Title page

Title: Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine in insulin-naïve subjects with type 2 diabetes (SUSTAIN 4): a randomised open-label clinical trial

Authors: Vanita R Aroda,[1] Stephen C Bain ,[2] Bertrand Cariou ,[3] Milivoj Piletic,[4] Ludger Rose,[5] Mads Axelsen,[6] Everton Rowe,[7] J Hans DeVries,[8]

Author affiliations: [1]MedStar Health Research Institute, Hyattsville, MD, USA; [2]School of Medicine, Swansea University, Wales, UK; [3]CHU Nantes, l'Institut du Thorax, Nantes, France; [4]General Hospital, Novo Mesto, Slovenia; [5]Münster Institute for Diabetes Research, Münster, Germany; [6]Novo Nordisk A/S, Søborg, Denmark; [7]Novo Nordisk Inc., Princeton, NJ, USA; [8]Academic Medical Center, University of Amsterdam, the Netherlands.

Contact details for corresponding author:

Prof J Hans DeVries, Academic Medical Center, Department of Endocrinology, Room F4-215, PO Box 2260, 1100 DD, Amsterdam, the Netherlands
j.h.devries@amc.uva.nl
+31205666525

Panel: Research in context

Evidence before this study

- *Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue in development for the treatment of type 2 diabetes (T2D), with a pharmacokinetic profile suitable for once-weekly dosing.*
- *It is structurally similar to liraglutide, an approved once-daily GLP-1 analogue, with modifications to extend its half-life and dosing profile.*
- *The design of this trial was based on preclinical safety and pharmacology findings, and the clinical phase 1 and 2 trials, which have supported further assessment of semaglutide in a phase 3 clinical trial programme.*
- *Results from the phase 2 dose-finding trial and one of the phase 1 semaglutide trials, indicate that an adjusted dose-escalation regimen is likely to offer a more acceptable gastrointestinal (GI) tolerability profile, whilst maintaining efficacy, than starting at the final dose.*

Added value of this study

- *This phase 3a trial demonstrates that semaglutide combines substantial lowering of HbA_{1c} with substantial weight loss, compared with basal insulin glargine as a reference active comparator. The safety profile of gradually titrated semaglutide appears to be similar to currently available GLP-1 receptor agonists (GLP-1RAs), consisting primarily of GI events, with a lower risk of hypoglycaemia compared with insulin glargine.*

Implications of all the available evidence

- *Semaglutide, administered once weekly, appears to be a valuable treatment for patients with T2D inadequately controlled on metformin, with or without sulphonylureas, as it exhibits both significant improvements in glycaemic control and an extent of weight loss that appears greater than has been reported for other GLP-1RAs. A combination of glucose-lowering effect and weight loss is particularly important in addressing the underlying pathophysiology of T2D. Semaglutide has an acceptable safety profile, which is similar to that of other GLP-1RAs.*

Summary (max 300 words, currently 254 words including funding statement)

Background

Despite a broad range of pharmacological options for type 2 diabetes (T2D) treatment, optimal glycaemic control remains challenging for many patients and new therapies remain necessary. Semaglutide is a glucagon-like peptide-1 (GLP-1) analogue in phase 3a development for T2D.

Methods

SUSTAIN 4 (ClinicalTrials.gov: NCT02128932) was a randomised, phase 3a, open-label trial assessing the non-inferiority of once-weekly 0·5 and 1·0 mg semaglutide compared with once-daily insulin glargine in insulin-naïve subjects with T2D inadequately controlled with metformin, with or without sulphonylureas. Primary endpoint was change in HbA_{1c} from baseline at week 30.

Findings

The trial was conducted from 4 August 2014 to 3 September 2015. In total, 1089 adults were randomised. From a mean baseline HbA_{1c} of 8·2% to week 30, 0·5 and 1·0 mg semaglutide achieved superior reductions of 1·2% and 1·6%, versus 0·8% with insulin glargine; estimated treatment difference (ETD) [95% CI] –0·38% [–0·52, –0·24] and –0·81% [–0·96, –0·67], both p<0·0001. Semaglutide 0·5 and 1·0 mg achieved superior weight loss of 3·5 kg and 5·2 kg versus 1·2 kg gain with insulin glargine (ETD –4·62 [–5·27; –3·96] and –6·33 [–6·99; –5·67] kg, both p<0·0001). Mean daily insulin glargine dose at week 30 was 29·2 IU/day. Severe or blood glucose-confirmed hypoglycaemia was reported by 4·4% and 5·6% of subjects treated with semaglutide 0.5 and 1·0 mg versus 10·6% with insulin glargine (p=0·0021 and 0·0202)). The proportion of subjects reporting severe hypoglycaemia was 0.6%, 1.4% and 1.4%, respectively. Proportions of subjects discontinuing treatment prematurely due to adverse events (mainly gastrointestinal) were 5·5%, 7·5% and 1·1%, respectively.

Interpretation

Semaglutide resulted in superior HbA_{1c} and weight reduction with fewer hypoglycaemic episodes, compared with insulin glargine. Semaglutide was well-tolerated, with a similar safety profile to other GLP-1RAs.

Funding: Novo Nordisk A/S

Introduction

Type 2 diabetes (T2D) is a complex disorder that requires individualised treatment strategies. Due to the progressive nature of T2D, most patients will require treatment intensification, which can be in the form of additional antihyperglycaemic agents either as an oral or an injectable therapy.[1] Currently, the most commonly used injectable treatments for patients failing to meet targets on oral therapy are basal insulins or glucagon-like peptide 1 receptor agonists (GLP-1RAs).[1]

Basal insulin, while effective in controlling hyperglycaemia for many patients,[2,3] is associated with adverse effects such as hypoglycaemia and weight gain.[4] By contrast, GLP-1RAs stimulate insulin secretion and inhibit the release of glucagon from pancreatic islets in a glucose-dependent manner,[5] resulting in effective glucose lowering that is comparable to basal insulin therapy while limiting hypoglycaemia.[6] GLP-1RAs have also been shown to reduce body weight.[6] While GLP-1RAs were initially used once- or twice-daily, recent efforts have focused on the development of once-weekly GLP-1RAs, with the potential to improve adherence and quality of life for patients.[6,7]

Semaglutide, a GLP-1 analogue currently in development, is structurally similar to liraglutide, an approved once-daily GLP-1 analogue. Structural modifications of the semaglutide molecule include amino acid substitutions at position 8 (alanine to α-aminoisobutyric acid) and position 34 (lysine to arginine), and acylation of the lysine in position 26 with a spacer and C-18 fatty diacid chain.[8] The substitution at position 8 renders semaglutide less susceptible to degradation by dipeptidyl peptidase-4 (DPP-4), while the lysine acylation improves binding to albumin.[8] These modifications extend the half-life of semaglutide to approximately 1 week,[8] enabling once-weekly administration.[9,10]

Here, we report the findings from the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes 4 (SUSTAIN 4) phase 3a trial, which aimed to evaluate the efficacy, safety and tolerability of subcutaneous (s.c.) semaglutide at doses of 0·5 mg and 1·0 mg once weekly compared with once-daily insulin glargine titrated to fasting glucose target. The trial cohort were insulin-naïve subjects with T2D, with inadequate glycaemic control on metformin, with or without sulphonylureas.

