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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 Basal Insulin

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ABSTRACT

Introduction: Once-weekly semaglutide is a glucagon-like peptide-1 (GLP-1) analogue that is currently available as 1.0 mg and 0.5 mg dose for the treatment of type 2 diabetes (T2D). Currently, no head-to-head trial investigating once-weekly semaglutide as an add-on to basal insulin vs other GLP-1 receptor agonists (GLP-1 RAs) is available. The aim of this study was to conduct a 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 basal insulin.

Methods: A systematic literature review was performed to identify all trials of GLP-1 RAs as an add-on to basal insulin in patients with T2D.

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Data at 24 ± 4 weeks were extracted for efficacy and safety outcomes (feasible for analysis in an NMA), including the change from baseline in glycated hemoglobin (HbA_{1c}), body weight, and systolic blood pressure, and the incidence of nausea, vomiting, and diarrhea. Data were synthesized using a NMA and a Bayesian framework.

Results: In total, eight studies were included across the base-case analyses. The results demonstrate that once-weekly semaglutide 1.0 mg was associated with significantly greater reductions in HbA_{1c} ($- 0.88\%$ to $- 1.39\%$ vs comparators) and weight ($- 1.49$ to $- 4.69$ kg vs comparators) and similar odds of experiencing nausea, vomiting, or diarrhea vs all GLP-1 RA comparators. Once-weekly semaglutide 1.0 mg was also equally effective at reducing systolic blood pressure compared with liraglutide 1.8 mg. Once-weekly semaglutide 0.5 mg significantly reduced HbA_{1c} vs the majority of other GLP-1 RAs, except liraglutide 1.8 mg QD. The odds of experiencing nausea were significantly lower with once-weekly semaglutide 0.5 mg compared with all GLP-1 RA comparators.

Conclusion: Once-weekly semaglutide 1.0 mg as an add-on to basal insulin is likely to be the most efficacious GLP-1 RA for reducing HbA_{1c} and weight from baseline after 6 months of treatment. The efficacy of once-weekly semaglutide is not associated with a significant increase in the incidence of gastrointestinal side-effects vs other GLP-1 RAs.

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INTRODUCTION

Type 2 diabetes (T2D) is a chronic and progressive disease associated with microvascular and macrovascular complications leading to increased morbidity and mortality [1, 2].

Glycemic control is the key goal in the management of T2D, with targets of glycated hemoglobin (HbA$_{1c}$) < 7.0% (53 mmol/L) or ≤ 6.5% (48 mmol/mol) defined in treatment guidelines [3–6]. Despite clear clinical guidelines for achieving glycemic control in patients with T2D [3, 7, 8], glycemic control remains suboptimal in many patients with T2D receiving insulin treatment. For example, in patients with T2D receiving basal insulin across Europe and the US, it has been estimated that 78.1% and 72.2% had inadequate glycemic control 3 and 24 months post-initiation [9]. There is significant clinical inertia in the initiation and intensification of insulin therapy among patients with poor glycemic control, and it has been estimated that only one-third achieve glycemic control 3 years after the initiation of basal insulin [10]. For patients who are inadequately controlled on basal insulin, treatment options include the intensification of insulin therapy by adding either rapid-acting bolus insulin, another oral anti-diabetic medication (OAD), or injectable glucagon-like peptide-1 receptor agonists (GLP-1 RAs) [3, 6, 7].

GLP-1 RAs are incretin mimetics that improve glycemic control with a favorable effect on body weight and a low incidence of hypoglycemia [11, 12]; GLP-1 RAs improve glycemic control when used at different stages along the T2D treatment cascade [3, 7, 13]. The differing mechanism of actions mean that GLP-1 RAs can complement basal insulin therapy for the management of day-to-day blood glucose control without incurring the increased risk of hypoglycemia and weight gain associated with the addition of a bolus insulin [13]. As such, it has been suggested that the combination treatment of a GLP-1 RA and basal insulin allows achievement of the goals of anti-diabetic therapy: robust glycemic control without an increase in hypoglycemia and weight gain [14, 15]. Combination therapy with GLP-1 RAs and basal insulin is also more effective when compared to other anti-diabetic treatment regimens [14].

Semaglutide is a new once-weekly GLP-1 analogue available at either a 1.0 mg or 0.5 mg dose. The clinical efficacy of once-weekly semaglutide has been extensively studied in 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 [16–22]. Specifically, the efficacy and safety of once-weekly semaglutide as an add-on to basal insulin (± OADs) has been investigated in the SUSTAIN 5 clinical trial [20]. In this trial, once-weekly semaglutide (+ basal insulin ± metformin) provided a superior reduction in HbA$_{1c}$ levels and body weight compared with placebo (+ basal insulin ± metformin) and allowed a significantly greater proportion of patients to achieve target HbA$_{1c}$ levels [20].

Given the number of treatment options available for the management of T2D, it is important for decision makers to understand the relative clinical benefits of all treatment options to allow for an informed treatment decision. So far, no head-to-head trials between once-weekly semaglutide and other GLP-1 RAs in patients inadequately controlled on basal insulin (± OADs) have been conducted. As each GLP-1 RA may demonstrate unique advantages and disadvantages, it is important to understand the relative efficacy and safety of each GLP-1 RA [23]. The aim of the current study was to conduct a systematic literature review (SLR) and network meta-analysis (NMA) to assess the relative efficacies and safety of GLP-1 RAs as an add-on to basal insulin (± OADs) in the treatment of T2D.

METHODS

The trials included across the analyses were derived from a SLR, for which the methodology

has been reported in Witkowski et al. [24] (while the search strategy and PICOS criteria have been previously presented in the sister publication within this journal, they are replicated in Tables S1 and Table S2 of the Electronic supplementary material, ESM, for convenience). Briefly, searches of databases (MEDLINE®, Embase, and the Cochrane Library; see Table S1 of the ESM) and conference proceedings were performed via Ovid on April 5, 2016 (updated in October 3, 2016 and August 16, 2017). Studies were then screened independently by two reviewers against the PICOS (population, interventions, comparators, outcomes, study design) selection criteria for inclusion in the SLR (Table S2 of the ESM).

An NMA was performed 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 approved for the treatment of T2D—liraglutide once-daily (QD), dulaglutide once-weekly (QW), exenatide twice-daily (BID), exenatide QW, lixisenatide QD, and albiglutide QW; despite a withdrawal notice, albiglutide is included as the reason for withdrawal was not related to the safety of the medicine [25]. In order to reduce variability between the populations across the different trials, the definition of the add-on to basal insulin population was aligned as closely as possible with the population included in SUSTAIN 5—patients inadequately controlled on basal insulin (100% received basal insulin) with or without metformin (approximately 83% of patients also received metformin). As relatively few trials have been conducted in patients inadequately controlled on basal insulin ± metformin, trials with patients inadequately controlled on basal insulin with up to two OADs were included for feasibility assessment. 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 outlined in the PICOS criteria of the SLR (Table S2 of the ESM) was then examined. All studies included in the NMA were assessed for

risk of bias using a seven-criteria checklist as approved by the National Institute of Health and Care Excellence (NICE) [26].

Statistical Analysis

As previously described in the sister publication, analyses of continuous outcomes (using a normal likelihood, identity link, shared parameter model) and dichotomous outcomes (using a binomial likelihood [assuming a normal distribution], logit link model) considered feasible for assessment were implemented on WinBUGS (MRC Biostatistics Unit, Cambridge, UK [27]) using a Bayesian framework with the inclusion of vague prior distributions, and three Markov Monte Carlo chains. Both fixed-effects (FE) and random-effects (RE) models were run for each outcome and the model with the best fit (based on the deviance information criterion [DIC] and the average posterior residual deviance) was used. All NMAs were formally assessed for inconsistency using Bucher's method (as outlined by the NICE Technical Support Document 4) [28]; briefly, the inconsistency assessment with Bucher's method compares direct and indirect (NMA) estimates, and the difference between these estimates is a measure of inconsistency.

