or no)
- baseline dyslipidemia (yes or no)
- baseline T2D (yes or no)
- sex (male or female) and
- BMI (≥ 27 to < 35 kg/m² or ≥ 35 kg/m²)

6.4. Blinding

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

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

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 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 dose escalation period, 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 these 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 or 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 and initiation of another antihyperglycemic medication may be considered (Section 6.9.6).

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

For this study, any dose of orforglipron ≥ 3 capsules within a 24-hour time period will be considered an overdose and should be reported per criteria described in Section 10.3.

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, orforglipron no longer has a clinical effect or can no longer be detected systemically (at least 7 days).

6.9. Prior and Concomitant Therapy

Prior therapies of interest including chronic weight management therapies and antihyperglycemic medication 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 obesity-related health problems, including hypertension, dyslipidemia, and T2D. Since weight reduction is expected to improve these comorbidities, study participants may require a dose reduction or complete withdrawal of certain concomitant medications. Investigators should closely monitor for the need for adjustment of concomitant medications (especially anti-hypertensives, as incretin therapies are commonly associated with a reduction in blood pressure) throughout the study.

During the study, a medication (treatment) intensity CRF pertaining to concomitant medications taken for obesity-related comorbidities will be collected at intervals specified in the SoA to understand the investigator's assessment of changes in medication intensity, 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 drug administration by at least 2 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 are provided in Section [10.9.2](#)).

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

Non-T2D participants who develop diabetes during the study may initiate medication for glucose control, with the exception of DPP-4 inhibitors or GLP-1 RAs or other incretin-based therapies (for example, tirzepatide). Initiation of metformin or sodium-glucose cotransporter 2 inhibitor (SGLT-2i) for the treatment of diabetes is permitted but should not be initiated during the study for the treatment of other conditions (for example, metformin for polycystic ovary syndrome or diabetes prevention; SGLT-2i for heart failure or chronic kidney disease).

6.9.3. Prohibited or Restricted Use Medications

The following medications are prohibited:

- GLP-1 RA or other incretin-based therapies (for example, tirzepatide), and DPP-4 inhibitors (Section [10.9.1.1](#)).

- Those intended to promote weight loss, including prescribed, over the counter, or alternative remedies. Examples are provided in Section 10.9.1.2.
- 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 10.9.1.4. 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:

- Weight gain medications, Examples are provided in Section 10.9.1.3.
- Moderate CYP3A inducers or inhibitors. Examples are provided in Section 10.9.2.2.

6.9.4. Prohibited 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.

6.9.5. Rescue Therapy for Severe, Persistent Hyperglycemia

Criteria for Severe, Persistent Hyperglycemia

Glycemic rescue criteria will be primarily determined from weekly fasting SMBG values recorded in participant eDiaries. Investigators will be trained on how to apply decision criteria for the timing and method of intervention in participants who do not reach glycemic targets during the treatment period. Participants should continue administering assigned study intervention. An additional therapeutic intervention should be considered in participants who meet the following criteria:

≥2 confirmed values over at least 2 consecutive weeks are:	Time period in the study
>270 mg/dL (15.0 mmol/L)	at any time from Week 0 and prior to Week 9
>240 mg/dL (13.3 mmol/L)	at any time from Week 9 to Week 16
>200 mg/dL (11.1 mmol/L)	at any time after Week 16
One value	Time period in the study
HbA1c ≥8.5% (69 mmol/mol)	on and after Week 24
Note: Investigators should first confirm that the study participant is fully compliant with the assigned study intervention and that he or she does not have an acute condition causing severe hyperglycemia.	

Rescue Medication

For participants treated with study intervention who meet criteria for severe persistent hyperglycemia, the investigator will decide, in consultation with the participant, on an appropriate glucose-lowering intervention (rescue therapy) that is not a prohibited medication listed in Section 10.9. Investigators should follow Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020).

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

Short-term treatment with insulin not as rescue therapy

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

6.9.6. Antihyperglycemic Medications after Permanent Discontinuation of Study Intervention

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

Exceptions: GLP-1 RAs or other incretin-based therapies (for example, tirzepatide), insulin (except as rescue medication for severe, persistent hyperglycemia [Section 6.9.5]), pramlintide (amylin analogs), and DPP-4 inhibitors are prohibited medications.

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 secondary efficacy endpoints at the final visit of the treatment period.

A participant must be permanently discontinued from study intervention if

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

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

- the participant has intolerable GI symptoms despite management as described in Section 6.6.1
- BMI ≤ 18.5 kg/m² is reached at any time during the treatment period

Note: The investigator should contact the sponsor's designated medical monitor to discuss whether it is medically appropriate for the participant to continue study intervention.

- initiation of other weight management medications (Section 10.9.1.2) 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 (MHP) for consultation. If a participant's psychiatric disorder can be adequately treated with psycho- and/or pharmacotherapy (see Section 10.9.1.3 for restricted use medications), then the participant, at the discretion of the investigator (in agreement with the MHP), may be continued in the study on study intervention.

7.1.1. Liver Chemistry Stopping Criteria

See Section 8.2.5.3 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.

If study intervention interruption is	then
3-6 consecutive doses	participant resumes the study intervention at the last administered dose level, unless doing so results in intolerable GI symptoms. See Section 6.6.1 for management of GI symptoms. If the dose interruption occurred immediately prior to a scheduled dose escalation visit, the participant should proceed with the next escalation.
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 last administered dose level should be resumed.
due to an AE (including recurrent GI symptoms), a clinically significant laboratory value, or a participant's personal circumstances*	The event is to be documented and followed according to the procedures in Section 8.3.
due to intolerable persistent GI AE	Participant should be treated as suggested in Section 6.6.1.

* Travel, hospitalizations, or planned or unplanned procedures.

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

7.2. Participant Discontinuation/Withdrawal from the Study

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

Female participants will be withdrawn 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

- if the participant, for any reason, requires treatment with a therapeutic agent that is prohibited by the protocol and has been demonstrated to be effective for treatment of the study indication. In this case, discontinuation from the study occurs prior to introduction of the new agent.

At the time of discontinuing from the study, if possible, the participant will complete procedures for an early discontinuation visit and post-treatment follow-up, if applicable, as shown in the SoA (Section 1.3). 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 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 (Section 1.3).

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 8.1.2.6.

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

The independent Clinical Endpoint Committee adjudicating events is described in Section 10.1.5.

8.1.1. Primary Efficacy Assessments

The primary efficacy endpoint includes change in the percent change in body weight and percentage of participants achieving $\geq 5\%$ body weight reduction.

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

The following secondary efficacy assessments will be collected according to the SoA.

8.1.2.1. Body Mass Related Parameters

Body Weight

- Body weight will be measured as described above (see Section 8.1.1).
- Body mass index (kg/m^2) will be derived using body weight in kilograms divided by the square height in meters.

Waist Circumference

Waist circumference will be collected according to the SoA.

Waist circumference should be measured in the horizontal plane and at the umbilicus level according to JASSO guideline. For further comments, see Appendix 8 (Section 10.8).

Measurement of Visceral Adipose Tissue (VAT), Subcutaneous Adipose Tissue (SAT), and VAT/SAT Ratio

Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) will be collected according to the SoA (Section 1.3).

Single slice imaging will be performed at the umbilicus level in a supine position using computerized tomography (CT) at each site in about 40% of total participants. The assessments will include VAT, SAT, and VAT/SAT ratio and will be calculated using software.

