ORIGINAL ARTICLE

Retatrutide, a Triple Hormone Receptor Agonist, for Treatment of Obesity

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ABSTRACT

BACKGROUND

Retatrutide is a triple-receptor agonist of glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon receptors.

METHODS

In this phase 3, randomized, double-blind trial, we assigned adults with obesity without diabetes to receive a once-weekly subcutaneous injection of retatrutide (at a dose of 4 mg, 9 mg, or 12 mg) or placebo for 80 weeks. Primary outcomes (evaluated in the 9-mg and 12-mg groups each vs. placebo) were the percent change in body weight and the change in the WOMAC pain score (ranging from 1 to 10, with higher scores indicating worse pain) in the subgroup of 574 participants with knee osteoarthritis and the change in the apnea–hypopnea index in the 243 participants with obstructive sleep apnea. For weight-related end points, intercurrent events were handled by a treatment-regimen estimand (intention-to-treat [ITT]). For end points in participants with knee osteoarthritis or obstructive sleep apnea, a hybrid-treatment estimand was applied, with a hypothetical strategy for intercurrent events suggesting treatment failure; ITT results are also reported.

RESULTS

A total of 2339 participants underwent randomization. The mean percent change in body weight in the retatrutide groups was –17.6% (4-mg dose), –23.7% (9-mg dose), and –25.0% (12-mg dose) versus –3.9% in the placebo group (differences, –19.8 and –21.0 percentage points, respectively; P<0.001 for both comparisons). Among the participants with knee osteoarthritis, the corresponding changes in the pain score in the retatrutide groups for the hybrid estimand were –3.2, –3.5, and –3.6 versus –1.9 with placebo (differences, –1.6 and –1.8 points; both P<0.001); the corresponding changes for the ITT estimand were –3.4, –3.9, and –4.1 versus –2.5 with placebo (differences, –1.4 and –1.6 points; both P<0.001). Among the participants with obstructive sleep apnea, the corresponding changes in events per hour in the retatrutide groups for the hybrid-treatment estimand were –22.9, –34.3, and –31.7 versus –9.9 (differences, –24.4 and –21.9; both P<0.001); the corresponding changes for the ITT estimand were –22.8, –34.3, and –32.1 versus –9.6 (differences, –24.7 and –22.5; both P<0.001). The most common adverse events were gastrointestinal.

CONCLUSIONS

In adults with obesity, retatrutide resulted in significant weight reduction, reduced pain in participants with knee osteoarthritis, and reduced apnea–hypopnea events in participants with obstructive sleep apnea. (Funded by Eli Lilly; TRIUMPH-1 ClinicalTrials.gov number, NCT05929066.)

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Obesity, the most prevalent chronic disease of our time, affects the health of more than 1 billion people worldwide.[1] Nutrient-stimulated hormone receptor modulators[2] — including the mono-receptor agonists liraglutide,[3] semaglutide,[4,5] and orforglipron[6] and the dual-receptor agonist tirzepatide[7,8] — target currently known neuroendocrine pathophysiological mechanisms underlying obesity.[9,10] The action of these drugs results in substantial weight reduction and improved health outcomes. Recent studies of these medications have shown prevention[11,12] and mitigation of cardiometabolic complications of obesity, including type 2 diabetes,[13-16] cardiovascular disease,[17,18] and metabolic dysfunction-associated steatohepatitis,[19,20] as well as reductions in other obesity-related diseases, including knee osteoarthritis[21] and obstructive sleep apnea.[22] Because obesity is a heterogeneous disease, medications that act through multiple mechanisms may provide the possibility of greater weight reduction and improved health outcomes.

Retatrutide is a triple-receptor agonist targeting the G-protein–coupled receptors for glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1, and glucagon.[23] In a phase 2 trial involving participants with obesity, once-weekly subcutaneous retatrutide (at a dose of 12 mg) resulted in a mean weight reduction of 24.2% at 48 weeks[24] and improved multiple cardiometabolic measures, including waist circumference, systolic and diastolic blood pressure, glycated hemoglobin, and lipid levels.[24] In a substudy,[25] the same regimen of retatrutide resulted in a significant reduction in liver fat.[25] In our current phase 3 trial (TRIUMPH-1), we evaluated the efficacy and safety of retatrutide with respect to obesity as well as knee osteoarthritis and obstructive sleep apnea in participants with obesity without diabetes.

Methods

Trial Design and Data Monitoring

We conducted this multicenter, randomized, placebo-controlled, double-blind, trial at 131 sites in 11 countries (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial consisted of 5 weeks of screening, 80 weeks of treatment, and 4 weeks of follow-up. After 80 weeks of treatment, the first eligible participants (approximately 500 participants) entered a 24-week treatment extension.

Eli Lilly, the manufacturer of retatrutide, performed the trial monitoring, along with the collection and analysis of the data. All the authors had access to the data and analyses, interpreted the data, and reviewed the manuscript. The first draft of the manuscript was written by the first author. The first and last authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol, available at NEJM.org.

Participants

Adults (≥18 years of age) with obesity who did not have diabetes were eligible to participate in the trial. Obesity was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 30 or a BMI ranging from 27 to less than 30 in participants with at least one complication of obesity. Enrollment was enriched for participants with a BMI of at least 35 (target enrollment, 80%). Participants with moderate or severe knee osteoarthritis (pain plus radiographic evidence) or obstructive sleep apnea (a score on the apnea–hypopnea index [AHI] of ≥15 with or without positive airway pressure therapy) were eligible for one of two basket trials as subpopulations of the participants with obesity. Full eligibility criteria are provided in the Supplementary Appendix.

Procedures

The participants were randomly assigned in a 1:1:1:1 ratio to receive 80 weeks of once-weekly subcutaneous retatrutide (at a dose of 4 mg, 9 mg, or 12 mg) or placebo, with randomization stratified according to prediabetes status, sex, and eligibility for either basket trial. All the participants received counseling with respect to physical activity and healthy diet without purposeful caloric restriction. A fixed dose escalation protocol was used to reach the assigned dose. Up to two permanent dose reductions were permitted to ameliorate gastrointestinal adverse events during the first 20 weeks and at any time to address inadequate food or fluid intake, a BMI 22 or less, or excessive weight loss as perceived by either the participant or the investigator. Details regarding the trial procedures have been published previously[26] and are described in the protocol. In the extension phase, the participants received retatrutide at a maximum-tolerated dose of 9 mg or 12 mg.

