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Effect of once-weekly semaglutide versus thrice-daily insulin aspart, both as add-on to metformin and optimized insulin glargine treatment in participants with type 2 diabetes (SUSTAIN 11): A randomized, open-label, multinational, phase 3b trial

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Abstract

Aim: To compare the efficacy and safety of once-weekly (OW) semaglutide versus thrice-daily (TID) insulin aspart (IAsp) in participants with inadequately controlled type 2 diabetes (T2D) treated with insulin glargine (IGlar) and metformin.

Materials and Methods: SUSTAIN 11 (NCT03689374) was a randomized (1:1), parallel, open-label, multinational, phase 3b trial. After a 12-week run-in to optimize once-daily IGlar U100, 1748 adults with T2D (HbA1c >7.5% to ≤10.0%) were randomized to OW semaglutide or TID IAsp as add-on to optimized IGlar and metformin for 52 weeks. The primary outcome was change in HbA1c from randomization to week 52. Confirmatory secondary endpoints included the occurrence of severe hypoglycaemic episodes and change in body weight (BW). Safety was assessed.

Results: HbA1c (randomization: 8.6% [70.0 mmol/mol]) decreased by 1.5% points (16.6 mmol/mol) and 1.2% points (13.4 mmol/mol) with semaglutide (n = 874) and IAsp (n = 874), respectively (estimated treatment difference [ETD] −0.29% points [95% confidence interval {CI} −0.38; −0.20]; $P < .0001$ for non-inferiority). Few severe hypoglycaemic episodes were recorded in either group, with no statistically significant difference between the groups. Change in BW from randomization (87.9 kg) to week 52 was in favour of semaglutide (−4.1 kg) versus IAsp (+2.8 kg) (ETD −6.99 kg [95% CI −7.41; −6.57]). A higher proportion of participants experienced adverse events with semaglutide (58.5%) versus IAsp (52.1%); most were mild to moderate.

Conclusions: In this basal insulin-treated population, OW semaglutide improved glycaemic control to a greater extent than TID IAsp and provided numerically greater weight loss.

KEYWORDS
GLP-1 analogue, glycaemic control, hypoglycaemia, insulin therapy, type 2 diabetes, weight control

1 | INTRODUCTION

Treatment guidelines for type 2 diabetes (T2D) recommend a patient-centric, individualized approach. Goals include minimizing hypoglycaemia and weight gain, and reducing the risk of complications such as atherosclerotic cardiovascular (CV) disease.[1,2] While some clinical guidelines recommend a glucagon-like peptide-1 receptor agonist (GLP-1RA) as the first injectable antihyperglycaemic during treatment intensification,[3,4] many patients are prescribed basal insulin (BI).[5] When patients have insufficient control with BI, either a GLP-1RA or bolus insulin can be considered.[1-4]

Systematic reviews and meta-analyses of randomized clinical trials indicate that treatment with long- or short-acting GLP-1RA/insulin combinations is associated with similar HbA1c reductions, greater weight loss, lower hypoglycaemia risk and lower insulin dose versus basal-plus and basal–bolus insulin (BBI) regimens.[6,7] In short-term (26-30 weeks) studies, improved quality of life (QoL) was observed with a once-daily GLP-1RA/insulin compared with BBI.[8-10]

Subcutaneous (s.c.) once-weekly (OW) semaglutide (Novo Nordisk A/S) is a long-acting GLP-1RA approved for T2D treatment.[11,12] In the SUSTAIN clinical trial programme, OW semaglutide 1.0 mg consistently showed superior HbA1c and body weight (BW) reductions versus placebo (including as add-on to BI in SUSTAIN 5) and a range of active comparators, including dipeptidyl peptidase-4 inhibitors (DPP-4is), sodium-glucose co-transporter-2 inhibitors, other GLP-1RAs and insulin glargine (IGlar).[13-21] The semaglutide safety profile was similar to that of other GLP-1RAs,[13-21] and, in SUSTAIN 4, there were fewer hypoglycaemic episodes with OW semaglutide versus IGlar, both as add-on to stable treatment with metformin ± sulphonylurea.[16] Additionally, CV benefits and positive effects on some kidney outcomes have been shown with OW semaglutide in participants with T2D.[22,23] Compared with BBI, the lower number of injections required with OW semaglutide may also enhance treatment adherence and QoL.[8,24,25]

The SUSTAIN 11 trial (NCT03689374) compared the efficacy and safety of OW semaglutide versus thrice-daily (TID) insulin aspart (IAsp; a rapid-acting insulin analogue), both as add-on to metformin and IGlar U100, in adults with T2D.

2 | MATERIALS AND METHODS

2.1 | Trial design

SUSTAIN 11 was a 52-week, randomized, open-label, multicentre, multinational, active-controlled, two-armed phase 3b trial conducted in 21 countries (see the supporting information in the supplementary appendix). It was conducted in compliance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice guidelines,[26] and the Declaration of Helsinki[27] (for the protocol, see the supporting information). Some trial design elements (such as the insulin titration regimen and selection of confirmatory secondary endpoints) were informed by the requirements of the German Drug Regulatory Affairs Act.[28,29]

2.2 | Participants

Adults with inadequately controlled T2D (HbA1c >7.5% to ≤10.0%; >58 to ≤86 mmol/mol) with IGlar and metformin ± one additional oral antihyperglycaemic drug (OAD), who were willing to undergo individualized treatment intensification toward an HbA1c target of 6.5% to 7.5% (48-58 mmol/mol), were enrolled. The exclusion criteria included the use of other glucose-lowering agents; for the full eligibility criteria, see the supporting information. All the participants provided written informed consent.