Model convergence (assessed using standard diagnostic methods for evaluating 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 (release 13, 2013; StataCorp. LP, College Station, TX, USA) using the "indirect" command [29]. The results of the NMA are presented as mean treatment differences or odds ratios (ORs) and an associated 95% credible interval (CrI). Unless the CrI excludes the null value (for treatment differences) or 1 (for ORs), it is assumed that there is no difference. Two ranking outcomes, median rank and the surface under the cumulative ranking curve (SUCRA), are also presented.

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

RESULTS

Identified Publications

A total of 107 publications reporting on 75 unique trials were included within the SLR (Table S3 of the ESM) as demonstrated in the sister article within this journal; the PRISMA diagram is replicated in Fig. S1 of the ESM. Of these 75 trials, 12 trials were considered to be relevant for inclusion in the current analysis [20, 30–40]. All 12 trials considered in the NMA formed a connected network. It should be noted that the insulin lispro arms from Diamant et al. [32] and HARMONY-6 [39] were deemed to be similar enough to combine into a single treatment node. The 12 trials were next examined for time points for which data were available for at least one outcome (Fig. S2 in the ESM). All 12 trials (100%) reported on an 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 (75%) 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 12 trials are presented in Table 1. Overall, the risk of bias across the 12 studies was considered to be low; however, the highest risk of bias across the studies was associated with elements of study blinding and omissions (Figure S3 in the ESM). In total, eight trials were deemed sufficiently homogeneous to combine for analysis, while four studies were identified as potential outliers due to study design and patient characteristics: the GetGoal-Duo 1 trial [33] screened patients who were newly initiated on basal insulin and were only included in the study if they were uncontrolled after 12 weeks; the GetGoal-O trial [38] was conducted exclusively in elderly patients; and both the GetGoal-L-C trial [37] and the GetGoal L-Asia trial [36] were conducted primarily (> 85%) in an Asian population (GLP-1 RAs are known to be more effective in Asian patients than in Caucasian patients, which may influence the relative treatment effects [41]). It was therefore decided that these studies should be excluded from the base-case analysis in order to limit the clinical heterogeneity of the NMA, yielding a total of eight studies; however, the impact of excluding those trials was to be explored in sensitivity analyses.

NMA Results

For the analysis, outcome-specific evidence networks were possible for 10 of the 20 outcomes of interest assessed for feasibility; note that it was not feasible to perform an analysis of the incidence of hypoglycemia as no connected network could be formed. Of the eight trials considered in the base-case analysis, all trials reported data on the change from baseline in HbA_{1c}, the proportion of patients achieving $HbA_{1c} < 7\%$ and $\leq 6.5\%$, fasting plasma glucose (FPG), weight, and the incidence of nausea, vomiting, and diarrhea; only two trials (LIRA-ADD2BASAL [40] and SUSTAIN 5 [20]) reported the change from baseline in systolic blood pressure (SBP), and three trials (GetGoal-Duo 2 [34], GetGoal-L [35], and SUSTAIN 5 [20]) reported the proportion of patients achieving $\geq 5\%$ weight loss. The evidence networks are shown in Fig. 1.

The FE model was preferred for all outcomes analyzed in the base case; no important differences between the FE and RE models were observed in terms of DIC and average posterior residual deviance (Table S4 of the ESM). However, the NMA for the change from baseline in SBP was unstable and failed to converge. As outlined in the methodology, a Bucher indirect comparison was therefore performed for this outcome.

The results of the NMA are presented as treatment differences or ORs (once-weekly semaglutide vs comparator) in Fig. 2a–h (the full matrix of relative treatment effects results are shown in Tables S12–S20 of the ESM). The associated treatment ranks (SUCRA and median rank) are presented, where available, in Tables 2 and 3.

Table 1 Study design and patient characteristics of trials included in the NMA

Trial	Number of patients	Randomized treatment	Background therapy	Prior therapy with 2/1 OADs, n (%)	Females, n (%)	Mean age, years (SD)	Mean baseline weight, kg (SD)	Mean baseline HbA$_{1c}$, % (SD)	Mean baseline duration of diabetes, years (SD)	Treatment duration, weeks (total trial duration)
AWARD-9 [30]: phase 3, double-blind, parallel trial, 40 sites globally	150	DULA 1.5 mg QW	IGlar ± MET	134 (89.3)/ NR	65 (43.3)	60.2 (9.5)	93.3 (17.5)	8.4 (0.9)	13 (7.5)	28 (31)
	150	Placebo		131 (87.3)/ NR	62 (41.3)	60.6 (10.1)	92.6 (17.1)	8.3 (0.8)	13.3 (7.7)	
Buse et al. [31]: phase 3, double-blind, parallel trial, 59 sites globally	123	Placebo	IGlar ± MET ± PG	97/8 (7)	44 (36)	59 (10)	93.4 (21.2)	8.5 (0.96)	12 (7)	(30)
	138	EXE 10 µg BID		93/23 (17)	67 (49)	59 (9)	95.4 (20.4)	8.32 (0.85)	12 (7)	
Diamant et al. [32]: phase 3, open-label, parallel trial, 108 sites globally	312	ILispro starting dose 24.6 U QD changing to dose 42.1 U QD	IGlar + MET ± SU	NR/99 (38)	130 (49.429657794676768)	59.4 (9.3)	89.4 (17)	8.2 (0.9)	11 (8, 15)	30 (44)
	315	EXE 10 µg BID		NR/85 (34)	119 (48.178137651821 9)	59.5 (9.6)	91.1 (16.6)	8.3 (1)	12 (8, 17)	
GetGoal-Duo 1 [33]: phase 3, open-label, parallel trial, 140 sites, 25 countries	223	Placebo	IGlar + MET ± PG or RG	196 (87.9)/27 (12)	110 (53.7)	56 (10)	86.8 (20.4)	7.6 (0.5)	8.7 (5.8)	24 (38.5)
	223	LIXI 20 µg QD		196 (87. 92)/ 27 (12)	114 (53.7)	56 (10)	87.3 (21.8)	7.6 (0.5)	9.6 (6)	

Table 1 continued

Trial	Number of patients	Randomized treatment	Background therapy	Prior therapy with 2/1 OADs, n (%)	Females, n (%)	Mean age, years (SD)	Mean baseline weight, kg (SD)	Mean baseline HbA$_{1c}$, % (SD)	Mean baseline duration of diabetes, years (SD)	Treatment duration, weeks (total trial duration)
GetGoal-Duo 2 [34]: phase 3, open-label, parallel trial, 199 sites globally	298	LIXI 20 µg QD	IGlar ± MET	NR	160 (53.7)	59.8 (8.6)	90.1 (17.4)	7.8 (0.6)	11.89 (6.43)	26 (38)
	298	IGlar QD	IGlar ± MET	NR	163 (54.7)	60.2 (8.6)	88.4 (15.9)	7.7 (0.6)	12.33 (6.75)	
	298	IGlu TID	IGlar ± MET	NR	166 (55.7)	59.4 (9.5)	90 (17.2)	7.8 (0.6)	12.41 (6.8)	
GetGoal-L [35]: phase 3, double-blind, parallel trial, 111 sites globally	167	Placebo	IGlar/IDet/NPH ± MET	NR (78)/NR	85 (50.9)	57 (10)	88.9 (20.8)	8.4 (0.8)	12.4 (6.3)	24 (25)
	329	LIXI 20 µg QD		NR (80)/NR	182 (55.5)	57 (10)	87.1 (20)	8.4 (0.9)	12.5 (7)	
GetGoal-L-Asia [36]: phase 3, double-blind, parallel trial, 57 sites in multiple Asian countries	154	LIXI 20 µg QD	IGlar/IDet/NPH ± SU	108 (70.1)/NR	85 (55.2)	58.7 (10.2)	65.93 (13)	8.54 (0.73)	13.7 (7.7)	24 (27)
	157	Placebo		111 (70.7)/NR	77 (49.0)	58 (10.1)	65.6 (12.47)	8.52 (0.78)	14.1 (7.7)	

