Supplementary Appendix

Supplement to: Jastreboff AM, Kaplan LM, Frías JP, et al. Triple–hormone-receptor agonist retatrutide for obesity — a phase 2 trial. N Engl J Med. DOI: 10.1056/NEJMoa2301972

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

SUPPLEMENTARY APPENDIX

CONTENTS

List of the Retatrutide Phase 2 Obesity Trial Investigators (Study J1I-MC-GZBF; NCT04881760)

1. Dr. Adil Fatakia, Tandem Clinical Research, LLC, 1151 Barataria Blvd Suite 3200, Marrero, LA, 70072, United States.
2. Dr. Evelyne Davidson, New Phase Research and Development, 6914 Office Park Circle, Knoxville, TN, 37909, United States.
3. Dr. Susan Brian, Cotton O'Neil Diabetes and Endocrinology Center, 3520 SW 6th Ave, Topeka, KS, 66606, United States.
4. Dr Stanley Hsia, Velocity Clinical Research, Huntington Park, 6011 Pacific Boulevard, Suite 116, Huntington Park, CA, 90255, United States.
5. Dr Amina Haggag, Anaheim Clinical Trials, LLC, 2441 W. La Palma Avenue, Suite 140, Anaheim, CA, 92801, United States.
6. Dr Julio Rosenstock, Velocity Clinical Research, Dallas, 7777 Forest Lane Suite C-685, Dallas, TX, 75230, United States.
7. Dr Juan Frias, Velocity Clinical Research, Huntington Park, 2010 Wilshire Blvd. Suite 302, Los Angeles, CA, 90057, United States.
8. Mrs Andrea Kessler, Perseverance Research Center, 11000 N. Scottsdale Rd Suite 110, Scottsdale, AZ, 85254, United States.
9. Dr Diana Widicus. Springfield Diabetes & Endocrine Center. 1118 Legacy Pointe. Springfield, IL, 62711, United States.
10. Dr Sandro Bacchelli, Encore Medical Research – Weston, 2771 Executive Park Drive Suite 5, Weston, FL, 33331, United States.
11. Dr Cathy Barnes, Suncoast Clinical Research, Inc. 5604 Gulf Drive, New Port Richey, FL, 34652, United States.
12. Dr Mae Sheikh-Ali, East Coast Institute for Research, LLC, 3550 University Blvd South Suite 101, Jacksonville, FL, 32216, United States.
13. Timothy Smith, StudyMetrix Research, 3862 Mexico Road, St. Peters, MO, 63303, United States.
14. Dr Lisa Connery, Alliance for Multispecialty Research, LLC, 1010 24th Ave. NW Suite 110, Norman, OK, 73069, United States.
15. Dr Valerie Espinosa, Texas Diabetes & Endocrinology, P.A, 6500 N. Mopac Expwy Bldg. 3, Ste. 200, Austin, TX, 78731, United States.
16. Dr Amer Al-Karadsheh, ENDOCRINE IPS, PLLC, 10837 Katy Freeway Suite 160, Houston, TX, 77079, United States.
17. Dr Sumana Gangi, Southern Endocrinology Associates, 1621 North Belt Line Rd Suite A, Mesquite, TX, 75149, United States.
18. Dr Wayne Ho, Southern California Dermatology, Inc., 1125 E. 17th St. Suite W244-W248, Santa Ana, CA, 92701, United States.
19. Dr Michelle Mangual, San Juan City Hospital, Paseo Dr. Jose Celso Barbosa 3rd Floor Room FP-04 San Juan City Hospital, San Juan, PR, 00935, United States.
20. Paul Norwood, Valley Research, 550 E. Herndon Ave Suite 101, Fresno, CA, 93720, United States.
21. Dr. Helen Stacey, Diablo Clinical Research, Inc., 2255 Ygnacio Valley Road Suite M, Walnut Creek, CA, 94598, United States.
22. Dr Ronald Chochinov, Coastal Metabolic Research Centre, 3454 Loma Vista Road, Ventura, CA, 93003, United States.

23. Ms Lisa Malak, Amici Clinical Research LLC, 34 East Somerset Street Somerset County, Raritan, NJ, 08869, United States.
24. Dr Rocio Harbison, Juno Research, 7400 Fannin Street Suite 855, Houston, TX , 77054, United States.
25. Dr Paola Mansilla-Letelier, Private Practice – Dr. Paola Mansilla-Letelier, Ave Albolote, Plaza Real Shopping Center, Suite 302, Guaynabo, PR, 00970, United States.
26. Dr Gregorio Cortes-Maisonet, GCM Medical Group, PSC – Hato Rey Site, 62, Calle José Martí Urb. Floral Park, San Juan, PR, 00917, United States.
27. Dr Ronald Brazg, Rainier Clinical Research Center, 800 Southwest 39th Street #110, Renton, WA, 98057, United States.
28. Dr Murray Gordon, Allegheny Endocrinology Associates, 420 East North Avenue, Pittsburgh, PA, 15212, United States.

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
   - ≥30 kg/m^2 and ≤50 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)

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 ≥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 ≥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 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^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) 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

    - ≥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)

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 ≥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^2 vs. $<$ 36 kg/m^2]) 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 [≥ 36 kg/m^2 vs. < 36 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

ICE	Strategy to Handle ICE	Assumptions for Missingness	Methods to Handle Missing Values at Endpoint
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.