2.3 | Treatments and randomization

Participants underwent a 2-week screening period, followed by 12-week run-in, 52-week treatment and 5-week follow-up periods (Figure S1). At run-in start, participants were transferred from their previous once- or twice-daily BI injections to s.c. once-daily IGlar (U100).[30] Self-measured plasma glucose (SMPG) profiles were used to optimize the IGlar dose during run-in and throughout the trial. For further details on the titration algorithms, see the supporting information. Participants continued metformin treatment (1500-3000 mg or maximum tolerated dose) throughout the trial unless related safety concerns arose; additional OADs were discontinued.

At run-in end, participants with HbA1c of more than 7.5% to 10.0% or less (>58 to ≤86 mmol/mol) were randomized 1:1 to receive OW semaglutide 1.0 mg or TID IAsp 100 U/ml injections from week 0 (randomization/baseline) to week 52 (end of treatment [EOT]). Participants randomized to OW semaglutide underwent dose escalation as per label.[11,12] Semaglutide dose reduction from 1.0 to 0.5 mg was allowed for safety concerns or unacceptable intolerability.

Participants randomized to IAsp were initiated at 4 U TID. Dose adjustments of both IGlar and IAsp were based on SMPG measurements according to the titration guidelines (supporting information) and individualized treatment goals, at the investigator's discretion. Persistent and/or unacceptable hyperglycaemia was initially managed with adjustment of insulin doses, followed by rescue medication, at

the investigator's discretion. Initiation of a sulphonylurea, incretin-based therapy (GLP-1RA or DPP-4i) or prandial insulin was not permitted. For further details on treatments and randomization, see the supporting information.

2.4 | Endpoints

The primary endpoint was change in HbA1c (% points) from randomization to EOT. For further information on the primary estimand (hypothetical estimand), see the supporting information. Confirmatory secondary efficacy endpoints were: time to first event adjudication committee (EAC)-confirmed severe hypoglycaemic episode; time to first EAC-confirmed severe hypoglycaemic episode requiring hospitalization or documented medical help, or that was life-threatening; and change in BW (kg) from randomization to EOT. For other prespecified supportive secondary endpoints evaluating glycaemic control, hypoglycaemia, anthropometric and patient-reported outcomes, see the supporting information. The following hypoglycaemic episodes were assessed: severe, documented symptomatic, asymptomatic and pseudo-hypoglycaemia (≤3.9 mmol/L cut-off [>3.9 mmol/L for pseudo-hypoglycaemia], American Diabetes Association [ADA] 2013 definition)[31]; clinically significant hypoglycaemia (<3.0 mmol/L cut-off, ADA 2018 definition)[32]; symptomatic or asymptomatic blood glucose (BG)-confirmed hypoglycaemia (<3.1 mmol/L cut-off). Safety endpoints included the occurrence of: adverse events (AEs); serious AEs (≥0.5% in any arm) by system organ class (SOC); AEs with fatal outcome by SOC; and AEs leading to premature treatment discontinuation. An external independent committee (blinded to treatment allocation) adjudicated the following events: severe hypoglycaemic episode, acute pancreatitis and all deaths (for either association with severe hypoglycaemic episode [ADA definition] or acute pancreatitis). All AEs were coded using the Medical Dictionary for Regulatory Activities version 23.1.[33]

2.5 | Statistical analysis

SUSTAIN 11 was designed to jointly confirm the non-inferiority of the primary endpoint (with >99.9% power) and superiority of the confirmatory severe hypoglycaemic endpoints and confirmatory body weight endpoint with semaglutide versus IAsp (with 85% power). An estimated sample size of 1736 randomized participants was required to ensure sufficient power, based on a two-sided significance level of .05 with the following assumptions: no treatment difference for the primary endpoint with a non-inferiority margin of 0.3% points and a standard deviation of 1.1% points, and for the secondary confirmatory hypoglycaemia endpoints, incidence rates for EAC-confirmed severe hypoglycaemia of 1.0 per 100 patient years of risk (100-PYR) for semaglutide and 4.0 per 100-PYR for IAsp and incidence rates for EAC-confirmed severe hypoglycaemic episodes requiring hospitalization, documented medical help, or that were life-threatening of 0.675 per 100-PYR for semaglutide and 2.7 per 100-PYR for IAsp.

Hierarchical testing was used to preserve the overall type 1 error (Figure S2), with the testing order, designed to accommodate the requirements of the German reimbursement authorities, was: (a) non-inferiority of semaglutide versus IAsp for change in HbA1c; (b) superiority of semaglutide versus IAsp for occurrence of EAC-confirmed severe hypoglycaemic episodes; (c) superiority of semaglutide versus IAsp for occurrence of EAC-confirmed severe hypoglycaemic episodes requiring hospitalization or documented medical help, or that were life-threatening; (d) superiority of semaglutide versus IAsp for change in BW; and (e) superiority of semaglutide versus IAsp for change in HbA1c. If the corresponding null hypothesis of no treatment difference was not rejected, confirmatory testing stopped and subsequent testing in the hierarchy was not performed. For the other efficacy endpoints, which were not part of the testing hierarchy (i.e. not confirmatory), estimated treatment differences (ETDs), 95% confidence intervals (CIs) and the associated *P* values (not tested for multiplicity) are provided.

The primary endpoint, confirmatory secondary BW endpoint and supportive secondary endpoints were analysed using analysis of covariance (ANCOVA) with treatment as a fixed factor and baseline values as a covariate, based on on-treatment data from the full analysis set (FAS) or from the safety analysis set (SAS, pulse data only). Before analysis, missing data were multiple imputed using observed data from participants within the same group defined by randomized treatment. The confirmatory secondary hypoglycaemic endpoints were analysed using a Cox proportional hazards model with treatment as a fixed factor, based on on-treatment data from the FAS. Safety outcomes were summarized descriptively, using on-treatment data from the SAS, except for AEs with fatal outcome, which were evaluated using in-trial data from the SAS. Summaries of treatment-emergent hypoglycaemic episodes are presented as an overview, including all episodes and episodes by severity. For further information on statistical analyses, see the supporting information.