END POINTS AND ASSESSMENTS

The end points were assessed from baseline to 80 weeks in the main trial and until 104 weeks in the extension study. The primary end points were the percent change in body weight (in the main trial), the change in the score on the pain subscale (which ranges from 0 to 10, with higher scores indicating worse pain) on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (in the knee osteoarthritis basket), and the change in the apnea-hypopnea index (AHI), which measures the average number of apneas and hypopneas per hour of sleep (in the obstructive sleep apnea basket) at week 80 for retatrutide at a dose of 9 mg, 12 mg, or both, as compared with placebo. The primary end point for the extension study was the percent change in body weight at week 104 comparing retatrutide 12 mg (80 weeks) followed by retatrutide up to 12 mg (24 weeks) versus placebo (80 weeks) followed by retatrutide up to 12 mg (24 weeks).

Key secondary end points of the main trial, as controlled for type I error, were the percent change in body weight with retatrutide at a once-weekly dose of 4 mg; the achievement of the weight-reduction thresholds of 5% or more to 35% or more (in 5% increments) with retatrutide at doses of 4 mg, 9 mg, or 12 mg; cardiometabolic measures (waist circumference, systolic blood pressure, triglycerides, non–high-density lipoprotein [HDL] cholesterol, fasting insulin, high-sensitivity C-reactive protein) with retatrutide at doses of 4 mg, 9 mg and 12 mg; and the change in participant-reported outcomes regarding the physical-function domain score on the 36-Item Short Form Health Survey, version 2 (SF-36v2). Other evaluations included the physical-function and psychosocial composite scores on the Impact of Weight on Quality of Life Lite–Clinical Trials version [IWQOL-Lite-CT] with retatrutide at doses of 9 mg and 12 mg. All end points were compared between retatrutide and placebo.

Key secondary end points for the subgroup of participants with a BMI of 35 or higher, as controlled for type I error, included the percent change in body weight and the achievement of weight-reduction thresholds of 5% or more or 35% or more (in 5% increments) with retatrutide at a dose of 4 mg, 9 mg, or 12 mg, as compared with placebo. Additional end points in the main trial included anthropometric targets (BMI of <25 or <30 and a waist-to-height ratio of <0.5), shifts in BMI category, change in glycemic status (normoglycemia, prediabetes, or type 2 diabetes), and levels of glycated hemoglobin and fasting glucose. Safety assessments through week 80 and the 4-week follow-up included adverse events, serious adverse events, and laboratory assessments.

STATISTICAL ANALYSIS

We determined that a sample of approximately 2300 participants would provide the trial with more than 99% power to show the superiority of retatrutide (at doses of 9 mg and 12 mg) to placebo for the percent change in body weight, the primary end point in the main trial. The overall familywise type I error was controlled at a two-sided alpha level of 0.05 within each of the two families: the main protocol paired with the knee osteoarthritis basket, and the main protocol paired with the obstructive sleep apnea basket.

The knee osteoarthritis and obstructive sleep apnea baskets were subpopulations of the main population with obesity; because the two baskets addressed distinct, nonoverlapping populations, no additional multiplicity adjustment was applied across the two families. Within each family, the two-sided alpha level was initially assigned as 0.025 to the main protocol and 0.025 to the basket; within the main protocol and each basket, multiplicity across the primary and key secondary end points was controlled by means of a graphical testing procedure. Details regarding the statistical analysis are provided in the Supplementary Appendix.

Efficacy analyses were performed in the population of all the participants who had undergone randomization. Safety analyses were performed in the safety population, which included all the participants who had received at least one dose of retatrutide or placebo.

Two estimands were predefined for weight-related end points, the treatment-regimen estimand, which estimates the mean treatment effect regardless of treatment discontinuation or initiation of prohibited weight-management treatments (on the basis of the treatment policy strategy, consistent with intention-to-treat analysis), and a hypothetical efficacy estimand, which estimates a treatment effect on the assumption that all the participants had received retatrutide or placebo for 80 weeks as intended by the protocol and did not have intercurrent events, such as initiation of

prohibited weight-management treatments (consistent with the hypothetical strategy).

Two estimands were prespecified for end points related to knee osteoarthritis and obstructive sleep apnea: we used a hybrid-treatment estimand with a hypothetical strategy for imputation of values related to intercurrent events associated with treatment failure and treatment policy strategy elsewhere, and we used a predefined hypothetical efficacy estimand to estimate a treatment effect on the assumption that all the participants had received retatrutide or placebo for 80 weeks as intended and did not have intercurrent events. We also report an intention-to-treat estimand that applies a treatment-policy strategy to all related intercurrent events. Additional methodologic details are described in the Supplementary Appendix.

RESULTS

PARTICIPANTS

From July 2023 through April 2026, a total of 2339 participants underwent randomization. Overall, 84.7% of the participants completed the trial (87.7 to 89.7% in the retatrutide groups and 72.4% in the placebo group). A total of 77.1% of the participants adhered to their trial-group assignment, including 75.3 to 87.0% of those in the retatrutide groups and 63.9% of those in the placebo group (Fig. S2).

In the retatrutide groups, treatment discontinuation because of adverse events occurred in 4.1% of those receiving the 4-mg dose, in 6.5% of those receiving the 9-mg dose, and in 11.1% of those receiving the 12-mg dose, as compared with 4.6% of those receiving placebo; corresponding treatment discontinuations owing to perceived excessive or sufficient weight loss (as determined by the participant or the site investigator) were reported in 0.3%, 1.0%, and 5.3% of the participants in the retatrutide groups, as compared with no participants in the placebo group. Corresponding permanent dose reductions occurred in 7.5%, 18.4%, and 22.5% of the participants in the retatrutide groups, as compared with 0.5% of those in the placebo group; the most common reasons were perceived excessive weight loss, having a BMI of 22 or less, and gastrointestinal events (Table S1).

