

## Supplementary Appendix

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

# SUPPLEMENTARY APPENDIX

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## **Inclusion and Exclusion Criteria**

### **Inclusion Criteria**

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

#### **Age**

1. Participant must be 18 to 75 years of age inclusive, at the time of signing the informed consent.

#### **Type of Participant and Disease Characteristics**

2. Have a BMI of
  - $\geq 30 \text{ kg/m}^2$  and  $\leq 50 \text{ kg/m}^2$
  - $\geq 27 \text{ kg/m}^2$  and  $< 30 \text{ kg/m}^2$  with at least 1 of the following weight-related comorbidities
    - hypertension: on BP-lowering medication or having systolic BP  $\geq 130 \text{ mmHg}$  or diastolic BP  $\geq 80 \text{ mmHg}$  at screening
    - dyslipidemia: on lipid-lowering medication or having low-density lipoprotein (LDL)  $\geq 160 \text{ mg/dL}$  (4.1 mmol/L) or triglycerides  $\geq 150 \text{ mg/dL}$  (1.7 mmol/L), or high-density lipoprotein (HDL)  $< 40 \text{ mg/dL}$  (1.0 mmol/L) for men or HDL  $< 50 \text{ mg/dL}$  (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)
3. In the investigator's opinion, are well motivated, capable, and willing to
  - learn how to self-inject study drug, as required for this protocol (visually impaired persons who are not able to perform the injections must have the assistance of a sighted individual trained to inject the study drug; persons with physical limitations who are not able to perform the injections must have the assistance of an individual trained to inject the study drug)
  - inject study drug (or receive an injection from a trained individual if visually impaired or with physical limitations), and
  - follow study procedures for the duration of the study, including, but not limited to, follow lifestyle advice (for example, dietary changes and physical activity plan), maintain a study drug administration log, and complete required questionnaires.

In addition, a subgroup of approximately 100-125 participants will meet the following inclusion criterion

4. Have liver fat content  $\geq 10\%$  by MRI-PDFF

#### **Sex**

5. Male and/or female  
Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.  
Males, women of childbearing potential and women not of childbearing potential (for definitions, see Section 10.5 of protocol [Appendix 5]) can participate in this study considering the following:

- males agree to refrain from sperm donation and to use contraceptive methods as described in Section 10.5 of protocol (Appendix 5) throughout the study and for 5 half-lives of study drug plus 90 days, corresponding to 4 months after the last injection.
- women of childbearing potential must have negative pregnancy tests at Visit 1 and Visit 4 as indicated in the SoA and agree to use contraceptive methods as described in Section 10.5 of protocol (Appendix 5) throughout the study and for 5 half-lives of study drug plus 30 days, corresponding to 2 months after the last injection. Female participants should not be breastfeeding.

**Note:** Hormone replacement therapy in postmenopausal women and contraceptives containing an estrogen and a progestin (oral or transdermal system) in premenopausal women are allowed but women must be on stable therapy for 3 months prior to screening.

### **Informed Consent**

6. Capable of giving signed informed consent as described in Section 10.1 of protocol (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 apply:

#### **Medical Conditions**

##### ***Diabetes Related***

7. Have history of type 1 diabetes mellitus (T1D) or T2D, history of ketoacidosis, or hyperosmolar state/coma
8. Have at least 1 laboratory value suggestive of diabetes during screening, including 1 or more of HbA1c  $\geq 6.5\%$  (48 mmol/mol), fasting serum glucose  $\geq 126$  mg/dL (7.0 mmol/L), or random glucose  $\geq 200$  mg/dL (11.1 mmol/L)

##### ***Obesity Related***

9. Have a self-reported change (increase or decrease) in body weight  $>5$  kg within 3 months prior to screening
10. Have a prior or planned surgical treatment for obesity (excluding liposuction or abdominoplasty, if performed  $>1$  year prior to screening)
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) <45 mL/min/1.73 m<sup>2</sup>, 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) 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 thyroid-stimulating hormone outside of the range of 0.4 to 6.0 mIU/L at screening visit

**Note:** Participants receiving treatment for hypothyroidism may be included, provided their thyroid hormone replacement dose has been stable for at least 6 months.

**Note:** Thyroid-stimulating hormone values above the normal range can, in some participant, suggest subclinical hypothyroidism. If, in the investigator's opinion, the participant has subclinical hypothyroidism and may require initiation of thyroid hormone replacement during the study, the participant should be excluded from the study.

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)
17. 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

18. Have a lifetime history of suicide attempt
19. Have a Patient Health Questionnaire-9 (PHQ-9) score of 15 or more at Visit 1
20. On the C-SSRS at Visits 1, 3, or 4, 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

21. Have uncontrolled hypertension (systolic BP above or equal to 160 mmHg and/or diastolic BP above or equal to 100 mmHg). If a participant is on anti-hypertensive therapies, doses must be stable for 30 days prior to screening. For participants with uncontrolled hypertension at the screening visit, antihypertensive medication may be started or adjusted. Blood pressure must meet the protocol criterion for hypertension control by Visit 3 with stable treatment for at least 30 days
22. Have an elevated resting pulse rate (>100 bpm) at baseline
23. 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)
24. 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.
25. Have NYHA Functional Classification III or IV CHF
26. Have an electrocardiogram (ECG) considered by the investigator indicative of active cardiac disease or with abnormalities that may interfere with the interpretation of changes in ECG intervals at screening
27. Have acute or chronic hepatitis, or signs and symptoms of any other liver disease other than NAFLD, or any of the following, as determined by the central laboratory during screening
  - ALT level >3.0X upper limit of normal (ULN) for the reference range
  - alkaline phosphatase (ALP) level >1.5X ULN for the reference range, or
  - total bilirubin level (TBL) >1.5X ULN for the reference range (except for cases of known Gilbert’s Syndrome)
28. Have a serum calcitonin level (at Visit 1) of
  - $\geq 20$  ng/L, if eGFR  $\geq 60$  mL/min/1.73 m<sup>2</sup> or

- $\geq 35$  ng/L if eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> (as determined by central laboratory at Visit 1)
29. Have a family or personal history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia (MEN) syndrome type 2
  30. 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
  31. Have any other condition not listed in this section (for example, hypersensitivity or intolerance) that is a contraindication to GLP-1RA
  32. 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
  33. Alcohol consumption  $> 14$  units/week for women and  $> 21$  units/week for men
  34. 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.
  35. Have had a transplanted organ (corneal transplants [keratoplasty] are allowed) or are awaiting an organ transplant
  36. Have any hematological condition that may interfere with HbA1c measurement (for example, hemolytic anaemias and sickle cell disease)
  37. Have had a blood donation of  $\geq 500$  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, hemolytic anaemia, sickle cell anaemia, or have a hemoglobin value  $< 11$  g/dL (males) or  $< 10$  g/dL (females), or any other condition known to interfere with HbA1c methodology
  38. Have a history of atopy (severe or multiple allergic manifestations) or clinically significant multiple or severe drug allergies, or intolerance to topical corticosteroids, or severe posttreatment hypersensitivity reactions (including, but not limited to, erythema multiforme major, linear immunoglobulin A dermatosis, toxic epidermal necrolysis, anaphylaxis, angioedema, or exfoliative dermatitis)
  39. Have a fasting serum triglyceride level of  $> 500$  mg/dL at screening. If a participant is on lipid-lowering therapies, doses must be stable for 30 days prior to screening
  40. 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

41. Have a history of symptomatic gallbladder disease within the past 2 years, defined by the presence of gallstones on an imaging study and abdominal pain attributed to the gallstones by the participant's physician; subjects who had a procedure to remove the gallstones and/or the gallbladder (cholecystectomy), with no long-term complications, are eligible for participation as long as the procedure was completed at least 3 months prior to screening
42. Have a history of documented human immunodeficiency virus (HIV) infection

***Prior/Concomitant Therapy***

43. 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) or have evidence of a significant, active autoimmune abnormality (for example, lupus or rheumatoid arthritis) that has required (within the last 3 months) or is likely to require, in the opinion of the investigator, concurrent treatment with systemic glucocorticoids (excluding topical, intraocular, intranasal, intraarticular, or inhaled preparations) during the course of the study
44. 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

**Examples:**

- 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.

45. Have taken within 3 months prior to screening medications (prescribed or over the counter) or alternative remedies intended to promote weight loss

**Examples include, but are not limited to:**

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

- Sanorex® (mazindol)
  - Apidex® or Lomaira™ (phentermine)
  - Qsymia™ (phentermine/topiramate combination)
  - Contrave® (naltrexone/bupropion)
46. Use of metformin, or any other glucose-lowering medication, whether prescribed for polycystic ovarian syndrome or diabetes prevention is not permitted
47. Have started implantable or injectable contraceptives, such as Depo Provera® and Nexplanon®, within 18 months prior to screening. Intrauterine devices, including levonorgestrel-releasing intrauterine systems, are allowed if the participant has been using the device for at least 3 months

***Prior/Concurrent Clinical Study Experience***

48. Have known allergies to GLP-1R agonists or LY3437943
49. Are currently enrolled in any other clinical study involving an investigational product (IP) or any other type of medical research judged not to be scientifically or medically compatible with this study
50. Within the last 30 days, have participated in a clinical study and received treatment, whether active or placebo. If the study involved an IP, 5 half-lives or 30 days, whichever is longer, should have passed
51. Have previously completed or withdrawn from this study or any other study investigating LY3437943 and have previously received the IP

***Other Exclusions***

52. 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
53. Are Lilly employees

## STATISTICAL ANALYSIS METHODS

In this study, the efficacy estimand was used to estimate the treatment effect for all randomized participants and is based on the newly released ICH E9 (R1) for estimands and sensitivity analyses. A supplemental “hybrid estimand” was also investigated for the primary endpoint.

### ***Efficacy estimand***

This estimand represents the average treatment effect of retatrutide relative to placebo at 24 weeks, as an adjunct to diet and physical activity counseling, in the randomized participants had they remained on their randomized treatment for the entire planned 24 weeks treatment duration. This estimand uses a hypothetical strategy to handle intercurrent events (permanent treatment discontinuation) [ICH E9(R1)] and is intended to provide an estimation of the achievable study treatment effect when participants take the treatment as planned. The efficacy analysis set (EAS), which includes data from all randomized subjects and excludes data after treatment discontinuation and subjects who discontinued study treatment due to inadvertent enrollment, was used in the analyses guided by the efficacy estimand. The resulting missing values (discarded after treatment discontinuation, or unobserved) were implicitly handled by using a mixed model for repeated measures (MMRM) under the assumption of missing at random. Dose reductions were not considered as intercurrent events and data after dose reduction and prior to permanent treatment discontinuations were included in the EAS.

For MMRM the independent variables of analysis model include treatment group, visit, treatment-by-visit interaction, stratification factors (sex [female vs. male] and baseline BMI [ $\geq 36$  kg/m<sup>2</sup> vs.  $< 36$  kg/m<sup>2</sup>]) as fixed effects, and baseline body weight as a covariate. Dose-pooling was implemented in MMRM to replace the fixed effect of treatment group with the preplanned time-varying treatment doses at each timepoint to derive a more efficient estimator when the same treatment regimen over time is shared across the treatment groups due to preplanned titration (Qu et al. 2021). For example, in RETA 4.0 mg (2.0 mg) and RETA 8.0 mg (2.0 mg) arms, the planned doses in the first 4 weeks are both 2.0 mg. Therefore, pooling all the participants in these 2 groups can provide a more efficient estimation for the effect of 2.0 mg and can also increase the estimation precision for the doses at later timepoints.

A logistic regression model with treatment group, stratification factors as fixed effects, and baseline body weight as a covariate, was used for binary outcomes of body weight change. Multiple imputation was used to impute the missing continuous-valued body weight percent change before deriving the binary endpoint (Ma et al. 2022). Missing values due to treatment discontinuation or unobserved was imputed from the observations in the EAS within the same treatment arm.

### ***Hybrid estimand***

Hybrid estimand is defined as the treatment difference in the mean percent change in body weight from baseline at Week 24 between retatrutide and placebo for the study target population with ICEs handled differently according to the reasons of the events as follows:

- Category 1: The ICEs of permanent discontinuation of study drug due to reasons unlikely related to the efficacy/safety outcomes will be handled by the hypothetical strategy.
- Category 2: The ICEs of permanent discontinuation of study drug due to lack of efficacy before study treatment discontinuation will be handled by the hypothetical strategy.
- Category 3: All other ICEs will be handled by the treatment policy strategy.

In this study, following ICH E9 (R1) guidance, a plan was made to collect informative treatment disposition reasons, through eCRF, for why data intended for collection are missing and classify them into categories 1 through 3 as shown in Statistical analysis methods Table 1. (ICH 2019).

Statistical analysis methods Table 1 Treatment Disposition Reasons

Disposition Reason	Associated Sub-Categories	Category
Adverse event		3
Protocol deviation	Due to epidemic/pandemic	1
	Other	3
Pregnancy		3
Lack of efficacy		2
Other		3
Withdrawal by subject	Concern about study procedures/perceived risks	3
	Scheduling conflicts	1
	Subject is moving or has moved	1
	Personal issue unrelated to trial	1
	Due to epidemic/pandemic	1
	Other (option to include a specify field)	3
Physician decision	Concern about study procedures/perceived risks	3
	Scheduling conflicts	1
	Subject is moving or has moved	1
	Due to epidemic/pandemic	1
	Other (option to include a specify field)	3
Study terminated by sponsor		1
Site terminated by sponsor		1
Study terminated by IRB/ERB		1

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

To estimate the “hybrid estimand”, multiple imputation was used to impute the corresponding missing potential outcome according to the missingness patterns (Statistical analysis methods Table 2) with ICEs handled differently according to the reasons of the events. When participants have missing values without ICEs, the missing values was be imputed using data from participants who do not have ICE or missing values.

