An indirect treatment comparison of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg using multilevel network meta-regression

Ildiko Lingvay,1 Robert Bauer,2 James Baker-Knight,2 Jack Lawson,2 Richard Pratley,3

1 Department of Internal Medicine/Endocrinology, Department of Clinical Sciences, UT Southwestern Medical Center, University of Texas, Dallas, TX, USA
2 Novo Nordisk A/S, Søborg, Denmark
3 AdventHealth Translational Research Institute, Orlando, FL, USA

Corresponding author’s contact information
James Baker-Knight, Senior Global HEOR Manager
+45 3075 2650 (direct)
JMKG@novonordisk.com

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Name and address of person to whom reprint requests should be addressed

James Baker-Knight
Novo Nordisk A/S
Novo Alle 1
2880 Bagsvaerd
Denmark.

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All authors contributed to the conception, drafting, and critical editing of the manuscript. R.B. conducted the statistical analyses.
Abstract

**Aims:** Currently no head-to-head data are available comparing semaglutide 2.0 mg with dulaglutide 3.0 mg or 4.5 mg. We conducted an indirect treatment comparison (ITC) of their effects on glycated haemoglobin (HbA\(_{1c}\)) and body weight in patients with type 2 diabetes (T2D).

**Materials and methods:** Multilevel network meta-regression (ML-NMR) was conducted, based on a connected evidence network of published results from the AWARD-11 trial and individual patient data (IPD) from the SUSTAIN FORTE and SUSTAIN 7 trials.

**Results:** Semaglutide 2.0 mg significantly reduced HbA\(_{1c}\) versus dulaglutide 3.0 mg and 4.5 mg, with estimated treatment differences (ETD) of -0.44%-points (95% credible interval [CrI]: -0.68, -0.19) and -0.28%-points (95% CrI: -0.52, -0.03), respectively. Semaglutide 2.0 mg also significantly reduced body weight versus dulaglutide 3.0 mg and 4.5 mg with ETDs of -3.29 kg (95% CrI: -4.62, -1.96) and -2.57 kg (95% CrI: -3.90, -1.24), respectively. Odds of achieving HbA\(_{1c}\) <7.0% were significantly greater for semaglutide 2.0 versus dulaglutide 3.0 mg (odds ratio [OR]: 2.23 [95% CrI: 1.15, 3.90]), while this did not reach significance for semaglutide 2.0 mg versus dulaglutide 4.5 mg (OR: 1.58 [95% CrI: 0.82, 2.78]). Sensitivity analyses supported the main analysis findings.

**Conclusions:** This ITC demonstrated significantly greater reductions from baseline in HbA\(_{1c}\) and body weight with semaglutide 2.0 mg vs dulaglutide 3.0 mg and 4.5 mg. The findings of this study provide important comparative effectiveness information until randomised head-to-head studies become available.

**Keywords**

semaglutide, dulaglutide, HbA\(_{1c}\), body weight, diabetes, multilevel network meta regression
Introduction

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) provide an effective treatment option for people with type 2 diabetes (T2D), offering improved glycaemic control alongside weight management and cardiovascular benefits.\(^1\) Current treatment guidelines recommended GLP-1 RAs across the treatment pathway for patients with T2D not adequately controlled on metformin alone, and as a preferred option for those with established cardiovascular disease regardless of glycated haemoglobin (HbA\(_{1c}\)) level.\(^2\) Semaglutide and dulaglutide are both long-acting GLP-1 RAs, which are available for once-weekly (QW) administration via subcutaneous injection. However, they differ in molecular structure, resulting in potential differences in their metabolic effects.\(^3\)-\(^5\) Understanding the impact of these differences on clinical outcomes is important for clinicians.