Methods

Study design

SUSTAIN 4 was a phase 3a, randomised, open-label, active-controlled, parallel-group, multicentre, multinational, three-armed trial (ClinicalTrials.gov no. NCT02128932). The trial was conducted at 196 participating sites located in Argentina, Croatia, France, Germany, India, Macedonia, Mexico, the Netherlands, Romania, Slovakia, Slovenia, South Africa, UK and the USA. This trial was conducted in compliance with the International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. This analysis is based on the completed trial after 30 weeks, and no interim analyses were planned.

Participants

Insulin naïve subjects who were ≥18 years old, diagnosed with T2D and on stable treatment with metformin alone or in combination with sulphonylureas 90 days prior to screening were included in the trial. Eligible subjects had an HbA_{1c} value of 7·0–10·0% (53–86 mmol/mol). Key exclusion criteria included a history of chronic or idiopathic acute pancreatitis, a screening calcitonin value of ≥50 ng/L, any personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2, severely impaired renal function (estimated glomerular filtration rate [eGFR] <30 ml/min/1·73 m^2), heart failure (New York Heart Association class IV) or any acute coronary or cerebrovascular events within the last 90 days. Subjects with known proliferative retinopathy or maculopathy requiring acute treatment were also excluded, and any cases of retinopathy identified in the trial were likely to be new cases. Retinopathy was not explicitly screened for during the trial itself. Full eligibility criteria are included in Supplementary Material 1. Written informed consent was obtained from all participants. The protocol was approved by all local ethics committees and institutional review boards.

Randomisation and masking

Subjects were randomly assigned with a 1:1:1 ratio to receive once-weekly s.c. semaglutide (0·5 mg or 1·0 mg) or once-daily insulin glargine using an interactive voice/web response system. Both investigators and subjects were unblinded, apart from members of the external event adjudication committee (EAC).

Procedures

Following a 2-week screening period, subjects received once-weekly s.c. semaglutide (0·5 mg or 1·0 mg; Novo Nordisk A/S, Bagsværd, Denmark) or once-daily insulin glargine (Lantus® U100, Sanofi, Gentilly, France) for 30 weeks, followed by a 5-week follow-up period. Subjects who stopped treatment prematurely were encouraged to remain in the trial and complete follow up. Semaglutide dosing was selected based on the findings of the phase 2 dose-finding trial,[11] and subjects followed a fixed dose-escalation regimen. In those allocated to receive semaglutide 0·5 mg, this dose was reached after 4 weeks of once-weekly 0·25 mg semaglutide. In the semaglutide 1·0 mg arm, this dose was reached after 4 weeks of once-weekly 0·25 mg semaglutide, followed by 4 weeks of once-weekly 0·5 mg semaglutide.

Subjects in the insulin glargine arm started on a dose of 10 IU once daily. Protocol instructions were to titrate the insulin dose weekly to a pre-breakfast self-measured plasma glucose (SMPG) target of 4·0–5·5 mmol/L (72–99 mg/dL) (Supplementary Material 2). Titration was according to the lowest value of each subject's fasting 1-point profile SMPG levels 3 days prior to visits or phone contacts. Injections were administered in the thigh, abdomen or upper arm. For semaglutide, injections could be done at any time of the day, but on the same day each week. In all treatment groups, prior background metformin and/or sulphonylurea treatment was continued throughout the trial.

Subjects with unacceptable hyperglycaemia (defined as any fasting SMPG measurement >15·0 mmol/L [270 mg/dL] from randomisation to end of week 5, 13·3 mmol/L [240 mg/dL] from week 6 to end of week 11 or 11·1 mmol/L [200 mg/dL] after week 12) were to be offered rescue treatment (intensification of existing background medication and/or initiation of new medication, preferably excluding GLP-1RAs, DPP-4 inhibitors or amylin analogues) as add-on to their randomised treatment at the discretion of the investigator, in accordance with current American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) treatment recommendations.[1]

Outcomes

The primary endpoint was change in HbA_{1c} from baseline to week 30 (end of treatment). The confirmatory secondary endpoint was change in body weight from baseline to week 30. Other secondary efficacy endpoints included proportion of subjects who achieved HbA_{1c} <7·0% (53 mmol/mol[12]) or ≤6·5% (48 mmol/mol[13]) by end of treatment, proportion of subjects achieving HbA_{1c} <7·0% (53 mmol/mol) without severe (by ADA classification [event requiring assistance of another person to actively administer carbohydrates,

glucagon, or take other corrective actions][14]) or blood-glucose (BG)-confirmed symptomatic hypoglycaemia (plasma glucose ≤3·1 mmol/L or 56 mg/dL) and no weight gain, change from baseline in fasting plasma glucose (FPG), mean 8-point SMPG profiles and postprandial increment, proportion of subjects who achieved ≥5% and ≥10% weight loss by end of treatment , change from baseline in body mass index (BMI), waist circumference, fasting blood lipids, systolic and diastolic blood pressure (BP), plasminogen activator inhibitor-1 [PAI-1], C-reactive protein [CRP] and patient-reported outcomes (PROs; Short Form [SF]-36v2™ health survey and Diabetes Treatment Satisfaction Questionnaire [DTSQ]).

Safety endpoints included the number of treatment-emergent adverse events (AEs), the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes during exposure and pulse rate. Other safety measurements were change in laboratory parameters (haematology, biochemistry, calcitonin, urinalysis, and urinary albumin-to-creatinine ratio) and examinations (ECG and physical examination) at week 30, the occurrence and level of anti-semaglutide antibodies, and semaglutide pharmacokinetics (to be included in a future population pharmacokinetic analyses across semaglutide phase 3a trials).

The need for a Data Monitoring Committee (DMC) was considered by Novo Nordisk in accordance with the guidance given by Food and Drug Administration and the European Medicines Agency and it was decided that the trial did not meet the need for a DMC.

An independent EAC validated predefined events in a blinded manner (Supplementary Material 3).

Statistical analysis

The trial was powered to the primary objective (change in HbA_{1c} level at 30 weeks) of demonstrating non-inferiority for both doses of semaglutide, separately tested against insulin glargine, under the following assumptions: no treatment difference; a non-inferiority margin of 0.3%; 1:1:1 randomisation; standard deviation of 1.1%; one-sided 0.025 significance level; and a 30% dropout rate. Based on this sample size of 1047 subjects was specified, ensuring at least 90% power for each of the HbA_{1c} non-inferiority tests. Further, this ensured 99% power to detect a difference between semaglutide 1.0 mg vs insulin glargine of 1.5 kg in change in body weight, with a standard deviation of 4 kg. Conservatively assuming independence between the two endpoints, the joint power is 80%.

To preserve the overall type 1 error rate, a pre-specified hierarchical testing was performed (Supplementary Figure 1): non-inferiority in change in HbA_{1c} for semaglutide 1.0 mg vs insulin glargine; superiority in change in body weight for semaglutide 1.0 mg vs insulin glargine; non-inferiority in change in HbA_{1c} for semaglutide 0.5 mg vs insulin glargine; superiority in change in HbA_{1c} for semaglutide 1.0 mg vs insulin glargine; superiority in change in body weight for semaglutide 0.5 mg vs insulin glargine; and superiority in change in HbA_{1c} for semaglutide 0.5 mg vs insulin glargine. Superiority for either change in HbA_{1c} or in body weight was considered established if the upper limit of the 2-sided 95% confidence interval for the estimated difference was below 0% or 0 kg, respectively.

