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ORIGINAL RESEARCH

A Systematic Literature Review and Network Meta-Analysis Comparing Once-Weekly Semaglutide with Other GLP-1 Receptor Agonists in Patients with Type 2 Diabetes Previously Receiving 1–2 Oral Anti-Diabetic Drugs

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ABSTRACT

Introduction: Once-weekly semaglutide is a new glucagon-like peptide-1 (GLP-1) analogue administered at a 1.0 or 0.5 mg dose. As head-to-head trials assessing once-weekly semaglutide as an add-on to 1–2 oral anti-diabetic drugs (OADs) vs other GLP-1 receptor agonists (GLP-1 RAs) are limited, a network meta-analysis (NMA) was performed. The objective was to assess the relative efficacy and safety of once-weekly semaglutide vs GLP-1 RAs in patients with type 2 diabetes (T2D) inadequately controlled on 1–2 OADs.
Methods: A systematic literature review (SLR) was conducted in order to identify trials of GLP-1 RAs in patients inadequately controlled on 1–2 OADs. Data at 24 ± 4 weeks were extracted for efficacy and safety outcomes (feasible for analysis in a NMA), which included the key outcomes of change from baseline in glycated hemoglobin (HbA_{1c}), systolic blood pressure (SBP), and weight, as well as discontinuation due to adverse events (AEs). Data were synthesized using a NMA and a Bayesian framework.
Results: In total, 26 studies were included across the base case analyses. Once-weekly semaglutide 1.0 mg was associated with significantly greater reductions in HbA_{1c} and weight vs all GLP-1 RA comparators. Once-weekly semaglutide 0.5 mg also achieved significantly greater reductions in HbA_{1c} and weight compared with the majority of other GLP-1 RAs. Both doses of once-weekly semaglutide were associated with similar odds of discontinuation due to AEs compared with other GLP-1 RAs.
Conclusion: Overall, once-weekly semaglutide 1.0 mg as an add-on to 1–2 OADs is the most efficacious GLP-1 RA in terms of the reduction of HbA_{1c} and weight from baseline after 6 months of treatment. In addition, the analysis suggests that once-weekly semaglutide is well tolerated and not associated with an increase in discontinuations due to AEs compared with other GLP-1 RAs.
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Keywords: GLP-1 receptor agonist; Glycemic control; HbA_{1c}; Network meta-analysis; Semaglutide; Systematic review; Systolic blood pressure; Type 2 diabetes; Weight

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INTRODUCTION

Type 2 diabetes (T2D) is a chronic and progressive metabolic disorder characterized by hyperglycemia. When maintained over an extended period of time, hyperglycemia is associated with an increased risk of macrovascular (e.g., stroke, myocardial infarction [MI], heart failure) and microvascular (e.g., neuropathy, nephropathy, retinopathy) complications resulting in increased morbidity and mortality [1, 2].

Glycemic control is an important clinical goal in the management of T2D and is assessed by measuring glycated hemoglobin (HbA_{1c}). Current treatment guidelines recommend that a target HbA_{1c} level of $< 7\%$ (53 mmol/mol) or $\leq 6.5\%$ (48 mmol/mol) should be achieved while minimizing the risk of hypoglycemia [3–6]; however, up to 50% of patients across Europe and the USA do not meet their glycemic targets [7, 8]. There are many reasons for poor glycemic control, including delays in treatment intensification, poor patient treatment adherence, and the limited efficacy and side effects of some medications [9]. Weight control and management of cardiovascular risk are also important factors in the treatment of T2D [4]. Obesity or excess weight are the main risk factors for developing T2D, and it is estimated that between 80 and 90% of adults are overweight or obese at the time of diagnosis [10]. However, insulin and oral anti-diabetic drugs (OADs), in particular thiazolidinediones (TZD) and sulfonylureas (SU), can result in undesired weight gain [11]. Increased weight gain is associated with an increased risk of cardiovascular disease (CVD) and adults with T2D have a 2–3 times higher risk of cardiovascular mortality than those without [12]. Lastly, blood pressure can serve as a surrogate marker of cardiovascular (CV) risk outcomes in patients with T2D, and guidelines recommend adequate blood pressure control to reduce CV risk [13–15].

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are incretin mimetics that improve glycemic control and have demonstrated superiority over commonly used oral and injectable anti-diabetic medications while significantly reducing the risk of hypoglycemia [16]. Unlike other anti-diabetic agents, GLP-1 RAs also provide significant weight reduction [16, 17], and, importantly, a CV risk reduction in patients with T2D has also been observed with some GLP-1 RAs [16, 17]. GLP-1 RAs are typically recommended as either second- or third-line agents (i.e., as an add-on therapy to one or two OADs) in the treatment intensification algorithm recommended by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) [3]. Specifically, GLP-1 RAs are recommended above all other classes in the hierarchy for obese patients with T2D by the American Association of Clinical Endocrinologists (AACE), the Canadian Diabetes Association, and UK guidelines [14, 18, 19], and Finnish clinical guidelines recommend semaglutide and liraglutide for reducing the risk of CV events [20].

Semaglutide is a new once-weekly (QW) GLP-1 analogue available at 1.0 mg or 0.5 mg doses that has been extensively studied throughout the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) clinical trial program, for which data from seven global phase 3 trials have been published [21–27]. The efficacy and safety of once-weekly semaglutide as an add-on therapy to 1–2 OADs was evaluated in SUSTAIN 2, SUSTAIN 3, SUSTAIN 4, and SUSTAIN 7, and superiority with both doses of once-weekly semaglutide vs comparator was shown for all trials with HbA_{1c} as the primary endpoint [22–24, 27]. Importantly, SUSTAIN 3 and SUSTAIN 7 compared once-weekly semaglutide with the once-weekly GLP-1 RAs exenatide (SUSTAIN 3 [23]) and dulaglutide (SUSTAIN 7 [27]). The SUSTAIN program established that once-weekly semaglutide is well tolerated, and that the safety profile is similar to other GLP-1 RAs [26]. SUSTAIN 6, a 2-year placebo-controlled cardiovascular outcomes trial assessing the CV safety of once-weekly semaglutide as an add-on to standard-of-care (SoC) in patients with T2D, showed improved long-term CV outcomes with semaglutide [26]. Once-weekly semaglutide + SoC demonstrated a significant 26% reduction in the risk of major adverse CV events (CV death, non-fatal MI, or non-fatal stroke) vs placebo + SoC [26].

Given the increasing number of treatments for patients with T2D, it is important to understand the relative clinical benefits of each treatment to allow recommendations on their use; however, few head-to-head trials and meta-analyses have been performed for GLP-1 RAs [28]. While SUSTAIN 3 and SUSTAIN 7 provide compelling data on the efficacy and safety of once-weekly semaglutide vs exenatide QW and dulaglutide QW, it is important to consider all available GLP-1 RAs, as they may each provide unique advantages and disadvantages [28]. Accordingly, the objective of this study was to conduct a systematic literature review (SLR) and network meta-analysis (NMA) to assess the efficacy and safety of once-weekly semaglutide vs other GLP-1 RAs in patients with T2D inadequately controlled on 1–2 OADs.

METHODS

Systematic Review

An SLR was performed in accordance with PRISMA guidelines [29] to identify trials of GLP-1 RAs in patients with T2D who are inadequately controlled on 1–2 OADs. Searches of MEDLINE®, Embase, and the Cochrane Library were performed via Ovid on April 5, 2016, with updates occurring on October 3, 2016 and August 16, 2017 (Table S1 in the Electronic supplementary material, ESM). Searches of conference proceedings were also carried out for the EASD (2014–2016), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR; 2014–2017), the International Diabetes Federation (IDF; 2013 and 2015), and the ADA Scientific Sessions (2014–2017).