Semaglutide and dulaglutide have both been investigated extensively as part of the SUSTAIN and AWARD clinical trial programmes, respectively. A head-to-head trial, SUSTAIN 7, compared the efficacy and safety of semaglutide and dulaglutide at lower doses (semaglutide 0.5 mg vs dulaglutide 0.75 mg) and higher doses (semaglutide 1.0 mg vs dulaglutide 1.5 mg) in patients with T2D inadequately controlled with metformin.\(^4\) Superiority of semaglutide compared with dulaglutide was demonstrated with regard to reducing HbA\(_{1c}\) and body weight at week 40.\(^4\) The two treatments had similar safety profiles, with similar proportions of patients experiencing gastrointestinal (GI) adverse events and discontinuing treatment due to adverse events.\(^4\)

Semaglutide was initially approved for use at maintenance doses of 0.5 mg and 1.0 mg by the Food and Drug Administration (FDA) in 2017\(^6\) and European Medicines Agency (EMA) in 2018;\(^7\) and dulaglutide was initially approved at doses of 0.75 mg and 1.5 mg by the FDA and EMA in 2014.\(^8,9\) However, T2D is a progressive disease, and treatment intensification is often required for maintenance of glycaemic control and minimisation of complications.\(^10\) The results of SUSTAIN 7 and other trials in the SUSTAIN and AWARD programmes indicate that higher doses of GLP-1 RAs are associated with greater reductions in HbA\(_{1c}\), although there is a need to balance treatment benefits.
with adverse events, particularly GI adverse events. Therefore, higher maintenance doses of semaglutide and dulaglutide have recently been investigated to provide potential treatment options for patients already receiving GLP-1 RAs who require further treatment intensification. Dulaglutide 3.0 mg and 4.5 mg were investigated in AWARD-11 and subsequently approved in 2020 and 2021 by the FDA and EMA, respectively. Semaglutide 1.0 mg has previously been compared with dulaglutide 3.0 mg and 4.5 mg using a Bucher indirect treatment comparison (ITC). Semaglutide 2.0 mg has also been investigated in SUSTAIN FORTE, and is currently under review by the FDA and EMA.

While SUSTAIN 7 provides a head-to-head comparison between lower doses of semaglutide and dulaglutide, there are currently no head-to-head data comparing the higher doses of the two treatments. The objective of this study was to compare the efficacy of semaglutide 2.0 mg with dulaglutide 3.0 mg and 4.5 mg doses using an ITC based on aggregate and individual patient data (IPD) from SUSTAIN FORTE and SUSTAIN 7 and published aggregate data from AWARD-11.

Methods

A multilevel network meta-regression (ML-NMR) was conducted in a Bayesian framework to compare efficacy outcomes of dulaglutide 3.0 mg and 4.5 mg with semaglutide 2.0 mg using data from the SUSTAIN FORTE, SUSTAIN 7, and AWARD-11 randomised controlled trials (RCTs). ML-NMR has been recently introduced as a methodology for conducting ITCs when IPD are available for some, but not all, included trials in a connected evidence network. When implemented in a Bayesian framework, ML-NMR retains the flexibility and extensibility of Bayesian network meta-analysis (NMA), allowing prior information to be used, data types with differing likelihoods to be included, and the analysis to be embedded in a probabilistic cost-effectiveness framework. Unlike other methods for ITC that allow for population adjustment (e.g. matching-adjusted indirect comparison [MAIC] and simulated treatment comparison methods), ML-NMR enables comparisons across multiple studies. It also allows comparison in any target population within a given covariate...
distribution, meaning that comparisons can be made in each of the included trial populations in a connected evidence network. A shared effect modifier assumption was chosen to make the model estimable. Therefore, it was assumed that the potential effect modifier interaction coefficients are identical for all dulaglutide dose levels. This assumption was necessary as data for the high doses of dulaglutide (3.0 mg and 4.5 mg) were only available on aggregate level and for one trial (AWARD-11).

