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Original article

# Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10)

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## ABSTRACT

**Aims.** – SUSTAIN 10 compared the efficacy and safety of the anticipated most frequent semaglutide dose (1.0 mg) with the current most frequently prescribed liraglutide dose in Europe (1.2 mg), reflecting clinical practice.

**Methods.** – In this phase 3b, open-label trial, 577 adults with type 2 diabetes (HbA<sub>1c</sub> 7.0–11.0%) on 1–3 oral antidiabetic drugs were randomized 1:1 to subcutaneous once-weekly semaglutide 1.0 mg or subcutaneous once-daily liraglutide 1.2 mg. Primary and confirmatory secondary endpoints were changes in HbA<sub>1c</sub> and body weight from baseline to week 30, respectively.

**Results.** – Mean HbA<sub>1c</sub> (baseline 8.2%) decreased by 1.7% with semaglutide and 1.0% with liraglutide (estimated treatment difference [ETD] –0.69%; 95% confidence interval [CI] –0.82 to –0.56,  $P < 0.0001$ ). Mean body weight (baseline 96.9 kg) decreased by 5.8 kg with semaglutide and 1.9 kg with liraglutide (ETD –3.83 kg; 95% CI –4.57 to –3.09,  $P < 0.0001$ ). The proportions of subjects achieving glycaemic targets of  $< 7.0\%$  and  $\leq 6.5\%$ , weight loss of  $\geq 5\%$  and  $\geq 10\%$ , and a composite endpoint of HbA<sub>1c</sub>  $< 7.0\%$  without severe or blood glucose-confirmed symptomatic hypoglycaemia and no weight gain were greater with semaglutide vs liraglutide (all  $P < 0.0001$ ). Both treatments had similar safety profiles, except for more frequent gastrointestinal disorders (the most common adverse events [AEs]) and AEs leading to premature treatment discontinuation with semaglutide vs liraglutide (43.9% vs 38.3% and 11.4% vs 6.6%, respectively).

**Conclusion.** – Semaglutide was superior to liraglutide in reducing HbA<sub>1c</sub> and body weight. Safety profiles were generally similar, except for higher rates of gastrointestinal AEs with semaglutide vs liraglutide.

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**Abbreviations:** AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; BMI, body mass index; bpm, beats per minute; CI, confidence interval; CKD-EPI, The Chronic Kidney Disease Epidemiology Collaboration; CoV, coefficient of variation; CV, cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; DTSQs, Diabetes Treatment Satisfaction Questionnaire status version; E, number of events; EASD, European Association for the Study of Diabetes; eGFR, estimated glomerular filtration rate; exenatide ER, exenatide extended release; ETD, estimated treatment difference; ETR, estimated treatment ratio; FAS, full analysis set; FPG, fasting plasma glucose; GI, gastrointestinal; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; KDIGO, Kidney Disease Improving Global Outcomes; max., maximum; MedDRA, Medical Dictionary for Regulatory Activities; MET, metformin; min., minimum; MTD, maximum tolerated dose; n, number of subjects; N, total number of subjects; OAD, oral antidiabetic drug; OD, once daily; OR, odds ratio; OW, once weekly; PRO, patient-reported outcome; R, event rate per 100 exposure-years; SAS, safety analysis set; s.c., subcutaneous; SD, standard deviation; SE, standard error; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; SF-36v2<sup>®</sup>, Short-Form 36 Health Survey version 2<sup>®</sup>; SMBG, self-measured blood glucose; SU, sulfonylurea; SUSTAIN, Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes; TEAE, treatment-emergent adverse event; T2D, type 2 diabetes.

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## Introduction

There are currently a variety of treatment options for type 2 diabetes (T2D); despite this, a large proportion of subjects do not achieve HbA<sub>1c</sub> treatment targets [1]. Furthermore, optimal treatment of T2D should involve patient-oriented treatment goals extending beyond glycaemic control, to include minimizing unwanted effects like weight gain and hypoglycaemia, and reducing the risk of complications such as cardiovascular (CV) events [2,3].