The evaluation of efficacy was based on a modified intention to treat (mITT), comprising all randomised subjects who were exposed to at least one dose of trial product, as specified in the trial protocol; the evaluation used data collected before the initiation of any rescue medication or before premature treatment discontinuation. Safety was evaluated based on the same set of subjects. For safety, only data collected before premature treatment discontinuation with an ascertainment window of 42 days were used to define treatment-emergent adverse events. Supportive analyses using all data collected during the trial were performed for both efficacy and safety.

Analysis methods for HbA_{1c} and body weight and other continuous endpoints assessed over time included a mixed model for repeated measurements (MMRM), with factors for treatment, country, stratum (metformin ± sulphonylurea) and baseline value, all nested within visits. An unstructured covariance matrix was assumed for measurements within the same subject. Outcomes evaluating the secondary HbA_{1c} and body weight targets were analysed using logistic regression. All p-values were two-sided test of the null hypothesis of no treatment difference. All statistical testing was done at the 0.05 significance level.

The robustness of the analyses of HbA_{1c} and body weight was assessed by handling missing data in various ways, including a comparator-based multiple imputation model where missing data points were imputed based on observed data in the insulin glargine arm. Sensitivity analyses also included an MMRM analysis on the mITT population using all data, regardless of whether obtained while the subjects had discontinued the trial product and/or whether the subject had been administered rescue medication (supplementary materials).

Role of the funding source

The sponsor designed the trial and developed the protocol in consultation with the first and last authors. The sponsor provided logistical support during the trial and obtained the data. The authors interpreted the data and wrote the report together with medical writing services provided by the sponsor. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

The trial was conducted from 4 August 2014 to 3 September 2015, with subjects recruited between 4 Aug 2014 and 16 Dec 2014. In total, 1089 adults with T2D were randomised to one of the semaglutide doses or insulin glargine, of whom 1082 (99%) were exposed to trial medication (Figure 1). In all, 1020 (94%) of randomised subjects completed the trial and 952 (88%) completed treatment. The proportion of subjects completing randomised treatment without the need for rescue medication was 82·6% with semaglutide 0·5 mg, 82·2% with semaglutide 1·0 mg, and 91·4% with insulin glargine. A total of 49 (13·5%) subjects in the semaglutide 0·5 mg group discontinued treatment prematurely, compared with 55 (15·3%) in the semaglutide 1·0 mg group. Fewer subjects (26 [7·2%]) discontinued treatment prematurely in the insulin glargine group. Most treatment discontinuations were due to AEs (mostly GI with semaglutide and of other causes with insulin glargine). Baseline characteristics were similar between all groups. Overall, 52% of subjects were on sulphonylureas (Table 1).

Mean HbA_{1c} (baseline 8·2%, SD 0·89%) decreased significantly over time in all three groups, with most of the decrease occurring by week 12 (Figure 2A). By week 30, mean HbA_{1c} decreased significantly with semaglutide 0·5 mg and 1·0 mg by 1·2% and 1·6%, respectively, versus 0·8% in the insulin glargine group; estimated treatment differences (ETD) versus insulin glargine (95% confidence interval [CI]) –0·38% (–0·52; –0·24) and –0·81% (–0·96 to –0·67); p<0.0001 for both; Figure 2B, Table 2). The mean insulin glargine dose at end of treatment was 29·2 IU/day. Results from the sensitivity analyses for HbA_{1c} confirm the primary analysis results and are provided in Supplementary Figure 1a.

HbA_{1c} <7% (<53 mmol/mol) was achieved by 57% and 73% of 0·5 mg and 1·0 mg semaglutide treated subjects, respectively, versus 38% in the insulin glargine group (p<0·0001; Table 2). HbA_{1c} ≤6·5% (≤48 mmol/mol) was achieved by 37% and 54% of 0.5 mg and 1.0 mg semaglutide-treated subjects, respectively, versus 18% in the insulin glargine group (p<0·0001 for both; Table 2).

The number of subjects achieving HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and without weight gain was 169 (47% of subjects) in the semaglutide 0·5 mg group and 231 (64%) in the semaglutide 1·0 mg group versus 56 (16%) in the insulin glargine group (p<0·0001 for both).

Mean FPG was reduced with all three groups (Table 2, Figure 2C–D). In the semaglutide 0·5 mg and insulin glargine groups, FPG decreased by a comparable amount (ETD 0·08 mmol/L [p=0·6243]) while, in the semaglutide 1.0 mg group, FPG decreased significantly more than with insulin glargine (ETD –0·61 mmol/L [p=0·0002]).

Mean 8-point SMPG was also reduced in all three groups. The decrease from baseline in the semaglutide 0·5 mg and insulin glargine groups was similar (ETD –0·04 mmol/L [p=0·7816]), while in the semaglutide 1·0 mg group, the decrease was significantly greater than for insulin glargine (ETD –0·57 mmol/L [p<0·0001]; Figure 2G and Table 2). Mean 8-point SMPG postprandial increments decreased in the semaglutide 0·5 mg and 1·0 mg groups significantly more than with insulin glargine (ETD –0·39 [p=0·0029] and –0·65 [p<0·0001], respectively; Table 2).

At week 30, mean body weight decreased significantly with semaglutide 0.5 mg and 1.0 mg by 3·5 kg and 5·2 kg, respectively, versus an increase of 1·2 kg in the insulin glargine group (ETD [95% CI] –4·62 kg [–5·27; –3·96] and –6·33 kg [–6·99; –5·67], respectively; p<0·0001 for both; Figure 2E–F, Table 2). A body weight reduction of ≥5% was observed in 37% and 51% of 0·5 mg and 1·0 mg semaglutide-treated subjects, respectively, versus 4% in the insulin glargine group (p<0·0001 for both; Table 2). A body weight reduction of ≥10% was observed in 7% and 16% of 0·5 mg and 1·0 mg semaglutide-treated subjects, respectively, versus 1% in the insulin glargine group (p=0.002 and p<0.0001, respectively, Table 2). Results from the sensitivity analyses for body weight confirmed this finding and are shown in Supplementary Figure 1b. BMI and waist circumference were significantly reduced with both doses of semaglutide compared with insulin glargine (Table 2).

Changes in lipid levels, and in levels of CRP and PAI-1, are detaild in supplementary tables 1 and 2.

Both systolic BP and diastolic BP decreased in the three treatment groups (Table 2). Systolic BP decreased to a significantly greater extent (by –1·7 mmHg) in the semaglutide 0·5 mg and 1·0 mg groups compared with the insulin glargine group (ETD –2·97 mmHg and –3·50

mmHg, respectively). Corresponding changes in diastolic BP were smaller and were not significant in either case (ETD 0·06 mmHg and 0·45 mmHg, respectively).

Pulse increased significantly with semaglutide 0·5 mg and 1·0 mg by 2·3 bpm and 3·1 bpm, respectively, versus a <0·1 bpm decrease with insulin glargine (Table 2). Overall treatment satisfaction (as per DTSQ; baseline 26·9 ± 7·01) improved by 4·6, 5·6 and 3·7 points with semaglutide 0·5 mg, semaglutide 1·0 mg and insulin glargine, respectively (ETD 0·87 [p=0·0254] and 1·38 [p=0·0005]; Supplementary Figure 2). The frequency with which subjects felt that their blood sugars had been unacceptably high was reduced to a significantly greater extent in the semaglutide 0·5 mg and 1·0 mg groups, compared with insulin glargine (ETD –0·44 [p=0·0011] and –0·71 [p<0·0001]). Results from the SF-36v2™ questionnaire were significantly improved with semaglutide 1·0 mg compared with insulin glargine in two of the eight domains (Supplementary Figure 3): role-emotional (ETD 1·67, p=0·0257) and general health (ETD 1·15, p=0·0291).