Data sources

Published aggregate data were available from AWARD-11, and aggregate and IPD were available from SUSTAIN FORTE and SUSTAIN 7. SUSTAIN FORTE reported a comparison between semaglutide 1.0 mg and semaglutide 2.0 mg, SUSTAIN 7 compared semaglutide 1.0 mg with dulaglutide 1.5 mg, and AWARD-11 compared dulaglutide 3.0 mg and 4.5 mg with dulaglutide 1.5 mg. Therefore, the three trials formed the connected evidence network shown in Figure 1, in which SUSTAIN 7 was used as an anchoring trial. Missing data in the studies for which IPD were available were imputed using multiple imputation and the multiply imputed data sets were incorporated into the ML-NMR model as described in Gelman et al.

Outcomes assessed

Outcomes assessed were change from baseline in HbA1c and change from baseline in body weight, corresponding with the primary and secondary confirmatory outcomes in all included trials. These outcomes were assessed at 40 weeks in SUSTAIN FORTE and SUSTAIN 7, and at 36 weeks in AWARD-11. For these continuous outcomes, mean treatment differences with associated 95% credible intervals (CrIs) were calculated. Proportions of patients achieving HbA1c <7.0% were also assessed and, for this dichotomous outcome, treatment odds ratios (ORs) with associated 95% CrIs were calculated. Statistical significance was determined as CrI not crossing zero.
Study and patient characteristics

Study characteristics and inclusion criteria of the SUSTAIN FORTE, SUSTAIN 7, and AWARD-11 trials used in the analysis are shown in Table 1. SUSTAIN FORTE and SUSTAIN 7 were multinational, Phase IIIb trials: SUSTAIN FORTE was a double-blind trial and SUSTAIN 7 was open-label. AWARD-11 was a double-blind, multinational, Phase III trial. There were some differences in terms of trial design and inclusion criteria among the studies; notably, there were differences in HbA\textsubscript{1c} inclusion criteria among the trials.

While baseline characteristics were generally similar among the trials (Table 2), the analysis was conducted using a connected network in which SUSTAIN 7 was used as an anchoring trial, making robust analysis possible despite some differences. Although there is little evidence to suggest that differences in baseline characteristics (age, sex, diabetes duration, glycaemic control and BMI) result in effect modification for semaglutide vs dulaglutide, ML-NMR takes into account both potential effect modifiers and prognostic factors across trials, allowing adjustment for baseline covariates. Therefore, in the main analysis, baseline HbA\textsubscript{1c}, BMI, and diabetes duration were adjusted for as potential effect modifiers. An unadjusted analysis was also conducted as a sensitivity analysis.

ML-NMR also allows comparison in each of the included trial populations in a connected evidence network. For the main analysis, the patient population considered was that of AWARD-11, which is in line with the approach that would be used in other population-adjusted methods (e.g. MAIC) in which IPD would be used to match baseline summary statistics to aggregate data. The impact of using different populations was explored in sensitivity analyses.

Analyses were based on results for the trial product estimand in SUSTAIN FORTE and SUSTAIN 7, and the efficacy estimand in AWARD-11. These estimands were similar in that they were defined in all trials as including patients on treatment without rescue therapy. This means that they target the treatment effect when all patients continue to use the treatment for the planned duration of the trial without rescue medication, thus reflecting effect when treatment is used as intended.
Sensitivity analyses

Three sensitivity analyses were conducted to assess the findings of the main analysis. For the first sensitivity analysis (sensitivity analysis 1) the impact of using the SUSTAIN 7 patient population as the target population was explored. In another analysis (sensitivity analysis 2), the impact of using the patient population from SUSTAIN FORTE was explored. To explore the impact of adjustment for potential effect modifiers, an unadjusted analysis (sensitivity analysis 3) using standard Bayesian NMA methodology was also conducted.

To account for the difference in timing of assessments between AWARD-11 (36 weeks) and the SUSTAIN trials (40 weeks), an additional sensitivity analysis was conducted using SUSTAIN 7 and SUSTAIN FORTE results corresponding to week 36 (obtained from linear interpolation between the week 28 and week 40 visits). Sensitivity analyses 1 and 2, exploring the impact of using the SUSTAIN 7 and SUSTAIN FORTE patient populations, respectively, as the target populations, were also conducted using the interpolated 36-week data from SUSTAIN 7 and SUSTAIN FORTE.

