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Retatrutide Once Weekly in Adults with Knee Osteoarthritis Pain and Obesity

Thomas J. Schnitzer, MD, PhD[1], David J. Hunter, MBBS, PhD, FRACP[2], Philip G. Conaghan, MBBS, PhD, FRACP, FRCP[3], Arya M. Sharma, MD, DSc (hon), FRCPC[4], Sue D. Pedersen, MD, FRCPC, DABOM[5], Kaiyi Chen[6], So Young Park[6], Nune Makarova[6], Kathryn Giblin[6], Tammy Forrester[6] for the TRIUMPH-4 and TRIUMPH-1-OA Investigators

[1]Departments of Physical Medicine and Rehabilitation, Internal Medicine/Rheumatology and Anesthesiology, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA

[2]Department of Rheumatology, Royal North Shore Hospital and Sydney Musculoskeletal Health, Faculty of Medicine and Health, Kolling Institute, University of Sydney, Sydney, Australia

[3]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, & NIHR Leeds Biomedical Research Centre, Leeds, UK

[4]Department of Medicine, University of Alberta, Edmonton, Alberta, Canada

[5]C-ENDO Diabetes and Endocrinology Clinic, and University of Calgary, Calgary, Canada

[6]Eli Lilly and Company, Indianapolis, Indiana USA

Corresponding author: Thomas Schnitzer MD, PhD

Northwestern University Feinberg School of Medicine - Physical Medicine and Rehabilitation
710 N Lake Shore Drive, Chicago, Illinois 60611
United States

tjs@northwestern.edu

The TRIUMPH-4 and TRIUMPH-1-OA investigators are listed in the Supplementary Appendix.

Abstract

Background: The efficacy and safety of retatrutide, an investigational triple agonist of glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors for painful knee osteoarthritis (OA) in people with obesity are unknown.

Methods: Two phase 3 trials enrolled adults with painful knee OA and BMI ≥27 kg/m^2 without diabetes. Participants were randomly assigned to once-weekly subcutaneous retatrutide (TRIUMPH-4, N=445: 9-mg, 12-mg; TRIUMPH-1-OA, N=574: 4-mg, 9-mg, 12-mg) or placebo. TRIUMPH-4 co-primary endpoints were change in WOMAC pain score (range, 0-10, higher=more pain) and percent change in bodyweight at week 68; TRIUMPH-1-OA primary endpoint was change in WOMAC pain score at week 80. For non-pain-related endpoints, intercurrent events were handled by a treatment policy strategy (treatment-regimen estimand [TRE]). For pain-related outcomes, a hybrid-treatment estimand was applied with a hypothetical strategy for participants with intercurrent events suggesting treatment failure and treatment policy strategy elsewhere. We also report an intention-to-treat estimand that applied a treatment policy strategy for all intercurrent events (hereafter ITT).

Results: In TRIUMPH-4 (68 weeks), mean change in WOMAC pain (hybrid-treatment estimand) was -3.96 (9-mg), -3.74 (12-mg) and -2.12 (placebo) (difference vs. placebo [95% CI] -1.83 [-2.37,-1.30], -1.61 [-2.16,-1.07], respectively); differences by ITT estimand: -1.70 [-2.19,-1.22]; -1.38 [-1.91,-0.85]) (P <0.001). Mean percent change in bodyweight was -20.0% (9-mg), -23.7% (12-mg) and -4.6% (placebo) (differences: -15.4 [-18.7,-12.1]; -19.2 [-22.4,-15.9]) (P <0.001). In TRIUMPH-1-OA (80 weeks), mean change in WOMAC pain (hybrid-treatment estimand) was -3.22 (4-mg), -3.48 (9-mg), -3.64 (12-mg) and -1.87 (placebo) (differences: -1.35 [-1.92,-0.78]; -1.61 [-2.20,-1.02]; -1.77 [-2.34,-1.20]); and differences by ITT estimand: -0.96 [-1.61,-0.30]; -1.41 [-2.07,-0.75]; -1.64 [-2.26,-1.02]) (P≤0.005). In both trials, serious adverse events (AEs) were more common with retatrutide than placebo, and gastrointestinal AEs were most common.

Conclusions: In participants with painful knee OA and obesity, retatrutide treatment resulted in significant reductions in both WOMAC pain scores and bodyweight.

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Osteoarthritis (OA), a progressive joint disease, often includes pain that limits quality of life and confers substantial socioeconomic burdens on patients, healthcare systems, and society.[1-3] Obesity is a risk factor in both OA onset and progression.[1-3] Excess bodyweight increases mechanical loading on weight-bearing joints; further, 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 an important component of knee OA management; each pound of bodyweight lost is associated with an approximately 4-fold load reduction across the knee.[6] Biomechanical and clinical benefits increase with weight loss; progressively greater weight reduction is associated with lower maximum knee compressive forces and greater symptom improvements.[7] Clinical guidelines include weight reduction alongside exercise, pharmacologic therapies such as nonsteroidal anti-inflammatory agents, intra-articular injections, and surgical interventions.[8,9]

Current pharmacologic therapies may provide modest efficacy but limited tolerability and safety. A study of semaglutide suggested improved knee OA pain,[10] highlighting the possibility that additional obesity therapeutics might address both excess bodyweight and knee OA symptoms.

Retatrutide is an investigational triple-receptor agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide-1 (GLP-1), and glucagon receptors. In phase 2 clinical trials in patients with obesity, retatrutide demonstrated average weight reductions from 8.7%–24.2%, versus 2.1% with placebo (percentage point difference: -6.6 to -22.1), at 48 weeks.[11] The two trials presented here, one published in part previously,[12] evaluated the efficacy, tolerability, and safety of once-weekly injectable retatrutide in adults with painful knee OA and obesity.

Methods

Study Design

These two phase 3, multicenter, randomized, parallel-arm, double-blind clinical trials were conducted in North America, Europe and Australia-- TRIUMPH-4, in 49 centers and 5 countries; TRIUMPH-1-OA in 66 centers and 7 countries (**Table S1**). We report these studies together to demonstrate replication across independent populations. The study design and primary outcome results for TRIUMPH-1-OA were previously reported;[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 participants. Refer to the Trial Oversight and Author Responsibilities section of the **Supplementary Appendix** for details.

Participants

Both trials included adults (≥18 years of age) with a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) Pain subscale score (numeric rating scale [NRS] 0 to 10 [higher number=more pain], Version 3.1) of ≥4 and ≤9 (moderate-to-severe OA pain) in the index knee, with ongoing pain (>12 weeks prior to screening and presence of index knee pain for >15 days over the previous month), American College of Rheumatology radiographic criteria for evidence of knee OA,[13] and at least one self-reported unsuccessful dietary effort to lose bodyweight. Both trials enrolled participants with obesity, defined as BMI ≥27 kg/m^2 with at least one obesity-related complication. Key exclusion criteria for both trials were weight change >5 kg within 90 days prior to screening, any conditions that could confound obesity or OA knee pain assessments, and diabetes. Enrollment of female participants was capped at approximately 70% to ensure adequate representation of male participants. Approximately 80% of participants

in both trials were patients with BMI >35 kg/m^2. See complete eligibility criteria for both trials in the **Supplementary Appendix**

Trial Procedures

TRIUMPH-4 participants were randomly assigned 1:1:1 to receive subcutaneous retatrutide (9-mg or 12-mg) or placebo once weekly for 68 weeks. TRIUMPH-1-OA participants were randomly assigned 1:1:1:1 to receive either subcutaneous retatrutide (4-mg, 9-mg, or 12-mg) or placebo each week for 80 weeks. Randomization in both studies was stratified by baseline WOMAC pain severity (severe [≥7], moderate [<7]), prediabetes status, and sex. Additional study details are available in the **Supplementary Appendix**.

