Supplementary Appendix

Supplement to: Wharton S, Blevins T, Connery L, et al. Daily oral GLP-1 receptor agonist orforglipron for adults with obesity. N Engl J Med 2022;387:877-88. DOI: 10.1056/NEJMoa2302392

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

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Author Contributions

DR and AH contributed to the study design. MK provided medical oversight during the trial. SR and RL were responsible for the statistical analyses. MK and Gary Grant (Eli Lilly and Company) wrote the first draft of the manuscript. SR, RL, XM, KJM, AH, DR, EP, and CK are the guarantors of this work and, as such, take responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in interpretation of the data and critical review of the manuscript, had access to the data and approved of this manuscript to be submitted for publication.

Full Exclusion and inclusion criteria

INCLUSION CRITERIA

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

Age

1. Participants must be 18 or the legal age of consent in the jurisdiction in which the study is taking place to 75 years of age inclusive, at the time of signing the informed consent

Type of Participant and Disease Characteristics

2. Have an HbA1c <6.5%

Weight

3. Have a BMI of
    - ≥30 kg/m^2
    - ≥27 kg/m^2 and <30 kg/m^2 with at least 1 of the following weight-related comorbidities
        - hypertension: on BP-lowering medication or having systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg at screening
        - dyslipidemia: on lipid-lowering medication or having 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) for men or HDL <50 mg/dL (1.3 mmol/L) for women at screening
        - cardiovascular disease: (for example, ischemic cardiovascular disease, New York Heart Association [NYHA] Functional Classification Class I-II heart failure. See Section **Error! Reference s ource not found.**)

- obstructive sleep apnea (only in participants >30 years of age)

4. Have had a stable body weight for the 3 months prior to randomization (5% body weight gain and/or loss)

Sex and Contraceptive/Barrier Requirements

5. Male and/or female

Contraceptive use by participants should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

Women not of childbearing potential (for definitions, see Section Error! Reference source not f ound.) and men can participate in this study considering the following:

a. Male participants:

- Males who agree to use highly effective/effective methods of contraception may participate in this trial.
- Please refer to Section **Error! Reference source not found.** (Appendix 4) for definitions a nd additional guidance related to contraception.

b. Female participants:

- Women of childbearing potential (WOCBP) are excluded from this trial.
- Women not of childbearing potential (WNOCBP) may participate in this trial.
- Please refer to Appendix 4 for definitions and additional guidance related to contraception.

Note: Hormone replacement therapy in postmenopausal women is allowed but women must be on stable therapy for 3 months prior to screening/Visit 1.

Informed Consent

6. Capable of giving signed informed consent as described in Section **Error! Reference source n ot found.** (Appendix 1), which includes compliance with the requirements and restrictions listed in the ICF and in this protocol

Exclusion Criteria
Participants are excluded from the study if any of the following criteria applies:

Medical Conditions

Diabetes Related

7. Have any prior diagnosis of type 1 diabetes mellitus (T1DM or T2DM, or rare forms of diabetes mellitus
8. Have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more of HbA1c ≥6.5% (48 mmol/mol), fasting serum glucose ≥126 mg/dL (7.0 mmol/L), or random glucose ≥200 mg/dL (11.1 mmol/L)

Obesity Related

9. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty, if performed >1 year prior to screening)
10. 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)

11. Have or plan to have endoscopic and/or device-based therapy for obesity or have had device removal within the last 6 months prior to screening including but not limited to
    - mucosal ablation
    - gastric artery embolization
    - intragastric balloon, and
    - duodenal-jejunal endoluminal liner.

Other Medical

12. Have renal impairment measured as estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2, calculated by Chronic Kidney Disease Epidemiology (CKD-EPI) as determined by central laboratory during screening
13. Have a known clinically significant gastric emptying abnormality (for example, severe gastroparesis or gastric outlet obstruction), have undergone gastric bypass (bariatric) surgery or restrictive bariatric surgery (for example, Lap-Band®), or chronically take drugs that directly affect GI motility
14. Have a history of acute or chronic pancreatitis. A participant with a history of acute pancreatitis caused by gallstones may be included in the study if the participant has a cholecystectomy to resolve the problem
15. Have a history of significant active or unstable Major Depressive Disorder (MDD) or other severe psychiatric disorder (for example, schizophrenia, bipolar disorder, or other serious mood or anxiety disorder) within the last 2 years

    Note: Participants with MDD or generalized anxiety disorder whose disease state is considered stable for the past 2 years and expected to remain stable throughout the course of the study, in the opinion of the Investigator, may be considered for inclusion if they are not on excluded medications.

16. Have a lifetime history of suicide attempt
17. Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1 or 3, prior to randomization
18. On the C-SSRS at Visit 1 or 3, prior to randomization:

    - a "yes" answer to Question 4 (Active Suicidal Ideation with Some Intent to Act, Without Specific Plan) on the "Suicidal Ideation" portion of the C-SSRS

    or

    - a "yes" answer to Question 5 (Active Suicidal Ideation with Specific Plan and Intent) on the "Suicidal Ideation" portion of the C-SSRS

    or

    - a "yes" answer to any of the suicide-related behaviors (actual attempt, interrupted attempt, aborted attempt, preparatory act, or behavior) on the "Suicidal Behavior" portion of the C-SSRS

    and

    - the ideation or behavior occurred within the past month.

19. Have poorly controlled hypertension (that is, mean seated systolic BP ³160 mm Hg or mean seated diastolic BP ³100 mm Hg) at screening, renal artery stenosis, or evidence of labile BP including symptomatic postural hypotension. Participants on antihypertensive medications must be on a stable dose for at least 3 months prior to screening and must meet the protocol criterion for hypertension control

20. Have an elevated resting pulse rate (PR) (>100 bpm) at screening and baseline

21. Have any of the following cardiovascular conditions within 3 months prior to Screening:
    - acute myocardial infarction
    - cerebrovascular accident (stroke)
    - unstable angina, or
    - hospitalization due to congestive heart failure (CHF).

22. Ongoing or history of frequent intermittent or chronic tachyarrhythmia syndromes (such as atrial fibrillation, supraventricular tachycardia, and positional orthostatic tachycardia syndrome).

    Note: Participants with history of premature atrial contractions or premature ventricular contractions may be included.