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have emerged as effective treatments for T2D and are incorporated into the clinical guidelines [2,3]. The 2018 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) consensus report and the 2019 ADA Standards of Care treatment guidelines recommend preferred treatments, following metformin (MET), as either GLP-1RAs or sodium–glucose cotransporter-2 inhibitors (SGLT-2is), particularly in adults with T2D and additional CV risk factors (e.g. GLP-1RAs or SGLT-2is for established atherosclerotic disease or SGLT-2is for chronic kidney disease or heart failure) [2,3]. In addition to improving glycaemic control, some drugs in the GLP-1RA class also provide weight loss, have CV benefits, improve renal outcomes, and minimize hypoglycaemic risk [2–7]. Several GLP-1RAs are currently available, both short- and long-acting, as once-daily (OD) or once-weekly (OW) injections [8], with different molecular sizes and structures that result in varying efficacy and safety profiles [9,10].

Semaglutide (Novo Nordisk A/S) is a long-acting glucagon-like peptide-1 (GLP-1) analog, approved for the treatment of T2D in a subcutaneous (s.c.), OW formulation [11,12]. The efficacy and safety of semaglutide OW has been investigated in the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) phase 3 clinical trial program across the continuum of care in subjects with T2D. In the SUSTAIN trials semaglutide consistently demonstrated superior reductions in HbA<sub>1c</sub> and body weight vs placebo and a range of active comparators, including other GLP-1RAs (exenatide extended release [ER] and dulaglutide) and basal insulin glargine, with a safety profile similar to that of other GLP-1RAs [4,13–18]. Furthermore, and in line with findings with the GLP-1 analog liraglutide in the LEADER trial [5], the SUSTAIN 6 trial demonstrated that semaglutide significantly reduced the risk of major adverse CV events, compared with placebo, in subjects with T2D and high CV risk [4].

The aim of the SUSTAIN 10 trial (NCT03191396) was to compare the efficacy and safety of OW semaglutide 1.0 mg with OD liraglutide 1.2 mg in adults with T2D. These doses were chosen to reflect clinical practice regarding use of GLP-1RAs in Europe: OW semaglutide 1.0 mg is expected to be the most frequently prescribed dose, whereas OD liraglutide 1.2 mg is currently the most frequently prescribed dose [19].

## Methods

### Trial design

SUSTAIN 10 was a 30-week, randomized, multicentre, multinational, active-controlled, parallel-group, open-label, two-armed phase 3b trial conducted in 11 European countries (Bulgaria, Czech Republic, Finland, France, Hungary, Italy, Poland, Slovenia, Spain, Sweden, United Kingdom). The trial design is shown in Figure S1 (see supplementary materials associated with this article on line) and a full list of trial investigators is shown in Table S1 (see supplementary materials associated with this article on line). The trial was conducted in compliance with the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical

Practice guidelines [20], and the Declaration of Helsinki [21]. Subjects provided consent before the commencement of any trial-related activities. The protocol is available in the Appendix (see supplementary materials associated with this article on line).

### Participants

Key inclusion criteria were age  $\geq 18$  years; T2D with HbA<sub>1c</sub> 7.0–11.0%; and stable daily doses of any of the following antidiabetic drug(s) or combination regimens 90 days prior to screening: biguanides (MET  $\geq 1500$  mg or maximum tolerated dose [MTD]), sulfonylurea (SU) or SGLT-2i (for both SU and SGLT-2i:  $\geq 0.5$  maximum approved dose according to local label or MTD as documented in subject medical record). Key exclusion criteria were renal impairment, measured as estimated glomerular filtration rate (eGFR)  $< 30$  mL/min/1.73 m<sup>2</sup>; presence of New York Heart Association Class IV heart failure; proliferative retinopathy or maculopathy requiring acute treatment, verified by fundus photography or dilated funduscopy within the 90 days prior to randomization; impaired liver function (alanine aminotransferase  $\geq 2.5$  times upper limit of normal at screening); and presence or history of malignant neoplasms within the past 5 years prior to screening. Full trial eligibility criteria are listed in Table S2 (see supplementary materials associated with this article on line).