Following a study screening hierarchy for exclusion, all titles and abstracts identified through the literature searches were screened by two reviewers to assess whether they met the PICOS (population, interventions, comparators, outcomes, study design) selection criteria (Table S2 in the ESM). It should be noted that the PICOS criteria were slightly broader than what was required for the current analysis and included additional populations of interest. This is because the SLR was designed to support another NMA assessing the efficacy and safety of once-weekly semaglutide and other GLP-1 RAs in patients who are inadequately controlled on basal insulin. Once title and abstract screening were completed, the reviewers reconciled any existing discrepancies between their selections of studies. The same two reviewers independently screened full-text articles for all studies identified as included at the title and abstract screening phase. When a consensus could not be reached between the two reviewers during reconciliation processes, a senior reviewer provided arbitration. In addition, data from digital curves were extracted using digital extraction tools. Any discrepancies observed between the data extracted by the two analysts were adjudicated by a third reviewer.

NMA Methodology

A NMA was performed, in accordance with guidance from the National Institute for Health and Care Excellence (NICE), ISPOR, and the Cochrane Institute [30–34], to compare the efficacy and safety of GLP-1 RAs in patients with T2D. In the analysis, the primary intervention of interest was once-weekly semaglutide (0.5 mg and 1.0 mg), and the primary comparators of interest were all other licensed doses of GLP-1 RAs—liraglutide once-daily (QD), dulaglutide QW, exenatide twice-daily (BID), exenatide QW, lixisenatide QD, and albiglutide QW. While albiglutide is soon to be withdrawn from the market, it remains a comparator of interest as the reason for withdrawal was not related to the safety of the medicine [35]. GLP-1 RAs were often taken with other background anti-diabetic medications in the trials. In order to reduce variability between populations across the different trials, the definition of the add-on to 1–2 OADs population was aligned as closely as possible to the relevant SUSTAIN trials of once-weekly semaglutide (the primary intervention of interest). Therefore, studies assessing GLP-1 RAs as an add-on to one OAD (defined as > 90% of patients inadequately controlled on metformin monotherapy, i.e., sufficiently similar to the patient population in SUSTAIN 2 or 7) or as an add-on to 1–2 OADs (defined as < 100% of

patients inadequately controlled on two OADs, i.e., sufficiently similar to the patient population in SUSTAIN 3 and 4) were considered for inclusion. Trials involving patients inadequately controlled on one OAD that was not metformin were also excluded in order to reflect SoC and align with international guidelines [3].

All trials identified in the SLR were examined for data on at least one outcome of interest, and the ability to form a best-case connected network was assessed. The feasibility of generating evidence networks for each of the 20 outcomes of interest (Table S2 in the ESM) was examined next; the outcomes of interest included glycemic control outcomes (e.g., change from baseline in HbA_{1c}, proportion of patients achieving $HbA_{1c} < 7\%$ [53 mmol/mol] or $\leq 6.5\%$ [48 mmol/mol]), weight outcomes (e.g., change from baseline in weight, body mass index [BMI], proportion of patients achieving weight loss of ≥ 5 or $\geq 10\%$), SBP, fasting plasma glucose (FPG), postprandial plasma glucose, proportion of patients achieving $HbA_{1c} < 7\%$ without weight gain and without hypoglycemia, and safety outcomes (including the incidence of discontinuations due to adverse events [AEs], nausea, vomiting, diarrhea, pancreatitis, and hypoglycemia [overall, severe, non-severe, nocturnal]).

All analyses of continuous outcomes were performed using a normal likelihood, identity link, shared parameter model, to account for both arm-level and trial-level data reported within the included studies. For the analysis of dichotomous outcomes, a binomial likelihood (assuming a normal distribution), logit link model was used. For each outcome, both fixed effects (FE) and random effects (RE) models were run, and the model with the better fit (based on the deviance information criterion [DIC] and average posterior residual deviance) was used. Exploratory meta-regression analyses were also performed to determine whether a covariate-adjusted model would provide a significantly better model fit. The NMA models were implemented using WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) [36] and employed a Bayesian framework with the use of uninformative prior distributions. Three Markov Monte Carlo chains were used, starting from different initial values of selected unknown parameters. Convergence for all models was assessed using standard diagnostic methods for evaluating convergence [37]. In addition, autocorrelation plots were assessed to detect the presence of autocorrelation in the chains. Following this, model convergence inferences were made from data obtained by sampling for a further 20,000 iterations using all the samples. If models failed to converge, the feasibility of a Bucher indirect comparison was considered. Bucher indirect comparisons were calculated in STATA 13 (StataCorp., College Station, TX, USA), using the indirect command [38].

The results of the NMA are presented as mean treatment differences or odds ratios (ORs) and an associated 95% credible interval (CrI). For continuous outcomes of interest, a treatment which offers a greater mean reduction from baseline is favored—for example a reduction in HbA_{1c} (%), SBP (mmHg), and weight (kg). For dichotomous outcomes, a treatment which offers an increase in the OR is favored—for example, higher odds for achieving a HbA_{1c} level < 7%. Where reducing the probability of achieving an outcome is favorable (e.g., a reduction in discontinuations due to AEs), a treatment which offers a reduction in the OR is favored. In Bayesian statistics, it is considered that differences exist only where the CrI does not include the null value for treatment differences or one for ORs. In certain cases, once-weekly semaglutide may achieve a numerical reduction/increase against a comparator, but unless the CrI excludes the null value (for treatment differences) or one (for ORs), it is assumed that there is no difference.

In addition to the mean treatment difference or OR, the median ranks of each treatment (and associated 95% CrI) are provided, where a treatment with a median rank of 1 is considered the best. If two drugs share a ranking, then both are assigned one value lower (e.g., if two drugs are both ranked as the second highest, they will both be given the median rank score of 3). An additional ranking outcome is also presented—the surface under the cumulative ranking curve (SUCRA). The SUCRA is a numerical summary statistic of cumulative ranking probability plots

(the probability a treatment is among the top *n* treatments [between the first and *n*th rank]) [39]. A higher SUCRA value indicates an increased possibility that a treatment is in the top rank. A treatment which is 'certain to be the best' will have a SUCRA value of 1 (i.e., 100%), and a treatment 'certain to be the worst' will have a value of 0 (i.e., 0%) [39]. This simplifies information about the effect of each treatment into a single value, allowing the complex results from NMA networks to be expressed with relatively few numbers. When the median rank and SUCRA values are in accordance (e.g., if a treatment has the highest median rank and the highest SUCRA score), this adds further weight to the interpretation.

NMAs combine all available evidence from clinical trials to estimate treatment effects. As this involves combining direct and indirect measures of effect, it is important to examine whether or not these two 'sources' of evidence are consistent with one another. Accordingly, all NMAs were formally assessed for inconsistency using Bucher's method (as outlined by the NICE technical support document [TSD] 4) [33]. Informal assessments were also performed by comparing the results of the NMA with the data reported across the studies included in the evidence networks. In the event of evidence of a substantial inconsistency that may change the conclusions based on the analysis selected (direct, simple indirect, or NMA), the following three steps were taken [33]: (1) data were verified for accuracy; (2) if data were found to be correct, meta-regression or restricted analyses were performed to address the imbalance driving the issue; (3) if the second step failed, or was infeasible, further analyses were considered, within the limitations of avoiding bias.