23. Have a history of NYHA Functional Classification III or IV CHF (see Section **Error! R eference source not found.**)

24. Have an electrocardiogram (ECG) considered by the Investigator with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening

25. Have a personal or family history of long QT syndrome, family history of sudden death in a first-degree relative (parents, siblings, or children) before the age of 40 years, or a personal history of unexplained syncope within the last year. Use of prescription or over-the-counter medications known to significantly prolong the QT or QTc interval at screening

26. Have a history of clinically significant gallbladder disease. However, participants with cholecystectomy may be included in the study

27. Have signs and symptoms of any other liver disease other than non-alcoholic fatty liver disease, or any of the following, as determined by the central laboratory during screening
    - ALT level >3.0X ULN for the reference range
    - ALP level >1.5X ULN for the reference range, or
    - TBL >1.5X ULN for the reference range (except for cases of known Gilbert's Syndrome)

28. Have evidence of hypothyroidism or hyperthyroidism based on clinical evaluation and/or an abnormal thyroid-stimulating hormone that, in the opinion of the Investigator, would pose a risk to patient safety. Subjects on a stable dose of thyroid replacement therapy for at least the prior 3 months who are clinically euthyroid and who are anticipated to remain on this dose throughout the trial period may be eligible if they meet the other criteria

29. Have a known self or family history (first-degree relative) of multiple endocrine neoplasia type 2A or type 2B, thyroid C-cell hyperplasia, or medullary thyroid carcinoma

30. Have a serum calcitonin level (at Visit 1) of

    - ≥20 ng/L, if eGFR ≥ 60 mL/min/1.73 m^2 or
    - ≥35 ng/L if eGFR < 60 mL/min/1.73 m^2 (as determined by central laboratory at Visit 1)

31. Have evidence of a significant, uncontrolled endocrine abnormality (for example, thyrotoxicosis or adrenal crises), in the opinion of the Investigator

32. Have a history of an active or untreated malignancy or are in remission from a clinically significant malignancy (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) for less than 5 years

33. Have evidence of human immunodeficiency virus (HIV) and/or positive HIV antibodies historically or at screening

34. Evidence of hepatitis B and/or positive hepatitis B surface antigen.

35. Hepatitis C as defined by presence of hepatitis C virus (HCV) RNA or positive hepatitis C antibody (anti-HCV). Participants treated for hepatitis C (and diagnosed as cured) must have an RNA test at screening and also be RNA negative for at least 3 years prior to screening to be eligible for the study

36. Have a history of any other condition (such as known drug or alcohol abuse, diagnosed eating disorder, or other psychiatric disorder) that, in the opinion of the Investigator, may preclude the participant from following and completing the protocol

37. Have an average weekly alcohol intake that exceeds 21 units per week (males) and 14 units per week (females) [1 unit = 12 oz or 360 mL of beer; 5 oz or 150 mL of wine; 1.5 oz or 45 mL of distilled spirits]

38. Have a history of use of marijuana or tetrahydrocannabinol (THC-containing products within 3 months of enrollment or unwillingness to abstain from marijuana or THC-containing products use during the trial

    Note: If a participant has used cannabidiol oil during the past 3 months but agrees to refrain from use for the duration of the study, the participant can be enrolled.

39. Have had a transplanted organ (corneal transplants [keratoplasty] are allowed) or are awaiting an organ transplant

40. Have had any exposure to GLP-1 analogs, or other related compounds within the prior 3 months or any prior history of hypersensitivity/allergies to these medications. Have known or suspected hypersensitivity to trial product(s), to selective GLP-1 RAs or GIP/GLP-1 or GLP-1/Gcg dual receptor agonists.

    - Participants who previously took GLP-1 analogs or related compounds and who discontinued those medications for intolerability or lack of efficacy should not be randomized.

41. Have had a blood donation of ³500 mL within the previous 8 weeks of study screening or a blood transfusion or severe blood loss within the prior 3 months, or have known hemoglobinopathy (for example, hemolytic anemia, sickle cell anemia), or have a hemoglobin value <11 g/dL (males) or <10 g/dL (females)

42. Triglycerides >500 mg/dL (5.7 mmol/L). If the patient is on lipid-lowering therapies, doses must be stable for 3 months prior to screening

43. Have evidence of a significant active, uncontrolled medical condition, or a history of any medical problem capable of constituting a risk when taking the study medication or interfering with the interpretation of data, as judged by the screening Investigator at screening

44. Have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that, in the opinion of the Investigator, is likely to require concurrent treatment with systemic glucocorticoids in the next 9 months

45. Have difficulty swallowing capsules

Prior/Concomitant Therapy

46. Unless otherwise specified, all concomitant medications should be at a stable dose for at least 3 months prior to randomization

47. Are receiving or have received within 3 months prior to screening chronic (>2 weeks) systemic glucocorticoid therapy (excluding topical, intraocular, intranasal, single intraarticular injection, or inhaled preparations)

48. Have current treatment with or history of treatment with (within 3 months prior to screening) medications that may cause significant weight gain including, but not limited to, tricyclic antidepressants, atypical antipsychotics, and mood stabilizers. However, participants at a stable dose (greater than 6 months and with no expectation that the dose will change within the next year) and who are weight stable for the last 6 months on these medications may be included in the study.

    Examples of medications causing weight gain that must be at stable doses for at least 6 months and with no expectation of changing within the next year include
    - imipramine
    - amitriptyline
    - mirtazapine
    - paroxetine
    - phenelzine
    - chlorpromazine
    - thioridazine
    - clozapine
    - olanzapine
    - valproic acid and its derivatives, and
    - lithium.

    Note: Selective serotonin reuptake inhibitors other than paroxetine are permitted.

49. Have taken within 3 months prior to screening medications (prescribed or over the counter) or alternative remedies (including herbal/nutritional supplements) intended to promote weight reduction

    Examples include, but are not limited to:

    - Saxenda® (liraglutide 3.0 mg) or other GLP-1 RA
    - Xenical®/Alli® (orlistat)
    - Meridia® (sibutramine)
    - Acutrim® (phenylpropanolamine)
    - Sanorex® (mazindol)

- Adipex® or Lomaira™ (phentermine)
- BELVIQ® [lorcaserin]
- Qsymia™ (phentermine/topiramate combination)
- Contrave® (naltrexone/bupropion)
- Wegovy™ (semaglutide 2.4 mg), and
- other similar body weight reduction medication, including OTC medications, for example, allī®.

