ORIGINAL ARTICLE

Retatrutide Once Weekly in Adults with Knee Osteoarthritis Pain and Obesity

T.J. Schnitzer,[1] D.J. Hunter,[2] P.G. Conaghan,[3,4] A.M. Sharma,[5] S.D. Pedersen,[6,7] K. Chen,[8] S.Y. Park,[8] N. Makarova,[8] K. Giblin,[8] and T. Forrester,[8] for the TRIUMPH-4 and TRIUMPH-1-OA Investigators*

ABSTRACT

BACKGROUND

Retatrutide, an investigational triple agonist of GIP, GLP-1, and glucagon receptors, may be useful for the treatment of painful knee osteoarthritis in persons with obesity.

METHODS

In two phase 3 trials, adults without diabetes who had painful knee osteoarthritis and a body-mass index of at least 27 were randomly assigned to receive once-weekly subcutaneous retatrutide (9 or 12 mg in TRIUMPH-4 and 4, 9, or 12 mg in TRIUMPH-1-OA) or placebo. In TRIUMPH-4, the primary end points were the change in the WOMAC pain score (range, 0 to 10, with higher scores indicating worse pain) and the percent change in body weight at week 68. In TRIUMPH-1-OA, the primary end point was the change in the WOMAC pain score at week 80. For non–pain-related end points, intercurrent events were handled with a treatment-policy strategy. For pain-related end points, a hybrid-treatment estimand was applied, with a hypothetical strategy for intercurrent events that suggested treatment failure and a treatment-policy strategy elsewhere. We also report results for an intention-to-treat (ITT) estimand.

RESULTS

A total of 445 participants underwent randomization in TRIUMPH-4 and 574 in TRIUMPH-1-OA. At 68 weeks, the mean changes in the WOMAC pain score (hybrid-treatment estimand) with retatrutide in TRIUMPH-4 were –3.96 (9 mg) and –3.74 (12 mg), versus –2.12 with placebo (difference vs. placebo, –1.83 [95% confidence interval {CI}, –2.37 to –1.30] and –1.61 [95% CI, –2.16 to –1.07], respectively). For the ITT estimand, the corresponding differences from placebo were –1.70 (95% CI, –2.19 to –1.22) and –1.38 (95% CI, –1.91 to –0.85) (P<0.001 for all comparisons). The mean percent changes in body weight with retatrutide were –20.0% (9 mg) and –23.7% (12 mg), versus –4.6% with placebo (difference vs. placebo, –15.4 percentage points [95% CI, –18.7 to –12.1] and –19.2 percentage points [95% CI, –22.4 to –15.9]; P<0.001 for both comparisons). At 80 weeks, the mean changes in the WOMAC pain score (hybrid-treatment estimand) with retatrutide in TRIUMPH-1-OA were –3.22 (4 mg), –3.48 (9 mg), and –3.64 (12 mg), versus –1.87 with placebo (difference vs. placebo, –1.35 [95% CI, –1.92 to –0.78], –1.61 [95% CI, –2.20 to –1.02], and –1.77 [95% CI, –2.34 to –1.20], respectively). For the ITT estimand, the corresponding differences from placebo were –0.96 (95% CI, –1.61 to –0.30), –1.41 (95% CI, –2.07 to –0.75), and –1.64 (95% CI, –2.26 to –1.02) (P≤0.005 for all comparisons). In both trials, serious adverse events were more common with retatrutide than with placebo, and the most common adverse events were gastrointestinal.

CONCLUSIONS

In participants with painful knee osteoarthritis and obesity, treatment with retatrutide resulted in significantly greater reductions in both the WOMAC pain score and body weight than placebo. (Funded by Eli Lilly; TRIUMPH-4 and -1 ClinicalTrials.gov numbers, NCT05931367 and NCT05929066.)

The authors' full names, academic degrees, and affiliations are listed at the end of the article. Thomas J. Schnitzer can be contacted at tjs@northwestern.edu or at Northwestern University Feinberg School of Medicine–Physical Medicine and Rehabilitation, 710 N. Lake Shore Dr., Chicago, IL 60611.

*A complete list of the TRIUMPH-4 and TRIUMPH-1-OA investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Osteoarthritis, a progressive joint disease, often involves pain that limits quality of life and confers substantial socioeconomic burdens on patients, health care systems, and society.[1-3] Obesity is a risk factor in both the onset and progression of osteoarthritis.[1-3] Excess body weight increases mechanical loading on weight-bearing joints; furthermore, increased joint stress accelerates cartilage degeneration and possible malalignment.[1,3,4] Excess adiposity may also contribute to a systemic, low-grade inflammatory state.[5]

Weight reduction is considered to be an important component of the management of knee osteoarthritis; for each pound of body weight lost, the load across the knee is reduced by approximately a factor of 4.[6] Biomechanical and clinical benefits increase with weight loss; progressively greater weight reduction is associated with lower maximum knee compressive forces and greater reductions in symptoms.[7] Clinical guidelines include weight reduction alongside exercise, pharmacologic therapies (such as nonsteroidal antiinflammatory agents), intraarticular injections, and surgical interventions.[8,9]

Current pharmacologic therapies may provide modest efficacy but are limited by side effects and safety. Data from a recent trial suggest that treatment with semaglutide led to reductions in knee osteoarthritis pain,[10] a finding that highlights the possibility that additional obesity therapeutics may address both excess body weight and symptoms of knee osteoarthritis.

Retatrutide is an investigational triple agonist of the glucose-dependent insulinotropic polypeptide (GIP), glucagon-like peptide-1 (GLP-1), and glucagon receptors. In phase 2 clinical trials involving patients with obesity, retatrutide led to average weight reductions at 48 weeks that ranged from 8.7 to 24.2%, as compared with 2.1% with placebo (difference vs. placebo, −6.6 to −22.1 percentage points).[11] We conducted the TRIUMPH-4 and TRIUMPH-1-OA trials to evaluate the efficacy and safety of once-weekly injectable retatrutide in adults with painful knee osteoarthritis and obesity.

METHODS

TRIAL DESIGN

We conducted these phase 3, double-blind, randomized, controlled trials in Australia, Europe, and North America, at 49 centers in 5 countries for TRIUMPH-4 and at 66 centers in 7 countries for TRIUMPH-1-OA (see Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). We report the results of these trials together to show replication of the results across independent populations. The trial design and the results for the primary end point in TRIUMPH-1-OA were reported previously[12]; those results are also included here.

