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Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis

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ABSTRACT

BACKGROUND

Weight reduction has been shown to alleviate symptoms of osteoarthritis of the knee, including pain. The effect of glucagon-like peptide-1 receptor agonists on outcomes in knee osteoarthritis among persons with obesity has not been well studied.

METHODS

We conducted a 68-week, double-blind, randomized, placebo-controlled trial at 61 sites in 11 countries. Participants with obesity (a body-mass index [BMI; the weight in kilograms divided by the square of the height in meters] of ≥30) and a clinical and radiologic diagnosis of moderate knee osteoarthritis with at least moderate pain were randomly assigned, in a 2:1 ratio, to receive once-weekly subcutaneous semaglutide (2.4 mg) or placebo, in addition to counseling on physical activity and a reduced-calorie diet. The primary end points were the percentage change in body weight and the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores reflecting worse outcomes) from baseline to week 68. A key confirmatory secondary end point was the physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2 (on a scale of 0 to 100, with higher scores indicating greater well-being).

RESULTS

A total of 407 participants were enrolled. The mean age was 56 years, the mean BMI 40.3, and the mean WOMAC pain score 70.9. A total of 81.6% of the participants were women. The mean change in body weight from baseline to week 68 was −13.7% with semaglutide and −3.2% with placebo (P<0.001). The mean change in the WOMAC pain score at week 68 was −41.7 points with semaglutide and −27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points vs. 6.5 points; P<0.001). The incidence of serious adverse events was similar in the two groups. Adverse events that led to permanent discontinuation of the trial regimen occurred in 6.7% of the participants in the semaglutide group and in 3.0% in the placebo group, with gastrointestinal disorders being the most common reason for discontinuation.

CONCLUSIONS

Among participants with obesity and knee osteoarthritis with moderate-to-severe pain, treatment with once-weekly injectable semaglutide resulted in significantly greater reductions in body weight and pain related to knee osteoarthritis than placebo. (Funded by Novo Nordisk; STEP 9 ClinicalTrials.gov number, NCT05064735.)

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CME

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Osteoarthritis of the knee represents the most prevalent form of osteoarthritis[1] and leads to chronic pain, reduced mobility, disability, and impaired quality of life.[2-5] Obesity is a major risk factor for the development and progression of osteoarthritis of the knee.[6-8] Obesity-related knee osteoarthritis arises from a combination of increased mechanical stress on weight-bearing joints, metabolic dysfunction, and obesity-induced inflammation.[7,8] Weight reduction alleviates symptoms — with a 2% improvement in Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain, function, and stiffness scores with every 1% reduction in body weight[9] — and may reduce the risk of structural progression.[10]

Treatment guidelines recommend weight reduction and physical activity as first-line management for obesity-related knee osteoarthritis.[11-13] Clinically important weight reduction requires a combination of a reduced-calorie diet and patient-centered physical-activity interventions, which may be challenging to adhere to[14] but have been shown to improve patient-reported outcomes related to pain.[15-17] Bariatric surgery may reduce knee pain in persons with obesity, although data from randomized, controlled trials are lacking.[18] There remains an unmet need for weight-management medications that can facilitate nonsurgical, sustained weight reduction and reduce pain in persons with obesity-related knee osteoarthritis. The effect of glucagon-like peptide-1 (GLP-1) receptor agonists in persons with obesity and knee osteoarthritis in this population has not been well established.[16,19]

Semaglutide, administered subcutaneously once weekly, is a GLP-1 receptor agonist that is approved in several countries for weight management in persons with a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 30 or greater, or 27 or greater for those with at least one weight-related coexisting condition. In the United States, this antiobesity medication is approved for reducing the risk of major adverse cardiovascular events in adults with established cardiovascular disease and overweight or obesity. The Semaglutide Treatment Effect in People with Obesity (STEP) 9 trial assessed whether a 2.4-mg dose of semaglutide would be superior to placebo as an adjunct to lifestyle modifications in reducing body weight and pain related to knee osteoarthritis in participants with obesity, clinical and radiologic diagnosis of moderate knee osteoarthritis, and pain that is at least moderately severe.

Methods

Trial Design and Oversight

The STEP 9 trial was a multicenter, double-blind, randomized, placebo-controlled trial conducted at 61 sites across 11 countries, in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines.[20,21] The protocol (available with the full text of this article at NEJM.org) was approved by independent ethics committees or institutional review boards at the participating institutions.

The sponsor (Novo Nordisk) designed the trial, prepared the protocol and statistical analysis plan, and performed the statistical analyses. The investigators were responsible for trial-related medical decisions and data collection. The authors interpreted the aggregated data, participated in writing the first and subsequent drafts of the manuscript (with assistance from a medical writer funded by the sponsor, who wrote the first draft under the direction of the authors in accordance with Good Publication Practice guidelines), and made the decision to submit the manuscript for publication. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Participants

Participants were 18 years of age or older and had obesity (BMI ≥30), a clinical diagnosis of knee osteoarthritis according to American College of Rheumatology criteria (knee pain with three or more of the following factors: an age of >50 years, stiffness for <30 minutes in the morning, crepitus, bony tenderness, bony enlargement, and no palpable warmth),[22] with moderate radiographic changes (Kellgren–Lawrence grade 2 or 3)[23] in the target knee. Eligible participants also had pain related to knee osteoarthritis, with a WOMAC pain score at randomization of at least 40 (on a scale of 0 to 100, with higher scores reflecting worse outcomes). For eligibility and efficacy assessments, the trial used the WOMAC numerical rating scale, version 3.1, with a 24-hour recall period; scores were normalized and expressed on a scale of 0 to 100, with higher scores reflecting worse outcomes (additional information is provided in the

Supplementary Appendix, available at NEJM.org). Participants who were receiving analgesic agents had to complete a 72-hour washout period before randomization. Full eligibility criteria are provided in the Supplementary Appendix. All the participants provided written informed consent.