Measurements of the adipose area will be performed centrally.

8.1.2.2. Hypertension Related Parameters

The following hypertension related parameters will be collected according to the SoA (Section 1.3).

- Blood pressure (measured at site)
 - Systolic blood pressure (mmHg)
 - Diastolic blood pressure (mmHg)
- Proportion of participants diagnosed with hypertension at baseline who had improvement in hypertension at 72 weeks (SBP<130 mmHg and DBP<80 mmHg)

8.1.2.3. Dyslipidemia Related Parameters

The following dyslipidemia related parameters will be collected according to the SoA (Section 1.3).

- Fasting lipids (measured at central laboratory)
 - TC, non-HDL-C, TG, LDL-C (direct), HDL-C, VLDL-C (mg/dL)
 - FFA (μEq/L)
- Proportion of participants diagnosed with dyslipidemia at baseline who had improvement in dyslipidemia at 72 weeks:
 - LDL-C <160 mg/dL (4.1 mmol/L),
 - TG < 150 mg/dL (1.7 mmol/L), or
 - HDL-C ≥40 mg/dL (1.0 mmol/L)

8.1.2.4. Glucose Control Related Parameters

The following glucose control related parameters will be collected according to the SoA (Section 1.3).

- Fasting glucose (mg/dL) (measured at central laboratory)
- HbA1c (%) (measured at central laboratory)
- Fasting serum insulin (pmol/L) (measured at central laboratory)
- C-peptide (ng/mL) (measured at central laboratory)

- Homeostatic Model Assessment for Beta Cell and Insulin Sensitivity (HOMA2-%B and HOMA2-%S): Fasting glucose and insulin values will be used to calculate beta-cell function and insulin sensitivity using the updated Homeostasis Model Assessment (HOMA2) (Wallace et al. 2004).
- 7-Point Self-Monitored Blood Glucose Profiles: Participants with T2D at baseline are required to perform two 7-point SMBG profiles on 2 days during the 2 weeks before Visits 3, 9, and 21 (refer to the SoA in Section 1.3). Participants will test and record SMBG concentrations in their study diaries before each meal (breakfast, lunch, and dinner), approximately 2 hours after the start of each meal, and at bedtime. The 7-point SMBG profiles will be entered in the eDiary and analyzed.
- Proportion of participants diagnosed with T2D at baseline who had improvement in T2D at 72 weeks, <6.5% (48 mmol/mol) in HbA1c. The definition of T2D at baseline is followed by Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020) (see Section 5.1 Inclusion criteria).
- Time to onset of T2D that participants with nonT2D at baseline who diagnosed incident diabetes from baseline to 72 weeks.

Fasting glucose samples must be obtained after 8 hours or more without eating, drinking (other than water) or performing any significant physical activity.

8.1.2.5. Other Parameters

The following parameters will be collected according to the SoA (Section 1.3).

- hsCRP (mg/dL) (measured at central laboratory)
- Uric acid (mg/dL) (measured at central laboratory)
- Adiponectin (µg/dL) (both high molecular weight and total adiponectin, measured at central laboratory)
- Leptin (ng/dL) (measured at central laboratory)
- Urinary albumin/creatinine ratio (mg/gCre) (measured at central laboratory)
- eGFR (mL/min/1.73 cm²) (creatinine measured at central laboratory) calculated using the Japanese Society of Nephrology formula: $194 \times \text{Cr}^{-1.094} \times \text{Age}^{-0.287}$ [if female; $\times 0.739$]
- Changes in medications for obesity-related health problems
 - Antihypertensive medication (decrease, no change, increase)
 - Lipid-lowering medication (decrease, no change, increase)
 - Concomitant OAD (decrease, no change, increase) (only apply to participants with T2D at baseline)
- Change in glycemic category (normo-glycaemia, borderline type, T2D)
 - Normo-glycemia: FG <110 mg/dL (6.1 mmol/L) and HbA1c <6.0% (42 mmol/mol)

- Borderline type: FG ≥ 110 mg/dL (6.1 mmol/L) and < 126 mg/dL (7.0 mmol/L), and HbA1c $\geq 6.0\%$ (42 mmol/mol) and $< 6.5\%$ (48 mmol/mol)
- T2D: FG ≥ 126 mg/dL (7.0 mmol/L) and HbA1c $\geq 6.5\%$ (48 mmol/mol)
- Proportion of participants who achieved 0, 1, 2 or 3 improvements of obesity-related health problems (hypertension, dyslipidemia, and T2D) at Week 72 from baseline
 - Improvement of hypertension: Proportion of participants diagnosed with hypertension at baseline who had improvement in hypertension at 72 weeks (Section 8.1.2.2)
 - Improvement of dyslipidemia: Proportion of participants diagnosed with dyslipidemia at baseline who had improvement in dyslipidemia at 72 weeks (Section 8.1.2.3)
 - Improvement of T2D: Proportion of participants diagnosed with T2D at baseline who had improvement in T2D at 72 weeks (Section 8.1.2.4)

8.1.2.6. Patient-Reported Outcomes Assessments

The self-reported questionnaires will be translated into Japanese, linguistically validated, and administered according to the SoA (Section 1.3). At these visits, the questionnaires should be completed before the participant has discussed their medical condition or progress in the study with the investigator and/or site staff, if the participant is not adversely affected by their fasting condition.

Short-Form 36 Version 2, Acute, 1-Week Recall Version

The Short-Form Health Survey Version 2 (SF-36v2) acute, 1-week recall version is a 36-item, generic, patient-administered measure designed to assess the following 8 domains:

- Physical functioning
- Role-physical
- Bodily pain
- General health
- Vitality
- Social functioning
- Role-emotional
- Mental health

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

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

The Impact of Weight on Quality of Life-Lite Clinical Trials version (IWQOL-Lite-CT) is a 20-item, obesity-specific patient-reported outcome instrument developed for use in obesity clinical trials. It 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 (Kolotkin et al. 2017, 2019). The three domain scores and total score range from 0 to 100 with higher scores indicating greater functioning.

EQ-5D-5L

Generic health-related quality of life will be assessed using the EuroQol – 5 Dimension – 5 Level (EQ-5D-5L) (EuroQoL Group 2015). The EQ-5D-5L is a standardized 5-item 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 comprises 5 dimensions of health:

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

The 5L version, introduced in 2005, scores each dimension at 5 levels for a total of 3125 possible health states.

- no problems
- slight problems
- moderate problems
- severe problems
- unable to perform/extreme problems,

In addition to the health profile, a single health state index value can be derived based on a formula that attaches weights to each of the levels in each dimension. This index value ranges between <0 (where 0 is a health state equivalent to death; negative values are valued as worse than dead) to 1 (perfect health) (Dolan 1997).

In addition, the EQ visual analog scale (VAS) records the respondent’s self-rated health status on a vertical graduated (0 to 100) scale.

In conjunction with the health state data, it provides a composite picture of the respondent’s health status. The EQ-5D-5L is used worldwide and is available in more than 170 different languages. Details on the instrument, and scoring, organizing, and presenting the data collected will follow C2H guidelines (Ikeda et al. 2015; C2H 2019).

Patient Global Impression of Status-Physical Function Weight

The PGIS-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 on a 5-point scale ranging from "not at all limited" to "extremely limited".

Patient Global Impression of Change-Physical Function Weight

The PGIC-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 medication. The responses are based on a 5-point scale ranging from "much better" to "much worse".