Results

In total, 1,842 patients were randomly assigned to a dulaglutide dose in AWARD-11 (3.0 mg, n=616; 4.5 mg, n=614; 1.5 mg, n=612). In SUSTAIN 7, 599 out of 1,199 patients were randomly assigned to the highest available doses of semaglutide or dulaglutide (semaglutide 1.0 mg, n=300; dulaglutide 1.5 mg, n=299). In SUSTAIN FORTE, 961 patients were randomly assigned to either dose of semaglutide (semaglutide 1.0 mg, n=481; semaglutide 2.0 mg, n=480).

Change in HbA1c

In the main analysis, semaglutide 2.0 mg was significantly more effective at reducing HbA1c from baseline compared with dulaglutide 3.0 mg and 4.5 mg with estimated treatment differences (ETDs) of \(-0.44\text{-points} (95\% \text{ CrI: } -0.68, -0.19)\) and \(-0.28\text{-points} (95\% \text{ CrI: } -0.52, -0.03)\), respectively (Figure 2A). Sensitivity analyses adjusting for different target populations (sensitivity analyses 1 and
2) and without adjustment for potential effect modification (sensitivity analysis 3) supported the findings of the main analysis (Figure 2A), although in sensitivity analysis 1, the difference between treatment did not reach statistical significance. Sensitivity analyses conducted using SUSTAIN 7 and SUSTAIN FORTE results corresponding to week 36 also supported the findings of the main analysis (Figure 3A).

**Change in body weight**

In the main analysis, semaglutide 2.0 mg was significantly more effective at reducing body weight from baseline compared with dulaglutide 3.0 mg and 4.5 mg with ETDs of \(-3.29\) kg (95% CrI: \(-4.62, -1.96\)) and \(-2.57\) kg (95% CrI: \(-3.90, -1.24\)), respectively (Figure 2B). Sensitivity analyses adjusting for different target populations (sensitivity analyses 1 and 2) and without adjustment for potential effect modification (sensitivity analysis 3) supported the findings of the main analysis (Figure 2B). Sensitivity analyses conducted using SUSTAIN 7 and SUSTAIN FORTE results corresponding to week 36 also supported the findings of the main analysis (Figure 3B).

**Patients achieving HbA1c <7.0%**

In the main analysis, the proportion of patients achieving HbA1c <7.0% was significantly greater for semaglutide 2.0 compared with dulaglutide 3.0 mg, with an odds ratio (OR) of 2.23 (95% CrI: 1.16, 3.90), while this did not reach significance for semaglutide 2.0 mg versus dulaglutide 4.5 mg (OR: 1.58 [95% CrI: 0.82, 2.78]) (Figure 2C). Sensitivity analyses adjusting for different target populations (sensitivity analyses 1 and 2) and without adjustment for potential effect modification (sensitivity analysis 3) supported the findings of the main analysis (Figure 2C). Sensitivity analyses conducted using SUSTAIN 7 and SUSTAIN FORTE results corresponding to week 36 also supported the findings of the main analysis (Figure 3C).
Discussion

This study indirectly compared the effect of two high-dose GLP-1 RAs (semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg), on reducing HbA1c and body weight from baseline in patients with T2D using ML-NMR. In this study, semaglutide 2.0 mg provided significantly greater reductions from baseline in HbA1c and body weight vs dulaglutide 3.0 mg and 4.5 mg. In addition, significantly greater proportions of patients achieving HbA1c <7.0% with semaglutide 2.0 mg vs dulaglutide 3.0 mg, and comparable proportions of patients achieved HbA1c <7.0% with semaglutide 2.0 mg and dulaglutide 4.5 mg. Results of the main analysis were supported by sensitivity analyses, and consistent regardless of the target population used in the ML-NMR.