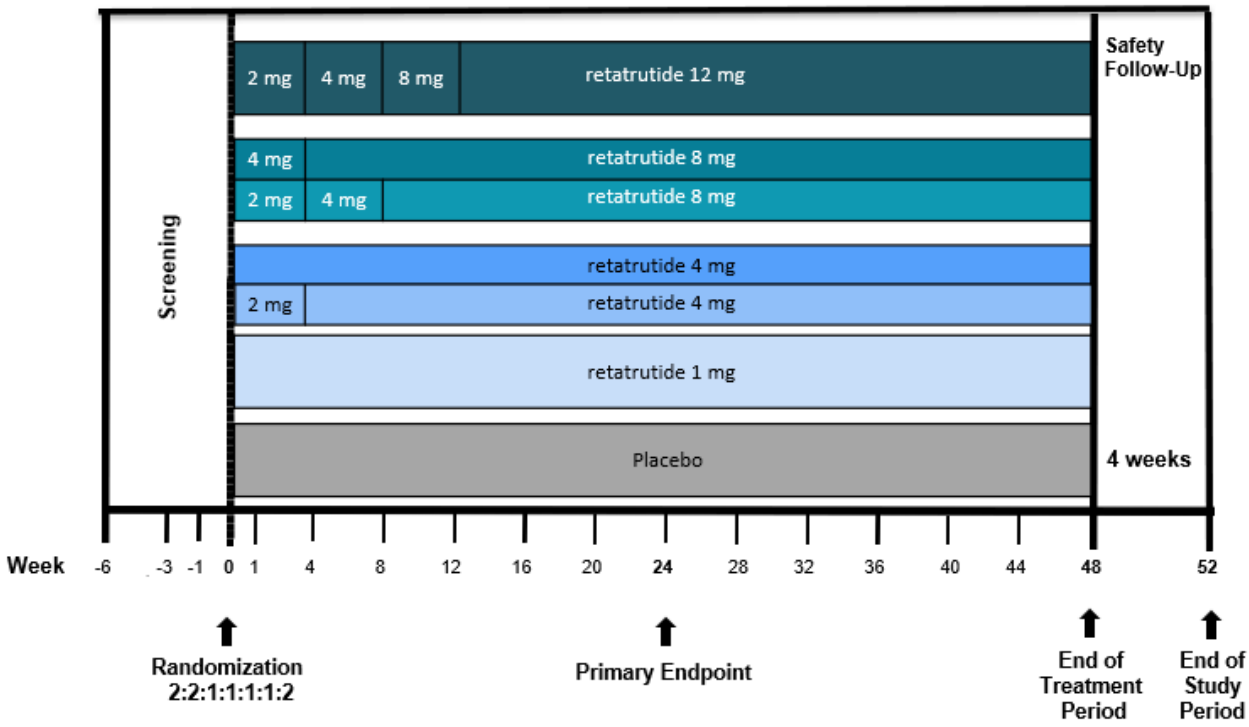


Figure S1. Study design schematic. This is a Phase 2, multicenter, randomized, placebo-controlled, double-blinded clinical trial investigating the efficacy and safety of 1 mg, 4 mg, 8 mg and 12 mg retatrutide (with different initial doses [ID], 2 mg versus 4 mg) administered once weekly (QW) subcutaneously compared with placebo for weight management as an adjunct to lifestyle intervention, in participants who have obesity, or overweight with ≥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.