PROMIS Short Form v1.0 Sleep Disturbance 8b

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." 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 standard deviation (SD) of 10 (Northwestern 2016).

8.2. Safety Assessments

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

8.2.1. Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the cardiovascular, respiratory, gastrointestinal, and neurological systems.
- Height, weight, and waist circumference will also be measured and recorded, per Appendix 7 (Section 10.7).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2. Vital Signs

For each participant, vital signs measurements should be conducted according to the SoA (Section 1.3) and 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 (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.

Electrocardiograms will initially be interpreted by a qualified physician (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 significant findings from ECGs that result in a diagnosis and that occur after signing of the ICF should be reported to Lilly or its designee as an AE via the eCRF.

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 and any alert reports.

8.2.4. Clinical Safety Laboratory Tests

See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and the SoA (Section 1.3) 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 Appendix 2 (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. 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 8.2.5.1)	Initiate comprehensive evaluation (see Section 8.2.5.2)	Interrupt or discontinue study drug (see Section 8.2.5.3)
ALT or AST ≥ 3 x ULN	X		
ALP ≥ 2 x ULN	X		
TBL ≥ 2 x ULN ^b	X		
ALT or AST ≥ 5 x ULN	X	X	
ALP ≥ 2.5 x ULN	X	X	
ALT or AST ≥ 3 x ULN with hepatic signs or symptoms ^a	X	X	X
ALT or AST ≥ 5 x ULN for more than 2 weeks	X	X	X
ALT or AST ≥ 8 x ULN	X	X	X
ALT or AST ≥ 3 x ULN and TBL ≥ 2 x ULN ^b or INR ≥ 1.5	X	X	X
ALP ≥ 3 x ULN	X	X	X
ALP ≥ 2.5 x ULN and TBL ≥ 2 x ULN ^b	X	X	X
ALP ≥ 2.5 x ULN with hepatic signs or symptoms ^a	X	X	X

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

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

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

If this laboratory value is observed...	Then...		
	Initiate or continue close hepatic monitoring	Initiate comprehensive hepatic evaluation	Interrupt or discontinue study drug
ALT or AST ≥ 2 x baseline	X		
ALP ≥ 2 x baseline	X		
TBL ≥ 2 x ULN ^b	X		
ALT or AST ≥ 3 x baseline or ≥ 250 U/L (whichever occurs first)	X	X	
ALP ≥ 2.5 x baseline	X	X	
ALT or AST ≥ 2 x baseline or ≥ 250 U/L	X	X	X

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

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

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

8.2.5.1. 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 <1.5 x ULN)	Participants with elevated baseline (ALT, AST, or ALP ≥ 1.5 x ULN)
ALT or AST ≥ 3 x ULN or	ALT or AST ≥ 2 x baseline
ALP ≥ 2 x ULN or	ALP ≥ 2 x baseline
TBL ≥ 2 x ULN ^a	TBL ≥ 2 x ULN ^a

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

Close hepatic monitoring should include these actions:

- Laboratory tests ([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.

8.2.5.2. 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.

8.2.5.3. 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 [8.2.5.1](#) and [8.2.5.2](#).

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.

8.2.6. 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.

8.2.7. 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 8.3.3.14 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.

8.2.8. 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. Laboratory results are provided to the sponsor via the central laboratory.

8.2.9. Diabetic Retinopathy Screening and Evaluation

Baseline fundus photography should be performed on participants who remain eligible with T2D based on screening activities performed at baseline between Visit 2 and Visit 3, unless dilated fundoscopy or fundus photography (evaluated by an ophthalmologist or optometrist) had been performed within 90 days prior to Visit 1 for any reason unrelated to this trial. In this case the fundoscopy/fundus photography do not need to be repeated unless visual function has worsened since the last examination. Participants with any degree of diabetic retinopathy or macular edema on the baseline assessment that warrants treatment based on the clinical judgement of the ophthalmologist will be excluded (See exclusion criterion #9).

If the applicable fundus photography or dilated fundoscopy was performed before the participant signed the ICF, it must be documented in the medical records that the reason for performing the examination was not related to this trial.

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

Fundus photography should be performed in both eyes (unless precluded due to severe cataract, prosthesis, or other conditions). For participants with a contraindication to pharmacological pupil dilation (for example, closed angle glaucoma), a non-dilated fundoscopic examination performed by an ophthalmologist or optometrist is allowed.

Photographs may be performed at the study site if equipment and staff trained in collecting the required views are available; otherwise, they should be referred to an ophthalmologist or other suitable qualified health care provider.

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

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

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

The definitions of the following events can be found in Appendix 3, Section 10.3:

- AEs
- SAEs
- Product complaints (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 (see Section 7).

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

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

For product complaints, 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 Appendix 3, 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 eCRF	N/A
Serious Adverse Event					
SAE and SAE updates – prior to start of study intervention and deemed reasonably possibly related to study procedures	Signing of the ICF	Start of intervention	Within 24 hours of awareness	SAE eCRF	SAE paper form
SAE and SAE updates - after start of study intervention	Start of intervention	Participation in study has ended	Within 24 hours of awareness	SAE eCRF	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 hours (see Section 8.3.2)	Pregnancy paper form	SAE paper form
Product Complaints					
PC associated with an SAE or might have led to an SAE	Start of study intervention	End of study intervention	Within 24 hours of awareness	Product Complaint form	N/A
PC not associated with an SAE	Start of study intervention	End of study intervention	Within 1 business day of awareness	Product Complaint form	N/A
Updated PC information	—	—	As soon as possible upon site awareness	Originally completed Product Complaint form with all changes signed and dated by the investigator	N/A
PC (if investigator becomes aware)	Participation in study has ended	N/A	Promptly	Product Complaint form	

Abbreviations: AE = adverse event; eCRF = electronic case report form; ICF = informed consent form; N/A = not applicable; PC = product complaint; SAE = serious adverse event.

^a Serious adverse events 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 post-study pregnancy related SAE considered reasonably related to the study intervention by the investigator will be reported to the sponsor as described in protocol Section 8.3.1. While the investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will be withdrawn from the study. The follow up on the pregnancy outcome should continue independent of study discontinuation.

8.3.3. Adverse Events of Special Interest

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 clinical endpoint committee (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 10.3.1 must be reported as SAEs.

8.3.3.3. Hypotension, Orthostatic hypotension, and Syncope

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

8.3.3.4. Hypoglycemia

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

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

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

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

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

Hypoglycemia Definitions and Categories

Level 1 hypoglycemia - 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 Persistent Hyperglycemia

Criteria for severe, persistent hyperglycemia are provided in Section [6.9.5](#).

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

8.3.3.6. Severe Gastrointestinal Adverse Events

Orforglipron may cause severe GI AEs, such as nausea, vomiting, and diarrhea. Information about severe 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 [6.9.6](#).

8.3.3.7. Acute Renal Events

Renal safety will be assessed based on repeated renal functional assessment as well as assessment of AEs suggestive of acute renal failure or worsening of preexisting chronic renal failure. GI AEs have been reported with 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, frequent vomiting, or symptoms of dehydration.

8.3.3.8. Pancreatitis

Diagnosis of Acute Pancreatitis

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

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

If acute pancreatitis is suspected, the investigator should:

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

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

and

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

Discontinuation for Acute Pancreatitis

If acute pancreatitis is suspected by the investigator, the participant must temporarily discontinue use of the study intervention. In this case, the participant with T2D needs to receive an appropriate alternative glucose-lowering regimen. Afterwards, if pancreatitis is confirmed by the adjudication committee, the study intervention must be permanently discontinued, and the participant needs to be followed throughout the duration of the study. If the case is not confirmed, then the participant can restart the study intervention if the investigator deems as clinically appropriate as described in Section 6.6.