Table 1 continued

| Trial	Number of patients	Randomized treatment	Background therapy	Prior therapy with 2/1 OADs, n (%)	Females, n (%)	Mean age, years (SD)	Mean baseline weight, kg (SD)	Mean baseline HbA₁c, % (SD)	Mean baseline duration of diabetes, years (SD)	Treatment duration, weeks (total trial duration)
GetGoal-L-C [37]: phase 3, double-blind, parallel trial, 51 sites in multiple Asian countries	224	LIXI 20 µg QD	IGlar/IDet/NPH ± MET	NR	119 (53.1)	53.9 (9.9)	74.2 (14.1)	7.9 (0.66)	10.3 (6.1)	24 (34)
	224	Placebo		NR	126 (56.2)	56.2 (9.1)	74.6 (13.3)	7.9 (0.70)	10.2 (6.2)	
GetGoal-O [38]: phase 3, double-blind, parallel trial, 73 sites globally	176	LIXI 20 µg QD	BI ± OADs ± SU ± MET	NR	84 (46.7)	74.0 (4.0)	80.8 (14.5)	8.1 (0.7)	13.6 (7.3)	24 (28)
	174	Placebo		NR	84 (48.3)	74.4 (3.8)	80.1 (16.8)	8.1 (0.7)	14.6 (7.9)	
HARMONY-6 [39]: phase 3, open-label, parallel trial, 210 sites globally	292	ALBI 30 mg QW	IGlar ± MET ± TZDs	203 (71.2/18 (6)	153 (54)	54.8 (9.1)	92.5 (21.5)	8.5 (0.9)	11 (7)	52
	294	ILispro		195 (69.4/19 (7)	145 (52)	56.3 (8.9)	91.6 (21)	8.4 (0.9)	11 (6)	

Table 1 continued

Trial	Number of patients	Randomized treatment	Background therapy	Prior therapy with 2/1 OADs, n (%)	Females, n (%)	Mean age, years (SD)	Mean baseline weight, kg (SD)	Mean baseline HbA1c, % (SD)	Mean baseline duration of diabetes, years (SD)	Treatment duration, weeks (total trial duration)
LIRA-ADD2BASAL [40]: phase 3, double-blind, parallel trial,	225	Placebo	BI (IGlar or IDet) ± MET	(93.3)/NR	89 (39.6)	57.5 (11.1)	91.9 (19.3)	8.3 (0.9)	12.1 (6.8)	26 (29)
	226	LIRA 1.8 mg QD		(92)/NR	105 (46.7)	59.3 (9.2)	90.2 (20)	8.2 (0.8)	12.1 (7.1)	
SUSTAIN 5 [20]: phase 3a, double-blind, parallel trial 76 sites globally	132	SEMA 0.5 mg QW	BI ± MET	NR/NR	58 (43.9)	59.1 (10.3)	92.7 (range 50.4, 162.8)	8.36 (0.83)	12.91 (7.59)	30 (43)
	131	SEMA 1.0 mg QW		NR/NR	54 (41.2)	58.5 (9.0)	92.5 (range 48.5, 165.6)	8.31 (0.82)	13.74 (7.82)	
	133	Placebo		NR/NR	62 (46.6)	58.8 (10.9)	89.9 (range 47.5, 157.3)	8.42 (0.88)	13.30 (7.98)	

ALBI albiglutide, BG biguanide, BI basal insulin, BID twice daily, DULA dulaglutide, EXE exenatide, HbA1c glycated hemoglobin, IDet insulin detemir, IGlar insulin glargine, ILispro insulin lispro, LIRA liraglutide, LIXI lixisenatide, MET metformin, NPH neutral protamine Hagedorn (isophane insulin), NR not reported, OAD oral anti-diabetic drug, PG pioglitazone, QD once daily, QW once weekly, RG rosiglitazone, SD standard deviation, SEMA semaglutide, SITA sitagliptin, SU sulfonylureas, TZD thiazolidinediones
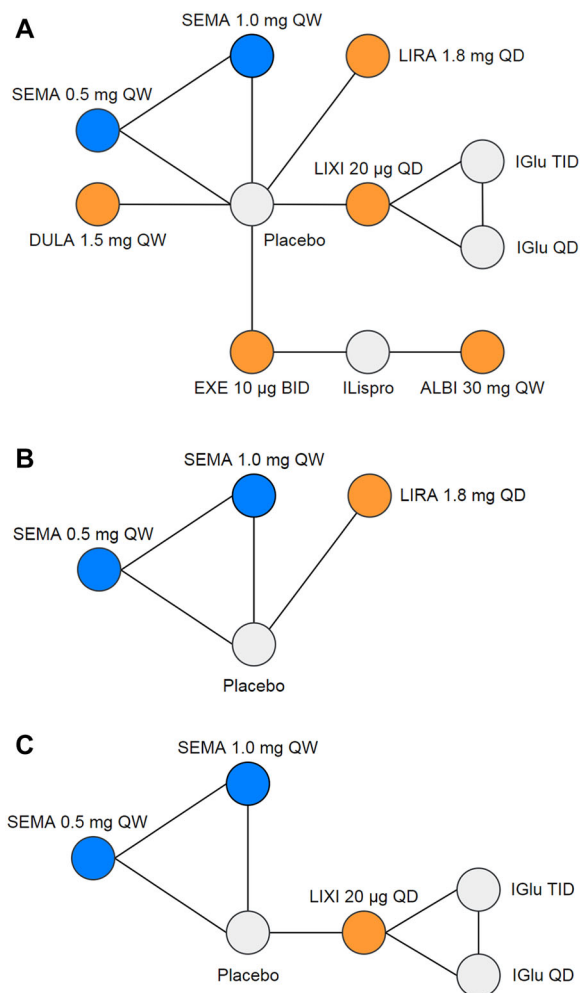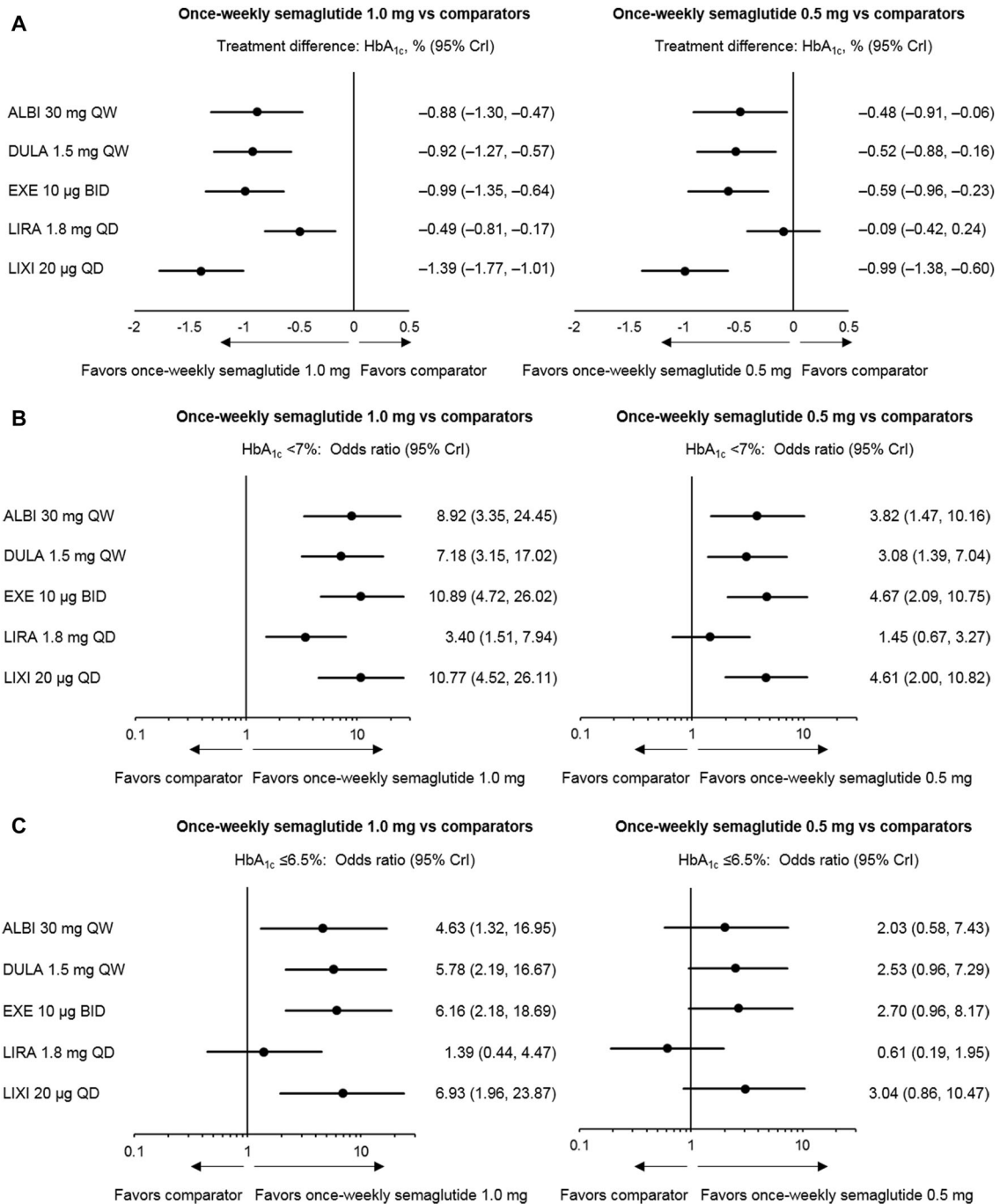
Fig. 1 Evidence networks for all outcomes. *Blue nodes* indicate a primary intervention of interest, orange nodes indicate a primary comparator of interest, and gray nodes indicate a secondary comparator. **a** The evidence network for the change from baseline in HbA_{1c}, weight, and FPG, the proportions of patients with $HbA_{1c} < 7\%$ or $\leq 6.5\%$, and the incidence of nausea, vomiting, and diarrhea. **b** The evidence network for the change from baseline in SBP. **c** The evidence network for the proportion of patients with $\geq 5\%$ weight loss. *ALBI* albiglutide, *BID* twice-daily, *DULA* dulaglutide, *EXE* exenatide, *IGlu* insulin glulisine, *ILispro* insulin lispro, *LIRA* liraglutide, *LIXI* lixisenatide, *QD* once-daily, *QW* once-weekly, *SEMA* semaglutide, *TID* thrice-daily