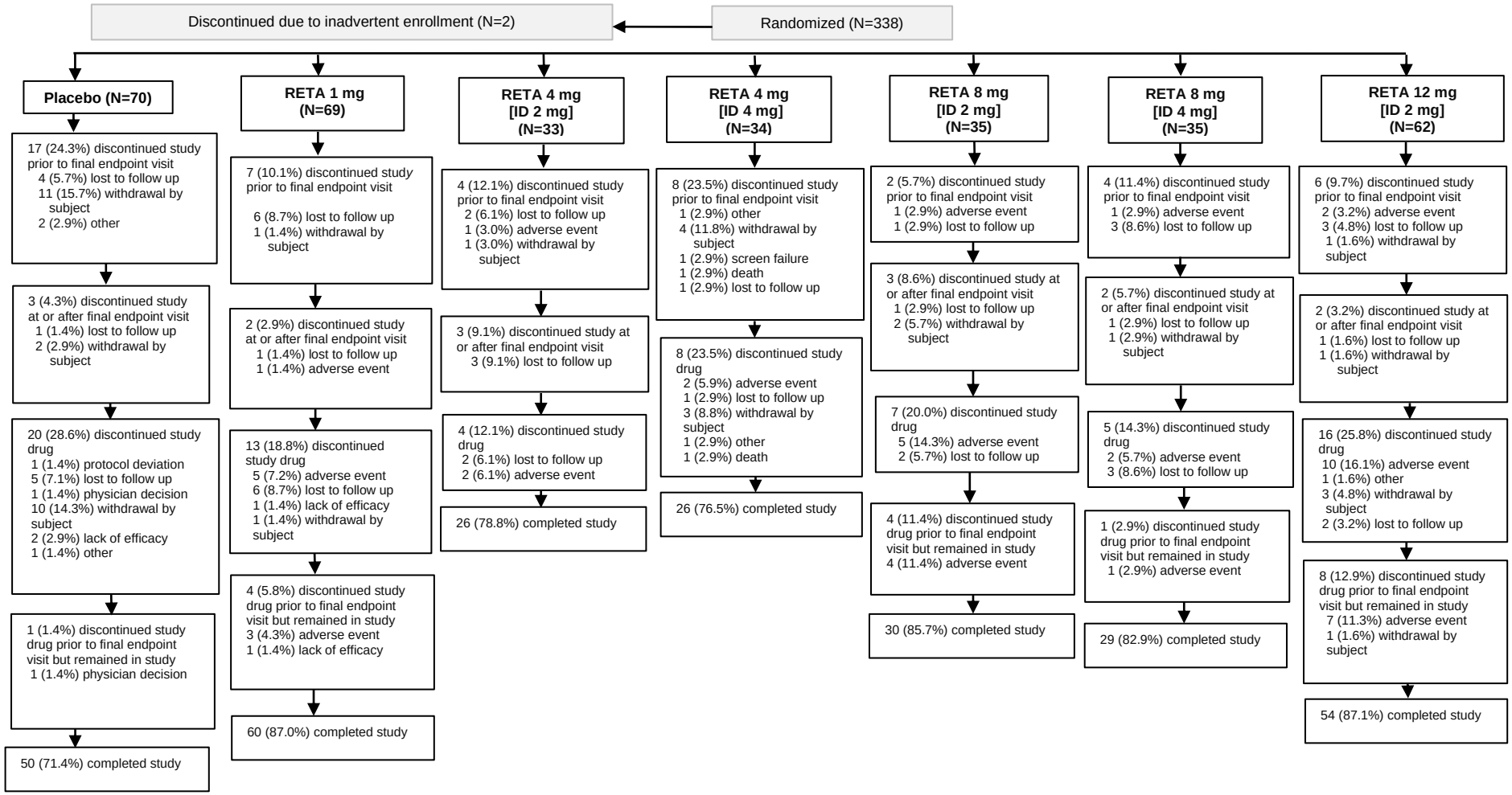


Figure S2. Consort diagram. Participant disposition from randomization. Mean duration of follow up in the study was 46.3 to 51.9 weeks across retatrutide groups and 46.2 weeks in the placebo group. Mean duration of follow up on treatment was 41.4 to 46.5 weeks across retatrutide groups and 41.9 weeks 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.

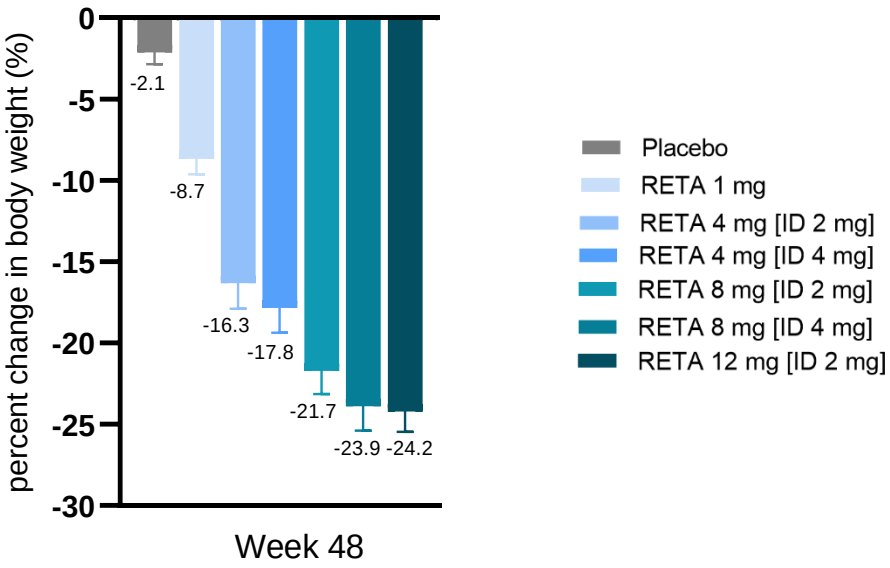


Figure S3. Percent change in weight at week 48. Least-squares means (standard error) are presented and shows the percent change in body weight from baseline at week 48 derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Abbreviations include ID, initial dose; RETA,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