Case Adjudication and Data Entry

An independent CEC will adjudicate all suspected cases of acute pancreatitis and all AEs of severe or serious abdominal pain of unknown etiology. The investigator must first report these events as an AE

as described in Section 8.3.1 and then report them as an endpoint on the CRF with all required source documents provided for adjudication to the CEC (see Section 10.1.5). Clinical event reporting begins after randomization. The CEC will be blinded to treatment assignment.

Asymptomatic Elevation of Serum Amylase and/or Lipase

Serial measures of pancreatic enzymes have limited clinical value for predicting episodes of acute pancreatitis in asymptomatic participants (Nauck et al. 2017; Steinberg et al. 2017a, 2017b). Therefore, further diagnostic follow-up of cases of asymptomatic elevation of pancreatic enzymes (lipase and/or pancreatic amylase $\geq 3 \times$ ULN) is not mandated but may be performed based on the investigator's clinical judgment and assessment of the participant's overall clinical condition.

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

8.3.3.9. Thyroid Malignancies and C-Cell Hyperplasia

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

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

Calcitonin Measurements

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

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

Calcitonin measurements in participants with $eGFR \geq 60$ mL/min/1.73 m²

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

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

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

A significant increase in calcitonin for participants with eGFR <60 mL/min/1.73 m² is defined as a *serum calcitonin value* ≥ 35 ng/L AND $\geq 50\%$ over the screening value. If a participant's laboratory results meet these criteria, these clinically significant laboratory results should be recorded as an AE.

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

Diabetic Retinopathy

Diabetic retinopathy and macular edema will be monitored using retinal fundus photography and additional ophthalmological follow-up as warranted throughout the study (Section 8.2.9).

Diabetic retinopathy will be assessed as nonproliferative (mild, moderate, or severe), proliferative, and diabetic macular edema as present or absent. All TEAEs of new or worsening diabetic retinopathy, macular edema, and other related complications will also be assessed.

8.3.3.10. Malignancies

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

8.3.3.11. Hepatic Disorders

All events of hepatic disorders or other suspected events related to hepatic disorders should be evaluated and additional diagnostic tests performed as needed. In cases of elevated liver markers, hepatic monitoring should be initiated as outlined in Section 8.2.5.

8.3.3.12. 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.

8.3.3.13. Hypersensitivity Reactions

Refer to Section 8.2.8.

8.3.3.14. 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 8.2.7). 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 (NIMH) trial group (TASA) for the purpose of being counterpart to the Columbia Classification Algorithm of Suicide Assessment (C-CASA) 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.

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

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

8.3.3.15. 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 PK samples should be collected regardless of study week at which the discontinuation occurs (even after Week 48).

The date and time of the most recent orforglipron dose prior to collecting the PK sample must be recorded on the eCRF from the study e-Diary. 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.

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 pharmacodynamic response.

8.6. Genetics

A whole blood sample will be collected for pharmacogenetic analysis as specified in the SoA (Section 1.3) where local regulations allow.

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

Samples will be used to investigate variable response to orforglipron and to investigate genetic variants thought to play a role in obesity disease, T2D, and related clinical traits or complications, including nonalcoholic steatohepatitis. Assessment of variable response may include evaluation of AEs or differences in pharmacodynamic, 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
- Pharmacodynamics
- 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 LY3509270
- pathways associate with diabetes mellitus, obesity, and related clinical traits or complications, including nonalcoholic steatohepatitis,
- mechanism of action of LY3509270
- research method or validating diagnostic tools or assay(s) related to obesity, diabetes mellitus, or related clinical traits or complications.

Samples will be collected according to the schedule described in the SoA (Section 1.3).

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 statistical analysis plan (SAP) will be finalized prior to 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 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 6 mg orforglipron compared to placebo with respect to the percent change from baseline in body weight and the percentage of participants who achieve 5% or more body weight reduction from baseline at Week 72.
- $H_{2,0}$: No difference in 12 mg orforglipron compared to placebo with respect to the percent change from baseline in body weight and the percentage of participants who achieve 5% or more body weight reduction from baseline at Week 72.
- $H_{3,0}$: No difference in 36 mg orforglipron compared to placebo with respect to the percent change from baseline in body weight and the percentage of participants who achieve 5% or more body weight reduction from baseline at Week 72.

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.

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

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

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

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

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

9.3. Statistical Analyses

9.3.1. General Considerations

Statistical analyses 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 non-missing measurement at or before randomization visit (prior to the first dose 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 analysis of covariance (ANCOVA) with robust inference (Ye et al. 2022). The model will include treatment group and strata as a factor variable, baseline value (of the dependent variable), and interaction (strata x treatment and baseline x treatment).

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

For categorical measures, summary statistics will include sample size, frequency, and percentages. A logistic regression model with treatment and stratification factors as fixed effects and the continuous baseline value as a covariate will be used to examine the treatment difference in binary efficacy outcomes. Fisher's exact test or Pearson's chi-square test will be used for treatment comparisons in other categorical outcomes.

Unless specified otherwise, safety assessments will be guided by an estimand comparing safety of 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 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 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(s)/Estimand(s) Analysis

The primary analyses will be conducted to evaluate the primary endpoints using the "treatment regimen" estimand. The assessments will be conducted using the randomized participants and the treatment regimen estimand data point set (Section 9.2).

For percent change in body weight at Week 72, missing data will be imputed and then will be analyzed using an ANCOVA model. Achieving 5% or more of body weight reduction from baseline at Week 72 will be analyzed using a logistic regression model. Both models are specified in Section 9.3.1.

Supplemental analysis will be guided by the "efficacy" estimand and conducted using the randomized participants and the efficacy estimand data point set (Section 9.2).

Percent change in body weight will be analyzed using a mixed model for repeated measures model characterizing percent change in body weight over time. Achieving 5% or more of body weight reduction over time will be analyzed using a logistic regression model. Both models are specified in Section 9.3.1.

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

The “treatment regimen” estimand will be used for the secondary endpoints (Section 9.2).

Continuous data will use an ANCOVA model and binary data will use a logistic regression model. Both models are specified in Section 9.3.1. Time to onset of T2D will use a cox proportional hazards model.

9.3.5. 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.

9.3.6. 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. Other Analyses

Subgroup Analyses

Subgroup analyses of the primary endpoints will be made to assess consistency of the intervention effect of orforglipron across the following subgroups using the “treatment regimen” estimand:

- Age group (<65, ≥65 years)
- Hypertension at baseline (yes, no)
- Dyslipidemia at baseline (yes, no)
- T2D at baseline (yes, no)
- Sex (female, male)
- Baseline BMI (≥ 27 to < 35 kg/m² or ≥ 35 kg/m²)

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.

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 236 participants (59 per treatment group) provides more than 80% power to demonstrate superiority of 6 mg, 12 mg, and/or 36 mg orforglipron to placebo with regards to 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. Additionally, a difference of at least 7.5% mean body weight reduction from baseline at 72 weeks for 12 mg and 36 mg orforglipron compared with placebo, a common SD of 10%, and a dropout rate of 20% are assumed for the statistical power calculation.