The proportion of subjects reporting treatment-emergent AEs was 69·9%, 73·3% and 65·3% with semaglutide 0·5, 1·0 mg and insulin glargine, respectively, with 6·1%, 4·7% and 5·0% of subjects reporting serious AEs (Table 3).

AEs with fatal outcome were reported in four subjects treated with 0·5 mg semaglutide (3 subjects with cardiovascular death [EAC-confirmed] and 1 pancreatic carcinoma [detected 149 days into the trial]) and 2 subjects treated with insulin glargine (2 subjects with cardiovascular death [EAC-confirmed]), with none in the semaglutide 1.0 mg arm. Diabetic retinopathy was reported by 1 subject (0.3%) each in the semaglutide 0.5 mg and insulin glargine groups and none in the semaglutide 1.0 mg group. Only 1 subject (0.3%) in the insulin glargine group reported proliferative retinopathy.

The proportion of subjects discontinuing treatment prematurely due to AEs was 5·5% for the semaglutide 0·5 mg group and 7·5% for the 1·0 mg group; both were higher than insulin glargine (1·1%; Supplementary Figure 6). The most frequent AEs (Table 3) and the majority of AEs leading to premature treatment discontinuation in the semaglutide groups were gastrointestinal (GI) events. In the semaglutide groups, GI events were mainly mild or moderate in severity and diminished in frequency over time (Figure 3). Nausea was reported in 21·3%, 22·2% and 3·6% of subjects in the semaglutide 0·5 mg, 1·0 mg and insulin glargine groups, respectively. Vomiting was reported in 6·6%, 10·3% and 3·1%, and diarrhoea was reported in 16·3%, 19·2% and 4·4% of subjects in the semaglutide 0·5 mg, 1·0 mg and insulin glargine groups, respectively. Compared with insulin glargine, lipase and

amylase levels both increased significantly more in both semaglutide groups compared to glargine, without a clear dose-dependent effect (Supplementary Figure 7).

Severe or BG-confirmed hypoglycaemia was reported by 4·4% of subjects receiving 0·5 mg semaglutide and 5·6% of those receiving 1·0 mg semaglutide, compared with 10·6% of those receiving insulin glargine ($p<0·0001$ for both). Most of these episodes were reported in subjects receiving sulphonylurea as background medication; 8.1%, 8.6% and 18.1% of these subjects experienced severe or BG-confirmed hypoglycaemia compared with 0.6%, 2.3% and 2.3% of those not receiving sulphonylurea as background medication. The proportion of subjects reporting severe hypoglycaemia was 0.6%, 1.4% and 1.4%, respectively. Nocturnal severe or BG-confirmed hypoglycaemia was reported by 1·1% of subjects receiving 0·5 mg semaglutide and 0·8% of those receiving 1·0 mg semaglutide, compared with 2·2% of subjects receiving insulin glargine.

A total of three cases of cholelithiasis were reported (none classified as severe); one in the semaglutide 0.5 mg group and two in the semaglutide 1.0 mg group. In one of the subjects receiving semaglutide 0.5 mg, this was categorised as a serious AE (SAE). Two pancreatic AEs were reported, both in the semaglutide 0·5 mg group, and were adjudicated as mild, acute pancreatitis. Both subjects discontinued treatment prematurely and symptoms resolved after treatment discontinuation.

EAC-confirmed neoplasms were reported by 8 subjects treated with semaglutide 0.5 mg, 2 subjects on semaglutide 1.0 mg and 3 subjects on insulin glargine. These included 4 subjects with malignant neoplasms (skin, nasopharyngeal, pancreatic and renal/adrenal) in the semaglutide 0.5 mg group, none in the semaglutide 1.0 mg group and one in the insulin glargine group. Calcitonin levels were comparable between groups with no apparent change during the trial. A decline in eGFR was observed in all three arms during the first 12 weeks of treatment, and then stayed stable over remaining duration of the trial (Supplementary Figure 4). EAC-confirmed cardiovascular adverse events are detailed in supplementary table 3.

Discussion

In this multicentre, randomised, phase 3a trial, both semaglutide 0·5 mg and 1·0 mg achieved superiority over insulin glargine in improving overall glycaemic control and inducing body weight loss in subjects with T2D after 30 weeks of treatment, with non-inferiority as the primary analysis.

A greater proportion of subjects in both the semaglutide 0·5 mg and 1·0 mg groups achieved HbA_{1c} targets set by the ADA/EASD and the American Association of Clinical Endocrinologists compared with those in the insulin glargine group. This observation compares favourably with previous findings for liraglutide,[15] and for other once-weekly GLP-1RAs such as dulaglutide and exenatide,[16,17] compared with insulin glargine. Furthermore, semaglutide led to substantial weight loss (3·5–5·2 kg versus baseline), with more subjects on semaglutide 0·5 mg and 1·0 mg experiencing clinically significant (≥5%) weight reduction, compared with insulin glargine. Trials with other GLP-1RAs have reported reductions of –0·4–2·5 kg.[18-21] The weight reduction achieved with semaglutide compared with insulin glargine (4.6–6.3 kg) also compared favourably to that reported with other long-acting GLP-1RAs (2.6–4.0 kg).[16,17,22] However, comparisons of these trials should be made with caution due to the differences in study design and patient populations between individual trials.

Consistent with these findings, the secondary composite endpoint (HbA_{1c} <7% without severe or BG-confirmed symptomatic hypoglycaemia and without weight gain) was achieved by nearly half of subjects in the semaglutide 0·5 mg group and nearly two-thirds in the semaglutide 1·0 mg group versus less than one-fifth in the insulin glargine group. The combination of glycaemic control and body weight reduction with a low potential for hypoglycaemia, delivered with a once-weekly injection, is a promising finding given that a high proportion of patients with diabetes are overweight/obese and many other treatments are either weight-neutral or associated with weight gain accompanied by hypoglycaemia and/or the need to be injected daily.[2,23]

No new safety issues were identified for semaglutide, and its safety profile seems comparable to that of other GLP-1RAs. As expected for a therapy with a glucose-dependent mechanism of action, hypoglycaemia incidence in the semaglutide arms was lower than in the insulin glargine group, consistent with previous findings both for once-daily[15] and once-weekly[24] GLP-1RAs. Furthermore, the majority of hypoglycaemic events observed were

reported in subjects receiving sulphonylureas in addition to metformin, indicating that the background therapy has contributed to these events.[4]

A comparable proportion of subjects reported SAEs across all three treatment groups. As was previously observed with other GLP-1RAs, the main GI side effects reported in the semaglutide groups were nausea and diarrhoea. As has been observed with other GLP-1RAs, GI AE profiles with semaglutide were higher than with insulin glargine, and their frequency diminished over time, as has been seen with liraglutide.[15,25] Premature treatment discontinuation was more frequent with semaglutide, driven primarily by these GI events. Dose escalation has been shown to partially ameliorate such AEs.[6,9,11] Rates of diarrhoea in the current trial were higher than have been previously reported for liraglutide[25] or exenatide.[16] There was also an increase in heart rate in the semaglutide arms and a reduction in systolic BP, consistent with previous trials of other long-acting GLP-1RAs.[6] Both liraglutide (LEADER trial) and semaglutide (SUSTAIN 6 trial) have recently been shown to reduce cardiovascular risk.[26,27] One potential mechanism may relate to modification of the progression of atherosclerosis; the contribution of cardiovascular risk factors to this outcome requires further research.[26,27]

The rate of pancreatitis in the trial was low, with two events being reported. Although acute pancreatitis has been reported following treatment with GLP-1RAs, a causal link has not been demonstrated.[28] Lipase and amylase levels increased with semaglutide, with a similar magnitude compared with other GLP-1RAs.[29] In the SUSTAIN 6 trial, no elevated rates of acute pancreatitis with semaglutide compared with placebo were seen despite higher lipase and amylase levels.[27] The rate of cholelithiasis in the current trial was also low, with only three cases reported.

