Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis[1]
STEP 9 (2024) Trial Summary

SUMMARY

- Adults with severe knee pain associated with moderate osteoarthritis (OA) and obesity (BMI ≥30kg/m^2) experienced a 10.5% reduction in body weight with taking semaglutide 2.4mg subcut q1wk vs placebo over 68 weeks. Participants also reported greater improvements in pain intensity, using the validated *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) *Numeric Rating Scale 3.1*. Importantly, both treatment arms were administered in conjunction with diet and exercise counselling.
  - Secondary endpoints included an assessment of functional improvement, usually considered by many to be the primary goal of pain management strategies. More patients experienced improved function total scores on the WOMAC in the semaglutide arm, and a greater percent were deemed to have clinically meaningful improvement (**NNT≈5**/68wk).
- This trial focused on two primary outcomes, with the first, weight loss, being a surrogate outcome, and the second, pain intensity, being a subjective patient-important outcome. Previous studies have already shown that weight loss can improve pain intensity in OA,[2] and this study further supports that conclusion. However, the study was not designed to determine whether there are any additional causal effects between the mechanism of action for semaglutide and analgesia.
- Although the study was not designed to conduct a full safety analysis, no concerning safety signals beyond the known occurrence of GI adverse effects were identified.
- Study limitations include the high likelihood of unblinding due to weight loss, with the potential for subsequent enhanced treatment effects on pain given the subjective reporting. Additionally, the inclusion and exclusion criteria for this study were strict, making generalizability of these results difficult. Finally, although not followed long-term, other studies have suggested that weight gain may recur if semaglutide is discontinued. It is unknown if pain and functional benefits will persist long-term, & if related to weight loss, then weight regain vs indefinite use of semaglutide needs to be considered.

Bottom Line:

- Patients experiencing severe pain from knee OA while living with obesity may be encouraged by reinforcing that weight loss can assist with reducing pain and improving function. Recognizing that weight loss utilizing lifestyle modification alone can be difficult for some to achieve, if cost is not prohibitive, semaglutide together with lifestyle modification may be considered to aid with weight reduction. Although causality for a semaglutide mechanism for pain is not established and it is off-label for the indication of OA, results are supportive for further investigation (larger, longer trials) for use in this area.

BACKGROUND

- Semaglutide is a GLP1 agonist that has been marketed in Canada since 2021. It is now indicated for treatment of type 2 diabetes, and also as an adjunct to lifestyle modification for people with an elevated BMI (BMI ≥30 or ≥27 + a weight-related coexisting condition). The **SELECT** trial (see RxFiles Trial Summary) showed CV benefit in patients with elevated BMI and established CV disease. The manufacturer has also pursued numerous phase 3 trials to assess the benefit of semaglutide in a variety of populations (**STEP 1-8** & **STEP TEENS**).
- Weight loss and physical activity are guideline-recommended 1st line for knee OA. Studies have suggested that in people with knee OA and obesity, a total body weight loss of ~5% can result in clinically significant improvement in function & pain.[2] An earlier network meta-analysis found that a) for each 1% ↓ in body weight, there is a 2% ↓in WOMAC pain, function, and stiffness scores, and also that b) a 25% weight reduction is needed to obtain a 50% decrease in WOMAC score.[3]
- One other GLP1 agonist, liraglutide 3mg subcut daily vs placebo, has been investigated for treating OA knee pain benefit, however in this 52 week study, there was minimal weight loss compared to placebo (-3.9kg; -6.9,-1) and no statistically significant improvement in pain intensity.[4]

STEP 9 TRIAL DESIGN AND POPULATION (SEE ORIGINAL ARTICLE/SUPPLEMENT FOR FULL CRITERIA)

DESIGN:

