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ORIGINAL RESEARCH

An Indirect Comparison of Basal Insulin Plus Once-Weekly Semaglutide and Fully Optimised Basal–Bolus Insulin in Type 2 Diabetes

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ABSTRACT

Introduction: To date, there have been few head-to-head comparisons between semaglutide once-weekly (OW) and short-acting mealtime insulin in participants with type 2 diabetes (T2D) treated with basal insulin and requiring treatment intensification. This indirect comparison evaluated the effects of these regimens on glycated haemoglobin (HbA_{1c}), body weight, hypoglycaemia, and other clinically relevant outcomes.

Methods: A post-hoc, unanchored, individual participant data meta-analysis was conducted on the basis of data from single treatment arms in the SUSTAIN 5 and DUAL 7 trials. Semaglutide 0.5 mg OW and 1.0 mg OW plus basal insulin were compared with an optimised (treat-to-target) basal–bolus regimen of insulin glargine and insulin aspart over 26 weeks, using regression adjustment to account for baseline differences between the trials.

Results: Over 26 weeks, semaglutide 1.0 mg OW plus basal insulin reduced mean HbA_{1c} by significantly more than the basal–bolus regimen (treatment difference: − 0.36%; $p = 0.003$), while semaglutide 0.5 mg OW plus basal insulin was comparable with basal–bolus insulin (treatment difference: 0.08%, $p = 0.53$). Both doses of semaglutide were associated with significant weight loss relative to insulin intensification (treatment differences: 6.8–9.4 kg; $p < 0.001$). At both doses, semaglutide intensification required less basal insulin per day than bolus intensification, and more participants on semaglutide met HbA_{1c} targets of $< 7.0\%$ and $\leq 6.5\%$ without hypoglycaemia or weight gain (odds ratio [OR] for $< 7.0\%$, 21.9; OR for $\leq 6.5\%$, 16.2; both $p < 0.001$).

Conclusions: In T2D uncontrolled by basal insulin, intensification with semaglutide 1.0 mg OW was associated with better glycaemic control, weight loss, and reduced hypoglycaemia versus a basal–bolus regimen, while limiting the treatment burden associated with frequent injections. Clinicians could consider treatment intensification with semaglutide when T2D is uncontrolled by basal insulin, especially when weight management is a priority. Effective glycaemic control coupled with weight

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management can alleviate the burden of diabetes-associated complications.

Keywords: Type 2 diabetes; Semaglutide; Insulin; Basal–bolus

Key Summary Points

Why carry out this study?

In patients with type 2 diabetes (T2D) uncontrolled on basal insulin, treatment can be intensified with either semaglutide or bolus insulin, but these alternatives have only been compared in one study to date.

This indirect comparison evaluated the effects of these treatment intensification strategies on glycated haemoglobin (HbA_{1c}), body weight, hypoglycaemia, and other clinically relevant outcomes.

What was learned from the study?

In participants with T2D uncontrolled by basal insulin, intensification with semaglutide 1.0 mg OW was associated with better glycaemic control, weight loss, reduced hypoglycaemia, reduced low-density lipoprotein (LDL), and reduced total cholesterol versus basal–bolus insulin; basal–bolus insulin was associated with larger improvements in high-density lipoprotein (HDL) cholesterol, triglycerides and fasting plasma glucose (FPG).

As an antidiabetic medication that can support weight management in T2D, semaglutide may reduce the risk of disease progression.

Clinicians could consider treatment intensification with semaglutide rather than bolus insulin when T2D is uncontrolled by basal insulin, especially when weight management is a high clinical priority.

INTRODUCTION

Type 2 diabetes (T2D) is a progressive disease associated with several complications, including retinopathy, neuropathy, nephropathy, heart attack, and stroke [1]. Various pharmacological treatments are available for T2D, including biguanides, sulfonylureas, meglitinide, thiazolidinedione, dipeptidyl peptidase 4 inhibitors, sodium-glucose cotransporter 2 inhibitors, glucagon-like peptide 1 receptor antagonists (GLP-1 RAs) and α-glucosidase inhibitors [2]. However, treatment regimens are frequently complex, which can limit adherence, especially in patients who face additional challenges in self-management, such as social disadvantage, poor education, or psychiatric disorders [3]. Adverse effects of some treatments, such as weight gain, can also serve as barriers to optimal pharmaceutical management of T2D [4].

As a progressive disease, T2D requires intensification of treatment over time [5]. Treatment progression is tailored to the needs of each patient, and, where possible, American Diabetes Association (ADA) guidelines recommend that GLP-1 RAs be initiated prior to insulin therapy [5]. However, in practice, some patients initiate basal insulin prior to GLP-1 RAs, and there will sometimes be a need to intensify treatment from basal insulin and metformin [6]. The ADA and European Association for the Study of Diabetes (EASD) have issued guidance on treatment intensification for patients in this situation, which can involve either multiple doses of insulin or the addition of GLP-1 RAs [5].