PROCEDURES

Participants were randomly assigned in a 2:1 ratio, with the use of an interactive Web-response system, to receive once-weekly subcutaneous semaglutide or visually identical placebo for 68 weeks, followed by a 7-week follow-up period during which the participants did not receive semaglutide or placebo. Block randomization was used (with a block size of six), with no stratification factors. Throughout the trial, participants in both groups received counseling on a reduced-calorie diet and physical activity (additional details are provided in the Supplementary Appendix). Semaglutide was initiated at a dose of 0.24 mg, with dose escalation intended to reach the 2.4-mg target at week 16. Participants who had unacceptable side effects with a 2.4-mg dose could continue to receive a lower dose (1.7 mg), provided that the investigator considered the treatment to be safe. The protocol recommended that participants make at least one additional attempt to escalate to the target dose of 2.4 mg, at the investigator's discretion.

Treatment with other antiobesity medications was not permitted; the use of other interventions for knee osteoarthritis was permitted. Although pain medication could be used throughout the trial, opioid use was an exclusion criterion at baseline, and use was discouraged during the trial. During the washout periods (24 to 72 hours before visits), acetaminophen could be used for pain management at a maximum of 4 g per day; no pain medication could be used within the 24 hours before a visit. Participants kept an electronic diary to record pain and pain-medication use. The worst daily knee pain was recorded in the electronic diary with the use of a numerical rating scale ranging from 0 to 10, with higher scores indicating worse pain. Additional details are provided in the Supplementary Appendix.

END POINTS AND ASSESSMENTS

All the end points were assessed from baseline to week 68. The primary end points were the percentage change in body weight and the change in WOMAC pain score. Confirmatory secondary end points were the percentage of participants with a body-weight reduction of at least 5% or at least 10%, the change in the WOMAC physical-function score, and the change in physical-function score on the 36-Item Short Form Health Survey (SF-36), version 2.0. The supportive secondary end points included changes in waist circumference, WOMAC stiffness score, WOMAC total score, pain intensity (as reported in the pain diary with the numerical rating scale), and pain-medication use. Exploratory end points included the change in the 6-minute walk distance. The SF-36 (acute version with a 7-day recall period) used norm-based scoring, on a scale of 0 to 100, with higher scores reflecting better outcomes.

Because the incidence of mild and moderate adverse events with a 2.4-mg dose of semaglutide has been characterized in previous trials,[24-31] a targeted approach to collection of safety data was used. Investigators recorded only serious adverse events, adverse events leading to discontinuation of semaglutide or placebo, adverse events warranting invasive knee procedures, medication error (i.e., an unintended failure with the investigational product, including administration of the wrong drug, incorrect route of administration, missed doses, or drug misuse or abuse by the participant [e.g., drug overdose to maximize the effect or with the intention to cause harm]), acute pancreatitis, coronavirus disease 2019, and pregnancy or pregnancy-related adverse events. Blood pressure was measured as part of the safety assessments.

STATISTICAL ANALYSIS

The two primary end points were tested at a significance level of 5%, with the alpha split between the two end points (1% for the percentage change in body weight and 4% for the change in WOMAC pain score). If superiority was confirmed for both primary end points, the confirmatory secondary end points could be tested at a 5% significance level in a prespecified hierarchical manner, as described in the Supplementary Appendix. Supportive secondary and exploratory end-point analyses were not controlled for multiplicity and should not be used to infer definitive treatment effects.

The full analysis population included all the participants who underwent randomization (according to the intention-to-treat principle). The safety analysis population included all the participants who underwent randomization and re-

ceived at least one dose of semaglutide or placebo. Observation periods included the in-trial period (the interval between the date a participant had undergone randomization and that participant's last date of contact with the trial site, regardless of treatment discontinuation or rescue intervention) and the on-treatment period (any period during which a participant had received semaglutide or placebo within the previous 2 weeks, excluding any period of temporary interruption of the assigned regimen).

The efficacy end points were analyzed with the use of two estimands.[32] A treatment policy estimand, which is consistent with an intention-to-treat analysis, is a precise description of the treatment effect in a "real world" setting, regardless of adherence, unacceptable adverse events, or additional interventions. The treatment policy estimand was used to assess efficacy in the full analysis population regardless of adherence to the assigned regimen, use of other interventions, or adherence to pain-medication washout and was used for statistical inference, including confirmatory testing. Multiple imputation was performed to account for missing data at week 68, with the use of the available data from the participants in each group. The primary end points were also analyzed with the use of the trial product estimand, which assessed efficacy if the trial regimen was followed as intended (i.e., without discontinuations or the use of other interventions). Additional details regarding estimands and analysis methods are provided in the Supplementary Appendix. Pain medication use was assessed with descriptive statistics. The change in the 6-minute walk distance was assessed post hoc according to the treatment policy estimand. In addition, a post hoc analysis was conducted of the change in the WOMAC pain score, stratified according to BMI at baseline (<35, 35 to <40, or ≥40). The analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL PARTICIPANTS

From October 2021 through March 2022, a total of 407 participants underwent randomization; 271 were assigned to receive semaglutide, and 136 to receive placebo. Most of the participants completed the treatment period (86.7% in the semaglutide group and 77.9% in the placebo group) and the trial (90.8% and 89.7%, respectively) (Fig. S1 in the Supplementary Appendix). Among the 235 participants in the semaglutide group who completed the treatment period, at the last treatment visit, 211 (89.8%) were receiving the full 2.4-mg dose, 9 (3.8%) were receiving 1.7 mg to less than 2.4 mg, and 11 (4.7%) were receiving less than 1.7 mg; 4 participants (1.7%) did not report the dose.