- Two-arm, randomized, double-blind, placebo-controlled trial, multicenter (61 sites, 11 countries), phase 3 superiority trial. Followed for 68wk.
- Allocation concealed (used an interactive Web-response system); used block randomization, no stratification; 2:1 ratio for treatment vs control.
- ITT analysis conducted for efficacy endpoints, and "on-treatment" analysis utilized for safety analysis.
- Used an "estimand" approach to assess outcomes based on "real world" approach (i.e. likely to be non-adherent or use of add-on other therapies) and compared this to the "trial product" (i.e. results with following the trial protocol closely).
- **Roles:**
  - **Sponsor**: Novo Nordisk was heavily involved (designed the trial, prepared the protocol & statistical analysis plan, did the statistical analysis, funded a medical writer, performed the safety surveillance).
  - **Investigators**: responsible for applying the exclusion criteria, making medical decisions around dose adjustments and AE, data collection, and reminding patients about the importance of adherence to regimen and lifestyle approaches.
  - **Authors**: interpreted the aggregated data, worked on manuscript alongside sponsor's medical writer, decision to submit for publication.
- **Washout:** Patients had to complete a 72hr washout period from analgesics before randomization (could use acetaminophen up to 24hr), however once in the study could use other OA interventions (though opioids discouraged). Prior to visits x72hr, patients were to again withhold any analgesics (specific agents not defined), except could take acetaminophen (up to 4g/day) up to 24hr prior. No "pain medication" could be used within 24hr before a visit.
- **Timeline:** Screened x2wk, then randomized. While enrolled and on tx, follow-up visits were q4wk up to 16wk (for dose escalation), then visits were q8wk (AE assessed & diet/activity counselling at each visit, amended protocol to also do WOMAC + pain & medication diary) for 68wk (52wk on target dose). There was a 7wk follow-up period at end of trial after agent stopped to further assess safety.
- Well designed trial, although participants and investigators were likely able to identify treatment arm given the difference in weight loss and AE, which could alter results by influencing subjective self-reporting. Potential risk of bias by having the manufacturer so closely involved.

POPULATION:

- **INCLUSION:** Adults (≥18yr) with mod-severe pain with knee OA* (with moderate radiologic changes in target knee, Kellgren-Lawrence grade 2/3, one or both knees), obesity (BMI≥30kg/m^2), baseline WOMAC **pain** intensity subscale ≥40 (normalized scale to 0-100, higher = worse outcomes), and willing to stop other analgesics before all visits.
  - * OA diagnosed by American College of Rheumatology criteria (i.e. knee pain + ≥3 of: age >50yr, morning stiffness <30min, crepitus, bony tenderness, bony enlargement, no palpable warmth).

- **EXCLUSIONS included:** MANY! Hx of DM, HbA1c ≥6.5%, baseline opioid/cannabis/pain patch use, hx of chronic pancreatitis, pancreatitis within 180d, personal or family hx of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma, malignant neoplasm in past 5yr, previous joint replacement in target knee, arthroscopy/injections in target knee in last 3mo, elective surgery scheduled during trial, symptomatic hip OA, chronic widespread pain, neuropathic pain, hx or planned obesity tx with surgery or a weight loss device (unless >1yr since procedure), self-report of recent wt change >5kg within 90d, uncontrolled thyroid dx, tx with GLP1 agonist in past 90d, ESRD, hx of MI / stroke / UA / TIA in past 60d, HF NYHA class IV, hx of psychiatric conditions… (See other notes of interest for remainder of list).
- **POPULATION at baseline (recruitment from Oct 2021 to Mar 2022; screened 785 patients, generally well balanced:**
  - **N=407 enrolled** (271 semaglutide, 136 placebo); protocol suggested would screen 420 subjects to achieve 375 total subjects to achieve desired power of 90% for change in WOMAC (sufficiently powered to detect a difference)
  - Mean age 56yr, female 81.6%, white 60.9%, baseline BMI 40.3 (41% had severe obesity with BMI ≥40; mean body wt = 108.6kg), waist circumference 118.7cm, WOMAC **pain** intensity score = 70.9 ("severe" pain, normalized to 0-100 scale, =35.5/50 if not normalized), other WOMAC baseline scores (stiffness & function) not reported. BP 132/82. Concurrent conditions: HTN 48%, dyslipidemia 30%, CVD 5.2.
    - The groups were ?relatively well balanced at baseline: in sema group: were a few more women, pain scores slightly higher, more use of acetaminophen at baseline. Notably: In sema group vs placebo = BMI ≥40 → 44% vs 34.6%, BMI 35-<40 → 31% vs 41.2%; and the subgroup analysis suggested the BMI ≥40 group had slightly more pain reduction than the BMI 35-<40 group.
  - **Completed the tx period**: 235 (86.7%) semaglutide, 77.9% placebo; completed the full trial period: 90.8% vs 89.7%.
    - At tx period end: 211 (89.8%) were on 2.4mg, 9 (3.8%) on 1.7mg to <2.4mg, and 4 (1.7%) did not report dose (seems to have been tolerated relatively well)