Retatrutide was initiated at 2-mg once weekly (or matching placebo); dose escalations occurred every 4 weeks until reaching the targeted maintenance dose (**Fig. S1**). Dose reductions were permitted for managing gastrointestinal adverse events, inadequate oral intake, excessive weight loss, or reaching BMI ≤22 kg/m^2.

Endpoints and Assessments

In TRIUMPH-4, co-primary endpoints were change in WOMAC Pain subscale score (Version 3.1, NRS 0–10) and percent change in bodyweight from baseline to week 68. Key secondary endpoints, also controlled for type 1 error, included bodyweight reductions of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25%, change from baseline in WOMAC Physical Function subscale scores at Weeks 36 and 68, and change in WOMAC Pain scores at Week 36. In TRIUMPH-1-OA, the primary endpoint was the change in WOMAC Pain scores from baseline to Week 80. Key secondary endpoints, also controlled for type 1 error, included percent change in bodyweight from baseline at Week 80, change from baseline in WOMAC Physical Function scores at Weeks 36, 68, and 80, and change in WOMAC Pain scores at Weeks 36 and 68. In both studies, for

participants with a baseline BMI ≥35 kg/m^2, change in WOMAC Pain scores and percent change in bodyweight were chosen as key secondary endpoints, controlled for type 1 error.

Key secondary analyses of pooled data from TRIUMPH-4 and TRIUMPH-1-OA, controlled for type 1 error, included achievement of ≥50% reduction in WOMAC Physical Function and WOMAC Pain scores at Week 68.

Additional secondary endpoints in both trials not controlled for type 1 error can be found in the respective Statistical Analysis Plans in the **Supplementary Appendix**.

Safety assessments included treatment-emergent adverse events, serious adverse events, and discontinuation of retatrutide.

Statistical Analysis

For the TRIUMPH-4 co-primary endpoints, a planned sample size of 435 participants (n=145/group) provided >90% power to demonstrate superiority of retatrutide 9-mg and 12-mg versus placebo. Similarly, a planned sample size of 560 participants (n=140/group) provided >90% power for the TRIUMPH-1-OA primary endpoint.

For both trials, efficacy analyses included all randomized participants. For non-pain-related endpoints, two estimands were predefined- the treatment regimen estimand (TRE), 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 (EE), which estimates a treatment effect on the assumption that all the participants had received retatrutide or placebo as intended by the protocol and did not have intercurrent events, such as initiation of prohibited weight-management treatments (consistent with the hypothetical strategy per ICH E9 (R1) addendum).

For endpoints related to knee OA presented in this report (WOMAC pain and physical function subscale scores, and Average Pain Intensity [API]-NRS score), two estimands were prespecified: 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 a hypothetical efficacy estimand to estimate a treatment effect on the assumption that all the participants had received retatrutide or placebo for 68 or 80 weeks as intended and did not have intercurrent events. We also report an intention-to-treat (ITT) estimand that applies a treatment-policy strategy to all related intercurrent events.

Graphical testing for multiple comparisons was used within each trial, controlling for family-wise error rate at a two-sided significance level of 0.05 (**Tables S2-4, Figs. S2-4)**. Pre-specified pooled key secondary endpoints were controlled for a two-sided submission-wise error rate[14,15] (the probability of a false positive claim on any endpoint, considering that a claim on any endpoint should be based on significant results from associated hypotheses across both trials) of no more than 0.05. Results for exploratory endpoints or 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 (ES) was calculated by the treatment difference divided by the pooled standard deviation (SD), where the pooled SD represents the combined variability of the two treatment groups. Additional statistical methods appear in the **Supplementary Appendix**.

Results

Study Participants

In TRIUMPH-4, between August 1, 2023 and November 14, 2025, 1394 participants were screened; 445 were enrolled and randomized to study intervention. In TRIUMPH-1-OA, between July 10, 2023 and April 30, 2026, 1729 participants were screened, 574 were enrolled and

randomized. Representativeness of trial participants are included in **Table S5**. Baseline demographics and clinical characteristics of participants in both trials were similar in the treatment groups (**Table 1, Table S1**). In TRIUMPH-4, 380/445 (85.4%) completed the study and 320/445 (71.9%) completed treatment (9-mg: 112 [75.7%]; 12-mg: 105 [70.9%]; placebo: 103 [69.1%]); and in TRIUMPH-1-OA, 479/574 (83.4%) completed the study, and 433/574 (75.4%) completed treatment (4-mg: 123 [86.0%]; 9-mg: 114 [79.7%]; 12-mg: 106 [73.6%]; placebo: 90 [62.5%]) (**Fig. S5)**. Treatment discontinuations due to adverse events were 18/148 (12.2%, 9-mg), 27/148 (18.2%, 12-mg) and 6/149 (4.0%, placebo) in TRIUMPH-4, and 4/143 (2.8%, 4-mg), 12/143 (8.4%, 9-mg), 22/144 (15.3%, 12-mg), and 9/144 (6.3%, placebo) in TRIUMPH-1-OA. Of these, approximately one-half in TRIUMPH-4 and one-third in TRIUMPH-1-OA were considered due to gastrointestinal events (**Table S6)**. The percentage of participants who reached their assigned dose and received their assigned dose at study end, respectively, were TRIUMPH-4: 9-mg: 136/147 (92.5%), 112/147 (76.2%); 12-mg: 133/148 (89.9%), 99/148 (66.9%); TRIUMPH-1-OA: 4-mg: 141/143 (98.6%), 134/143 (93.7%); 9-mg: 135/143 (94.4%), 107/143 (74.8%); 12-mg: 128/144 (88.9%), 95/144 (66.0%).

Efficacy

Primary Endpoints

In TRIUMPH-4, for the hybrid-treatment estimand, the mean change in WOMAC pain scores from baseline to week 68 was -3.96 with 9-mg, -3.74 with 12-mg retatrutide, and -2.12 with placebo (estimated treatment difference [ETD] vs. placebo [95% CI]: 9-mg: -1.83 [-2.37,-1.30]; 12-mg: -1.61 [-2.16,-1.07], all p<0.001**; Table 2, Fig. 1**). These changes correspond to a Cohen's d ES of 0.79 and 0.68, respectively. For the ITT estimand, the mean change in WOMAC pain scores from baseline to week 68 was -4.30 (9-mg), -3.97 (12-mg) and -2.59 (placebo) (ETD vs placebo [95% CI]: 9-mg: -1.70 [-2.19,-1.22]; 12-mg: -1.38 [-1.91,-0.85]; all p<0.001; **Table S7**). For the TRE, the mean percent change in bodyweight from baseline to

week 68 was -20.0% (9-mg) and -23.7% (12-mg) and -4.6% (placebo) (ETD vs. placebo [95% CI], percentage point, 9-mg: -15.4 [-18.7,-12.1]; 12-mg: -19.2 [-22.4,-15.9]; all p<0.001; **Table 2, Fig. 1**). Similar results were observed with the EE (hypothetical estimand) (**Table S8, Fig. 1**).