Semaglutide 1.0 mg has previously been compared with dulaglutide 3.0 mg and 4.5 mg using a Bucher ITC. In the analysis, significantly greater reductions in HbA1c were demonstrated with semaglutide 1.0 mg vs dulaglutide 3.0 mg, and comparable reductions in HbA1c were shown for semaglutide 1.0 mg and dulaglutide 4.5 mg. Significantly greater reductions in body weight were also demonstrated with semaglutide 1.0 mg vs both doses of dulaglutide. However, in the absence of a head-to-head trial comparing semaglutide 2.0 mg with dulaglutide 3.0 mg and 4.5 mg, this is the first comparison of these doses of semaglutide and dulaglutide. The results provide comparison of two high dose GLP-1 RAs, which have been shown in clinical trials to provide greater reductions in HbA1c and body weight than their lower dose equivalents, thereby providing additional options for patients who require treatment intensification.

Strengths of this study include the comparison method used. As discussed in a recent report by the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU), ML-NMR provides a means of conducting a population-adjusted analysis using a connected evidence network, as opposed to only two trials, in situations where IPD are available for some, but not all included trials. The report recommends development of a new Technical Support Document (TSD) recommending ML-NMR as the preferred population-adjusted approach for anchored
While there were some differences in baseline characteristics of patients enrolled across the three included trials, based on subgroup analyses of SUSTAIN 7, there is little evidence to suggest that differences in baseline characteristics (age, sex, diabetes duration, glycaemic control and BMI) result in effect modification for semaglutide vs dulaglutide. The main analysis adjusted for baseline HbA1c, BMI, and diabetes duration as potential effect modifiers, thereby accounting for differences in baseline characteristics among trials. However, a sensitivity analysis conducted without adjustment for potential effect modifiers supported the findings of the main analysis, confirming no appreciable impact of effect modification on the results of the analysis. The ML-NMR approach allows comparison in any target population within a given covariate distribution, meaning that comparisons can be made in each of the included trial populations in a connected evidence network. Comparisons were conducted using the AWARD-11 population in the main analysis. As only published aggregate data were available for AWARD-11, this is in line with the approach that would be used in other population-adjusted methods, such as MAIC, in which IPD would be used to match baseline summary statistics to aggregate data. This is also aligned with the MAIC conducted as a supplementary analysis in the recent publication indirectly comparing semaglutide 1.0 mg with dulaglutide 3.0 mg and 4.5 mg. The impact of using the SUSTAIN FORTE and SUSTAIN 7 populations was explored in supplementary analyses, all of which supported the findings of the main analysis.

The current study focused only on efficacy outcomes and did not evaluate differences between treatments in terms of safety outcomes, which are highly relevant to clinical decision making. However, a quantitative ITC of safety outcomes is intrinsically more difficult, due to cross-trial differences in the assessment of adverse events. In all included trials, a similar safety profile was observed across treatment arms; adverse event rates were comparable between semaglutide 1.0 mg and dulaglutide 1.5 mg treatment arms in SUSTAIN 7, dulaglutide 1.5 mg, 3.0 mg, and 4.5 mg treatment arms in AWARD-11, and semaglutide 1.0 mg and 2.0 mg treatment arms in SUSTAIN FORTE. Furthermore, the current study did not evaluate differences in cardiovascular outcomes between treatments. While cardiovascular outcomes trials have demonstrated cardiovascular
benefits of semaglutide 0.5 mg and 1.0 mg\textsuperscript{23} and dulaglutide 1.5 mg\textsuperscript{24} among people with T2D at high cardiovascular risk, cardiovascular outcomes for semaglutide 2.0 mg and dulaglutide 3.0 mg and 4.5 mg are yet to be fully established.