Finally, this article does not contain any new studies with human subjects or animals performed by any of the authors.

RESULTS

Identified Publications

A total of 1273 unique citations of potential interest were identified in the electronic searches. Of these, 85 citations were considered to meet the SLR PICOS criteria. A further 22 citations were identified through hand searching of conference abstracts or were provided by the sponsor in the form of clinical study reports (CSR). Therefore, a total of 107 publications reporting on 75 unique trials were included within the SLR (a list of these trials is provided in Table S3 of the ESM and a PRISMA flow diagram of the SLR is shown in Fig. S1 of the ESM). Of these 75 trials, 41 trials were considered to be relevant for inclusion in the current analysis [22–24, 27, 40–70]. The process of excluding the other 34 trials is detailed in Fig. S2 of the ESM.

All 41 trials considered in the NMA formed a connected network, which allowed for the comparison of once-weekly semaglutide with dulaglutide QW (0.75 mg and 1.5 mg), liraglutide QD (1.2 mg and 1.8 mg), exenatide QW (2 mg dose), exenatide QD (5 μg and 10 μg), albiglutide 30 mg, and lixisenatide 20 μg. Placebo, sitagliptin, insulin glargine, and the fixed combination of insulin glargine and lixisenatide are secondary comparators that connect primary comparators of interest. All other secondary comparators were removed from the network, including comparators from the DUAL-1 trial (insulin degludec and the fixed combination of insulin degludec and liraglutide), as they do not contribute to any connections between primary comparators of interest in the network. This resulted in a total of 34 trials [22–24, 27, 40–69] remaining within the network.

Within this network, there are multiple arms of insulin glargine and lixisenatide. While the insulin glargine arms were assessed as similar enough to combine into a single treatment node, important differences in the titration strategies between the lixisenatide arms were observed. Accordingly, lixisenatide treatment arms in the network were pooled into one-step (10 μg QD starting dose followed by escalation to 20 μg QD after 15 days) or two-step (10 μg QD starting dose for 1 week, followed by 15 μg QD for 1 week and then 20 μg maintenance dose) arms. Note that the GET GOAL-M trial is included in the network but the lixisenatide arms were not pooled because the primary

objective of this trial was to investigate morning vs evening administration.

The 34 trials within the network were next examined for time points for which data were available for at least one outcome (Fig. S3 of the ESM). All 34 trials (100%) reported on at least one outcome of interest between 20 and 28 weeks. Based on this, it was decided to analyze each outcome at 24 ± 4 weeks (approximately 6 months) of treatment—it was assumed that the level of response to treatment within 4 weeks of the target week was unlikely to vary considerably. Overall, the majority of trials (82%) reported at either 24 or 26 weeks (range: week 23–28) in the analysis at 24 ± 4 weeks.

The study design and patient characteristics of the 34 trials are presented in Table S4. Overall, the risk of bias across the 34 studies was considered to be low; however, the highest risk of bias across the studies was associated with elements of study blinding and dropouts. Generally, most trials were deemed sufficiently homogeneous to combine for analysis; however, eight studies were considered to be potential outliers due to study design and patient characteristics: Derosa [44] enrolled treatment-naive patients who were instructed to take metformin for 8 months prior to treatment randomization; Van Gaal [68] specifically enrolled young (mean age of 43 years) and obese (mean BMI of 36.8 kg/m^2) patients; and five studies (Araki [41], GetGoal-M Asia [52], Inagaki [59], Ji [60], Lew [63], and Zang [69]) enrolled only Asian patients. It was therefore decided to exclude these studies from the base-case analysis, yielding a total of 26 studies; however, the impact of excluding these trials was explored in sensitivity analyses.

NMA Results

For the analysis, outcome-specific evidence networks were possible for 8 of the 20 outcomes of interest assessed for feasibility. It should be noted that, due to a paucity of data, it was not possible to conduct NMAs on the majority of the safety outcomes included in the SLR PICOS criteria (Table S2 in the ESM). Twenty-six trials were considered in the base-case analysis, and the evidence network is shown in Fig. 1.

In the base-case analysis of the change from baseline in HbA_{1c} and FPG, and the proportion of patients achieving a $HbA_{1c} < 7\%$ or $\leq 6.5\%$, the RE model provided a better fit than the FE model in terms of DIC and the average posterior residual deviance (Table S5 of the ESM). For the base-case analyses assessing the change from baseline in SBP and weight as well as the proportion of patients discontinuing due to AEs, the FE model was preferred; no important differences between the FE and RE models were observed in terms of DIC and average posterior residual deviance (Table S5 of the ESM).

Exploratory meta-regression analyses were performed on four outcomes (change from baseline in HbA_{1c}, FPG, weight, and SBP) to validate the use of unadjusted models in the base case. Overall, meta-regression analysis did not result in a significant improvement in model fit or a reduction in the between-study SD (for the RE model). Therefore, regression may have resulted in overfitting.

The results of the NMA are presented as treatment differences or ORs (once-weekly semaglutide vs comparator) in Fig. 2a–g (the full matrix of relative treatment effect results are shown in Tables S14–S21 in the ESM). The associated treatment ranks (SUCRA and median rank) are also presented in Tables 1 and 2.

Glycemic Control

All 26 trials reported data on the change from baseline in HbA_{1c} (Table S6 in the ESM). The evidence network for the change from baseline in HbA_{1c} is shown in Fig. 1. The results (Fig. 2a, Table S14 of the ESM) showed that once-weekly semaglutide 1.0 mg was associated with a significantly greater reduction in HbA_{1c} vs all GLP-1 RA comparators. The analyses also suggested that once-weekly semaglutide 0.5 mg can provide significantly greater reductions in HbA_{1c} vs the majority of GLP-1 RA comparators (11 out of 13). It should be noted that inconsistency ($p = 0.006$) was detected in one loop of evidence (insulin glargine, exenatide 2 mg QW, and once-weekly semaglutide 1.0 mg) within the