INTERVENTION/COMPARISON:

- **Semaglutide 2.4mg** vs **placebo** as control (2:1 stratification) – given subcut once weekly x 68wk (goal of 52wk at target dose)
  - Adjunct to lifestyle modifications - All received counseling on a reduced-calorie diet + physical activity
  - Semaglutide started at 0.24mg, ↑ q4wk, goal to reach 2.4mg by week 16 (but could reduce to 1.7mg if AE but were to try to escalate to 2.4mg a second time if safe at investigator's discretion).
  - Patients kept electronic diary to document pain (worst daily knee pain using NRS) & pain-medication use.
  - Used ITT (all randomized); safety analysis was all randomized + received ≥1 dose.
  - **Treatment Policy Estimand (1')**: description of the tx effect in a real-world setting (regardless of adherence, AE, other interventions such as medication or joint replacement) → used in the full analysis population (regardless of adherence, other interventions, whether they did the washout properly)
  - Used multiple imputation to account for missing data at end.
  - **Trial Product Estimand (2')**: Assessed efficacy if the trial regimen was followed (results similar to tx policy).
  - "In trial period" = randomization to last date of contact (whether d/c prescription or rescue intervention); "On tx period" = received drug + 2wk, excluding any period of temporary interruption of the regimen).

OUTCOMES – over 68 weeks:

- **Primary:** 1) % of change in body weight; 2) mean change in the self-reported WOMAC pain score (*Western Ontario & McMaster Universities Osteoarthritis Index*) from baseline to week 68.
- **Secondary**:
  - "**Confirmatory**": Change in physical-function score using the SF-36 (Short Form Health Survey v2.0, scale 0-100, higher=better outcomes); # of participants with ≥5% and with ≥10% body wt decrease; change in WOMAC physical-function score
  - "**Supportive**": MANY! Included: change in waist circumference, WOMAC stiffness score, WOMAC total score, SF-36 components
    - Protocol amended to include numerous others, including stated pain intensity (NRS from diary), stated pain medication use, and numerous endpoints relating to clinically meaningful changes
  - "**Exploratory**": Change in 6min walking distance (protocol also noted use of and change in analgesics, only graph data reported).
  - **Safety**: Noted AE previously described, so used a "targeted approach" to collect safety data (only SAE, AE leading to D/C, AE warranting invasive knee procedures, medication error including wrong route of administration/missed dose/drug misuse or overuse, acute pancreatitis, COVID-19, pregnancy, or pregnancy-related AE). Also monitored BP.
- **Subgroup analysis** (not pre-specified): change in WOMAC pain score by BMI – little difference; there was ↓ WOMAC pain in all subgroups, though slightly less in the BMI 35-<40 group; BMI<35: -17.8 (-28.1,-7.4), BMI 35-<40: -10.3 (-19.7, -0.9), BMI≥40: -17.7 (-26.7, -8.8).