### Randomization

Subjects with T2D inadequately controlled on 1–3 oral antidiabetic drug(s) (OADs) were randomized 1:1 to treatment with either s.c. OW semaglutide 1.0 mg or s.c. OD liraglutide 1.2 mg (both supplied by Novo Nordisk A/S, Bagsværd, Denmark). Subjects were stratified based on background medication of SU and SGLT2-i (SU  $\pm$  MET; SGLT-2i  $\pm$  MET; SU and SGLT-2i  $\pm$  MET; MET monotherapy).

### Treatments

Following a 2-week screening period, the treatment period was 30 weeks, with a 5-week safety data collection follow-up to accommodate for the long half-life of semaglutide. After randomization, all subjects followed a dose-escalation regimen. The semaglutide maintenance dose was reached after an 8-week escalation period consisting of 4 weeks of 0.25 mg OW, followed by 4 weeks of 0.5 mg OW. The liraglutide maintenance dose was reached after 1 week of 0.6 mg OD. In the event of unacceptable gastrointestinal (GI) adverse events (AEs) with liraglutide, escalation from 0.6 mg to 1.2 mg could be extended over 2 weeks at the discretion of the investigator. Both medications were administered by injections to the thigh, abdomen, or upper arm, at any time of day and irrespective of meals. Semaglutide injections were administered OW preferably on the same day, while liraglutide injections were administered OD at the same time every day. Subjects were intended to continue on stable, pre-trial background medication dose(s) throughout treatment, unless rescue criteria were met or a safety concern relating to the background medication arose.

Rescue medication (intensification of antidiabetic background medication and/or initiation of new antidiabetic medication) was offered if subjects experienced persistent and unacceptable hyperglycaemia (fasting plasma glucose [FPG] levels  $\geq 13.3$  mmol/L from week 8 to the end of week 15, or  $\geq 11.1$  mmol/L from week 16 to the end of treatment). Rescue medication was prescribed at the investigators' discretion according to ADA/EASD 2012 and 2015 guidelines [22,23]; GLP-1RAs, dipeptidyl peptidase-4 inhibitors (DPP-4is), and amylin analogs were not permitted.

## Endpoints

The primary endpoint was change in HbA<sub>1c</sub> (%-point, hereafter referred to as '%') from baseline to week 30. The confirmatory secondary endpoint was change in body weight (kg) from baseline to week 30. Other pre-specified supportive secondary efficacy endpoints included changes from baseline to week 30 in: FPG; mean postprandial increment across all meals and mean 7-point profile based on self-measured blood glucose (SMBG); fasting blood lipids (total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, and triglycerides); body mass index (BMI); waist circumference; and systolic and diastolic blood pressure.

Pre-specified clinical treatment targets included subjects who, after 30 weeks of treatment, achieved HbA<sub>1c</sub> < 7.0% (ADA) [24] or ≤ 6.5% (American Association of Clinical Endocrinologists) [25]. In addition, the proportions of subjects achieving HbA<sub>1c</sub> reduction ≥ 1%; weight loss ≥ 3%, ≥ 5%, or ≥ 10%; a composite endpoint of HbA<sub>1c</sub> < 7.0% without severe (ADA classification) [26] or blood glucose (BG)-confirmed symptomatic hypoglycaemic episodes and no weight gain; and composite endpoints of HbA<sub>1c</sub> reduction of ≥ 1% and weight loss of ≥ 3%, ≥ 5%, or ≥ 10%. Supportive secondary endpoints for patient-reported outcomes (PROs) included changes from baseline to week 30 in Short-Form 36 Health Survey version 2<sup>®</sup> (SF-36v2<sup>®</sup>) and Diabetes Treatment Satisfaction Questionnaire status version (DTSQs) scores [27,28].

Safety endpoints included the number of treatment-emergent adverse events (TEAEs, classified as events that had an onset date, or increase in severity, during the 'on-treatment' observation period) and the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycaemic episodes. Other safety endpoints included change from baseline to week 30 in haematology, biochemistry, calcitonin, pulse rate, electrocardiogram category, physical examination category, and eye examination category. All AEs were coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA).

## Statistical analysis

The primary estimand was defined as the treatment difference between semaglutide and liraglutide at week 30 for all randomized subjects if all subjects completed treatment and did not initiate rescue medication. This estimand was considered clinically relevant as it assessed the glycaemic benefit a subject with T2D was expected to achieve if they initiated and continued treatment with semaglutide vs liraglutide.