Percent change from baseline in body weight was analyzed using analysis of heterogeneous covariance (ANHECOVA) with terms of treatment group, stratification factors (sex [female vs. male] and baseline BMI [ $\geq 36 \text{ kg/m}^2$  vs.  $< 36 \text{ kg/m}^2$ ]), and continuous covariate of baseline value, along with the interaction between treatment group and the stratification factors and that between treatment group and the baseline value. The heteroscedasticity is also considered by introducing

treatment specific variance estimates. This formulation has been shown to provide the optimal efficiency gain regardless of randomization schemes within the class of linear model adjustment (Ye et al. 2009).

A similar logistic regression model described under the efficacy estimand was used for binary efficacy outcomes of body weight change guided by the hybrid estimand. Multiple imputation was used to impute the missing continuous-valued body weight percent change before deriving the binary endpoint (Ma et al. 2022) and the imputation strategy is shown in Statistical analysis methods Table 2.

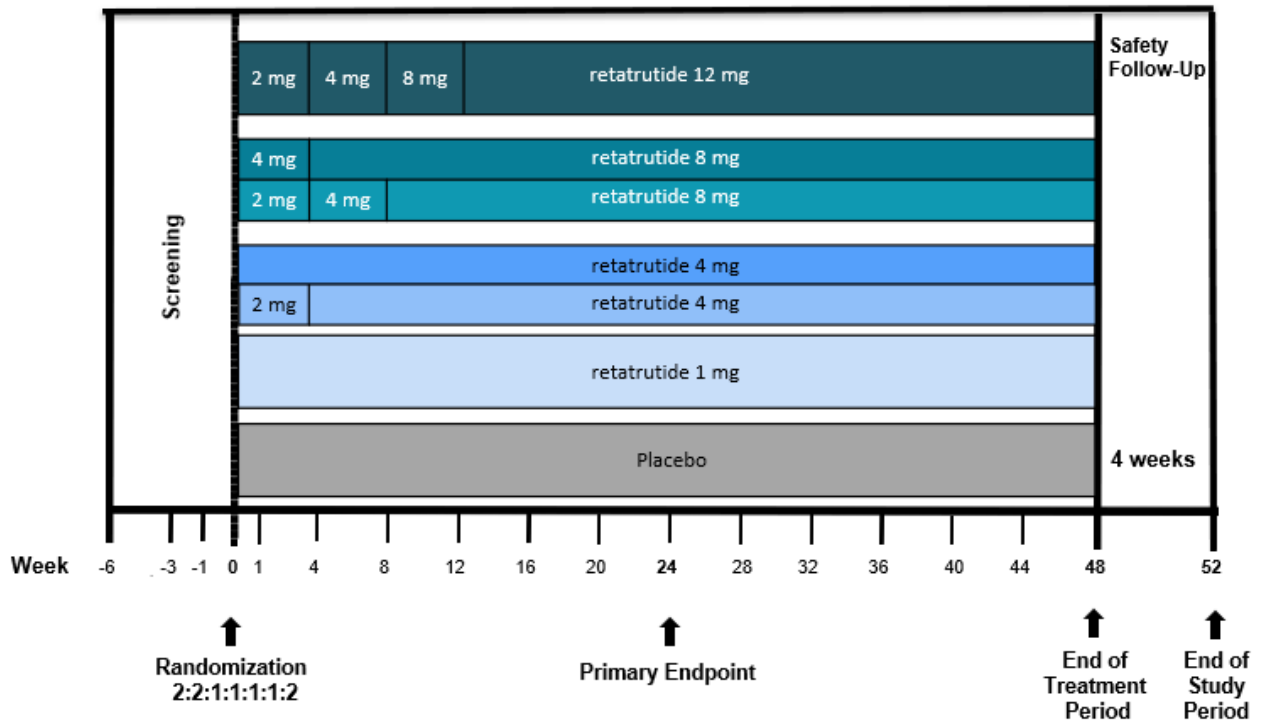
Statistical analysis methods Table 2 Strategy to Handle ICE and Missingness for Hybrid Estimand

<b>ICE</b>	<b>Strategy to Handle ICE</b>	<b>Assumptions for Missingness</b>	<b>Methods to Handle Missing Values at Endpoint</b>
Category 1: Treatment discontinuation due to reasons unlikely related to efficacy/safety outcome	Hypothetical	MAR	Data collected after the ICE were set to missing. Missing values will be imputed using all non-missing data (excluding data collected after ICEs) from the same treatment arm.
Category 2: Treatment discontinuation due to lack of efficacy	Hypothetical	MAR	Data collected after the ICE were set to missing. Missing values will be imputed using all non-missing data (excluding data collected after ICEs) from the same treatment arm.
Category 3: All other treatment discontinuations	Treatment policy	MNAR Considers that these participants could not adhere to their assigned treatment and may not benefit from the assigned treatment.	Missing values will be imputed using the jump-to-reference (placebo) imputation approach.

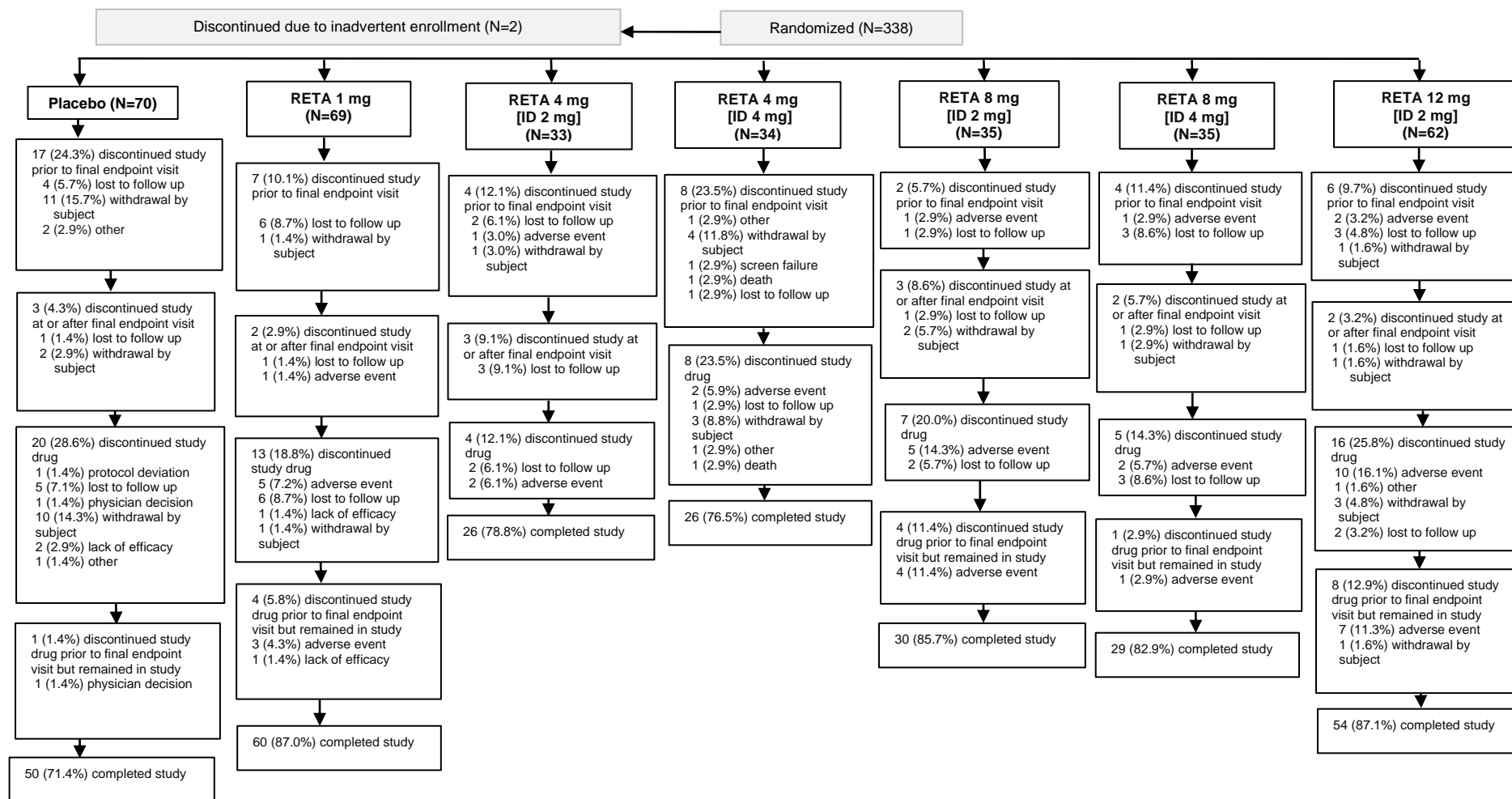
Abbreviations: ICE = intercurrent event; MAR = missing at random; MNAR = missing not at random.

Safety analyses were performed with data in the safety analysis set that consists of all the data from the 48-week treatment period and 4-week safety follow-up from subjects who took at least one study treatment.

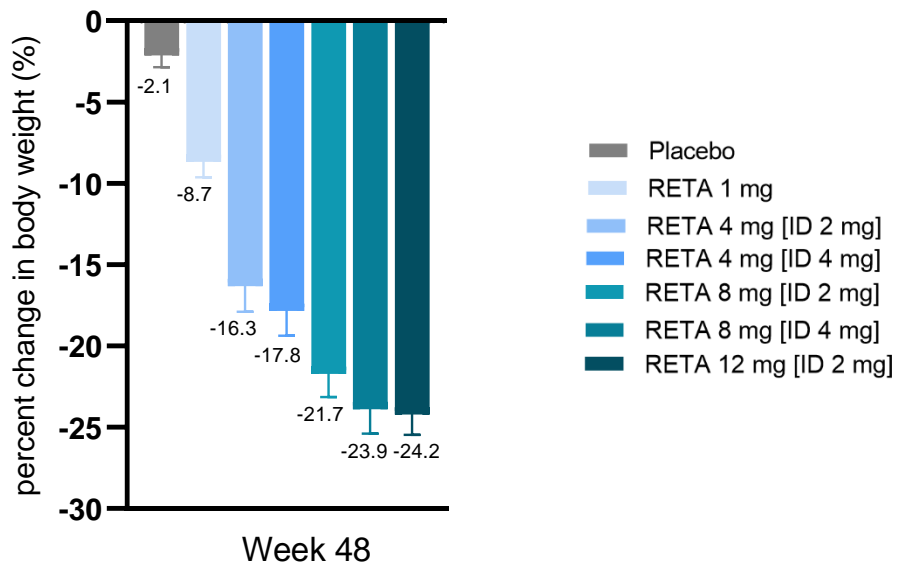
More details on analysis methods are provided in the statistical analysis plan in the Supplementary Material available at [nejm.org](http://nejm.org).



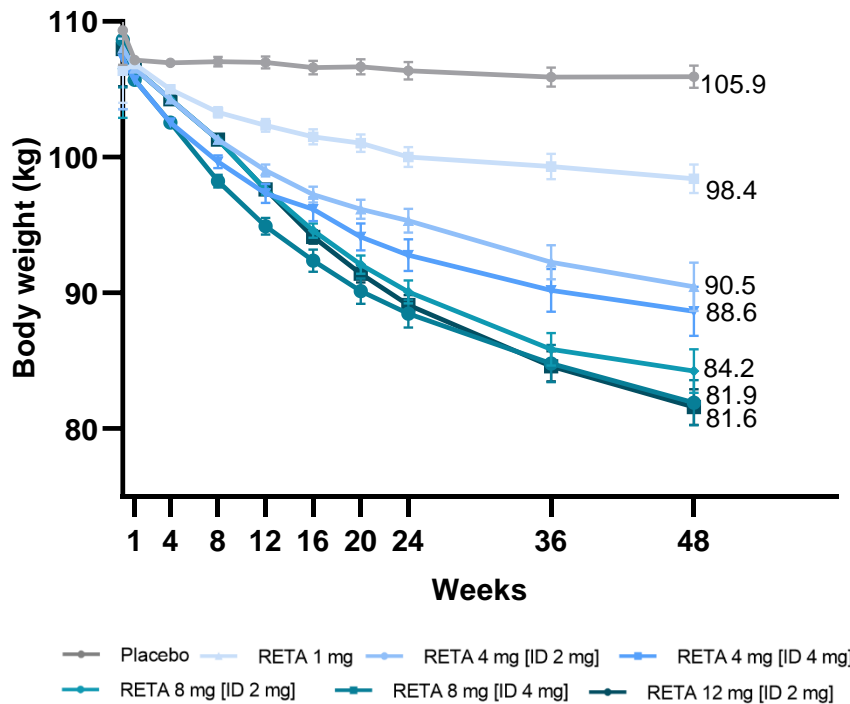
**Figure S1. Study design schematic.** This is a Phase 2, multicenter, randomized, placebo-controlled, double-blinded clinical trial investigating the efficacy and safety of 1 mg, 4 mg, 8 mg and 12 mg retatrutide (with different initial doses [ID], 2 mg versus 4 mg) administered once weekly (QW) subcutaneously compared with placebo for weight management as an adjunct to lifestyle intervention, in participants who have obesity, or overweight with  $\geq 1$  weight-related complication (excluding type 2 diabetes). All randomized participants were planned to undergo a 48-week treatment period. After the 48-week treatment period, participants proceeded to a four-week safety follow-up.