RESULTS Follow up over 68 weeks

Clinical Endpoints	semaglutide n=271	placebo n=136	Absolute Difference	NNT/NNH /68wk	Comments
PRIMARY ENDPOINTS –					- "Alpha split" for 5% significance level between 2 end points (1% change in body weight, 4% change in WOMAC pain). If both superior (they were), would test confirmatory endpoints at 5% significance (hierarchal manner). "Supportive" & "Exploratory" not controlled for multiplicity & not used to infer treatment effects. - Change in actual body weight about ~25lbs difference. - Clinically meaningful difference in WOMAC , started to see difference at ~wk16 - 6/18 AE leading to D/C were GI related - no stat sig differences for other safety areas (note that the protocol for gradual dose escalation would help with GI AE) - rate for D/C tx: 34/271 sema (12.5%, mostly due to AE) vs 29/136 placebo (21.3%, mostly due to "other" – not defined, not effective?)
% of change in body weight	-13.7%	-3.2%	-10.5% (-12.3, -8.6)	-	
Mean change in the WOMAC **pain** score (normalized to 0-100)	-41.7 points	-27.5 points	-14.1 points (-20. -8.3)	-	
SELECT SECONDARY ENDPOINTS – (* indicates supportive outcomes)					
SF-36 physical-fx score	12 points	6.5 points	5.6 points (3.1,8)	-	
% of patients with meaningful (≥11.4pt) improvement in SF-36v2*	58%	29.4%	28.6% (18, 39.3) **OR** 3.3 (2, 5.4)	NNT≈4	
WOMAC **physical-fx** score	-41.5 points	-26.7 points	-14.9 points(-20.4,-9.3)	-	
% of patients with meaningful (≥41.2pt) improvement in WOMAC **physical-fx** score*	50.4%	29%	21.4% (10.6, 32.2) **OR** 2.5 (1.5, 4.1)	NNT≈5	
% of patients with body weight ↓ ≥5%	85.2%	33.6%	51.6% (41.6, 61.6) **OR** 11.4 (6.6, 19.6)	NNT≈2	
WOMAC **total** score*	-41.8 points	-26.9 points	-14.9 points(-20.5,-9.3)	-	
NRS Pain intensity*	-2.5 points	-1.4 points	-1 point (-1.6, -0.5)	-	
Safety/Other Outcomes –					
SAE	27 (10%)	11 (8.1%)	1.9% (-4.7, 7.3)	NNH≈53 NS	
Serious GI event	4 (1.5%)	1 (0.7%)	0.7% (-2.7, 3.1)		
AE leading to D/C	18 (6.7%)	4 (3%)	3.7 (-1.3, 7.7)	NNH≈27 NS	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:

- WOMAC is a validated tool in OA, considers pain, stiffness, and function
- Lifestyle counseling was provided for both groups, presumably equally - reduced confounding?
- Primary estimand helps with generalizability of findings to real world; Trial product estimand results were similar to treatment protocol estimand: this is reassuring for accuracy of results
- Trial was sufficiently powered (adequate sample size) to detect a difference

LIMITATIONS:

- Weight loss would have been likely to unblind to treatment group (some had over 20% wt reduction in tx arm), could influence the **subjective reports** relating to WOMAC/SF-36 & perhaps also motivation related to lifestyle interventions (though the authors said, "*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*.")
- Unclear why the weighted tx arm 2:1 with placebo. If the participants knew they had 2:1 odds of being in treatment arm, this could enhance the placebo effect
- Actual adherence to diet & exercise unknown/not reported
- Most clinically important would have been measuring functional improvement as a primary outcome, clinically meaningful outcomes were included (after protocol amendment) as supportive outcomes only.
- Many exclusion criteria, including those with diabetes, and those with complex chronic pain (e.g. widespread, neuropathic component). Exclusion of so many people limits generalizability (screened 785 patients, enrolled 407 → ~52%).
- Trial not designed to assess safety (though they note prior studies had already done this); numerically had more serious malignant neoplasms, GI event, acute gallbladder disease, however not statistically significant different; trial too small to be reassuring or show a difference if there is one.