Efficacy endpoints were evaluated based on the full analysis set (FAS, which included all randomized subjects) from the 'on-treatment without rescue medication' observation period; safety endpoints were analyzed using the safety analysis set (SAS, which included data from all subjects exposed to at least one dose of trial product) from the 'on-treatment' or 'in-trial' observation periods. See Table S3 and protocol (see supplementary materials associated with this article on line) for the definitions of the observation periods.

Three confirmatory hypotheses were tested using the following hierarchical testing procedure [29]:

- 1 HbA<sub>1c</sub> non-inferiority of semaglutide 1.0 mg vs liraglutide 1.2 mg (non-inferiority margin of 0.3);
- 2 Body weight superiority of semaglutide 1.0 mg vs liraglutide 1.2 mg;
- 3 HbA<sub>1c</sub> superiority of semaglutide 1.0 mg vs liraglutide 1.2 mg [Figure S2 (see supplementary materials associated with this article on line)].

The Type-I error rate for testing the three confirmatory hypotheses relating to HbA<sub>1c</sub> and body weight was preserved at an overall one-sided alpha ( $\alpha$ ) level of 2.5%. A sample size of 288 subjects was needed in each of the semaglutide and liraglutide groups (total planned randomized: 576 subjects), to provide at least 90% power to reject all three confirmatory hypotheses and, thus, confirm HbA<sub>1c</sub> superiority and body weight superiority of semaglutide vs liraglutide across efficacy and in-trial assumptions.

The primary analysis addressed the primary estimand, which was based on the FAS using measurements up to and including week 30 from the 'on-treatment without rescue medication' observation period.

In the primary analysis, imputation of missing data was handled using multiple imputation assuming that missing data were missing at random. Missing data were imputed as intermittent values using a Markov Chain Monte Carlo method to obtain a monotone missing data pattern. This imputation was done for each treatment group separately and 500 copies of the dataset were generated. A sequential regression approach for imputing monotonely missing values at planned visits was implemented starting with the first visit after baseline and sequentially continued to the last planned visit (week 30). A linear model was applied to each treatment group. This model used the background medication stratification factor (SU ± MET, SGLT-2i ± MET, SU and SGLT-2i ± MET, and MET monotherapy) as a categorical effect, and baseline and post-baseline HbA<sub>1c</sub> values (observed and imputed) prior to the visit in question as covariates. An analysis of covariance with treatment and background medication stratification factor as categorical effects and baseline HbA<sub>1c</sub> as a covariate were used to analyze HbA<sub>1c</sub> at week 30 for each of the 500 data sets generated as part of the imputation of missing values. Rubin's rule was used to combine the analysis results in order to draw inference. Sensitivity analyses (tipping-point, retrieved drop-out [superiority only], and per-protocol [non-inferiority only] analyses) were conducted on the primary analysis, see Table S3 (see supplementary materials associated with this article on line) for details.

The secondary confirmatory endpoint of change from baseline to week 30 in body weight was analyzed in the same way as the primary endpoint, but using baseline and post-baseline body weight measurements as covariates (instead of HbA<sub>1c</sub>). Sensitivity analyses (tipping-point and retrieved drop-out analyses) were also conducted on the secondary confirmatory endpoint, see Table S3 (see supplementary materials associated with this article on line) for details.

Continuous endpoints were analyzed separately using a similar model approach as for the primary endpoint, with associated baseline values as covariates (instead of HbA<sub>1c</sub>). The binary endpoints were analyzed using a logistic regression model with treatment and stratification factor as fixed factors and baseline values as covariates. Before analysis, missing data for individual components were imputed separately using the same approach as for continuous endpoints and subsequently dichotomized. The PRO questionnaires (SF-36v2<sup>®</sup> and DTSQs) were used to evaluate quality of life and treatment satisfaction; see Table S3 (see supplementary materials associated with this article on line) for further details on the PRO questionnaires.

Safety outcomes were summarized descriptively based on the SAS using data from the 'on-treatment' observation period, except neoplasms and diabetic retinopathy, which were reported using data from the 'in-trial' observation period. Summaries of treatment-emergent hypoglycaemic episodes were presented as an overview, including all episodes and episodes by severity.