The first of these intensification strategies generally involves adding one or more daily doses of bolus insulin at mealtimes [5, 7]. However, this increases treatment complexity, requiring regular dose adjustments and multiple daily injections [8]. Treatment regimens with more frequent injections have been linked to lower compliance with therapy [9], especially in patients with limited self-management ability [5]. Increasing the dose of insulin can also increase the risk of hypoglycaemia and weight gain [8, 10].

An alternative treatment intensification strategy is joint therapy with basal insulin and GLP-1 RAs [11–13]. GLP-1 RAs are an established treatment option for T2D, offering improved glycaemic control alongside weight management and cardiovascular benefits [14, 15]. Some GLP-1 RAs allow once-weekly (OW) dosing to minimize treatment burden, which can facilitate adherence and improve quality of life (QoL) [12]. Recent ADA and EASD guidelines support the use of joint therapy with GLP-1 RAs and basal insulin in T2D [5, 7], and the risk of weight gain and hypoglycaemia is reported to be lower than for optimised basal–bolus treatment [16].

Semaglutide is a long-acting GLP-1 RA currently available in OW doses of 0.5 mg and 1.0 mg, and was approved for use in T2D by the Food and Drug Administration (FDA) in 2017 and the European Medicines Agency (EMA) in 2018 [17, 18]. Semaglutide OW has been investigated extensively in the SUSTAIN clinical trial programme, including as part of joint therapy with basal insulin, and has been found to improve glycaemia and body weight compared with GLP-1 RAs exenatide and dulaglutide as well as placebo [19–23]. Notably, SUSTAIN 5 compared semaglutide 0.5 mg OW and 1.0 mg OW with placebo in adult participants with T2D already receiving basal insulin and metformin; semaglutide plus basal insulin was found to reduce glycated haemoglobin (HbA_{1c}) and body weight relative to placebo plus basal insulin, with low rates of adverse events [12].

SUSTAIN 11 is a recently completed randomised controlled trial (RCT) comparing semaglutide OW plus basal insulin with fully optimised basal–bolus insulin [24]. In SUSTAIN 11, semaglutide OW plus basal insulin was noninferior to basal–bolus insulin in supporting glycemic control ($p < 0.0001$), and was associated with numerically greater weight loss [24]. It is important to expand the evidence base for these treatment regimens, to help physicians choose the most appropriate treatment intensification strategy when basal insulin therapy is insufficient [25]. The objective of this study was to indirectly compare OW semaglutide plus basal insulin with fully optimised basal–bolus insulin, using individual participant data (IPD) from SUSTAIN 5 [12] and DUAL 7 (a trial comparing optimised basal–bolus insulin with fixed-ratio insulin in T2D) [26]. Outcomes considered included HbA_{1c}, body weight, hypoglycaemia, insulin dose, fasting plasma glucose (FPG) and serum lipids.

METHODS

A post-hoc, unanchored, individual participant data meta-analysis (IPD-MA) was conducted to assess change in HbA_{1c} and other outcomes of interest, using data from single treatment arms in the SUSTAIN 5 and DUAL 7 RCTs. IPD-MA is an established approach for performing indirect treatment comparisons that compares treatment arms from multiple trials using IPD, and is only possible when IPD are available from all included trials [27]. Relative to traditional meta-analyses relying on aggregate data, IPD-MA has been described as a "gold standard", offering improved data quality control, easier adjustment for potential bias, and exploration of a wider range of outcomes [27, 28]. IPD-MA has been used previously for assessing the effect of glucose control medication [29].

This article compares data from previously published studies. There were no human or animal participants.

Data Sources

Study design and participant recruitment for SUSTAIN 5 and DUAL 7 have been reported in full previously [12, 26].

SUSTAIN 5 compared semaglutide 0.5 mg OW and 1.0 mg OW with placebo in adult participants with T2D already receiving basal insulin and metformin [12]. To minimise heterogeneity and ensure the availability of IPD, other studies by the same sponsor were considered as sources for comparison with a basal–bolus regimen. DUAL 7 [26], which compared an optimised basal–bolus regimen of insulin glargine (IGlar) and insulin aspart (IAsp) with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira), was suitable for an indirect comparison with