The trials were approved by the ethical review board at each site. Written informed consent was obtained from all the participants. Eli Lilly, the trial sponsor, was involved in the trial design and conduct; collection, management, analyses, and interpretation of the data; preparation, review, and approval of the manuscript; and the decision to submit the manuscript for publication. The sponsor did not have the right to veto publication or to control the decision about where to submit the manuscript. Final decisions about manuscript submission were made by the authors, including employees of the sponsor. Additional details about trial oversight and author responsibilities are provided in the Supplementary Appendix. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocols, available at NEJM.org.

PARTICIPANTS

Both trials included adults (≥18 years of age) with ongoing pain in the index knee (defined as chronic pain over a period of >12 weeks before screening and the presence of pain on >15 days in the month before screening), radiographic evidence of knee osteoarthritis according to the criteria of the American College of Rheumatology,[13] and at least one previous participant-reported unsuccessful dietary effort to lose body weight. Pain in the index knee was assessed with the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), version 3.1, which uses a numeric rating scale ranging from 0 to 10, with higher numbers indicating worse pain. Eligible participants had a score of at least 4 but no more than 9, indicative of moderate-to-severe osteoarthritis pain. Both trials enrolled participants with obesity, which was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of at least 27 in TRIUMPH-4 and as a BMI of at least 30, or at least 27 with one or more

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

Characteristic	TRIUMPH-4				TRIUMPH-1-OA				
	Retatrutide, 9 mg (N=148)	Retatrutide, 12 mg (N=148)	Placebo (N=149)	Total (N=445)	Retatrutide, 4 mg (N=143)	Retatrutide, 9 mg (N=143)	Retatrutide, 12 mg (N=144)	Placebo (N=144)	Total (N=574)
Age — yr	55.1±9.6	54.8±9.9	55.6±9.8	55.2±9.7	56.3±9.4	56.4±9.3	55.7±9.2	56.0±8.7	56.1±9.1
Female sex — no. (%)†	94 (63.5)	94 (63.5)	94 (63.1)	282 (63.4)	108 (75.5)	108 (75.5)	109 (75.7)	110 (76.4)	435 (75.8)
Race or ethnic group — no. (%)†									
White	97 (65.5)	101 (68.2)	97 (65.1)	295 (66.3)	105 (73.4)	104 (72.7)	105 (72.9)	107 (74.3)	421 (73.3)
American Indian or Alaska Native	36 (24.3)	31 (20.9)	33 (22.1)	100 (22.5)	18 (12.6)	16 (11.2)	17 (11.8)	20 (13.9)	71 (12.4)
Black or African American	11 (7.4)	8 (5.4)	9 (6.0)	28 (6.3)	16 (11.2)	12 (8.4)	15 (10.4)	12 (8.3)	55 (9.6)
Multiple	0	3 (2.0)	0	3 (0.7)	1 (0.7)	0	1 (0.7)	0	2 (0.3)
Asian	0	1 (0.7)	1 (0.7)	2 (0.4)	0	4 (2.8)	1 (0.7)	2 (1.4)	7 (1.2)
Native Hawaiian or other Pacific Islander	0	1 (0.7)	1 (0.7)	2 (0.4)	0	2 (1.4)	1 (0.7)	0	3 (0.5)
Hispanic or Latino	61 (41.2)	45 (30.4)	55 (36.9)	161 (36.2)	32 (22.4)	35 (24.5)	31 (21.5)	32 (22.2)	130 (22.6)
Not reported	4 (2.7)	3 (2.0)	8 (5.4)	15 (3.4)	3 (2.1)	5 (3.5)	4 (2.8)	3 (2.1)	15 (2.6)
WOMAC pain score‡	6.02±1.29	5.88±1.25	5.94±1.24	5.95±1.26	6.10±1.22	5.93±1.11	6.04±1.31	5.83±1.33	5.97±1.25
WOMAC physical function score‡	5.99±1.47	5.72±1.56	5.56±1.60	5.75±1.55	5.86±1.67	5.86±1.31	5.96±1.56	5.64±1.73	5.83±1.58
Average pain intensity score§	5.81±1.56	5.61±1.59	5.59±1.65	5.67±1.60	5.58±1.78	5.55±1.50	5.58±1.81	5.51±1.63	5.56±1.68
Kellgren–Lawrence grade — no. (%)¶									
0	0	0	0	0	0	0	1 (0.7)	0	1 (0.2)
1	0	0	0	0	0	0	0	1 (0.7)	1 (0.2)
2	55 (37.2)	50 (33.8)	55 (36.9)	160 (36.0)	48 (33.6)	55 (38.5)	56 (38.9)	53 (36.8)	212 (36.9)
3	93 (62.8)	96 (64.9)	94 (63.1)	283 (63.6)	95 (66.4)	88 (61.5)	87 (60.4)	90 (62.5)	360 (62.7)
4	0	2 (1.4)	0	2 (0.4)	0	0	0	0	0
Body weight — kg	112.4±22.7	113.5±22.4	112.2±23.1	112.7±22.7	111.9±22.5	111.0±21.1	114.3±26.3	112.8±23.7	112.5±23.5
BMI‖									
Mean	40.5±7.2	40.3±7.0	40.5±6.8	40.4±7.0	40.9±6.6	40.5±6.6	41.0±7.5	40.7±6.9	40.8±6.9
≥35 — no. (%)	125 (84.5)	124 (83.8)	125 (83.9)	374 (84.0)	119 (83.2)	117 (81.8)	116 (80.6)	123 (85.4)	475 (82.8)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding.
† Sex, race, and ethnic group were reported by the participants.
‡ Scores on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) range from 0 to 10 on each subscale (pain and physical function), with higher scores indicating worse symptoms.
§ Average pain intensity was assessed on a numeric rating scale ranging from 0 to 10, with higher scores indicating worse pain.
¶ Grades on the Kellgren–Lawrence scale range from 0 (no radiographic evidence of osteoarthritis) to 4 (large osteophytes and marked narrowing of joint space).
‖ The body-mass index (BMI) is the weight in kilograms divided by the square of the height in meters.