3 | RESULTS

3.1 | Patient disposition and characteristics at randomization

From October 2018 (first patient first visit) to October 2019 (last patient first visit), 2968 patients were screened; 1748 were randomized. In the semaglutide arm, 850 (97.3%) participants completed the trial, 826 (94.5%) completed treatment and 24 (2.7%) participants withdrew from the trial. In the IAsp arm, 831 (95.1%) participants completed the trial, 806 (92.2%) completed treatment and 43 (4.9%) withdrew from the trial (Figure S3).

Characteristics at randomization and concomitant illnesses and complications present at screening were generally balanced between the two arms (Table 1).

TABLE 1 Participant characteristics at randomization

	Semaglutide	Insulin aspart	Total
Number of participants (N)	874	874	1748
Age, y	60.8 (9.4)	61.5 (9.5)	61.2 (9.4)
Sex			
Male	445 (50.9)	449 (51.4)	894 (51.1)
Race			
White	674 (77.1)	691 (79.1)	1365 (78.1)
Black or African American	21 (2.4)	14 (1.6)	35 (2.0)
Asian	176 (20.1)	166 (19.0)	342 (19.6)
Other	3 (0.3)	3 (0.3)	6 (0.3)
Ethnicity			
Hispanic or Latino	23 (2.6)	22 (2.5)	45 (2.6)
Not Hispanic or Latino	851 (97.4)	852 (97.5)	1703 (97.4)
HbA1c, %	8.6 (0.7)	8.5 (0.7)	8.6 (0.7)
mmol/mol	70.3 (7.7)	69.8 (7.7)	70.0 (7.7)
Diabetes duration, y	13.4 (6.8)	13.4 (6.5)	13.4 (6.7)
Body weight, kg	87.6 (18.1)	88.1 (18.4)	87.9 (18.2)
Body mass index, kg/m^2	31.4 (5.5)	31.7 (5.5)	31.5 (5.5)
Renal function, ml/min/1.73 m^2			
Normal (≥90)	533 (61.0)	549 (62.8)	1082 (61.9)
Mild impairment (60 to <90)	282 (32.3)	272 (31.1)	554 (31.7)
Moderate impairment (30 to <60)	55 (6.3)	52 (5.9)	107 (6.1)
Severe impairment (15 to <30)	3 (0.3)	1 (0.1)	4 (0.2)
End-stage impairment (<15)	1 (0.1)	0	1 (0.1)
Selected concomitant illnesses at screening			
Hypertension	690 (78.9)	686 (78.5)	1376 (78.7)
Dyslipidaemia[a]	246 (28.1)	266 (30.4)	512 (29.3)
Hyperlipidaemia[a]	235 (26.9)	220 (25.2)	455 (26.0)
Obesity[b]	175 (20.0)	188 (21.5)	363 (20.8)
Hepatic steatosis	88 (10.1)	93 (10.6)	181 (10.4)
Hypercholesterolaemia[a]	69 (7.9)	64 (7.3)	133 (7.6)
Previous myocardial ischaemia	45 (5.1)	61 (7.0)	106 (6.1)
Coronary artery disease	51 (5.8)	52 (5.9)	103 (5.9)
Benign prostatic hyperplasia	48 (5.5)	52 (5.9)	100 (5.7)
History of diabetes complications at screening			
Diabetic retinopathy	146 (16.7)	131 (15.0)	277 (15.8)
Diabetic neuropathy	258 (29.5)	249 (28.5)	507 (29.0)
Diabetic nephropathy	109 (12.5)	85 (9.7)	194 (11.1)
Macroangiopathy[c]	114 (13.0)	100 (11.4)	214 (12.2)
Concomitant antidiabetes medication			
Mean metformin dose, mg	2059 (473.2)	2061 (462.9)	2060 (468.0)

Note: Data are mean (standard deviation), with the exception of data on sex, race, ethnicity, renal function, concomitant illnesses at screening and history of diabetes complications at screening, which are presented as n (%). Data for participant characteristics were measured at the last assessment before dosing.

[a]For participants to be classified as having concomitant dyslipidaemia, hyperlipidaemia or hypercholesterolaemia, a formal diagnosis listed in the medical history was required, and this classification was therefore not based on laboratory assessments of lipids.

[b]For participants to be classified as having concomitant obesity, a formal diagnosis listed in the medical history was required; this requirement resulted in a discrepancy with the usual definition of obesity, as approximately 58% of participants had a body mass index of >30 kg/m^2.

[c]Included peripheral vascular disease.

3.2 | Insulin and semaglutide doses

Total estimated daily BI dose decreased from randomization to EOT with semaglutide and IAsp (observed baselines: 40.2 and 40.9 U; estimated EOT values: 30.8 and 34.8 U, respectively); decreases were greater with semaglutide versus IAsp (estimated ratios to baseline: 0.84 vs. 0.95, respectively; estimated treatment ratio [ETR] 0.88 [95% CI 0.85; 0.92], $P < .0001$). Total estimated daily insulin dose at EOT (basal plus study medication in the IAsp group) was lower with semaglutide versus IAsp (30.8 and 67.6 U; estimated ratios to baseline: 0.84 vs. 1.85, respectively; ETR 0.46 [95% CI 0.44; 0.47], $P < .0001$). Descriptive observed insulin data can be found in Table S1.

Mean dose of semaglutide was 0.86 mg at EOT (71.9%, 26.9% and 1.1% of participants who remained on treatment were on 1.0, 0.5 and 0.25 mg doses, respectively, at EOT).