In TRIUMPH-1-OA, for the hybrid-treatment estimand, mean change in WOMAC pain from baseline to week 80 was -3.22 (4-mg) [key secondary endpoint], -3.48 (9-mg), and -3.64 (12-mg) and -1.87 (placebo) (ETD vs. placebo [95% CI]: 4-mg: -1.35 [-1.92,-0.78]; 9-mg: -1.61 [-2.20,-1.02]; 12-mg: -1.77 [-2.34,-1.20]; all p<0.001; **Table 2, Fig. 1**), corresponding to Cohen's d ES of 0.55, 0.63, and 0.72, respectively. For the ITT estimand, mean change in WOMAC pain from baseline to week 80 was -3.41 (4-mg) [key secondary endpoint], -3.86 (9-mg), -4.10 (12-mg) and -2.46 (placebo) (ETD vs. placebo [95% CI]: 4-mg: -0.96 [-1.61,-0.30], p=0.005; 9-mg: -1.41 [-2.07,-0.75], p<0.001; 12-mg: -1.64 [-2.26,-1.02], p<0.001; **Table S7**). Similar results were observed with the EE (**Table S8, Fig. 1**).

Key Secondary Endpoints

In TRIUMPH-4 and TRIUMPH-1-OA, for the hybrid-treatment estimand, the mean change from baseline in the WOMAC Physical Function score was significantly greater in participants treated with retatrutide (**Table 2, Fig. 2**). Changes in WOMAC pain scores also significantly improved at week 36 (**Table 2**). Similar results were observed with the ITT estimand (**Table S7**) and EE (**Table S8, Fig. S6**).

Similar findings were also observed in participants with a baseline BMI ≥35 kg/m^2 for the hybrid-treatment estimand (**Table 2**) and EE (**Table S8**).

At week 68 in TRIUMPH-4, for the TRE, a significantly greater proportion of participants treated with 9-mg or 12-mg retatrutide achieved bodyweight reduction targets of ≥5%, ≥10%, ≥15%, ≥20%, and ≥25% (**Table 2**). The same was observed in the EE (**Table S8, Fig. S7).** In TRIUMPH-1-OA, for the TRE, mean percent change in bodyweight from baseline to week 80

was -17.5% (4-mg), -22.9% (9-mg), -24.8% (12-mg) and -4.3% (placebo) (ETD vs. placebo, percentage point, 4-mg: -13.2 [-16.1,-10.4]; 9-mg: -18.6 [-21.4,-15.8]; 12-mg: -20.6 [-23.6,-17.5]; all p<0.001) (**Table 2, Fig. 1**).

Pooled Key Secondary Endpoints

In pooled analyses at Week 68, for the hybrid-treatment estimand, 63.2% to 69.6% of retatrutide and 37.8% of placebo participants achieved a ≥50% reduction in WOMAC Pain, and 63.5% to 64.6% and 33.1%, respectively, for Physical Function (**Table 2, Table S9, Fig. S8**). Results for the ITT estimand were 66.8% to 75.2% of retatrutide and 44.7% of placebo participants for WOMAC Pain, and 69.9% to 70.7% of retatrutide and 37.7% of placebo participants for WOMAC Physical Function (**Table S10**).

Additional Secondary Endpoints

In TRIUMPH-4 and TRIUMPH-1-OA, daily Average Pain Intensity is presented using the hybrid-treatment estimand, EE and ITT estimand for retatrutide and placebo (**Fig. S9)**. Pain medication use reported in the daily diary decreased over time in all treatment groups (**Fig. S10**). Cardiometabolic data from both trials, including blood pressure, percent change in lipid parameters, hsCRP, and fasting insulin using the TRE and EE, are found in **Table S11 and Fig. S11**.

Adverse Events and Tolerability

In TRIUMPH-4 and TRIUMPH-1-OA, the most frequent adverse events were nausea, diarrhea, and constipation in retatrutide-treated participants (**Table S12**). The majority of gastrointestinal events were mild-to-moderate in severity and typically occurred during the dose escalation period (**Fig. S12**). Treatment discontinuation due to gastrointestinal adverse events occurred in 9/147 (6.1%) to 12/148 (8.1%) of participants receiving retatrutide and 2/149 (1.3%) receiving

placebo in TRIUMPH-4, and 2/143 (1.4%) to 8/144 (5.6%) receiving retatrutide and 0/144 (0.0%) receiving placebo in TRIUMPH-1-OA (**Table 3)**.

Fourteen participants receiving 9-mg and 16 receiving 12-mg retatrutide in TRIUMPH-4 and 6 participants receiving 4-mg, 14 receiving 9-mg, and 21 receiving 12-mg retatrutide in TRIUMPH-1-OA reported a serious adverse event (**Table 3 and Table S13**). In TRIUMPH-4, one death occurred in retatrutide 9-mg and 12-mg groups each; these deaths were assessed by investigators as unrelated to study treatment. No deaths occurred in TRIUMPH-1-OA (**Table S14**).

Discussion

In both trials presented here, retatrutide significantly improved WOMAC pain scores compared with placebo in patients with obesity and knee OA.

In both trials, in analyses using the hybrid treatment estimand, the changes in WOMAC pain scores with retatrutide (Cohen's d effect size range 0.55 to 0.79) represent a possible improvement relative to that typically achieved with existing approved interventions, which provide symptom control alone. Though direct comparisons are not feasible owing to different study types and varied analyses, previous studies reported pain-reduction Cohen's d effect sizes of 0.37 for maximum-dose ibuprofen, 0.31 for maximum-dose tramadol,[16] 0.61 for intra-articular glucocorticoids versus oral placebo,[17,18] and 0.50 for semaglutide versus placebo based on improvement in WOMAC pain score.[10]

Weight reduction interventions have generally been associated with improvements in OA-related pain, with prior studies suggesting that clinical benefits are typically observed with bodyweight reductions of approximately 5–10%; greater weight reduction can lead to further reductions in pain and improvement in physical function.[7] Non-pharmacologic treatment such as low-calorie diets have demonstrated a 34.4% reduction in knee pain.[19] A study with liraglutide

(3-mg) did not show a clear benefit for knee OA pain with weight reduction of approximately 4%.[20] A study report of GLP-1 receptor agonist, semaglutide (2.4-mg), found that 65.2% of treated participants achieved ≥50% reduction in WOMAC pain score from baseline to Week 68 with weight reduction of 13.7%.[10] A network meta-analysis study of bariatric surgery reported a 62.7% reduction in knee pain with weight reduction of 28%.[19] The findings from these studies reinforce the association between weight reduction and improvement in knee OA symptoms.