Most participants were women (81.6%) and White (60.9%), and the mean age was 56 years (Table 1 and Table S1). At baseline, the mean body weight was 108.6 kg, the BMI 40.3, the waist circumference 118.7 cm, and the WOMAC pain score 70.9. A higher percentage of participants (41.0%) had severe obesity (BMI ≥40) than other weight categories (the BMI was 35 to <40 in 34.4% of the participants, 30 to <35 in 24.3%, and <30 in 0.2%). Overall, the characteristics of the participants at baseline were balanced between the two groups. The representativeness of the trial population is shown in Table S2.

PRIMARY END POINTS

The mean change from baseline in body weight at week 68 was −13.7% in the semaglutide group and −3.2% in the placebo group (estimated difference, −10.5 percentage points; 95% confidence interval [CI], −12.3 to −8.6; P<0.001) (Fig. 1). The results for the trial product estimand were similar (estimated difference, −12.1 percentage points; 95% CI, −13.8 to −10.5) (Fig. S2).

The mean change from baseline in the WOMAC pain score at week 68 was −41.7 points in the semaglutide group and −27.5 points in the placebo group (estimated difference, −14.1 points; 95% CI, −20.0 to −8.3; P<0.001) (Fig. 1). The results of the trial product estimand were similar (estimated difference, −14.8 points; 95% CI, −20.1 to −9.4) (Fig. S3).

CONFIRMATORY SECONDARY END POINTS

At week 68, the percentages of participants who had body-weight reductions from baseline of at least 5% and at least 10% were significantly higher in the semaglutide group (87.0% and 70.4%, respectively) than in the placebo group (29.2% and 9.2%, respectively) (Fig. 2A and Table S3). Over a period of 68 weeks, participants in the semaglutide group had a greater decrease (improvement) from baseline in WOMAC physical-function score than participants in the placebo group (mean change,

Table 1. Characteristics of the Participants at Baseline.*

Characteristic	Semaglutide (N=271)	Placebo (N=136)	Total (N=407)
Age — yr	56±10	56±10	56±10
Female sex — no. (%)	228 (84.1)	104 (76.5)	332 (81.6)
Race or ethnic group — no. (%)†			
White	168 (62.0)	80 (58.8)	248 (60.9)
Asian	16 (5.9)	6 (4.4)	22 (5.4)
Black	18 (6.6)	13 (9.6)	31 (7.6)
American Indian or Alaska Native	37 (13.7)	11 (8.1)	48 (11.8)
Other	32 (11.8)	26 (19.1)	58 (14.3)
Body weight — kg	108.7±24.1	108.5±24.5	108.6±24.2
Body-mass index			
Mean	40.5±7.3	40.0±7.1	40.3±7.2
Distribution — no. (%)			
<30	0	1 (0.7)	1 (0.2)
30 to <35	67 (24.7)	32 (23.5)	99 (24.3)
35 to <40	84 (31.0)	56 (41.2)	140 (34.4)
≥40	120 (44.3)	47 (34.6)	167 (41.0)
Waist circumference — cm‡	118.3±15.8	119.7±15.9	118.7±15.8
WOMAC pain score§	72.8±15.6	67.2±16.0	70.9±16.0
Systolic blood pressure — mm Hg¶	132±14	131±15	132±15
Diastolic blood pressure — mm Hg¶	82±10	82±10	82±10
Coexisting conditions — no. (%)‖			
Hypertension	128 (47.2)	68 (50.0)	196 (48.2)
Dyslipidemia	80 (29.5)	44 (32.4)	124 (30.5)
Gastroesophageal reflux disease	31 (11.4)	15 (11.0)	46 (11.3)
Asthma	19 (7.0)	19 (14.0)	38 (9.3)
Cardiovascular disease	13 (4.8)	8 (5.9)	21 (5.2)

* Plus–minus values are means ±SD. Data are shown for the full analysis population, which consisted of all the participants who had undergone randomization. Additional information about baseline characteristics is provided in Table S1 in the Supplementary Appendix. Percentages may not total 100 because of rounding.
† Race or ethnic group was reported by the participants. The "Other" category includes participants for whom race or ethnic group was not reported.
‡ Data on waist circumference were available for 405 participants (270 in the semaglutide group and 135 in the placebo group).
§ The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain scores were normalized and expressed on a scale of 0 to 100, with higher scores reflecting worse outcomes.
¶ Data on blood pressure were available for 404 participants (269 in the semaglutide group and 135 in the placebo group).
‖ Included are the coexisting conditions reported in more than 5% of the participants in the total trial population; additional information is provided in Table S1.

–41.5 points vs. –26.7 points; estimated difference, –14.9 points; 95% CI, –20.4 to –9.3; P<0.001) (Fig. S4A). At week 68, participants in the semaglutide group also had a greater increase (improvement) in SF-36 physical-function score from baseline than those in the placebo group (mean change, 12.0 points vs. 6.5 points; estimated difference, 5.6 points; 95% CI, 3.1 to 8.0; P<0.001) (Fig. S4C).