Overall, the percentage of participants in the retatrutide groups who completed dose escalation and reached their assigned target dose was 97.8% with the 4-mg dose, 94.2% with the 9-mg dose, and 89.9% with the 12-mg dose (Fig. S3 and Table S2). At week 80, the corresponding percentage of participants who continued to receive their assigned dose was 74.5%, 58.7%, and 54.0%.

In the main trial, the demographic and clinical characteristics of the participants were generally similar in the two groups at baseline (Table 1 and Table S3). The mean BMI was 40, and 77.4% of the participants had a BMI of 35 or higher. The knee osteoarthritis basket included 574 participants (24.5%), and the obstructive sleep apnea basket included 243 participants (10.4%) (Table S4). The extension phase included 532 participants (Table S4). The representativeness of the trial population is shown in Table S5.

BODY-WEIGHT OUTCOMES

In the retatrutide groups, the mean percent change in body weight from baseline to week 80 as calculated with the treatment-regimen estimand was –17.6% with the 4-mg dose, –23.7% with the 9-mg dose, and –25.0% with the 12-mg dose, as compared with –3.9% with placebo (Fig. 1A, Table 2, and Figs. S4 and S5). All retatrutide doses were superior to placebo with respect to body weight, with between-group differences (as measured in percentage points) of –13.7 with the 4-mg dose, –19.8 with the 9-mg dose, and –21.0 with the 12-mg dose ($P<0.001$ for all comparisons). The corresponding mean percent changes in body weight from baseline to week 80 for the efficacy-estimand calculation were –19.0%, –25.9%, and –28.3%, as compared with 2.2% with placebo (Fig. 1A and Table S6). Weight reduction appeared to be greater among women than among men at 80 weeks (treatment-regimen estimand, –26.3% and –22.3%, respectively, at the 12-mg dose) (Fig. S6).

Weight reduction of 35% or more was seen in 5.7 to 21.1% of the participants in the retatrutide groups and in 0.2% of those in the placebo group with the treatment-regimen estimand (Table 2 and Fig. S7). Results that were calculated with the efficacy estimand are shown in Figure S7 and Table S6.

As calculated with the treatment-regimen estimand in the retatrutide groups, the BMI target of less than 30 was met in 40.1 to 57.1% of the participants, and the BMI target of less than 25 was met in 12.0 to 26.3% of the participants, as compared with 9.2% and 1.6% of the participants, respectively, in the placebo group; a target waist-

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

Characteristic	Retatrutide			Placebo N=587
	4 mg (N=584)	9 mg (N=584)	12 mg (N=584)	
Age — yr	48.3±12.0	48.8±12.4	48.4±12.2	48.7±12.1
Female sex — no. (%)†	382 (65.4)	383 (65.6)	383 (65.6)	385 (65.6)
Body weight — kg	113.3±26.2	112.2±24.1	113.0±23.9	112.3±24.7
Body-mass index‡				
Mean	40.3±7.3	40.0±7.2	40.0±6.8	39.8±6.9
≥35 — no. (%)	462 (79.1)	451 (77.2)	449 (76.9)	448 (76.3)
Waist circumference — cm	118.4±16.2	118.0±15.7	118.8±15.5	118.2±16.0
Systolic blood pressure — mm Hg	127.3±13.4	126.7±13.5	126.3±12.7	127.0±12.5
Lipid measures — mg/dl				
Triglycerides	133.8±67.2	131.0±57.1	138.1±103.7	134.6±63.3
Non-HDL cholesterol	142.9±35.1	144.2±36.5	144.3±36.4	145.5±37.3
Prediabetes — no. (%)§	199 (34.1)	225 (38.5)	207 (35.4)	214 (36.5)
Fasting insulin — mIU/liter	22.2±17.0	21.8±17.6	22.7±16.1	22.1±16.2
High-sensitivity C-reactive protein — mg/liter	6.6±8.0	6.6±10.4	6.5±8.1	6.1±6.6
SF-36v2 acute form physical functioning domain score¶	46.1±9.3	46.6±9.3	45.7±10.0	46.0±9.4
IWQOL-Lite-CT‖				
Physical function composite score	52.3±25.9	52.2±25.1	51.0±26.3	49.9±25.3
Psychosocial composite score	54.6±24.4	54.1±24.3	52.8±24.3	53.2±23.9

* Plus–minus values are means ±SD. HDL denotes high-density lipoprotein.
† Sex was reported by the participants.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The diagnosis of prediabetes required at least two values within the following ranges: fasting glucose, 100 to 125 mg per deciliter; 2-hour glucose, 140 to 199 mg per deciliter; or glycated hemoglobin, 5.7 to 6.4%, according to the 2023 American Diabetes Association Standards of Medical Care in Diabetes.
¶ Scores on the 36-Item Short Form Health Survey, version 2 (SF-36v2), for the physical functioning domain are rated on a 3-point Likert scale ranging from "limited a lot" to "not limited at all." Each domain score was transformed to a scale of 0 to 100, with higher scores indicating better levels of function.
‖ Scores on the Impact of Weight on Quality of Life–Lite Clinical Trials (IWQOL-Lite-CT) are rated on either a 5-point frequency scale ("never" to "always") or a 5-point truth scale ("not at all true" to "completely true"). Total scores range from 0 to 100, with higher scores indicating better functioning.

to-height ratio of less than 0.5 was met in 10.1 to 20.4% of the participants in the retatrutide groups and in 0.9% of those in the placebo group (Fig. 1B, Fig. S8, Table S7). Results as calculated with the efficacy estimand are shown in Figures S8 and S9 and Table S6.

Results for participants with a BMI of 35 or higher are shown in Figures S10 and S11 and Table S7 for the treatment-regimen estimand; results for the efficacy estimand are shown in Figures S10 and S11 and Table S6. Waterfall plots of the percent change in weight are shown in Figure S12. The use of prohibited medications is shown in Table S8.

In the extension phase, the mean percent change in body weight from baseline to week 104 among the participants who switched to a maximum tolerated dose of 9 mg or 12 mg from placebo was –18.9%, –25.7%, –28.7%, and –29.9%, respectively (for the treatment-regimen estimand) and –19.2%, –27.9%, –29.5%, and –30.3%, respectively (for the efficacy estimand) (Fig. S13).