Patients with a BMI ≥35 kg/m^2 have reported greater multi-morbidity and challenges related to OA treatment.[3,21] Such patients may be denied surgical care for OA or experience greater post-surgical complications from joint replacement surgery.[21] In both TRIUMPH-4 and TRIUMPH-1-OA, participants with a baseline BMI ≥35 kg/m^2 demonstrated significant improvements in WOMAC pain score, physical function, and weight reduction.

Weight reduction is linked to a reduction in cardiovascular risk and other metabolic conditions along with decreased risk of initiation and progression of OA.[22] The severity of OA disability has been associated with significant increases in all-cause mortality and serious CVD events.[23] In the overall TRIUMPH-1 population (N=2339) which included TRIUMPH-1-OA participants, retatrutide treatment improved cardiometabolic parameters, including triglycerides, non-HDL cholesterol, systolic blood pressure, hsCRP, and fasting insulin.[12] The cardiometabolic findings from the two OA studies were consistent with the TRIUMPH-1 results.

Safety and tolerability of retatrutide were generally similar to phase 2 results with retatrutide and generally similar to those with other GLP-1 and GIP/GLP-1 receptor agonists. Treatment discontinuation due to adverse events ranged from 2.8%–18.2% with retatrutide and 4.0%–6.2% with placebo. The most frequent adverse events were gastrointestinal, mostly mild-to-moderate in severity, and primarily occurred during dose escalation and more commonly with retatrutide 9-mg and 12-mg. Dysesthesia events occurred in 6.3%–20.9% with retatrutide and 0.7% with placebo, were generally mild, and rarely led to treatment discontinuation.

The mechanisms responsible for pain reduction with GLP-1 treatment are incompletely understood. Weight reduction leads to decreased loading of the knee and appears to be a multiple of the actual weight lost.[6] Some data suggest that adipose tissue reduction may decrease systemic inflammatory mediators hinting that GLP-1 receptor agonists may provide anti-inflammatory activity.[24,25] Further study is necessary to determine the extent to which these or other mechanisms might be involved, directly or indirectly, in observed pain reduction. Questions remain whether treatment with retatrutide could potentially alter the progression of OA and may reduce the need for total joint replacement.

These two trials have several limitations. The earliest assessment of the WOMAC pain and physical function was at Week 16, limiting knowledge of treatment effect onset. Inflammatory biomarkers, such as hsCRP, were assessed only at baseline and trial completion, precluding evaluation of temporal changes. The two studies in this present report were limited by design to people with overweight or obesity and OA; therefore, effects on a broader OA population are unknown. Our trials were not designed to assess avoidance of knee replacement, OA progression, or disease modification.

In conclusion, these two studies demonstrated that patients with knee OA and obesity treated with retatrutide 4-mg, 9-mg, and 12mg had improved WOMAC pain scores and reduced bodyweight.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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Meeting Presentation

Part of the data from this study will be presented at the American College of Rheumatology; November 6-11, 2026.

References

1. Chen L, Zheng JJY, Li G, et al. Pathogenesis and clinical management of obesity-related knee osteoarthritis: Impact of mechanical loading. J Orthop Translat 2020;24:66-75. (In eng). DOI: 10.1016/j.jot.2020.05.001.
2. Duong V, Abdel Shaheed C, Ferreira ML, et al. Risk factors for the development of knee osteoarthritis across the lifespan: A systematic review and meta-analysis. Osteoarthritis Cartilage 2025;33(10):1162-1179. (In eng). DOI: 10.1016/j.joca.2025.03.003.
3. Raud B, Gay C, Guiguet-Auclair C, et al. Level of obesity is directly associated with the clinical and functional consequences of knee osteoarthritis. Scientific Reports 2020;10(1):3601. DOI: 10.1038/s41598-020-60587-1.
4. Mocanu V, Timofte DV, Zară-Dănceanu CM, Labusca L. Obesity, Metabolic Syndrome, and Osteoarthritis Require Integrative Understanding and Management. Biomedicines 2024;12(6) (In eng). DOI: 10.3390/biomedicines12061262.
5. Soták M, Clark M, Suur BE, Börgeson E. Inflammation and resolution in obesity. Nat Rev Endocrinol 2025;21(1):45-61. (In eng). DOI: 10.1038/s41574-024-01047-y.
6. Messier, S.P., Gutekunst, D.J., Davis, C. and DeVita, P. Weight loss reduces knee-joint loads in overweight and obese older adults with knee osteoarthritis. Arthritis & Rheumatism 2005, 52: 2026-2032. DOI: 10.1002/art.21139.
7. Messier SP, Resnik AE, Beavers DP, et al. Intentional Weight Loss in Overweight and Obese Patients With Knee Osteoarthritis: Is More Better? Arthritis Care Res (Hoboken) 2018;70(11):1569-1575. (In eng). DOI: 10.1002/acr.23608.
8. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27(11):1578-1589. (In eng). DOI: 10.1016/j.joca.2019.06.011.
9. Brophy RH, Fillingham YA. AAOS Clinical Practice Guideline Summary: Management of Osteoarthritis of the Knee (Nonarthroplasty), Third Edition. J Am Acad Orthop Surg 2022;30(9):e721-e729. (In eng). DOI: 10.5435/jaaos-d-21-01233.
10. Bliddal H, Bays H, Czernichow S, et al. Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. N Engl J Med 2024;391(17):1573-1583. (In eng). DOI: 10.1056/NEJMoa2403664.
11. Jastreboff AM, Kaplan LM, Frías JP, et al. Triple-Hormone-Receptor Agonist Retatrutide for Obesity - A Phase 2 Trial. N Engl J Med 2023;389(6):514-526. (In eng). DOI: 10.1056/NEJMoa2301972.
12. Jastreboff AM, Kaplan LM, Davies MJ, et al. Retatrutide, a Triple Hormone Receptor Agonist, for Treatment of Obesity. N Engl J Med. 2026 Sep 29. doi: 10.1056/NEJMoa2604169. Epub ahead of print. PMID: 42814954..
13. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29(8):1039-49. (In eng). DOI: 10.1002/art.1780290816.
14. Bretz F, Xi D. Commentary on “Statistics at FDA: Reflections on the Past Six Years.” Stat Biopharm Res. 2019;11(1), 20–25. https://doi.org/10.1080/19466315.2018.1562369.
15. Vandemeulebroecke M, Häring DA, Hua E, Wei X, Xi D. New strategies for confirmatory testing of secondary hypotheses on combined data from multiple trials. Clin Trials 2024;21(2):171-179. (In eng). DOI: 10.1177/17407745231214382.
16. da Costa BR, Pereira TV, Saadat P, et al. Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid treatment for knee and hip osteoarthritis: network meta-analysis. BMJ 2021;375:n2321. (In eng). DOI: 10.1136/bmj.n2321.