The sample size also provides more than 80% power to demonstrate superiority of 6 mg, 12 mg, and/or 36 mg orforglipron to placebo in terms of percentage of participants achieving at least 5% body weight reduction at 72 weeks, conducted in parallel using a Fisher's exact test, each at a 2-sided significance level of 0.016, assuming 30% placebo-treated participants and 65% orforglipron-treated participants achieving the goal and a dropout rate of 20%.

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 (CIOMS) International Ethical Guidelines
 - Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
 - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (for example, advertisements) must be submitted to an institutional review board (IRB)/independent ethics committee (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 (CFR), 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 CFR 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.

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

10.1.4. Data Protection

- Participants will be assigned a unique identifier by the sponsor. Any participant 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.
- The participant must be informed 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 data protection, information security, and data integrity. These processes include appropriate contingency plan(s) for appropriate and timely response in the event of a data security breach.

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 cardiovascular events and pancreatic AEs will be performed for this study. Sections 8.3.3.1 and 8.3.3.8 outline additional information on cardiovascular 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 data set would result in analyses lacking scientific rigor (for example, underpowered) or compromise the integrity of the overall analyses (for example, trial not yet unblinded), the summary of results will be submitted within 1 year after the end of the study globally or as soon as available, whichever is earlier.

Data

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

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

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

Data and documents, including the study protocol, statistical analysis plan, clinical study report, and blank or annotated case report forms, 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 (QTLs) 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 QTLs 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 (CTA) 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 (EDC) 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 (COAs)

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 electronic COA (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 systems 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 systems. Prior to decommissioning, the investigator will receive or access an archival copy of pertinent data for retention.

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

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

10.1.8. Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. 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 Section [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 Participant Visit ^a
Exploratory biomarkers	Sponsor or Designee	7 years
Pharmacokinetic	Sponsor or Designee	1 years
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 the central laboratory unless otherwise stated.
- 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.
- 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 each laboratory safety report.

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

Clinical Laboratory Tests	Comments
Hematology	Assayed by Lilly-designated laboratory
Hemoglobin	
Hematocrit	
Erythrocyte count (RBCs - red blood cells)	
Mean cell volume	
Mean cell hemoglobin	
Mean cell hemoglobin concentration	
Leukocytes (WBCs - white blood cells)	
Differential	
Absolutes Count of:	
Neutrophils, segmented	
Lymphocytes	
Monocytes	
Eosinophils	
Basophils	
Platelets	
Cell morphology (RBCs and WBCs)	To be performed if abnormalities are detected.

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

Hormones (female)	Assayed by Lilly-designated laboratory unless stated otherwise.
Serum Pregnancy	
Urine Pregnancy	Assayed and evaluated locally
Follicle stimulating hormone (FSH)	
Urine Chemistry	Assayed by Lilly-designated laboratory
Albumin	
Creatinine	
Calculations	Generated by Lilly-designated laboratory.
eGFR (CKD-EPI)	Japanese Society of Nephrology coefficient-modified Chronic Kidney Disease - Epidemiology equation
Urinary albumin/creatinine ratio (UACR)	
Other Testing	Assayed by Lilly-designated laboratory.
Thyroid Stimulating Hormone (TSH)	
Adiponectin (high molecular weight and total)	Results will not be provided to investigative sites.
Leptin	Results will not be provided to investigative sites.
Insulin	Results will not be provided to investigative sites.
C-peptide	Results will not be provided to investigative sites.
Calcitonin	
Hemoglobin A1c (HbA1c)	
Cystatin C	Results will not be provided to investigative sites.
Free Fatty Acids	Results will not be provided to investigative sites.
Pancreatic Amylase	
Lipase	
High sensitivity C-Reactive Protein (hsCRP)	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)	

Abbreviations: CKD-EPI = Chronic Kidney Disease Epidemiology; EDTA = ethylenediaminetetraacetic acid; eGFR = estimated glomerular filtration rate; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; PK = pharmacokinetic, RBC = red blood cells; UACR = urine albumin/creatinine ratio; VLDL = very low-density lipoprotein cholesterol; WBC = white blood cells.

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

Purpose of collecting samples after a systemic hypersensitivity event

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

When to collect samples after a systemic hypersensitivity event occurs

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

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

Timing	Laboratory Test ^a
Collect from 30 minutes to 4 hours after the start of the event. Note: The optimal collection time is from 1 to 2 hours after the start of event.	Total tryptase

^a All samples for hypersensitivity testing will be assayed by 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 pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New condition detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Medication error, misuse, or abuse of IMP, including signs, symptoms, or clinical sequelae.
- Lack of efficacy or failure of expected pharmacological action per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfill the definition of an AE or SAE.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments that are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.
- The disease/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 pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

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

10.3.3. Definition of Product Complaints

Product Complaint

- A product complaint 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 product complaints:
 - Deficiencies in labeling information, and
 - Use errors for device or drug-device combination products due to ergonomic design elements of the product.
- Product complaints related to study interventions used in clinical trials are collected in order 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 product complaint or problem with the study intervention so that the situation can be assessed.
- An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint and as an AE/SAE.

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

AE, SAE, and Product Complaint Recording

- When an AE/SAE/product complaint 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/product complaint 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 product complaint information is reported on the Product Complaint Form.
- Note:** An event may meet the definition of both a product complaint and an AE/SAE. In such cases, it should be reported as both a product complaint 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 product complaints.

- 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 adverse event 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 adverse event 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 adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

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

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 one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

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

10.3.5. Reporting of SAEs

SAE Reporting via an Electronic Data Collection Tool

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

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 site training documents.

10.3.6. Regulatory Reporting Requirements**SAE Regulatory Reporting**

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards 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, IRBs/IECs, 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 Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

10.4. Appendix 4: Contraceptive and Barrier Guidance

10.4.1. Definitions

Word/Phrase	Definition
Women of childbearing potential (WOCBP)	Adult females are considered WOCBP unless they are WNOCBP.
Women not of childbearing potential (WNOCBP)	Females are considered WNOCBP if they • have a congenital anomaly such as Müllerian agenesis resulting in confirmed infertility. • are infertile due to surgical sterilization, or • are postmenopausal. Acceptable surgical sterilization methods are hysterectomy, bilateral salpingo-oophorectomy, bilateral salpingectomy, or bilateral oophorectomy.
Postmenopausal state	The postmenopausal state is defined as a woman: • at any age at least 6 weeks post-surgical bilateral oophorectomy with or without hysterectomy, confirmed by operative note; or • aged at least 40 years and up to 55 years with an intact uterus, not on hormone therapy^a, who has had cessation of menses for at least 12 consecutive months without an alternative medical cause, AND with a follicle stimulating hormone ≥ 40 mIU/mL; or • 55 years or older not on hormone therapy, who has had at least 12 months of spontaneous amenorrhea, or • aged at least 55 years with a diagnosis of menopause prior to starting hormone replacement therapy. ^a Women should not be taking medications during amenorrhea such as oral contraceptives, hormonal replacement therapy (HRT), gonadotropin-releasing hormone, anti-estrogens, SERMs, or chemotherapy that could induce transient amenorrhea. Females on HRT and those whose menopausal status cannot be confirmed will be required to comply with the protocol contraception requirements if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Females

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

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

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

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

Examples of different forms of contraception:

Methods	Examples
Highly effective contraception (less than 1% failure rate)	• fallopian tubal sterilization methods other than bilateral salpingectomy (laparoscopic bipolar electrocoagulation, plastic ring application on the uterine tubes, fallopian tube ligation, hysteroscopic sterilization). Note: Bilateral salpingectomy is indicative of permanent sterilization. Please see the WNOCBP definition above. • combination oral contraceptive pill • progestin-only contraceptive pill (mini-pill) • ^aimplanted contraceptives

	• ^ainjectable contraceptives • contraceptive patch (only women <198 pounds or 90 kg) • 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 drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore, where local regulations and IRB/IEC allow, a whole blood sample will be collected for DNA analysis from consenting participants.
- DNA samples will be used for research related to orforglipron or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases. They may also be used to develop tests/assays orforglipron, study interventions related to this drug class, or diabetes, obesity, and related traits or complications, including nonalcoholic steatohepatitis and related diseases. Genetic research may consist of the analysis of one 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 study disease or related conditions.
- The results of genetic analyses may be reported in the clinical study report (CSR) or in a separate study summary.
- The sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.