SUPPORTIVE SECONDARY AND EXPLORATORY END POINTS

A greater percentage of participants in the semaglutide group than in the placebo group had a body-weight reduction of at least 15% (47.8% vs. 2.5%) and at least 20% (23.3% vs. 0%) (Fig. 2A). A greater percentage of participants in the semaglutide group also had a reduction in the WOMAC

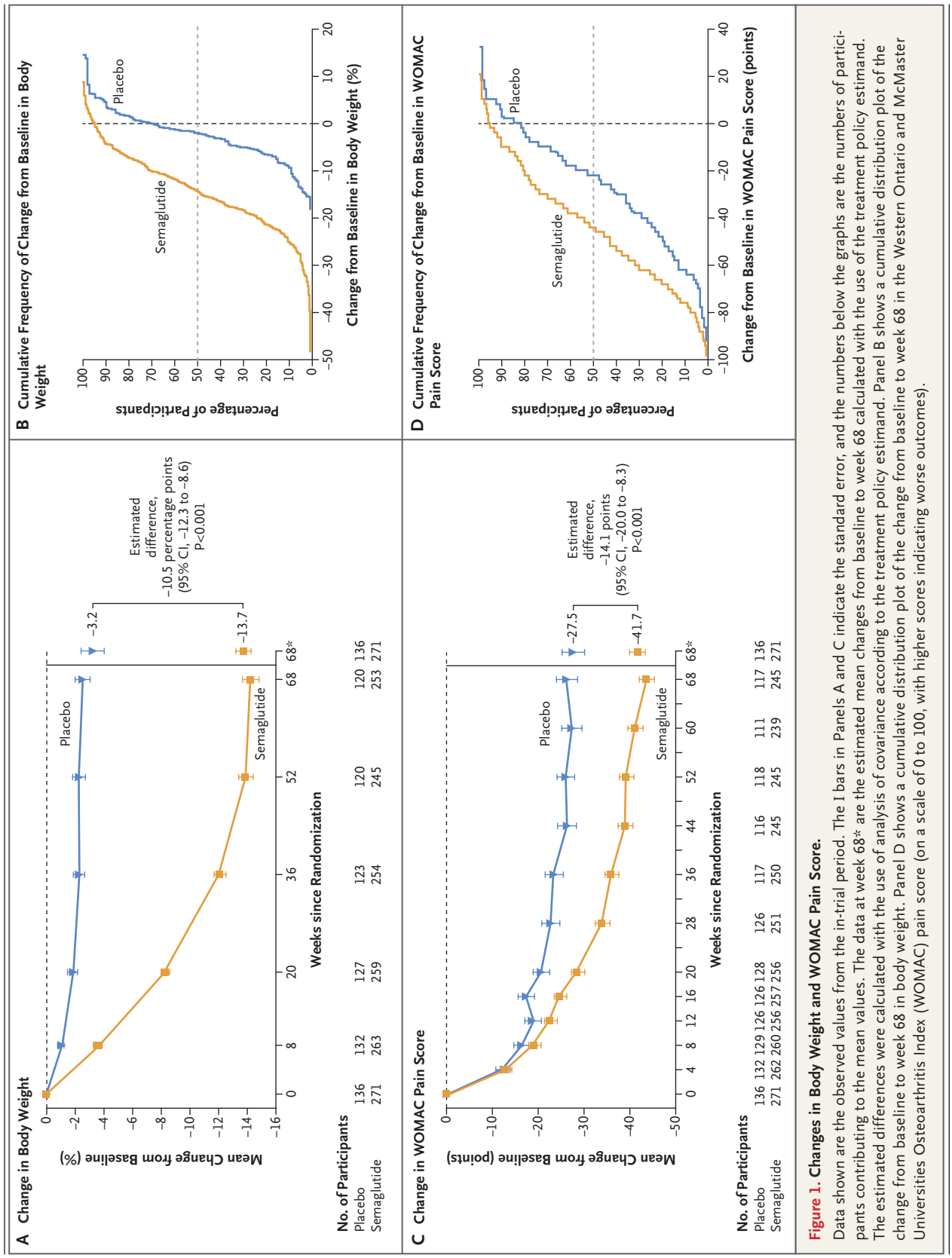

Figure 1. Changes in Body Weight and WOMAC Pain Score.

Data shown are the observed values from the in-trial period. The I bars in Panels A and C indicate the standard error, and the numbers below the graphs are the numbers of participants contributing to the mean values. The data at week 68* are the estimated mean changes from baseline to week 68 calculated with the use of the treatment policy estimand. The estimated differences were calculated with the use of analysis of covariance according to the treatment policy estimand. Panel B shows a cumulative distribution plot of the change from baseline to week 68 in body weight. Panel D shows a cumulative distribution plot of the change from baseline to week 68 in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain score (on a scale of 0 to 100, with higher scores indicating worse outcomes).

pain score of at least 30% and at least 50% (Fig. 2B). In addition, treatment with semaglutide resulted in a greater reduction in waist circumference over a period of 68 weeks than placebo (difference, −6.9 cm; 95% CI, −9.1 to −4.7) (Fig. S5).

The results of subgroup analyses indicated greater improvements in WOMAC pain scores with semaglutide than with placebo in all subgroups defined according to BMI at baseline (Table S4). Semaglutide resulted in greater reductions over a 68-week period than placebo in pain intensity according to the score on the numerical rating scale for daily knee pain (difference, −1.0 point; 95% CI, −1.6 to −0.5) (Fig. S6).

Semaglutide resulted in greater reductions over a period of 68 weeks than placebo in the WOMAC stiffness score (estimated difference, −15.9 points; 95% CI, −23.2 to −8.6) and WOMAC total score (estimated difference, −14.9 points; 95% CI, −20.5 to −9.3) (Figs. S7 and S8). Greater improvements from baseline to week 68 in the 6-minute walk distance were reported in the semaglutide group than in the placebo group (mean change, 56.8 m and 14.2 m, respectively; estimated difference, 42.6 m; 95% CI, 25.6 to 59.7).

The percentage of participants who were using nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen decreased during the trial in both groups, although to a greater extent in the semaglutide group (Fig. 3). Acetaminophen use was more prevalent at baseline in the semaglutide group but reached a level similar to that in the placebo group by approximately week 36. NSAID use was similarly prevalent at baseline in the two groups but was lower in the semaglutide group by approximately week 16. Only 23 participants (8.5%) in the semaglutide group and 13 (9.6%) in the placebo group reported taking opioids at any time during the trial; of these participants, 12 in the semaglutide group and 7 in the placebo group reported codeine use.