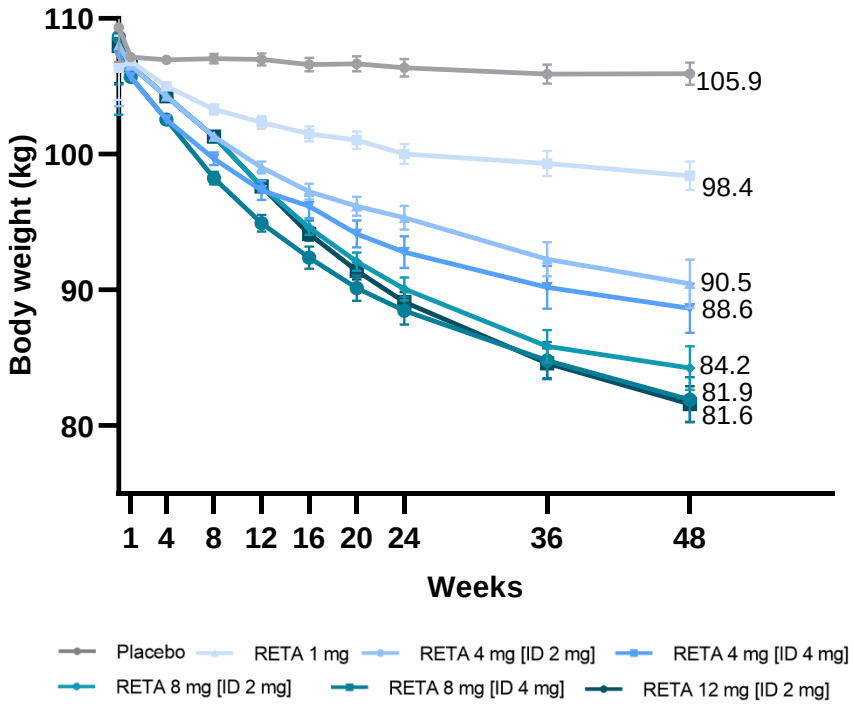
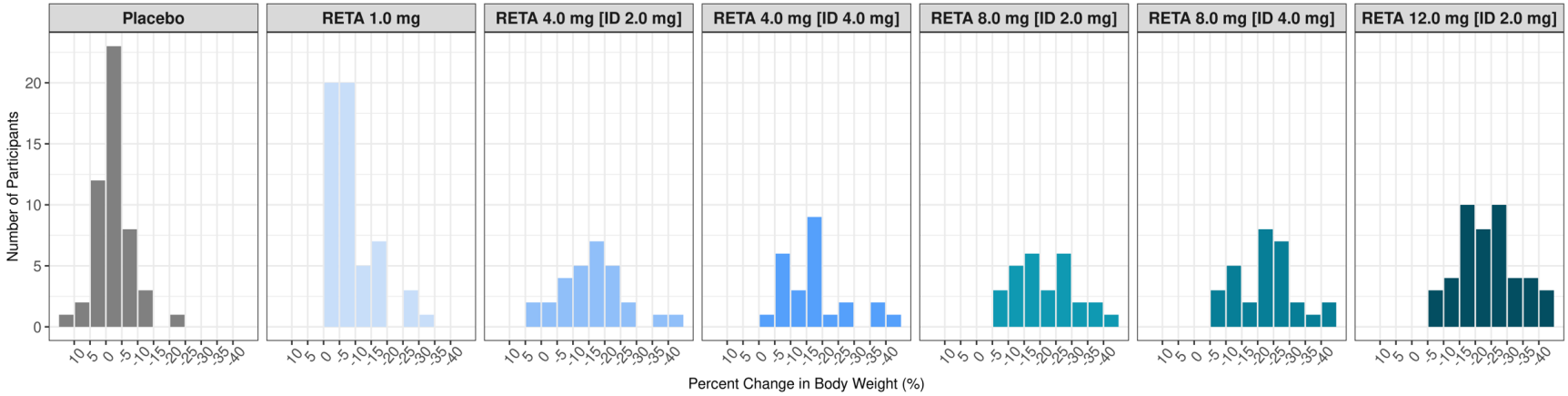


Figure S4. Body weight in kilograms over time. Least-squares mean body weight in kilograms from baseline to 48 weeks, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Mean baseline body weight: placebo, 109.2 kg; retatrutide 1mg, 106.4 kg; retatrutide 4 mg [ID 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)

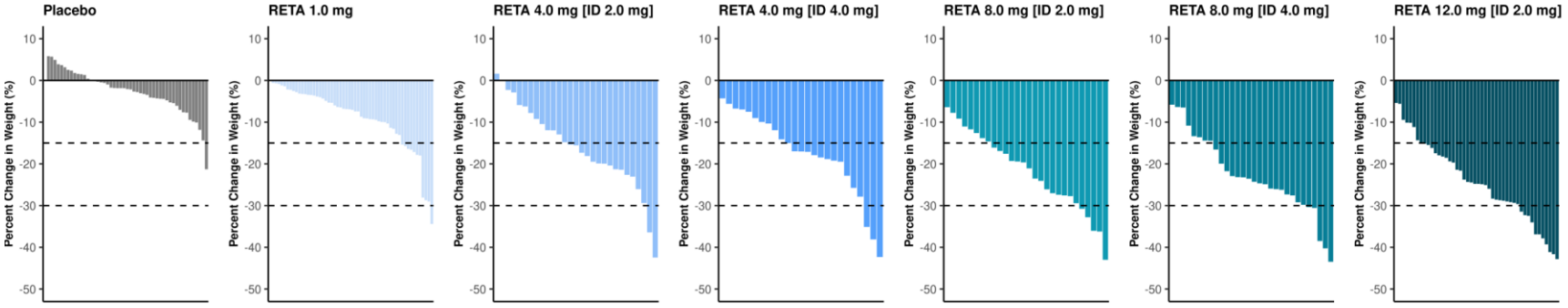


Figure S5. Histogram and waterfall plots for percent change in weight at 48 weeks. Histogram (Panel A) and waterfall plot (Panel B) for percent change in weight at week 48 for individuals in all treatment groups; data were censored after discontinuation of study treatment. At week 48, body weight reduction 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.