50. Use of metformin, or any other glucose-lowering medication, whether prescribed for polycystic ovarian syndrome or diabetes prevention, is not permitted
51. Are currently taking a central nervous system stimulant (for example, Ritalin-SRÒ) with the exception of caffeinated beverages at screening
52. Are receiving strong CYP3A inhibitors or CYP3A inducers or drugs that are P-gp/BCRP substrates with narrow therapeutic index. Please see Section **Error! R eference source not found.** for details
53. Evidence of regular use of known drugs of abuse in the opinion of the Investigator

Prior/Concurrent Clinical Study Experience

54. Are currently enrolled in any other clinical study involving an IP or any other type of medical research judged not to be scientifically or medically compatible with this study
55. Have participated, within the last 90 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, at least 5 elimination half-lives or 90 days, whichever is longer, should have passed. Also, if have participated within the last 6 months, whether on active drug or placebo, in a clinical study that contained a GLP-1 RA
56. Have previously completed or withdrawn from this study or any other study investigating LY3502970

Other Exclusions

57. Are women of childbearing potential
58. Are women acting as a surrogate, who are currently pregnant or breastfeeding, or who intend to become pregnant or to breastfeed at any time during the study or within 20 weeks after receiving the last dose of study drug
59. Are Investigator site personnel directly affiliated with this study and/or their immediate families. Immediate family is defined as a spouse, parent, child, or sibling, whether biological or legally adopted
60. Are employees of Eli Lilly and Company (Lilly) or are employees of a third-party organization involved in the study, which requires exclusion of their employees
61. Are, in the opinion of the Investigator or Sponsor, unsuitable for inclusion in the study

Exclusions Specifically for ABPM

The following additional exclusions apply only to participation in ABPM collections. A participant who qualifies for the study based on the above inclusion/exclusion parameters but does not qualify for ABPM may still participate in the study. Not being able or willing to participate in ABPM procedures is not considered a protocol deviation.

62. Participants with hypertension should have well-controlled BP (<140/90), regardless of antihypertensive treatment. Participants receiving treatment for hypertension should be on a stable antihypertensive regimen for at least 3 months prior to screening

Note: If the Investigator anticipates a need to add antihypertensive medication during the course of the study, the participant should not be included in the ABPM procedures.

63. Participant works rotation shifts or works during the hours of 2200 to 0700
64. Participant performs strenuous manual labor that cannot be avoided during the monitoring period
65. Participant has a nondominant arm circumference of >55 cm at Visit 1
66. Participant is unable to obtain a valid baseline ABPM reading
67. Chronic use of nonsteroidal anti-inflammatory agents or cyclooxygenase-2 (COX-2) inhibitors, as well as other agents, prescription or over-the-counter, known to affect BP, are permitted; however, use of these agents on an as needed basis (PRN) during the 48-hour period immediately prior to or during each 24-hour ABPM recording is prohibited. Examples include, but are not limited to, decongestants (pseudoephedrine, ephedrine, phenylephrine, naphazoline, and oxymetazoline) and multi-symptom cold remedies
68. Male participants must abstain from use of phosphodiesterase type 5 (PDE-5) inhibitors (that is, tadalafil, vardenafil, and sildenafil) or yohimbine (herbal aphrodisiac) during the 48-hour period immediately prior to or during each 24-hour ABPM recording, since these medications may confound the BP measurements.

STATISTICAL ANALYSIS METHODS

Primary Estimand:

The primary efficacy assessment, guided by the "efficacy estimand", was conducted using the efficacy analysis set for the primary endpoint and secondary endpoints. For the "efficacy estimand", the hypothetical strategy is used to handle the intercurrent events (ICEs or permanent discontinuation of study drug), so only data collected before the occurrence of any ICEs were used in the MMRM analysis. Through the mixed model for repeated measures (MMRM) the potential efficacy measures (after the ICEs) had participants not had ICEs will be implicitly imputed. To confirm efficacy of orforglipron with adequate statistical power, the evaluation of the primary efficacy endpoint for orforglipron 36 mg and 45 mg compared to placebo were made by pooling 2 dose escalation regimens, i.e., combine 36mg-1 and 36mg-2 for 36mg and combine 45mg-1 and 45mg-2 for 45mg.

Supplementary tables and figures

Table S1. Representativeness of study participants.

Disease under investigation	**Obesity (BMI≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with ≥1 weight-related comorbidity without diabetes**
Special considerations related to:	
Sex and gender	According to WHO statistics, in 2016, 39% of men and 40% of women worldwide were overweight and 11% of men and 15% of women had obesity.
Age	Worldwide, obesity and overweight affect all adult age groups. In the United States in 2018, the prevalence of obesity was highest among adults aged 40 to 59 years (44%), followed by those ≥60 (42%), and those aged 20 to 39 years (39%).
Race or ethnic group	In terms of race and ethnicity, in 2018 the prevalence of obesity in the United States was highest in non-Hispanic Black adults (50%), followed by Hispanic adults (46%), non-Hispanic White adults (41%) and non-Hispanic Asian adults (16%). Without regard to obesity, in 2018 the United States population was 60% non-Hispanic White, 18% Hispanic or Latino, 13% non-Hispanic Black or African American, and 6% non-Hispanic Asian.
Geography	The prevalence of obesity is higher in the Oceania region, United States, Middle Eastern countries, South America (Brazil, Argentina), Canada, Australasia, Europe, and the Russian Federation. Rates are lowest in low- to middle-income countries.
Overall representativeness of this trial	The GZGI phase 2 trial was conducted in adults ≥18 years of age in 3 countries across 2 continents: Canada, Hungary, and the United States. The United States, which has a higher prevalence of obesity than Canada and Hungary, represented 71% of the study population. Women represented approximately 59% of the trial population and men 41%. The average age was 54 years (range 22 to 75 years), with 15% of participants aged ≥65 years. This is in line with the higher prevalence of obesity in the 40 to 59 year age group. In this trial, most of the participants were White (91%); only 7% were Black or African-American, and 14% were Hispanic or Latino.