## Results

Between June and November 2017, 767 subjects were screened, of whom 577 were randomized and 576 were exposed to treatment (Fig. 1). Of the FAS, a total of 287 (99.0%) subjects in the OW semaglutide 1.0 mg arm and 282 (98.3%) subjects in the OD liraglutide 1.2 mg arm completed the trial; 249 (85.9%) and 261 (90.9%) completed treatment, respectively.

Baseline characteristics and background medications were generally similar in each treatment group. The overall mean age was 59.5 years, HbA<sub>1c</sub> 8.2%, body weight 96.9 kg, and diabetes duration 9.3 years. Most subjects (94.8%) received biguanides; 46.8% of subjects received SU and 24.6% received SGLT-2i. Few subjects in either treatment arm required rescue medication (4 subjects with semaglutide vs 12 subjects with liraglutide; all subjects except one in the liraglutide group were treatment completers; Table 1; Fig. 1). Diabetes complications at screening are shown in Table S4 (see supplementary materials associated with this article on line).

Mean HbA<sub>1c</sub> (baseline 8.2%) decreased over time for both treatment arms (Fig. 2a), and from baseline to week 30 (Fig. 2b) by 1.7% with semaglutide and 1.0% with liraglutide (estimated treatment difference (ETD) at week 30  $-0.69\%$  [95% confidence interval (CI)  $-0.82$  to  $-0.56$ ],  $P < 0.0001$  for superiority). The results of the primary analysis were supported by the sensitivity analyses.

FPG was reduced with both semaglutide and liraglutide from baseline to week 30, but changes were significantly greater with semaglutide (ETD  $-1.24$  mmol/L [95% CI  $-1.54$  to  $-0.93$ ],  $P < 0.0001$ , Fig. 2c). Observed SMBG 7-point profile (at baseline and week 30) and change in mean 7-point SMBG profile from baseline to week 30 are shown in Fig. 2d and e, respectively; reductions in the mean profile were greater with semaglutide vs liraglutide (ETD  $-0.89$  mmol/L [95% CI  $-1.15$  to  $-0.64$ ],

$P < 0.0001$ ). Reductions in the SMBG increment from baseline to week 30 were also greater with semaglutide vs liraglutide (ETD  $-0.53$  mmol/L [95% CI  $-0.77$  to  $-0.28$ ],  $P < 0.0001$ ; data not shown).