**Figure S2. Consort diagram.** Participant disposition from randomization. Mean duration of follow up in the study was 46.3 to 51.9 weeks across retatrutide groups and 46.2 weeks in the placebo group. Mean duration of follow up on treatment was 41.4 to 46.5 weeks across retatrutide groups and 41.9 weeks in the placebo group. Note: One participant in the placebo group was reported to have completed the study treatment on the disposition form but was reported to have withdrawn study drug due to the SAE of blood calcitonin increased on the AE form. This participant is not included in the number of participants who discontinued study drug in the placebo group. Abbreviations include AE, adverse event; ID, initial dose; RETA, retatrutide; SAE, serious adverse event.

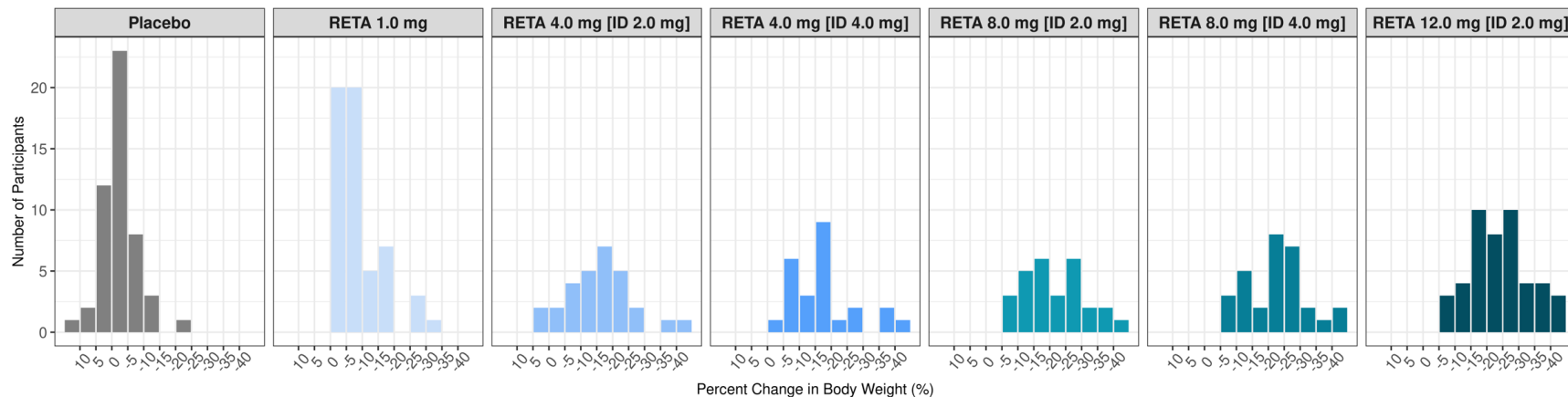


**Figure S3. Percent change in weight at week 48.** Least-squares means (standard error) are presented and shows the percent change in body weight from baseline at week 48 derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Abbreviations include ID, initial dose; RETA, retatrutide.

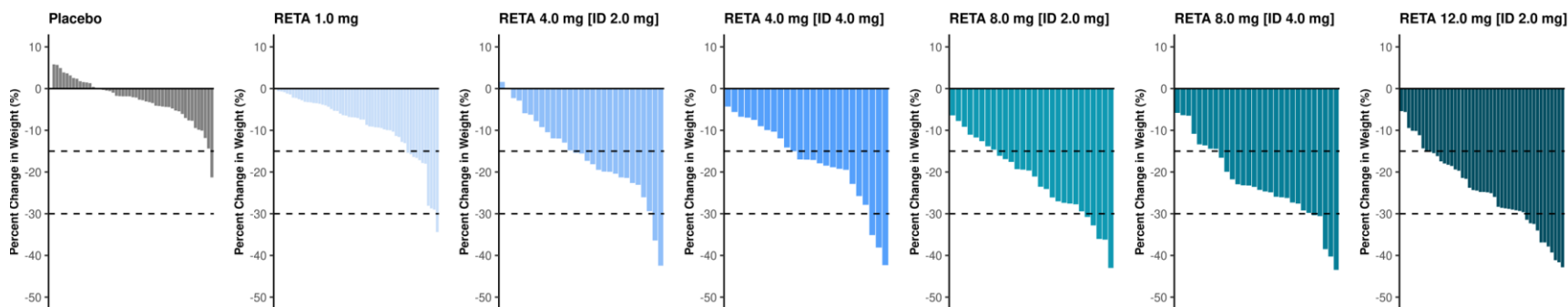


**Figure S4. Body weight in kilograms over time.** Least-squares mean body weight in kilograms from baseline to 48 weeks, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Mean baseline body weight: placebo, 109.2 kg; retatrutide 1mg, 106.4 kg; retatrutide 4 mg [ID 2mg], 108.0 kg; retatrutide 4 mg [ID 4mg], 107.0 kg; retatrutide 8 mg [ID 2 mg], 106.5 kg; retatrutide 8 mg [ID 4 mg], 108.6 kg; retatrutide 12 mg [ID 2 mg], 108.0 kg; Total, 107.7 kg. Error bars indicate standard error. Abbreviations include ID, initial dose; RETA, retatrutide.

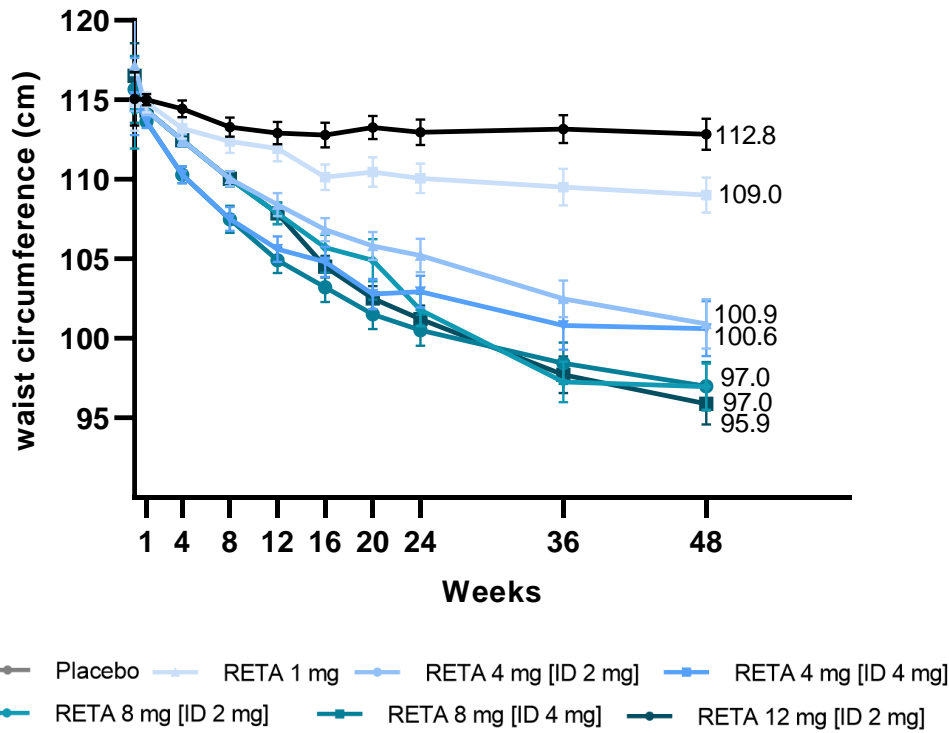
A)



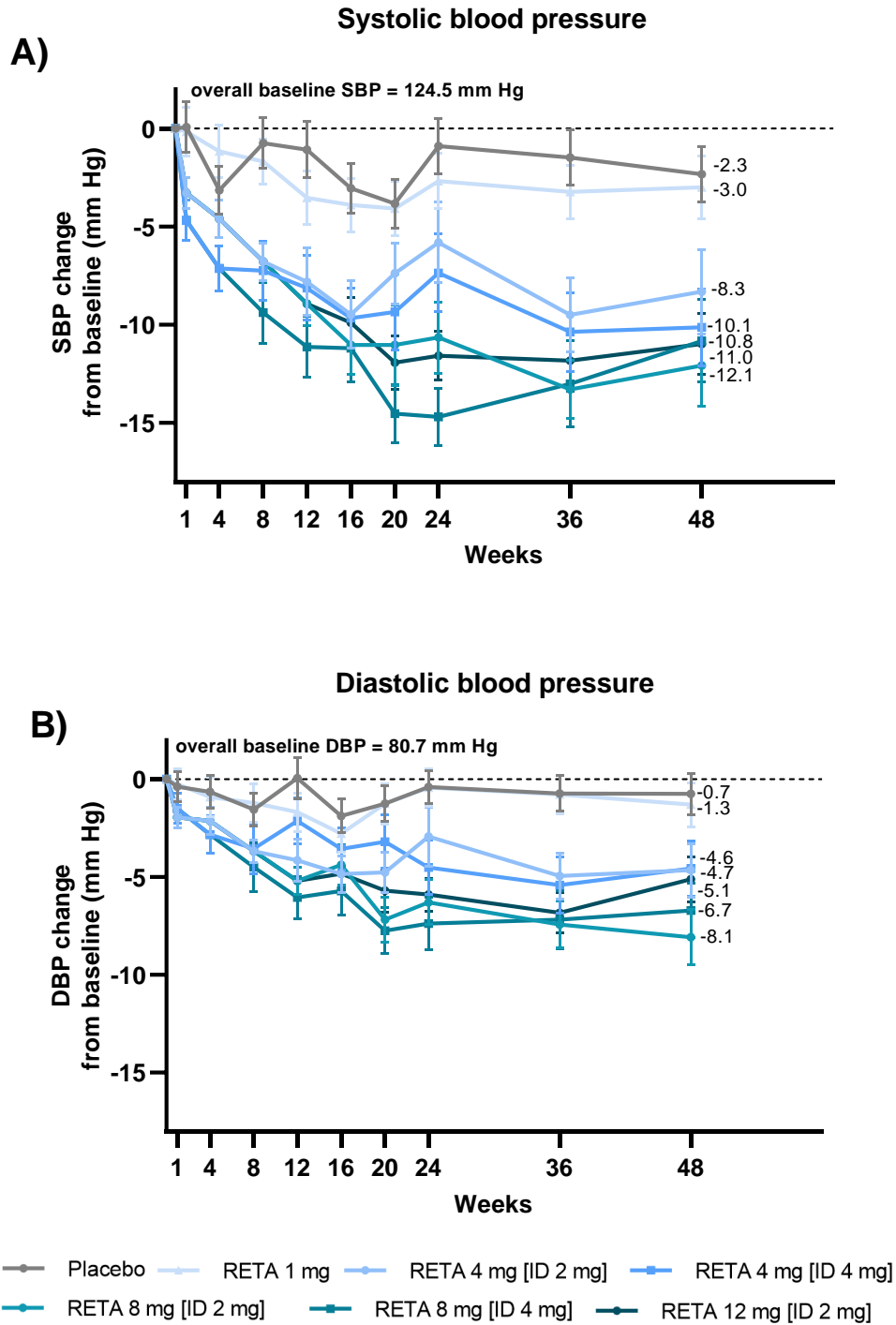
B)