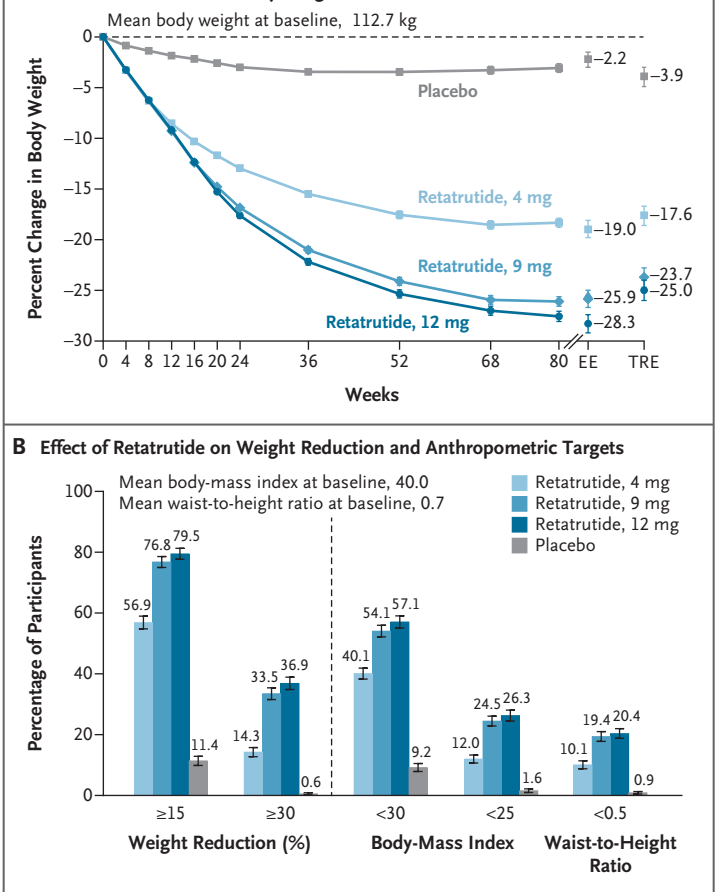


Figure 1. Effect of Retatrutide on Body Weight.

Panel A shows the percent change in body weight from baseline to week 80 (controlled for type I error). The curves on the left show changes from week 0 to week 80 on the basis of observed means during treatment according to the efficacy estimand data-point set; the I bars indicate standard errors. The data at the right of the curves show a model-based estimate with 95% confidence intervals derived from a mixed model for repeated measures for the efficacy estimand (EE) and a model-based estimate with 95% confidence intervals derived from an analysis of covariance for the treatment-regimen estimand (TRE; P<0.001 for all comparisons with placebo). Panel B shows the percentage of participants with reductions in body weight of 15% or more and 30% or more (controlled for type I error), along with the percentage of participants who reached the body-mass index targets of less than 30 or less than 25 and the waist-to-height ratio target of less than 0.5 (not controlled for type I error) at week 80 for the treatment-regimen estimand. Data are model-based estimates, and standard errors are derived from a logistic-regression model with imputed data. P<0.001 for all comparisons with placebo for weight-reduction thresholds. Data regarding the percentage of participants with body-weight reductions of at least 5%, 10%, 20%, 25%, and 35% are provided in Figure S7, and data for the efficacy estimand are provided in Figure S8.

HEALTH OUTCOMES

For the hybrid-treatment estimand, the mean change in the WOMAC pain subscale score (in points) at week 80 for the knee osteoarthritis basket was –3.5 and –3.6 with retatrutide 9 mg and 12 mg, respectively, and –1.9 with placebo, for a difference of –1.6 and –1.8 points, respectively (P<0.001 for both comparisons) (Fig. S14). In the obstructive sleep apnea basket, the mean change in the AHI events per hour at week 80 was –34.3 and –31.7 with retatrutide 9 mg and 12 mg, respectively, and –9.9 with placebo, for a difference of –24.4 and –21.9, respectively (P<0.001 for both comparisons) (Fig. S14).

For the intention-to-treat estimand, the mean change in the WOMAC pain subscale score at week 80 in the knee osteoarthritis basket was –3.9 and –4.1 with retatrutide 9 mg and 12 mg, respectively, as compared with –2.5 with placebo, for a difference of –1.4 and –1.6 points (P<0.001 for both comparisons). In the obstructive sleep apnea basket, the mean change in the AHI events per hour at week 80 was –34.3 and –32.1 with retatrutide 9 mg and 12 mg, respectively, as compared with –9.6 with placebo, for a difference of –24.7 and –22.5 points (P<0.001 for both comparisons).

In the overall population at week 80, retatrutide treatment improved cardiometabolic measures, including waist circumference, systolic blood pressure, fasting insulin, high-sensitivity C-reactive protein, triglycerides, and non-HDL cholesterol (Table 2, Fig. 2A, Figs. S15 to S19, and Table S7). Among the 36.1% of participants who had prediabetes at baseline, a reversion to normoglycemia occurred in 89.4 to 93.2% of the participants in the retatrutide groups and in 54.2% of those in the placebo group (Fig. 2B). The glycemic status at 80 weeks among the participants with normoglycemia at baseline is shown in Figure S20.

Changes in the IWQOL-Lite-CT physical function and psychosocial composite scores were higher in the retatrutide groups than in the placebo group, as were scores on the SF-36v2 (P<0.001 for all comparisons) (Table 2).

SAFETY

During the treatment period, at least one adverse event was reported in 87.0 to 89.2% of the participants in the retatrutide groups and in 80.7% of those in the placebo group (Table 3). The most frequently reported adverse events with retatrutide were gastrointestinal (nausea, diarrhea, and constipation), which were mostly transient and mild or moderate in severity; these events occurred most commonly during dose escalation (Fig. S21).