The samples will be retained while research on 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

Hepatic Evaluation Testing

See Section 8.2.5 for guidance on appropriate test selection.

The Lilly-designated central laboratory must 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 ^a
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 ^b
Basophils	Hepatitis C virus (HCV) testing:
Eosinophils	HCV total antibody ^a
Platelets	HCV RNA ^b
Cell morphology (RBC and WBC)	Hepatitis D virus (HDV) testing:
Hepatic Clinical Chemistry Panel	HDV total antibody ^a
Total bilirubin	HDV IgM antibody
Direct bilirubin	HDV RNA ^b
Alkaline phosphatase (ALP)	Hepatitis E virus (HEV) testing:
Alanine aminotransferase (ALT)	HEV IgG antibody
Aspartate aminotransferase (AST)	HEV IgM antibody
Gamma-glutamyl transferase (GGT)	HEV RNA ^b
Creatine kinase (CK)	Anti-nuclear antibody (ANA)
Hepatic Coagulation Panel	Anti-smooth muscle antibody (ASMA) or anti-actin antibody
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 ^c	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 antibody	
EBV DNA ^b	

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

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

^c Availability of acetaminophen protein adducts testing is limited, so testing may be performed at central labs, if needed.

10.7. Appendix 7: Measurement of Height, Weight, Waist Circumference, Vital Signs, Electrocardiogram, Computed Tomography

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

Measuring Height

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

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

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

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

Measuring Weight

- Body weight measurements should be done in a consistent manner using a calibrated electronic scale capable of measuring weight in **kilograms (kg) 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 (kg) to the nearest one-tenth kg.

Measuring Waist Circumference

- Waist circumference should be measured in the horizontal plane and at the umbilicus level according to JASSO guideline.

- Measurements should be taken at the end of a normal expiration using a nonstretchable 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 eCRF. 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 light clothing (if available, patient gowns could also be used).

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

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

Vital Sign Measurements (Blood Pressure and Heart Rate)

- Vital sign measurements (blood pressure and heart rate, measured by pulse) should be taken before obtaining an ECG tracing and before collection of blood samples for laboratory testing
- The participant should sit quietly for 5 minutes before vital signs measurements are taken
- For each parameter, three measurements will be taken using the same arm, preferably the nondominant arm
- The recordings should be taken at least 1 minute apart. Each measurement of sitting pulse and blood pressure needs to be recorded in the eCRF
- Blood pressure must be taken with a same type of sphygmomanometer (for example, sphygmomanometer, mercury manometer) throughout the study.
- If blood pressure and pulse measurements are taken separately, pulse should be taken prior to blood pressure.

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

Electrocardiogram

- All digital ECGs will be obtained using centrally provided ECG machines and will be electronically transmitted to a designated central ECG laboratory.
- 12-lead ECGs should be obtained after the subject has rested in a supine position for approximately 5 to 10 minutes.
- Electrocardiograms should be collected prior to collection of blood samples for laboratory testing, including PK samples.
- Triplicate ECGs should be obtained approximately 1 minute apart, with all 3 tracings to be obtained within approximately 5 minutes. Measurements that deviate substantially from previous readings should be repeated immediately.

Computerized Tomography

- Single slice imaging will be performed at the umbilicus level in a supine position using CT scanner at each site.
- To obtain consistent and quality data for central review, investigators participating in the study will be provided with detailed instructions on the CT acquisition protocol to be used.
- The CT acquisition protocol will include sequences for measurement of the following:
 - VAT
 - SAT
 - VAT/SAT
- Measurements of the adipose tissue area will be performed by a central reader blinded to the clinical and pathological data.

10.8. Appendix 8: JASSO Guidelines

Eleven obesity-related health problems

The JASSO guideline defines 11 health disorders for diagnosis of “Obesity Disease” to subjects who need weight reduction from medical reason.

- 1) Glucose intolerance disorder (T2D, impaired glucose tolerance [IGT], and so on)
- 2) Dyslipidemia
- 3) Hypertension
- 4) Hyperuricemia and Gout
- 5) Cardiovascular disease, myocardial infarction and Angina
- 6) Cerebral infarction and transient ischemic attack (TIA)
- 7) Non-alcoholic fatty liver disease (NAFLD)
- 8) Menstruation disorder and infertility
- 9) Obstructive sleep apnea syndrome (OSAS) and obesity-hypoventilation syndrome
- 10) Motor dysfunction: arthritis/osteoarthritis (knee, hip joint, supine and so on)
- 11) Obesity-related renal disease

Physical activity

The JASSO guideline indicated the amount of physical activity according to the purpose of weight loss:

- for prevention of weight gain; 150 to 250 minutes (1,200 to 2,000 kcal) per week
- for weight loss:
 - moderate intensity physical activity less than 150 minutes per week to provide only modest weight loss
 - moderate intensity physical activity between 225 and 420 minutes per week to provide 5 to 7.5 kg weight loss
 - greater amounts of physical activity to provide more weight loss

For example, moderate intensity physical activities (3-6 METs) are slightly fast walking (4 km/hour) and bicycle commuting (<16 km/hour), etc.

Before starting exercise therapy, participants will be confirmed the degree of obesity-related health problems such as lifestyle related diseases, orthopedic diseases, the presence or absence of treatment, medical history, and exercise habits, and discussed contents of physical activities that can be safely implemented according to the participant’s situation (JASSO 2022).

10.9. Appendix 9: Prohibited Medications or Medications with Special Use Restrictions

10.9.1. 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.

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

10.9.1.1. Glucose-lowering Medications

Participants without T2D 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, GLP-1 receptor agonists, GIP/GLP-1 receptor agonists and DPP-4 inhibitor are prohibited within 90 days prior to Visit 1 and throughout the study. The following medications are examples:

- dulaglutide
- liraglutide
- semaglutide
- exenatide

- tirzepatide
- sitagliptin
- saxagliptin
- linagliptin
- alogliptin

10.9.1.2. Weight Loss Medications

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

- mazindol
- Bofu tsusho san (Chinese herbal medicine)
- liraglutide
- semaglutide
- orlistat
- sibutramine
- phenylpropanolamine
- phentermine
- lorcaserin
- phentermine/topiramate
- naltrexone/bupropion
- ingested material that transiently occupies space in the stomach, for example, Plenity®
- over-the-counter medications, for example, alli®

10.9.1.3. Weight Gain Medications

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

- imipramine
- amitriptyline
- mirtazapine
- paroxetine
- phenelzine
- chlorpromazine
- thioridazine

- clozapine
- olanzapine
- quetiapine
- valproic acid (and its derivatives)
- lithium

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

10.9.1.4. 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. Participants who chronically use these drugs should be excluded.