The trial population was heterogeneous, encompassing a broad range in terms of age, duration of diabetes and level of HbA_{1c} control at baseline. The population was also ethnically diverse compared with other phase 3a programmes in T2D (77% of subjects were White, 11% Asian and 9% Black or African American).

The limitations of this trial included the open-label design, which was due to the different dosing frequency and titration of glargine compared with semaglutide. This should be especially considered when interpreting endpoints that are prone to subjectivity, such as GI AEs and the PROs, in quality of life in the current trial, although the reduced frequency of dosing with semaglutide may improve both adherence and quality of life compared with once-daily treatments and is perceived to do so by patients.[6,7] The trial duration was short,

limiting the conclusions that can be drawn regarding the long-term efficacy and tolerability of semaglutide compared with insulin glargine. In addition, real-world patient populations may be expected to have received multiple oral antidiabetic therapies before being considered for insulin treatment. Research in populations with longer baseline diabetes duration and a longer history of treatment may therefore be of relevance.

Another limitation of the current trial was the extent to which insulin glargine was titrated. All insulin adjustments were at the discretion of the investigators and were not reinforced by a titration committee. The mean pre-breakfast fasting SMPG at week 30 (7·1 mmol/L) suggests that a more rigorous titration could have been enforced, but that may possibly have come at the expense of more hypoglycaemia and body weight gain. Many patients may have found it challenging to achieve an SMPG level below 5.5 mmol/l. The overall mean insulin dose reported here was in line with that reported in trials comparing other weekly GLP-1RAs and insulin glargine,[17,22] and the insulin dose at the end of the trial (29·2 IU/day at 30 weeks) appears to be consistent with clinical practice. It is possible that more frequent titrations or discontinuations of sulphonylureas would have allowed more aggressive insulin titration.

In summary, semaglutide was associated with superior glycaemic control and reduced body weight, with low hypoglycaemia rates, compared with insulin glargine in patients with T2D receiving metformin with or without sulphonylureas. However, it should be noted that insulin glargine did not achieve titration targets, reflecting a potential limitation of titration often observed in clinical practice. No unexpected safety issues were identified and semaglutide showed a similar safety profile to that of other GLP-1RAs. Combined with its cardiovascular risk reduction effect recently noted in the SUSTAIN 6 trial, semaglutide appears to be an effective once-weekly therapeutic option for patients with T2D who are unable to achieve glycaemic control on metformin with or without sulphonylureas.

Authors' contributions

VRA JHD and MA participated in the trial design. VRA, SCB, BC, MP, LR and JHD took part in the conduct of the trial and the data collection. MA and ER took part in the data analysis. All authors interpreted the data and participated in writing the manuscript together with medical writing services provided by the sponsor. All the authors have read the manuscript critically and approved the submitted version.

Conflicts of interest

In conducting this study, SCB has received personal fees from Novo Nordisk. VA, SCB, BC, MP, LR and JHD have previously received honoraria and VA, SCB (to his institution) and JHD have previously received research grants from Novo Nordisk. VA has previously received honoraria from Adocia, the American Diabetes Association, AstraZeneca, Janssen, Medscape, Sanofi and Tufts, and reseatch grants from AztraZeneca/Bristol-Myers Squibb, Calibra, Eisai, Elcelyx, Janssen, Sanofi and Theracos (all paid to her institution). SCB has previously received honoraria and research grants (paid to his institution) from Boehringer Ingerheim, Cellnovo, Eli Lilly, Jensen, MSD and Sanofi. BC has previously received honoraria from Amgen, AstraZeneca, Eli Lilly, Sanofi-Regeneron, Novartis and Merck, and research grants from Pfizer, Sanofi and Sanofi-Regeneron. MP has previously received honoraria from Eli Lilly. LR has previously received honoraria from AstraZeneca and Eli Lilly. MA is full-time employee of, and owns stock in, Novo Nordisk A/S, and ER has been a full-time employee of Novo Nordisk Inc. JHD has previously received honoraria from GlaxoSmithKline and MSD, and funding from Eli Lilly (to his institution).

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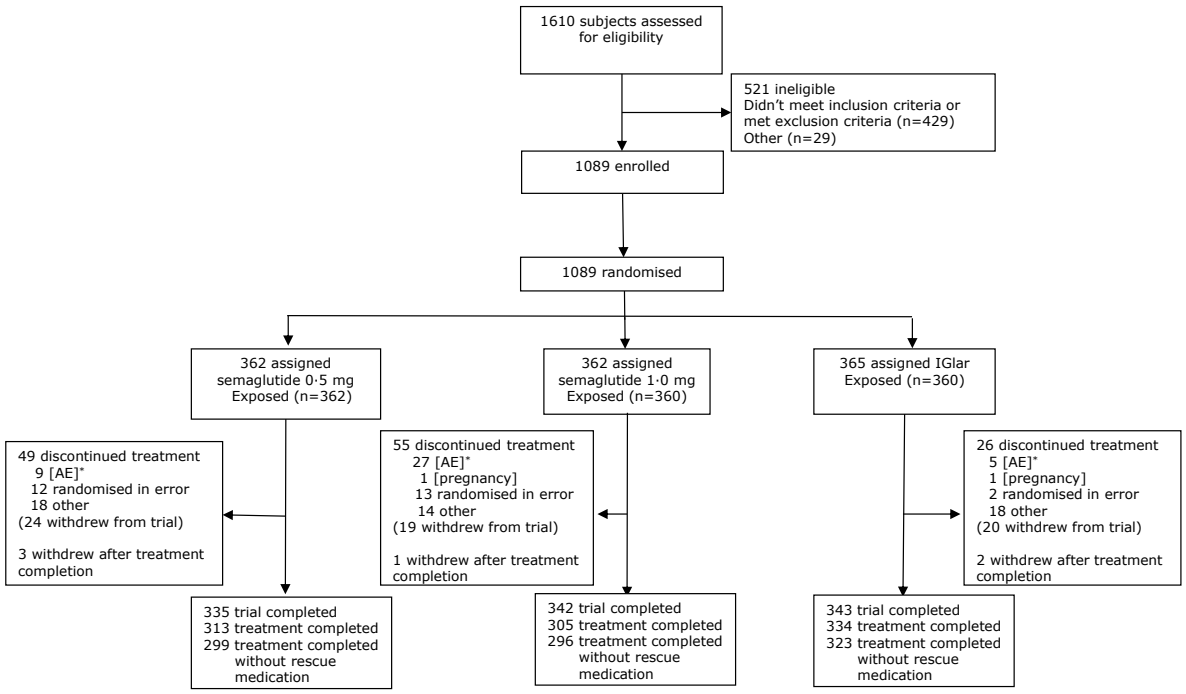
Figures