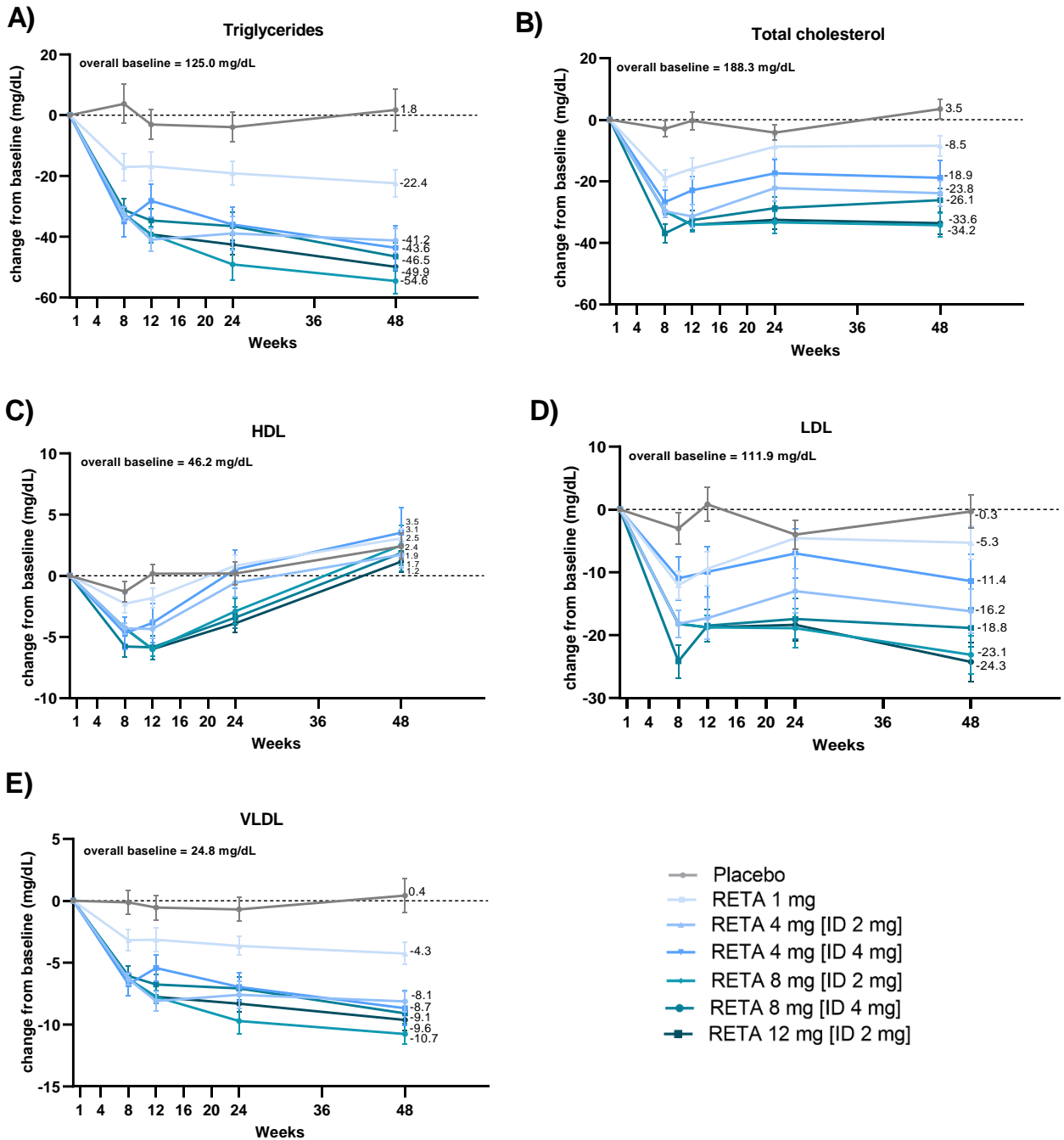
**Figure S5. Histogram and waterfall plots for percent change in weight at 48 weeks.** Histogram (Panel A) and waterfall plot (Panel B) for percent change in weight at week 48 for individuals in all treatment groups; data were censored after discontinuation of study treatment. At week 48, body weight reduction was observed in 100% (RETA 1mg), 93% (RETA 4mg [ID 2mg]), 100% (RETA 4mg [ID 4mg]), 100% (RETA 8mg [ID 2mg]), 100% (RETA 8mg [ID 4mg]), 100% (RETA 12mg), vs. 70% in placebo. Abbreviations include ID, initial dose; RETA, retatrutide.



**Figure S6. Waist circumference in centimeters over time.** Least-squares mean waist circumference in centimeters from baseline to 48 weeks, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Mean baseline waist circumference: placebo, 115.1 cm; retatrutide 1mg, 114.8 cm; retatrutide 4 mg [ID 2mg], 117.2 cm; retatrutide 4 mg [ID 4mg], 115.2 cm; retatrutide 8 mg [ID 2 mg], 114.3 cm; retatrutide 8 mg [ID 4 mg], 115.6 cm; retatrutide 12 mg [ID 2 mg], 116.5 cm; Total, 115.5 cm. Error bars indicate standard error. Abbreviations include ID, initial dose; RETA, retatrutide.



**Figure S7. Change from baseline in systolic and diastolic blood pressure.** Least-squares means (standard error) are presented and shows the change in blood pressure from baseline to week 48 derived from a mixed-model for repeated-measures (MMRM) analysis for the safety analysis set. Abbreviations include DBP, diastolic blood pressure; ID, initial dose; SBP, systolic blood pressure; RETA, retatrutide.

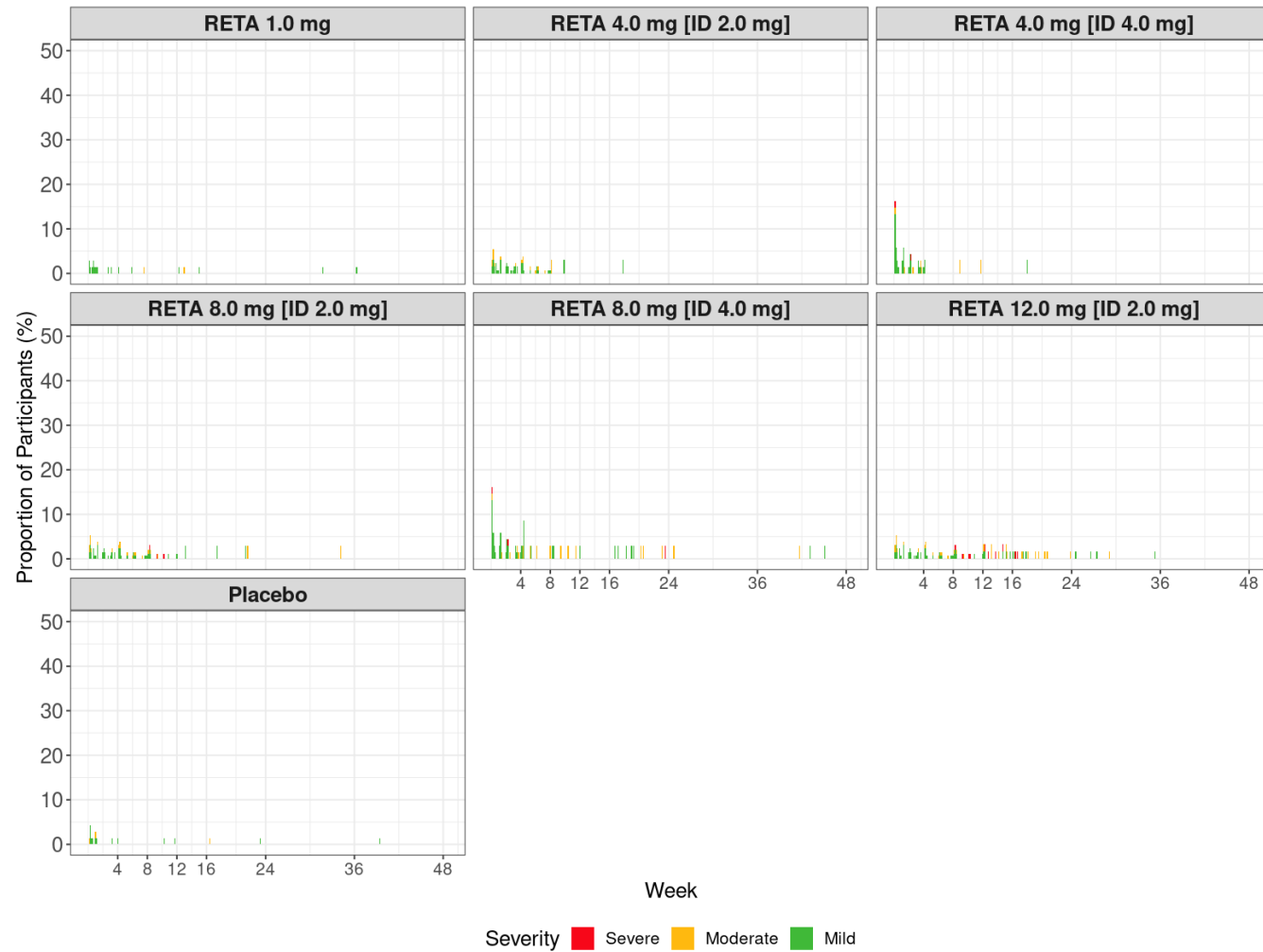


**Figure S8. Change from baseline for lipid parameters.** Least-squares means (standard error) are presented and shows the change in lipids from baseline to week 48, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Abbreviations include HDL, high density lipoproteins; ID, initial dose; LDL, low density lipoproteins; RETA, retatrutide; VLDL, very low density lipoproteins.

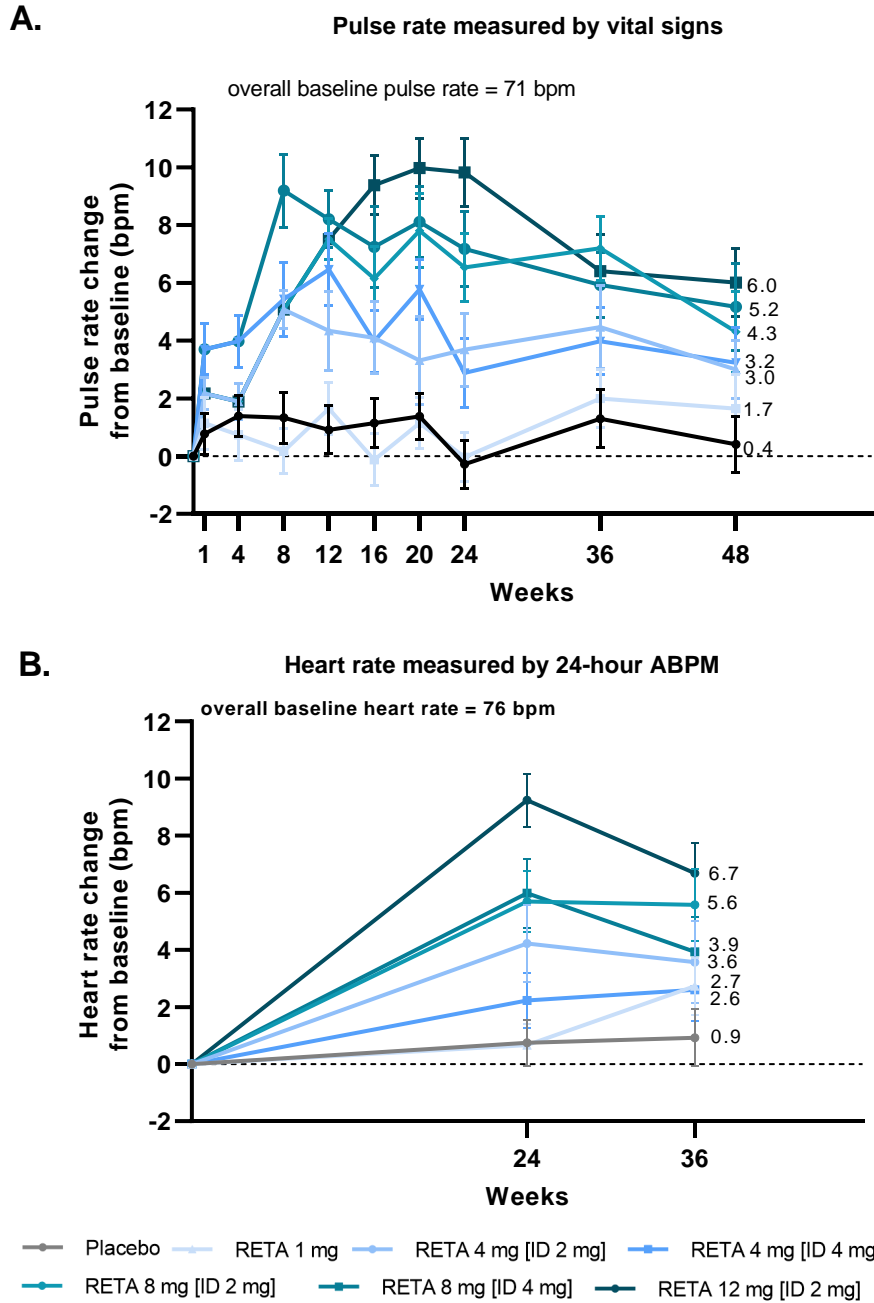
A)



B)



**Figure S9. Incidence of nausea, diarrhea, and vomiting combined over time.** Prevalence (Panel A) and incidence (Panel B) of nausea, diarrhea, and vomiting combined over time. Events were classified as mild (shown in green), moderate (shown in yellow), severe (shown in red). For incidence, all events for each participant were counted with the first day of each event shown. Abbreviations include ID, initial dose; RETA, retatrutide.



**Figure S10. Change from baseline in heart rate.** Change from baseline in pulse rate (vital signs) through 48 weeks of treatment (Panel A) and heart rate by ABPM through 36 weeks of treatment (Panel B). Least-squares means (standard error) are presented, derived from a mixed-model for repeated-measures (MMRM) analysis for the safety analysis set. Abbreviations include ABPM, ambulatory blood pressure monitoring; bpm, beats per minute; ID, initial dose; RETA, retatrutide.