Glycemic Control

All eight trials considered in the base-case analysis reported data on the change from baseline in HbA_{1c} (Table S5 of the ESM). The

evidence network for the change from baseline in HbA_{1c} is shown in Fig. 1a. Once-weekly semaglutide 1.0 mg was associated with a significantly greater reduction in HbA_{1c} vs all GLP-1 RA comparators included in the analysis (Fig. 2a, Table S12 of the ESM). Furthermore, based on the 0.3 percentage-points margin for clinical superiority suggested by the FDA [42] and European Medicines Agency (EMA; [43]), the improvements in HbA_{1c} achieved with once-weekly semaglutide 1.0 mg were clinically meaningful vs all primary comparators. The analysis also suggested that once-weekly semaglutide 0.5 mg can provide significantly greater reductions in HbA_{1c} vs all GLP-1 RA comparators except liraglutide 1.8 mg QD. An additional sensitivity analysis using the same statistical approach as in the base-case analysis was performed to validate the legitimacy of excluding four trials [33, 36–38] from the base-case analysis on the basis of heterogeneity. The evidence network for the sensitivity analysis is shown in Fig. S4 of the ESM. The results of the analysis demonstrate that the inclusion of the outlier trials had little impact on the results and the overall interpretation of the analysis (Table S21 of the ESM).

NMAs were also feasible for the proportion of patients with HbA_{1c} levels $< 7\%$ or HbA_{1c} level $\leq 6.5\%$ using the same evidence network as shown in Fig. 1a. Data supporting these analyses are shown in Table S6 of the ESM. In line with the results seen for change from baseline in HbA_{1c}, analysis of the proportion of patients achieving HbA_{1c} targets showed that once-weekly semaglutide 1.0 mg had significantly higher odds of achieving a HbA_{1c} level $< 7\%$ vs all GLP-1 RA comparators (Fig. 2b, Table S13 of the ESM). Once-weekly semaglutide 0.5 mg also demonstrated significantly higher odds of achieving a HbA_{1c} level $< 7\%$ vs all GLP-1 RA comparators, except liraglutide 1.8 mg QD, to which it was comparable. Once-weekly semaglutide 1.0 mg had higher odds of achieving a HbA_{1c} level $\leq 6.5\%$ vs the majority of GLP-1 RA comparators, except liraglutide 1.8 mg, to which it was comparable; once-weekly semaglutide 0.5 mg had similar odds vs all GLP-1 RA comparators (Fig. 2c, Table S14 of the ESM).

A Once-weekly semaglutide 1.0 mg vs comparators
Treatment difference: HbA$_{1c}$, % (95% CrI)

ALBI 30 mg QW	−0.88 (−1.30, −0.47)
DULA 1.5 mg QW	−0.92 (−1.27, −0.57)
EXE 10 µg BID	−0.99 (−1.35, −0.64)
LIRA 1.8 mg QD	−0.49 (−0.81, −0.17)
LIXI 20 µg QD	−1.39 (−1.77, −1.01)

Favors once-weekly semaglutide 1.0 mg   Favors comparator

Once-weekly semaglutide 0.5 mg vs comparators
Treatment difference: HbA$_{1c}$, % (95% CrI)

ALBI 30 mg QW	−0.48 (−0.91, −0.06)
DULA 1.5 mg QW	−0.52 (−0.88, −0.16)
EXE 10 µg BID	−0.59 (−0.96, −0.23)
LIRA 1.8 mg QD	−0.09 (−0.42, 0.24)
LIXI 20 µg QD	−0.99 (−1.38, −0.60)

Favors once-weekly semaglutide 0.5 mg   Favors comparator

B Once-weekly semaglutide 1.0 mg vs comparators
HbA$_{1c}$ <7%: Odds ratio (95% CrI)

ALBI 30 mg QW	8.92 (3.35, 24.45)
DULA 1.5 mg QW	7.18 (3.15, 17.02)
EXE 10 µg BID	10.89 (4.72, 26.02)
LIRA 1.8 mg QD	3.40 (1.51, 7.94)
LIXI 20 µg QD	10.77 (4.52, 26.11)

Favors comparator   Favors once-weekly semaglutide 1.0 mg

Once-weekly semaglutide 0.5 mg vs comparators
HbA$_{1c}$ <7%: Odds ratio (95% CrI)