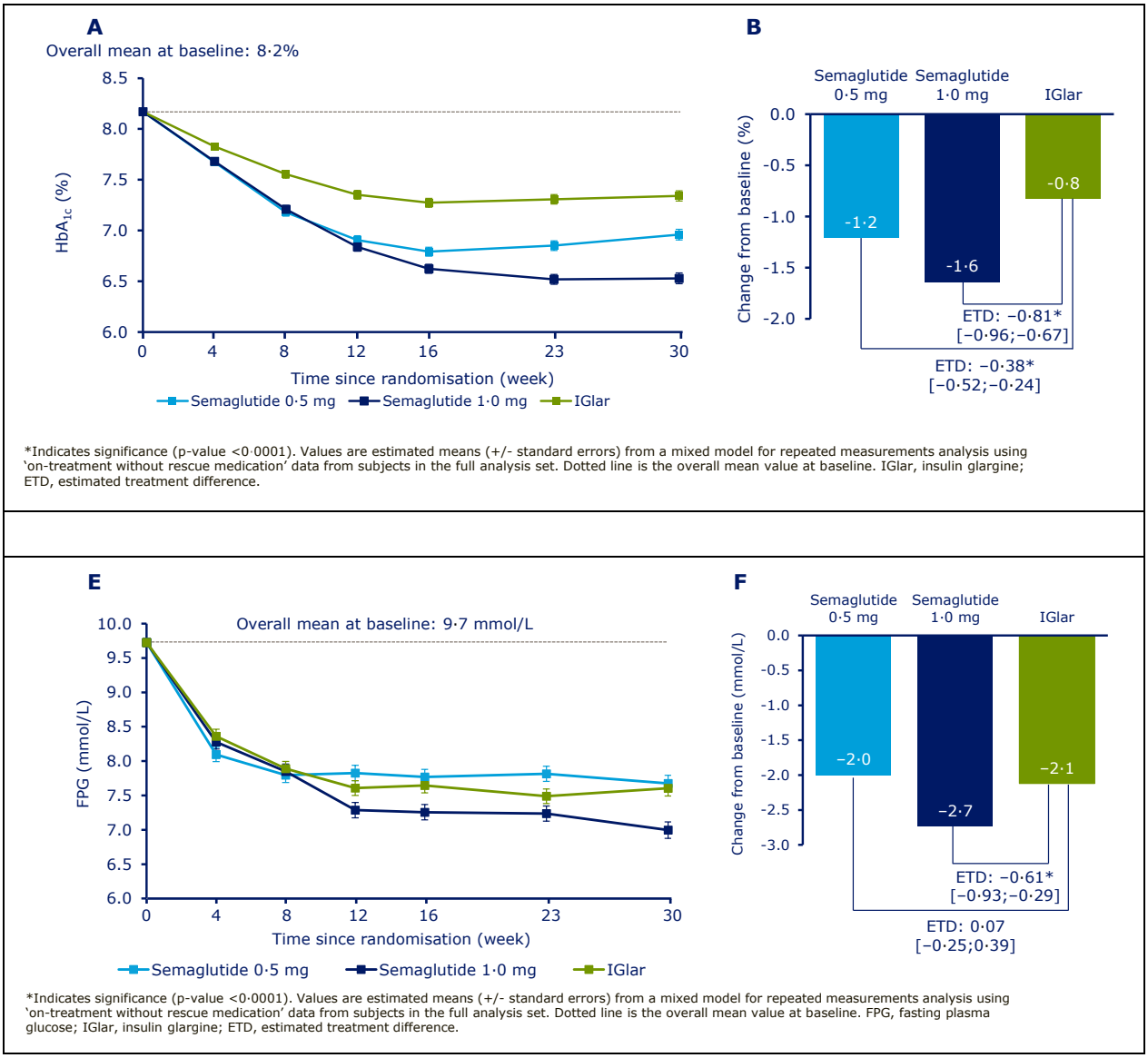
Figure 1. Participant flow



Subjects completing the trial are defined as those with a follow-up visit. Reasons for subjects not exposed to treatment were withdrawal by the subject or loss to follow-up

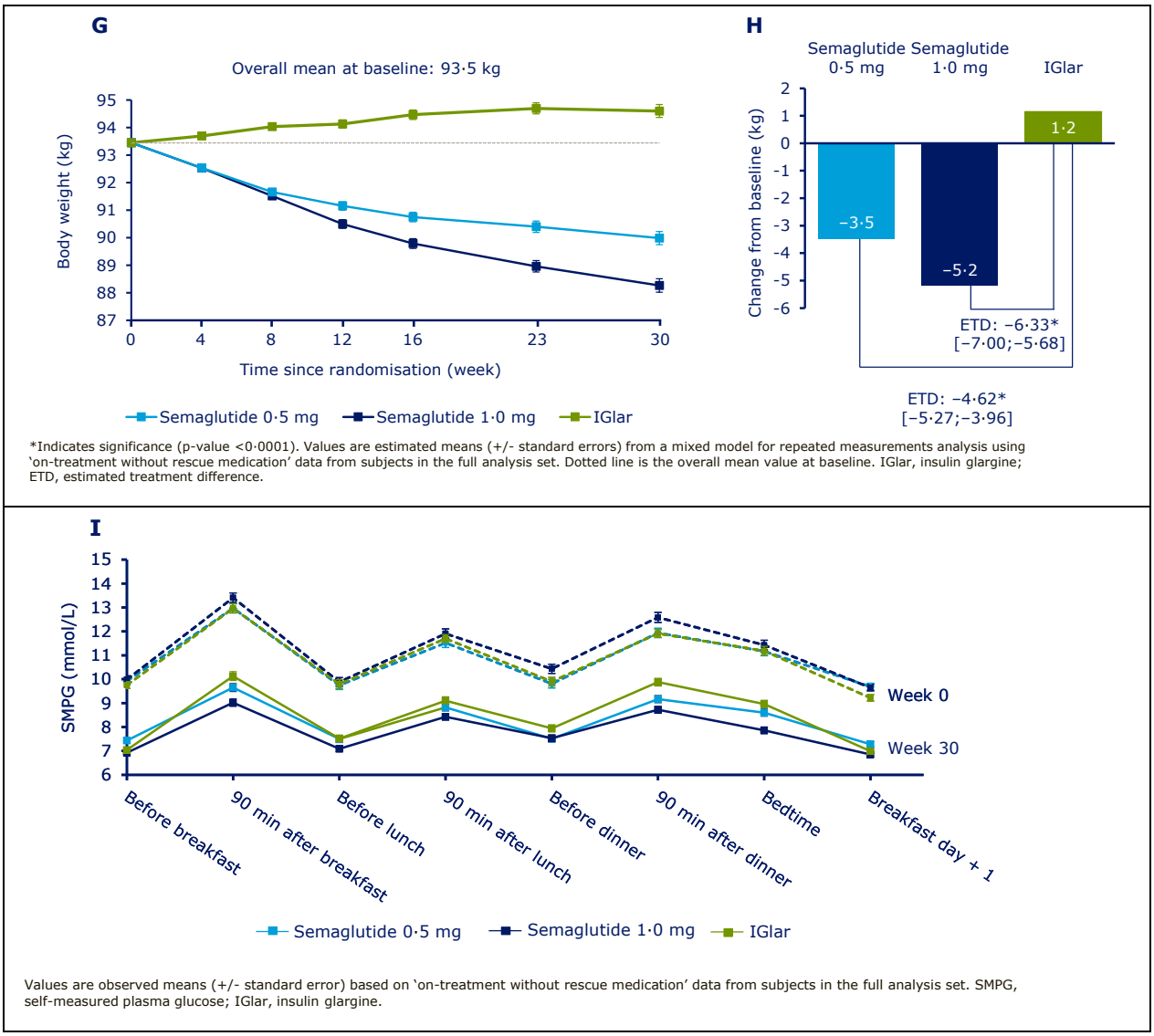
**Reflects primary reason for treatment discontinuation, as judged by the investigator*

Figure 2. Semaglutide 0·5 mg and 1·0 mg once weekly, compared with insulin glargine: change in mean HbA_{1c} by week (A), mean HbA_{1c} after 30 weeks (B), overall mean fasting plasma glucose over time (C), mean fasting plasma glucose after 30 weeks (D), change in mean body weight by week (E), mean body weight after 30 weeks (F) and mean 8-point SMPG profile at baseline and week 30 (G)



*Indicates significance (p-value <0·0001). Values are estimated means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline. IGlar, insulin glargine; ETD, estimated treatment difference.