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Table 2. Primary and Key Secondary End Points.*

End Point	TRIUMPH-4			TRIUMPH-1-OA			
	Retatrutide, 9 mg (N=148)	Retatrutide, 12 mg (N=148)	Placebo (N=149)	Retatrutide, 4 mg (N=143)	Retatrutide, 9 mg (N=143)	Retatrutide, 12 mg (N=144)	Placebo (N=144)
Primary end points							
Change in WOMAC pain score	−3.96±0.18	−3.74±0.18	−2.12±0.21	—	−3.48±0.21	−3.64±0.20	−1.87±0.21
Difference from placebo (95% CI); P value	−1.83 (−2.37 to −1.30); P<0.001	−1.61 (−2.16 to −1.07); P<0.001	—	—	−1.61 (−2.20 to −1.02); P<0.001	−1.77 (−2.34 to −1.20); P<0.001	—
Percent change in body weight	−20.0±0.9	−23.7±1.0	−4.6±1.3	—	—	—	—
Difference from placebo (95% CI); P value	−15.4 (−18.7 to −12.1); P<0.001	−19.2 (−22.4 to −15.9); P<0.001	—	—	—	—	—
Key secondary end points							
Change in WOMAC pain score†	—	—	—	−3.22±0.20	—	—	−1.87±0.21
Difference from placebo (95% CI); P value	—	—	—	−1.35 (−1.92 to −0.78); P<0.001	—	—	—
Percent change in body weight‡	—	—	—	−17.5±1.0	−22.9±1.0	−24.8±1.2	−4.3±1.0
Difference from placebo (95% CI); P value	—	—	—	−13.2 (−16.1 to −10.4); P<0.001	−18.6 (−21.4 to −15.8); P<0.001	−20.6 (−23.6 to −17.5); P<0.001	—
Percentage of participants reaching weight-reduction threshold (no./total no.)§							
≥5%	89.9±2.6 (119/131)	95.0±2.1 (127/131)	41.9±4.6 (40/115)	—	—	—	—
Risk difference (95% CI); P value	48.0 (37.5 to 58.6); P<0.001	53.1 (43.1 to 63.2); P<0.001	—	—	—	—	—
≥10%	81.5±3.3 (109/131)	83.9±3.2 (113/131)	22.5±4.3 (14/115)	—	—	—	—
Risk difference (95% CI); P value	59.0 (48.5 to 69.5); P<0.001	61.4 (50.6 to 72.1); P<0.001	—	—	—	—	—
≥15%	63.7±4.0 (85/131)	75.6±3.7 (103/131)	15.2±3.9 (8/115)	—	—	—	—

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Risk difference (95% CI); P value	48.6 (37.5 to 59.7); P<0.001	60.4 (49.8 to 71.1); P<0.001	—	—	—	—	—
≥25%	33.7±3.8 (47/131)	45.1±4.1 (64/131)	3.1±2.1 (1/115)	—	—	—	—
Risk difference (95% CI); P value	30.7 (22.0 to 39.4); P<0.001	42.1 (33.2 to 51.0); P<0.001	—	—	—	—	—
Change in the WOMAC physical function score	−3.64±0.20	−3.57±0.20	−1.80±0.22	−3.21±0.18	−3.42±0.21	−3.48±0.19	−1.53±0.22
Difference from placebo (95% CI); P value	−1.83 (−2.40 to −1.27); P<0.001	−1.77 (−2.34 to −1.20); P<0.001	—	−1.68 (−2.23 to −1.12); P<0.001	−1.89 (−2.49 to −1.29); P<0.001	−1.95 (−2.52 to −1.38); P<0.001	—
Change in the WOMAC pain score at wk 36	−3.57±0.16	−3.24±0.19	−1.93±0.19	−3.15±0.17	−2.88±0.18	−2.90±0.19	−1.87±0.20
Difference from placebo (95% CI); P value	−1.64 (−2.11 to −1.17); P<0.001	−1.31 (−1.83 to −0.79); P<0.001	—	−1.28 (−1.79 to −0.76); P<0.001	−1.01 (−1.53 to −0.49); P<0.001	−1.03 (−1.56 to −0.49); P<0.001	—
Change in the WOMAC pain score at wk 68	—	—	—	−3.11±0.18	−3.18±0.20	−3.17±0.20	−1.72±0.21
Difference from placebo (95% CI); P value	—	—	—	−1.38 (−1.91 to −0.85); P<0.001	−1.46 (−2.02 to −0.90); P<0.001	−1.45 (−2.00 to −0.90); P<0.001	—
Results in participants with baseline BMI ≥35							
Change in the WOMAC pain score	−4.12±0.19	−3.91±0.20	−2.12±0.22	−3.18±0.21	−3.46±0.23	−3.65±0.21	−1.95±0.23
Difference from placebo (95% CI); P value	−2.00 (−2.58 to −1.42); P<0.001	−1.79 (−2.37 to −1.22); P<0.001	—	−1.23 (−1.84 to −0.62); P<0.001	−1.51 (−2.15 to −0.88); P<0.001	−1.71 (−2.32 to −1.09); P<0.001	—
Percent change in body weight	−21.6±1.0	−25.6±1.0	−3.4±1.7	−16.3±1.1	−22.6±1.2	−24.8±1.2	−3.4±1.0
Difference from placebo (95% CI); P value	−18.2 (−22.2 to −14.2); P<0.001	−22.2 (−26.1 to −18.2); P<0.001	—	−13.0 (−15.8 to −10.2); P<0.001	−19.3 (−22.2 to −16.3); P<0.001	−21.4 (−24.5 to −18.3); P<0.001	—

* Plus–minus values are model-based means ±SE, and other data are model-based estimates and 95% confidence intervals. The treatment-regimen estimand was used for weight-related end points; for pain-related end points, the hybrid-treatment estimand was applied, with a hypothetical strategy used for participants who had intercurrent events associated with treatment failure and a treatment-policy strategy used elsewhere. Differences from placebo for end points expressed as percentages are given in percentage points. Unless otherwise specified, results in TRIUMPH-4 were assessed at week 68 and those in TRIUMPH-1-OA at week 80.

† This was a key secondary end point for the 4-mg dose of retatrutide as compared with placebo in TRIUMPH-1-OA.

‡ This was a key secondary end point in TRIUMPH-1-OA.

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

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complications of obesity (hypertension, dyslipidemia, obstructive sleep apnea, or cardiovascular disease), in TRIUMPH-1-OA. Key exclusion criteria for both trials were a weight change of more than 5 kg within 90 days before screening, any conditions that could confound assessments of obesity or osteoarthritis knee pain, and diabetes. Enrollment of female participants was capped at approximately 70% to ensure adequate representation of male participants. Approximately 80% of the participants in both trials had a BMI above 35. Complete eligibility criteria for both trials are listed in the Supplementary Appendix.

PROCEDURES

TRIUMPH-4 participants were randomly assigned in a 1:1:1 ratio to receive subcutaneous retatrutide at a dose of 9 mg or 12 mg or placebo once weekly for 68 weeks. TRIUMPH-1-OA participants were randomly assigned in a 1:1:1:1 ratio to receive subcutaneous retatrutide at a dose of 4 mg, 9 mg, or 12 mg or placebo once weekly for 80 weeks. Randomization in both trials was stratified according to the WOMAC pain score at baseline (≥7 [severe pain] vs. <7 [moderate pain]), the presence of prediabetes (yes or no), and sex. Additional details about trial procedures are provided in the Supplementary Appendix.