ALBI 30 mg QW	3.82 (1.47, 10.16)
DULA 1.5 mg QW	3.08 (1.39, 7.04)
EXE 10 µg BID	4.67 (2.09, 10.75)
LIRA 1.8 mg QD	1.45 (0.67, 3.27)
LIXI 20 µg QD	4.61 (2.00, 10.82)

Favors comparator   Favors once-weekly semaglutide 0.5 mg

C Once-weekly semaglutide 1.0 mg vs comparators
HbA$_{1c}$ ≤6.5%: Odds ratio (95% CrI)

ALBI 30 mg QW	4.63 (1.32, 16.95)
DULA 1.5 mg QW	5.78 (2.19, 16.67)
EXE 10 µg BID	6.16 (2.18, 18.69)
LIRA 1.8 mg QD	1.39 (0.44, 4.47)
LIXI 20 µg QD	6.93 (1.96, 23.87)

Favors comparator   Favors once-weekly semaglutide 1.0 mg

Once-weekly semaglutide 0.5 mg vs comparators
HbA$_{1c}$ ≤6.5%: Odds ratio (95% CrI)

ALBI 30 mg QW	2.03 (0.58, 7.43)
DULA 1.5 mg QW	2.53 (0.96, 7.29)
EXE 10 µg BID	2.70 (0.96, 8.17)
LIRA 1.8 mg QD	0.61 (0.19, 1.95)
LIXI 20 µg QD	3.04 (0.86, 10.47)

Favors comparator   Favors once-weekly semaglutide 0.5 mg

Fig. 2 Forest plots 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 target HbA$_{1c}$ < 7% or **c** HbA$_{1c}$ ≤ 6.5%, **d** change from baseline in FPG, **e** change from baseline in weight, and the incidence of **f** nausea, **g** vomiting, and **h** diarrhea. *ALBI* albiglutide, *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, *QD* once-daily, *QW* once-weekly
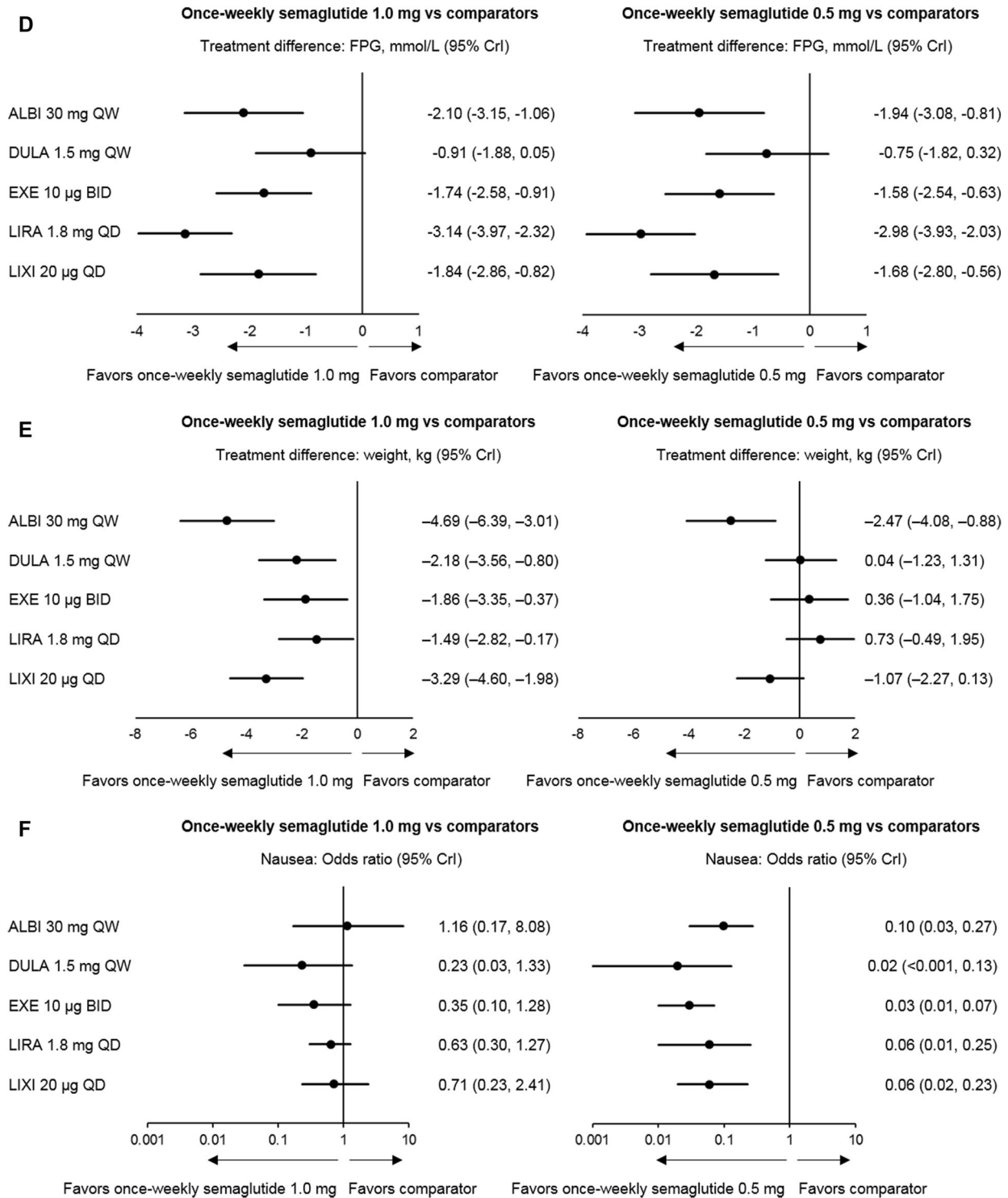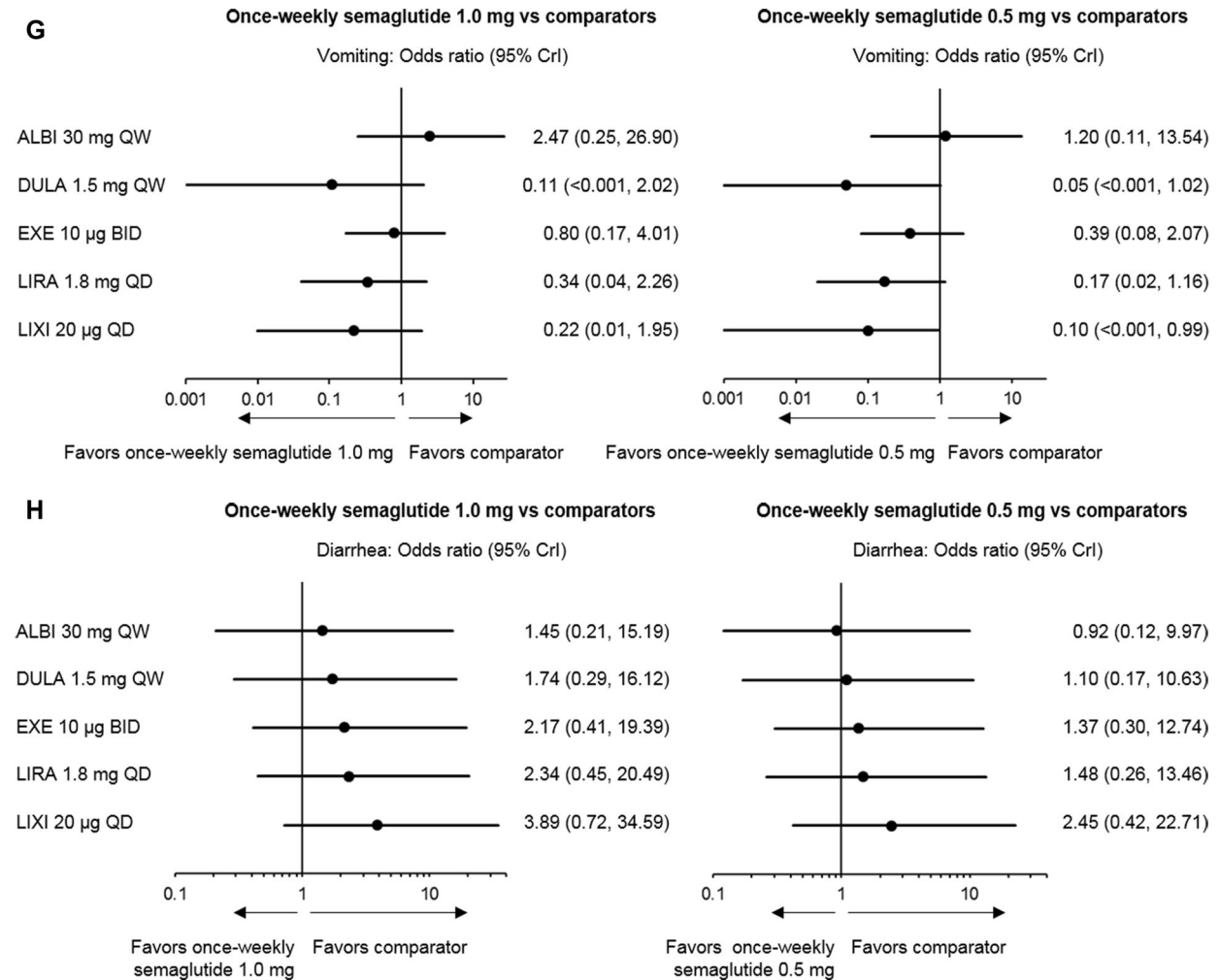
D