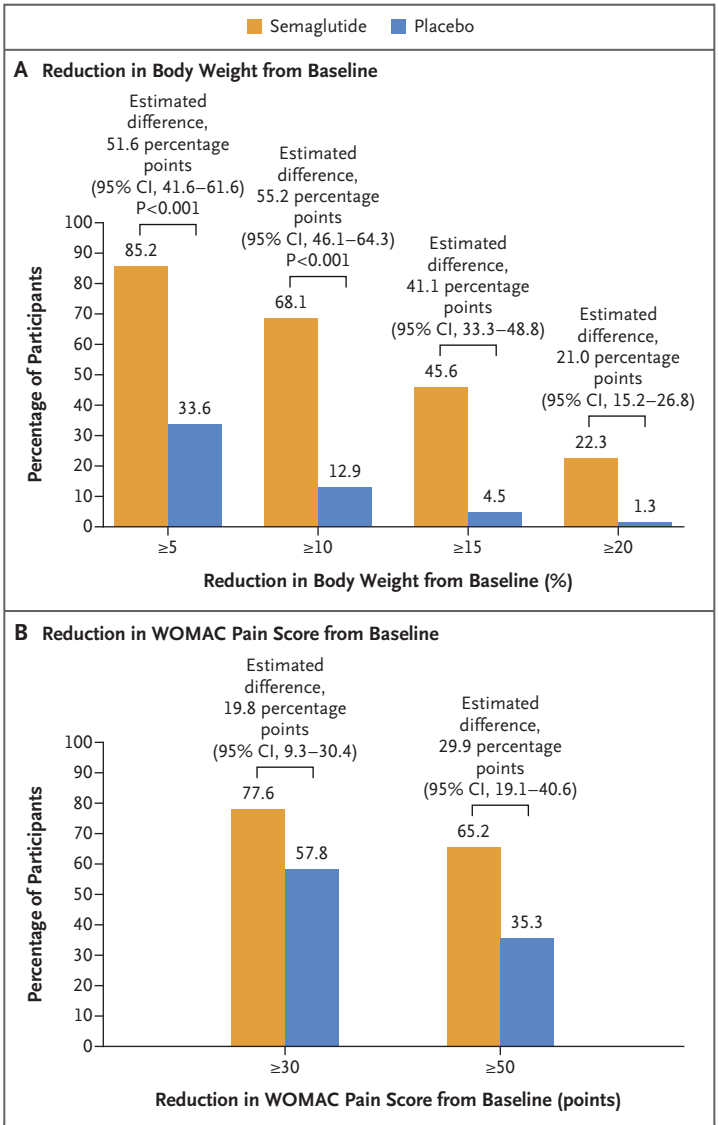

Figure 2. Reduction in Body Weight and WOMAC Pain Score at Week 68.

The estimated percentages and differences were derived from a logistic-regression model according to the treatment policy estimand. The confidence intervals for the differences were obtained with the use of the delta method. P values are reported for confirmatory secondary end-point analyses only, on the basis of odds ratios estimated from the same logistic-regression model. The odds ratios for these end points are provided in Table S3 in the Supplementary Appendix.

SAFETY

Safety was assessed in 269 participants in the semaglutide group and in 135 participants in the placebo group. The incidence of serious adverse events was similar in the two groups (10.0% in the semaglutide group and 8.1% in the placebo group) (Table 2). The most frequently reported serious adverse events were neoplasms (benign, malignant, or unspecified; nine events reported among 9 participants [3.3%] in the semaglutide group and three events reported among 3 participants [2.2%] in the placebo group) and gastrointestinal disorders (five events reported among 4 participants [1.5%] in the semaglutide group and one event reported in 1 participant [0.7%] in the placebo group) (Table S5). Adverse events leading to permanent discontinuation of