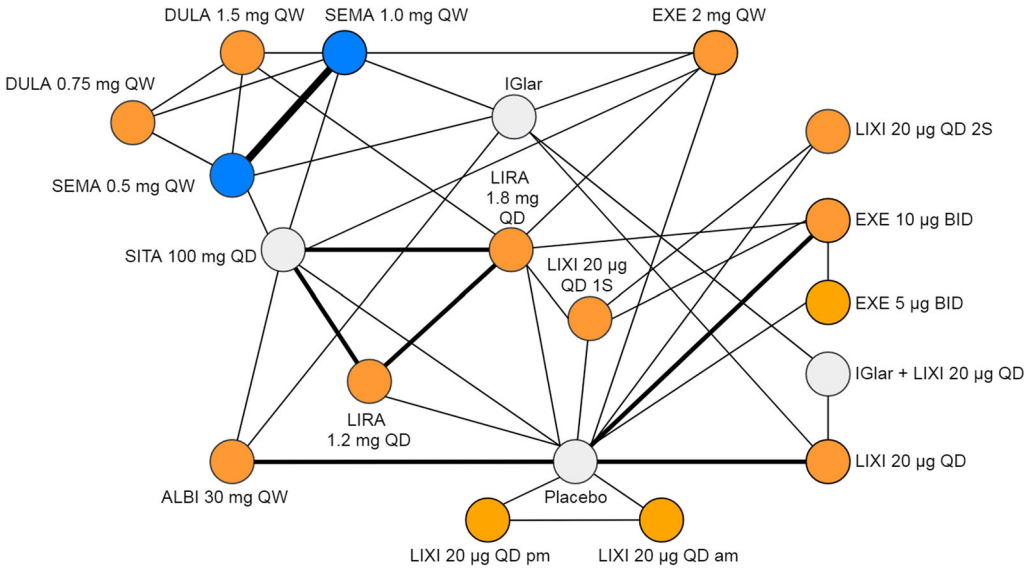
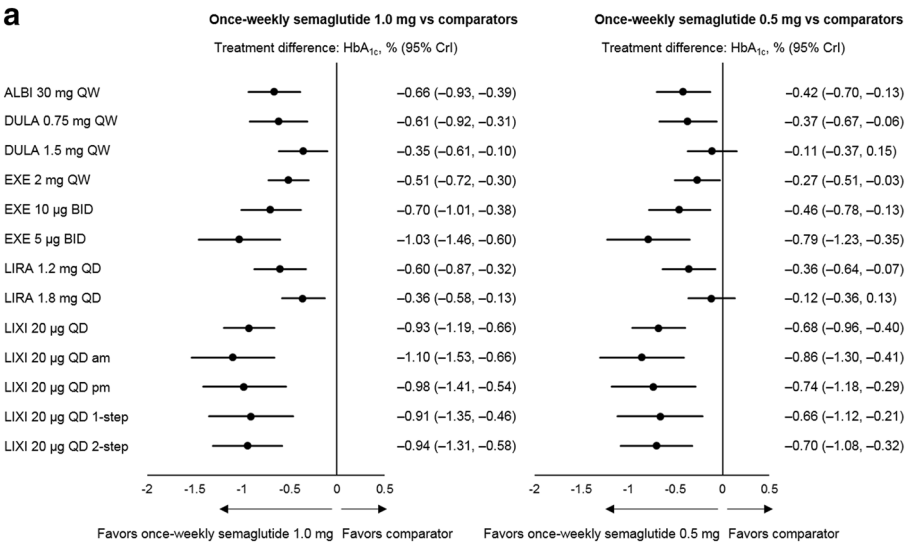


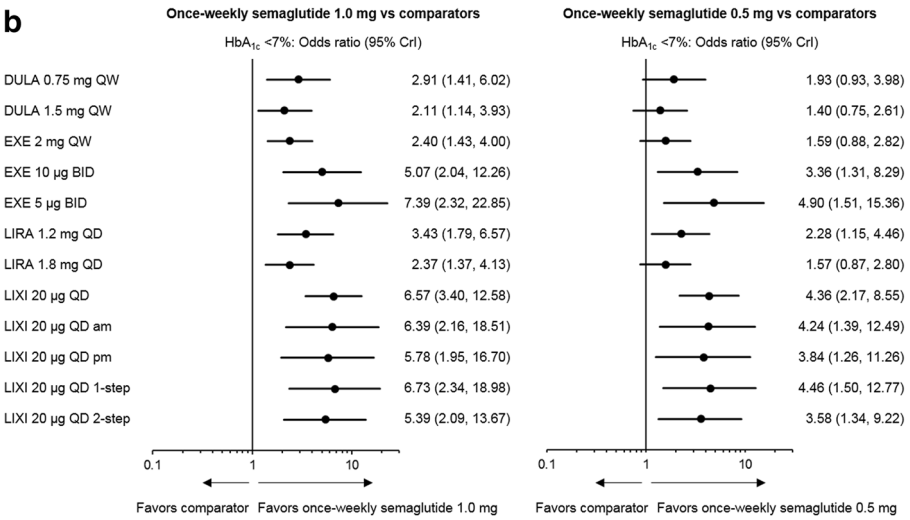
Fig. 1 Base-case evidence network. *Line thickness* corresponds to the number of trials contributing to the comparison between two interventions—the *thickest* equates to three trials, while the *thinnest* equates to one trial. *Blue nodes* indicate a primary intervention of interest, *orange nodes* indicate a primary comparator of interest, and *gray nodes* indicate a secondary comparator. *1S* one step, *2S* two steps, *ALBI* albiglutide, *am* morning, *BID* twice-daily, *DULA* dulaglutide, *EXE* exenatide, *IGlar* insulin glargine, *LIRA* liraglutide, *LIXI* lixisenatide, *pm* evening, *QD* once-daily, *QW* once-weekly, *SEMA* semaglutide

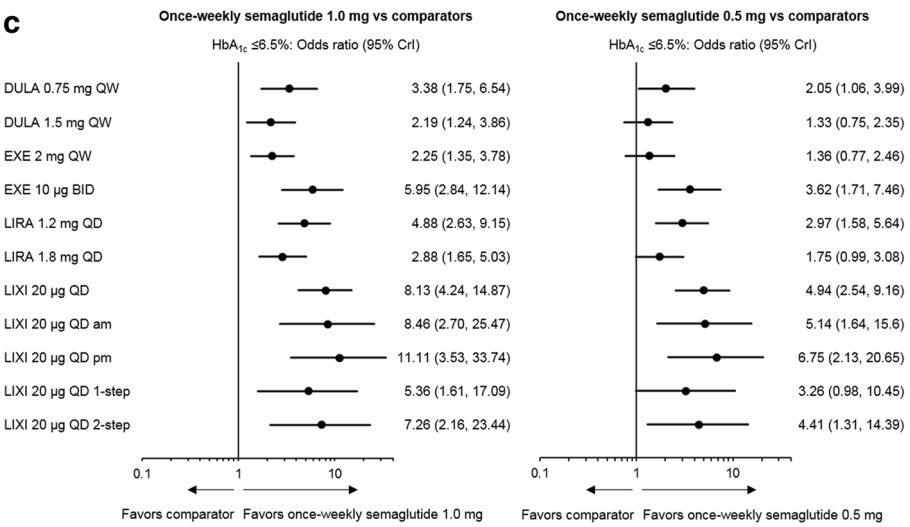
network for the change from baseline in HbA_{1c}. When considering the treatment comparison between once–weekly semaglutide 1.0 mg and exenatide 2 mg QW, the direction of the treatment effect is the same for the direct effect (− 0.36; 95% CI − 0.52, − 0.20), indirect effect (− 0.74; 95% CI − 0.96, − 0.52), and NMA (− 0.51; 95% CI − 0.72, − 0.30). Furthermore, while the magnitude of effect differs, the treatment difference between once-weekly semaglutide 1.0 mg and exenatide 2 mg QW (in favor of once-weekly semaglutide 1.0 mg) remains significant in each analysis. In accordance with the protocol outlined to address inconsistency, restricted analyses were performed to assess the impact that the presence of this inconsistency may have. This involved removing trials (DURATION-3) and arms (the exenatide 2 mg QW arm of SUSTAIN 3 or the insulin glargine arm of SUSTAIN 4) within the loop of evidence. Together, these analyses demonstrate that this inconsistency is unlikely to have a large impact on the wider network, as excluding these trials/arms (one at a time) had a minimal effect on the overall results of the NMA.

An additional sensitivity analysis was performed to validate the legitimacy of excluding eight outlier trials [41, 44, 52, 59, 60, 63, 68, 69] (on the basis of heterogeneity) from the base-case analyses of the change from baseline in HbA_{1c}. When compared with the base-case analysis, the inclusion of the outlier trials resulted in an additional treatment node for lixisenatide (lixisenatide 10–20 µg) in the network (Fig. S5 in the ESM). The same statistical approach as used in the base-case analyses was taken for this analysis. The inclusion of these outlier trials had little impact on the results and overall interpretation (Table S22 of the ESM).