3.3 | Glycaemic control

Mean HbA1c (mean at randomization: 8.6% [70.0 mmol/mol]) decreased from randomization to EOT by 1.5% points (16.6 mmol/mol) with semaglutide and by 1.2% points (13.4 mmol/mol) with IAsp (ETD −0.29% points [95 CI −0.38; −0.20], −3.2 mmol/mol [95% CI −4.1; −2.2]; $P < .0001$ for non-inferiority; Figure 1A). Superiority was not tested because the confirmatory statistical testing hierarchy was not completed (Figure S2). These results were supported by sensitivity analyses (Table S2). At EOT, greater proportions of participants treated with semaglutide versus IAsp achieved an HbA1c of 7.5% or less (≤58.0 mmol/mol; estimated odds ratio [OR] 1.68 [95% CI 1.35; 2.10]), an HbA1c of less than 7.0% (<53.0 mmol/mol; estimated OR 1.72 [95% CI 1.40; 2.10]), and an HbA1c of 6.5% or less (≤48.0 mmol/mol; estimated OR 1.90 [95% CI 1.51; 2.39]; Table S3).

Regarding other glycaemic endpoints, change from baseline to EOT in fasting BG favoured semaglutide versus IAsp (all $P < .0001$), mean seven-point self-monitoring of BG (SMBG) was similar between treatment arms ($P = .5631$), and postprandial increment favoured IAsp versus semaglutide ($P < .0001$) (Table S4 and Figure S4A,B).

3.4 | Hypoglycaemia

Few EAC-confirmed severe hypoglycaemic episodes were reported with semaglutide (four events) and IAsp (seven events; estimated rate ratio [ERR] 0.58 [95% CI 0.15; 2.20]; $P = .4231$) (Figure S5A, Table 2).

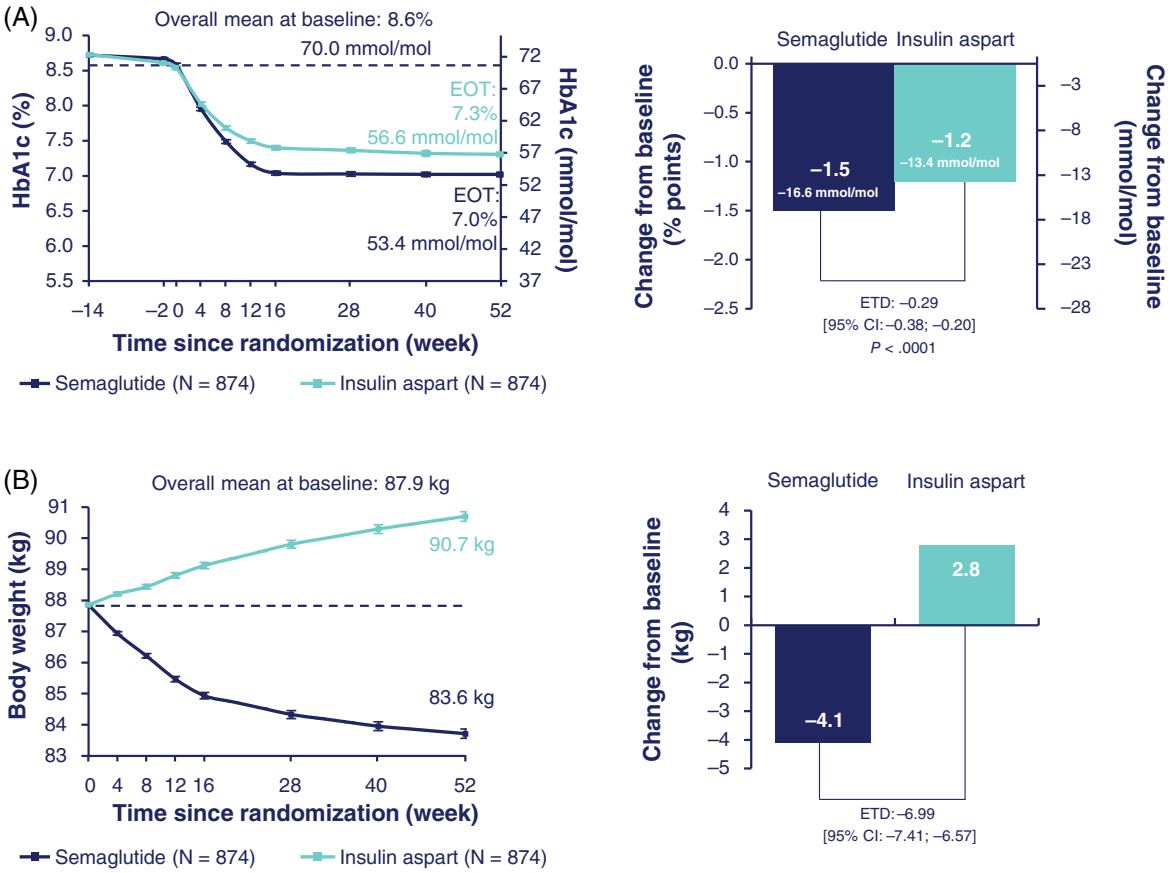

FIGURE 1 Change in A, HbA1c (primary endpoint) and B, body weight (secondary endpoint) from randomization to EOT. Primary and secondary endpoints from randomization to week 52. A, Change in HbA1c. Mean estimates (±SE) are from an ANCOVA where missing data were multiple imputed using data from participants within the same group defined by randomized treatment. The dashed line is the overall average value at randomization. B, Change in body weight. Mean (±SE) estimates are from an ANCOVA where missing data were multiple imputed using data from participants within the same group defined by randomized treatment. The dashed line is the overall average value at randomization. ANCOVA, analysis of covariance; CI, confidence interval; EOT, end of treatment; ETD, estimated treatment difference; SE, standard error.