Once-weekly semaglutide 1.0 mg vs comparators
Treatment difference: FPG, mmol/L (95% CrI)

Once-weekly semaglutide 0.5 mg vs comparators
Treatment difference: FPG, mmol/L (95% CrI)

	1.0 mg	0.5 mg
ALBI 30 mg QW	-2.10 (-3.15, -1.06)	-1.94 (-3.08, -0.81)
DULA 1.5 mg QW	-0.91 (-1.88, 0.05)	-0.75 (-1.82, 0.32)
EXE 10 µg BID	-1.74 (-2.58, -0.91)	-1.58 (-2.54, -0.63)
LIRA 1.8 mg QD	-3.14 (-3.97, -2.32)	-2.98 (-3.93, -2.03)
LIXI 20 µg QD	-1.84 (-2.86, -0.82)	-1.68 (-2.80, -0.56)

Favors once-weekly semaglutide 1.0 mg   Favors comparator   Favors once-weekly semaglutide 0.5 mg   Favors comparator

E

Once-weekly semaglutide 1.0 mg vs comparators
Treatment difference: weight, kg (95% CrI)

Once-weekly semaglutide 0.5 mg vs comparators
Treatment difference: weight, kg (95% CrI)

	1.0 mg	0.5 mg
ALBI 30 mg QW	−4.69 (−6.39, −3.01)	−2.47 (−4.08, −0.88)
DULA 1.5 mg QW	−2.18 (−3.56, −0.80)	0.04 (−1.23, 1.31)
EXE 10 µg BID	−1.86 (−3.35, −0.37)	0.36 (−1.04, 1.75)
LIRA 1.8 mg QD	−1.49 (−2.82, −0.17)	0.73 (−0.49, 1.95)
LIXI 20 µg QD	−3.29 (−4.60, −1.98)	−1.07 (−2.27, 0.13)

Favors once-weekly semaglutide 1.0 mg   Favors comparator   Favors once-weekly semaglutide 0.5 mg   Favors comparator

F

Once-weekly semaglutide 1.0 mg vs comparators
Nausea: Odds ratio (95% CrI)

Once-weekly semaglutide 0.5 mg vs comparators
Nausea: Odds ratio (95% CrI)

	1.0 mg	0.5 mg
ALBI 30 mg QW	1.16 (0.17, 8.08)	0.10 (0.03, 0.27)
DULA 1.5 mg QW	0.23 (0.03, 1.33)	0.02 (<0.001, 0.13)
EXE 10 µg BID	0.35 (0.10, 1.28)	0.03 (0.01, 0.07)
LIRA 1.8 mg QD	0.63 (0.30, 1.27)	0.06 (0.01, 0.25)
LIXI 20 µg QD	0.71 (0.23, 2.41)	0.06 (0.02, 0.23)

Favors once-weekly semaglutide 1.0 mg   Favors comparator   Favors once-weekly semaglutide 0.5 mg   Favors comparator

Fig. 2 continued

G Once-weekly semaglutide 1.0 mg vs comparators
Vomiting: Odds ratio (95% CrI)

ALBI 30 mg QW — 2.47 (0.25, 26.90)
DULA 1.5 mg QW — 0.11 (<0.001, 2.02)
EXE 10 μg BID — 0.80 (0.17, 4.01)
LIRA 1.8 mg QD — 0.34 (0.04, 2.26)
LIXI 20 μg QD — 0.22 (0.01, 1.95)

0.001 0.01 0.1 1 10

Favors once-weekly semaglutide 1.0 mg   Favors comparator

Once-weekly semaglutide 0.5 mg vs comparators
Vomiting: Odds ratio (95% CrI)

ALBI 30 mg QW — 1.20 (0.11, 13.54)
DULA 1.5 mg QW — 0.05 (<0.001, 1.02)
EXE 10 μg BID — 0.39 (0.08, 2.07)
LIRA 1.8 mg QD — 0.17 (0.02, 1.16)
LIXI 20 μg QD — 0.10 (<0.001, 0.99)

0.001 0.01 0.1 1 10

Favors once-weekly semaglutide 0.5 mg   Favors comparator

H Once-weekly semaglutide 1.0 mg vs comparators
Diarrhea: Odds ratio (95% CrI)

ALBI 30 mg QW — 1.45 (0.21, 15.19)
DULA 1.5 mg QW — 1.74 (0.29, 16.12)
EXE 10 μg BID — 2.17 (0.41, 19.39)
LIRA 1.8 mg QD — 2.34 (0.45, 20.49)
LIXI 20 μg QD — 3.89 (0.72, 34.59)

0.1 1 10

Favors once-weekly semaglutide 1.0 mg   Favors comparator

Once-weekly semaglutide 0.5 mg vs comparators
Diarrhea: Odds ratio (95% CrI)

ALBI 30 mg QW — 0.92 (0.12, 9.97)
DULA 1.5 mg QW — 1.10 (0.17, 10.63)
EXE 10 μg BID — 1.37 (0.30, 12.74)
LIRA 1.8 mg QD — 1.48 (0.26, 13.46)
LIXI 20 μg QD — 2.45 (0.42, 22.71)

0.1 1 10

Favors once-weekly semaglutide 0.5 mg   Favors comparator

Fig. 2 continued

A NMA was also performed for FPG using the same evidence network as shown in Fig. 1a (Table S7 of the ESM). In line with the results achieved relating to reductions in HbA_{1c}, the analysis of the change from baseline in FPG demonstrated that once-weekly semaglutide 1.0 mg and 0.5 mg were both associated with significantly greater reductions in FPG compared with the majority of GLP-1 RA comparators, except dulaglutide 1.5 mg, to which they were comparable (Fig. 2d, Table S15 of the ESM).