Serious adverse events were reported in 7.7 to 10.5% of the participants in the retatrutide

groups and in 5.5% of those in the placebo groups (Table 3). In the retatrutide groups, four deaths occurred: three (0.5%) in the 9-mg group and one (0.2%) in the 12-mg group; two deaths (0.3%) occurred in the placebo group (Table 3 and Table S9). The most prevalent adverse events of special interest that were more commonly reported with retatrutide were dysesthesia, injection-site reactions, and hypotension. Reported hypotension was more common in participants receiving antihypertensive drugs (Tables S10 and S11). These events were mostly mild or moderate in severity and were deemed by the investigator to be nonserious events. Ten participants had an adjudication-confirmed major adverse cardiovascular event. Among the participants receiving retatrutide, these events were reported in 1 participant (0.2%) in the 4-mg group, 5 participants (0.9%) in the 9-mg group, and 3 participants (0.5%) in the 12-mg group, as compared with 1 participant (0.2%) in the placebo group (Table 3). The mean pulse rate increased with retatrutide, peaking at 20 weeks in the 9-mg and 12-mg groups and decreased thereafter (Table S12 and Fig. S22). Serious or severe ketoacidosis events and malnutrition serious adverse events were rarely reported and were balanced between the retatrutide and placebo groups. No cases of medullary thyroid cancer or drug-induced liver injury were reported. Urinary tract infections were reported in 7.5 to 8.7% of the participants in the retatrutide groups and in 5.3% of those in the placebo group; of these events, 92% occurred in women, were generally mild or moderate in severity, and did not lead to treatment discontinuation.

DISCUSSION

In this trial involving adults with obesity, the use of triple-receptor agonist retatrutide resulted in a mean weight reduction of up to 25.0% (according to the treatment-regimen estimand) and 28.3% (according to the efficacy estimand) at 80 weeks, with more than one third of the participants losing at least 30% of their body weight. In the extension phase of the trial, retatrutide treatment was associated with a mean weight reduction of up to 29.9% (treatment-regimen estimand) and 30.3% (efficacy estimand) at 104 weeks. Participants in the retatrutide group had a significant decrease in knee pain (>60% according to the hybrid-treatment estimand) in those with knee osteoarthritis and in AHI events per hour (>50% with the hybrid-treatment estimand) in those with obstructive sleep apnea, and improved quality of life and cardiometabolic measures in the overall trial population.

It has been hypothesized that treating obesity with therapies that target multiple nutrient-stimulated hormone pathways may facilitate greater weight reduction and broader health improvement.[27] Therapies that target these pathways have transformed the treatment of obesity, with average weight reductions of 12 to 22%.[4-7] Weight reductions of 30 to 35% or greater have previously been attainable with bariatric surgery[28] or combination pharmacotherapy.[29,30] In this trial, weight loss of at least 35% was reported in nearly a quarter of the participants (21% with the treatment-regimen estimand and 27% with the efficacy estimand). Given the degree of weight reduction in response to retatrutide, these data support the possibility of treating to a defined target as is done for other diseases (e.g., a glycated hemoglobin target of <6.5% for type 2 diabetes), rather than to a relative percent change in weight.

At 80 weeks, among all the participants who received the 12-mg dose of retatrutide, a BMI of less than 30 was reported in approximately 60% and a BMI of less than 25 was reported in more than 25% (according to both the treatment-regimen estimand and the efficacy estimand) (Fig. S8) Among the participants with less severe obesity (class 1; BMI, 30 to <35) at baseline, a BMI of less than 30 was observed in more than 90% of those receiving either the 9-mg or 12-mg dose of retatrutide, as compared with approximately 20% in the placebo group; less than 10% were reported to continue to a BMI in the class 1 obesity range with retatrutide, as compared with 60% with placebo. No participants progressed to class 2 obesity (BMI, 35 to <40) with retatrutide, as compared with approximately 20% with placebo. A BMI of less than 25 was observed in more than half the participants in the retatrutide groups, as compared with 6.3% in the placebo group. Even though anthropometric targets such as BMI and waist-to-height ratio do not fully define obesity, they provide a first step toward a treat-to-target approach. Additional studies are needed to define treatment targets that best reflect the lowest overall risk of adverse health outcomes.

Treatment with retatrutide resulted in improved measures of health. Patients with obesity have a 60% lifetime risk of knee osteoarthritis, which results in pain, disability, and reduced qual-

Table 2. Primary and Key Secondary Efficacy End Points.*

End Point	Retatrutide			Placebo (N=587)
	4 mg (N=584)	9 mg (N=584)	12 mg (N=584)	
Primary end point				
Main trial				
Percent change in body weight at 80 wk	−17.6 (−18.6 to −16.7)†	−23.7 (−24.7 to −22.8)	−25.0 (−26.0 to −24.0)	−3.9 (−4.9 −3.0)
Difference vs. placebo (95% CI) — percentage points	−13.7 (−15.0 to −12.4)†	−19.8 (−21.2 to −18.4)	−21.0 (−22.5 to −19.6)	—
Extension phase				
No. of participants	183	131	109	109
Percent change in body weight at 104 wk	−25.7 (−27.3 to −24.1)‡	−28.7 (−30.6 to −26.8)‡	−29.9 (−31.9 to −27.8)	−18.9 (−20.4 to −17.4)
Difference vs. placebo (95% CI) — percentage points	−6.8 (−9.0 to −4.6)‡	−9.8 (−12.2 to −7.4)‡	−11.0 (−13.5 to −8.4)	—
Knee osteoarthritis basket§				
No. of participants	143	143	144	144
Change in WOMAC pain subscale score at 80 wk — points¶	−3.2 (−3.6 to −2.8)†	−3.5 (−3.9 to −3.1)	−3.6 (−4.0 to −3.3)	−1.9 (−2.3 to −1.4)
Difference vs. placebo — points (95% CI)	−1.3 (−1.9 to −0.8)†	−1.6 (−2.2 −1.0)	−1.8 (−2.3 to −1.2)	—
Obstructive sleep apnea basket§				
No. of participants	60	61	60	62
Change in apnea–hypopnea index at 80 wk — events/hr‖	−22.9 (−29.7 to −16.0)†	−34.3 (−40.8 to −27.7)	−31.7 (−38.2 to −25.2)	−9.9 (−17.5 to −2.2)
Difference vs. placebo (95% CI) — events/hr	−13.0 (−23.0 to −3.0)†	−24.4 (−34.1 to −14.7)	−21.9 (−32.2 to −11.5)	—
Key secondary end points in the overall population				
Percentage of participants reaching weight reduction threshold **				
≥5%	88.3±1.5 [478/530]	92.9±1.2 [503/528]	94.0±1.1 [495/519]	39.7±2.5 [155/429]
≥10%	74.8±1.9 [405/530]	87.3±1.5 [475/528]	86.8±1.5 [461/519]	21.7±2.0 [76/429]
≥15%	56.9±2.1 [310/530]	76.8±1.8 [422/528]	79.5±1.8 [428/519]	11.4±1.5 [39/429]
≥20%	39.6±2.1 [214/530]	64.3±2.0 [359/528]	66.8±2.0 [363/519]	6.4±1.1 [23/429]
≥25%	25.0±1.8 [131/530]	46.7±2.0 [263/528]	53.0±2.1 [291/519]	2.6±0.7 [10/429]
≥30%	14.3±1.5 [71/530]	33.5±1.9 [189/528]	36.9±2.0 [204/519]	0.6±0.3 [1/429]
≥35%	5.7±1.1 [23/530]	18.3±1.6 [102/528]	21.1±1.7 [117/519]	0.2±0.2 [0/429]