A limitation of this study is comparison of estimands across trials, as there are subtle differences in the handling of intercurrent events, with different criteria for initiation of rescue medication. Furthermore, it was not possible to conduct an analysis based on the results of the treatment policy estimand in SUSTAIN FORTE\textsuperscript{14} and SUSTAIN 7,\textsuperscript{4} similar to the treatment-regimen estimand in AWARD-11,\textsuperscript{11} which included efficacy data for patients regardless of treatment discontinuation or rescue medication. This was because confidence intervals and standard errors for estimates on treatment level for the treatment-regimen estimand from AWARD-11 have not been published. However, the trial product estimand may be seen as the more relevant estimand for comparisons between treatments, as it provides estimates of treatment effects without potential confounding due to intercurrent events.

Despite the limitations, the ML-NMR approach allowed for a robust ITC of changes in HbA\textsubscript{1c} and body weight associated with semaglutide 2.0 mg compared with dulaglutide 3.0 mg and 4.5 mg, and showed consistent results regardless of the target population used in analyses. As for any ITC, a head-to-head trial would be required to fully validate the findings.

**Conclusion**

This ITC demonstrated significantly greater reductions from baseline in HbA\textsubscript{1c} and body weight with semaglutide 2.0 mg vs dulaglutide 3.0 mg and 4.5 mg. The findings of this study, and particularly the results provided in different trial populations, provide important comparative effectiveness information until randomised head-to-head studies become available.
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Data availability

Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in References.
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Legends for figures and tables

Figure 1: Network of evidence for semaglutide vs high dose dulaglutide
Abbreviations: QW, once-weekly.

Figure 2: Efficacy outcomes of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg
Change in HbA1c from baseline (A); change in bodyweight (kg) from baseline (B); proportion of patients achieving target HbA1c (C). Main analysis, sensitivity analyses 1–3.
Abbreviations: CrI, credible interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; OR, odds ratio.

Figure 3: Efficacy outcomes of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg utilising SUSTAIN 7 results corresponding to week 36
Change in HbA1c from baseline (A); change in bodyweight (kg) from baseline (B); proportion of patients achieving target HbA1c (C). Main analysis, sensitivity analyses 1 and 2.
Abbreviations: CrI, credible interval; ETD, estimated treatment difference; HbA1c, glycated haemoglobin; OR, odds ratio.
Table 1: Overview of study characteristics and inclusion criteria of included trials

†Note SUSTAIN 7 also included semaglutide 0.5 mg and dulaglutide 0.75 mg, however these were not treatments of interest for the current analysis.

Abbreviations: BMI, body mass index; HbA1c, glycated haemoglobin; RCT, randomised controlled trial; T2D, type 2 diabetes.

Table 2: Characteristics of enrolled patients reported in SUSTAIN FORTE, SUSTAIN 7, and AWARD 11

†Note SUSTAIN 7 also included semaglutide 0.5 mg and dulaglutide 0.75 mg, however these were not treatments of interest for the current analysis.

‡Fasting plasma glucose in SUSTAIN FORTE and SUSTAIN 7, fasting serum glucose in AWARD-11.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; SD, standard deviation; T2D, type 2 diabetes.
Figures

Figure 1: Network of evidence for semaglutide vs high dose dulaglutide

Abbreviations: QW, once-weekly
Figure 2: Efficacy outcomes of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg
Change in HbA$_{1c}$ from baseline (A); change in bodyweight (kg) from baseline (B); proportion of patients achieving target HbA$_{1c}$ (C).
Abbreviations: Crl, credible interval; ETD, estimated treatment difference; HbA$_{1c}$, glycated haemoglobin; OR, odds ratio.
A)

Change in HbA1c, %

| Analysis                                | ETD      | 95% CI       |
|----------------------------------------|----------|--------------|
| Main analysis (dulaglutide 3.0 mg)     | -0.42    | [-0.65; -0.19] |
| Sensitivity analysis 1 (dulaglutide 3.0 mg) | -0.39    | [-0.63; -0.15] |
| Sensitivity analysis 2 (dulaglutide 3.0 mg) | -0.44    | [-0.68; -0.20] |
| Main analysis (dulaglutide 4.5 mg)     | -0.25    | [-0.49; -0.02] |
| Sensitivity analysis 1 (dulaglutide 4.5 mg) | -0.23    | [-0.47; 0.01] |
| Sensitivity analysis 2 (dulaglutide 4.5 mg) | -0.28    | [-0.52; -0.04] |