**Table S1. Vital Signs and Clinical Laboratory Results of the Participants at Baseline**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2mg] (N=33)	RETA 4 mg [ID 4mg] (N=34)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)	Total (N= 338)
Blood pressure, mmHg								
Systolic	126.2 ± 12.6	126.1 ± 14.6	127.2 ± 12.4	126.5 ± 13.3	126.3 ± 12.8	122.3 ± 12.2	118.7 ± 15.5	124.6 ± 13.8
Diastolic	83.5 ± 9.5	79.7 ± 9.2	80.9 ± 8.5	81.0 ± 8.7	82.1 ± 9.1	80.4 ± 9.3	78.2 ± 11.3	80.8 ± 9.6
Pulse, beats/min	74.0 ± 10.8	71.1 ± 11.3	68.3 ± 11.1	71.4 ± 10.2	72.0 ± 11.3	69.1 ± 9.3	69.3 ± 9.3	71.0 ± 10.6
Lipid parameters, mg/dL**								
Total	188.2 (22.5)	189.0 (18.7)	188.1 (19.1)	191.0 (18.3)	184.9 (22.5)	189.4 (17.9)	187.5 (22.0)	188.3 (20.3)
HDL cholesterol	46.2 (19.2)	44.5 (29.0)	51.3 (27.9)	46.2 (22.2)	42.9 (28.8)	47.0 (23.0)	47.0 (26.0)	46.2 (25.5)
LDL cholesterol	112.4 (39.5)	112.7 (26.9)	109.9 (27.9)	111.0 (26.2)	110.9 (32.2)	116.2 (25.8)	110.0 (34.3)	111.9 (31.4)
Triglycerides	118.5 (47.0)	133.3 (46.3)	113.4 (41.8)	142.7 (52.9)	132.8 (43.3)	112.2 (45.5)	124.7 (48.3)	125.0 (47.0)
HbA1c, %	5.5 ± 0.4	5.5 ± 0.4	5.6 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4
Fasting glucose, mg/dL	94.9 ± 9.6	94.3 ± 9.7	93.6 ± 7.8	91.4 ± 10.4	94.1 ± 11.9	94.0 ± 9.2	93.2 ± 9.1	93.8 ± 9.7
Fasting insulin, mU/L**	15.0 (59.2)	14.8 (60.5)	15.6 (60.7)	17.1 (80.9)	16.0 (71.6)	14.9 (62.5)	14.8 (72.5)	15.3 (65.4)

Plus-minus values are mean ± standard deviation. Abbreviations include HDL, high-density lipoprotein; ID, initial dose; LDL, low-density lipoprotein; RETA, retatrutide. \*\*Lipid parameters and fasting insulin are presented as geometric mean (%CV).

**Table S2. Representativeness of study**

	<b>Details</b>
<b>Disease under investigation</b>	Obesity (BMI≥30 kg/m <sup>2</sup> ) or overweight (BMI ≥27 kg/m <sup>2</sup> )
Special considerations related to	
<b>Sex and gender</b>	According to WHO statistics, in 2016, 39% of men and 40% of women worldwide had overweight and 11% of men and 15% of women had obesity.
<b>Age</b>	Worldwide, obesity and overweight affect all adult age groups. In the United States, the prevalence of obesity is highest among adults aged 40 to 59 years (45%), followed by those ≥60 (43%), and those aged 20 to 39 years (40%).
<b>Race or ethnic group</b>	In terms of race and ethnicity, in the United States, the prevalence of obesity is highest in Black adults (49.6%), followed by Hispanic adults (44.8%), White adults (42.2%) and Asian adults (17.4%). Without regard to obesity, the United States population is currently 58% White, 19% Hispanic or Latino, 12% Black or African American, and 6% Asian.
<b>Geography</b>	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.
Other considerations	
<b>Overall representativeness of this trial</b>	Study GZBF was conducted in adults ≥18 years of age in the United States. Although the United States has a higher prevalence of obesity than most other countries, this study cannot be considered representative of the global population living with obesity. In Study GZBF, to ensure adequate representation of male participants, female enrollment was capped at 60%. Women represented approximately 48% of the trial population and men 52%. The average age was 48 years (range 18 to 76 years), with 10% of participants aged ≥65 years. This is in line with the higher prevalence of obesity in the 40-to-59-year age group in the United States. All demographic measures were self-reported. In terms of race and ethnicity, Study GZBF was representative of the prevailing demographics in the United States, with approximately 35% Latin-Americans and 8% African Americans.

Data was collected from relevant peer reviewed journal review articles.

**Table S3. Baseline demographics and characteristics in sex subgroups**

	Placebo (N=34)	RETA 1 mg (N=33)	RETA 4 mg [ID 2mg] (N=16)	RETA 4 mg [ID 4mg] (N=16)	RETA 8 mg [ID 2 mg] (N=17)	RETA 8 mg [ID 4 mg] (N=17)	RETA 12 mg [ID 2 mg] (N=30)	Total (N=163)
<b>Female participants (48.2%)</b>								
Age, years	47.4 ± 13.8	53.0 ± 13.4	55.4 ± 11.0	47.0 ± 13.5	42.7 ± 13.9	46.4 ± 10.7	45.8 ± 14.0	48.4 ± 13.5
Race, n (%)								
American Indian or Alaska Native	0	0	0	0	0	0	1 (3.3)	1 (0.6)
Asian	0	0	0	0	1 (5.9)	0	1 (3.3)	2 (1.2)
Black or African American	5 (14.7)	3 (9.1)	3 (18.8)	2 (12.5)	3 (17.6)	1 (5.9)	1 (3.3)	18 (11.0)
White	28 (82.4)	29 (87.9)	13 (81.2)	14 (87.5)	13 (76.5)	15 (88.2)	25 (83.3)	137 (84.0)
Multiple	1 (2.9)	0	0	0	0	1 (5.9)	2 (6.7)	4 (2.5)
Hispanic or Latino, n (%)	10 (29.4)	8 (24.2)	4 (25.0)	7 (43.8)	7 (41.2)	5 (29.4)	10 (33.3)	51 (31.3)
Body weight, kg	102.5 ± 21.4	98.0 ± 16.8	94.8 ± 17.2	95.9 ± 18.2	100.5 ± 17.1	98.9 ± 17.2	101.9 ± 20.7	99.5 ± 18.7
BMI, kg/m <sup>2</sup>	38.3 ± 6.5	37.8 ± 6.3	37.4 ± 6.4	37.2 ± 5.1	37.3 ± 4.8	37.1 ± 5.2	38.3 ± 6.5	37.8 ± 5.9
BMI category, n (%)								
<30	2 (5.9)	2 (6.1)	0	0	1 (5.9)	1 (5.9)	1 (3.3)	7 (4.3)
≥30 to <35	11 (32.4)	12 (36.4)	7 (43.8)	7 (43.8)	4 (23.5)	7 (41.2)	12 (40.0)	60 (36.8)
≥35 to <40	8 (23.5)	8 (24.2)	3 (18.8)	4 (25.0)	6 (35.3)	4 (23.5)	4 (13.3)	37 (22.7)
≥40	13 (38.2)	11 (33.3)	6 (37.5)	5 (31.2)	6 (35.3)	5 (29.4)	13 (43.3)	59 (36.2)
Waist circumference, cm	112.1 ± 14.9	110.7 ± 13.9	113.9 ± 16.7	109.6 ± 12.7	109.3 ± 12.2	110.0 ± 12.0	112.8 ± 15.8	111.4 ± 14.1
Blood pressure, mmHg								
Systolic	121.6 ± 11.7	120.3 ± 12.9	130.4 ± 13.7	127.6 ± 13.3	126.6 ± 13.5	123.1 ± 13.8	115.5 ± 17.9	122.3 ± 14.5
Diastolic	81.8 ± 10.1	76.8 ± 8.0	80.3 ± 8.1	81.3 ± 6.9	82.0 ± 8.6	82.0 ± 8.5	77.6 ± 13.9	79.9 ± 9.9
Pulse, beats/min	74.2 ± 10.5	69.3 ± 8.7	66.7 ± 10.3	69.6 ± 10.7	73.6 ± 11.7	71.4 ± 7.9	71.5 ± 8.8	71.2 ± 9.8
Prediabetes, n (%)#	11 (32.4)	15 (45.5)	9 (56.3)	6 (37.5)	7 (41.2)	8 (47.1)	8 (26.7)	64 (39.3)
HbA1c, %	5.6 ± 0.4	5.6 ± 0.4	5.7 ± 0.3	5.6 ± 0.4	5.5 ± 0.3	5.6 ± 0.4	5.5 ± 0.4	5.6 ± 0.4
Fasting glucose, mg/dL	92.8 ± 11.0	93.5 ± 9.6	93.7 ± 7.7	90.3 ± 8.7	88.7 ± 10.4	93.7 ± 9.1	90.5 ± 8.6	92.0 ± 9.5

<b>Male participants (51.8%)</b>	<b>Placebo (N=36)</b>	<b>RETA 1 mg (N=36)</b>	<b>RETA 4 mg [ID 2mg] (N=17)</b>	<b>RETA 4 mg [ID 4mg] (N=18)</b>	<b>RETA 8 mg [ID 2 mg] (N=18)</b>	<b>RETA 8 mg [ID 4 mg] (N=18)</b>	<b>RETA 12 mg [ID 2 mg] (N=32)</b>	<b>Total (N=175)</b>
Age, years	48.6 ± 11.4	48.4 ± 13.1	46.4 ± 11.2	46.6 ± 15.0	49.4 ± 12.7	51.0 ± 11.3	45.9 ± 10.4	48.0 ± 12.0
Race†, n (%)								
American Indian or Alaska Native	0	0	0	1 (5.6)	0	0	0	1 (5.6)
Asian	2 (5.6)	0	0	0	0	0	0	2 (1.1)
Black or African American	3 (8.3)	3 (8.3)	1 (5.9)	0	1 (5.6)	0	1 (3.1)	9 (5.1)
White	31 (86.1)	32 (88.9)	16 (94.1)	16 (88.9)	17 (94.4)	18 (100.0)	31 (96.9)	161 (92.0)
Multiple	0	0	0	1 (5.6)	0	0	0	1 (0.6)
Native Hawaiian or other pacific islander	0	1 (2.8)	0	0	0	0	0	1 (0.6)
Hispanic or Latino, n (%)	12 (33.3)	15 (41.7)	5 (29.4)	7 (38.9)	8 (44.4)	7 (38.9)	12 (37.5)	66 (37.7)
Body weight, kg	115.5 ± 18.5	114.0 ± 19.6	120.5 ± 27.8	116.9 ± 19.2	112.2 ± 24.2	117.9 ± 20.2	113.7 ± 21.4	115.4 ± 20.9
BMI, kg/m <sup>2</sup>	36.4 ± 5.2	37.2 ± 5.5	37.2 ± 5.5	37.6 ± 4.4	37.4 ± 7.2	36.8 ± 5.9	36.6 ± 5.5	37.0 ± 5.5
BMI category, n (%)								
<30	3 (8.3)	1 (2.8)	0	0	1 (5.6)	1 (5.6)	1 (3.1)	7 (4.0)
≥30 to <35	13 (36.1)	14 (38.9)	8 (47.1)	9 (50.0)	7 (38.9)	7 (38.9)	12 (37.5)	70 (40.0)
≥35 to <40	12 (33.3)	12 (33.3)	4 (23.5)	4 (22.2)	6 (33.3)	5 (27.8)	12 (37.5)	55 (31.4)
≥40	8 (22.2)	9 (25.0)	5 (29.4)	5 (27.8)	4 (22.2)	5 (27.8)	7 (21.9)	43 (24.6)
Waist circumference, cm	118.0 ± 12.4	118.6 ± 14.6	120.6 ± 16.4	119.9 ± 14.0	119.1 ± 14.9	120.9 ± 11.1	120.0 ± 16.5	119.4 ± 14.2
Blood pressure, mmHg								
Systolic	130.6 ± 12.0	131.4 ± 14.1	124.3 ± 10.6	125.6 ± 13.6	126.0 ± 12.5	121.5 ± 10.9	121.8 ± 12.4	126.6 ± 12.9
Diastolic	85.2 ± 8.8	82.3 ± 9.5	81.4 ± 9.0	80.8 ± 10.3	82.3 ± 9.9	78.8 ± 10.0	78.8 ± 8.3	81.7 ± 9.4
Pulse, beats/min	73.9 ± 11.2	72.7 ± 13.2	69.9 ± 11.8	73.0 ± 9.9	70.6 ± 11.0	66.9 ± 10.1	67.2 ± 9.5	70.9 ± 11.3
Prediabetes, n (%)#	15 (41.7)	12 (33.3)	6 (35.3)	4 (22.2)	4 (22.2)	7 (38.9)	11 (34.4)	59 (33.7)
HbA1c, %	5.5 ± 0.4	5.5 ± 0.4	5.6 ± 0.4	5.4 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4	5.5 ± 0.4
Fasting glucose, mg/dL	96.6 ± 7.7	95.1 ± 9.8	93.5 ± 8.1	91.9 ± 11.8	99.3 ± 11.2	94.4 ± 9.6	95.8 ± 9.0	95.4 ± 9.5

Plus-minus values are mean ± standard deviation. Abbreviations include BMI, body mass index; ID, initial dose; RETA, retatrutide. # Prediabetes was defined by HbA1c ≥5.7 and <6.5%.

**Table S4. Body weight and anthropometric measures at week 24**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=34)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)
<b>Primary endpoint</b>							
Percent change in weight, %	-1.6 (-2.7, -0.5)	-7.2 (-8.5, -5.9)	-11.8 (-13.3, -10.2)	-13.9 (-15.9, -11.9)	-16.7 (-18.4, -15.1)	-17.9 (-19.7, -16.1)	-17.5 (-18.8, -16.1)
<b>Secondary endpoints</b>							
<i>Percent of participants*</i>							
Weight reduction ≥5%	26	59	87	94	100	100	97
Weight reduction ≥10%	3	25	59	72	83	94	90
Weight reduction ≥15%	1	10	29	44	51	68	70
<i>Change from baseline</i>							
Weight, kg	-1.4 (-2.6, -0.1)	-7.8 (-9.2, -6.3)	-12.5 (-14.2, -10.7)	-15.0 (-17.3, -12.7)	-17.7 (-19.4, -16.1)	-19.3 (-21.3, -17.3)	-18.7 (-20.1, -17.2)
BMI, kg/m <sup>2</sup>	-0.5 (-1.0, -0.1)	-2.6 (-3.2, -2.1)	-4.4 (-5.0, -3.8)	-5.2 (-6.0, -4.4)	-6.2 (-6.8, -5.6)	-6.7 (-7.4, -6.0)	-6.5 (-7.0, -6.0)
Waist circumference, cm	-2.5 (-4.1, -1.0)	-5.4 (-7.3, -3.6)	-10.3 (-12.3, -8.2)	-12.5 (-14.5, -10.6)	-13.7 (-15.7, -11.7)	-15.0 (-16.9, -13.1)	-14.3 (-16.0, -12.6)
<b>Pre-specified exploratory endpoints</b>							
<i>Percent of participants*</i>							
Weight reduction ≥20%	0	3	6	14	26	30	31
Weight reduction ≥25%	0	0	0	9	21	11	15
Weight reduction ≥30%	0	0	0	0	0	1	5

Data are least squares means (95% CI), unless otherwise stated. Abbreviations include BMI, body mass index; ID, initial dose; RETA, retatrutide; SE, standard error. \* The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.