17. Bannuru RR, Schmid CH, Kent DM, Vaysbrot EE, Wong JB, McAlindon TE. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. Ann Intern Med 2015;162(1):46-54. (In eng). DOI: 10.7326/m14-1231.
18. Jüni P, Hari R, Rutjes AWS, Fischer R, Silletta MG, Reichenbach S, da Costa BR. Intra-articular corticosteroid for knee osteoarthritis. Cochrane Database of Systematic Reviews 2015(10). DOI: 10.1002/14651858.CD005328.pub3.
19. Panunzi S, Maltese S, De Gaetano A, Capristo E, Bornstein SR, Mingrone G. Comparative efficacy of different weight loss treatments on knee osteoarthritis: A network meta-analysis. Obes Rev 2021;22(8):e13230. (In eng). DOI: 10.1111/obr.13230.
20. Gudbergsen H, Overgaard A, Henriksen M, et al. Liraglutide after diet-induced weight loss for pain and weight control in knee osteoarthritis: a randomized controlled trial. Am J Clin Nutr 2021;113(2):314-323. (In eng). DOI: 10.1093/ajcn/nqaa328.
21. King LK, March L, Anandacoomarasamy A. Obesity & osteoarthritis. Indian J Med Res 2013;138(2):185-93. (In eng).
22. Nadolsky K, Garvey WT, Agarwal M, et al. American Association of Clinical Endocrinology Consensus Statement: Algorithm for the Evaluation and Treatment of Adults with Obesity/Adiposity-Based Chronic Disease – 2025 Update. Endocrine Practice 2025;31(11):1351-1394. DOI: 10.1016/j.eprac.2025.07.017.
23. Hawker GA, Croxford R, Bierman AS, Harvey PJ, Ravi B, Stanaitis I, Lipscombe LL. All-cause mortality and serious cardiovascular events in people with hip and knee osteoarthritis: a population based cohort study. PLoS One 2014;9(3):e91286. (In eng). DOI: 10.1371/journal.pone.0091286.
24. Phillips CL, Grayson BE. The immune remodel: Weight loss-mediated inflammatory changes to obesity. Exp Biol Med (Maywood) 2020;245(2):109-121. (In eng). DOI: 10.1177/1535370219900185.
25. Lee YS, Jun HS. Anti-Inflammatory Effects of GLP-1-Based Therapies beyond Glucose Control. Mediators Inflamm 2016;2016:3094642. (In eng). DOI: 10.1155/2016/3094642.

Figure 1. Changes from Baseline in WOMAC Pain Subscale Score and Bodyweight

Figure 1. Panel A. TRIUMPH-4: Change in WOMAC Pain Score from baseline to week 68. Panel B. TRIUMPH-1-OA: Change in WOMAC Pain Score from baseline to week 80. Panel C. TRIUMPH-4: Percent change in bodyweight from baseline to week 68. Panel D. TRIUMPH-1-OA: Percent change in bodyweight from baseline to week 80.

Figures display results of three (C-D) or four (A-B) separate analyses combined into one panel. The curves on the left show changes from week 0 to week 68 (TRIUMPH-4) or week 80 (TRIUMPH-1-OA) on the basis of (i) observed means during treatment according to the efficacy estimand data-point set in which data points affected by intercurrent events (ICEs) were excluded from the calculation of observed means. The error bars indicate standard errors. The data points at the right of the curves at week 68 or 80 show (ii) the results of a MBE, with 95% CIs derived from MMRM according to the efficacy estimand (hypothetical, EE) — an analysis for the primary end point of the trial, (iii) a MBE with 95% CIs derived from ANCOVA according to the hybrid-treatment estimand (HYB) for panels A-B or treatment-regimen estimand (TRE) for panels C-D, and (iv) a MBE with 95% CIs derived from ANCOVA according to the intention-to-treat estimand (ITT) for panels A-B. P<0.001 for all comparisons with placebo. Numbers below the graph show the number of participants contributing to each mean.

Abbreviations: CI=confidence interval; EE=efficacy estimand; HYB=hybrid-treatment estimand; ITT=intention-to-treat estimand; MBE=model-based estimate; MMRM=mixed model repeated measures; OA=osteoarthritis; PBO=placebo; RETA=retatrutide; SE=standard error; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

Figure 2. Changes in WOMAC Physical Function Scores from Baseline

Figure 2. Panel A. TRIUMPH-4:

Observed change from baseline in WOMAC Physical Function subscale score from baseline to Week 68. Panel B. TRIUMPH-1-OA: Observed change from baseline in WOMAC Physical Function subscale score from baseline to Week 80.

The curves on the left show changes from week 0 to week 68 (TRIUMPH-4) or week 80 (TRIUMPH-1-OA) on the basis of observed means during treatment according to the efficacy estimand data-point set in which data points affected by intercurrent events were excluded from the calculation of observed means. The error bars indicate standard errors. The data at the right of the curves at Week 68 or 80 show the results of MBE (95% CI) of mean change according to the efficacy estimand (hypothetical; EE), hybrid-treatment estimand (HYB), and intention-to-treat estimand (ITT). Numbers below the graph show the number of participants contributing to each mean. For all treatment comparisons in panels A and B, p<0.001 compared to placebo.

Abbreviations: CI=confidence interval; EE=efficacy estimand; HYB=hybrid-treatment estimand; ITT=intention-to-treat estimand; MBE=model-based estimate; OA=osteoarthritis; PBO=placebo; RETA=retatrutide; SE=standard error; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

Table 1. Baseline Demographics and Clinical Characteristics

	TRIUMPH-4				TRIUMPH-1-OA				
	RETA 9-mg N=148	RETA 12-mg N=148	Placebo N=149	Total N=445	RETA 4-mg N=143	RETA 9-mg N=143	RETA 12-mg N=144	Placebo N=144	Total N=574
Age, years	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, n (%)†	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, n (%)†									
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)
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)
Ethnicity, n (%)†									
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)
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	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)
API-NRS 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, n (%)									
0					0	0	1 (0.7)	0	1 (0.2)
1					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
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, kg/m^2	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)
BMI ≥35 kg/m^2, n (%)	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)

Data presented as mean (standard deviation), unless noted. WOMAC based on NRS 0 to 10; API-NRS based on a scale of 0-10.

Abbreviations: API-NRS=Average Pain Intensity-Numeric Rating Scale; BMI=body mass index; NRS=numeric rating scale; OA=osteoarthritis; RETA=retatrutide; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index.

† Sex, race, and ethnicity were reported by the participants.