Retatrutide was initiated at a dose of 2 mg once weekly; dose escalations occurred every 4 weeks until the target maintenance dose was reached (Fig. S1 in the Supplementary Appendix). Dose reductions were permitted for management of gastrointestinal adverse events or in cases of inadequate oral intake, excessive weight loss, or a reduction in BMI to 22 or lower.

END POINTS AND ASSESSMENTS

In TRIUMPH-4, the primary end points were the change in the WOMAC pain score and the percent change in body weight from baseline to week 68. Key secondary end points, which were controlled for type I error, included body-weight reductions of at least 5%, at least 10%, at least 15%, at least 20%, and at least 25%; the change from baseline in the score on the WOMAC physical function subscale (range, 0 to 10, with higher scores indicating worse symptoms) at weeks 36 and 68; and the change from baseline in the WOMAC pain score at week 36. In TRIUMPH-1-OA, the primary end point was the change in the WOMAC pain score from baseline to week 80 with the 9-mg and 12-mg doses of retatrutide as compared with placebo. Key secondary end points, controlled for type I error, included the change in the WOMAC pain score from baseline to week 80 with 4 mg of retatrutide as compared with placebo; the percent change in body weight from baseline to week 80; the change from baseline in the WOMAC physical function score at weeks 36, 68, and 80; and the change from baseline in the WOMAC pain score at weeks 36 and 68. In both trials, the change in the WOMAC pain score and the percent change in body weight from baseline to week 68 (TRIUMPH-4) or to week 80 (TRIUMPH-1-OA) among participants with a BMI of at least 35 were additional key secondary end points, controlled for type I error.

In key secondary analyses of pooled data from TRIUMPH-4 and TRIUMPH-1-OA, controlled for type I error, we assessed the percentage of participants with a reduction of at least 50% in the WOMAC physical function score and the percentage of participants with a reduction of at least 50% in the WOMAC pain score at week 68. For both trials, additional secondary end points that were not controlled for type I error included the daily average pain intensity, assessed on a numeric rating scale; the use of pain medication as reported by the participants in a daily diary; and measures of cardiometabolic health (the change from baseline in blood pressure and the percent changes from baseline in levels of lipids, high-sensitivity C-reactive protein, and fasting insulin). A complete list of secondary end points that were not controlled for type I error in each trial is provided in the respective statistical analysis plans in the Supplementary Appendix. Safety assessments included adverse events, serious adverse events, and discontinuation of retatrutide.

STATISTICAL ANALYSIS

For TRIUMPH-4, we calculated that a sample size of 435 participants (145 in each group) would provide the trial with more than 90% power to show the superiority of retatrutide (at doses of 9 mg and 12 mg) to placebo for the two primary end points. For TRIUMPH-1-OA, a sample size of 560 participants (140 in each group) was calculated to provide more than 90% power to show the superiority of retatrutide (at 9 mg and 12 mg) to placebo for the primary end point.

For both trials, efficacy analyses included all the participants who underwent randomization.

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For non–pain-related end points, two estimands were prespecified: a treatment-regimen estimand, which estimates the mean treatment effect regardless of treatment discontinuation or the initiation of prohibited treatment for weight management (on the basis of the treatment-policy strategy, consistent with the intention-to-treat analysis), and a hypothetical efficacy estimand, which estimates a treatment effect under the assumption that all the participants received retatrutide or placebo as intended according to the protocol and did not have intercurrent events, such as initiation of prohibited weight-management treatment (consistent with the hypothetical strategy recommended in the International Council for Harmonisation E9 [R1] addendum).[14]

For end points related to knee osteoarthritis for which results are reported here (WOMAC pain and physical function scores and the average pain intensity on a numeric rating scale), two estimands were prespecified: the first was a hybrid-treatment estimand, with a hypothetical strategy used for imputation of values related to intercurrent events associated with treatment failure and a treatment-policy strategy used elsewhere, and the second was a hypothetical efficacy estimand to estimate a treatment effect under the assumption that all the participants received retatrutide or placebo for 68 or 80 weeks as intended and did not have intercurrent events. We also report results for an intention-to-treat estimand that applies a treatment-policy strategy to all related intercurrent events.

Graphical testing for multiple comparisons was used within each trial, which controlled the familywise error rate at a two-sided significance level of 0.05 (Tables S2 through S4 and Figs. S2 through S4). Prespecified key secondary end points in pooled analyses were controlled for a two-sided submission-wise error rate[15,16] (i.e., the probability of a false positive claim for any end point, given that a claim for any end point should be based on significant results from associated hypotheses across both trials) of no more than 0.05. Results for exploratory end points and subgroups are reported as point estimates and 95% confidence intervals, which have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Cohen's d effect size was calculated as the treatment difference divided by the pooled standard deviation, where the pooled standard deviation represents the combined variability of the two trial groups in the comparison. Additional statistical methods are described in the Supplementary Appendix.

RESULTS

TRIAL PARTICIPANTS

In TRIUMPH-4, a total of 1394 participants were screened between August 1, 2023, and November 14, 2025, and 445 underwent randomization: 148 were assigned to each retatrutide group and 149 to the placebo group. In TRIUMPH-1-OA, 1729 participants were screened between July 10, 2023, and April 30, 2026, and 574 underwent randomization: 143 were assigned to each of the 4-mg and 9-mg groups and 144 to each of the 12-mg and placebo groups. The representativeness of the trial participants is summarized in Table S5. In both trials, the demographic and clinical characteristics of the participants at baseline were similar among the trial groups (Table 1 and Table S1).

In TRIUMPH-4, 380 of 445 participants (85.4%) completed the trial, and 320 of 445 (71.9%) completed the assigned course of retatrutide or placebo (112 of 148 [75.7%] in the 9-mg group, 105 of 148 [70.9%] in the 12-mg group, and 103 of 149 [69.1%] in the placebo group). In TRIUMPH-1-OA, 479 of 574 participants (83.4%) completed the trial, and 433 of 574 participants (75.4%) completed the assigned course of retatrutide or placebo (123 of 143 [86.0%] in the 4-mg group, 114 of 143 [79.7%] in the 9-mg group, 106 of 144 [73.6%] in the 12-mg group, and 90 of 144 [62.5%] in the placebo group) (Fig. S5). Discontinuation of retatrutide or placebo due to adverse events occurred in 19 participants (12.8%) in the 9-mg group (including 1 participant who died), 27 participants (18.2%) in the 12-mg group, and 6 participants (4.0%) in the placebo group in TRIUMPH-4 and in 4 participants (2.8%) in the 4-mg group, 12 participants (8.4%) in the 9-mg group, 22 participants (15.3%) in the 12-mg group, and 9 participants (6.2%) in the placebo group in TRIUMPH-1-OA (Table S6). Of these discontinuations, approximately one half in TRIUMPH-4 and one third in TRIUMPH-1-OA were considered to be due to gastrointestinal events. The percentage of participants who reached their assigned dose was 92.5% (136 of 147 participants) in the 9-mg group and 89.9% (133 of 148 participants) in the 12-mg group in TRIUMPH-4 and 98.6% (141 of 143 participants) in the 4-mg group, 94.4%

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Figure 1 (facing page). Changes from Baseline in WOMAC Pain Subscale Scores and Body Weight.