*Indicates significance (p-value <0·0001). Values are estimated means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline. FPG, fasting plasma glucose; IGlar, insulin glargine; ETD, estimated treatment difference.

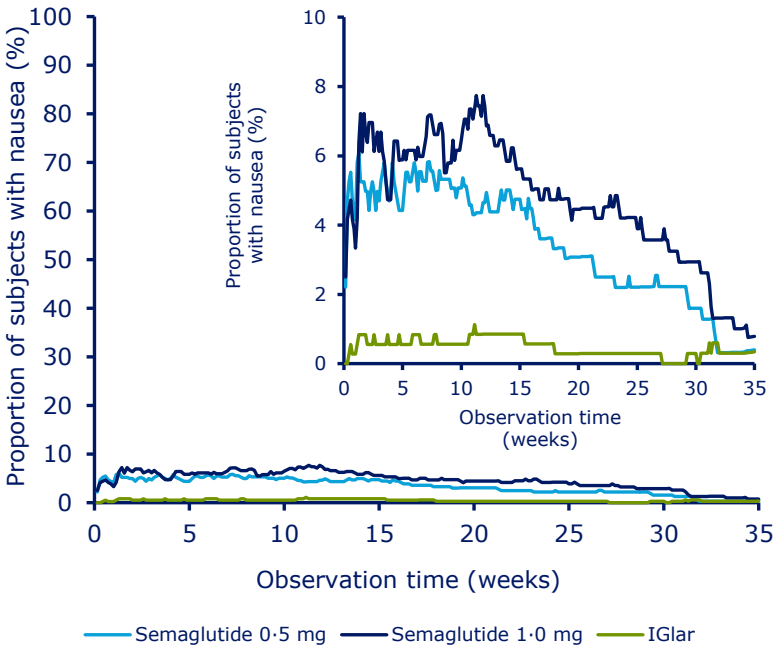


*Indicates significance (p-value <0·0001). Values are estimated means (+/- standard errors) from a mixed model for repeated measurements analysis using 'on-treatment without rescue medication' data from subjects in the full analysis set. Dotted line is the overall mean value at baseline. IGlar, insulin glargine; ETD, estimated treatment difference.

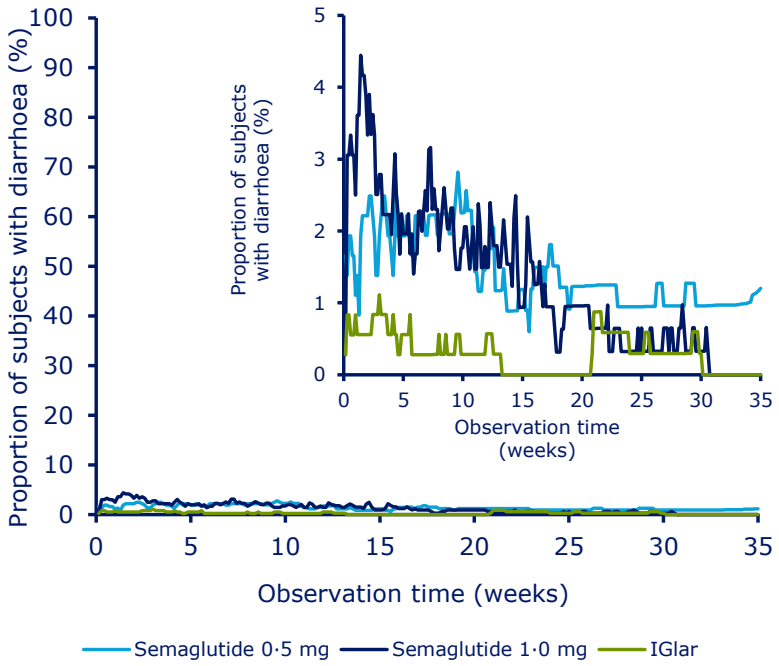
Values are observed means (+/- standard error) based on 'on-treatment without rescue medication' data from subjects in the full analysis set. SMPG, self-measured plasma glucose; IGlar, insulin glargine.

Figure 3. Time course of nausea (A) and diarrhoea (B)

A



B



Treatment-emergent AEs by week. IGlar, insulin glargine.

Table 1. Baseline characteristics of trial populations

	Semaglutide 0·5 mg N=362	**Semaglutide 1·0 mg** N=360	**Insulin glargine** N=360
Age* years, mean (SD)	56·5 (10·3)	56·7 (10·4)	56·2 (10·6)
Sex, n (%)			
Female	165 (45·6)	178 (49·4)	165 (45·8)
Male	197 (54·4)	182 (50·6)	195 (54·2)
HbA_{1c},* %, mean (SD)	8·1 (0·85)	8·3 (0·94)	8·1 (0·88)
HbA_{1c},* mmol/mol, mean (SD)	65·4 (9·28)	66·6 (10·30)	65·4 (9·58)
Diabetes duration,* years, mean (SD)	7·8 (5·14)	9·3 (7·17)	8·6 (6·29)
Body weight,* mean, kg (SD)	93·7 (21·39)	94·0 (22·48)	92·6 (21·52)
BMI,* kg/m^2, mean (SD)	33·1 (6·45)	33·0 (6·51)	33·0 (6·51)
eGFR (MDRD),* mL/min/1·73 m^2, mean (SD)	97·9 (25·94)	98·0 (27·55)	99·7 (26·46)

Oral antidiabetes treatment, n (%)[†]			
Metformin monotherapy	176 (48·6)	175 (48·6)	172 (47·8)
Metformin + SU	186 (51·4)	185 (51·4)	188 (52·2)
Ethnicity, n(%)			
Hispanic or Latino	61 (16·9)	74 (20·6)	78 (21·7)
Not Hispanic or Latino	301 (83·1)	286 (79·4)	281 (78·1)
NA[‡]	0	0	1 (0·3)
Race, n(%)			
American Indian or Alaska Native	1 (0·3)	0 (0·0)	1 (0·3)
Asian	42 (11·6)	39 (10·8)	38 (10·6)
Black or African American	32 (8·8)	34 (9·4)	33 (9·2)
White	279 (77·1)	279 (77·5)	276 (76·7)
Other	3 (0·8)	3 (0·8)	5 (1·4)
NA[‡]	5 (1·4)	5 (1·4)	7 (1·9)