UNCERTAINTIES:

- What happens when the drug is stopped? (prior studies suggest weight gain is likely to recur →in **STEP 1** extension, weight regain was 2/3 of wt loss within 1 year of discontinuation)
- Cost-benefit analysis? (patients without another indication or coverage may need to pay out of pocket, does the benefit outweigh the cost?)
- Would there be any analgesic effect with semaglutide in patients who do not have an elevated BMI? (trial discussion suggested may be a mechanism for semaglutide to reduce inflammation, however trial not designed to show this)
- How does semaglutide compare to usual care in a broader population?
- How do the psychological components related to pain change with body weight reduction/semaglutide? (only SF-36 physical function scores reported)

Other notes of interest:

- **Additional exclusion criteria**: (continued) … known / suspected hypersensitivity to ingredient, pregnant / breastfeeding / planning pregnancy / childbearing potential without contraception, recent participation in another trial (within 90d other than COVID-19), other household members in the trial, hx of MDD within 2yr, other psychiatric d/o (schizophrenia, bipolar), hx suicide attempt or behaviour within 30d, known/suspected alcohol or drug abuse, anything else the investigator deems might jeopardize the subject's safety or adherence to the protocol.
- WOMAC NRS 3.1 scoring= pain (50 points), stiffness (20 points), physical function (170 points) (these were all normalized to a 0-100 scale when reported as individual & total components)
- Additional decrease in body weight % in sema vs placebo: 47.8% had ≥15% wt reduction (vs 2.5%) and 23.3% had ≥20% wt reduction (vs 0%).
- % of pt using NSAID/acetaminophen decreased in both groups (but more in the sema group) → acetaminophen was more prevalent in sema group at baseline
- Numerous Protocol amendments: added pain diary, changed how often different measures assessed (added pain intensity measures, didn't look at 1° endpoints at wk28, added clinical meaningful endpoints)
- Total withdrawal: 90.8% vs 89.7% completed the trial (similar rates); also similar rates of withdrawal from trial
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Costs: semaglutide **WEGOVY** ✗ ⊗ 2.4mg subcut wkly **$460**/30d + potentially cost associated with lifestyle measures (diet & exercise)

RxFILES RELATED LINKS

- Non-insulin Type 2 Diabetes Agents chart
- Weight Loss chart
- **SELECT** Trial Summary

ACKNOWLEDGEMENTS: Prepared By: Amy Wiebe, BSP (Initial version –Oct 2025). **Reviewers:** Loren Regier

References:

1) Bliddal H, Bays H, Czernichow S, et al (the STEP 9 Study Group). Once-Weekly Semaglutide in Persons with Obesity and Knee Osteoarthritis. NEJM. 2024;391(17):1573-83. DOI: 10.1056/NEJMoa2403664.
2) Troy T, Ngo H, Pham L. Weight Loss in Patients With Overweight or Obesity and Knee Osteoarthritis. *Am Fam Physician.* 2024;110(6):641-42.
3) Panunzi S, Maltese S, De Gaetano A, et al. Comparative efficacy of different weight loss treatments on knee osteoarthritis: a network meta-analysis. Obes Rev 2021;22(8):e13230.
4) 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):314–23. https://doi.org/10.1093/ajcn/nqaa328.

Abbreviations: ✗ =Non-formulary in SK ⊗=not covered by NIHB 1°=primary **ACR**=American College of Rheumatology **AE**=adverse events **BMI**=body mass index **BP**=blood pressure **CV**=cardiovascular **CVD**=cardiovascular disease **d**=day **D/C**=discontinuation **d/o**=disorder **fx**=function **GI**=gastrointestinal **GLP1**=glucagon-like peptide-1 receptor agonist **HF**=heart failure **HTN**=hypertension **hx**=history **ITT**=intention to treat **kg**=kilogram **lbs**=pounds **MDD**=major depressive disorder **MI**=myocardial infarction **NSAID**=non-steroidal anti-inflammatory drug(s) **NRS**=numerical rating scale **NYHA**=New York Heart Association **OA**=osteoarthritis **OR**=odds ratio **SAE**=serious adverse event **sema**=semaglutide **SF-36**=Short Form Health Survey **subcut**=subcutaneous **TIA**=transient ischemic attack **tx**=treatment **UA**=unstable angina **vs**=versus **wk**=week(s) **WOMAC**=Western Ontario and McMaster Universities Osteoarthritis Index **wt**=weight **yr**=year(s)