Change in waist circumference (95% CI) — cm	−15.7 (−6.7 to −14.8)	−20.1 (−21.1 to −19.2)	−21.6 (−22.6 to −20.5)	−4.6 (−5.5 to −3.6)
Change in systolic blood pressure (95% CI) — mm Hg	−7.6 (−8.6 to −6.5)	−9.8 (−10.8 to −8.7)	−10.4 (−11.6 to −9.2)	−1.9 (−3.6 to −0.3)
Percent change in triglycerides (95% CI)	−30.9 (−33.1 −28.6)	−36.4 (−38.6 −34.2)	−38.0 (−40.0 to −35.9)	−3.0 (−6.0 to 0.1)
Percent change in non-HDL cholesterol (95% CI)	−16.7 (−18.3 to −15.0)	−21.9 (−23.7 to −20.2)	−20.6 (−22.5 to −18.7)	−4.6 (−6.9 −2.2)
Percent change in fasting insulin (95% CI)	−43.10 (−45.96 to −40.10)	−51.91 (−54.44 to −49.25)	−54.50 (−57.23 to −51.59)	−11.03 (−16.41 to −5.30)
Percent change in high-sensitivity C-reactive protein (95% CI)	−57.7 (−60.9 to −54.2)	−61.6 (−64.7 to −58.2)	−62.6 (−65.8 to −59.0)	−24.9 (−30.7 to −18.7)
Change in physical functioning domain score on SF-36v2 (95% CI)	5.8 (5.2 to 6.4)	6.5 (5.9 to 7.1)	6.2 (5.6 to 6.8)	2.6 (1.8 to 3.4)
Change in composite physical function score on IWQOL-Lite-CT (95% CI)	24.0 (22.3 to 25.7)	27.2 (25.5 to 29.0)	27.6 (26.0 to 29.3)	13.1 (10.8 to 15.5)
Change in composite psychosocial score on IWQOL-Lite-CT (95% CI)	24.1 (22.4 to 25.7)	27.8 (26.2 to 29.4)	27.2 (25.5 to 28.8)	12.1 (10.0 to 14.3)

* Data are model-based estimates and 95% confidence intervals or standard errors, derived from an analysis of covariance for the treatment-regimen estimand. The primary and key secondary end points were tested under a multiplicity-control procedure. The confidence intervals were not adjusted for multiplicity and should not be used for hypothesis testing. All the end points were evaluated at week 80 unless otherwise specified. Treatment differences as compared with placebo were significant for all primary and key secondary end points with $P<0.001$, except for the change in events per hour on the apnea–hypopnea index for the 4-mg dose of retatrutide, with $P=0.01$.

† This end point for the 4-mg dose of retatrutide is a key secondary end point (controlled for type I error), not a primary end point.

‡ This end point for the 4-mg and 9-mg doses of retatrutide was a prespecified end point (not controlled for type I error), not a primary end point.

§ The health-related end points related to knee osteoarthritis and obstructive sleep apnea were calculated with a hybrid-treatment estimand with a hypothetical strategy used for imputation of values related to intercurrent events associated with treatment failure and treatment policy strategy elsewhere.

¶ Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) range from 0 to 10, with higher scores indicating more severe symptoms.

‖ The apnea–hypopnea index measures the average number of apneas and hypopneas per hour of sleep.

** Data are model-based estimates and standard errors derived from the logistic regression model with imputed data. The number of participants divided by the total denominator is derived from the treatment-regimen estimand data-points set.