Table 1 Inclusion criteria in DUAL 7 and SUSTAIN 5

Study	Duration	Inclusion criteria	Exclusion criteria	*N*	Randomised treatment
DUAL 7	26 weeks	T2D Age ≥ 18 years HbA1c of 7.0–10.0% Stable treatment with IGlar (20–50 U) and metformin BMI ≤ 40 kg/m^2 eGFR > 60 mL/min/1.73 m^2	Hypersensitivity to trial product Pregnant or breastfeeding Treatment with other antidiabetic or investigational drugs Selected complications (e.g. heart attack, stroke, malignancy, maculopathy, retinopathy, and liver or renal impairment)	506	IDegLira, *n* = 252 IGlar + IAsp, *n* = 254
SUSTAIN 5	30 weeks	T2D Age ≥ 18 years HbA1c of 7.0–10.0% Stable treatment with basal insulin, with or without metformin eGFR > 30 mL/min/1.73 m^2	Hypersensitivity to trial product Pregnant or breastfeeding Treatment with other antidiabetic or investigational drugs Selected complications (e.g. heart attack, stroke, malignancy, maculopathy, retinopathy, and liver or renal impairment)	397	Semaglutide 0.5 mg OW + basal insulin, *n* = 132 Semaglutide 1.0 mg OW + basal insulin, *n* = 132 Placebo + basal insulin, *n* = 133

BMI body mass index, *eGFR* estimated glomerular filtration rate, *HbA$_{1c}$* glycated haemoglobin, *IAsp* insulin aspart, *IDegLira* insulin degludec/liraglutide, *IGlar* insulin glargine, *OW* per week, *T2D* type 2 diabetes

SUSTAIN 5, and the authors were able to access IPD from both studies. Other studies with available IPD were also considered, including the ONSET trials [30–32]; however, these each used a run-in period of 8 weeks, representing a fundamental design difference to SUSTAIN 5. In both SUSTAIN 5 and DUAL 7, the primary endpoint was change in HbA_{1c} from baseline to the end of the study.

Notably, the relevant study arms of SUSTAIN 5 and DUAL 7 capture treatment intensification strategies as they might be used in real-world clinical practice. In the semaglutide plus basal insulin arm of SUSTAIN 5, participants with a baseline HbA_{1c} of ≤ 8% reduced their insulin dose by 20% at the start of the trial to reduce the risk of hypoglycaemia; these participants could uptitrate their dose between week 10 and week 16. For all other participants, the basal insulin dose was not to be altered except to meet pre-defined clinical needs, and the semaglutide dose was fixed at 0.5 mg OW or 1.0 mg OW. In the optimised basal–bolus arm of DUAL 7, the basal insulin dose was adjusted twice weekly and the bolus insulin dose was titrated weekly, targeting a prebreakfast self-monitored plasma glucose range of 4.0–-5.0 mmol/L and a bedtime range of 4.0–-6.0 mmol/L. Among participants receiving metformin, the dose was to be kept stable in both trials.

The two trials had similar inclusion criteria, with some minor discrepancies (Table 1), and baseline characteristics were similar between

Table 2 Baseline characteristics in DUAL 7 and SUSTAIN 5

	DUAL 7	SUSTAIN 5	
	IGlar + IAsp (n = 254)	Semaglutide 0.5 mg OW + basal insulin (n = 110)[a]	Semaglutide 1.0 mg OW + basal insulin (n = 110)[a]
Age, years[b]	58.0 (8.6)	58.4 (10.4)	58.6 (8.4)
Female, n (%)	137 (53.9)	46 (41.8)	43 (39.1)
Race (%)[c]			
White	235 (92.5)	92 (83.6)	83 (75.5)
Black	6 (2.4)	3 (2.7)	9 (8.2)
Asian	3 (1.2)	14 (12.7)	17 (15.5)
Other	10 (3.9)	1 (0.9)	1 (0.9)
Body weight, kg[b]	88.2 (17.2)	94.4 (19.7)	92.9 (22.0)
BMI,[b] kg/m^2	31.7 (4.5)	33.1 (5.9)	32.0 (6.4)
T2D duration, years[b]	13.2 (6.8)	12.7 (7.4)	13.5 (7.6)
Basal insulin, U[b]	33.0 (10.4)	46.3 (34.1)	43.8 (34.8)
Baseline HbA_{1c}, %[b]	8.2 (0.8)	8.4 (0.8)	8.3 (0.8)
eGFR,[b] mL/min/1.73 m^2	90.8 (13.7)	91.5 (18.4)	92.4 (16.1)
FPG, mmol/L[b]	8.2 (2.5)	9.1 (3.5)	8.6 (2.8)

BMI body mass index, *eGFR* estimated glomerular filtration rate, *FPG* fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *HDL* high-density lipoprotein, *IAsp* insulin aspart, *IGlar* insulin glargine, *OW* once weekly, *SD* standard deviation, *T2D* type 2 diabetes

[a]Full analysis set, excluding participants from SUSTAIN 5 not on metformin

[b]Population mean (SD)