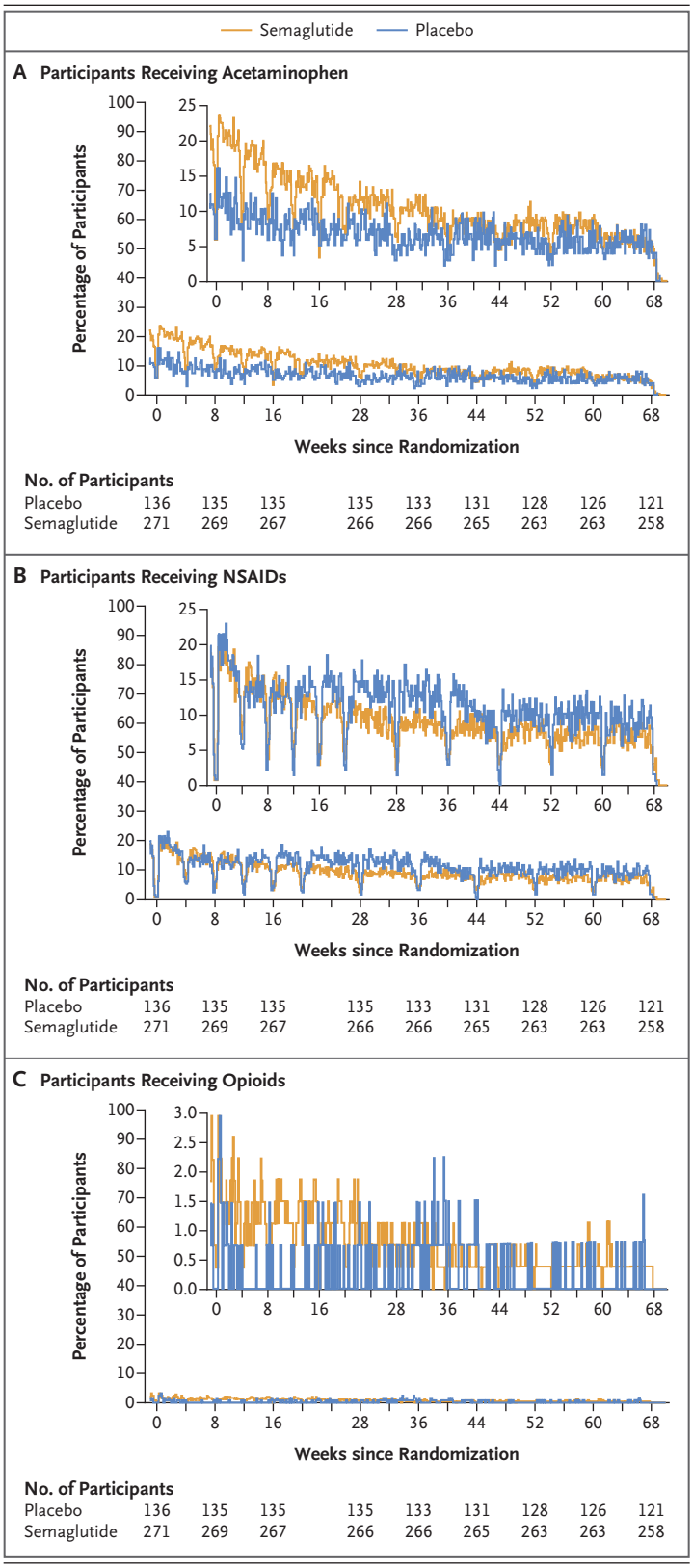

Figure 3. Use of Pain Medication According to Type.

Data shown are the observed data from the in-trial period, including a 7-day prerandomization period. The numbers below the graphs are the numbers of participants contributing to the analysis at each time point. Current opioid use was an exclusion criterion at randomization, and initiation or use of opioids was discouraged during the trial; three cases of ongoing use of opioids at randomization (which represented protocol deviations) were identified. The inset in each panel shows the same data on an enlarged y axis. NSAID denotes nonsteroidal antiinflammatory drug.

the trial regimen were reported in 6.7% of the participants in the semaglutide group and in 3.0% of those in the placebo group. Gastrointestinal disorders (in 2.2% in the semaglutide group and in 0% in the placebo group) and neoplasms (benign, malignant, or unspecified; in 1.9% and 1.5%, respectively) were the most common event types that led to discontinuation of the trial regimen (Table S6). There were no unexpected findings with respect to the safety focus areas (Table 2). Among the participants who were receiving semaglutide or placebo at week 68, the systolic and diastolic blood pressure were reduced from baseline by a mean (±SD) of 8±15 mm Hg and 3±9 mm Hg, respectively, in the semaglutide group and 0±13 mm Hg and 1±9 mm Hg, respectively, in the placebo group.

DISCUSSION

The STEP 9 trial, which involved persons with obesity and moderate-to-severe pain due to knee osteoarthritis, showed that semaglutide was superior to placebo in reducing pain related to knee osteoarthritis as well as body weight and was associated with improved physical function. Although previous studies have indicated a benefit of weight reduction with respect to symptoms,[9] this randomized trial used full blinding of the participants to the trial-group assignment and also showed larger effects. Weight reductions and safety outcomes with semaglutide were consistent with those reported in previous STEP trials.[24-31]

Treatment with semaglutide resulted in greater improvements than placebo across all pain-related end points, a finding that is in line with those from an observational study involving adults

Table 2. Adverse Events.*

Adverse Event	Semaglutide (N=269)	Placebo (N=135)	Relative Risk (95% CI)	Risk Difference (95% CI)†
	no. of participants (%)			
Any serious adverse event	27 (10.0)	11 (8.1)	1.23 (0.64 to 2.40)	1.9 (–4.7 to 7.3)
Adverse event leading to permanent discontinuation of semaglutide or placebo				
Any event	18 (6.7)	4 (3.0)	2.26 (0.82 to 6.30)	3.7 (–1.3 to 7.7)
Gastrointestinal disorder	6 (2.2)	0	—	2.2 (–0.8 to 4.8)
Fatal event	0	0	—	—
Safety focus areas				
Coronavirus disease 2019	51 (19.0)	32 (23.7)	0.80 (0.54 to 1.19)	–4.7 (–13.7 to 3.4)
Serious neoplasm‡	10 (3.7)	6 (4.4)	0.84 (0.32 to 2.18)	–0.7 (–5.9 to 3.1)
Serious malignant neoplasm‡	8 (3.0)	2 (1.5)	2.01 (0.49 to 8.31)	1.5 (–2.5 to 4.5)
Serious gastrointestinal event‡	4 (1.5)	1 (0.7)	2.01 (0.31 to 13.33)	0.7 (–2.7 to 3.1)
Serious acute gallbladder disease‡	3 (1.1)	1 (0.7)	1.51 (0.22 to 10.49)	0.4 (–3.0 to 2.6)
Serious cardiovascular disorder‡	3 (1.1)	2 (1.5)	0.75 (0.15 to 3.75)	–0.4 (–4.2 to 2.0)
Medication error§	2 (0.7)	4 (3.0)	0.25 (0.05 to 1.16)	–2.2 (–6.7 to 0.4)
Serious acute renal failure‡	0	1 (0.7)	0.00 (0.00 to 1.93)	–0.7 (–4.1 to 0.8)
Serious psychiatric disorder‡	0	1 (0.7)	0.00 (0.00 to 1.93)	–0.7 (–4.1 to 0.8)
Acute pancreatitis	0	0	—	—
Pregnancy or pregnancy-related adverse event‡	0	0	—	—
Joint replacement	2 (0.7)	0	—	—

* Shown are adverse events that occurred during the on-treatment period with any dose of semaglutide or placebo that was administered within the previous 49 days, unless indicated otherwise (the on-treatment period was any period during which a participant had received semaglutide or placebo within the previous 2 weeks, excluding any period of temporary interruption of the assigned regimen). Adverse events are shown for the safety analysis population, which included all the participants who had undergone randomization and received at least one dose of semaglutide or placebo. Additional information on serious adverse event types, adverse event types leading to discontinuation of semaglutide or placebo, and malignant neoplasms according to type is provided in Tables S5, S6, and S7, respectively.