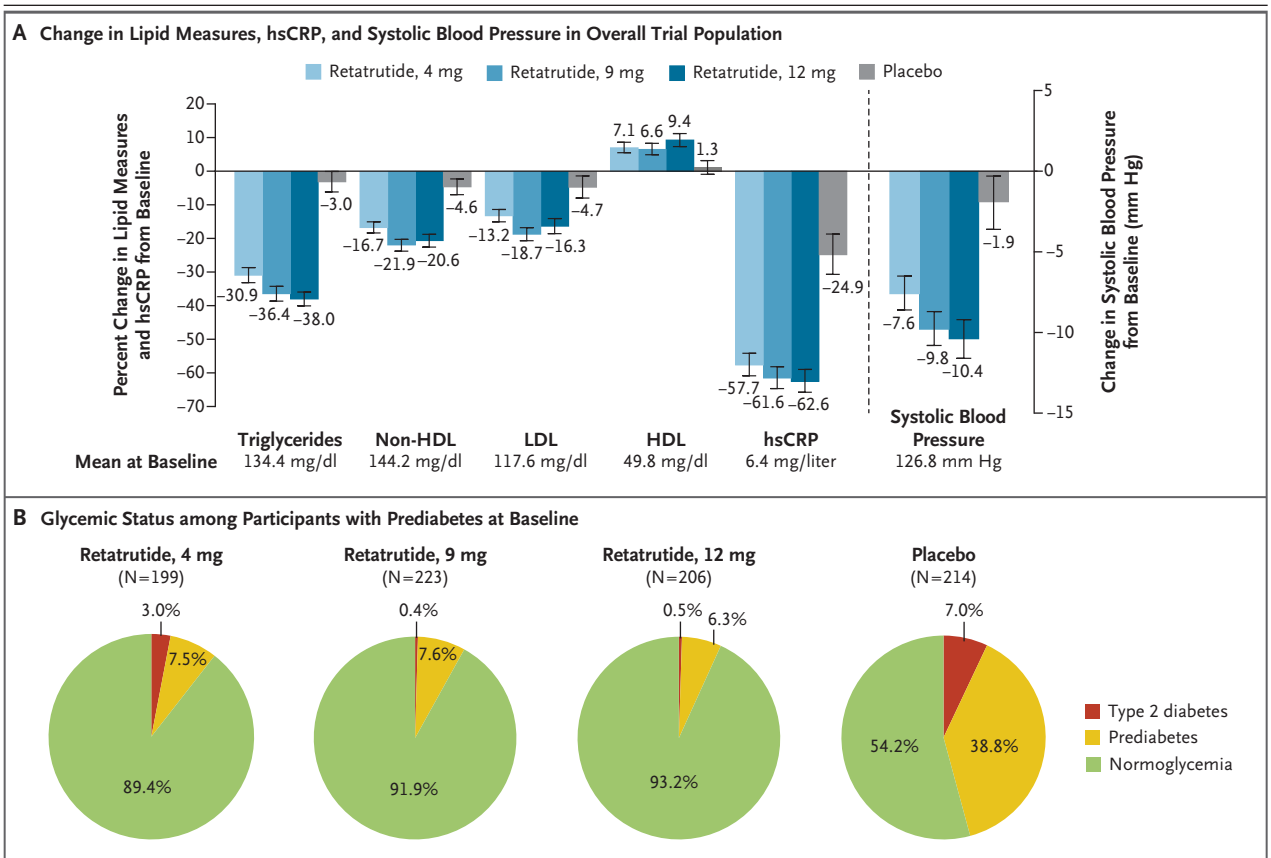


Figure 2. Effect of Retatrutide on Health Outcomes.

Data are model-based estimates with 95% confidence intervals at week 80, as calculated with the treatment-regimen estimand unless otherwise specified. Panel A shows the percent change in lipid measures, the percent change in the high-sensitivity C-reactive protein (hsCRP), and the change in systolic blood pressure (SBP) in the overall trial population (controlled for type I error except for low-density lipoprotein [LDL] and high-density lipoprotein [HDL]). P<0.001 for all comparisons with placebo. Data for the efficacy estimand are provided in Figures S16 to S18. Panel B shows the percentage of participants with normoglycemia, prediabetes, and type 2 diabetes at week 80 among the participants who had prediabetes at baseline for the treatment-regimen data- points set. Type 2 diabetes was adjudicated by a clinical end-point committee; participants with an adjudicated diagnosis of type 2 diabetes at any time during the trial were classified as having type 2 diabetes at week 80. Remaining glycemic status at week 80 was assessed at the last postbaseline laboratory visit at which each participant had at least one of the following: measurement of fasting glucose, oral glucose tolerance, or glycated hemoglobin. Classification as prediabetes required at least two values within the following ranges: fasting glucose level, 100 to 125 mg per deciliter; 2-hour glucose level, 140 to 199 mg per deciliter; or glycated hemoglobin level, 5.7 to 6.4%, all according to the 2023 American Diabetes Association Standards of Medical Care in Diabetes. Data for the efficacy estimand are provided in Figure S20.

ity of life; weight reduction is associated with a reduction in the WOMAC pain score.[21,31] In this trial, retatrutide resulted in a reduction in pain of up to 61.6% (hybrid-treatment estimand).[32,33] With respect to obstructive sleep apnea, which is often associated with obesity,[34] effective treatment (before the recent approval of tirzepatide for this indication[22]) often relied on mechanical interventions or bariatric surgery.[35] In this trial, retatrutide resulted in significant improvement in the AHI events per hour, with a mean decrease of up to 57.3% (hybrid-treatment estimand).

Cardiometabolic measures improved across all retatrutide groups, including systolic blood pressure, diastolic blood pressure, triglycerides, low-density lipoprotein cholesterol, and high-sensitivity C-reactive protein, with reversion to normoglycemia occurring in more than 90% of the participants who had prediabetes at baseline. Participant-reported outcomes supported improvements in quality of life, including physical function and psychosocial domains.

The safety of retatrutide was generally similar to that seen in a phase 2 trial[24] and to that reported with therapies that were based on nutrient-stimulated hormone pathways.[4,7] The most