NMAs were also feasible for three other outcomes: HbA_{1c} level < 7%, HbA_{1c} level ≤ 6.5%, and FPG. The evidence networks and data supporting these analyses are shown in Fig. S4 and Tables S7–S9 in the ESM. The analyses of the proportion of patients achieving a HbA_{1c} level < 7% or ≤ 6.5% suggested that the improved HbA_{1c} reduction observed with once-weekly semaglutide 1.0 mg vs other GLP-1 RAs


a
Once-weekly semaglutide 1.0 mg vs comparators
Treatment difference: HbA1c, % (95% CrI)
ALBI 30 mg QW −0.66 (−0.93, −0.39)
DULA 0.75 mg QW −0.61 (−0.92, −0.31)
DULA 1.5 mg QW −0.35 (−0.61, −0.10)
EXE 2 mg QW −0.51 (−0.72, −0.30)
EXE 10 µg BID −0.70 (−1.01, −0.38)
EXE 5 µg BID −1.03 (−1.46, −0.60)
LIRA 1.2 mg QD −0.60 (−0.87, −0.32)
LIRA 1.8 mg QD −0.36 (−0.58, −0.13)
LIXI 20 µg QD −0.93 (−1.19, −0.66)
LIXI 20 µg QD am −1.10 (−1.53, −0.66)
LIXI 20 µg QD pm −0.98 (−1.41, −0.54)
LIXI 20 µg QD 1-step −0.91 (−1.35, −0.46)
LIXI 20 µg QD 2-step −0.94 (−1.31, −0.58)
-2 -1.5 -1 -0.5 0 0.5
Favors once-weekly semaglutide 1.0 mg Favors comparator
Once-weekly semaglutide 0.5 mg vs comparators
Treatment difference: HbA1c, % (95% CrI)
−0.42 (−0.70, −0.13)
−0.37 (−0.67, −0.06)
−0.11 (−0.37, 0.15)
−0.27 (−0.51, −0.03)
−0.46 (−0.78, −0.13)
−0.79 (−1.23, −0.35)
−0.36 (−0.64, −0.07)
−0.12 (−0.36, 0.13)
−0.68 (−0.96, −0.40)
−0.86 (−1.30, −0.41)
−0.74 (−1.18, −0.29)
−0.66 (−1.12, −0.21)
−0.70 (−1.08, −0.32)
-2 -1.5 -1 -0.5 0 0.5
Favors once-weekly semaglutide 0.5 mg Favors comparator


b
Once-weekly semaglutide 1.0 mg vs comparators
HbA1c <7%: Odds ratio (95% CrI)
DULA 0.75 mg QW 2.91 (1.41, 6.02)
DULA 1.5 mg QW 2.11 (1.14, 3.93)
EXE 2 mg QW 2.40 (1.43, 4.00)
EXE 10 µg BID 5.07 (2.04, 12.26)
EXE 5 µg BID 7.39 (2.32, 22.85)
LIRA 1.2 mg QD 3.43 (1.79, 6.57)
LIRA 1.8 mg QD 2.37 (1.37, 4.13)
LIXI 20 µg QD 6.57 (3.40, 12.58)
LIXI 20 µg QD am 6.39 (2.16, 18.51)
LIXI 20 µg QD pm 5.78 (1.95, 16.70)
LIXI 20 µg QD 1-step 6.73 (2.34, 18.98)
LIXI 20 µg QD 2-step 5.39 (2.09, 13.67)
0.1 1 10
Favors comparator Favors once-weekly semaglutide 1.0 mg
Once-weekly semaglutide 0.5 mg vs comparators
HbA1c <7%: Odds ratio (95% CrI)
1.93 (0.93, 3.98)
1.40 (0.75, 2.61)
1.59 (0.88, 2.82)
3.36 (1.31, 8.29)
4.90 (1.51, 15.36)
2.28 (1.15, 4.46)
1.57 (0.87, 2.80)
4.36 (2.17, 8.55)
4.24 (1.39, 12.49)
3.84 (1.26, 11.26)
4.46 (1.50, 12.77)
3.58 (1.34, 9.22)
0.1 1 10
Favors comparator Favors once-weekly semaglutide 0.5 mg


c
Once-weekly semaglutide 1.0 mg vs comparators
HbA1c ≤6.5%: Odds ratio (95% CrI)
DULA 0.75 mg QW 3.38 (1.75, 6.54)
DULA 1.5 mg QW 2.19 (1.24, 3.86)
EXE 2 mg QW 2.25 (1.35, 3.78)
EXE 10 µg BID 5.95 (2.84, 12.14)
LIRA 1.2 mg QD 4.88 (2.63, 9.15)
LIRA 1.8 mg QD 2.88 (1.65, 5.03)
LIXI 20 µg QD 8.13 (4.24, 14.87)
LIXI 20 µg QD am 8.46 (2.70, 25.47)
LIXI 20 µg QD pm 11.11 (3.53, 33.74)
LIXI 20 µg QD 1-step 5.36 (1.61, 17.09)
LIXI 20 µg QD 2-step 7.26 (2.16, 23.44)
0.1 1 10
Favors comparator Favors once-weekly semaglutide 1.0 mg
Once-weekly semaglutide 0.5 mg vs comparators
HbA1c ≤6.5%: Odds ratio (95% CrI)
2.05 (1.06, 3.99)
1.33 (0.75, 2.35)
1.36 (0.77, 2.46)
3.62 (1.71, 7.46)
2.97 (1.58, 5.64)
1.75 (0.99, 3.08)
4.94 (2.54, 9.16)
5.14 (1.64, 15.6)
6.75 (2.13, 20.65)
3.26 (0.98, 10.45)
4.41 (1.31, 14.39)
0.1 1 10
Favors comparator Favors once-weekly semaglutide 0.5 mg

◀**Fig. 2** Forest plot of the NMA results: once-weekly semaglutide 0.5 or 1.0 mg vs comparator. Treatment differences are considered significant when the 95% CrI excludes the null value. Odds ratios are considered significant when the 95% CrI excludes 1. The NMA results are presented as forest plots for **a** change from baseline in HbA_{1c}, **b** proportion of patients achieving a HbA_{1c} level < 7%, **c** proportion of patients achieving a HbA_{1c} level ≤ 6.5%, **d** change from baseline in FPG, **e** change from baseline in weight, **f** change from baseline in SBP, and **g** proportion of patients discontinuing due to AEs. *AE* adverse event, *ALBI* albiglutide, *am* morning, *BID* twice-daily, *CrI* credible interval, *DULA* dulaglutide, *EXE* exenatide, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *LIRA* liraglutide, *LIXI* lixisenatide, *NMA* network meta-analysis, *pm* evening, *QD* once-daily, *QW* once-weekly, *SBP* systolic blood pressure

increases the probability of achieving these recommended glycemic targets. In line with the results from the analysis of the change from baseline in HbA_{1c}, once-weekly semaglutide 1.0 mg was associated with significantly higher odds of achieving a HbA_{1c} level < 7 or ≤ 6.5% vs all GLP-1 RA comparators (Fig. 2b, c, Tables S15 and S16 in the ESM). Furthermore, once-weekly semaglutide 0.5 mg was also associated with higher odds of achieving these HbA_{1c} targets vs most GLP-1 RA comparators (8 out of 12 for HbA_{1c} level < 7%; 7 out of 12 for HbA_{1c} level ≤ 6.5%). The analysis of the change from baseline FPG showed some significant differences in favor of once-weekly semaglutide 1.0 mg vs exenatide (2 mg QW and 10 μg BID) and lixisenatide (20 μg and 20 μg in two steps), while once-weekly semaglutide 0.5 mg was associated with a comparable reduction in FPG vs all GLP-1 RA comparators (Fig. 2d, Table S17 in the ESM).