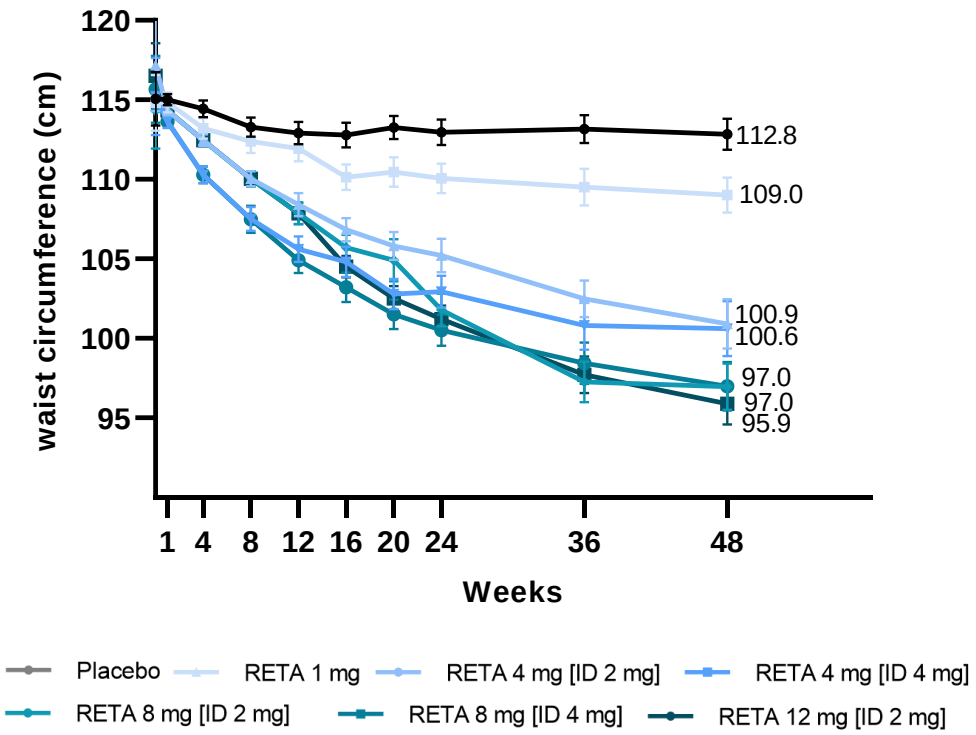


Figure S6. Waist circumference in centimeters over time. Least-squares mean waist circumference in centimeters from baseline to 48 weeks, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Mean baseline waist circumference: placebo, 115.1 cm; retatrutide 1mg, 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.

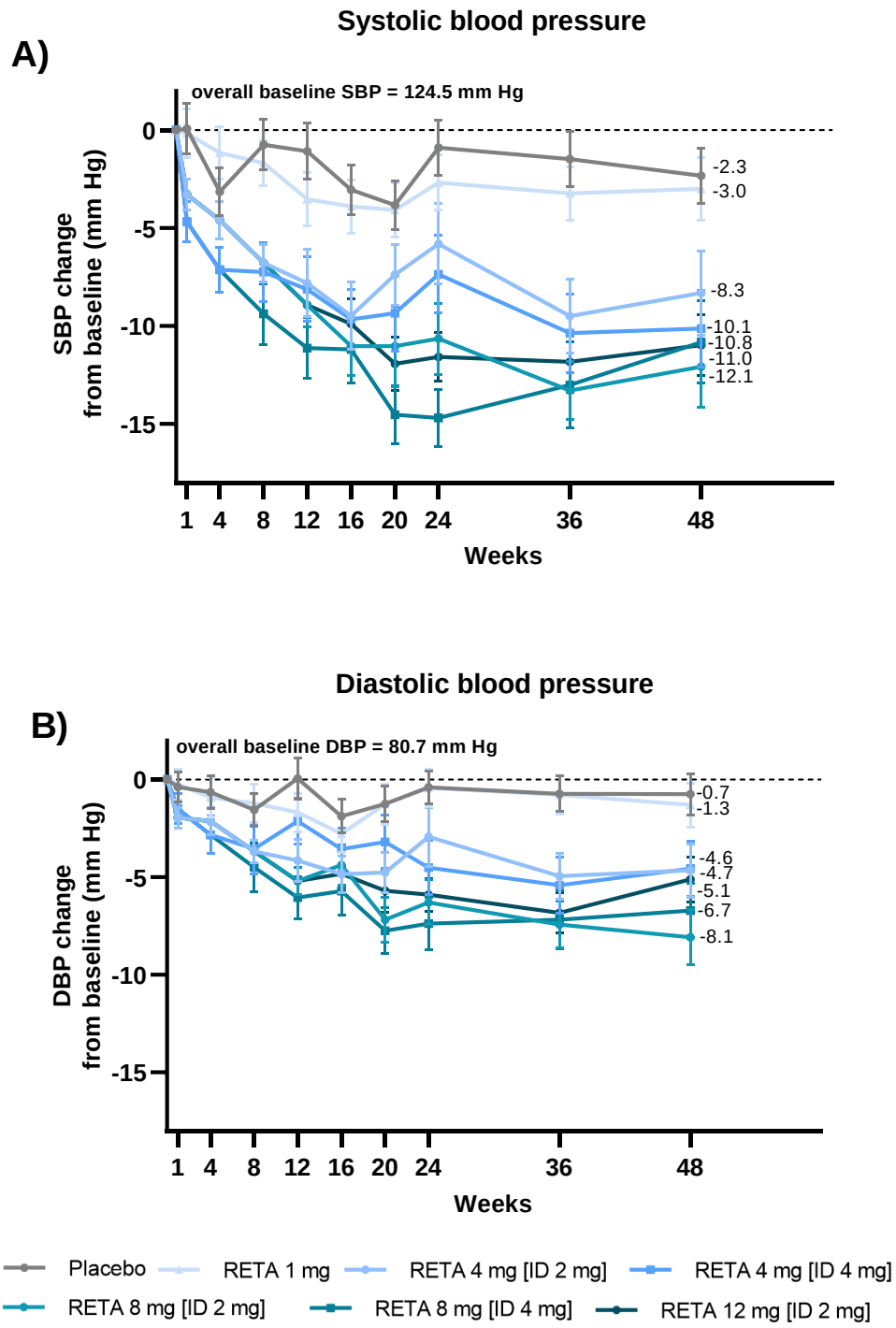


Figure S7. Change from baseline in systolic and diastolic blood pressure. Least-squares means (standard error) are presented and shows the change in blood pressure from baseline to week 48 derived from a mixed-model for repeated-measures (MMRM) analysis for the safety analysis set. Abbreviations include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