[c]Race groups are non-exclusive—some subjects identify with more than one category

treatment groups (Table 2). In DUAL 7, participants with a body mass index (BMI) of > 40 kg/m^2 were excluded, while 11.5% of participants in SUSTAIN 5 had a BMI above this threshold. However, mean BMI was similar across the trials (31.7 kg/m^2 in DUAL 7 and 33.1 and 32.0 kg/m^2 in the semaglutide 0.5 mg and 1.0 mg arms of SUSTAIN 5, respectively) (Table 2). Likewise, the lower limit for estimated glomerular filtration rate (eGFR) differed between the two trials (> 60 mL/min/1.73 m^2 in DUAL 7 and > 30 mL/min/1.73 m^2 in SUSTAIN 5), but mean eGFR was similar (90.8 mL/min/1.73 m^2 in DUAL 7 and 91.5 and 92.4 mL/min/1.73 m^2 in the semaglutide 0.5 mg and 1.0 mg arms of SUSTAIN 5, respectively) (Table 2).

All participants in DUAL 7 received metformin during the trial, but some participants in SUSTAIN 5 did not. To account for this, participants in SUSTAIN 5 not on metformin were excluded from the analysis. Treatment duration also differed between the trials (30 weeks in SUSTAIN 5 vs 26 weeks in DUAL 7). Therefore, week 26 data for SUSTAIN 5 were interpolated from data for week 23 and week 30.

Endpoints

Change in HbA_{1c} from baseline over 26 weeks was assessed by calculating the differences of the means across treatment arms. Other endpoints included change in body weight,

attainment of HbA_{1c} targets (< 7.0% and ≤ 6.5%), severe or blood-glucose-confirmed symptomatic hypoglycaemic episodes (plasma glucose level < 3.1 mmol/L, or requiring the assistance of another person), attainment of HbA_{1c} targets without hypoglycaemia or weight gain, basal insulin dose, FPG, blood pressure, and serum lipids. All of the endpoints in the present analysis were pre-specified endpoints in the SUSTAIN 5 and DUAL 7 trials.

Analysis Methods

The primary analysis was based on the on-treatment observation period for all randomised participants treated with either semaglutide OW plus basal insulin or IGlar + IAsp, excluding those in SUSTAIN 5 not on metformin. No adjustments were made for multiplicity. The analysis was unanchored, as SUSTAIN 5 and DUAL 7 did not share a common comparator [33]. Unanchored comparisons cannot make use of within-trial randomisation, so an alternative way to address systematic error is needed. IPD-MA is a preferred method for unanchored comparisons as it allows adjustment for clinically relevant variables at the IPD level, reducing bias relative to a traditional meta-analysis [28]. Identifying the key factors is vital, as including too many factors leads to loss of precision and wide confidence intervals. According to National Institute for Health and Care Excellence (NICE) guidance, clinically relevant factors should be selected a priori [34]. For the present study, this was done on the basis of clinical input; the factors identified are reported in Table 7 (supplementary material). Variables selected were those widely recognised to have an impact on T2D treatment outcomes (e.g. age and gender) or where there was a strong clinical rationale for a link to a particular outcome (e.g. baseline body weight as an effect modifier for weight loss); this approach to selecting variables of interest has been used previously in indirect comparisons of diabetes treatments [35].

For continuous endpoints, including HbA_{1c}, analysis of covariance (ANCOVA) was used to estimate the differences between the SUSTAIN 5 and DUAL 7 treatment arms (Table 7, supplementary material). ANCOVA is the preferred method of adjustment in studies with baseline and follow-up measurements [36]. To account for variables evaluated to potentially modify the effect of treatment (effect modifiers), population adjustment was performed in the statistical analysis to provide estimates applicable to a SUSTAIN 5 population. Before statistical analysis, missing values were imputed within each trial using data from participants within the same treatment group. In each subsequent statistical analysis, inferences were performed using Rubin's rule across multiple imputations [37]. For dichotomous endpoints, following standard practice, logistic regression was used to estimate the differences between treatment arms and to adjust for relevant variables (Table 7, supplementary material). These included the proportions of participants achieving HbA_{1c} targets of < 7.0% and ≤ 6.5%; the proportions achieving these HbA_{1c} targets without severe or blood-glucose-confirmed symptomatic hypoglycaemia; and the proportions achieving these targets without either hypoglycaemia or weight gain. The number of severe and blood-glucose-confirmed hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function, with the logarithm of the time covered by the on-treatment observation period as an offset. Negative binomial regression is the standard approach to analysing hypoglycaemic events in diabetes trials [38]. Insulin usage was analysed on a logarithmic scale and back-transformed to determine the treatment ratios between daily insulin dose with semaglutide OW plus basal insulin and daily insulin dose with IGlar + IAsp.