TABLE 2 Secondary hypoglycaemia outcomes (A) and proportions of participants achieving composite endpoints relating to HbA1c targets and hypoglycaemia episodes after 52 weeks of treatment (B)

(A) Secondary hypoglycaemia outcomes

	Semaglutide (N = 874)			Insulin aspart (N = 874)			Statistical analyses	
	n (%)	E	R	n (%)	E	R	ERR [95% CI]	*P* value
Exposure time (y)	938.3			916.8				
EAC-confirmed severe hypoglycaemic episodes	4 (0.5)	4	0.4	6 (0.7)	7	0.8	0.58 [0.15; 2.20]	.4231
EAC-confirmed severe hypoglycaemic episodes requiring hospitalization, documented help or that were life-threatening	2 (0.2)	2	0.2	4 (0.5)	4	0.4	0.49 [0.09; 2.65]	Not tested[a]
EAC-confirmed severe or BG-confirmed symptomatic hypoglycaemic episodes (BG ≤3.9 mmol/L)	330 (37.8)	1420	151	528 (60.4)	5616	613	0.25 [0.20; 0.30]	<.0001
EAC-confirmed severe or BG-confirmed symptomatic hypoglycaemic episodes (BG <3.1 mmol/L)	139 (15.9)	254	27.1	328 (37.5)	1744	190	0.14 [0.11; 0.18]	<.0001
EAC-confirmed severe or clinically significant[b] hypoglycaemic episodes (BG <3.0 mmol/L)	169 (19.3)	339	36.1	379 (43.4)	2270	248	0.15 [0.12; 0.19]	<.0001

(B) Participants achieving composite endpoints after 52 weeks of treatment

	Semaglutide		Insulin aspart		Statistical analyses	
	Proportion achieving endpoint (%)	Estimated odds of endpoint	Proportion achieving endpoint (%)	Estimated odds of endpoint	OR [95% CI]	*P* value
HbA1c <7.0% at week 52 without an EAC-confirmed severe or clinically significant hypoglycaemic episode (BG <3.0 mmol/L)	40.4	0.7	20.3	0.2	2.90 [2.32; 3.63]	<.0001
HbA1c <7.0% at week 52 without an EAC-confirmed severe or clinically significant hypoglycaemic episode (BG <3.0 mmol/L) and no weight gain	36.6	0.6	5.5	0.1	11.06 [7.91; 15.46]	<.0001
HbA1c ≤7.5% without an EAC-confirmed severe hypoglycaemic episode	74.7	3.2	65.1	1.9	1.68 [1.35; 2.10]	<.0001
HbA1c ≤7.5% without an EAC-confirmed severe hypoglycaemic episode requiring hospitalization, documented medical help or that was life-threatening	75.0	3.2	65.2	1.9	1.70 [1.36; 2.12]	<.0001

Note: (A) All episodes were analysed using a Cox proportional hazards model with treatment group as a categorical fixed factor. Data are presented from the on-treatment full analysis set. (B) Data are presented from the on-treatment full analysis set. The binary endpoints were analysed using a logistic regression model with treatment as a fixed factor and baseline values as covariates. Before analysis, missing data for individual components were imputed separately using observed data from participants within the same group defined by randomized treatment. For continuous variables, missing values were imputed using a regression model including randomized treatment group and data from randomization and all previous visits as covariates, and subsequently were dichotomized. For hypoglycaemic episodes, episodes in the remaining unobserved part of the observation period were imputed using a Bayes Poisson log-link model with treatment as a fixed factor and baseline value as a covariate, and the logarithm of the time period covered by the participant's on-treatment observation period as offset and subsequently the total number of hypoglycaemic episodes were dichotomized. Severe hypoglycaemic episodes were classified as per the American Diabetes Association definition.

Abbreviations: BG, blood glucose; CI, confidence interval; E, number of events; EAC, event adjudication committee; ERR, estimated rate ratio; n, number of participants experiencing ≥1 event; OR, odds ratio; R, event rate per 100 exposure-years.

[a]Not tested because of the positioning of the endpoint in the hierarchical testing order.

[b]Clinically significant hypoglycaemic episodes did not need to be symptomatic.

Superiority for semaglutide versus IAsp for the time to first EAC-confirmed severe hypoglycaemic episode from randomization to EOT was not confirmed (hazard ratio 0.65 [95% CI 0.18; 2.30]; $P = .50$ for superiority). Consequently, further confirmatory testing was not performed for subsequent confirmatory endpoints lower in the testing hierarchy (shown in Figure S2).

Few EAC-confirmed severe hypoglycaemic episodes that required hospitalization, documented help or were life-threatening were reported in either the semaglutide (two events) or the IAsp (four events) arms (ERR 0.49 [95% CI 0.09; 2.65]; superiority not tested; Figure S5B, Table 2).

Fewer events of EAC-confirmed severe or clinically significant hypoglycaemic episodes (BG <3.0 mmol/L; with no requirement to be symptomatic) occurred with semaglutide (339 events) versus IAsp (2270 events; Table 2; $P < .0001$). Four composite endpoints, including an HbA1c of <7.0% or ≤7.5% and hypoglycaemic episodes of various definitions, also favoured semaglutide versus IAsp (all $P < .0001$; Table 2).

3.5 | Body weight

Mean BW decreased from randomization (87.9 kg) to EOT by 4.1 kg with semaglutide but increased by 2.8 kg with IAsp (ETD −6.99 kg [95% CI −7.41; −6.57]; Figure 1B; superiority not tested). Sensitivity analyses supported these results (Table S2). At EOT, greater proportions of participants treated with semaglutide versus IAsp achieved weight loss of 5% or more from randomization (OR 24.15 [95% CI 15.90; 36.68]; $P < .0001$) or 10% or more (OR 35.98 [95% CI 13.25; 97.71]; $P < .0001$; Table S3). Percentage change in BW (ETD −8.03% [95% CI −8.52; −7.55]), absolute change in body mass index (ETD −2.54 kg/m^2 [95% CI −2.69; −2.39]) and absolute change in waist circumference (ETD −5.31 cm [95% CI −5.81; −4.80]) also favoured semaglutide versus IAsp (all $P < .0001$; Table S5).