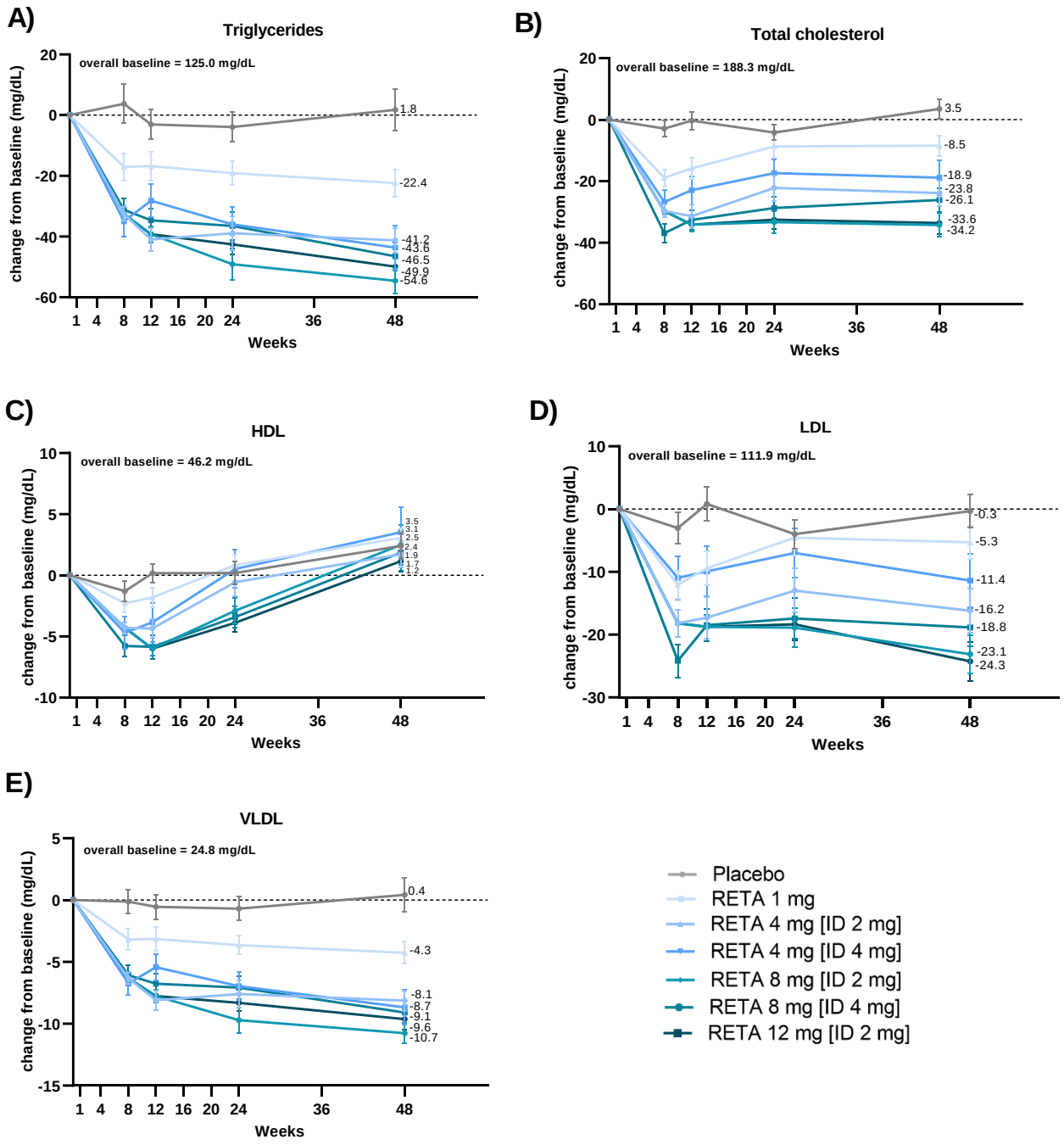


Figure S8. Change from baseline for lipid parameters. Least-squares means (standard error) are presented and shows the change in lipids from baseline to week 48, derived from a mixed-model for repeated-measures (MMRM) analysis for the efficacy estimand. Abbreviations include HDL, high density lipoproteins;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

A)


RETA 1.0 mg
RETA 4.0 mg [ID 2.0 mg]
RETA 4.0 mg [ID 4.0 mg]
RETA 8.0 mg [ID 2.0 mg]
RETA 8.0 mg [ID 4.0 mg]
RETA 12.0 mg [ID 2.0 mg]
Placebo
Proportion of Participants (%)
0
10
20
30
40
50
4
8
12
16
24
36
48
Week
Severity
Severe
Moderate
Mild

B)