Across these analyses, once-weekly semaglutide 1.0 mg was the highest ranked GLP-1 RA, achieving a median rank of 1 and a SUCRA score of 100% across all glycemic outcomes (Tables 2, 3). In line with the interpretation of SUCRA scores [44], this indicates that once-weekly semaglutide 1.0 mg is the most efficacious treatment within these networks. Despite the absence of lower-dose variants of the GLP-1 RA comparators from the analyses (e.g., dulaglutide 0.75 mg QW, exenatide 5 μg BID), once-weekly semaglutide 0.5 mg ranked highly in the analysis of these glycemic outcomes, achieving median ranks of 2–3 and SUCRA scores of 80–90% (Tables 2, 3).

Weight

All eight trials included in the base-case analysis reported data for the change from baseline in body weight (Table S8 of the ESM). The

Table 2 SUCRA results

Comparator	CFB in HbA$_{1c}$ (%)	HbA$_{1c}$ < 7% (%)	HbA$_{1c}$ ≤ 6.5% (%)	CFB in FPG (%)	CFB in weight (%)	≥ 5% weight loss (%)	Nausea (%)	Vomiting (%)	Diarrhea (%)
Semaglutide 0.5 mg QW	**90**	**90**	80	**90**	70	**80**	**80**	**70**	20
Semaglutide 1.0 mg QW	**100**	**100**	**100**	**100**	**100**	**100**	50	**50**	10
Albiglutide 30 mg QW	70	50	60	20	30		**60**	**70**	20
Dulaglutide 1.5 mg QW	60	60	40	80	70		0	0	30
Exenatide 10 µg BID	50	30	40	60	80		20	40	**40**
Insulin glulisine QD[a]	20	20	20	50	20	40	90	60	90
Insulin glulisine TID[a]	30	60	70	40	10	0	100	50	100
Insulin lispro[a]	40	30	30	10	0		10	100	70
Liraglutide 1.8 mg	80	80	**90**	0	**90**		30	20	**40**
Lixisenatide 20 µg QD	20	30	30	50	50	60	40	10	**60**
Placebo[a]	0	0	0	50	30	20	70	90	80

The highest and second highest SUCRA values of the primary comparators per outcome are highlighted in green and blue, respectively. The calculation of SUCRA scores for the change from baseline in SBP was not possible as the analysis was performed via a Bucher indirect comparison only

BID twice-daily, *CFB* change from baseline, *CrI* credible interval, *FPG* fasting plasma glucose, *HbA$_{1c}$* glycated hemoglobin, *QD* once-daily, *QW* once-weekly, *SBP* systolic blood pressure, *SUCRA* surface under the cumulative ranking, *TID* thrice-daily

[a] Secondary comparators

Table 3 Median ranks

Comparator	CFB in HbA$_{1c}$	HbA$_{1c}$ < 7%	HbA$_{1c}$ ≤ 6.5%	CFB in FPG	CFB in weight	≥ 5% weight loss	Nausea	Vomiting	Diarrhea
Semaglutide 0.5 mg QW	**2 (2, 3)**	**2 (2, 3)**	3 (2, 7)	**2 (1, 3)**	4 (2, 6)	**2 (2, 4)**	**3 (1, 3)**	**4 (2, 8)**	9 (3, 11)
Semaglutide 1.0 mg QW	**1 (1, 1)**	**1 (1, 1)**	**1 (1, 2)**	**1 (1, 2)**	**1 (1, 1)**	**1 (1, 2)**	6 (5, 9)	**6 (4, 10)**	10 (5, 11)
Albiglutide 30 mg QW	4 (3, 7)	6 (4, 10)	5 (3, 10)	9 (4, 10)	8 (6, 10)		**5 (4, 10)**	**4 (2, 9)**	9 (5, 11)
Dulaglutide 1.5 mg QW	5 (4, 8)	5 (4, 9)	7 (4, 10)	3 (2, 5)	4 (2, 5)		11 (6, 11)	11 (5, 11)	8 (4, 11)
Exenatide 10 µg BID	6 (4, 8)	8 (5, 10)	7 (4, 10)	5 (4, 8)	3 (2, 5)		9 (7, 11)	7 (4, 10)	**7 (5, 10)**
Insulin glulisine QD[a]	9 (6, 11)	9 (5, 10)	9 (5, 10)	6 (4, 10)	9 (7, 10)	4 (4, 6)	2 (1, 3)	5 (1, 10)	2 (1, 6)
Insulin glulisine TID[a]	8 (4, 10)	5 (4, 8)	4 (2, 8)	7 (4, 10)	10 (7, 11)	6 (4, 6)	1 (1, 3)	6 (2, 10)	1 (1, 2)
Insulin lispro[a]	7 (5, 10)	8 (5, 10)	8 (4, 10)	10 (6, 10)	11 (9, 11)		10 (7, 11)	1 (1, 3)	4 (1, 8)
Liraglutide 1.8 mg	3 (2, 3)	3 (2, 4)	**2 (1, 4)**	11 (10, 11)	**2 (2, 4)**		8 (5, 11)	9 (5, 11)	**7 (4, 11)**
Lixisenatide 20 µg QD	9 (8, 10)	8 (5, 10)	8 (4, 10)	6 (4, 9)	6 (5, 7)	3 (1, 3)	7 (5, 9)	10 (7, 11)	**5 (3, 9)**
Placebo[a]	11 (10, 11)	11 (11, 11)	11 (11, 11)	6 (4, 9)	8 (7, 10)	5 (4, 6)	4 (4, 5)	2 (1, 4)	3 (2, 5)

The highest and second highest median ranks of the primary comparators per outcome are highlighted in green and blue, respectively. The calculation of median ranks for the change from baseline in SBP was not possible as the analysis was performed via a Bucher indirect comparison only

BID twice-daily, *CFB* change from baseline, *CrI* credible interval, *FPG* fasting plasma glucose, *HbA$_{1c}$* glycated hemoglobin, *QD* once-daily, *QW* once-weekly, *SBP* systolic blood pressure, *TID* thrice-daily

[a] Secondary comparators

evidence network for the change in body weight was the same as for the outcomes of glycemic control presented in Fig. 1a. The results showed that once-weekly semaglutide 1.0 mg was associated with a significantly greater reduction in body weight vs all GLP-1

Table 4 Matrix of results for the change from baseline in SBP

Treatment A	Treatment B			
	Placebo	Liraglutide 1.8 mg QD	Semaglutide 0.5 mg QW	Semaglutide 1.0 mg QW
Placebo				
Liraglutide 1.8 mg QD	− 5.02 (−7.45, −2.59)			
Semaglutide 0.5 mg QW	− 0.06 (−3.94, 3.82)	4.96 (0.38, 9.54)[a]		
Semaglutide 1.0 mg QW	−3.69 (− 7.82, 0.44)	1.33 (− 3.46, 6.12)[a]	−3.63 (− 9.30, 2.04)	

Treatment difference: treatment A (row) vs treatment B (column), mmHg (95% CI)

Green shaded cells indicate a significantly greater reduction (improvement) from baseline in the outcome with treatment A vs treatment B where the 95% CrI excludes the null value

Red shaded cells indicate a significantly greater increase (worsening) from baseline in the outcome with treatment A vs treatment B where the 95% CrI excludes the null value

CFB change from baseline, *CI* confidence interval, *QD* once-daily, *QW* once-weekly, *SBP* systolic blood pressure

[a] These two estimates are indirect comparisons. All remaining estimates in this matrix are trial-level direct comparisons

RA comparators (Fig. 2e, Table S16 of the ESM). Furthermore, once-weekly semaglutide 1.0 mg achieved a median rank of 1 and a SUCRA score of 100%, indicating that this treatment is the most efficacious option for a reduction in body weight within the network (Tables 2, 3). Overall, once-weekly semaglutide 0.5 mg was broadly comparable to all GLP-1 RA comparators. An additional sensitivity analysis, performed to validate the legitimacy of excluding four trials [33, 35–38] from the base-case analysis (Fig. S4 of the ESM), showed that the inclusion of the outlier trials had little impact on the results and interpretation of the analysis (Table S21 of the ESM). A NMA was also possible for the proportion of patients achieving ≥ 5% weight loss using data from three trials (GetGoal-Duo 2 [34], GetGoal-L [35], and SUSTAIN 5 [20]; Table S9); however, lixisenatide 20 μg QD was the only GLP-1 RA available for comparison (Fig. 1c). Overall, once-weekly semaglutide 1.0 mg and 0.5 mg had comparable odds of achieving ≥ 5% weight loss vs lixisenatide 20 μg QD (Table S17 of the ESM).