Favours semaglutide

Favours dulaglutide
Change in body weight, kg

| Analysis                        | ETD  | 95% Crl     |
|--------------------------------|------|-------------|
| Main analysis (dulaglutide 3.0 mg) | -3.03 | [-4.29; -1.79] |
| Sensitivity analysis 1 (dulaglutide 3.0 mg) | -3.09 | [-4.40; -1.78] |
| Sensitivity analysis 2 (dulaglutide 3.0 mg) | -3.05 | [-4.33; -1.79] |
| Main analysis (dulaglutide 4.5 mg) | -2.31 | [-3.56; -1.06] |
| Sensitivity analysis 1 (dulaglutide 4.5 mg) | -2.36 | [-3.68; -1.04] |
| Sensitivity analysis 2 (dulaglutide 4.5 mg) | -2.33 | [-3.60; -1.06] |

Favours semaglutide

Favours dulaglutide
Figure 3: Efficacy outcomes of semaglutide 2.0 mg versus dulaglutide 3.0 mg and 4.5 mg utilising SUSTAIN 7 results corresponding to week 36
Change in HbA₁c from baseline (A); change in bodyweight (kg) from baseline (B); proportion of patients achieving target HbA₁c (C).
Crl, credible interval; ETD, estimated treatment difference; HbA₁c, glycated haemoglobin; OR, odds ratio.
## Tables

**Table 1: Overview of study characteristics and inclusion criteria of included trials**

| Study name (Primary reference) NCT number | Study design | Inclusion criteria | Background medication | Duration of follow-up | Randomised treatment | Number of patients randomised | Completion date |
|------------------------------------------|--------------|--------------------|-----------------------|-----------------------|----------------------|-------------------------------|----------------|
| SUSTAIN FORTE\(^{14}\) NCT03989232    | Phase IIIb, double-blind, RCT Multinational | HbA\(_{1c}\): 8.0–10.0\% | No restriction | At least 6 months | Metformin ≥1,500 mg/day (or a maximal tolerated dose) ≥90 days with or without sulphonylurea (≥half the maximum approved dose according to local label or maximum tolerated or effective dose) | Semaglutide 2.0 mg | 480 | November 2020 |
|                                          |              | BMI: 8.0–10.0\%    |                       |                       | Semaglutide 1.0 mg   | 481                          |                |
| SUSTAIN 7\(^{4*}\) NCT02648204         | Phase IIIb, open-label, RCT Multinational | HbA\(_{1c}\): 7.0–10.5\% | No restriction | Not specified | Metformin ≥1,500 mg/day (or a maximal tolerated dose) ≥90 days | Semaglutide 1.0 mg | 300 | May 2017 |
|                                          |              | BMI: 7.0–10.5\%    |                       |                       | Dulaglutide 1.5 mg   | 299                          |                |
| AWARD-11\(^{11}\) NCT03495102         | Phase III, double-blind, RCT Multinational | HbA\(_{1c}\): 7.5–11.0\% | ≥25 kg/m\(^2\)       | At least 6 months | Metformin ≥1,500 mg/day for ≥3 months | Dulaglutide 3.0 mg | 616 | May 2019 |
|                                          |              | BMI: 7.5–11.0\%    |                       |                       | Dulaglutide 4.5 mg   | 614                          |                |
|                                          |              |                   |                       |                       | Dulaglutide 1.5 mg   | 612                          |                |

Abbreviations: BMI, body mass index; HbA\(_{1c}\), glycated haemoglobin; RCT, randomised controlled trial; T2D, type 2 diabetes