**Table S5. Primary and secondary endpoints from hybrid estimand**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=34)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)
<b>Primary endpoint (at 24 weeks)</b>							
Percent change in weight, %	-1.8 (-2.9, -0.7)	-6.9 (-8.2, -5.5)	-10.7 (-12.9, -8.6)	-13.8 (-16.1, -11.4)	-14.7 (-17.0, -12.3)	-16.2 (-18.2, -14.2)	-16.2 (-17.9, -14.4)
LSM difference from placebo, % (95% CI)		-5.1 (-6.8, -3.3)	-8.9 (-11.4, -6.5)	-12.0 (-14.5, -9.4)	-12.9 (-15.5, -10.3)	-14.4 (-16.7, -12.1)	-14.4 (-16.4, -12.3)
<b>Secondary endpoints (at 48 weeks)</b>							
Percent change in weight, %	-2.6 (-4.0, -1.2)	-8.1 (-9.9, -6.2)	-14.7 (-18.3, -11.0)	-15.7 (-19.3, -12.2)	-18.1 (-21.6, -14.7)	-20.5 (-23.7, -17.4)	-20.9 (-23.8, -17.9)
LSM difference from placebo, % (95% CI)		-5.5 (-7.8, -3.2)	-12.1 (-16.0, -8.2)	-13.2 (-16.9, -9.4)	-15.6 (-19.3, -11.9)	-18.0 (-21.4, -14.5)	-18.3 (-21.5, -15.0)
<b>Percent of participants*</b>							
Weight reduction ≥5%	28	61	80	87	83	93	89
Weight reduction ≥10%	10	26	66	66	73	82	82
Weight reduction ≥15%	2	17	49	53	57	66	72
<b>Prespecified exploratory endpoints (at 48 weeks)</b>							
<b>Percent of participants*</b>							
Weight reduction ≥20%	2	6	28	21	40	60	49
Weight reduction ≥25%	0	6	12	16	32	37	36
Weight reduction ≥30%	0	1	6	9	14	14	19

Data are least squares means (95% CI). Abbreviations include CI, confidence interval; ID, initial dose; LSM, least squares mean; RETA, retatrutide.  
 \* The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets

**Table S6. Pre-Specified Exploratory End Points at Weeks 36 and 48**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=34)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)
<b>Pre-specified exploratory endpoints (at 48 weeks)</b>							
<i>Percentage of participants, % *</i>							
Weight reduction ≥20%	1	6	31	29	50	70	64
Weight reduction ≥25%	0	6	13	19	36	43	48
Weight reduction ≥30%	0	1	6	10	16	17	26
<i>Change from baseline</i>							
Fasting glucose, mg/dL	3.1 (-0.8, 6.9)	-2.2 (-4.5, 0.1)	-7.2 (-11.1, -3.4)	-7.7 (-10.3, -5.0)	-8.9 (-12.8, -5.0)	-9.6 (-12.6, -6.7)	-10.6 (-12.7, -8.5)
Fasting insulin, mU/L	-1.3 (-3.4, 0.9)	-3.3 (-5.2, -1.4)	-7.1 (-8.9, -5.2)	-7.6 (-10.1, -5.2)	-6.6 (-9.2, -3.9)	-7.8 (-9.3, -6.2)	-8.9 (-10.1, -7.6)
Fasting HbA1c, %	0.0 (-0.1, 0.1)	-0.2 (-0.2, -0.1)	-0.2 (-0.3, -0.1)	-0.3 (-0.4, -0.3)	-0.5 (-0.6, -0.3)	-0.5 (-0.5, -0.4)	-0.4 (-0.5, -0.4)
<i>Percent change from baseline</i>							
Fasting triglycerides	1.4 (-9.3, 12.1)	-17.9 (-25.1, -10.8)	-33.0 (-39.4, -26.5)	-34.9 (-46.2, -23.6)	-43.6 (-50.1, -37.1)	-37.2 (-44.5, -29.9)	-39.9 (-46.7, -33.1)
Fasting total cholesterol	1.9 (-1.5, 5.2)	-4.5 (-8.0, -1.0)	-12.6 (-17.0, -8.3)	-10.0 (-15.8, -4.3)	-18.2 (-22.2, -14.1)	-13.9 (-17.8, -9.9)	-17.8 (-21.5, -14.2)
Fasting LDL cholesterol	-0.3 (-5.0, 4.4)	-4.7 (-9.3, -0.1)	-14.5 (-20.7, -8.3)	-10.2 (-17.6, -2.8)	-20.7 (-26.1, -15.3)	-16.8 (-22.2, -11.5)	-21.7 (-27.2, -16.2)
Fasting VLDL cholesterol	1.7 (-9.0, 12.4)	-17.2 (-24.3, -10.0)	-32.7 (-39.2, -26.3)	-35.0 (-46.2, -23.7)	-43.4 (-50.0, -36.8)	-36.7 (-43.9, -29.4)	-38.8 (-45.7, -31.8)
Fasting HDL cholesterol	5.2 (0.6, 9.8)	6.6 (3.2, 10.0)	3.7 (-0.8, 8.3)	7.6 (-1.0, 16.2)	5.4 (-1.6, 12.3)	4.0 (-2.4, 10.5)	2.5 (-1.3, 6.2)
<b>Pre-specified exploratory endpoints (at 36 weeks)</b>							
<i>Change from baseline with 24-hour ABPM</i>							
Systolic BP, mmHg	-2.9 (-5.4, -0.4)	-4.8 (-7.2, -2.3)	-8.7 (-12.7, -4.8)	-8.3 (-11.5, -5.1)	-8.8 (-11.6, -6.0)	-11.8 (-14.8, -8.8)	-8.8 (-11.9, -5.8)
Diastolic BP, mmHg	-1.0 (-2.6, 0.5)	-2.2 (-4.0, -0.5)	-3.2 (-6.0, -0.4)	-2.9 (-5.0, -0.8)	-3.4 (-5.1, -1.7)	-3.5 (-5.6, -1.4)	-2.8 (-4.6, -0.9)
Heart rate (beats/min)	0.9 (-1.0, 2.9)	2.7 (0.8, 4.7)	3.6 (0.8, 6.4)	2.6 (0.4, 4.8)	5.6 (3.1, 8.1)	3.9 (1.5, 6.4)	6.7 (4.6, 8.8)

Data are least squares means (95% CI), unless otherwise stated. Abbreviations include ABPM, ambulatory blood pressure monitoring; BP, blood pressure; CI, confidence interval; HbA1c, glycated hemoglobin; HDL, high-density lipoproteins; ID, initial dose; LDL, low-density lipoproteins; RETA, retatrutide; VLDL, very low-density lipoproteins. \* The percentage was calculated with the use of Rubin's rules by combining the percentages of participants who met the target in imputed data sets.

**Table S7. Prespecified Subgroup Analyses of Body Weight Change by Baseline BMI and Sex**

	Placebo	RETA 1 mg	RETA 4 mg [ID 2 mg]	RETA 4 mg [ID 4 mg]	RETA 8 mg [ID 2 mg]	RETA 8 mg [ID 4 mg]	RETA 12 mg [ID 2 mg]
<b>Percent change in weight at week 48, %</b>							
<i>BMI</i>							
<35 kg/m <sup>2</sup> (N=143)	-2.7 (-5.4, 0.0)	-8.2 (-10.6, -5.8)	-15.0 (-18.1, -11.9)	-15.9 (-19.5, -12.3)	-22.1 (-25.1, -19.1)	-21.3 (-25.6, -17.1)	-21.5 (-25.2, -17.7)
≥35 kg/m <sup>2</sup> (N=192)	-1.4 (-2.9, 0.0)	-8.9 (-11.8, -6.1)	-18.2 (-23.1, -13.4)	-19.1 (-23.5, -14.8)	-20.9 (-24.7, -17.1)	-26.5 (-30.5, -22.4)	-26.4 (-29.1, -23.7)
<i>Sex</i>							
Male (N=174)	-1.8 (-3.5, -0.1)	-7.8 (-9.9, -5.7)	-13.8 (-17.0, -10.6)	-15.1 (-19.8, -10.3)	-21.4 (-24.6, -18.3)	-19.8 (-24.1, -15.5)	-21.9 (-25.3, -18.6)
Female (N=161)	-2.6 (-4.7, -0.5)	-9.6 (-12.7, -6.5)	-18.8 (-24.1, -13.4)	-20.3 (-23.6, -17.1)	-22.8 (-26.9, -18.7)	-28.5 (-32.2, -24.9)	-26.6 (-30.1, -23.1)

Data are least squares means (95% CI). Abbreviations include BMI, body mass index; ID, initial dose; RETA, retatrutide; SE, standard error.

**Table S8. Metabolic and cardiovascular measures at week 24**

	Placebo (N=68)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=33)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)
<b>Percent Change from baseline</b>							
Fasting triglycerides (%)	-3.1 (-10.8, 4.6)	-15.3 (-21.3, -9.3)	-31.1 (-39.8, -22.4)	-28.8 (-37.8, -19.7)	-39.3 (-47.5, -31.0)	-29.2 (-36.3, -22.1)	-34.0 (-39.1, -29.0)
Fasting total cholesterol (%)	-2.2 (-4.8, 0.4)	-4.6 (-8.3, -0.9)	-11.8 (-16.1, -7.5)	-9.2 (-13.8, -4.6)	-17.7 (-21.3, -14.0)	-15.3 (-19.1, -11.4)	-17.3 (-20.5, -14.1)
Fasting LDL cholesterol (%)	-3.6 (-7.5, 0.4)	-4.1 (-9.2, 1.0)	-11.6 (-17.8, -5.4)	-6.3 (-13.1, 0.6)	-16.9 (-22.4, -11.3)	-15.6 (-21.3, -9.9)	-16.4 (-21.0, -11.8)
Fasting VLDL cholesterol (%)	-2.8 (-10.6, 4.9)	-14.7 (-20.7, -8.8)	-30.6 (-39.3, -21.8)	-28.1 (-37.1, -19.0)	-39.1 (-47.4, -30.9)	-28.5 (-35.7, -21.4)	-33.4 (-38.7, -28.2)
Fasting HDL cholesterol (%)	0.4 (-3.6, 4.4)	1.8 (-1.7, 5.3)	-1.2 (-6.0, 3.5)	1.1 (-5.5, 7.7)	-6.2 (-10.6, -1.9)	-7.4 (-11.0, -3.8)	-8.4 (-11.6, -5.1)
<b>Change from baseline</b>							
Fasting glucose (mg/dL)	3.4 (0.5, 6.2)	-3.4 (-5.7, -1.1)	-6.5 (-9.3, -3.6)	-9.0 (-11.7, -6.2)	-9.8 (-12.6, -7.1)	-9.9 (-12.8, -6.9)	-10.2 (-12.7, -7.8)
Fasting insulin (mU/L)	-0.8 (-2.8, 1.2)	-3.6 (-4.9, -2.4)	-6.3 (-7.8, -4.7)	-5.1 (-7.3, -3.0)	-6.6 (-8.4, -4.8)	-5.3 (-7.1, -3.6)	-6.5 (-8.1, -5.0)
Fasting HbA1c (%)	0.1 (0.0, 0.1)	-0.1 (-0.2, 0.0)	-0.2 (-0.3, -0.1)	-0.3 (-0.4, -0.2)	-0.4 (-0.5, -0.3)	-0.4 (-0.5, -0.3)	-0.3 (-0.4, -0.3)
<b>Change from baseline with 24-hour ABPM</b>							
Systolic BP (mmHg)	-3.4 (-5.7, -1.1)	-4.3 (-6.7, -1.9)	-4.5 (-9.4, 0.4)	-8.0 (-11.1, -4.8)	-10.2 (-13.0, -7.4)	-11.1 (-13.6, -8.5)	-9.4 (-12.9, -6.0)
Diastolic BP (mmHg)	-1.7 (-3.1, -0.3)	-2.0 (-3.7, -0.3)	-0.9 (-3.2, 1.5)	-2.4 (-4.4, -0.4)	-3.4 (-5.2, -1.7)	-3.1 (-4.7, -1.5)	-2.5 (-4.3, -0.6)
Heart rate (bpm)	0.8 (-0.8, 2.3)	0.7 (-0.8, 2.1)	4.2 (1.5, 6.9)	2.2 (0.3, 4.1)	5.7 (3.6, 7.8)	6.0 (3.6, 8.4)	9.2 (7.4, 11.1)

Data are least squares means (95% CI), unless otherwise stated. Abbreviations include ABPM, ambulatory blood pressure monitoring; BP, blood pressure, HbA1c, glycated hemoglobin; HDL, high-density lipoproteins; ID, initial dose; LDL, low-density lipoproteins; RETA, retatrutide; SE, standard error; VLDL, very low-density lipoproteins.