Systolic Blood Pressure

Only two trials (LIRA-ADD2BASAL [40] and SUSTAIN 5 [20]) reported data on the change from baseline in SBP and were included in an indirect comparison (Table S10 of the ESM). Therefore, only a comparison between once-weekly semaglutide and liraglutide 1.8 mg QD was possible (Fig. 1b). This analysis suggests that the change in SBP with once-weekly semaglutide 1.0 mg was comparable with liraglutide 1.8 mg in this population. In contrast, the change in SBP with liraglutide 1.8 mg QD was more effective than once-weekly semaglutide 0.5 mg (Table 4).

Adverse Events

It is important to consider whether the improved efficacy of once-weekly semaglutide vs other GLP-1 RA comparators is at the expense of an increase in adverse events (AEs). The most common AEs associated with the GLP-1 RA class compared with other anti-diabetic drug classes are gastrointestinal (GI)-related [45]. In this NMA, it was feasible to analyze three GI-related AEs: nausea, vomiting, and diarrhea. The data included in the base-case analysis of these outcomes are shown in Table S11 of the ESM and the evidence network (the same for each outcome) is presented in Fig. 1a. Overall, once-weekly semaglutide 1.0 mg was associated with similar odds of nausea, vomiting, or diarrhea vs all GLP-1 RA comparators (Fig. 2f–h, Tables S18–S20 of the ESM). Once-weekly semaglutide 0.5 mg was associated with similar odds of vomiting or diarrhea; however, the risk of nausea with once-weekly semaglutide 0.5 mg was significantly lower vs all other GLP-1 RA comparators.

DISCUSSION

The objective of this study was to demonstrate the efficacy and safety of once-weekly semaglutide vs other GLP-1 RAs in patients with T2D inadequately controlled on basal insulin (± OADs). The analyses demonstrated that once-weekly semaglutide 1.0 mg was associated with significantly greater reductions in HbA_{1c} and body weight vs all other GLP-1 RAs. This was reflected in a SUCRA score of 100%, indicating that once-weekly semaglutide 1.0 mg is the most efficacious treatment within these networks. Additional analyses showed that the significantly greater reductions in HbA_{1c} and body weight with once-weekly semaglutide 1.0 mg are also supported by significant improvements in FPG and significantly higher odds of achieving the HbA_{1c} targets of < 7% and ≤ 6.5% compared with other GLP-1 RAs. The analyses also demonstrated that once-weekly semaglutide 0.5 mg can provide significantly greater reductions in HbA_{1c} vs the majority of GLP-1 RA comparators. The increased efficacy of once-weekly semaglutide was not at the expense of reduced tolerability, as the GI-related side effects of nausea, vomiting, and diarrhea were comparable between once-weekly semaglutide and other GLP-1 RA comparators.

This is the first NMA to assess the efficacy and safety of once-weekly semaglutide as an add-on to basal insulin in patients with T2D vs other GLP-1 RAs. To our knowledge, no other study has performed a comparative analysis of GLP-1 RAs as an add-on to basal insulin; however, previous systematic reviews and meta-analyses have assessed the efficacy and safety of GLP-1 RAs compared with other anti-diabetic treatments in this population. In a systematic review of studies assessing the safety and efficacy of GLP-1 RAs (exenatide, liraglutide, lixisenatide) as an add-on to basal insulin, the majority of studies reported beneficial effects of such a combination compared with other treatment regimens [15]. In a meta-analysis comparing the efficacy and safety of a combination of GLP-1 RAs and basal insulin vs other anti-diabetic treatment regimens, the combination of a GLP-1 RA and basal insulin yielded a greater mean reduction in HbA_{1c} and body weight by

− 0.44% and − 3.22 kg, respectively, and a greater likelihood of patients achieving a HbA_{1c} level < 7% [14].

In this NMA, once-weekly semaglutide 1.0 mg was the most clinically effective GLP-1 RA for achieving glycemic targets and reducing HbA_{1c}, FPG, and body weight in patients who are receiving basal insulin. This was supported by SUCRA scores which indicated that once-weekly semaglutide is the most clinically efficacious in the evidence network. However, it is important that an increase in efficacy does not come at the expense of an increase in AEs. The most frequent AEs linked with GLP-1 RA therapy are GI-related (e.g., nausea, vomiting, and diarrhea); however, these AEs are thought to be dose dependent and can decline over time [45, 46]. In a NMA investigating the relative frequencies of GI-related AEs in association with various GLP-1 RAs (excluding semaglutide), it was demonstrated that taspoglutide (now withdrawn), albiglutide and lixisenatide were most commonly associated with nausea and vomiting, while lixisenatide and liraglutide ranked first and second for the incidence of diarrhea [45]. In our analysis, the risk of GI-related AEs with once-weekly semaglutide was similar to all other GLP-1 RA comparators, suggesting that the increased efficacy of once-weekly semaglutide vs other GLP-1 RAs is not associated with a higher risk of AEs.

The strengths of this study include the quality and homogeneity of trials included across the networks. All included data were derived from a SLR, ensuring that all evidence was captured for the analyses. Furthermore, the NMAs were performed according to previously published guidelines [28, 47–50], and the sensitivity analyses confirmed the robustness of the results and conclusions. This study was also subject to some limitations. Firstly, there was heterogeneity in the time points reported in the individual studies, which was addressed by using the well-established approach of applying a time window to the analyses [51–53]. Secondly, although the risk of publication bias in this analysis was considered low, four of the publications included across these analyses were open-label studies, which can introduce performance bias. Lastly, an analysis to assess the risk of hypoglycemia with

once-weekly semaglutide (in combination with insulin) compared with other GLP-1 RAs was not feasible. In general, GLP-1 RAs can complement basal insulin therapy without the increased risk of hypoglycemia associated with basal–bolus insulin therapy [13]; often, the addition of GLP-1 RAs allows for the insulin dose to be reduced, decreasing the risk of hypoglycemia and weight gain [15, 54]. Furthermore, in a meta-analysis assessing the efficacy and safety of GLP-1 RAs as an add-on to basal insulin vs basal insulin with or without rapid-acting insulin, insulin with GLP-1 RA was associated with a significantly lower risk of hypoglycemia compared with treatment intensification with a rapid-acting insulin [55]. For once-weekly semaglutide, the data from SUSTAIN 5 [20] suggest that the addition of once-weekly semaglutide 0.5 or 1.0 mg to basal insulin is not associated with a significant increase in hypoglycemia compared with placebo (data unpublished). Therefore, it is likely that once-weekly semaglutide will not increase the risk of hypoglycemia when added to basal insulin; however, comparative data with other GLP-1 RAs are required.

CONCLUSION

Overall, once-weekly semaglutide 1.0 mg as an add-on to basal insulin is the most efficacious GLP-1 RA in terms of reductions in HbA_{1c} and body weight from baseline after 6 months of treatment. Once-weekly semaglutide 0.5 mg is also efficacious in reducing HbA_{1c} compared with the majority of GLP-1 RA comparators in the analysis. The increased efficacy of once-weekly semaglutide vs other GLP-1 RA comparators was not associated with an increase in GI-related AEs.

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