Panel A shows the changes in the score on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale from baseline to week 68 among the participants in TRIUMPH-4; WOMAC pain scores range from 0 to 10, with higher scores indicating worse pain. Panel B shows the changes in the WOMAC pain score from baseline to week 80 among the participants in TRIUMPH-1-OA. Panel C shows the percent changes in body weight from baseline to week 68 among the participants in TRIUMPH-4, and Panel D the percent changes in body weight from baseline to week 80 among the participants in TRIUMPH-1-OA. The graphs display the results of three (Panels C and D) or four (Panels A and B) separate analyses combined into one panel. The curves on the left side of each graph show observed mean changes from baseline during the treatment period according to the efficacy estimand data-point set, in which data points affected by intercurrent events were excluded from the calculation of observed means. In all panels, plus–minus values are means ±SD, and the I bars indicate standard errors. The data points to the right of the curves are model-based estimates with 95% confidence intervals derived from a mixed model for repeated measures according to the efficacy estimand that followed the hypothetical strategy (EE) (which was used as an analysis of the primary end points), model-based estimates with 95% confidence intervals derived from analysis of covariance according to the hybrid-treatment estimand (HYB) for Panels A and B or the treatment-regimen estimand (TRE) for Panels C and D, and model-based estimates with 95% confidence intervals derived from analysis of covariance according to the intention-to-treat estimand (ITT) for Panels A and B. Numbers below each graph are the numbers of participants included in the calculation of the means. P<0.001 for all comparisons with placebo.

(135 of 143 participants) in the 9-mg group, and 88.9% (128 of 144 participants) in the 12-mg group in TRIUMPH-1-OA. The percentage of participants who were receiving their assigned dose at the end of the trial was 76.2% (112 of 147 participants) in the 9-mg group and 66.9% (99 of 148 participants) in the 12-mg group in TRIUMPH-4 and 93.7% (134 of 143 participants) in the 4-mg group, 74.8% (107 of 143 participants) in the 9-mg group, and 66.0% (95 of 144 participants) in the 12-mg group in TRIUMPH-1-OA.

EFFICACY

Primary End Points

In TRIUMPH-4, for the hybrid-treatment estimand, the mean change in the WOMAC pain score from baseline to week 68 was −3.96 with 9 mg of retatrutide and −3.74 with 12 mg, as compared with −2.12 with placebo; the estimated difference from placebo was −1.83 (95% confidence interval [CI], −2.37 to −1.30) for 9 mg of retatrutide and −1.61 (95% CI, −2.16 to −1.07) for 12 mg (P<0.001 for both comparisons) (Table 2 and Fig. 1). These changes corresponded to Cohen's d effect sizes of 0.79 and 0.68, respectively. For the intention-to-treat estimand, the mean change in the WOMAC pain score from baseline to week 68 was −4.30 in the 9-mg group and −3.97 in the 12-mg group, as compared with −2.59 in the placebo group; the estimated difference from placebo was −1.70 (95% CI, −2.19 to −1.22) with 9 mg of retatrutide and −1.38 (95% CI, −1.91 to −0.85) with 12 mg (P<0.001 for both comparisons) (Table S7). For the treatment-regimen estimand, the mean percent change in body weight from baseline to week 68 was −20.0% for 9 mg of retatrutide and −23.7% for 12 mg, as compared with −4.6% for placebo; the estimated difference from placebo was −15.4 percentage points (95% CI, −18.7 to −12.1) for 9 mg and −19.2 percentage points (95% CI, −22.4 to −15.9) for 12 mg (P<0.001 for both comparisons) (Table 2 and Fig. 1). Similar results were obtained with the efficacy estimand that followed the hypothetical strategy (Fig. 1 and Table S8).

In TRIUMPH-1-OA, for the hybrid-treatment estimand, the mean change in the WOMAC pain score from baseline to week 80 was −3.22 in the 4-mg retatrutide group, −3.48 in the 9-mg group, and −3.64 in the 12-mg group, as compared with −1.87 in the placebo group. The estimated difference from placebo was −1.35 (95% CI, −1.92 to −0.78) for 4 mg, −1.61 (95% CI, −2.20 to −1.02) for 9 mg, and −1.77 (95% CI, −2.34 to −1.20) for 12 mg (P<0.001 for all comparisons) (Table 2 and Fig. 1), which corresponded to Cohen's d effect sizes of 0.55, 0.63, and 0.72, respectively. For the intention-to-treat estimand, the mean change in the WOMAC pain score from baseline to week 80 was −3.41 with 4 mg of retatrutide, −3.86 with 9 mg, and −4.10 with 12 mg, as compared with −2.46 with placebo; the estimated difference from placebo was −0.96 (95% CI, −1.61 to −0.30) for 4 mg (P=0.005), −1.41 (95% CI, −2.07 to −0.75) for 9 mg (P<0.001), and −1.64 (95% CI, −2.26 to −1.02) for 12 mg (P<0.001) (Table S7). Similar results were obtained with the efficacy estimand that followed the hypothetical strategy (Fig. 1 and Table S8).