**Table S9. Short Form-36 Version 2 Health Survey (SF-36v2) acute form domain scores at Week 48**

	<b>Placebo</b>  (N=68)	<b>RETA 1 mg</b>  (N=68)	<b>RETA 4 mg [ID 2 mg]</b>  (N=33)	<b>RETA 4 mg [ID 4 mg]</b>  (N=33)	<b>RETA 8 mg [ID 2 mg]</b>  (N=35)	<b>RETA 8 mg [ID 4 mg]</b>  (N=35)	<b>RETA 12 mg [ID 2 mg]</b>  (N=61)
<u>Physical Functioning</u>							
Baseline	50.3 (48.7, 52.0)	51.7 (50.4, 53.0)	50.1 (46.7, 53.4)	49.9 (46.9, 52.9)	50.7 (48.2, 53.1)	49.1 (46.7, 51.6)	49.2 (47.3, 51.0)
Change from baseline	2.2 (1.0, 3.5)	2.9 (1.5, 4.4)	3.6 (1.6, 5.7)	3.2 (0.9, 5.5)	4.5 (2.0, 7.0)	4.8 (3.4, 6.3)	2.7 (0.8, 4.6)
<u>Role-Physical</u>							
Baseline	52.3 (50.8, 53.8)	53.9 (52.9, 54.9)	52.1 (49.4, 54.9)	51.6 (49.1, 54.1)	49.9 (46.9, 53.0)	51.4 (48.7, 54.1)	50.7 (48.7, 52.7)
Change from baseline	2.8 (1.6, 3.9)	2.1 (0.5, 3.7)	2.7 (1.0, 4.3)	2.0 (0.2, 3.7)	3.8 (2.2, 5.4)	3.7 (2.6, 4.8)	2.0 (0.6, 3.4)
<u>Bodily Pain</u>							
Baseline	52.2 (50.3, 54.1)	53.2 (51.5, 54.9)	53.4 (50.1, 56.7)	53.0 (50.4, 55.5)	51.5 (48.9, 54.0)	51.3 (48.4, 54.3)	51.2 (48.9, 53.4)
Change from baseline	1.6 (0.0, 3.2)	2.6 (1.1, 4.1)	3.9 (2.5, 5.4)	0.7 (-2.6, 4.0)	3.8 (0.9, 6.7)	2.2 (0.7, 3.6)	2.1 (0.0, 4.3)
<u>General Health</u>							
Baseline	52.4 (50.4, 54.1)	54.7 (53.2, 56.3)	54.1 (51.4, 56.8)	52.6 (50.0, 55.3)	53.3 (50.6, 55.9)	51.0 (48.1, 53.8)	49.8 (47.7, 51.8)
Change from baseline	1.7 (0.5, 2.9)	3.0 (1.4, 4.5)	3.6 (1.9, 5.4)	4.0 (2.4, 5.5)	2.7 (0.4, 4.9)	3.9 (2.5, 5.4)	4.2 (2.4, 5.9)
<u>Vitality</u>							
Baseline	55.7 (54.1, 57.4)	55.4 (53.6, 57.3)	55.0 (52.5, 57.6)	53.6 (50.4, 56.9)	54.8 (52.1, 57.5)	52.2 (49.0, 55.4)	53.7 (51.6, 55.7)
Change from baseline	1.7 (0.2, 3.3)	2.4 (0.8, 4.0)	3.8 (1.8, 5.8)	4.4 (2.6, 6.3)	2.3 (-0.3, 4.9)	1.9 (-0.4, 4.2)	2.9 (1.1, 4.6)
<u>Social Functioning</u>							
Baseline	54.7 (53.8, 55.7)	54.8 (53.7, 55.9)	54.3 (52.1, 56.5)	53.1 (50.7, 55.6)	53.2 (50.9, 55.5)	52.8 (50.2, 55.3)	52.5 (50.8, 54.2)
Change from baseline	1.5 (0.7, 2.2)	0.5 (-0.8, 1.8)	0.6 (-1.3, 2.4)	1.0 (-0.1, 2.1)	2.9 (1.7, 4.0)	1.3 (0.2, 2.5)	1.6 (0.7, 2.6)
<u>Role Emotional</u>							
Baseline	52.9 (51.6, 54.3)	52.7 (51.3, 54.0)	51.9 (49.0, 54.9)	52.6 (50.1, 55.2)	49.5 (46.2, 52.9)	52.4 (49.6, 55.1)	50.5 (48.4, 52.5)
Change from baseline	2.1 (1.3, 2.9)	1.6 (0.2, 3.0)	0.7 (-1.6, 2.9)	1.2 (-0.6, 2.9)	2.8 (1.7, 4.0)	1.7 (0.6, 2.7)	1.7 (0.4, 3.1)
<u>Mental Health</u>							
Baseline	50.9 (49.7, 52.2)	51.2 (50.1, 52.3)	49.9 (48.3, 51.5)	50.9 (48.6, 53.1)	50.0 (48.0, 52.0)	49.5 (47.4, 51.6)	50.7 (49.5, 51.8)
Change from baseline	0.1 (-1.0, 1.2)	0.5 (-0.8, 1.8)	-0.7 (-2.5, 1.1)	-0.3 (-1.4, 0.9)	0.4 (-0.9, 1.7)	-0.1 (-1.4, 1.3)	-0.2 (-1.7, 1.4)
<u>Physical Component</u>							
Baseline	51.6 (50.0, 53.1)	53.6 (52.3, 55.0)	52.6 (49.8, 55.5)	51.5 (48.9, 54.0)	51.7 (49.3, 54.2)	50.5 (47.7, 53.2)	50.1 (48.1, 52.0)
Change from baseline	2.3 (1.0, 3.7)	3.2 (1.6, 4.8)	4.8 (3.3, 6.2)	3.2 (1.6, 4.8)	4.6 (2.6, 6.7)	4.8 (3.6, 5.9)	3.2 (1.5, 4.9)

Data are least squares means (95% CI). Abbreviations include ID, initial dose; RETA, retatrutide; SE, standard error.

**Table S10.**

**Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group but < 5% of total participants**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=33)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)	Total (N=337)
<b>Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group but &lt; 5% of total participants (n, %)</b>								
Hypertension	2 (2.9)	6 (8.7)	1 (3.0)	0	3 (8.6)	0	4 (6.5)	16 (4.7)
Nasopharyngitis	3 (4.3)	6 (8.7)	0	2 (6.1)	3 (8.6)	1 (2.9)	0	15 (4.5)
Dizziness	2 (2.9)	1 (1.4)	1 (3.0)	2 (6.1)	0	3 (8.6)	5 (8.1)	14 (4.2)
Abdominal pain upper	2(2.9)	3 (4.3)	1 (3.0)	0	3 (8.6)	2 (5.7)	3 (4.8)	14 (4.2)
Dyspepsia	2 (2.9)	1 (1.4)	2 (6.1)	0	2 (5.7)	2 (5.7)	5 (8.1)	14 (4.2)
Gastroesophageal reflux disease	1(1.4)	1 (1.4)	2 (6.1)	3 (9.1)	3 (8.6)	0	4 (6.5)	14 (4.2)
Blood creatine phosphokinase increased	2 (2.9)	5 (7.2)	1 (3.0)	1 (3.0)	1 (2.9)	2 (5.7)	1 (1.6)	13 (3.9)
Headache	0	2 (2.9)	1 (3.0)	0	0	4 (11.4)	4 (6.5)	11 (3.3)
Sinusitis	4 (5.7)	2 (2.9)	1 (3.0)	1 (3.0)	1 (2.9)	1 (2.9)	0	10 (3.0)
Urinary tract infection	1 (1.4)	2 (2.9)	2 (6.1)	1 (3.0)	0	2 (5.7)	2 (3.2)	10 (3.0)
Upper respiratory tract infection	2 (2.9)	4 (5.8)	0	0	0	2 (5.7)	2 (3.2)	10 (3.0)
Abdominal pain	2 (2.9)	1 (1.4)	1 (3.0)	0	2 (5.7)	1 (2.9)	2(3.2)	9 (2.7)
Hyperesthesia	1 (1.4)	0	2 (6.1)	1 (3.0)	1 (2.9)	1 (2.9)	2 (3.2)	8 (2.4)
Abdominal distension	0	0	0	0	0	2 (5.7)	5 (8.1)	7 (2.1)
Rash	0	2 (2.9)	0	0	2 (5.7)	1 (2.9)	2 (3.2)	7 (2.1)
Amylase increased	2 (2.9)	0	2 (6.1)	0	1 (2.9)	0	2 (3.2)	7 (2.1)
Weight decreased	0	1 (1.4)	0	1 (3.0)	2 (5.7)	2 (5.7)	1 (1.6)	7 (2.1)
Hypotension	0	1 (1.4)	0	0	1 (2.9)	3 (8.6)	1 (1.6)	6 (1.8)
Dizziness postural	0	1 (1.4)	0	0	2 (5.7)	0	2 (3.2)	5 (1.5)
Sensitive skin	0	0	0	1 (3.0)	0	2 (5.7)	2 (3.2)	5 (1.5)
Pruritus	0	0	0	1 (3.0)	0	2 (5.7)	1 (1.6)	4 (1.2)
Anaemia	0	0	2 (6.1)	0	0	0	2 (3.2)	4 (1.2)
Allodynia	0	0	0	0	0	0	4 (6.5)	4 (1.2)
Erectile dysfunction	0	2 (5.6)	0	0	0	0	0	2 (1.1)
Feces hard	0	0	0	0	0	2 (5.7)	0	2 (0.6)
Vaginal infection	0	0	0	1 (6.7)	0	0	0	1 (0.6)

Data are number of participants (%). Abbreviations include ID, initial dose; RETA, retatrutide.

**Table S11. Serious adverse events**

<b>Subject age and sex</b>	<b>Treatment Arm</b>	<b>Dose at time of SAE</b>	<b>Description (MedDRA preferred term/reported term)</b>	<b>Days from first dose of study drug</b>	<b>Investigator assessment of relatedness to study drug</b>	<b>Action taken/ Event Outcome</b>	<b>Additional Comments on Medical History and Concurrent Illnesses</b>
60 y, female	Placebo	N/A	Bone contusion/ Bruised ribs	91	No	Drug Interrupted/ Recovered/Resolved	Injury related to motor vehicle accident
60 y, male	Placebo	N/A	Blood calcitonin increased/ Increase in serum calcitonin levels	176	Yes	Drug Withdrawn/ Not Recovered/Not Resolved	Increase from baseline value of 17.3 ng/L to 35.2 ng/L
58 y, male	Placebo	N/A	Coronary artery stenosis/ Worsening coronary artery stenosis	363	No	Not Applicable/ Recovering/Resolving	Coronary artery bypass graft surgery was performed
46 y, female	RETA 1 mg	1 mg	Chest discomfort/ Chest tightness / Pain	179	No	Dose Not Changed/ Recovered/Resolved	History of depression; cardiac event was ruled out
75 y, female	RETA 1 mg	1 mg	Cerebrovascular accident	65	No	Not Applicable/ Recovered/Resolved	Hypertension
74 y, male	RETA 1 mg	1 mg	Cerebrovascular accident/ Stroke	277	No	Drug Withdrawn/ Recovered/Resolved	Obstructive sleep apnea, reactive airway disease, past history of pontine stroke
37 y, female	RETA 4 mg [ID 4 mg]	4 mg	Drowning/ Drowning	292	No	Drug Withdrawn/ Fatal	The patient drowned while rafting which led to her death
42 y, female	RETA 4 mg [ID 4 mg]	4 mg	Clear cell renal cell carcinoma	175	No	Drug Withdrawn/ Recovered/Resolved	History of reoccurring urinary tract infections; presenting symptom was abdominal pain
32 y, female	RETA 8 mg [ID 2 mg]	8 mg	Cardiac failure/ Heart Failure	176	No	Drug Interrupted/ Recovered/Resolved	Prior COVID-19 infection was considered the underlying cause of heart failure by the investigator

49 y, female	RETA 8 mg [ID 4 mg]	8 mg	Vomiting/ Intractable vomiting	165	Yes	Not Applicable/ Recovered/Resolved	Laparoscopic cholecystectomy was performed
			Cholecystitis acute/ Acute cholecystitis	173	Yes	Drug Withdrawn/ Recovered/Resolved	
66 y, male	RETA 8 mg [ID 4 mg]	8 mg	COVID-19/ SARS-CoV-2 Omicron variant infection	289	No	Drug Withdrawn/ Recovered/Resolved	Acute renal failure was considered as possibly due to COVID-19- associated nephropathy (COVAN) secondary to COVID infection
			Acute kidney injury/ Acute renal failure	295	No	Drug Withdrawn/ Recovering/Resolving	
51 y, female	RETA 12 mg [ID 2 mg]	12 mg	Electrocardiogram QT prolonged/ Prolonged QT syndrome	134	Yes	Drug Withdrawn/ Recovered/Resolved	Severe vomiting (treated with ondansetron) leading to hypokalemia, dehydration, hypotension and shock liver with severe ALT/AST elevations. All events resolved with discontinuation of study drug
30 y, female	RETA 12 mg [ID 2 mg]	2 mg	Pancreatitis acute/ Acute pancreatitis	14	Yes	Drug Withdrawn/ Recovered/Resolved	Adjudicated as an event of acute pancreatitis, by Clinical Endpoint Committee

Abbreviations include ID, initial dose; RETA, retatrutide; SAE, serious adverse event; y, years; MedDRA, Medical Dictionary for Regulatory Activities.