Table 3. Adverse Events (Safety Population).*

Adverse Event	Retatrutide			Placebo (N=586)
	4 mg (N=584)	9 mg (N=583)	12 mg (N=582)	
	number of participants (percent)			
Any adverse event after the start of treatment	508 (87.0)	519 (89.0)	519 (89.2)	473 (80.7)
Serious adverse event	45 (7.7)	45 (7.7)	61 (10.5)	32 (5.5)
Death†	0	3 (0.5)	1 (0.2)	2 (0.3)
Leading to discontinuation from trial‡	6 (1.0)	8 (1.4)	16 (2.7)	10 (1.7)
Leading to discontinuation of retatrutide or placebo‡	24 (4.1)	38 (6.5)	65 (11.2)	27 (4.6)
Gastrointestinal disorder leading to discontinuation of retatrutide or placebo	13 (2.2)	22 (3.8)	27 (4.6)	7 (1.2)
Adverse event in ≥10% of participants§				
Nausea	167 (28.6)	224 (38.4)	247 (42.4)	87 (14.8)
Diarrhea	147 (25.2)	199 (34.1)	186 (32.0)	79 (13.5)
Constipation	139 (23.8)	151 (25.9)	152 (26.1)	64 (10.9)
Vomiting	62 (10.6)	133 (22.8)	147 (25.3)	28 (4.8)
Decreased appetite	75 (12.8)	78 (13.4)	96 (16.5)	34 (5.8)
Upper respiratory tract infection	83 (14.2)	71 (12.2)	76 (13.1)	68 (11.6)
Dizziness	29 (5.0)	52 (8.9)	70 (12.0)	18 (3.1)
Dyspepsia	46 (7.9)	52 (8.9)	63 (10.8)	22 (3.8)
Abdominal pain	41 (7.0)	34 (5.8)	60 (10.3)	11 (1.9)
Fatigue	43 (7.4)	62 (10.6)	59 (10.1)	21 (3.6)
Adverse event of special interest and other safety topics				
Dysesthesia: skin burning sensation and related adverse events	30 (5.1)	72 (12.3)	73 (12.5)	5 (0.9)
Injection-site reaction	32 (5.5)	52 (8.9)	71 (12.2)	22 (3.8)
Hypotension, orthostatic hypotension, and decrease in blood pressure	16 (2.7)	31 (5.3)	51 (8.8)	5 (0.9)
Severe or serious gastrointestinal adverse event	15 (2.6)	35 (6.0)	30 (5.2)	8 (1.4)
Cancer	12 (2.1)	5 (0.9)	11 (1.9)	6 (1.0)
Severe or serious arrhythmia or cardiac conduction disorder	1 (0.2)	4 (0.7)	5 (0.9)	5 (0.9)
Severe or serious gallbladder or biliary tract disorder	10 (1.7)	5 (0.9)	4 (0.7)	4 (0.7)
Adjudication-confirmed pancreatitis	1 (0.2)	3 (0.5)	4 (0.7)	2 (0.3)
Adjudication-confirmed major adverse cardiovascular event	1 (0.2)	5 (0.9)	3 (0.5)	1 (0.2)
Severe or serious hepatic disorder¶	0	0	3 (0.5)	0
Severe or serious ketoacidosis from inadequate nutritional intake or other type of metabolic acidosis and ketosis	1 (0.2)	1 (0.2)	2 (0.3)	1 (0.2)
Severe or serious acute renal event	2 (0.3)	0	2 (0.3)	0
Severe or serious hypersensitivity reaction‖	0	2 (0.3)	1 (0.2)	2 (0.3)
Thyroid cancer or C-cell hyperplasia**	1 (0.2)	0	1 (0.2)	0
Severe or serious depression or suicidal ideation or behavior	0	0	1 (0.2)	1 (0.2)
Severe or serious malnutrition	1 (0.2)	2 (0.3)	0	0

* Safety analyses were performed in the population of participants who had undergone randomization and received at least one dose of retatrutide or placebo. Adverse events are listed according to the preferred terms in the *Medical Dictionary for Regulatory Activities*, version 28.1.

† Deaths were adjudicated by an independent clinical end-point committee whose members determined whether the death was cardiovascular-related. Causes of death in the retatrutide group were one motor vehicle accident and two sudden deaths (one noncardiovascular and one of undetermined cause) in the 9-mg group and adjudicated cardiovascular death (in a participant with known heart failure 189 days after the discontinuation of retatrutide) in the 12-mg group. Causes of death in the placebo group were one motor vehicle accident and one gunshot wound. Additional details are provided in Table S7.

‡ Adverse events in this category exclude deaths. The denominator for these values is not the safety population but the randomly assigned population.

§ Adverse events that occurred during treatment in at least 10% of participants in any trial group are listed in descending order of incidence in the 12-mg retatrutide group.

¶ Three participants in the 12-mg retatrutide group had hepatic disorders, which included one case of acute cholestatic hepatitis A, one case of acute ischemic hepatitis most likely due to dehydration associated with *Clostridium difficile* colitis, and one case of an increase in hepatic enzymes associated with an exacerbation of gallstone disease.

‖ This category includes potential immediate and potential nonimmediate hypersensitivity reactions.

** There were no cases of medullary thyroid cancer or C-cell hyperplasia.

common adverse events were gastrointestinal. These events were generally mild or moderate in severity, occurred mostly during dose escalation, and were more common at higher doses. The 4-mg dose, which required a single dose-escalation step, resulted in a mean weight reduction of 19% and a BMI of less than 30 in more than 40% of the participants. Permanent dose reductions owing to perceived excessive weight loss or reaching a BMI of 22 or less occurred among more participants in the retatrutide groups than among those in the placebo group. We speculate that these observations highlight the need to reconsider the use of the maximum tolerated dose as the treatment strategy, thereby aiming for the minimum effective dose needed to reach treatment targets for each patient, as is common in the treatment of other chronic metabolic diseases.

Dizziness and reported symptoms of hypotension appeared to be dose-dependent and more frequent with retatrutide. Reported symptoms of hypotension were more common among participants who were receiving concurrent antihypertensive therapy. A few serious or severe events of ketosis or ketoacidosis occurred, with similar numbers across the retatrutide and placebo groups. Ten adjudicated-confirmed pancreatitis events were reported (1 with retatrutide 4 mg, 3 with retatrutide 9 mg, and 4 with retatrutide 12 mg, as compared with 2 in the placebo group). These small event numbers do not permit conclusions regarding a treatment effect, so additional data will be required from forthcoming trials. Major adverse cardiovascular events occurred in all groups (1 participant [0.2%] with retatrutide 4 mg, 5 participants [0.9%] with retatrutide 9 mg, and 3 participants [0.5%] with retatrutide 12 mg, as compared with 1 participant [0.2%] with placebo). This trial was not powered to assess cardiovascular safety; adequately powered, longer studies are needed to assess cardiovascular safety, such as TRIUMPH-Outcomes (NCT06383390), which is evaluating cardiovascular and kidney outcomes. Urinary tract infections were more frequent with retatrutide and occurred almost exclusively in women, without a clear temporal pattern.

The basket design is a strength that enabled simultaneous assessment of retatrutide for the treatment of obesity and two of its major complications within one trial. Prespecified analyses enabled comparison of clinical response according to subgroup, which suggested greater weight loss in women than in men.

Limitations of the trial include the absence of an active comparator, which may have contributed to greater attrition in the placebo group, as reflected by the use of the now more widely available obesity medications in this group.[4,7] Only 2% of the participants had a baseline BMI of less than 30, which limits generalizability to that population.

Treatment with retatrutide resulted in significant reductions in body weight and in pain from knee osteoarthritis and in events of obstructive sleep apnea in adults with obesity without diabetes.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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