Notes: Sex, race, and ethnicity was collected on the demographics electronic case report form at screening. Race and ethnicity, collected where permitted by local law, were reported by either the participant or participant's guardian using standardized categories aligned with regulatory guidance. Age was calculated based on birthdate provided at screening. Geography was based on the country of enrollment.

Table S2. Study and Treatment Discontinuation Details Among Participants.

	12mg N=50	24mg N=53	36mg-1 N=29	36mg-2 N=29	45mg-1 N=31	45mg-2 N=30	Placebo N=50
Discontinuation from the Study (Prior to Week 26) – no. (%)	4 (8.0)	2 (3.8)	0	3 (10.3)	4 (12.9)	2 (6.7)	4 (8.0)
Adverse event	1 (2.0)	0	0	3 (10.3)	1 (3.2)	2 (6.7)	0
Withdrawal by Subject	2 (4.0)	2 (3.8)	0	0	2 (6.5)	0	3 (6.0)
Lost to Follow Up	1 (2.0)	0	0	0	1 (3.2)	0	1 (2.0)
Discontinuation from the Study (After Week 26) – no. (%)	0	1 (1.9)	1 (3.4)	0	1 (3.2)	0	1 (2.0)
Withdrawal by Subject	0	1 (1.9)	1 (3.4)	0	1 (3.2)	0	0
Other	0	0	0	0	0	0	1 (2.0)
Discontinued study with a safety follow up visit	2 (4.0)	4 (7.5)	1 (3.4)	2 (6.9)	3 (9.7)	0	2 (4.0)
Adverse event	1 (2.0)	1 (1.9)	0	1 (3.4)	0	0	0
Withdrawal by subject	1 (2.0)	2 (3.8)	1 (3.4)	1 (3.4)	1 (3.2)	0	1 (2.0)
Other	0	1 (1.9)	0	0	2 (6.5)	0	1 (2.0)
Discontinued treatment – no. (%)	13 (26.0)	14 (26.4)	5 (17.2)	6 (20.7)	12 (38.7)	7 (23.3)	8 (16.0)
Adverse event	7 (14.0)	10 (18.9)	3 (10.3)	6 (20.7)	5 (16.1)	4 (13.3)	1 (2.0)
- GI Reaction	7 (14.0)	9 (17.0)	3 (10.3)	4 (13.8)	4 (12.9)	3 (10.0)	1 (2.0)
Withdrawal by Subject	5 (10.0)	4 (7.5)	2 (6.9)	0	4 (12.9)	1 (3.3)	5 (10.0)
Physician decision	0	0	0	0	0	1 (3.3)	0
Lost to Follow Up	1 (2.0)	0	0	0	1 (3.2)	0	1 (2.0)
Other	0	0	0	0	2 (6.5)	1 (3.3)	1 (2.0)

GI denotes gastrointestinal, N number of participants randomized, and no. number of participants in the specified category. GI included vomiting, nausea, diarrhoea, abdominal pain upper, constipation, abdominal discomfort, food poisoning, gastroesophageal reflux disease, regurgitation, and vomiting projectile.

Table S3. Percentage of participants achieving ≥5%, ≥10%, and ≥15% weight reduction (Efficacy Estimand)

	Orforglipron				
	12 mg	24 mg	36 mg	45 mg	Placebo
Number of participants at baseline	44	51	56	57	48
Week 26					
Percentage of participants who achieved a **≥5% body weight reduction**					
Observed % (n/N)	84.2 (32/38)	90.2 (37/41)	91.7 (44/48)	89.1 (41/46)	23.8 (10/42)
Model Estimated %	74.4	88.8	89.5	87.3	22.9
≥10% body weight reduction					
Observed % (n/N)	44.7 (17/38)	56.1 (23/41)	72.9 (35/48)	73.9 (34/46)	2.4 (1/42)
Model Estimated %	39.4	56.6	71.3	69.9	2.3
≥15% body weight reduction					
Observed % (n/N)	23.7 (9/38)	24.4 (10/41)	33.3 (16/48)	34.8 (16/46)	0 (0/42)
Model Estimated %	20.6	25.8	34.5	34.0	0.0
Week 36					
Percentage of participants who achieved a **≥5% body weight reduction**					
Observed % (n/N)	82.4 (28/34)	91.2 (31/34)	93.5 (43/46)	94.6 (35/37)	23.1 (9/39)
Model Estimated %	72.0	89.5	92.1	90.4	24.0
≥10% body weight reduction					
Observed % (n/N)	52.9 (18/34)	61.8 (21/34)	76.1 (35/46)	73.0 (27/37)	7.7 (3/39)
Model Estimated %	46.5	61.9	74.8	69.1	8.9
≥15% body weight reduction					
Observed % (n/N)	23.5 (8/34)	32.4 (11/34)	43.5 (20/46)	51.4 (19/37)	0 (0/39)
Model Estimated %	22.5	33.2	42.6	48.0	0.8

n = the number of participants who reached the weight reduction target; N = the number of participants with observed body weight measurements at the end point. Model estimated % were calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets. Only participants with a non-missing baseline value and at least one post-baseline value of the response variable were included in these analyses.

Table S4. Exploratory Endpoints (Efficacy Estimand)