Table 2. Primary and Key Secondary Endpoints – Treatment Regimen Estimand (Weight-related) and Hybrid-treatment Estimand (Pain-related)

	TRIUMPH-4			TRIUMPH-1-OA			
	RETA 9-mg N=148	RETA 12-mg N=148	Placebo N=149	RETA 4-mg N=143	RETA 9-mg N=143	RETA 12-mg N=144	Placebo N=144
Primary Endpoints							
Change in WOMAC Pain Score	-3.96 (0.18)	-3.74 (0.18)	-2.12 (0.21)		-3.48 (0.213)	-3.64 (0.197)	-1.87 (0.214)
Treatment comparison (95% CI); p value	-1.83 (-2.37, -1.30); p<.001	-1.61 (-2.16, -1.07); p<.001	--	-	-1.61 (-2.20, -1.02); p<.001	-1.77 (-2.34, -1.20); p<.001	--
Percent Change in Bodyweight	-20.0 (0.9)	-23.7 (1.0)	-4.6 (1.3)				
Treatment comparison (95% CI); p value	-15.4 (-18.7, -12.1); p<.001	-19.2 (-22.4, -15.9); p<.001	--				
Key Secondary Endpoints							
Change in WOMAC Pain Score				-3.22 (0.197)			-1.87 (0.214)
Treatment comparison (95% CI); p value				-1.35 (-1.92, -0.78); p<.001			
Percent Change in Bodyweight[a]				-17.5 (0.99)	-22.9 (1.01)	-24.8 (1.16)	-4.3 (1.04)
Treatment comparison (95% CI); p value				-13.2 (-16.1, -10.4); p<.001	-18.6 (-21.4, -15.8); p<.001	-20.6 (-23.6, -17.5); p<.001	--
Participants achieving bodyweight reduction, %±SE [n/N] [b]							
≥5%	89.9±2.6 [119/131]	95.0±2.1 [127/131]	41.9±4.6 [40/115]				
Risk difference (95% CI)	48.0 (37.5, 58.6); p<.001	53.1 (43.1, 63.2); p<.001	--				
≥10%	81.5±3.3 [109/131]	83.9±3.2 [113/131]	22.5±4.3 [14/115]				
Risk difference (95% CI)	59.0 (48.5, 69.5); p<.001	61.4 (50.6, 72.1); p<.001	--				
≥15%	63.7±4.0 [85/131]	75.6±3.7 [103/131]	15.2±3.9 [8/115]				
Risk difference (95% CI)	48.6 (37.5, 59.7); p<.001	60.4 (49.8, 71.1); p<.001	--				

≥20%	48.5±4.1 [66/131]	65.9±4.1 [91/131]	9.9±3.4 [5/115]				
Risk difference (95% CI)	38.7 (28.1, 49.2); p<.001	56.0 (45.6, 66.5); p<.001	--				
≥25%	33.7±3.8 [47/131]	45.1±4.1 [64/131]	3.1±2.1 [1/115]				
Risk difference (95% CI)	30.7 (22.0, 39.4); p<.001	42.1 (33.2, 51.0); p<.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)
Treatment comparison (95% CI); p value	-1.83 (-2.40, -1.27); p<.001	-1.77 (-2.34, -1.20); p<.001	—	-1.68 (-2.23, -1.12); <.001	-1.89 (-2.49, -1.29); <.001	-1.95 (-2.52, -1.38); <.001	--
Change in the WOMAC Pain score at Week 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)
Treatment comparison (95% CI)	-1.64 (-2.11, -1.17); p<.001	-1.31 (-1.83, -0.79); p<.001	--	-1.28 (-1.79, -0.76); <.001	-1.01 (-1.53, -0.49); <.001	-1.03 (-1.56, -0.49); <.001	--
Change in the WOMAC Pain score at Week 68				-3.11 (0.18)	-3.18 (0.20)	-3.17 (0.20)	-1.72 (0.21)
Treatment comparison (95% CI)				-1.38 (-1.91, -0.85); <.001	-1.46 (-2.02, -0.90); <.001	-1.45 (-2.00, -0.90); <.001	--
Change in the WOMAC Pain score in participants with BMI ≥35 kg/m^2	-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)
Treatment comparison (95% CI)	-2.00 (-2.58, -1.42); p<.001	-1.79 (-2.37, -1.22); p<.001	--	-1.23 (-1.84, -0.62); p<.001	-1.51 (-2.15, -0.88); p<.001	-1.71 (-2.32, -1.09); p<.001	--
Percent change in bodyweight in participants with BMI ≥35 kg/m^2	-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)
Treatment comparison (95% CI)	-18.2 (-22.2, -14.2); p<.001	-22.2 (-26.1, -18.2); p<.001	--	-13.0 (-15.8, -10.2); <.001	-19.3 (-22.2, -16.3); <.001	-21.4 (-24.5, -18.3); <.001	--
Achievement of bodyweight reduction thresholds in participants with BMI ≥35 kg/m^2, %±SE [n/N][b]							
≥5%	93.6±2.2 [106/113]	96.4±1.9 [107/110]	42.3±5.2 [36/94]				
Risk difference (95% CI)	51.3 (40.2, 62.4); p<.001	54.1 (43.2, 65.0); p<.001	--				

≥10%	85.5±3.3 [98/113]	88.4±3.1 [99/110]	21.2±4.5 [12/94]	
Risk difference (95% CI)	64.3 (53.2, 75.4); p<.001	67.2 (56.6, 77.9); p<.001	--	
≥15%	68.1±4.3 [78/113]	81.3±3.7 [92/110]	14.6±4.2 [7/94]	
Risk difference (95% CI)	53.5 (41.7, 65.3); p<.001	66.7 (55.7, 77.7); p<.001	--	
≥20%	53.3±4.6 [62/113]	70.9±4.2 [82/110]	9.5±3.6 [4/94]	
Risk difference (95% CI)	43.9 (32.3, 55.4); p<.001	61.4 (50.4, 72.5); p<.001	--	
≥25%	38.9±4.3 [45/113]	52.3±4.5 [62/110]	3.0±2.0 [1/94]	
Risk difference (95% CI)	35.9 (26.5, 45.3); p<.001	49.3 (39.5, 59.2); p<.001	--	

Pooled (TRIUMPH-4 and TRIUMPH-1-OA) Key Secondary Endpoints at Week 68

	RETA 9-mg N=291	RETA 12-mg N=292	Placebo N=293
Achievement of ≥50% reduction in the WOMAC Pain, %±SE [n/N][b,c]	69.6±2.8 [189/248]	63.2±3.0 [167/236]	37.8±3.0 [86/185]
Treatment comparison (95% CI); p value	31.79 (23.78, 39.81); p<.001	25.45 (17.02, 33.89); p<.001	--
Achievement of ≥50% reduction in the WOMAC Physical Function, %±SE [n/N][b,c]	64.6±2.9 [176/246]	63.5±3.0 [168/235]	33.1±3.0 [73/183]
Treatment comparison (95% CI); p value	31.41 (23.28, 39.55); p<.001	30.34 (21.91, 38.78); p<.001	--

Data presented as model-based estimate (standard error) unless specified. [a]Key secondary endpoint in TRIUMPH-1-OA. [b]Data are model-based estimates and standard errors derived from the 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 for non-pain-related endpoints and from the hybrid-treatment estimand data points set for pain-related endpoints. . [c]Endpoints are tested under SWER control based on pooled analysis of studies TRIUMPH-4 and TRIUMPH-1-OA. TRIUMPH-4 outcomes at Week 68 unless specified. TRIUMPH-1-OA outcomes at Week 80 unless specified. WOMAC based on NRS 0 to 10 (higher number=more pain). The widths of confidence intervals have not been adjusted for multiplicity and cannot be used to infer treatment effects. For the pain-related endpoints presented here (WOMAC pain and physical function scores), a hybrid-treatment estimand

was applied, with a hypothetical strategy used for imputation of values related to intercurrent events associated with treatment failure and treatment policy strategy elsewhere.