† The risk differences are expressed in percentage points.

‡ Shown are the number of events that were reported during the in-trial period (the interval between the date a participant had undergone randomization and that participant's last date of contact with the trial site, regardless of treatment discontinuation or rescue intervention).

§ Medication error was defined as an unintended failure with the investigational product, including administration of the wrong drug, incorrect route of administration, missed doses, or drug misuse or abuse by the participant (e.g., drug overdose to maximize the effect or with the intention to cause harm).

with knee osteoarthritis and type 2 diabetes, in which greater reductions in WOMAC total and pain scores were seen among participants who received GLP-1 receptor agonists than among those who did not receive these agents (mean BMI at baseline, 25).[19] In contrast, a trial of the GLP-1 receptor agonist liraglutide (administered subcutaneously once daily at a dose of 3.0 mg) that involved participants with overweight or obesity and knee osteoarthritis showed no significant differences in pain as compared with placebo (according to the Knee Injury and Osteoarthritis Outcome Score).[16] However, in the liraglutide trial, weight reduction was modest (mean change, –2.8 kg in the liraglutide group and 1.2 kg in the placebo group), which may have contributed to the lack of improvement in pain scores.

The use of analgesic agents decreased during the trial, with a greater reduction observed in the semaglutide group than in the placebo group, a finding that confirms that pain reduction with semaglutide was not due to increased

use of analgesic agents. These results suggest an NSAID-sparing effect of semaglutide, potentially limiting the adverse effects of NSAIDs[33] and reducing polypharmacy. Opioid use was discouraged and was low throughout the trial in both groups.

The trial was not designed to investigate the mechanism of action of semaglutide on knee osteoarthritis, so mechanistic conclusions cannot be drawn. Weight reduction is most likely a major contributor, as a result of reduced mechanical stress on the knee joints; previous studies have shown that weight reduction through various strategies can lead to considerable alleviation of knee pain and joint stiffness.[9] However, preclinical studies have shown that GLP-1 receptor agonists have antiinflammatory and antidegradative effects.[34,35]

The severity of obesity varied among the enrolled participants, and subgroup analyses indicated a benefit of semaglutide with respect to pain regardless of BMI values at baseline. However, overall mean BMI and pain scores at baseline were higher than in previous studies involving persons with knee osteoarthritis,[15,16,19] and a high percentage of participants (41%) had severe obesity (BMI ≥40) at baseline. Future studies could further explore the applicability of these findings to wider populations.

The limitations of this trial include a lack of imaging at follow-up and a lack of assessment of metabolic and inflammatory markers; therefore, the effect of semaglutide on the pathophysiology of knee osteoarthritis could not be determined. In addition, adherence to dietary and physical-activity recommendations was not assessed. Although most participants were women, knee osteoarthritis is known to be more prevalent among women than among men.[1] The prevalence of coexisting conditions at baseline, such as nonalcoholic fatty liver disease and obstructive sleep apnea, was lower than expected on the basis of previous epidemiologic data,[36] most likely because coexisting conditions were reported by the investigator and not objectively assessed. In addition, changes in outcomes were not assessed after the end of the treatment period; however, previous studies have shown weight regain after discontinuation of semaglutide,[28,37] a finding that suggests that longer-term treatment strategies may be needed to maintain benefits. Perceived trial-group assignment and the effect of such perception were not assessed; however, the magnitude and consistency of treatment benefit with semaglutide across outcomes suggests that perceived assignment was unlikely to account for the improvements observed.[38]

This randomized, double-blind, placebo-controlled trial showed that treatment with semaglutide alleviated pain related to osteoarthritis of the knee among persons with obesity and knee osteoarthritis. The findings support the use of once-weekly subcutaneous semaglutide at a dose of 2.4 mg for weight management and treatment of pain in persons with obesity and moderate-to-severe pain due to knee osteoarthritis.