	Orforglipron				Placebo
	12 mg	24 mg	36 mg	45 mg	
Glycated hemoglobin (%)					
Baseline	5.6 (0.1)	5.8 (0.1)	5.6 (0.1)	5.6 (0.1)	5.6 (0.1)
Change from baseline at Week 26	-0.4 (0.0)	-0.4 (0.0)	-0.4 (0.0)	-0.3 (0.0)	0.1 (0.0)
Change from baseline at Week 36	-0.4 (0.0)	-0.4 (0.0)	-0.4 (0.0)	-0.3 (0.0)	-0.1 (0.0)
Total cholesterol					
Baseline (mmol/L)	4.8 (0.2)	5.1 (0.2)	4.8 (0.1)	5.0 (0.1)	5.1 (0.2)
% Change from baseline at Week 26	-7.2 (2.2)	-7.6 (2.1)	-10.4 (1.9)	-7.8 (2.0)	-1.1 (2.2)
% Change from baseline at Week 36	-9.7 (2.2)	-8.8 (2.3)	-7.2 (2.0)	-6.2 (2.2)	-2.5 (2.3)
HDL					
Baseline (mmol/L)	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)	1.3 (0.1)	1.2 (0.1)
% Change from baseline at Week 26	-2.3 (2.1)	-2.5 (2.0)	-6.8 (1.8)	-6.1 (1.8)	-2.4 (2.0)
% Change from baseline at Week 36	0.5 (1.9)	-1.2 (1.9)	-1.6 (1.6)	-0.6 (1.8)	-3.6 (1.7)
LDL					
Baseline (mmol/L)	2.9 (0.1)	3.0 (0.1)	2.7 (0.1)	2.9 (0.1)	3.2 (0.1)
% Change from baseline at Week 26	-9.9 (3.5)	-7.7 (3.4)	-11.7 (3.1)	-8.2 (3.2)	-1.0 (3.6)
% Change from baseline at Week 36	-12.8 (3.4)	-10.2 (3.5)	-7.9 (3.2)	-8.2 (3.3)	-2.9 (3.6)
VLDL					
Baseline (mmol/L)	0.5 (0.0)	0.6 (0.0)	0.6 (0.0)	0.6 (0.0)	0.7 (0.1)
% Change from baseline at Week 26	-4.7 (4.9)	-12.0 (4.4)	-12.7 (4.1)	-9.5 (4.3)	1.9 (5.0)
% Change from baseline at Week 36	-11.4 (4.6)	-14.0 (4.5)	-12.3 (4.0)	-7.5 (4.5)	1.1 (5.0)
Triglycerides					
Baseline (mmol/L)	1.2 (0.1)	1.4 (0.1)	1.3 (0.1)	1.4 (0.1)	1.5 (0.1)
% Change from baseline at Week 26	-3.6 (5.1)	-12.5 (4.5)	-12.8 (4.2)	-9.6 (4.4)	2.1 (5.1)
% Change from baseline at Week 36	-11.9 (4.6)	-14.1 (4.5)	-11.9 (4.0)	-7.2 (4.5)	0.8 (4.9)
Systolic BP (mm Hg)					
Baseline	129.4 (1.7)	129.7 (1.5)	131.0 (1.5)	127.4 (1.5)	128.3 (1.6)
Change from baseline at Week 26	-5.4 (1.8)	-4.5 (1.8)	-10.1 (1.7)	-9.7 (1.7)	-3.8 (1.8)
Change from baseline at Week 36	-7.3 (1.8)	-6.9 (1.7)	-10.3 (1.5)	-12.1 (1.7)	-2.2 (1.7)
Diastolic BP (mm Hg)					
Baseline	82.8 (1.2)	82.2 (1.1)	81.2 (1.0)	79.2 (1.0)	81.2 (1.1)
Change from baseline at Week 26	-1.5 (1.1)	-0.3 (1.1)	-4.5 (1.0)	-2.7 (1.0)	-4.7 (1.1)
Change from baseline at Week 36	-2.7 (1.1)	-1.3 (1.1)	-4.4 (1.0)	-3.0 (1.0)	-3.1 (1.0)
Pulse rate (bpm)					
Baseline	73.8 (1.5)	72.4 (1.4)	69.5 (1.4)	70.2 (1.4)	69.3 (1.5)
Change from baseline at Week 26	5.4 (1.3)	6.7 (1.2)	6.0 (1.1)	8.1 (1.2)	-2.3 (1.2)
Change from baseline at Week 36	6.4 (1.4)	5.9 (1.4)	7.8 (1.3)	7.1 (1.3)	-2.0 (1.3)

Data are shown as least squares means (standard error). BP denotes blood pressure, HDL high-density lipoprotein, LDL low-density lipoprotein, and VLDL very low-density lipoprotein.

Table S5. Change From Baseline in Blood Pressure and Pulse Rate at Weeks 26 and 36 (Safety Analysis Set).

			Week 26		Week 36	
Treatment	**N**	**Baseline LSM (SE)**	**N**	**CFB LSM (SE)**	**N**	**CFB LSM (SE)**
Systolic Blood Pressure (mm Hg)						
Placebo	50	128.5 (1.56)	43	-3.6 (1.72)	43	-1.8 (1.62)
Orforglipron 12 mg	48	129.5 (1.60)	44	-5.4 (1.73)	44	-6.9 (1.62)
Orforglipron 24 mg	53	129.6 (1.52)	47	-4.8 (1.66)	46	-6.7 (1.57)
Orforglipron 36 mg	58	131.4 (1.45)	51	-9.2 (1.60)	50	-8.8 (1.51)
Orforglipron 45 mg	61	127.7 (1.42)	52	-8.8 (1.57)	51	-10.1 (1.49)
Diastolic Blood Pressure (mm Hg)						
Placebo	50	81.5 (1.07)	43	-4.7 (1.02)	43	-2.8 (0.98)
Orforglipron 12 mg	48	82.7 (1.10)	44	-1.5 (1.02)	44	-2.5 (0.98)
Orforglipron 24 mg	53	82.1 (1.04)	47	-0.4 (0.98)	46	-1.7 (0.95)
Orforglipron 36 mg	58	81.4 (1.00)	51	-4.4 (0.94)	50	-4.0 (0.91)
Orforglipron 45 mg	61	79.3 (0.97)	52	-2.7 (0.93)	51	-2.9 (0.90)
Pulse (beats/min)						
Placebo	50	69.6 (1.45)	43	-2.1 (1.21)	43	-1.8 (1.34)
Orforglipron 12 mg	48	73.9 (1.48)	44	4.6 (1.23)	44	5.3 (1.36)
Orforglipron 24 mg	53	71.9 (1.41)	47	5.5 (1.17)	46	3.2 (1.30)
Orforglipron 36 mg	58	69.3 (1.35)	51	6.2 (1.13)	50	7.4 (1.25)
Orforglipron 45 mg	61	69.8 (1.31)	52	7.2 (1.11)	51	6.0 (1.23)

Abbreviations: CFB = change from baseline; LSM = least squares mean; N = number of participants in the analysis population; SE = standard error.

Table S6. Changes in Antihypertensive and Lipid-lowering Medication Use.