Abbreviations: BMI=body mass index; CI=confidence interval; NRS=numeric rating scale; OA=osteoarthritis; RETA=retatrutide; SWER=submission wise error rate; WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3. Adverse Events

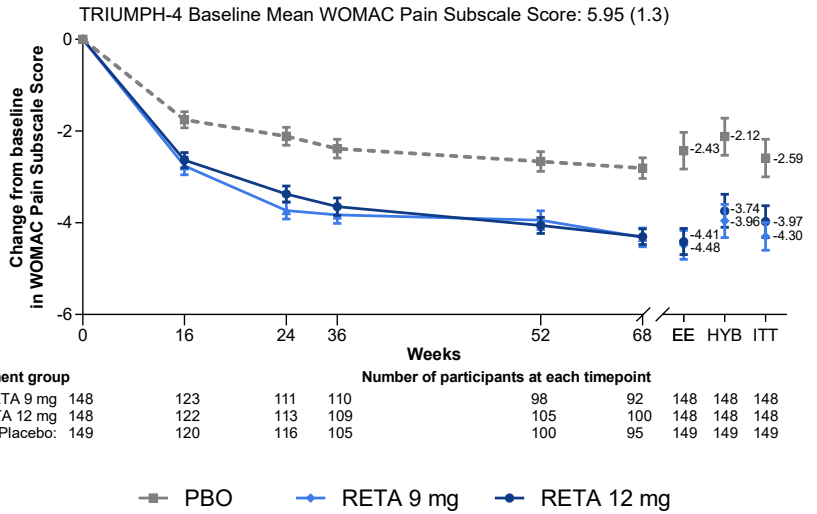
	TRIUMPH-4				TRIUMPH-1-OA				
	RETA 9-mg N=147	**RETA 12-mg N=148**	**Placebo N=149**	**Total N=444**	**RETA 4-mg N=143**	**RETA 9-mg N=143**	**RETA 12-mg N=144**	**Placebo N=144**	**Total N=574**
Any adverse event emerging during treatment	125 (85.0)	127 (85.8)	110 (73.8)	362 (81.5)	130 (90.9)	132 (92.3)	136 (94.4)	125 (86.8)	523 (91.1)
Deaths	1 (0.7)	1 (0.7)	0	2 (0.5)	0	0	0	0	0
Serious adverse events	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 events leading to discontinuation of study treatment	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 disorders leading to discontinuation of study treatment	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)
Treatment emergent 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 Reactions	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 disorders	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)
Malignancies	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 and serious Arrhythmias and cardiac conduction disorders	3 (2.0)	2 (1.4)	0	5 (1.1)	0	0	2 (1.4)	2 (1.4)	4 (0.7)
Severe and serious gallbladder and biliary tract disorders	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 and serious Malnutrition	1 (0.7)	1 (0.7)	0	2 (0.5)	1 (0.7)	1 (0.7)	0	0	2 (0.3)
Severe and serious acute renal events	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 and serious Hepatic disorders	0	0	0	0	0	0	1 (0.7)	0	1 (0.2)
Severe and serious hypersensitivity reactions	0	0	0	0	0	1 (0.7)	0	0	1 (0.2)
Thyroid Malignancies and C-Cell Hyperplasia	0	0	0	0	0	0	1 (0.7)	0	1 (0.2)
Severe and serious Depression, suicidal ideation, and behavior events	0	1 (0.7)	0	1 (0.2)	0	0	0	0	0
Severe and serious Ketoacidosis[a]	0	0	0	0	0	0	0	0	0

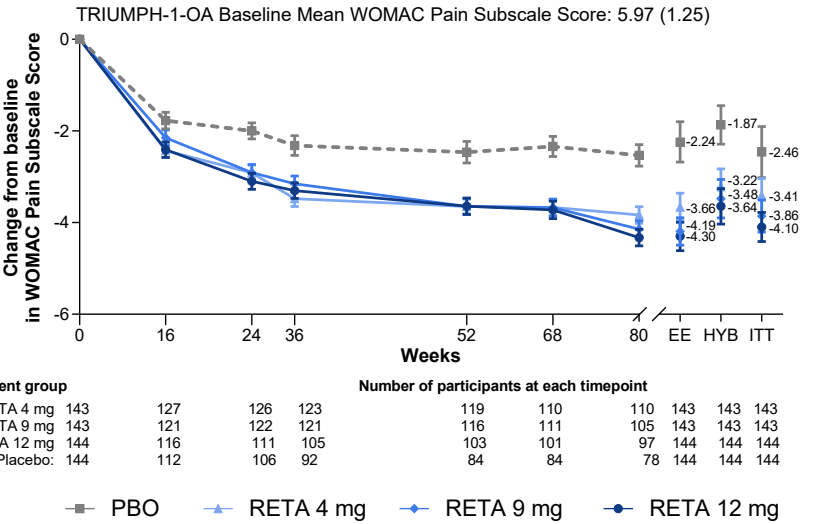
Data presented as number (%). [a]Due to inadequate nutritional intake and other types of metabolic acidosis and ketosis. Data are reported for the safety data points set. Safety population defined as all participants who were randomly assigned a study intervention and who received ≥1 dose of double-blind study intervention. MedDRA Version 28.1.

Abbreviations: AE=adverse event; n=number of participants in the specified category; N=all randomly assigned participants who took ≥1 dose of study drug; RETA=retatrutide; TE=treatment-emergent; TEAE=TE Adverse Events; CEC=clinical endpoint committee; MACE=major adverse cardiovascular event.

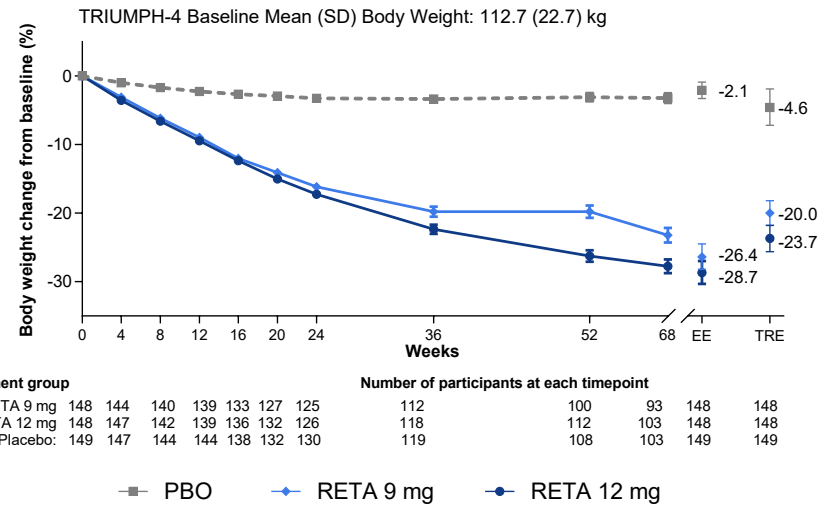
A.