3.6 | Blood pressure, pulse rate and lipids

Systolic blood pressure decreased from randomization to EOT by 3.0 mmHg with semaglutide but increased by 0.9 mmHg with IAsp; there was a difference between semaglutide and IAsp (ETD −3.9 [95% CI −5.0; −2.7]; $P < .0001$; Table S6 and Figure S4C). Diastolic blood pressure also decreased with semaglutide versus IAsp ($P < .0216$; Table S6 and Figure S4D). Pulse rate increased from randomization (75.2 beats per minute [bpm]) to EOT by 2.4 bpm with semaglutide and by 1.0 bpm with IAsp (ETD 1.4 bpm [95% CI 0.6; 2.1]; $P = .0003$). Changes in lipids were small and not statistically significant except for total cholesterol (Table S6).

3.7 | Patient-reported outcomes

At randomization, scores for all domains of the short version of the 36-item Short Form Health Survey version 2 (SF-36v2™), Diabetes Quality of Life Clinical Trial Questionnaire (DQLCTQ-R), and Treatment Related Impact Measure for Diabetes (TRIM-D) questionnaire were similar between the treatment arms.

Of the eight SF-36v2™ domains, from randomization to EOT, improvements were observed with seven domains with semaglutide, as well as the physical and mental component summary scores, and four domains with IAsp, as well as the physical component summary score; improvements with semaglutide versus IAsp were reported in four domains. The physical component summary score improved with semaglutide versus IAsp (1.3 vs. 0.4, respectively; ETD 0.95 [95% CI 0.37; 1.53]; $P = .0014$), while changes in the mental component summary score were similar (0.2 vs. −0.4, respectively; ETD 0.59 [95% CI −0.14; 1.32]; $P = .1114$; Table S7).

Of the eight DQLCTQ-R domains, improvements were observed from randomization to EOT in all domains with semaglutide and in four domains with IAsp. Improvements with semaglutide versus IAsp were recorded in all domains ($P < .05$; Table S7).

Of the five TRIM-D domains, improvements from randomization to EOT were reported in all domains (and in total score) with semaglutide, but in only one domain with IAsp. There was an improvement for all domains with semaglutide versus IAsp ($P < .0001$ for all; Table S7).

3.8 | Safety

In total, AEs were reported by 511 participants (58.5%) with semaglutide and 450 participants (52.1%) with IAsp. Most AEs were mild-to-moderate in severity (Table 3). The most commonly reported AEs in the semaglutide group were gastrointestinal (GI) disorders (Table 3), the most frequent of which were nausea, diarrhoea and vomiting (14.8%, 7.4% and 5.7% of participants, respectively, with semaglutide, and 0.8%, 2.7% and 0.6% of participants, respectively, with IAsp). GI AEs mostly had onset during the dose-escalation period with semaglutide, but were more evenly distributed over time with IAsp; in both arms, most GI AEs resolved by end-of-trial. More participants treated with semaglutide versus IAsp experienced an AE leading to premature treatment discontinuation (3.7% and 0.7%, respectively; Table 3); this difference was largely driven by GI AEs (1.7% and 0.0%, respectively).

Hypoglycaemic episodes by classification are shown in Table 4. In general, rates of hypoglycaemia were lower with semaglutide versus IAsp.

Slightly fewer serious AEs were reported with semaglutide versus IAsp (Table 3); overall, the most frequently reported serious AEs were cardiac disorders (1.7% and 2.1% with semaglutide and IAsp, respectively). Other serious AEs with semaglutide and IAsp were infections and infestations (1.9% and 1.7%, respectively) and neoplasms (benign, malignant and unspecified; 1.3% and 1.0%, respectively).

Three AEs with fatal outcome were reported during the run-in period and, postrandomization, 12 (1.4%) participants in the semaglutide arm and one (0.1%) participant in the IAsp arm died

TABLE 3 Overview of adverse events

	Semaglutide			Insulin aspart		
	n (%)	E	R	n (%)	E	R
Number of participants (N)	874			864		
AEs	511 (58.5)	1642	175	450 (52.1)	1260	137.4
Gastrointestinal disorders AEs by SOC	275 (31.5)	621	66.2	76 (8.8)	100	10.9
Nausea	129 (14.8)	174	18.5	7 (0.8)	7	0.8
Diarrhoea	65 (7.4)	98	10.4	23 (2.7)	29	3.2
Vomiting	50 (5.7)	78	8.3	5 (0.6)	6	0.7
Dyspepsia	36 (4.1)	46	4.9	3 (0.3)	3	0.3
Severity						
Mild	412 (47.1)	1132	120.6	375 (43.4)	902	98.4
Moderate	223 (25.5)	446	47.5	162 (18.8)	300	32.7
Severe	47 (5.4)	64	6.8	40 (4.6)	58	6.3
Serious AEs	65 (7.4)	102	10.9	84 (9.7)	124	13.5
Fatal[a]	12[a] (1.4)	14[a]	1.5	1 (0.1)	1	0.1
Serious AEs by SOC (≥0.5% in any treatment arm or of special interest)						
Infections and infestations	17 (1.9)	23	2.5	15 (1.7)	20	2.2
Cardiac disorders[b]	15 (1.7)	23	2.5	18 (2.1)	25	2.7
Neoplasms benign, malignant and unspecified (including cysts and polyps)	11 (1.3)	11	1.2	9 (1.0)	10	1.1
Nervous system disorders	7 (0.8)	8	0.9	12 (1.4)	12	1.3
Injury, poisoning and procedural complications	6 (0.7)	7	0.7	8 (0.9)	10	1.1
Gastrointestinal disorders	3 (0.3)	3	0.3	5 (0.6)	6	0.7
Metabolism and nutrition disorders	3 (0.3)	3	0.3	5 (0.6)	5	0.5
Musculoskeletal and connective tissue disorders	2 (0.2)	2	0.2	6 (0.7)	8	0.9
Eye disorders	2 (0.2)	2	0.2	5 (0.6)	5	0.5
General disorders and administration site conditions	4 (0.5)	4	0.4	3 (0.3)	3	0.3
Respiratory, thoracic and mediastinal disorders	2 (0.2)	2	0.2	4 (0.5)	5	0.5
Surgical and medical procedures	2 (0.2)	2	0.2	4 (0.5)	4	0.4
Vascular disorders	1 (0.1)	2	0.2	5 (0.6)	6	0.7
AEs leading to treatment discontinuation	32 (3.7)	32	3.4	6 (0.7)	6	0.7
AEs leading to treatment discontinuation by SOC (≥0.5% in any treatment arm)						
Gastrointestinal disorders	15 (1.7)	15	1.6	0	–	–
Neoplasms benign, malignant and unspecified (including cysts and polyps)	6 (0.7)	6	0.6	1 (0.1)	1	0.1