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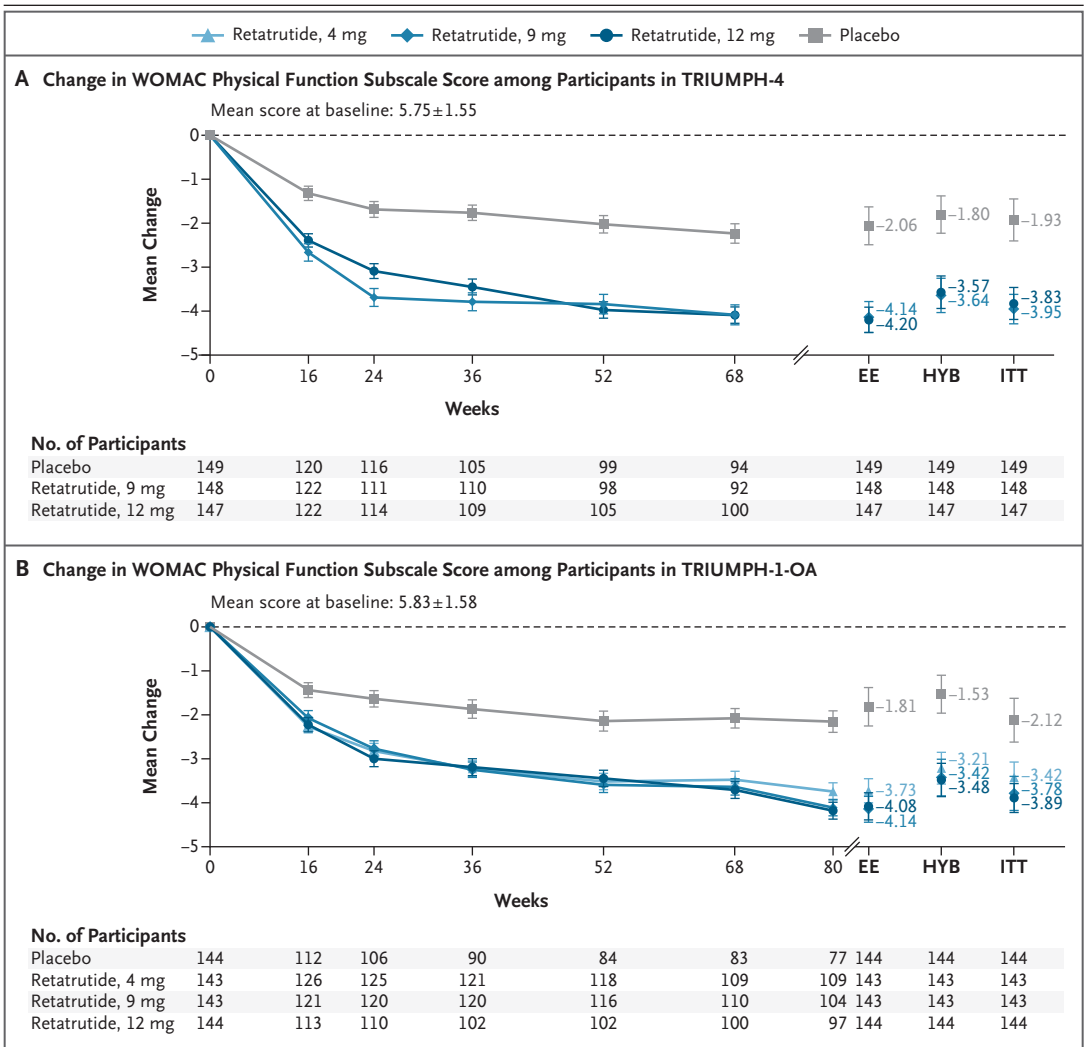


Figure 2. Changes from Baseline in WOMAC Physical Function Subscale Scores.

Panel A shows the observed changes in the score on the WOMAC physical function subscale (range, 0 to 10, with higher scores indicating worse symptoms) from baseline to week 68 among the participants in TRIUMPH-4. Panel B shows the observed changes in the WOMAC physical function score from baseline to week 80 among the participants in TRIUMPH-1-OA. The curves on the left side of each graph show observed mean changes from baseline during the treatment period according to the efficacy estimand data-point set, in which data points affected by intercurrent events were excluded from the calculation of observed means. In both panels, plus–minus values are means ±SD, and the I bars indicate standard errors. The data points to the right of the curves are model-based estimates with 95% confidence intervals according to the efficacy estimand that followed the hypothetical strategy, the hybrid-treatment estimand, and the intention-to-treat estimand. Numbers below each graph are the numbers of participants included in the calculation of the means. P<0.001 for all comparisons with placebo.

Key Secondary End Points

In both trials, for the hybrid-treatment estimand, the mean changes in the WOMAC physical function score from baseline to week 68 or week 80 were significantly greater among participants treated with retatrutide than among those who received placebo (Table 2 and Fig. 2). Changes in WOMAC pain scores at week 36 were also significantly greater with retatrutide than with placebo (Table 2). Similar results were observed with the intention-to-treat estimand (Table S7) and with the efficacy estimand that followed the hypothetical strategy (Table S8 and Fig. S6). The findings in the subgroup of participants with a

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Table 3. Pooled Analyses of Key Secondary End Points.*

End Point	Retatrutide, 9 mg (N=291)	Retatrutide, 12 mg (N=292)	Placebo (N=293)
Percentage of participants reaching ≥50% reduction in WOMAC pain score at wk 68 (no./total no.)	69.6±2.8 (189/248)	63.2±3.0 (167/236)	37.8±3.0 (86/185)
Difference from placebo (95% CI); P value	31.79 (23.78 to 39.81); P<0.001	25.45 (17.02 to 33.89); P<0.001	—
Percentage of participants reaching ≥50% reduction in WOMAC physical function score at wk 68 (no./total no.)	64.6±2.9 (176/246)	63.5±3.0 (168/235)	33.1±3.0 (73/183)
Difference from placebo (95% CI); P value	31.41 (23.28 to 39.55); P<0.001	30.34 (21.91 to 38.78); P<0.001	—

* Shown are results from pooled analyses of key secondary end points among the participants in TRIUMPH-4 and TRIUMPH-1-OA. Plus–minus values are model-based means ±SE, and other data are model-based estimates and 95% confidence intervals; values were derived from a logistic-regression model with imputed data. Differences from placebo are given in percentage points. End points were tested with control of the submission-wise error rate. The widths of the confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. For these pain-related end points, the hybrid-treatment estimand was applied.

baseline BMI of at least 35 were similar to those in the overall trial population for the hybrid-treatment estimand (Table 2) and for the efficacy estimand that followed the hypothetical strategy (Table S8).

In TRIUMPH-4, for the treatment-regimen estimand, the percentage of participants who reached a body-weight reduction target of at least 5%, at least 10%, at least 15%, at least 20%, or at least 25% at week 68 was significantly greater in the 9-mg and 12-mg retatrutide groups than in the placebo group (Table 2 and Table S9). Similar results were observed with the efficacy estimand that followed the hypothetical strategy (Fig. S7 and Table S8), and results for participants with a BMI of at least 35 at baseline were similar to those in the overall trial population (Table S9). In TRIUMPH-1-OA, for the treatment-regimen estimand, the mean percent change in body weight from baseline to week 80 was –17.5% in the 4-mg retatrutide group, –22.9% in the 9-mg group, and –24.8% in the 12-mg group, as compared with –4.3% in the placebo group; the estimated difference from placebo was –13.2 percentage points (95% CI, –16.1 to –10.4), –18.6 percentage points (95% CI, –21.4 to –15.8), and –20.6 percentage points (95% CI, –23.6 to –17.5), respectively (P<0.001 for all comparisons) (Table 2 and Fig. 1).