TRIUMPH-4 Baseline Mean WOMAC Pain Subscale Score: 5.95 (1.3)
Change from baseline in WOMAC Pain Subscale Score
0
-2
-4
-6
0
16
24
36
52
68
EE
HYB
ITT
Weeks
-2.43
-2.12
-2.59
-3.74
-3.96
-3.97
-4.30
-4.41
-4.48
Treatment group
Number of participants at each timepoint
RETA 9 mg 148 123 111 110 98 92 148 148 148
RETA 12 mg 148 122 113 109 105 100 148 148 148
Placebo: 149 120 116 105 100 95 149 149 149
PBO
RETA 9 mg
RETA 12 mg

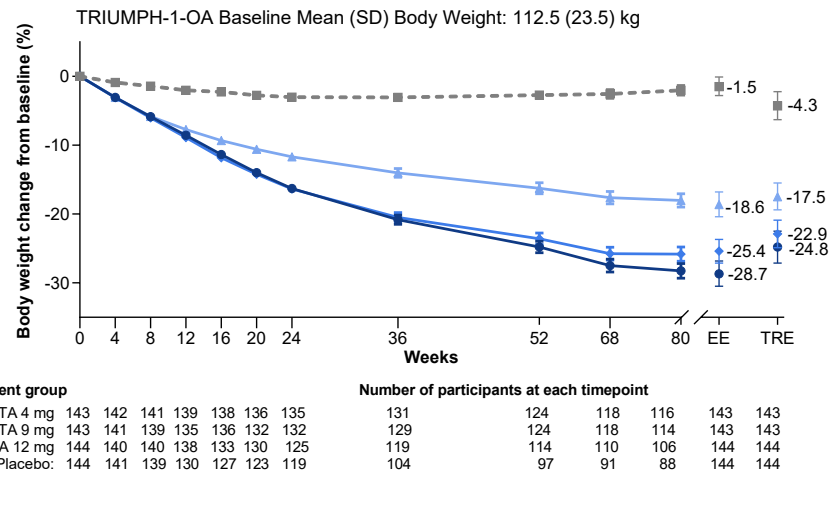
B.


TRIUMPH-1-OA Baseline Mean WOMAC Pain Subscale Score: 5.97 (1.25)
Change from baseline in WOMAC Pain Subscale Score
0
-2
-4
-6
0
16
24
36
52
68
80
EE
HYB
ITT
Weeks
-2.24
-1.87
-2.46
-3.22
-3.48
-3.41
-3.66
-3.64
-3.86
-4.19
-4.30
-4.10
Treatment group
Number of participants at each timepoint
RETA 4 mg 143 127 126 123 119 110 110 143 143 143
RETA 9 mg 143 121 122 121 116 111 105 143 143 143
RETA 12 mg 144 116 111 105 103 101 97 144 144 144
Placebo: 144 112 106 92 84 84 78 144 144 144
PBO
RETA 4 mg
RETA 9 mg
RETA 12 mg

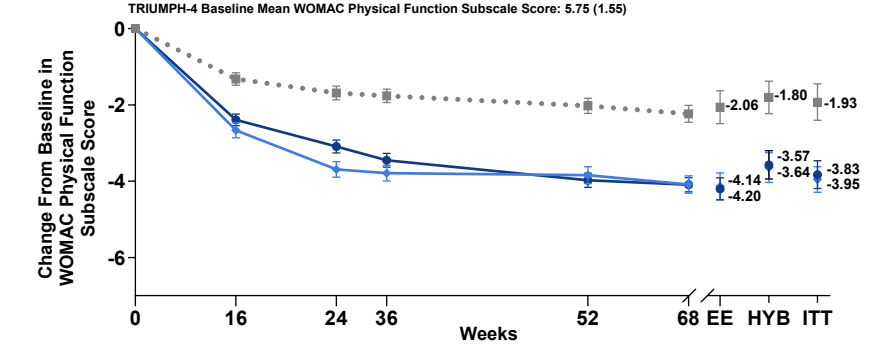
C.


TRIUMPH-4 Baseline Mean (SD) Body Weight: 112.7 (22.7) kg
Body weight change from baseline (%)
0
-10
-20
-30
0
4
8
12
16
20
24
36
52
68
EE
TRE
Weeks
-2.1
-4.6
-20.0
-23.7
-26.4
-28.7
Treatment group
Number of participants at each timepoint
RETA 9 mg 148 144 140 139 133 127 125 112 100 93 148 148
RETA 12 mg 148 147 142 139 136 132 126 118 112 103 148 148
Placebo: 149 147 144 144 138 132 130 119 108 103 149 149
PBO
RETA 9 mg
RETA 12 mg

D.

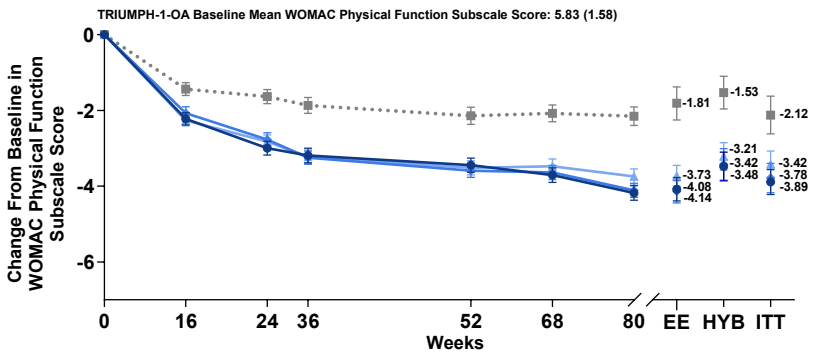

TRIUMPH-1-OA Baseline Mean (SD) Body Weight: 112.5 (23.5) kg
Body weight change from baseline (%)
0
-10
-20
-30
0
4
8
12
16
20
24
36
52
68
80
EE
TRE
Weeks
-1.5
-4.3
-18.6
-17.5
-22.9
-25.4
-24.8
-28.7
Treatment group
Number of participants at each timepoint
RETA 4 mg 143 142 141 139 138 136 135 131 124 118 116 143 143
RETA 9 mg 143 141 139 135 136 132 132 129 124 118 114 143 143
RETA 12 mg 144 140 140 138 133 130 125 119 114 110 106 144 144
Placebo: 144 141 139 130 127 123 119 104 97 91 88 144 144
PBO
RETA 4 mg
RETA 9 mg
RETA 12 mg

A.



Treatment group	Number of participants at each timepoint								
RETA 9 mg:	148	122	111	110	98	92	148	148	148
RETA 12 mg:	147	122	114	109	105	100	147	147	147
Placebo:	149	120	116	105	99	94	149	149	149

B.



Treatment group	Number of participants at each timepoint									
RETA 4 mg:	143	126	125	121	118	109	109	143	143	143
RETA 9 mg:	143	121	120	120	116	110	104	143	143	143
RETA 12 mg:	144	113	110	102	102	100	97	144	144	144
Placebo:	144	112	106	90	84	83	77	144	144	144