Note: Data from the on-treatment safety analysis set are presented, except for AEs with fatal outcomes, which are from the in-trial observation period.
Abbreviations: %, proportion of participants experiencing ≥1 event; AE, adverse event; E, number of events; IAsp, insulin aspart; n, number of participants experiencing ≥1 event; R, event rate per 100 exposure-years; SOC, system organ class.

[a]There was multiple reporting of one AE that led to fatal outcome, which resulted in 14 events but only 12 fatalities. Further details of fatalities are in Table S8.

[b]Serious cardiac disorders experienced by ≥1 subjects in the trial included acute myocardial infarction (n = 3 with semaglutide and n = 4 with IAsp), coronary artery disease (n = 4 with semaglutide and n = 1 with IAsp), coronary artery stenosis (n = 1 with semaglutide and n = 3 with IAsp), angina pectoris (n = 2 with IAsp), unstable angina (n = 1 with semaglutide and n = 1 with IAsp), coronary artery atherosclerosis (n = 1 with semaglutide), coronary artery occlusion (n = 1 with semaglutide) and myocardial ischaemia (n = 1 with IAsp).

(Table S8). During the treatment period, 11 AEs with fatal outcome occurred with semaglutide (onset of events: day 4 to day 346) and one AE with fatal outcome occurred with IAsp (onset at day 209). An AE with fatal outcome occurred during the follow-up period (onset at day 372) with semaglutide.

AEs with fatal outcome with semaglutide were distributed across multiple SOCs and preferred terms with no apparent pattern. These AEs with fatal outcome were primarily in participants with multiple longstanding pre-existing medical conditions. All fatal events were evaluated by the investigator as unlikely to be related to the trial drug.

TABLE 4 Hypoglycaemic episodes by classification

	Semaglutide			Insulin aspart		
	n (%)	E	R	n (%)	E	R
Number of participants (N)	874			864		
Exposure time (y)	938.3			916.8		
Severe or BG-confirmed symptomatic	139 (15.9)	254	27.1	328 (38.0)	1745	190.3
ADA classified	539 (61.7)	3544	377.7	664 (76.9)	11 017	1202
Severe hypoglycaemia	4 (0.5)	4	0.4	7 (0.8)	8	0.9
Documented symptomatic hypoglycaemia	328 (37.5)	1416	150.9	527 (61.0)	5609	611.8
Asymptomatic hypoglycaemia	413 (47.3)	2091	222.8	499 (57.8)	5329	581.2
Probable symptomatic hypoglycaemia	13 (1.5)	17	1.8	25 (2.9)	35	3.8
Pseudo-hypoglycaemia	13 (1.5)	16	1.7	15 (1.7)	34	3.7
Unclassifiable				2 (0.2)	2	0.2

Note: Hypoglycaemic episodes were defined according to the ADA 2013 definition using BG levels of 3.9 mmol/L as a cut-off (≤3.9 mmol/L to confirm severe, documented symptomatic and asymptomatic hypoglycaemia and BG levels of >3.9 mmol/L used to confirm pseudo-hypoglycaemia), according to the ADA 2018 definition (<3.0 mmol/L to confirm clinically significant hypoglycaemia), or using a BG cut-off level below which symptoms of hypoglycaemia occur in normal physiology (<3.1 mmol/L used to confirm symptomatic or asymptomatic BG-confirmed hypoglycaemia). Data are presented for the on-treatment safety analysis set.

Abbreviations: %, percentage of participants experiencing ≥1 event; ADA, American Diabetes Association; BG, blood glucose; E, number of events; N, number of participants experiencing ≥1 event; R, event rate per 100 years of exposure.

All deaths were adjudicated as 'death not associated with severe hypoglycaemia or acute pancreatitis', except for one event that could not be adjudicated because of insufficient information. There were two AEs with fatal outcome because of coronavirus disease 2019 (COVID-19)-related pneumonia, one in each treatment arm. For further details, see Table S8.

4 | DISCUSSION

The SUSTAIN 11 results showed that OW semaglutide was non-inferior ($P < .0001$) to TID IAsp for glycaemic control in BI-treated participants with uncontrolled T2D, with a greater decrease in HbA1c over 52 weeks observed with semaglutide versus IAsp. Furthermore, a greater proportion of participants achieved HbA1c targets of 7.5% or less, less than 7.0%, and 6.5% or less with semaglutide versus IAsp ($P < .0001$). Although the estimated BI dose decreased with both semaglutide and IAsp, the reduction in HbA1c was still greater with semaglutide.

Improvements in glycaemic control in both arms were accompanied by a very low (and lower than expected) risk for severe hypoglycaemia, which was probably a result of the comparatively conservative insulin titration algorithms (with broad limits for no adjustments between 4.0 and 6.9 mmol/L) and broad HbA1c targets (individualized targets ranged from 6.5% to 7.5%), as well as increased caution and awareness from investigators in the context of a population with advanced T2D. All other non-severe, clinically significant hypoglycaemic endpoints favoured semaglutide over IAsp.