\(^{1}\)Note SUSTAIN 7 also included semaglutide 0.5 mg and dulaglutide 0.75 mg, however these were not treatments of interest for the current analysis.
Table 2: Characteristics of enrolled patients reported in SUSTAIN FORTE, SUSTAIN 7, and AWARD-11

| Trial name (pooled treatment arms) | SUSTAIN FORTE | SUSTAIN 7† | AWARD-11 |
|-----------------------------------|---------------|------------|----------|
| Treatment                         | Semaglutide 2.0 mg and semaglutide 1.0 mg | Semaglutide 1.0 mg and dulaglutide 1.5 mg | Dulaglutide 1.5 mg, dulaglutide 3.0 mg and dulaglutide 4.5 mg |
| N                                 | 961           | 599        | 1,842    |
| Mean age (SD), years              | 58.0 (10.0)   | 55.6 (10.6) | 57.1 (10.0) |
| Female, %                         | 41.4          | 44.4       | 48.8     |
| Race, n (%)                       |               |            |          |
| White                             | 847 (88)      | 463 (77)   | 1,580 (86) |
| Asian                             | 69 (7)        | 93 (16)    | 45 (2.4)  |
| Black or African American         | 43 (4)        | 36 (6)     | 82 (4.5)  |
| American Indian or Alaska native | 1 (<1)        | 0          | 88 (4.8)  |
| Native Hawaiian or Pacific Islander | 0            | 0          | 5 (<1)    |
| Other                             | 1 (<1)        | 7 (1)      | 0        |
| Multiple                           | 0             | 0          | 42 (2.3)  |
| Mean HbA1c (SD), %                | 8.9 (0.6)     | 8.2 (0.9)  | 8.6 (1.0) |
| Mean body weight (SD), kg         | 99.3 (23.5)   | 94.5 (21.4) | 95.7 (20.3) |
| Mean BMI (SD), kg/m²              | 34.6 (7.0)    | 33.3 (6.5) | 34.2 (6.3) |
| Mean T2D duration (SD), years     | 9.5 (6.2)     | 7.5 (5.7)  | 7.6 (5.7) |
| Mean fasting glucose† (SD), mg/dL | 194.4 (50.0)  | 174.8 (44.0) | 184.1 (51.5) |
| Mean DBP (SD), mmHg               | 80.9 (9.4)    | 80.8 (8.9) | 78.7 (9.0) |
| Mean SBP (SD), mmHg               | 134.4 (14.0)  | 132.6 (14.1) | 131.8 (14.1) |
| Mean pulse rate (SD), beats/minute | 75.9 (10.1)  | 75.1 (10.5) | 75.5 (10.0) |
| Mean eGFR (SD), mL/min/1.73 m²    | 93.4 (16.9)   | 97.2 (16.0) | 93.5 (18.1) |
| Mean lipid levels (SD), mg/dL     | Not collected | 183.2 (44.7) | 177.5 (NR)§ |

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| Trial name | SUSTAIN FORTE | SUSTAIN 7† | AWARD-11 |
|------------|---------------|------------|-----------|
| Treatment (pooled treatment arms) | Semaglutide 2.0 mg and semaglutide 1.0 mg | Semaglutide 1.0 mg and dulaglutide 1.5 mg | Dulaglutide 1.5 mg, dulaglutide 3.0 mg and dulaglutide 4.5 mg |
| HDL cholesterol | Not collected | 45.0 (10.8) | 45.6 (NR)§ |
| LDL cholesterol | Not collected | 103.8 (38.8) | 93.4 (NR)§ |
| VLDL cholesterol | Not collected | Not collected | 34.5 (NR)§ |
| Triglycerides | Not collected | 183.3 (112.6) | 202.4 (NR)§ |

†Note SUSTAIN 7 also included semaglutide 0.5 mg and dulaglutide 0.75 mg, however these were not treatments of interest for the current analysis.
‡Fasting plasma glucose in SUSTAIN FORTE and SUSTAIN 7, fasting serum glucose in AWARD-11.
§Pooled data are not presented in the AWARD-11 publication. Mean values have been calculated as weighted average.

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NR, not reported; SD, standard deviation; T2D, type 2 diabetes; VLDL, very low-density lipoprotein.