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

10.9.2. Medications with Special Use Restrictions**10.9.2.1. 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. 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[®])

10.9.2.2. 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

10.10. Appendix 10: Definition and Management of Diabetes

Criteria for Diagnosis of T2D and nonT2D

Participants are categorized as those with T2D or nonT2D (including borderline-type diabetes and normoglycemia), as defined by Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020).

The T2D populations are defined who have diabetes according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020), history of ketoacidosis or hyperosmolar state/coma, or laboratory evidence of diagnostic of DM during screening including either HbA1c $\geq 6.5\%$ (48 mmol/mol), or glucose levels (fasting glucose ≥ 126 mg/dL and/or random glucose ≥ 200 mg/dL):

- a) Diagnosis of T2D
 - i. Both glucose level and HbA1c meets diabetic type criteria at Visit 1
 - ii. Only glucose level meets diabetic type criteria at Visit 1
 - ✧ With typical symptoms of DM or definite diabetic retinopathy
 - ✧ Without typical symptoms of DM or definite diabetic retinopathy, re-exam at Visit 2 and:
 - Both glucose level and HbA1c meet diabetic type criteria
 - Only glucose level meets diabetic type criteria
 - Only HbA1c meets diabetic type criteria
 - iii. Only HbA1c meets diabetic type criteria at Visit 1, re-exam at Visit 2 and
 - Both glucose level and HbA1c meet diabetic type criteria
 - Only glucose level meets diabetic type criteria
 - Only HbA1c meets diabetic type criteria
- b) Prior treatment (within 3 months prior to Visit 1) with DPP-4 inhibitors, oral GLP-1 RA, or any injectable therapy for T2D

The nonT2D populations are defined who have not diabetes according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020) and laboratory evidence of normoglycemia or borderline type during screening including either HbA1c, or glucose levels;

- a) Diagnosis of nonT2D
 - i. Normoglycemia
 - ✧ Meet both HbA1c $< 6.0\%$ (42 mmol/mol) and glucose level < 110 mg/dL at both Visit 1 and Visit 2
 - ii. Borderline type diabetes
 - ✧ Meet either HbA1c 6.0% - 6.4% (42- 46 mmol/mol) or glucose level 110-125 mg/dL at Visit 1 and Visit 2

Glycemic Classification

All participants without laboratory tests suggestive of diabetes will be classified as having T2D. In keeping with Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020), at least 2 abnormal tests at Visit 1 and Visit 2.

Definition and Management of Incident Diabetes

Definition of incident diabetes

Incident diabetes is defined when any 1 of the following occur after randomization according to Japanese Clinical Practice Guideline for Diabetes 2019 (Araki et al. 2020):

- 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 $\geq 6.5\%$ (48 mmol/mol)
 - FG ≥ 126 mg/dL (7.0 mmol/L)
 - Random glucose ≥ 200 mg/dL (11.1 mmol/L), if measured
- initiation of any medication for the treatment of diabetes

Confirmation of diabetes diagnosis

In the event 1 abnormal value is observed (HbA1c $\geq 6.5\%$ [48 mmol/mol]) OR fasting glucose ≥ 126 mg/dL (7.0 mmol/L) OR random glucose ≥ 200 mg/dL (11.1 mmol/L) 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.

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

- HbA1c $\geq 6.5\%$ (48 mmol/mol) is observed at 2 measurements any time during the study.
- FG value ≥ 126 mg/dL (7.0 mmol/L) is observed at a consecutive FG measurement (either at a scheduled or an unscheduled visit) following an isolated FG value ≥ 126 mg/dL (7.0 mmol/L).
 - If diabetes diagnosis has not been confirmed at the consecutive FG measurement, another FG 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 diabetes events

- Diabetes diagnosis and the onset date as assessed by investigator will be recorded in the AE eCRF and the dedicated endpoint eCRF.
- 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 eCRFs.
- All reported or suspected cases of incident diabetes will be adjudicated by an independent clinical endpoint committee (adjudication committee).

- Decisions of the adjudication committee regarding diabetes diagnosis and the onset date will be recorded in the dedicated adjudication eCRF.

Management of Diabetes

Non-T2D 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
- provided a diary to record hypoglycemic episodes per Section 8.3.3.4.

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-1R agonists, GIP/GLP-1RA, and any injectable therapy for T2DM, which are prohibited in the study. GLP-1RA, GIP/GLP-1RAs, DPP-4 inhibitors and any injectable therapy for T2DM should not be used in combination with orforglipron due to overlapping pharmacology and the potential for increased GI side effects. Monitoring for hypoglycemia includes capture of events as defined in Section 8.3.3.4. Date of diagnosis of diabetes will be captured in the electronic case report form (eCRF). If participants are diagnosed with T1DM (rather than T2DM), discontinuation of study intervention should occur as noted in Section 7.1.

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

Implementation of This Appendix

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

Exceptional Circumstances

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

Implementing Changes under Exceptional Circumstances

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"
- a change in the method of study intervention administration
- dispensation of additional study intervention during an extended treatment period
- alternate delivery of study intervention and ancillary supplies, and
- provision of their personal or medical information required prior to implementation of these activities.

Changes in Study Conduct during Exceptional Circumstances

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

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

Remote Visits

Types of remote visits

Telemedicine: Telephone or technology-assisted virtual visits, or both, are acceptable to complete appropriate assessments. Assessments to be completed in this manner include, but are not limited to, collection of AEs, SMBG values, and concomitant medications.

Mobile healthcare: Healthcare visits may be performed by a mobile healthcare provider at locations other than the study site when participants cannot travel to the site due to an exceptional circumstance if written approval is provided by the sponsor. Procedures performed at such visits include, but are not limited to, concomitant medications, SMBG values, vital signs (BP and PR), body weight, collection of blood samples, physical assessments, administration of PROs if validated for these types of visits, administration of study intervention, and collection of health information.

Other alternative locations: During exceptional circumstances, laboratory samples may be drawn locally, if needed outside of mobile health care visits.

Data capture

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

Safety reporting

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

Return to on-site visits

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

Local Laboratory Testing Option

Local laboratory testing may be conducted in lieu of central laboratory testing. However, central laboratory testing must be retained for: Visits 3, 10, and 15. 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, 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 the 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 visits to randomization visit: the participant will proceed to the next study visit per the usual Schedule of Activities, provided that randomization visit must be conducted within 30 days from first screening/lead-in 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 visits 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 Schedule of Activities 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 Schedule of Activities (Section 1.3). 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.

Allowed adjustments to visit windows are as follows:

Visit Number	Tolerance
Visit 2, 4 through 11, 13, 14, 16, 17, 19, 20, and Follow-up Visit	Within 3 days before or after the intended date per the Schedule of Activities.
Visit 3, 12, 15, 18 and 21	Within 7 days before or after the intended date per the Schedule of Activities.

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

Documentation

Changes to study conduct will be documented

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

Source documents at alternate locations

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

10.12. Appendix 12: Abbreviations and Definitions

Term	Definition
abuse	Use of a study intervention for recreational purposes or to maintain an addiction or dependence
AE	adverse event
AHM	antihyperglycemic medication
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AST	aspartate aminotransferase
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.
BCRP	breast cancer resistance protein
BG	blood glucose
BMI	body mass index
BP	blood pressure
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDK-EPI	Chronic Kidney Disease Epidemiology Collaboration
CEC	clinical endpoint committee
CFR	Code of Federal Regulations
CHF	congestive heart failure
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
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.