		Orforglipron				Placebo
Category	Change status	12 mg	24 mg	36 mg	45 mg	
Antihypertensive therapy	No use at both baseline and postbaseline period	34 (68.0)	32 (60.4)	29 (50.0)	36 (59.0)	31 (62.0)
	Increased	0	0	0	0	0
	Not changed	5 (10.0)	3 (5.7)	7 (12.1)	8 (13.1)	6 (12.0)
	Decreased	0	0	0	0	0
	Cannot be determined	4 (8.0)	11 (20.8)	9 (15.5)	9 (14.8)	6 (12.0)
	Not Applicable	7 (14.0)	7 (13.2)	13 (22.4)	8 (13.1)	7 (14.0)
Antiobesity medication	No use at both baseline and postbaseline period	50 (100.0)	53 (100.0)	54 (93.1)	61 (100.0)	50 (100.0)
	Increased	0	0	0	0	0
	Not changed	0	0	0	0	0
	Decreased	0	0	0	0	0
	Cannot be determined	0	0	4 (6.9)	0	0
	Not Applicable	0	0	0	0	0
Lipid lowering medication	No use at both baseline and postbaseline period	39 (78.0)	42 (79.2)	43 (74.1)	43 (70.5)	41 (82.0)
	Increased	0	0	0	0	0
	Not changed	4 (8.0)	2 (3.8)	5 (8.6)	6 (9.8)	4 (8.0)
	Decreased	0	0	0	0	0
	Cannot be determined	3 (6.0)	8 (15.1)	7 (12.1)	5 (8.2)	3 (6.0)
	Not Applicable	4 (8.0)	1 (1.9)	3 (5.2)	7 (11.5)	2 (4.0)
Antiemetic	No use at both baseline and postbaseline period	47 (94.0)	40 (75.5)	52 (89.7)	52 (85.2)	50 (100.0)
	Increased	0	0	0	0	0
	Not changed	0	0	0	0	0
	Decreased	0	0	0	0	0
	Cannot be determined	3 (6.0)	13 (24.5)	6 (10.3)	9 (14.8)	0
	Not Applicable	0	0	0	0	0
Antidiarrheal	No use at both baseline and postbaseline period	48 (96.0)	44 (83.0)	54 (93.1)	56 (91.8)	47 (94.0)
	Increased	0	0	0	0	0
	Not changed	0	0	0	0	0
	Decreased	0	0	0	0	0
	Cannot be determined	2 (4.0)	9 (17.0)	4 (6.9)	5 (8.2)	3 (6.0)
	Not Applicable	0	0	0	0	0

Table S7. Additional Safety Parameters at Week 26 (Safety Analysis Set).

	Orforglipron						
	12 mg (N=50)	**24 mg (N=53)**	**36 mg-1 (N=29)**	**36 mg-2 (N=29)**	**45 mg-1 (N=31)**	**45 mg-2 (N=30)**	**Placebo (N=50)**
Total serum lipase – IU/L							
Baseline	30.8 (2.1)	32.2 (2.2)	31.7 (2.8)	35.0 (3.2)	34.9 (3.1)	28.8 (2.5)	30.3 (2.1)
% Change from baseline	19.2 (6.2)	19.6 (6.0)	16.8 (8.0)	18.9 (8.3)	26.0 (8.8)	40.0 (9.1)	-6.6 (4.9)
Total serum amylase							
Baseline	23.9 (1.8)	24.9 (1.8)	24.9 (2.3)	24.0 (2.3)	24.9 (2.3)	22.5 (2.0)	22.8 (1.7)
% Change from baseline	9.0 (4.3)	9.9 (4.2)	14.0 (5.9)	10.4 (5.8)	12.1 (5.9)	18.6 (5.8)	-4.7 (3.7)
Serum calcitonin – ng/L							
Baseline	1.2 (0.2)	1.5 (0.2)	1.2 (0.2)	0.9 (0.2)	1.2 (0.3)	1.4 (0.3)	1.0 (0.2)
% Change from baseline	-4.2 (6.6)	10.1 (7.4)	4.7 (9.3)	25.5 (11.7)	14.1 (10.6)	35.7 (11.7)	9.1 (7.6)
Serum Alkaline Phosphatase (IU/L)							
Baseline	82.2 (3.4)	84.0 (3.2)	78.1 (4.0)	81.5 (4.3)	90.2 (4.6)	73.4 (3.7)	87.2 (3.4)
% Change from baseline	-1.2 (2.1)	-3.9 (2.0)	-5.4 (2.7)	-8.0 (2.7)	-3.8 (2.8)	-9.9 (2.5)	-4.9 (2.1)
Serum Alanine Aminotransferase (IU/L)							
Baseline	24.3 (1.8)	24.3 (1.7)	24.4 (2.3)	22.0 (2.1)	24.6 (2.3)	21.1 (1.9)	24.7 (1.8)
% Change from baseline	-22.3 (3.6)	-23.4 (3.4)	-27.9 (4.3)	-22.8 (4.8)	-24.1 (4.7)	-25.8 (4.3)	-14.2 (4.0)
Serum Aspartate Aminotransferase (U/L)							
Baseline	19.9 (1.0)	20.9 (1.0)	21.9 (1.4)	19.6 (1.3)	20.4 (1.3)	18.4 (1.1)	20.1 (1.0)
% Change from baseline	-9.3 (3.2)	-7.5 (3.2)	-12.4 (4.0)	-5.0 (4.6)	-7.7 (4.4)	-11.0 (3.9)	-4.4 (3.4)

Data are shown as least squares means (standard error). N denotes number of subjects in the analysis population.

Figure S1. Patient Disposition (CONSORT Diagram).