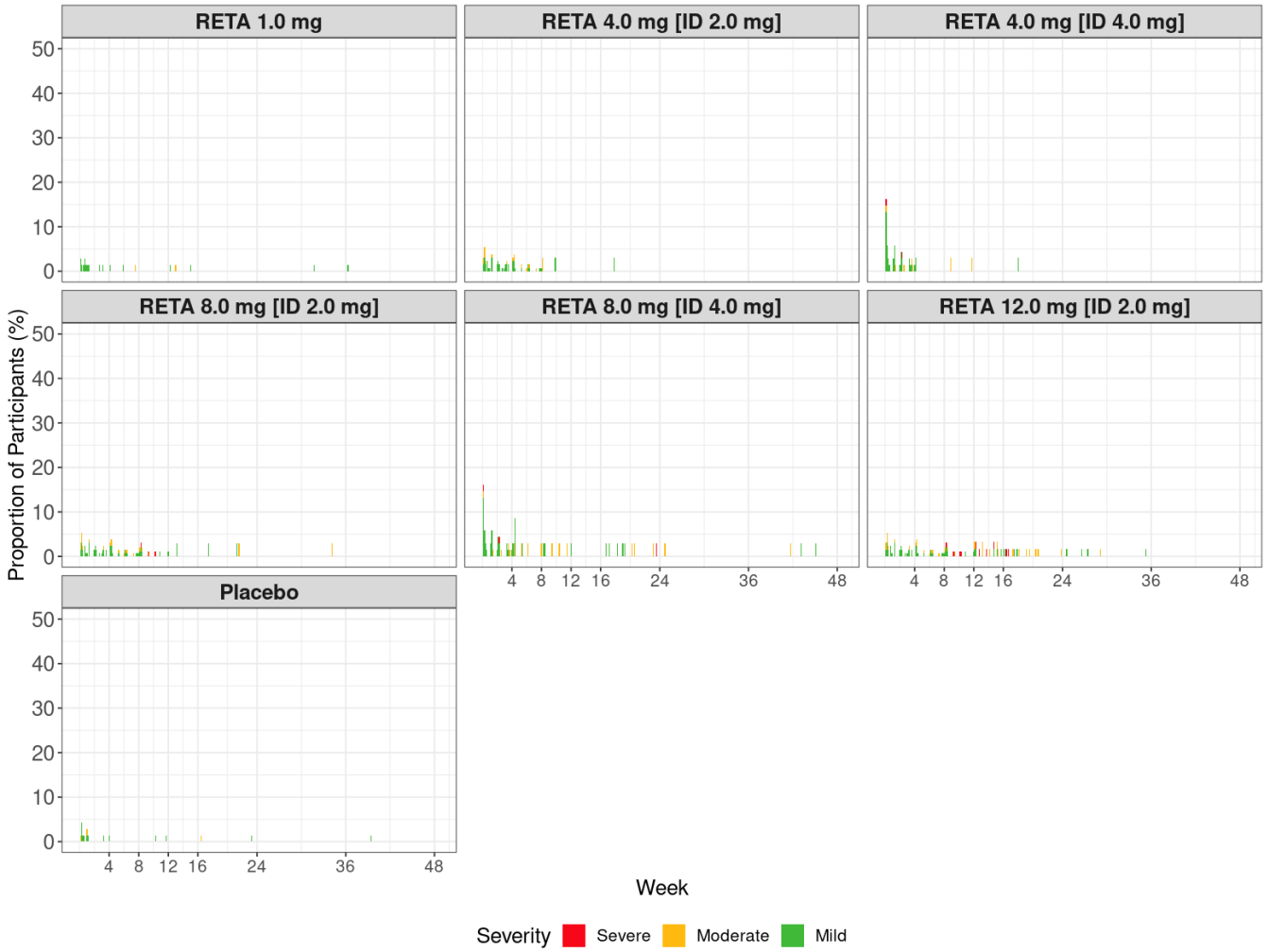


Figure S9. Incidence of nausea, diarrhea, and vomiting combined over time. Prevalence (Panel A) and incidence (Panel B) of nausea, diarrhea, and vomiting combined over time. Events were classified as mild (shown in green), moderate (shown in yellow), severe (shown in red). For incidence, all events for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