Across these analyses, once-weekly semaglutide 1.0 mg was the highest-ranked GLP-1 RA, achieving median ranks of 1–2 and SUCRA scores of 94–100% (Tables 1, 2). Together, these treatment ranks showed that once-weekly semaglutide 1.0 mg is likely to be the most clinically efficacious treatment within these networks. Once-weekly semaglutide 0.5 mg was also ranked highly within the networks, and achieved the second-highest SUCRA score and median rank for these four outcomes.

Weight

In total, 25 trials reported the change from baseline in weight (Table S10 in the ESM), and the evidence network is shown in Fig. S4 of the ESM. The results showed that once-weekly semaglutide 1.0 mg was associated with a significantly greater reduction in weight vs all GLP-1 RA comparators (Fig. 2e, Table S18 of the ESM). Once-weekly semaglutide 0.5 mg also provided significantly greater reductions in weight vs the majority of GLP-1 RA comparators (10 out of 13). Together, the SUCRA scores and median ranks show that once-weekly semaglutide 1.0 mg is the most efficacious GLP-1 RA in terms of weight reduction in the network (Tables 1, 2).

An additional sensitivity analysis was performed to validate the legitimacy of excluding eight outlier trials [41, 44, 52, 59, 60, 63, 68, 69] (on the basis of heterogeneity) from the base-case analyses of the change from baseline in weight (evidence network shown in Fig. S5 of the ESM). The inclusion of these outlier trials had little impact on the results and overall interpretation (Table S22 of the ESM).

Systolic Blood Pressure

Fifteen trials reported the change from baseline in SBP (Table S11 of the ESM), and the evidence network is shown in Fig. S4 of the ESM. Although fewer comparators were available in the analysis of SBP, once-weekly semaglutide 1.0 mg was associated with a small but significantly greater reduction in SBP vs all available GLP-1 RA comparators except dulaglutide 0.75 mg QW and liraglutide 1.2 mg QD (Fig. 2f, Table S19 of the ESM); once-weekly semaglutide 0.5 mg was associated with a comparable reduction in SBP vs all GLP-1 RA comparators.

An additional sensitivity analysis was performed to validate the legitimacy of excluding four outlier trials [41, 59, 60, 69] (on the basis of heterogeneity) from the base-case analyses of the change from baseline in SBP (evidence network shown in Fig. S5 of the ESM). The inclusion of these outlier trials had little impact on the results and overall interpretation (Table S22 of the ESM).

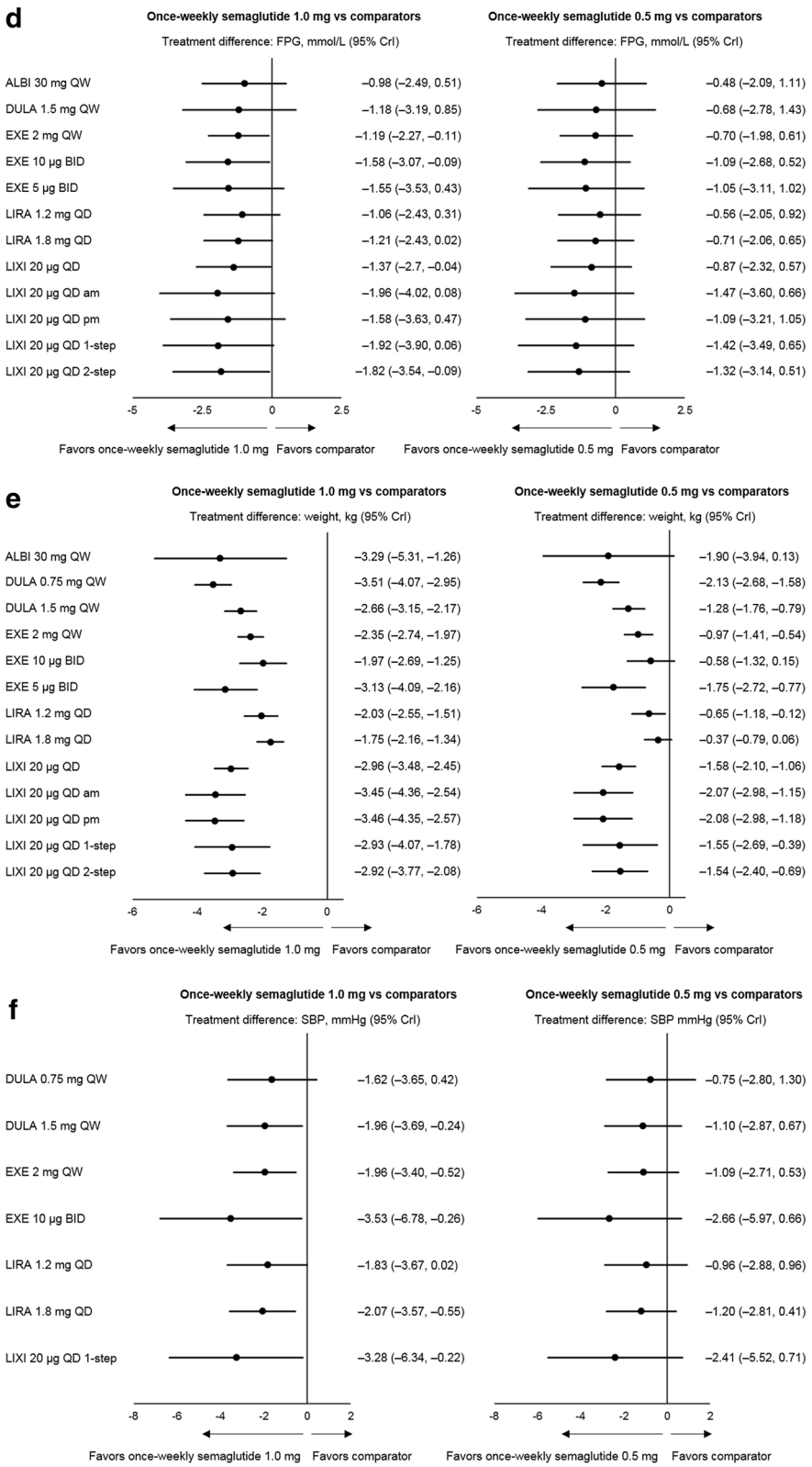


Fig. 2 continued

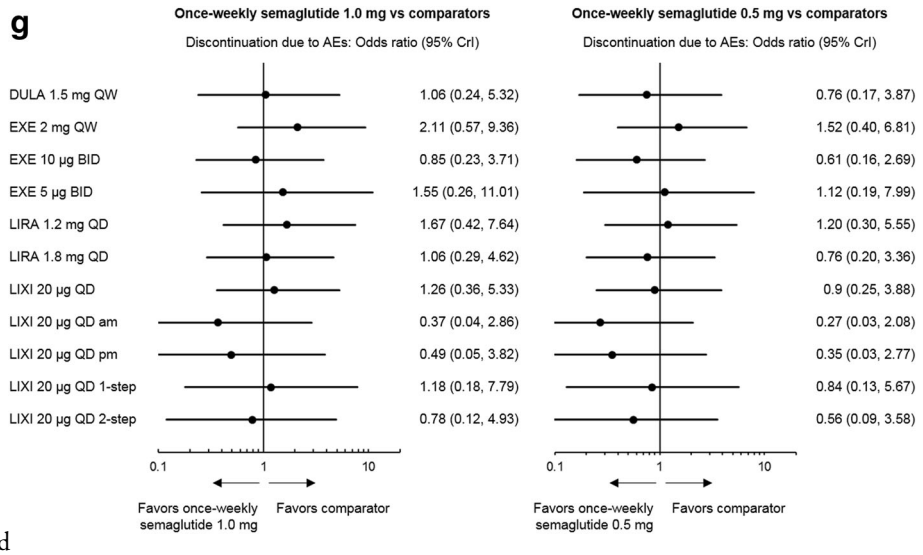


Fig. 2 continued

Composite Outcome (HbA_{1c} < 7%, no weight gain, and no hypoglycemia)