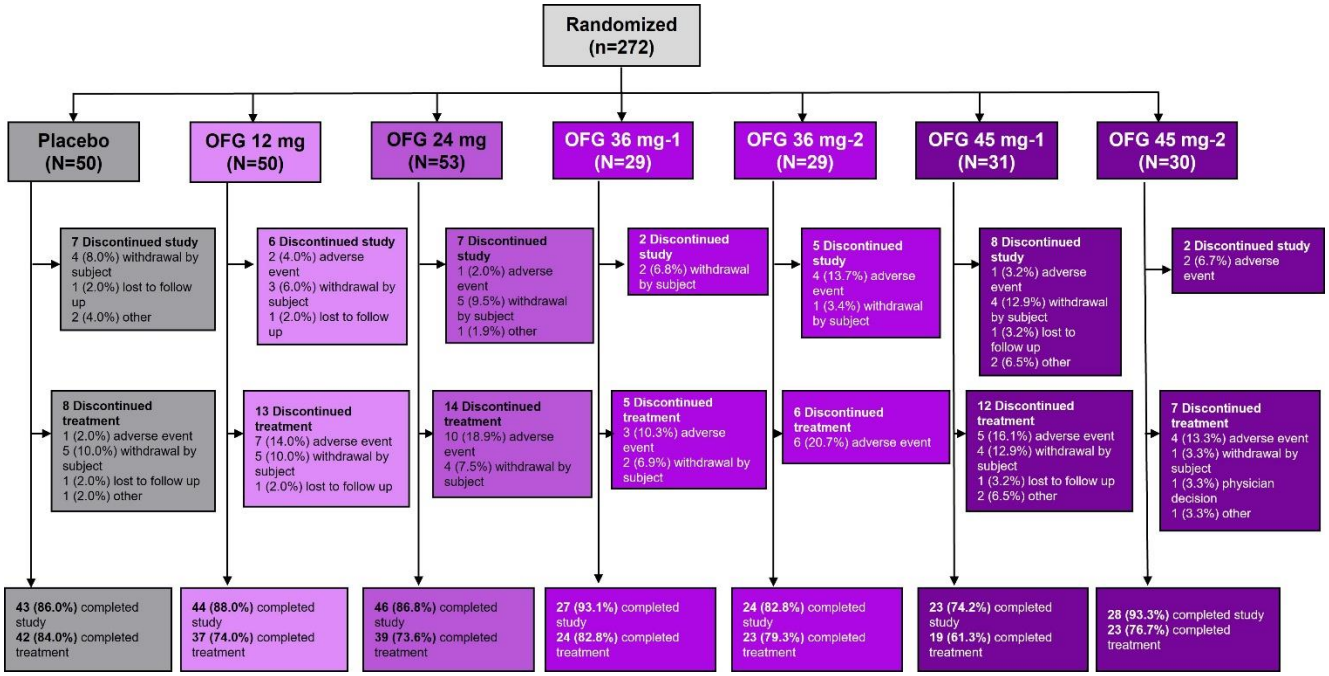
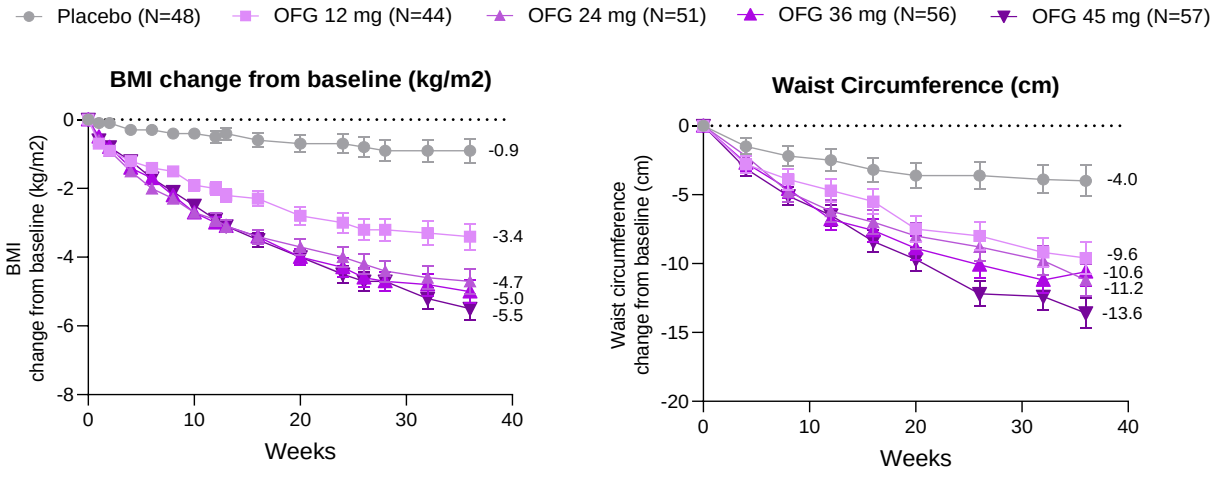
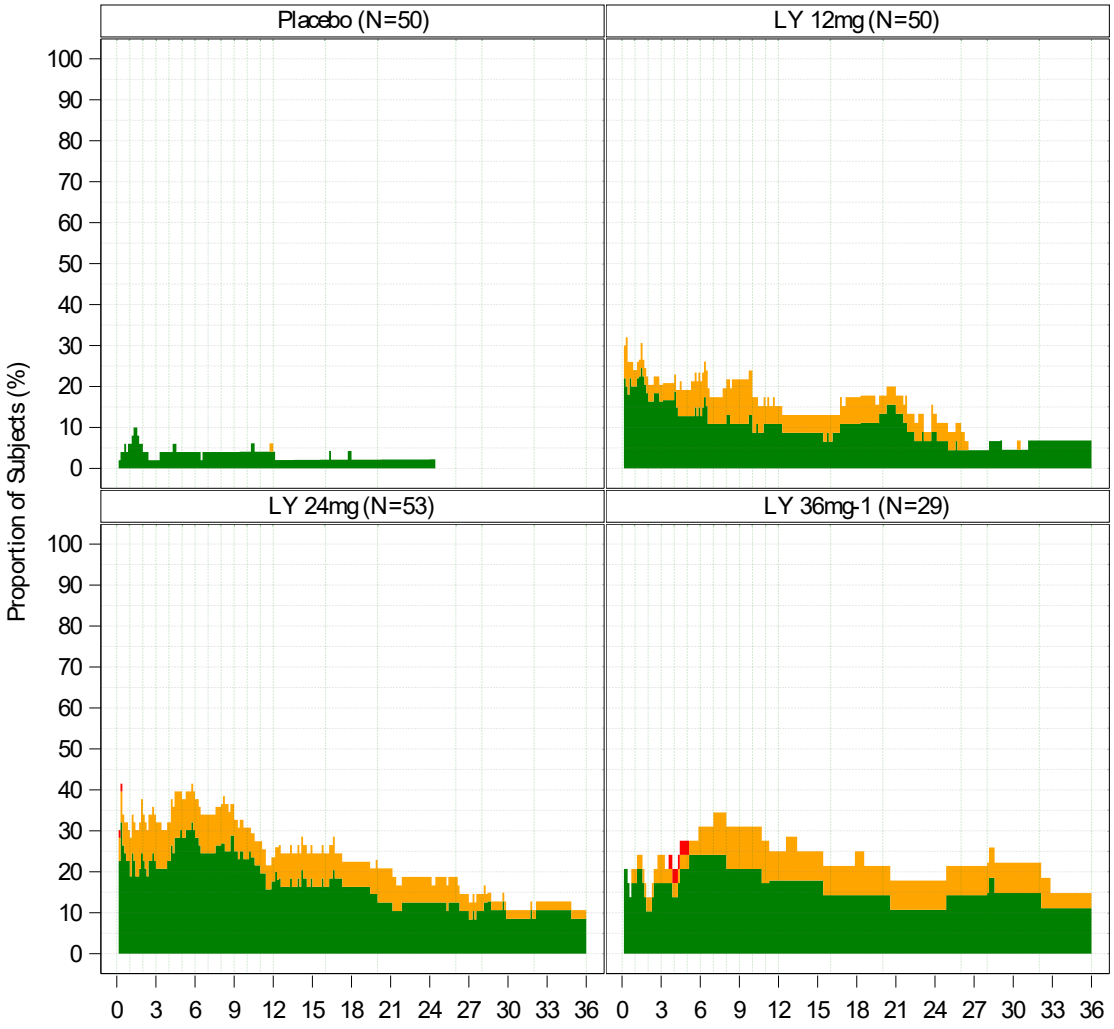