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APPENDIX

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REFERENCES

1. Long H, Liu Q, Yin H, et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol 2022;74:1172-83.
2. Hunter DJ, Bierma-Zeinstra S. Osteoarthritis. Lancet 2019;393:1745-59.
3. Kawano MM, Araújo ILA, Castro MC, Matos MA. Assessment of quality of life in patients with knee osteoarthritis. Acta Ortop Bras 2015;23:307-10.
4. Vitaloni M, Botto-van Bemden A, Sciortino Contreras RM, et al. Global management of patients with knee osteoarthritis begins with quality of life assessment: a systematic review. BMC Musculoskelet Disord 2019;20:493.
5. Shalhoub M, Anaya M, Deek S, et al. The impact of pain on quality of life in patients with osteoarthritis: a cross-sectional study from Palestine. BMC Musculoskelet Disord 2022;23:248.
6. Reyes C, Leyland KM, Peat G, Cooper C, Arden NK, Prieto-Alhambra D. Association between overweight and obesity and risk of clinically diagnosed knee, hip, and hand osteoarthritis: a population-based cohort study. Arthritis Rheumatol 2016;68:1869-75.
7. Raud B, Gay C, Guiguet-Auclair C, et al. Level of obesity is directly associated with the clinical and functional consequences of knee osteoarthritis. Sci Rep 2020;10:3601.
8. 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.
9. 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.
10. Salis Z, Gallego B, Nguyen TV, Sainsbury A. Association of decrease in body mass index with reduced incidence and progression of the structural defects of knee osteoarthritis: a prospective multicohort study. Arthritis Rheumatol 2023; 75:533-43.
11. Kolasinski SL, Neogi T, Hochberg MC, et al. 2019 American College of Rheumatology/Arthritis Foundation guideline for the management of osteoarthritis of the hand, hip, and knee. Arthritis Care Res (Hoboken) 2020;72:149-62.
12. Bannuru RR, Osani MC, Vaysbrot EE, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthritis Cartilage 2019;27:1578-89.
13. Gibbs AJ, Gray B, Wallis JA, et al. Recommendations for the management of hip and knee osteoarthritis: a systematic review of clinical practice guidelines. Osteoarthritis Cartilage 2023;31:1280-92.
14. Lemstra M, Bird Y, Nwankwo C, Rogers M, Moraros J. Weight loss intervention adherence and factors promoting adherence: a meta-analysis. Patient Prefer Adherence 2016;10:1547-59.
15. Messier SP, Beavers DP, Queen K, et al. Effect of diet and exercise on knee pain in patients with osteoarthritis and overweight or obesity: a randomized clinical trial. JAMA 2022;328:2242-51.
16. 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;113:314-23.
17. Christensen R, Henriksen M, Leeds AR, et al. Effect of weight maintenance on symptoms of knee osteoarthritis in obese patients: a twelve-month randomized controlled trial. Arthritis Care Res (Hoboken) 2015;67:640-50.
18. Heuts EAF, de Jong LD, Hazebroek EJ, Wagener M, Somford MP. The influence of bariatric surgery on hip and knee joint pain: a systematic review. Surg Obes Relat Dis 2021;17:1637-53.
19. Zhu H, Zhou L, Wang Q, et al. Glucagon-like peptide-1 receptor agonists as a disease-modifying therapy for knee osteoarthritis mediated by weight loss: findings from the Shanghai Osteoarthritis Cohort. Ann Rheum Dis 2023;82:1218-26.
20. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310:2191-4.
21. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2). Geneva:International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, step 4 version. November 9, 2016 (https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf).
22. Altman R, Asch E, Bloch D, et al. Development of criteria for the classification and reporting of osteoarthritis: classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039-49.
23. Kohn MD, Sassoon AA, Fernando ND. Classifications in brief: Kellgren–Lawrence classification of osteoarthritis. Clin Orthop Relat Res 2016;474:1886-93.
24. Davies M, Færch L, Jeppesen OK, et al. Semaglutide 2·4 mg once a week in adults with overweight or obesity, and type 2 diabetes (STEP 2): a randomised, double-blind, double-dummy, placebo-controlled, phase 3 trial. Lancet 2021;397:971-84.
25. Garvey WT, Batterham RL, Bhatta M, et al. Two-year effects of semaglutide in adults with overweight or obesity: the STEP 5 trial. Nat Med 2022;28:2083-91.
26. Kadowaki T, Isendahl J, Khalid U, et al. Semaglutide once a week in adults with overweight or obesity, with or without type 2 diabetes in an east Asian population (STEP 6): a randomised, double-blind, double-dummy, placebo-controlled, phase 3a trial. Lancet Diabetes Endocrinol 2022;10:193-206.
27. Wadden TA, Bailey TS, Billings LK, et al. Effect of subcutaneous semaglutide vs placebo as an adjunct to intensive behavioral therapy on body weight in adults with overweight or obesity: the STEP 3 randomized clinical trial. JAMA 2021;325:1403-13.
28. Rubino D, Abrahamsson N, Davies M, et al. Effect of continued weekly subcutaneous semaglutide vs placebo on weight loss maintenance in adults with overweight or obesity: the STEP 4 randomized clinical trial. JAMA 2021;325:1414-25.
29. Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med 2021;384:989-1002.
30. Mu Y, Bao X, Eliaschewitz FG, et al. Efficacy and safety of once weekly semaglutide 2·4 mg for weight management in a predominantly east Asian population with overweight or obesity (STEP 7): a double-blind, multicentre, randomised controlled trial. Lancet Diabetes Endocrinol 2024;12: 184-95.
31. Rubino DM, Greenway FL, Khalid U, et al. Effect of weekly subcutaneous semaglutide vs daily liraglutide on body weight in adults with overweight or obesity without diabetes: the STEP 8 randomized clinical trial. JAMA 2022;327:138-50.
32. Wharton S, Astrup A, Endahl L, et al. Estimating and reporting treatment effects in clinical trials for weight management: using estimands to interpret effects of intercurrent events and missing data. Int J Obes (Lond) 2021;45:923-33.
33. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013;382:769-79.
34. Mei J, Sun J, Wu J, Zheng X. Liraglutide suppresses TNF-α-induced degradation of extracellular matrix in human chondrocytes: a therapeutic implication in osteoarthritis. Am J Transl Res 2019;11:4800-8.
35. Meurot C, Martin C, Sudre L, et al. Liraglutide, a glucagon-like peptide 1 receptor agonist, exerts analgesic, anti-inflammatory and anti-degradative actions in osteoarthritis. Sci Rep 2022;12:1567.
36. Sarma S, Sockalingam S, Dash S. Obesity as a multisystem disease: trends in obesity rates and obesity-related complications. Diabetes Obes Metab 2021;23:Suppl 1:3-16.
37. Wilding JPH, Batterham RL, Davies M, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: the STEP 1 trial extension. Diabetes Obes Metab 2022;24:1553-64.
38. Bruggemeyer C, Nepal D, Putman M. Unintentional unblinding in rheumatic disease trials. Lancet Rheumatol 2023; 5(10):e633-e636.