It was also feasible to analyze the composite outcome of HbA_{1c} < 7%, no weight gain, and no hypoglycemia (data presented in Table S12 of the ESM and the evidence network is shown in Fig. S4 of the ESM). Although only an indirect comparison between once-weekly semaglutide 0.5 mg and 1.0 mg with lixisenatide 20 µg QD was possible, the results showed that both once-weekly semaglutide 0.5 and 1.0 mg were associated with significantly higher odds of achieving the composite outcome when compared with lixisenatide 20 µg QD (Table S20 of the ESM).

Safety Outcomes

For effective treatment, it is important to consider the risk of AEs, with gastrointestinal (GI) events commonly cited as reasons for discontinuing treatment with GLP-1 RAs [71, 72]. While it was not feasible to perform an analysis of the incidence of GI events (no connected network could be constructed) such as nausea or diarrhea, a comparison of the rates of discontinuation due to AEs was possible (data presented in Table S13 of the ESM, and the evidence network is shown in Fig. S4 of the ESM). This analysis showed that once-weekly semaglutide 0.5 mg and 1.0 mg were both associated with statistically similar odds of discontinuing due to AEs compared with other GLP-1 RAs (Fig. 2g, Table S21 of the ESM).

DISCUSSION

The objective of this analysis was to assess the relative efficacy and safety of once-weekly semaglutide vs other GLP-1 RAs in patients with T2D inadequately controlled on 1–2 OADs. The analyses showed that once-weekly semaglutide 1.0 mg was associated with significantly greater reductions in HbA_{1c} and weight vs all other GLP-1 RAs. Once-weekly semaglutide 1.0 mg also provided small but significantly greater reductions in SBP when compared with the majority of GLP-1 RAs available for comparison in this analysis. The analyses further demonstrated that once-weekly semaglutide 0.5 mg provides significantly greater reductions in HbA_{1c} and weight vs the majority of GLP-1 RA comparators. The improvements in HbA_{1c} achieved with once-weekly semaglutide 1.0 mg were clinically meaningful vs all GLP-1 RAs, based on the 0.3 percentage-points margin for clinical superiority suggested by the Food and Drug Administration (FDA; [73]) and the European Medicines Agency (EMA; [74]). Additional analyses suggested that the improved HbA_{1c} reduction with once-weekly semaglutide

Table 1 SUCRA results

Comparator	CFB in HbA_{1c}	HbA_{1c} <7%	HbA_{1c} ≤6.5%	CFB in FPG	CFB in weight	CFB in SBP	Discontinuations due to AEs
SEMA 0.5 mg QW	**89%**	**88%**	**94%**	**82%**	**94%**	**91%**	50%
SEMA 1.0 mg QW	**100%**	**100%**	**100%**	**94%**	**100%**	**100%**	31%
ALBI 30 mg QW	56%			65%	39%		
DULA 0.75 mg QW	61%	65%	63%		33%	73%	
DULA 1.5 mg QW	83%	82%	81%	53%	61%	64%	38%
EXE 2 mg QW	72%	71%	81%	53%	72%	64%	**69%**
EXE 10 µg BID	50%	41%	38%	35%	83%	27%	25%
EXE 5 µg BID	17%	18%		35%	44%		56%
IGlar†	56%	53%	56%	88%	0%	27%	100%
IGlar + LIXI 20 µg QD†	89%	88%	88%	100%	6%		88%
LIRA 1.2 mg QD	61%	59%	50%	59%	78%	64%	**63%**
LIRA 1.8 mg QD	83%	76%	69%	53%	89%	55%	38%
LIXI 20 µg QD	28%	24%	25%	41%	50%		44%
LIXI 20 µg QD am	11%	24%	19%	35%	33%		0%
LIXI 20 µg QD pm	22%	29%	13%	18%	33%		6%
LIXI 20 µg QD in one step	28%	35%	44%	18%	50%	27%	44%
LIXI 20 µg QD in two steps	22%	24%	25%	24%	50%		19%
SITA 100mg QD†	33%	18%	19%	35%	17%	18%	94%
Placebo†	0%	0%	0%	6%	17%	0%	81%

The highest and second highest SUCRA values of the primary comparators per outcome are highlighted in green and blue, respectively

AE adverse event, *ALBI* albiglutide, *am* morning, *BID* twice-daily, *CFB* change from baseline, *CrI* credible interval, *DULA* dulaglutide, *EXE* exenatide, *HbA_{1c}* glycated hemoglobin, *IGlar* insulin glargine, *LIRA* liraglutide, *LIXI* lixisenatide, *pm* evening, *QD* once-daily, *QW* once-weekly, *SBP* systolic blood pressure, *SEMA* semaglutide, *SITA* sitagliptin, *SUCRA* surface under the cumulative ranking

† Secondary comparators

increases the probability of achieving the recommended glycemic targets of < 7% or ≤ 6.5%. Finally, once-weekly semaglutide was associated with similar odds of discontinuation due to AEs compared with other GLP-1 RAs.

This study is the first to assess the relative efficacy and safety of once-weekly semaglutide as an add-on therapy to 1–2 OADs vs all available GLP-1 RAs. While three recent NMAs assessing the efficacy of GLP-1 RAs (not including once-weekly semaglutide) did not identify one particular treatment that was clearly more efficacious than the others, dulaglutide QW, exenatide QW and liraglutide QD were shown to be the most effective with respect to reducing HbA_{1c} and weight after 6 months [75–77]. Our analyses suggest that the new GLP-1 RA, once-weekly semaglutide 1.0 mg, is the most efficacious GLP-1 RA for reducing HbA_{1c}, achieving glycemic targets, and reducing weight. This assertion is supported by the SUCRA scores showing that once-weekly semaglutide 1.0 mg was the most efficacious in these networks, and by the observation that no other GLP-1 RA achieved significant improvements in these outcomes vs all other GLP-1 RAs. Although fewer comparators were available for analysis, once-weekly semaglutide 1.0 mg may also offer small improvements in SBP reduction compared with other GLP-1 RAs in this population.