Key Secondary End Points in Pooled Analyses

In pooled analyses at week 68, for the hybrid-treatment estimand, 63.2 to 69.6% of the participants in the retatrutide groups had a reduction of at least 50% in the WOMAC pain score, as compared with 37.8% of those in the placebo group; for the WOMAC physical function score, the corresponding numbers were 63.5 to 64.6% in the retatrutide groups, as compared with 33.1% in the placebo group (Table 3, Table S10, and Fig. S8). For the intention-to-treat estimand, 66.8 to 75.2% of the participants in the retatrutide groups had a reduction of at least 50% in the WOMAC pain score, as compared with 44.7% of those in the placebo group, and for the WOMAC physical function score, the corresponding numbers were 69.9 to 70.7% in the retatrutide groups, as compared with 37.7% in the placebo group (Table S11).

Additional Secondary End Points

In both trials, results for the daily average pain intensity were analyzed with the hybrid-treatment estimand, the efficacy estimand that followed the hypothetical strategy, and the intention-to-treat estimand for retatrutide and placebo (Fig. S9). Pain medication use as reported by participants in a daily diary decreased over time in all trial groups (Fig. S10). Cardiometabolic data from both trials, including changes in blood pressure and percent changes in levels of lipids, high-sensitivity C-reactive protein, and fasting insulin as calculated with the treatment-regimen estimand and the efficacy estimand that followed the hypothetical strategy, are shown in Table S9 and Figure S11.

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Table 4. Adverse Events.*

Event	TRIUMPH-4				TRIUMPH-1-OA				
	Retatrutide, 9 mg (N=147)	Retatrutide, 12 mg (N=148)	Placebo (N=149)	Total (N=444)	Retatrutide, 4 mg (N=143)	Retatrutide, 9 mg (N=143)	Retatrutide, 12 mg (N=144)	Placebo (N=144)	Total (N=574)
	number of participants (percentage)								
Any adverse event after the start of treatment	125 (85.0)	127 (85.8)	110 (73.8)	362 (81.5)	130 (90.9)	132 (92.3)	136 (94.4)	125 (86.8)	523 (91.1)
Death	1 (0.7)	1 (0.7)	0	2 (0.5)	0	0	0	0	0
Serious adverse event	14 (9.5)	16 (10.8)	3 (2.0)	33 (7.4)	6 (4.2)	14 (9.8)	21 (14.6)	10 (6.9)	51 (8.9)
Adverse event leading to discontinuation of retatrutide or placebo	19 (12.9)	27 (18.2)	6 (4.0)	52 (11.7)	4 (2.8)	12 (8.4)	22 (15.3)	9 (6.2)	47 (8.2)
Gastrointestinal disorder leading to discontinuation of retatrutide or placebo	9 (6.1)	12 (8.1)	2 (1.3)	23 (5.2)	2 (1.4)	6 (4.2)	8 (5.6)	0	16 (2.8)
Adverse events of special interest									
Dysesthesia	13 (8.8)	31 (20.9)	1 (0.7)	45 (10.1)	9 (6.3)	24 (16.8)	22 (15.3)	1 (0.7)	56 (9.8)
Injection-site reaction	13 (8.8)	9 (6.1)	4 (2.7)	26 (5.9)	11 (7.7)	17 (11.9)	20 (13.9)	8 (5.6)	56 (9.8)
Severe or serious gastrointestinal disorder	5 (3.4)	4 (2.7)	1 (0.7)	10 (2.3)	0	13 (9.1)	5 (3.5)	1 (0.7)	19 (3.3)
Cancer	7 (4.8)	2 (1.4)	1 (0.7)	10 (2.3)	2 (1.4)	3 (2.1)	6 (4.2)	3 (2.1)	14 (2.4)
Severe or serious arrhythmia or cardiac conduction disorder	3 (2.0)	2 (1.4)	0	5 (1.1)	0	0	2 (1.4)	2 (1.4)	4 (0.7)
Severe or serious gallbladder or biliary tract disorder	1 (0.7)	1 (0.7)	0	2 (0.5)	1 (0.7)	1 (0.7)	0	2 (1.4)	4 (0.7)
Adjudication-confirmed MACE	2 (1.4)	1 (0.7)	0	3 (0.7)	0	0	1 (0.7)	0	1 (0.2)
Severe or serious malnutrition	1 (0.7)	1 (0.7)	0	2 (0.5)	1 (0.7)	1 (0.7)	0	0	2 (0.3)
Severe or serious acute renal event	0	1 (0.7)	0	1 (0.2)	1 (0.7)	0	1 (0.7)	0	2 (0.3)
Adjudication-confirmed pancreatitis	0	0	0	0	0	2 (1.4)	0	0	2 (0.3)
Severe or serious hepatic disorder	0	0	0	0	0	0	1 (0.7)	0	1 (0.2)
Severe or serious hypersensitivity reaction	0	0	0	0	0	1 (0.7)	0	0	1 (0.2)
Thyroid cancer or C-cell hyperplasia	0	0	0	0	0	0	1 (0.7)	0	1 (0.2)
Severe or serious depression or suicidal ideation or behavior	0	1 (0.7)	0	1 (0.2)	0	0	0	0	0
Severe or serious ketoacidosis†	0	0	0	0	0	0	0	0	0

* Data are reported for the safety population, which included all the participants who underwent randomization and received at least one dose of retatrutide or placebo. Adverse events are listed according to the preferred term in the *Medical Dictionary for Regulatory Activities*, version 28.1. MACE denotes major adverse cardiovascular event.
† Ketoacidosis included events due to inadequate nutritional intake, as well as other types of metabolic acidosis and ketosis.

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SAFETY

In both trials, the most frequent adverse events were nausea, diarrhea, and constipation among the participants treated with retatrutide (Table S12). The majority of gastrointestinal events were mild to moderate in severity and typically occurred during the dose-escalation period (Fig. S12). In TRIUMPH-4, discontinuation of retatrutide or placebo due to gastrointestinal adverse events occurred in 9 of 147 participants (6.1%) in the 9-mg retatrutide group and in 12 of 148 participants (8.1%) in the 12-mg group, as compared with 2 of 149 (1.3%) in the placebo group; in TRIUMPH-1-OA, discontinuation due to gastrointestinal adverse events occurred in 2 of 143 participants (1.4%) in the 4-mg group, 6 of 143 participants (4.2%) in the 9-mg group, and 8 of 144 participants (5.6%) in the 12-mg group, as compared with no participants in the placebo group (Table 4).

A serious adverse event was reported in 14 participants (9.5%) in the 9-mg group and in 16 participants (10.8%) in the 12-mg group in TRIUMPH-4 and in 6 participants (4.2%) in the 4-mg group, in 14 participants (9.8%) in the 9-mg group, and in 21 participants (14.6%) in the 12-mg group in TRIUMPH-1-OA (Table 4 and Table S13). In TRIUMPH-4, one death occurred in each of the retatrutide groups; these deaths were assessed by the investigators as being unrelated to the trial treatment. No deaths occurred in TRIUMPH-1-OA (Table S14).