**Table S12. Additional safety measures**

	Normal range	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=33)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)
<b>Pulse, bpm</b>								
Baseline	60-100 bpm	74.0 (71.5, 76.5)	71.1 (68.5, 73.8)	68.3 (64.6, 72.1)	71.4 (67.9, 74.9)	72.0 (68.4, 75.7)	69.1 (66.0, 72.1)	69.3 (67.0, 71.6)
Week 48		71.4 (69.5, 73.3)	72.7 (70.4, 75.0)	74.0 (72.1, 76.0)	74.3 (71.8, 76.7)	75.3 (72.6, 78.1)	76.2 (73.2, 79.1)	77.0 (74.7, 79.3)
change at week 48		0.4 (-1.5, 2.3)	1.7 (-0.7, 4.0)	3.0 (1.1, 4.9)	3.2 (0.8, 5.6)	4.3 (1.5, 7.1)	5.2 (2.2, 8.1)	6.0 (3.7, 8.3)
<b>Pancreatic-amylase, U/L</b>	13 – 53 U/L							
Baseline		23.4 (21.4, 25.3)	23.2 (21.0, 25.3)	27.5 (24.3, 30.7)	25.0 (22.3, 27.7)	24.7 (21.7, 27.6)	21.2 (18.2, 24.2)	23.3 (20.5, 26.0)
Week 48		25.1 (23.4, 26.8)	26.0 (24.6, 27.5)	29.0 (26.1, 31.9)	27.9 (26.0, 29.8)	27.9 (26.0, 29.7)	27.2 (24.4, 30.1)	28.6 (26.2, 30.9)
% change at week 48		5.7 (-1.5, 12.9)	9.6 (3.6, 15.7)	22.3 (10.2, 34.4)	17.5 (9.6, 25.4)	17.5 (9.6, 25.3)	14.8 (2.9, 26.7)	20.4 (10.3, 30.4)
<b>Lipase, U/L</b>	13 – 60 U/L							
Baseline		28.7 (25.8, 31.6)	30.4 (27.0, 33.7)	34.3 (30.9, 37.8)	34.7 (30.7, 38.6)	30.5 (26.4, 34.5)	28.8 (25.4, 32.2)	27.5 (25.3, 29.8)
Week 48		30.3 (28.1, 32.6)	34.4 (31.6, 37.3)	41.2 (35.4, 47.0)	37.8 (33.3, 42.2)	38.4 (35.2, 41.6)	38.1 (32.7, 43.5)	38.1 (33.5, 42.6)
% change at week 48		0.9 (-6.6, 8.4)	14.6 (5.1, 24.0)	36.9 (17.6, 56.2)	25.7 (10.8, 40.5)	27.8 (17.1, 38.5)	26.7 (8.7, 44.7)	26.7 (11.6, 41.8)
<b>Aspartate aminotransferase, U/L</b>								
Baseline	≤31 - female	21.9 (20.5, 23.3)	21.6 (19.8, 23.4)	21.9 (19.4, 24.3)	22.1 (19.6, 24.7)	18.9 (17.1, 20.6)	23.2 (20.4, 26.1)	20.1 (18.5, 21.6)
Week 48	≤37 - male	22.4 (20.3, 24.5)	20.1 (19.0, 21.1)	19.4 (17.5, 21.3)	17.8 (16.3, 19.3)	17.4 (15.9, 19.0)	19.5 (17.5, 21.5)	19.1 (17.3, 20.8)
% change at week 48		5.0 (-5.0, 15.0)	-5.9 (-10.8, -0.9)	-9.0 (-17.9, -0.1)	-16.5 (-23.7, -9.2)	-18.2 (-25.4, -11.0)	-8.4 (-17.8, 1.0)	-10.5 (-18.6, -2.3)
<b>Alanine aminotransferase, U/L</b>								
Baseline	≤41 - female	23.6 (20.9, 26.4)	22.8 (20.2, 25.5)	24.3 (20.0, 28.6)	24.8 (20.7, 28.8)	20.4 (16.8, 24.1)	27.3 (22.2, 32.3)	23.3 (20.2, 26.4)
Week 48	≤33 - male	24.4 (21.9, 26.9)	20.9 (19.3, 22.5)	21.3 (18.8, 23.7)	18.8 (16.2, 21.4)	19.1 (16.6, 21.7)	20.7 (17.6, 23.8)	22.0 (19.7, 24.2)
% change at week 48		3.5 (-7.2, 14.3)	-11.3 (-18.1, -4.4)	-9.7 (-20.1, 0.8)	-20.2 (-31.4, -9.1)	-18.7 (-29.6, -7.8)	-12.2 (-25.5, 1.2)	-6.8 (-16.3, 2.8)
<b>Calcitonin, ng/L</b>								
Baseline	≤6.4 - female	1.5 (1.1, 1.9)	1.7 (1.3, 2.1)	1.3 (0.9, 1.7)	1.4 (0.8, 1.9)	2.1 (1.3, 2.9)	1.3 (0.8, 1.8)	1.7 (1.1, 2.1)
Week 48	≤9.5 - male	1.6 (1.4, 1.8)	1.6 (1.4, 1.7)	1.6 (1.4, 1.9)	1.7 (1.3, 2.0)	1.8 (1.5, 2.2)	1.9 (1.7, 2.2)	1.9 (1.6, 2.1)
% change at week 48		3.2 (-9.2, 15.6)	1.1 (-7.6, 9.8)	5.4 (-9.8, 20.5)	6.5 (-16.8, 29.9)	17.6 (-3.8, 39.1)	23.8 (8.1, 39.5)	21.9 (6.1, 37.7)
<b>Urine</b>								
<b>Albumin-to-Creatinine Ratio, g/kg</b>								
Baseline	≤30 g/kg	8.7 (6.7, 10.8)	8.7 (6.8, 10.6)	7.8 (5.7, 9.9)	8.5 (5.4, 11.5)	7.6 (5.6, 9.7)	9.1 (6.4, 11.8)	8.3 (6.9, 9.8)
Week 48		10.7 (7.9, 13.6)	7.7 (6.3, 9.0)	8.5 (6.2, 10.9)	11.0 (7.7, 14.3)	8.1 (6.4, 9.7)	7.6 (5.7, 9.6)	7.5 (6.4, 8.7)
% change at week 48		27.1 (-6.5, 60.8)	-9.2 (-24.9, 6.6)	0.9 (-26.7, 28.4)	30.6 (-8.4, 69.6)	-4.7 (-24.5, 15.1)	-9.9 (-33.1, 13.2)	-11.0 (-24.7, 2.7)
<b>eGFR (mL/min/1.73m<sup>2</sup>)</b>								
Baseline	>60 (mL/min/1.73m <sup>2</sup> )	89.4 (85.4, 93.4)	87.9 (83.7, 92.2)	84.5 (78.1, 90.9)	90.9 (84.9, 96.9)	94.8 (89.5, 100.1)	92.7 (87.7, 97.7)	93.6 (89.0, 98.1)
Week 48		90.2 (87.7, 92.7)	86.9 (85.1, 88.7)	92.8 (89.3, 96.3)	90.8 (87.1, 94.5)	93.7 (90.4, 96.9)	95.7 (92.3, 99.0)	97.1 (94.5, 99.6)
change at week 48		-0.3 (-2.8, 2.2)	-3.6 (-5.4, -1.8)	2.4 (-1.1, 5.9)	0.4 (-3.3, 4.0)	3.2 (-0.1, 6.5)	5.2 (1.9, 8.6)	6.6 (4.1, 9.1)

Data presented are LSM (95% CI). Note: except for pulse and eGFR, all other measures were analyzed with log-transformation. Abbreviations include eGFR, estimated glomerular filtration rate; ID, initial dose; LSM, least squares mean, RETA, retatrutide.

**Table S13. Details of cardiac arrhythmia and related AEs\* – all MedDRA preferred terms by dose group**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=33)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)	Total (N=337)
Participants with ≥ 1 AE of cardiac arrhythmia and related AEs	2 (2.9)	3 (4.3)	0	2 (6.1)	0	5 (14.3)	7 (11.3)	19 (5.6)**
Bundle branch block right	1 (1.4)	1 (1.4)	0	0	0	1 (2.9)	0	3 (0.9)
Palpitations	0	0	0	0	0	1 (2.9)	2 (3.2)	3 (0.9)
Tachycardia	1 (1.4)	0	0	0	0	0	2 (3.2)	3 (0.9)
Defect conduction intraventricular	0	0	0	0	0	1 (2.9)	1 (1.6)	2 (0.6)
Heart rate increased	0	0	0	0	0	1 (2.9)	1 (1.6)	2 (0.6)
Ventricular extrasystoles	0	0	0	0	0	1 (2.9)	1 (1.6)	2 (0.6)
Atrioventricular block first degree	0	0	0	1 (3.0)	0	0	0	1 (0.3)
Bradycardia	0	1 (1.4)	0	0	0	0	0	1 (0.3)
Electrocardiogram QT prolonged	0	0	0	0	0	0	1 (1.6)	1 (0.3)
Supraventricular extrasystoles	0	1 (1.4)	0	0	0	0	0	1 (0.3)
Syncope***	0	0	0	1 (3.0)	0	0	0	1 (0.3)

Data are number of participants (%). Abbreviations include AE, adverse events; ID, initial dose; RETA, retatrutide; MedDRA, Medical Dictionary for Regulatory Activities; \*Cardiac arrhythmia and related AEs were assessed by a predefined search using the following Standardized MedDRA Queries: arrhythmia related investigations, signs and symptoms; conduction defects; supraventricular tachyarrhythmias; ventricular tachyarrhythmias. \*\*21 events occurred in 19 participants. Of these 21 events, 13 were mild, 7 were moderate and 1 was severe. Of the 19 participants, 17 continued treatment and 2 discontinued treatment (12 mg group). The two events that led to treatment discontinuation were: 1) a severe and serious event of electrocardiogram QT prolonged; and 2) palpitations of moderate severity. \*\*\*The reported term for the AE of syncope was "orthostatic faintness."

**Table S14. Details of hyperesthesia and related AEs\* – all MedDRA preferred terms by dose group**

	Placebo (N=70)	RETA 1 mg (N=69)	RETA 4 mg [ID 2 mg] (N=33)	RETA 4 mg [ID 4 mg] (N=33)	RETA 8 mg [ID 2 mg] (N=35)	RETA 8 mg [ID 4 mg] (N=35)	RETA 12 mg [ID 2 mg] (N=62)	Total (N=337)
Participants with ≥ 1 AE of hyperesthesia and related AEs	1 (1.4)	1 (1.4)	2 (6.1)	2 (6.1)	1 (2.9)	5 (14.3)	8 (12.9)	20 (5.9)**
Hyperaesthesia	1 (1.4)	0	2 (6.1)	1 (3.0)	1 (2.9)	1 (2.9)	2 (3.2)	8 (2.4)
Sensitive skin	0	0	0	1 (3.0)	0	2 (5.7)	2 (3.2)	5 (1.5)
Allodynia	0	0	0	0	0	0	4 (6.5)	4 (1.2)
Skin burning sensation	0	1 (1.4)	0	0	0	1 (2.9)	0	2 (0.6)
Paraesthesia	0	0	0	0	0	1 (2.9)	0	1 (0.3)

Data are number of patients (%). Abbreviations include AE, adverse events; ID, initial dose; RETA, retatrutide; TEAE, treatment-emergent adverse event; MedDRA, Medical Dictionary for Regulatory Activities.

\*Hyperaesthesia and related AEs were assessed by a predefined search using the MedDRA preferred terms of allodynia, burning sensation, dysaesthesia, hyperaesthesia, hyperpathia, paraesthesia, pain of skin, sensitive skin, skin burning sensation, and skin discomfort.

\*\*Sixteen of 20 events resolved, 2 were resolving during the treatment period and 2 were unresolved at the 4-week safety follow-up visit.

**Table S15. Summary of end of treatment dosing status**

	<b>Placebo</b> (N=70)	<b>RETA 1 mg</b> (N=69)	<b>RETA 4 mg [ID 2 mg]</b> (N=33)	<b>RETA 4 mg [ID 4 mg]</b> (N=33)	<b>RETA 8 mg [ID 2 mg]</b> (N=35)	<b>RETA 8 mg [ID 4 mg]</b> (N=35)	<b>RETA 12 mg [ID 2 mg]</b> (N=62)
On target dose*	NA	56 (81.2)	28 (84.8)	24 (72.7)	23 (65.7)	29 (82.9)	40 (64.5)
Not on target dose**	NA	0 (0)	1 (3)	1 (3)	5 (14.3)	1 (2.9)	6 (9.7)
Discontinued treatment***	20 (28.6)	13 (18.8)	4 (12.1)	8 (24.2)	7 (20)	5 (14.3)	16 (25.8)

Data are number of participants (%). Abbreviations include ID, initial dose; NA; not available RETA, retatrutide.

\* Participants who were on the planned target dose at the last visit of the treatment period.

\*\* Participants who were not on the planned target dose at the last visit of the treatment period and did not discontinue study treatment.

\*\*\* Participants who discontinued study treatment prior to the last visit of the treatment period.

## References

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