To evaluate the robustness of the results, sensitivity analyses were conducted for key outcomes (HbA_{1c}, FPG, hypoglycaemic episodes, and body weight). To evaluate the impact of interpolating data for week 26 in SUSTAIN 5, analyses for these outcomes were repeated using data from week 23 and week 30. To assess the impact of differences in BMI inclusion criteria, analyses for these outcomes were repeated after excluding the participants in SUSTAIN 5 with a BMI of > 40 kg/m^2. An unadjusted analysis was

Table 3 Changes in HbA_{1c} and body weight after 26 weeks of treatment

	Semaglutide + basal insulin			Treatment difference (95% CI)
	n[a]	Mean at week 26[b]	Δ, week 26[b]	
Change in HbA_{1c} (%)				
IGlar + IAsp	233	6.8 (0.09)	− 1.4 (0.09)	–
Semaglutide 0.5 mg OW + basal insulin	101	7.0 (0.08)	− 1.4 (0.08)	0.08 (− 0.16, 0.31)
				$p = 0.53$
Semaglutide 1.0 mg OW + basal insulin	98	6.5 (0.08)	− 1.8 (0.08)	**− 0.36 (− 0.60, − 0.13)**
				p* = 0.003
Change in weight (kg)				
IGlar + IAsp	233	90.9 (0.3)	2.9 (0.3)	–
Semaglutide 0.5 mg OW + basal insulin	102	90.4 (0.4)	− 3.9 (0.4)	**− 6.8 (− 7.7, − 5.9)**
				p* < 0.001
Semaglutide 1.0 mg OW + basal insulin	98	87.1 (0.4)	− 6.5 (0.4)	**− 9.4 (− 10.3, − 8.5)**
				p* < 0.001

CI confidence interval, *HbA_{1c}* glycated haemoglobin, *IAsp* insulin aspart, *IGlar* insulin glargine, *OW* once weekly, *SE* standard error

*$p < 0.05$. Bold: favours semaglutide

[a]Subjects contributing to the analysis with data available for week 26 (DUAL 7) or for week 23 or 30, interpolated to week 26 (SUSTAIN 5)

[b]Estimated least-squares mean (SE)

conducted to explore the impact of the adjustment process, including variable selection.

RESULTS

Overall, 474 participants contributed data to the indirect comparison, including 254 who received IGlar + IAsp and 220 who received semaglutide OW plus basal insulin. Of the participants who received semaglutide, 110 received 0.5 mg OW and 110 received 1.0 mg OW.

Change from Baseline in HbA_{1c}

Semaglutide 0.5 mg OW plus basal insulin and IGlar + IAsp produced similar reductions in average HbA_{1c} over 26 weeks (Table 3). Participants who received semaglutide 1.0 mg OW plus basal insulin experienced a significantly greater average reduction in HbA_{1c} than those who received IGlar + IAsp (treatment difference: − 0.36%; 95% confidence interval [CI]: − 0.60, − 0.13; $p = 0.003$).

Change from Baseline in Body Weight

Participants who received semaglutide 0.5 mg OW plus basal insulin lost weight on average, while those who received IGlar + IAsp gained weight (treatment difference: − 6.8 kg; 95% CI: − 7.7, − 5.9; $p < 0.001$). The pattern was the same for semaglutide 1.0 mg OW plus basal insulin (treatment difference: − 9.4 kg; 95% CI: − 10.3, − 8.5; $p < 0.001$) (Table 3).

Frequency of Hypoglycaemic Events

Participants who received semaglutide plus basal insulin experienced severe or blood-glucose-confirmed hypoglycaemic episodes significantly less frequently than those who received IGlar + IAsp in both dose groups (rate ratio [RR] for semaglutide 0.5 mg OW, 0.02; RR for semaglutide 1.0 mg OW, 0.02; both $p < 0.001$) (Table 4).

Participants Achieving HbA_{1c} Targets Without Hypoglycaemia or Weight Gain

Participants who received semaglutide 0.5 mg OW plus basal insulin were significantly more likely than those who received IGlar + IAsp to achieve HbA_{1c} targets without experiencing hypoglycaemia or weight gain (odds ratio [OR] for $< 7.0\%$, 21.9; OR for $\leq 6.5\%$, 16.2; both $p < 0.001$) (Table 5). This was also true for those who received semaglutide 1.0 mg OW plus basal insulin (OR for $< 7.0\%$, 38.2; OR for $\leq 6.5\%$, 29.1; both $p < 0.001$). In addition to these composite endpoints, participants who received semaglutide 1.0 mg OW plus basal insulin were significantly more likely to meet these HbA_{1c} targets overall (OR for $< 7.0\%$, 1.83; OR for $\leq 6.5\%$, 1.87; both $p < 0.05$).

Basal Insulin Dose

Participants who received semaglutide 0.5 mg OW or 1.0 mg OW plus basal insulin used significantly less basal insulin per day on average than those who received IGlar + IAsp (ratio for 0.5 mg OW, 0.619; ratio for 1.0 mg OW, 0.571; both $p < 0.001$). Participants receiving IGlar + IAsp used an estimated mean of 44.8 international units (IU) of basal insulin daily; participants receiving semaglutide 0.5 mg OW plus basal insulin used 35.0 IU daily, and participants receiving semaglutide 1.0 mg OW plus basal insulin used 30.2 IU daily.