DISCUSSION

In both TRIUMPH-4 and TRIUMPH-1-OA, retatrutide led to significantly greater reductions in WOMAC pain scores than placebo in patients with obesity and knee osteoarthritis. In both trials, the changes in WOMAC pain scores with retatrutide as calculated with the hybrid-treatment estimand (with Cohen's d effect sizes ranging from 0.55 to 0.79) represent a possible improvement relative to the effects typically achieved with existing approved interventions, which provide symptom control alone. Although direct comparisons are not feasible owing to differences in the type of study and analyses, previous studies assessing pain reduction showed Cohen's d effect sizes of 0.37 for maximum-dose ibuprofen and 0.31 for maximum-dose tramadol as compared with oral placebo,[17] 0.61 for intraarticular glucocorticoids as compared with oral placebo,[18,19] and 0.50 for semaglutide as compared with placebo on the basis of the WOMAC pain score.[10]

Weight-reduction interventions have generally been associated with reductions in osteoarthritis-related pain, with previous studies suggesting that clinical benefits are typically observed with body-weight reductions of approximately 5 to 10%; greater weight reduction can lead to further reductions in pain and improvements in physical function.[7] Nonpharmacologic treatments such as low-calorie diets have been shown to reduce knee pain by 34.4%.[20] A trial of liraglutide (at a dose of 3 mg) did not show a clear benefit for knee osteoarthritis pain with weight reduction of approximately 4%.[21] In a trial evaluating the GLP-1 receptor agonist semaglutide (2.4 mg), 65.2% of treated participants had a reduction of at least 50% in the WOMAC pain score from baseline to week 68, with a mean weight reduction of 13.7% in the semaglutide group.[10] A network meta-analysis of bariatric surgery showed a 62.7% reduction in knee pain with a weight reduction of 28%.[20] The findings from these studies reinforce the association between reduction in body weight and reduction in the symptoms of knee osteoarthritis.

Patients with a BMI of at least 35 have been reported to have more coexisting conditions and greater challenges related to osteoarthritis treatment than those with lower BMIs.[3,22] Such patients may be denied surgical care for osteoarthritis or have greater postsurgical complications from joint-replacement surgery.[22] In both TRIUMPH-4 and TRIUMPH-1-OA, participants with a baseline BMI of 35 or higher had significant reductions in the WOMAC pain score, improvements in physical function, and reductions in body weight.

Weight reduction is linked to a reduction in the risk of cardiovascular disease and other metabolic conditions, along with decreased risk of the onset and progression of osteoarthritis.[23] The severity of osteoarthritis-related disability has been associated with significant increases in the risk of death and serious cardiovascular events.[24] In the overall TRIUMPH-1 population (2339 participants), which included the TRIUMPH-1-OA participants, treatment with retatrutide improved measures of cardiometabolic health, including systolic blood pressure and levels of triglycerides, non–high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, and fasting insulin.[12]

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The cardiometabolic findings from TRIUMPH-4 and TRIUMPH-1-OA were consistent with the overall TRIUMPH-1 results.

The safety profile of retatrutide was generally similar to those in phase 2 trials of retatrutide and to those of other GLP-1 and glucose-dependent insulinotropic polypeptide–GLP-1 receptor agonists. Discontinuation due to adverse events occurred in 2.8 to 18.2% of the participants who received retatrutide and in 4.0 to 6.2% of those who received placebo. The most frequent adverse events were gastrointestinal, which were mostly mild to moderate in severity, occurred primarily during dose escalation, and were more common with retatrutide at doses of 9 mg and 12 mg than with 4 mg of retatrutide or placebo. Dysesthesia events occurred in 6.3 to 20.9% of the participants who received retatrutide and in 0.7% of those who received placebo, were generally mild, and rarely led to discontinuation of retatrutide or placebo.

The mechanisms responsible for pain reduction with GLP-1 treatment are incompletely understood. Weight reduction leads to decreased loading on the knee, and the level of load reduction appears to be a multiple of the actual weight lost.[6] Some data suggest that reduction in adipose tissue may decrease systemic inflammatory mediators, findings that hint that GLP-1 receptor agonists may provide antiinflammatory activity.[25,26] Further study is necessary to determine the extent to which these or other mechanisms may be involved, directly or indirectly, in observed pain reduction. Questions remain about whether treatment with retatrutide could potentially alter the progression of osteoarthritis and reduce the occurrence of total joint replacement.

These trials have several limitations. The earliest assessment of the WOMAC pain and physical function scores after the baseline assessment occurred at week 16, which limits knowledge about the onset of a treatment effect. Inflammatory biomarkers, such as high-sensitivity C-reactive protein, were assessed only at baseline and at trial completion, timing that precludes evaluation of temporal changes. The two trials were limited by design to persons with overweight or obesity and osteoarthritis; therefore, effects on a broader population of persons with osteoarthritis are unknown. Our trials were not designed to assess avoidance of knee replacement, osteoarthritis progression, or disease modification.

In these trials, treatment with retatrutide at a dose of 4, 9, or 12 mg led to significantly greater reductions in the WOMAC pain score and in body weight than placebo among participants with knee osteoarthritis and obesity.

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AUTHOR INFORMATION

Thomas J. Schnitzer, M.D., Ph.D.,[1] David J. Hunter, M.B., B.S., Ph.D.,[2] Philip G. Conaghan, M.B., B.S., Ph.D.,[3,4] Arya M. Sharma, M.D., D.Sc.,[5] Sue D. Pedersen, M.D.,[6,7] Kaiyi Chen, Ph.D.,[8] So Young Park, Ph.D.,[8] Nune Makarova, M.D., M.P.H.,[8] Kathryn Giblin, M.D.,[8] and Tammy Forrester, M.S.[8]

[1] Departments of Physical Medicine and Rehabilitation, Anesthesiology, and Internal Medicine and Rheumatology, Northwestern University Feinberg School of Medicine, Chicago; [2] Department of Rheumatology, Royal North Shore Hospital and Sydney Musculoskeletal Health, Faculty of Medicine and Health, Kolling Institute, University of Sydney, Sydney; [3] Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, United Kingdom; [4] National Institute for Health and Care Research (NIHR) Leeds Biomedical Research Centre, Leeds, United Kingdom; [5] Department of Medicine, University of Alberta, Edmonton, Canada; [6] C-ENDO Diabetes and Endocrinology Clinic, Calgary, AB, Canada; [7] University of Calgary, Calgary, AB, Canada; [8] Eli Lilly, Indianapolis.

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