Reductions in HbA1c were accompanied by weight loss with semaglutide, whereas BW increases were observed with IAsp; there was a numerical treatment difference in BW of 6.99 kg at EOT for semaglutide versus IAsp. Furthermore, higher proportions of participants achieved weight-loss responses of 5% or higher or 10% or higher with semaglutide compared with IAsp ($P < .0001$). This reflects the known effects of GLP-1RAs and insulins on BW previously shown in other randomized clinical trials, with GLP-1RAs associated with weight loss and insulins with weight gain.[16,34,35]

In our study, decreases in systolic blood pressure were observed with semaglutide, in accordance with previous studies with GLP-1RAs,[13-22] whereas slight increases occurred with IAsp. The pulse increase observed in semaglutide-treated participants did not appear to be associated with any increase in arrythmia or adverse cardiac events. Such increases in pulse are a well-recognized effect of GLP-1RAs[36] and were also observed in SUSTAIN 6, a cardiovascular outcomes trial (CVOT) of OW semaglutide, in which a CV benefit was observed.[22]

QoL and treatment satisfaction, measured by the SF-36v2™, DQLCTQ-R and TRIM-D questionnaires, were generally greater with semaglutide than with IAsp. This may in part reflect the less burdensome injection schedule with semaglutide compared with IAsp (OW and TID, respectively), the need to assess BG less frequently, the greater decrease in estimated BI dose, and the overall better efficacy profile in terms of HbA1c and BW. Previous studies have indicated that the less intensive GLP-1RA plus BI dosing schedules may increase adherence compared with BBI.[8,37] The OW injection regimen of semaglutide may therefore be an additional benefit to patients in real-world clinical practice.

In SUSTAIN 11, both semaglutide and IAsp were generally well tolerated. As expected for a GLP-1RA, GI events were the most commonly reported AEs with semaglutide. Across treatment arms, serious AEs, including cardiac disorders, were reported by similar proportions of subjects and with comparable event rates.

An imbalance in AEs with fatal outcome was observed with semaglutide versus IAsp, which contrasts with previous, extensive data with OW semaglutide from clinical trials,[13-22] including the CVOT SUSTAIN 6[22] and real-world data.[38-41] There was no clustering of causes or any observed pattern regarding the timing of AEs with fatal outcome (Table S8). Deaths primarily occurred in participants with multiple, longstanding pre-existing medical conditions. All deaths were adjudicated by an independent and blinded external adjudication committee; none were associated with severe hypoglycaemia or acute pancreatitis. All were rated by the investigator as unlikely to be related to the trial drug. Two fatalities were related to COVID-19; however, the COVID-19 pandemic appeared to have a limited impact on the trial and did not affect participant safety, trial integrity or the overall conclusions. The safety profile of OW semaglutide in this trial was determined to be consistent with its well-established safety profile and consistent with the GLP-1RA drug class in general.[13-22]

Participants enrolled in this trial were slightly older than other SUSTAIN trial populations, had longer diabetes duration and late-stage, uncontrolled T2D, as reflected by higher baseline HbA1c.[13-21] Despite these differences, the effects of semaglutide on HbA1c and BW were comparable with those reported from other SUSTAIN trials.[13-21] In a systematic literature review and network meta-analysis, in participants with T2D previously receiving 1-2 OADs, OW semaglutide 1.0 mg showed greater reductions in HbA1c and BW, and was well tolerated, versus GLP-1RA comparators.[42] Our results are also mostly consistent with the systematic review and meta-analysis mentioned in the Introduction,[6] in which GLP-1RA/insulin combinations resulted in greater weight losses, lower hypoglycaemia risk and lower insulin dose versus basal-plus and BBI regimens.[6]

In this trial, glycaemic control was evaluated via change in HbA1c and seven-point SMBG profile. Although the measurement of glycaemic variability via continuous glucose monitoring would have provided additional useful information, the approach taken reflected clinical practice for many individuals with T2D at the time the trial commenced (2018), and, indeed, is still reflective of care for many patients with T2D today.

In conclusion, the combination of BI and a GLP-1RA is a common treatment choice in patients with advanced T2D,[43] and our results confirm that this is appropriate. Furthermore, evidence suggests that GLP-1RAs provide an alternative to the addition of bolus insulin to BI when individualizing T2D treatment.[44] SUSTAIN 11 was the first large, prospective, head-to-head trial comparing OW semaglutide with a rapid-acting insulin analogue, as add-on to metformin and optimized IGlar. Despite the challenging population, results support the established, favourable benefit–risk profile of OW semaglutide, which is in keeping with current guideline recommendations.[3,4] This provides useful information for both physicians and patients when making joint treatment decisions to optimize the management of T2D.

AUTHOR CONTRIBUTIONS

L.L.N. performed statistical analyses. All the authors acquired, analysed, or interpreted data; drafted and critically revised the manuscript. M.S.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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CONFLICT OF INTEREST

M.K. receives consulting fees from Abbott, Bayer AG, Boehringer Ingelheim, Eli Lilly, MSD, Novo Nordisk, and Sanofi. Payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events are received from Abbott, AstraZeneca, Bayer AG, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, and Novo Nordisk. M.S.K., J.L., and L.L.N. are employees of Novo Nordisk A/S. M.S.K. is a shareholder in Novo Nordisk A/S. K.S. receives consulting fees and support for attending meetings and/or travel from Eli Lilly and Sanofi. Payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events are provided from Bayer AG, Bioton, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi, and Servier. O.T. has nothing to disclose. S.J. receives payments or honoraria for lectures from Amgen, AstraZeneca, Bayer AG, Berlin Chemie, BMS, Boehringer Ingelheim, Eli Lilly, MSD, Novartis, Novo Nordisk, Pfizer, Roche, Sanofi, SCIARC, and VIFOR. S.J. participates on Data Safety Monitoring Boards or Advisory Boards for Amgen, AstraZeneca, Bayer AG, Boehringer Ingelheim, Eli Lilly, MSD, and Novo Nordisk. S.J. participates in the German Diabetes Association working groups on (i) diabetes prevention and (ii) diabetes and the heart.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/dom.14765.

DATA AVAILABILITY STATEMENT

The data sets analyzed during the current study are available on reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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