Other Outcomes

Additional outcomes are summarised in Table 6. Semaglutide 0.5 mg OW and 1.0 mg OW plus basal insulin significantly reduced mean low-density lipoprotein (LDL) cholesterol relative to IGlar + IAsp, and semaglutide 0.5 mg OW significantly reduced mean total cholesterol. However, semaglutide plus basal insulin also reduced mean high-density lipoprotein (HDL) cholesterol by significantly more than IGlar + IAsp at both doses. IGlar + IAsp significantly reduced mean triglycerides relative to semaglutide 1.0 mg OW plus basal insulin, but not relative to semaglutide 0.5 mg OW plus basal insulin.

IGlar + IAsp significantly reduced mean FPG relative to semaglutide 0.5 mg OW plus basal insulin. Semaglutide 1.0 mg OW plus basal insulin significantly reduced mean systolic blood pressure (SBP) relative to IGlar + IAsp. There were no other significant differences between the treatments.

Sensitivity Analyses

Across outcomes, the sensitivity analyses specified in the "Methods" section were compatible

Table 4 Severe or blood-glucose-confirmed hypoglycaemic episodes

	IGlar + IAsp	Semaglutide 0.5 mg OW + basal insulin	Semaglutide 1.0 mg OW + basal insulin
Rate (SE)[a]	730.8 (98.5)	15.0 (6.1)	11.1 (6.3)
Rate ratio	–	**0.02, $p < 0.001$***	**0.02, $p < 0.001$***

IAsp insulin aspart, *IGlar* insulin glargine, *OW* once weekly, *SE* standard error

*$p < 0.05$. Bold: favours semaglutide

[a]Estimated number of events per 100 participant years

Table 5 Attainment of HbA_{1c} targets without hypoglycaemia or weight gain

	IGlar + IAsp	Semaglutide 0.5 mg OW + basal insulin		Semaglutide 1.0 mg OW + basal insulin	
	R (%)[a]	*R* (%)[a]	Odds ratio (95% CI)[b]	*R* (%)[a]	Odds ratio (95% CI)[b]
$HbA_{1c} < 7.0\%$	162.1 (63.8)	68.2 (62.0)	0.91 (0.54, 1.53)	81.9 (74.4)	**1.83 (1.03, 3.25)**
			$p = 0.72$		***p* = 0.038***
$HbA_{1c} < 7.0\%$ without hypoglycaemia	58.0 (22.8)	62.4 (56.7)	**4.3 (2.6, 7.3)**	74.1 (67.4)	**7.5 (4.3, 13.1)**
			p* < 0.001		***p* < 0.001***
$HbA_{1c} < 7.0\%$ without hypoglycaemia or weight gain	11.8 (4.6)	57.2 (52.0)	**21.9 (10.4, 45.8)**	69.9 (63.5)	**38.2 (17.8, 82.0)**
			p* < 0.001		***p* < 0.001***
$HbA_{1c} \leq 6.5\%$	107.7 (42.4)	42.6 (38.7)	0.89 (0.53, 1.48)	61.3 (55.8)	**1.87 (1.11, 3.14)**
			$p = 0.65$		***p* = 0.018***
$HbA_{1c} \leq 6.5\%$ without hypoglycaemia	38.4 (15.1)	38.2 (34.7)	**3.13 (1.75, 5.58)**	53.9 (49.0)	**5.8 (3.3, 10.4)**
			p* = 0.001		***p* < 0.001***
$HbA_{1c} \leq 6.5\%$ without hypoglycaemia or weight gain	8.6 (3.4)	38.1 (34.6)	**16.2 (7.1, 36.9)**	52.7 (47.9)	**29.1 (12.7, 66.5)**
			p* < 0.001		***p* < 0.001***

CI confidence interval, *HbA1c* glycated haemoglobin, *IAsp* insulin aspart, *IGlar* insulin glargine, *OW* once weekly, *SE* standard error

*$p < 0.05$. Bold: favours semaglutide

[a]Average number of subjects achieving target across data imputations

[b]Odds ratio vs IGlar + IAsp

with the primary analysis (Tables 8 and 9, supplementary material). For change in HbA_{1c}, treatment differences across analyses ranged from − 0.29% to − 0.75% for semaglutide 1.0 mg OW plus basal insulin vs IGlar + IAsp; treatment differences ranged from 0.16% to − 0.14% for semaglutide 0.5 mg OW plus basal insulin vs IGlar + IAsp. For change in body weight, treatment differences across analyses ranged from − 8.79 to − 9.57 kg for semaglutide 1.0 mg OW plus basal insulin vs IGlar + IAsp; treatment differences ranged from − 6.54 to − 6.82 kg for semaglutide 0.5 mg OW plus basal insulin vs IGlar + IAsp. For change in FPG, treatment differences across analyses ranged from − 0.02 to − 0.12 mmol/L for semaglutide 1.0 mg OW plus basal insulin vs IGlar + IAsp; treatment differences ranged from 0.59 to 0.66 mmol/L for semaglutide 0.5 mg OW plus basal insulin vs IGlar + IAsp. All significance tests in sensitivity analyses produced results consistent with the primary analysis.