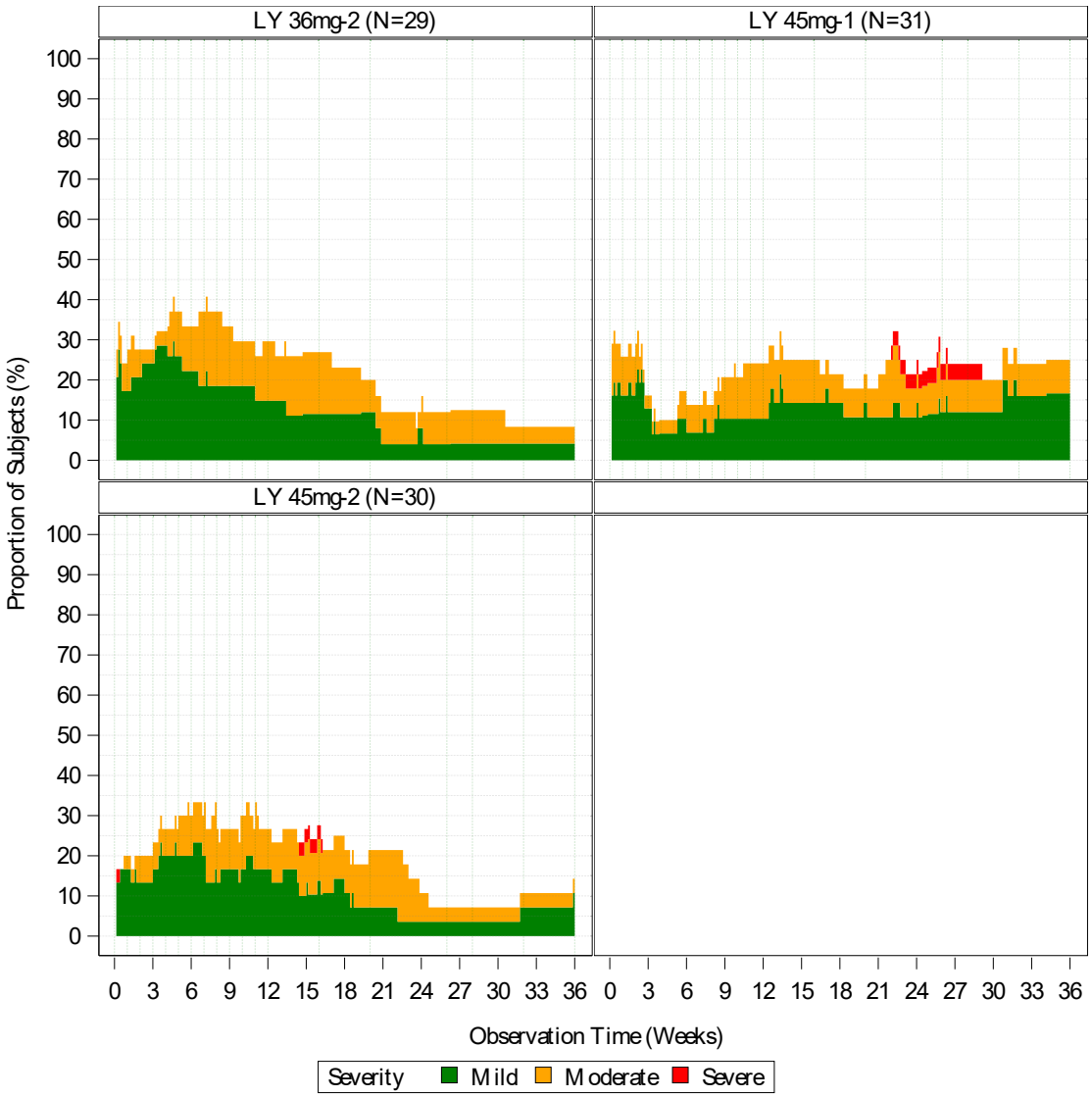
Figure S2. Change From Baseline in BMI and Waist Circumference.



Least square means are presented. Panel A shows the change from baseline in BMI (kg/m2) by week (efficacy estimand). Panel B shows change from baseline in waist circumference (cm) by week. 36mg-1 and 36mg-2 were pooled for 36 mg. 45mg-1 and 45mg-2 were pooled for 45 mg.

Figure S3.Prevalence of Nausea/Vomiting/Diarrhea/Constipation by Maximum Severity and Treatment Over Time (Safety Analysis Set).





Note: Proportions were based on the number of subjects at risk. N denotes number of subjects in specified treatment group.