*Values are means; [†]Metformin doses ≥1500 mg or maximum tolerated dose were allowed. SU doses ≥half of maximum dose allowed according to natio
site chose not to report ethnicity, and race was not collected in France sites (all counted as NA). BMI, body mass index; eGFR, estimated glomerular filtra
of Diet in Renal Disease; SD, standard deviation; SU, sulphonylurea

Table 2. Primary and selected secondary endpoints by treatment group

	Overall baseline, mean [SD]	**Semaglutide 0·5 mg**			**Semaglutide 1·0 mg**	
		Change from baseline at Week 30 Mean [SE]	ETD [95% CI]	p	Change from baseline at Week 30 Mean [SE]	ETD [95% CI]
Glycaemia endpoints						
HbA_{1c} (%)	8·2 [0·89]	−1·2 [0·05]	−0·38 [−0·52; −0·24]	<0·0001	−1·6 [0·05]	−0·81 [−0·96; −0·67]
HbA_{1c} (mmol/mol)	65·8 [9·74]	−13·2 [0·57]	−4·16 [−5·72; −2·60]	<0·0001	−17·9 [0·58]	−8·87 [−10·45; −7·30]
FPG (mmol/L)	9·7 [2·84]	−2·0 [0·12]	0·08 [−0·24; 0·40]	0·6243	−2·7 [0·12]	−0·61 [−0·93; −0·29]
8-point SMPG (mmol/L)						
Mean	10·9 [2·54]	−2·4 [0·10]	−0·04 [−0·30; 0·23]	0·7816	−2·9 [0·10]	−0·57 [-0·83; -0·31]

Increment	2·4 [1·95]	−0·6 [0·09]	−0·39 [−0·65; −0·13]	0·0029	−0·9 [0·10]	−0·65 [−0·91; −0·39]
Body weight endpoints						
Body weight (kg)	93·5 [21·79]	−3·5 [0·24]	−4·62 [−5·27; −3·96]	<0·0001	−5·2 [0·24]	−6·33 [−6·99; −5·67]
BMI (kg/m^2)	33·0 [6·49]	−1·2 [0·08]	−1·66 [−1·89; −1·43]	<0·0001	−1·9 [0·09]	−2·27 [−2·51; −2·04]
Waist circumference (cm)	109·2 [15·16]	−3·2 [0·30]	−3·42 [−4·24; −2·59]	<0·0001	−4·5 [0·31]	−4·76 [−5·59; −3·93]
Blood pressure and pulse rate						
DBP (mmHg)	79·9 [8·53]	−1·4 [0·43]	0·06 [−1·12; 1·24]	0·9183	−1·0 [0·44]	0·45 [−0·74; 1·64]
SBP (mmHg)	132·1 [15·31]	−4·6 [0·72]	−2·97 [−4·92; −1·03]	0·0028	−5·2 [0·73]	−3·50 [−5·46; −1·54]
Pulse rate (bpm)	74.5 [10.22]	2.3 [0.47]	2.36 [1.07; 3.65]	0.0004	3.1 [0.48]	3.19 [1.88; 4.50]

Treatment targets					
		Semaglutide 0·5 mg			**Semaglutide 1·0 mg**
	Subjects achieving target, n (%)	OR [95% CI]	p	Subjects achieving target, n (%)	OR [95% CI]
Proportion achieving HbA_{1c} targets					
<7·0% (<53 mmol/mol)	208 (57·5)	2·39 [1·73; 3·28]	<0·0001	264 (73·3)	5·78 [4·08; 8·19]
≤6·5% (≤48 mmol/mol)	135 (37·3)	3·02 [2·11; 4·33]	<0·0001	195 (54·2)	6·86 [4·76; 9·89]
Proportion achieving body weight reduction					
≥5%	134 (37·0)	13·37 [7·71; 23·20]	<0·0001	183 (50·8)	23·94 [13·80; 41·50]
≥10%	28 (7·5)	6·35 [2·42; 16·69]	0·0002	57 (15·8)	14·51 [5·70; 36·92]
Proportion achieving HbA_{1c} <7·0% without severe or BG–confirmed hypoglycaemia and without weight gain	169 (46·7)	5·39 [3·72; 7·81]	<0·0001	231 (64·2)	12·88 [8·73; 19·02]

Odds ratios are calculated from logistic regression models adjusted for treatment, country, stratification and baseline HbA1c. * baseline is for the entire t
body weight data imputed by MMRM; p-value is for a two-sided test of the null hypothesis that there is no difference. BMI, body mass index; BP, blood p
interval; FPG, fasting plasma glucose; SE, standard error; SMPG, self-monitored plasma glucose

Table 3. Adverse events overview

	Semaglutide 0·5 mg			Semaglutide 1·0 mg			
	N	(%)	E	N	(%)	E	N
Number of subjects	**362**	-	-	**360**	-	-	**360**
Serious adverse events	**22**	**6·1**	**31**	**17**	**4·7**	**23**	**18**
Fatal	**4**	**1·1**	**4**	**0**	**-**	**-**	**2**
Any adverse events	**253**	**69·9**	**1026**	**264**	**73·3**	**1151**	**235**
Severe	27	7·5	48	20	5·6	33	10
Moderate	108	29·8	201	110	30·6	233	104
Mild	221	61·0	777	230	63·9	885	193
GI adverse events	**149**	**41.2**	**345**	**156**	**43.3**	**525**	**54**
Severe	7	1·9	10	6	1·7	11	2
Moderate	36	9·9	49	51	14·2	90	15
Mild	132	36·5	286	137	38·1	424	44
Adverse events leading to premature treatment discontinuation	**20**	**5·5**	**29**	**27**	**7·5**	**45**	**4**
All GI adverse events	11	3·0	15	19	5·3	31	0
Nausea	3	0·8	3	7	1·9	7	0
Vomiting	3	0·8	3	7	1·9	7	0
Diarrhoea	1	0·3	1	9	2·5	9	0
Adverse events by preferred term (≥5% of subjects)							
Nausea	77	21·3	101	80	22·2	117	13

Diarrhoea	59	16·3	67	69	19·2	118	16
Nasopharyngitis	45	12·4	58	29	8·1	37	44
Lipase increased	36	9·9	39	30	8·3	32	15
Decreased appetite	25	6·9	34	23	6·4	23	1
Vomiting	24	6·6	28	37	10·3	119	11
Headache	19	5·2	40	23	6·4	33	20
Dyspepsia	12	3·3	24	24	6·7	39	2
Back pain	11	3	11	18	5	20	7
Upper respiratory tract infection	10	2·8	10	14	3·9	16	24
Gastro-oesophageal reflux disease	4	1·1	4	19	5·3	20	3
Other adverse events							
Pancreatitis	2	0·6	2	0	-	-	0
Cholelithiasis	1	0·3	1	2	0·6	2	0
Cardiovascular	3	0.8	3	3	0.8	4	4
Malignant neoplasms	4	1·1	4	0	-	-	1
Skin	1	0·3	1	0	-	-	1
Naso-pharyngeal	1	0·3	1	0	-	-	
Pancreatic	1	0·3	1	0	-	0	0
Renal/adrenal	1	0·3	1	0	-	-	0
Benign neoplasms	5	1·4	5	2	0·6	4	3

Summary of treatment-emergent AEs includes events that are collected from first exposure to the follow-up visit scheduled 5 weeks (+1 week visit wind
dose. E, number of events; N, number of subjects.. The 5% is calculated based on the total number of subjects in the safety analysis set

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