DISCUSSION

This study indirectly compared semaglutide OW plus basal insulin with fully optimised basal–bolus insulin (IGlar + IAsp) in adult participants also receiving metformin, assessing the effects of these therapies on HbA_{1c}, weight, basal insulin dose, and hypoglycaemia, among other outcomes. As recent treatment guidelines cite both of these regimens as viable strategies for intensification from basal insulin [5, 7], comparisons between them are of high clinical value.

Table 6 Additional outcomes over 26 weeks of treatment

	IGlar + IAsp	Semaglutide 0.5 mg OW + basal insulin		Semaglutide 1.0 mg OW + basal insulin	
	δ, week 26[a]	δ, week 26[a]	Treatment difference	Δ, week 26[a]	Treatment difference
SBP, mmHg	− 3.0 (0.8)	− 4.9 (1.2)	− 1.89, $p = 0.21$	− 8.9 (1.2)	**− 5.88, $p < 0.001$***
DBP, mmHg	− 1.6 (0.6)	− 1.3 (0.8)	0.29, $p = 0.76$	− 2.0 (0.8)	− 0.37, $p = 0.70$
FPG, mmol/L	− 2.4 (0.2)	− 1.7 (0.2)	*0.65, $p = 0.011$**	− 2.4 (0.2)	− 0.01, $p = 0.98$
Triglycerides, mmol/L	− 0.35 (0.06)	− 0.22 (0.09)	0.130, $p = 0.24$	0.14 (0.10)	*0.489, $p < 0.001$**
HDL, mmol/L	0.03 (0.01)	− 0.07 (0.02)	*− 0.095, $p < 0.001$**	− 0.04 (0.02)	*− 0.062, $p = 0.012$**
LDL, mmol/L	0.03 (0.05)	− 0.23 (0.07)	**− 0.258, $p = 0.003$***	− 0.21 (0.07)	**− 0.241, $p = 0.007$***
Total cholesterol, mmol/L	− 0.08 (0.06)	− 0.38 (0.08)	**− 0.300, $p = 0.004$***	− 0.26 (0.09)	− 0.177, $p = 0.10$

DBP diastolic blood pressure, *FPG* fasting plasma glucose, *HbA_{1c}* glycated haemoglobin, *HDL* high-density lipoprotein, *IAsp* insulin aspart, *IGlar* insulin glargine, *LDL* low-density lipoprotein, *OW* once weekly, *SBP* systolic blood pressure, *SE* standard error

*$p < 0.05$. Bold: favours semaglutide. Italic: favours IGlar + IAsp

[a]Estimated least-squares mean (SE)

In the present study, semaglutide 1.0 mg OW plus basal insulin reduced average HbA_{1c} to a significantly greater extent than the basal–bolus regimen; semaglutide 0.5 mg plus basal insulin was comparable with the basal–bolus regimen. Participants who received basal insulin plus semaglutide at either dose experienced significantly lower rates of hypoglycaemic events than those who received basal–bolus insulin, and had significantly greater odds of meeting HbA_{1c} targets of $\leq 6.5\%$ and $< 7.0\%$ without experiencing hypoglycaemia or weight gain. Participants who received semaglutide 1.0 mg OW plus basal insulin also had significantly greater odds of meeting these HbA_{1c} targets overall.

These findings suggest that intensification with semaglutide can provide comparable or superior glycaemic control to intensification with bolus insulin, alongside supporting patients to achieve weight loss. The impact on weight is notable, as weight loss is a crucial part of diabetes management [39] and can considerably reduce the risk of cardiovascular disease [40, 41]. Indeed, many antidiabetic therapies contribute to weight gain, and this has been recognised as a barrier to treatment intensification [4]. The present findings are consistent with research on T2D treatment intensification using other GLP-1 RAs, which also reportedly support glycaemic control and improve body weight versus intensification with bolus insulin [16, 42–44].

Semaglutide intensification was also associated with greater reductions in LDL cholesterol than the basal–bolus regimen, another important treatment goal [45]. In T2D, a 1 mmol/L reduction in LDL levels is associated with a 9% reduction in all-cause mortality and a 13% reduction in vascular mortality [46]. However, basal–bolus insulin treatment was associated with larger increases in HDL cholesterol and larger reductions in triglycerides. Low HDL cholesterol coupled with high triglycerides is a common pattern of dyslipidaemia in T2D, so this may be an important consideration in patients with this lipid profile [45].