Term	Definition
compliance	Adherence to all study-related, good clinical practice (GCP), and applicable regulatory requirements.
CONSORT	Consolidated Standards of Reporting Trials
CRF	case report form; a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor for each trial participant.
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computerized tomography
CTA	clinical trial agreement
CV	cardiovascular
CWM	chronic weight management
CYP3A4	cytochrome P450 3A4 enzyme
DBP	diastolic blood pressure
DMC	data monitoring committee. A data monitoring committee, or data monitoring board (DMB) 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.
DSM-V	Diagnostic and Statistical Manual of Mental Disorders, 5 th Edition
DPP-4	DPP-4 dipeptidylpeptidase-4 enzyme
ECG	electrocardiogram
eCOA	electronic clinical outcome assessment
eCRF	electronic case report form
ED	early discontinuation
EDC	electronic data capture
eGFR	estimated glomerular filtration rate (calculated by Japanese Society of Nephrology coefficient-modified CKD EPI equation)
EMA	European Medicines Agency
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.

Term	Definition
enter	Participants entered into a study are those who sign the informed consent form directly or through their legally acceptable representatives.
EQ-5D-5L	European Quality of Life 5 Dimensions 5 Level
ERB	ethical review board
FBG	fasting blood glucose
FDA	US Food and Drug Administration
FFA	free fatty acid
FG	fasting glucose
GCP	good clinical practice
GI	gastrointestinal
GIP	glucose-dependent insulintropic polypeptide
GLP-1	glucagon-like peptide-1
GLP-1 RA	GLP-1 receptor agonist
GLP-1R	GLP-1 receptor
HbA1c	glycated hemoglobin
HBcAb	hepatitis B core antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	HDL
HDL-C	high-density lipoprotein cholesterol
HOMA2-B	homeostasis model assessment estimates steady state beta cell function
HOMA2-IR	homeostasis model assessment estimates insulin resistance beta cell function
hsCRP	high-sensitivity C-reactive protein
IB	Investigator's Brochure
ICE	intercurrent event

Term	Definition
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IGT	impaired glucose tolerance
IRB	Institutional Review Board
IMP	Investigational Medicinal Product (see also “investigational product”) A medicinal product which is being tested or used as a reference, including as a placebo, in a clinical trial.
informed consent	A process by which a participant voluntarily confirms their willingness to participate in a particular study, after having been informed of all aspects of the study that are relevant to the participant’s decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
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 Trials version
IWRS	interactive web-response system
JASSO	Japan Society for the Study of Obesity
LDL	low density lipoprotein
LDL-C	low-density lipoprotein cholesterol
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.

Term	Definition
MEN2	multiple endocrine neoplasia syndrome type 2
MET	metabolic equivalent
MHP	mental health professional
MMRM	mixed model for repeated measures
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 carcinoma
NAFLD	non-alcoholic fatty liver disease
NIMH	National Institute of Mental Health
OATP	organic anion transporting polypeptide
OSAS	obstructive sleep apnea syndrome
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
PK/PD	pharmacokinetics/pharmacodynamics
P-gp	permeability glycoprotein
PGI-C	Patient Global Impression of Change
PGI-S	Patient Global Impression of Status
PHQ-9	Patient Health Questionnaire (9-item)
PI	principal investigator
PMDA	Pharmaceuticals and Medical Devices Agency
PT-INR	prothrombin time-international normalized ratio
QTL	quality tolerance limit
SAE	serious adverse event
SAP	statistical analysis plan
SAT	subcutaneous adipose tissue

Term	Definition
SBP	systolic blood pressure
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 Health Survey Version 2
SGLT-2i	sodium-glucose cotransporter 2 inhibitor
SIB	suicidal ideation or behavior
SMBG	self-monitoring of blood glucose
SoA	Schedule of Activities
STEPS	STEPwise approach to Surveillance
T1D	type 1 diabetes
T2D	type 2 diabetes
TASA	NIMH Trial Group
TBL	total bilirubin
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.
TG	triglyceride
TIA	transient ischemic attack
TSH	thyroid-stimulating hormone
Tx	treatment
TxP	treatment period
UACR	urine albumin/creatinine ratio
ULN	upper limit of normal
VAS	visual analog scale
VAT	visceral adipose tissue
VLDL-C	very low-density lipoprotein cholesterol

Term	Definition
WNOCBP	women not of childbearing potential
WOCBP	women of childbearing potential

10.13. Appendix 13: Protocol Amendment History

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

Amendment [a]

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.

The overall changes and rationale for the changes made to this protocol are described in the following table:

Amendment Summary for Protocol J2A-JE-GZPD Amendment (a)

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. - Divided the de-escalation and re-escalation table into 2 tables and positioned them with associated text. - Updated the de-escalation for participants currently taking 3 mg to indicate that these participants will be discontinued from study intervention. - Provided clarifications if re-escalation attempts are not tolerated. - Provided further clarification for participants assigned to the 6 mg arm. - Moved some text within Section 6.6.1.	Clarifications
1.1 Synopsis	Study Population: “less than” was changed to “approximately”.	Correction
1.3 Schedule of Activities	Fasting Visits: “antihypertensive medications” was changed to “antihyperglycemic medications”	Correction
1.3 Schedule of Activities	Prior treatments for indication: “T2D and” was deleted from “Includes prior T2D and weight management medications.”	Correction
1.3 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 GZGP protocol (b)
1.3 Schedule of Activities	PK Samples: “or post-dose” was changed to “post-dose”	Correction

Section # and Name	Description of Change	Brief Rationale
6.1 Study Intervention(s) Administered	Background Diabetes Therapy After End of Treatment Period: “PI” was changed to “investigator”	Clarification
6.6.1 Management of Gastrointestinal Symptoms During Dose Escalation	“AHM” was changed to “antihyperglycemic medications”	Correction
6.9 Prior and Concomitant Therapy	“AHM” was changed to “antihyperglycemic medications”	Correction
6.9.6 Antihyperglycemic Medications after Permanent Discontinuation of Study Intervention	“PI” was changed to “investigator”	Clarification
8.2.3 Electrocardiograms	“Single” was changed to “Triplicate”	Correction
8.2.3 Electrocardiograms	Added text “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 GZGP protocol (b)
8.6 Genetics	“clinical trials” was changed to “clinical traits”	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	“baseline” was changed to “randomization”	Clarification
10.4.2 Contraceptive Guidance	Examples of different forms of contraception: 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
10.7 Appendix 7: Measurement of Height, Weight, Waist Circumference, Vital Signs, Electrocardiogram, Computed Tomography	Electrocardiogram: “at least 10 minutes.” was changed to “approximately 5 to 10 minutes.”	Correction
10.9.1.4 Strong CYP3A Inhibitors or Inducers, Sensitive P-gp/BCRP Substrates, and OATP Inhibitors	“sofobuvir” was changed to “sofosbuvir”	Correction

Section # and Name	Description of Change	Brief Rationale
10.10 Appendix 10: Definition and Management of Diabetes Criteria for Diagnosis of T2D and nonT2D	Deleted “The duration of treatment in ATTAIN-J (Study GZPD) is determined by glycemic status at randomization.”	Correction
10.12 Appendix 12: Abbreviations and Definitions	“antihypertensive medications” was changed to “antihyperglycemic medications”	Correction
Throughout	Minor editorial changes have been made throughout	These are minor; therefore, they have not been individually summarized

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