It is important that improvements in efficacy are balanced with the risk of AEs. The most common AEs associated with the GLP-1 RA class are GI-related events (such as nausea, vomiting, and diarrhea), which are commonly cited as reasons for discontinuing GLP-1 RA therapy [71, 72]. Our analysis showed that once-weekly

Table 2 Median rank (95% CrI)

Comparator	CFB in HbA_{1c}	HbA_{1c} <7%	HbA_{1c} ≤6.5%	CFB in FPG	CFB in weight	CFB in SBP	Discontinuations due to AEs
SEMA 0.5 mg QW	**3 (2, 5)**	**3 (1, 6)**	**2 (2, 5)**	**4 (1, 13)**	**2 (2, 3)**	**2 (1, 6)**	9 (3, 16)
SEMA 1.0 mg QW	**1 (1, 2)**	**1 (1, 2)**	**1 (1, 2)**	**2 (1, 8)**	**1 (1, 1)**	**1 (1, 3)**	12 (5, 17)
ALBI 30 mg QW	9 (6, 13)			7 (2, 15)	12 (2, 18)		
DULA 0.75 mg QW	8 (4, 15)	7 (3, 14)	7 (3, 13)		13 (9, 17)	4 (1, 10)	
DULA 1.5 mg QW	4 (2, 8)	4 (2, 9)	4 (2, 8)	9 (1, 18)	8 (6, 12)	5 (2, 9)	11 (6, 17)
EXE 2 mg QW	6 (4, 10)	6 (3, 9)	4 (2, 8)	9 (4, 16)	6 (4, 9)	5 (2, 9)	**6 (4, 10)**
EXE 10 µg BID	10 (6, 14)	11 (6, 16)	11 (7, 15)	12 (5, 17)	4 (2, 7)	9 (2, 12)	13 (9, 17)
EXE 5 µg BID	16 (10, 18)	15 (7, 18)		12 (2, 18)	11 (6, 16)		8 (2, 16)
IGlar†	9 (6, 13)	9 (6, 14)	8 (6, 13)	3 (1, 8)	19 (19, 19)	9 (4, 11)	1 (1, 3)
IGlar + LIXI 20 µg QD†	3 (1, 7)	3 (1, 8)	3 (1, 7)	1 (1, 9)	18 (17, 18)		3 (1, 5)
LIRA 1.2 mg QD	8 (5, 12)	8 (5, 13)	9 (7, 13)	8 (3, 15)	5 (3, 7)	5 (2, 9)	**7 (5, 12)**
LIRA 1.8 mg QD	4 (2, 6)	5 (3, 9)	6 (4, 9)	9 (5, 15)	3 (2, 5)	6 (3, 8)	11 (8, 15)
LIXI 20 µg QD	14 (11, 18)	14 (10, 17)	13 (10, 16)	11 (5, 16)	10 (7, 13)		10 (6, 13)
LIXI 20 µg QD am	17 (11, 18)	14 (6, 17)	14 (7, 16)	12 (2, 18)	13 (8, 17)		17 (9, 17)
LIXI 20 µg QD pm	15 (8, 18)	13 (5, 17)	15 (9, 17)	15 (4, 18)	13 (8, 17)		16 (6, 17)
LIXI 20 µg QD in one step	14 (7, 18)	12 (6, 17)	10 (3, 16)	15 (4, 18)	10 (4, 16)	9 (2, 12)	10 (4, 16)
LIXI 20 µg QD in two steps	15 (10, 18)	14 (7, 17)	13 (5, 16)	14 (5, 18)	10 (6, 14)		14 (6, 17)
SITA 100mg QD†	13 (11, 17)	15 (10, 17)	14 (10, 16)	12 (6, 17)	16 (13, 17)	10 (8, 12)	2 (1, 4)
Placebo†	19 (18, 19)	18 (17, 18)	17 (16, 17)	17 (15, 18)	16 (13, 17)	12 (10, 12)	4 (3, 7)

The highest and second highest median ranks of the primary comparators per outcome are highlighted in green and blue, respectively

AE adverse event, *ALBI* albiglutide, *am* morning, *BID* twice-daily, *CFB* change from baseline, *CrI* credible interval, *DULA* dulaglutide, *EXE* exenatide, *FPG* fasting plasma glucose, *HbA_{1c}* glycated hemoglobin, *IGlar* insulin glargine, *LIRA* liraglutide, *LIXI* lixisenatide, *pm* evening, *QD* once-daily, *QW* once-weekly, *SBP* systolic blood pressure, *SEMA* semaglutide, *SITA* sitagliptin

† Secondary comparators

semaglutide was associated with a similar rate of discontinuation due to AEs when compared with other GLP-1 RAs. This is in agreement with the SUSTAIN clinical trial program, which has demonstrated that once-weekly semaglutide has a similar safety profile to other GLP-1 RAs [23, 27]. This suggests that the increase in efficacy with once-weekly semaglutide is well tolerated and not associated with an increased burden from AEs. It should be noted that it was not feasible to perform an analysis of the incidence of hypoglycemia (no connected network could be formed). While hypoglycemia is a well-defined barrier to glycemic control [78, 79], the incidence of hypoglycemia is known to be low with GLP-1 RAs (due to their glucose-dependent mechanism of action) and it is not typically cited as a reason for discontinuation of GLP-1 RAs [72]. Consistent with the class effect, the incidence of severe hypoglycemia with once-weekly semaglutide was low and comparable with dulaglutide QW in SUSTAIN 7 [27]. Furthermore, for the composite outcome ($HbA_{1c} < 7\%$, no weight gain, and no hypoglycemia) where the data only allowed an indirect comparison between once-weekly semaglutide and lixisenatide 20 µg QD, once-weekly semaglutide was associated with significantly higher odds of achieving this outcome compared with lixisenatide 20 µg QD. This suggests that the improvements in glycemic control with once-weekly semaglutide are not at the cost of increased rates of hypoglycemia.

The strengths of this study include the number and homogeneity of trials across the networks, and the alignment of the analyses with clinical practice and guidance from NICE, ISPOR, and the Cochrane institute [30–33, 80]. All of the trials included within the NMA were derived from a SLR, ensuring all available

evidence was captured. Furthermore, the robustness of the results and conclusions were demonstrated across a number of sensitivity and restricted analyses. Exploratory meta-regression analyses also validated the choice model used for the key analyses (change from baseline in HbA_{1c}, SBP, and weight). The analyses were also subject to some common limitations. These included heterogeneity in the time points reported across the trials, which was addressed using the well-accepted approach of applying a time-point window [75, 76, 81] and the potential publication bias within the trials included in the SLR. While the overall risk of bias was generally considered low, 18 studies included across the analyses were open-label trials, which could introduce performance bias. We were not able to include an analysis of certain other outcomes of interest (for example the incidence of hypoglycemia or postprandial glucose [PPG]), based on the limitations of available data. In the case of PPG, considerable heterogeneity in the available datasets precluded a robust comparative analysis. Some of the factors contributing to heterogeneity in PPG analysis included different methods of assessing PPG (2-h PPG after a standardized breakfast meal test vs self-monitored plasma glucose [SMPG] assessment), different time points of assessment (90 vs 120 min), and different SMPG profiles (7-point vs 8-point vs 9-point) among the included studies reporting data for PPG increments.

CONCLUSION

Overall, once-weekly semaglutide 1.0 mg as an add-on to 1–2 OADs is the most efficacious GLP-1 RA in terms of the reduction of HbA_{1c} and weight from baseline after 6 months of treatment. Once-weekly semaglutide 0.5 mg also significantly reduces HbA_{1c} and weight when compared with the majority of GLP-1 RA comparators. In addition, the similar rate of discontinuation due to AEs with once-weekly semaglutide relative to other GLP-1 RAs suggests that once-weekly semaglutide is well tolerated and not associated with an increase in burden from AEs.

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Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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