Notably, semaglutide OW plus basal insulin involves a simpler treatment regimen; dose

adjustments were not needed following titration, only 8 doses were administered per week rather than 28 doses per week with IGlar + IAsp, and participants were not required to time injections to coincide with meals. Although adherence was not assessed in the present study, the implications of this should not be disregarded, given the recognised impact of treatment burden on T2D treatment adherence [9]. Further study is also warranted to assess differences in cost-effectiveness between these treatment strategies.

The use of IPD-MA for the indirect treatment comparison is a major strength of the present study. Where head-to-head data are unavailable, IPD-MA can be a robust way to compare the efficacy of treatments [27]. The availability of IPD for both SUSTAIN 5 and DUAL 7 allowed regression adjustment for baseline differences using ANCOVA, which is not possible in traditional meta-analyses relying on aggregate data. As the studies included comparable populations within comparable, controlled settings, the results were robust to the details of the adjustment.

The main limitation of this study was that the data available necessitated the use of an unanchored, indirect treatment comparison. An unanchored approach means that within-trial randomization cannot be used to address potential bias resulting from differences between trial populations; as such, the IPD-MA regression adjustment was the main safeguard against this bias. In the present study, population adjustment was performed to indirectly estimate treatment effects that would be applicable to a SUSTAIN 5 population. For this purpose, it is essential to choose appropriate variables to include in the regression adjustment. Here, the variables of interest were chosen on the basis of clinical input, which is inherently subjective. As a safeguard against this limitation, we conducted an unadjusted analysis to explore the influence of the adjustment procedure on the study outcomes. Although we made a fairly extensive adjustment using several variables, this did not alter the results compared with the unadjusted analysis, indicating that the impact of adjustment was small in this study.

Another limitation was that the available data did not allow analysis of postprandial glucose; this should be considered in future research, as the primary purpose of bolus insulin is to minimise postprandial hyperglycaemia.

The two studies used in the analysis employed slightly different inclusion criteria for BMI and eGFR. However, the mean baseline values for these characteristics were similar between studies, and sensitivity analyses excluding participants in SUSTAIN 5 who did not meet the DUAL 7 criterion for BMI confirmed the main analysis. Other baseline differences, including gender and insulin dose, were adjusted for as shown in Table 7 (supplementary material). As a result of differences in study duration, data from SUSTAIN 5 for week 26 were interpolated from data for week 23 and week 30, but sensitivity analyses using the original visit data produced the same results as the main analysis.

Other limitations relate to the differing strategies for insulin titration used in the two studies. In DUAL 7, basal–bolus insulin was titrated regularly under close monitoring to meet predetermined glucose targets. In SUSTAIN 5, participants with a baseline HbA_{1c} of $\leq$ 8% reduced their basal insulin dose by 20% at the start of the trial and could uptitrate their dose between week 10 and week 16; otherwise, insulin was not titrated and the dose of semaglutide was fixed. This difference is relevant for several reasons. First, the present results may not generalise to patients with $HbA_{1c} \leq 8\%$ who start semaglutide without reducing their basal insulin dose; such patients may experience larger reductions in HbA_{1c} or more frequent or severe hypoglycaemia. Second, in clinical practice, glucose monitoring is likely to be less intensive and titration protocols are likely to be less strictly followed than in the DUAL 7 clinical trial. If this is the case, the real-world effect of IGlar + IAsp on HbA_{1c} (even using the same daily glucose targets) is likely to be smaller than the effect reported here. Third, this analysis compared basal insulin plus semaglutide with a specific basal–bolus titration regimen using specific daily glucose targets, not with basal–bolus insulin therapy per se. In principle, a basal–bolus regimen titrating to

stricter targets might produce a larger average reduction in HbA_{1c} than basal insulin plus semaglutide, but would be likely to increase the risk of hypoglycaemia [47]. The key finding here is that basal insulin plus semaglutide produced comparable or larger average reductions in HbA_{1c} than a basal–bolus insulin regimen with simultaneous benefits to weight loss and hypoglycaemia, which would not be attainable using more aggressive insulin titration.

CONCLUSION

In participants with T2D uncontrolled by basal insulin, intensification with semaglutide 1.0 mg OW was associated with better glycaemic control, weight loss, and reduced hypoglycaemia relative to intensification with bolus insulin, while limiting the treatment burden associated with frequent injections. Alongside the head-to-head data from SUSTAIN 11, these results may help clinicians to choose the most appropriate strategies for intensifying T2D treatment and limiting treatment burden when basal insulin therapy is insufficient.

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Data Availability. All data generated or analysed during this study are included in this published article or as supplementary information files.

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