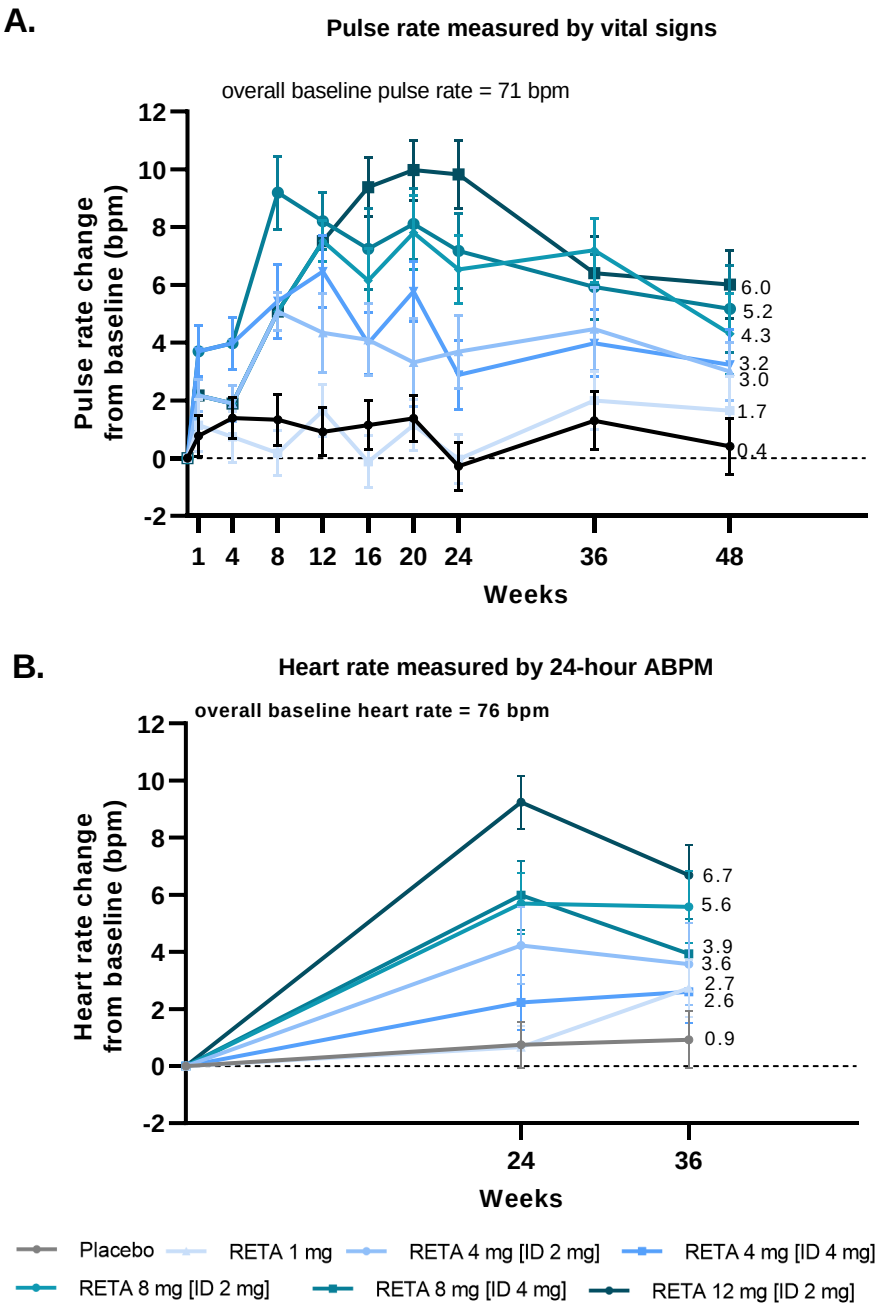


Figure S10. Change from baseline in heart rate. Change from baseline in pulse rate (vital signs) through 48 weeks of treatment (Panel A) and heart rate by ABPM through 36 weeks of treatment (Panel B). Least-squares means (standard error) are presented, derived from a mixed-model for repeated-measures (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

	Details
Disease under investigation	Obesity (BMI≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2)
Special considerations related to	
Sex and gender	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.
Age	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%).
Race or ethnic group	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.
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.
Other considerations	
Overall representativeness of this trial	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

Female participants (48.2%)	**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)
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^2	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

Male participants (51.8%)	**Placebo** (N=36)	**RETA 1 mg** (N=36)	**RETA 4 mg [ID 2mg]** (N=17)	**RETA 4 mg [ID 4mg]** (N=18)	**RETA 8 mg [ID 2 mg]** (N=18)	**RETA 8 mg [ID 4 mg]** (N=18)	**RETA 12 mg [ID 2 mg]** (N=32)	**Total** (N=175)
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^2	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)
Primary endpoint							
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)
Secondary endpoints							
*Percent of participants**							
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
Change from baseline							
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^2	-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)
Pre-specified exploratory endpoints							
*Percent of participants**							
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)
Primary endpoint (at 24 weeks)							
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)
Secondary endpoints (at 48 weeks)							
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)
*Percent of participants**							
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
Prespecified exploratory endpoints (at 48 weeks)							
*Percent of participants**							
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)
Pre-specified exploratory endpoints (at 48 weeks)							
*Percentage of participants, % **							
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
Change from baseline							
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)
Percent change from baseline							
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)
Pre-specified exploratory endpoints (at 36 weeks)							
Change from baseline with 24-hour ABPM							
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]
Percent change in weight at week 48, %							
BMI							
<35 kg/m^2 (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^2 (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)
Sex							
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)
Percent Change from baseline							
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)
Change from baseline							
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)
Change from baseline with 24-hour ABPM							
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

	Placebo (N=68)	RETA 1 mg (N=68)	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=61)
Physical Functioning							
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)
Role-Physical							
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)
Bodily Pain							
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)
General Health							
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)
Vitality							
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)
Social Functioning							
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)
Role Emotional							
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)
Mental Health							
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)
Physical Component							
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)
Treatment-emergent adverse events occurring in ≥5% of participants in any treatment group but < 5% of total participants (n, %)								
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)
Gastrooesophageal 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

Subject age and sex	Treatment Arm	Dose at time of SAE	Description (MedDRA preferred term/reported term)	Days from first dose of study drug	Investigator assessment of relatedness to study drug	Action taken/ Event Outcome	Additional Comments on Medical History and Concurrent Illnesses
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 Cholecystitis acute/ Acute cholecystitis	165 173	Yes Yes	Not Applicable/ Recovered/Resolved Drug Withdrawn/ Recovered/Resolved	Laparoscopic cholecystectomy was performed
66 y, male	RETA 8 mg [ID 4 mg]	8 mg	COVID-19/ SARS-CoV-2 Omicron variant infection Acute kidney injury/ Acute renal failure	289 295	No No	Drug Withdrawn/ Recovered/Resolved Drug Withdrawn/ Recovering/Resolving	Acute renal failure was considered as possibly due to COVID-19-associated nephropathy (COVAN) secondary to COVID infection
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)
Pulse, bpm								
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)
Pancreatic-amylase, U/L	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)
Lipase, U/L	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)
Aspartate aminotransferase, U/L								
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)
Alanine aminotransferase, U/L								
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)
Calcitonin, ng/L								
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)
Urine Albumin-to-Creatinine Ratio, g/kg								
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)
eGFR (mL/min/1.73m^2)								
Baseline	>60 (mL/min/1.73m^2)	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

	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)
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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