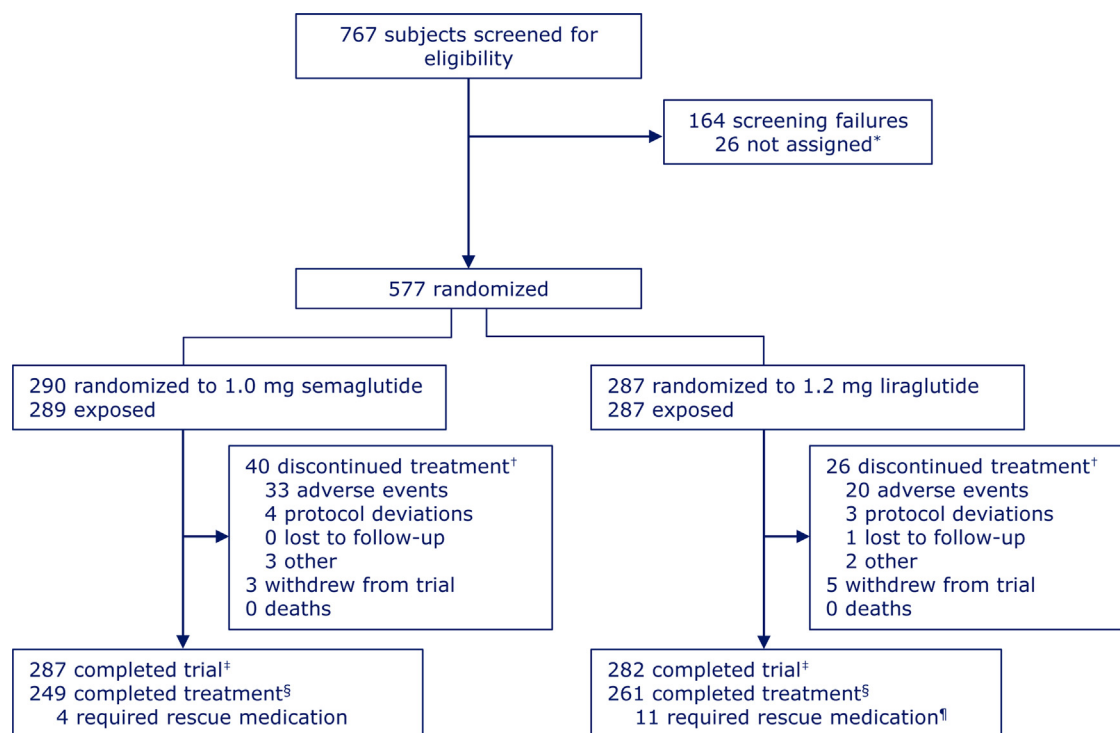
The proportions of subjects achieving HbA<sub>1c</sub>  $< 7.0\%$  and  $\leq 6.5\%$  at week 30 were 80% vs 46% and 58% vs 25%, respectively, with semaglutide vs liraglutide (estimated odds ratio [OR] 5.98 [95% CI 3.83 to 9.32] and 4.84 [95% CI 3.21 to 7.30], respectively,  $P < 0.0001$ ; Fig. 2f and g). A greater proportion of subjects achieved HbA<sub>1c</sub> reduction  $\geq 1\%$  with semaglutide vs liraglutide (83% vs 48% respectively, estimated OR 7.24 [95% CI 4.55 to 11.50],  $P < 0.0001$ ; Figure S3a [see supplementary materials associated with this article on line]).

Mean body weight (baseline 96.9 kg) decreased over time for both treatment arms (Fig. 3a), and from baseline to week 30 (Fig. 3b) by 5.8 kg vs 1.9 kg with semaglutide vs liraglutide (ETD  $-3.83$  kg [95% CI  $-4.57$  to  $-3.09$ ],  $P < 0.0001$ ). The results of the confirmatory analysis were supported by the sensitivity analyses.

The proportions of subjects achieving weight loss of  $\geq 5\%$  and  $\geq 10\%$  at week 30 were 56% vs 18% and 19% vs 4%, respectively, with semaglutide vs liraglutide (estimated OR 5.89 [95% CI 3.93 to 8.81] and 4.99 [95% CI 2.57 to 9.68], respectively, both  $P < 0.0001$ ; Fig. 3c and d). Similarly, a greater proportion of subjects also achieved weight loss  $\geq 3\%$  with semaglutide vs liraglutide (73% vs 34% respectively, estimated OR 5.22 [95% CI 3.57 to 7.62],  $P < 0.0001$ ; Figure S3b [see supplementary materials associated with this article on line]).

Changes in BMI and waist circumference from baseline to week 30 were also significantly greater with semaglutide than with liraglutide [Table S5 (see supplementary materials associated with this article on line)].

The composite endpoint of HbA<sub>1c</sub>  $< 7.0\%$  without severe or BG-confirmed symptomatic hypoglycaemia and without weight gain was achieved by a greater proportion of subjects treated with



**Fig. 1.** Subject disposition. One subject receiving liraglutide 1.2 mg discontinued treatment prematurely, the primary reason for which was a non-treatment-emergent adverse event. \*Screened subjects who withdrew consent before randomization; †includes only exposed subjects; ‡subjects who completed the trial according to the end-of-trial form; §subjects who completed treatment according to the end-of-treatment form; ¶one extra subject in the liraglutide group received rescue medication but did not complete treatment.

**Table 1**

Baseline characteristics – full analysis set.

	Semaglutide 1.0 mg (n = 290)	Liraglutide 1.2 mg (n = 287)	Total (N = 577)
Age, years	60.1 (10.5)	58.9 (10.0)	59.5 (10.2)
Sex, male	160 (55.2%)	167 (58.2%)	327 (56.7%)
Race, White	264 (91.0%)	268 (93.4%)	532 (92.2%)
HbA <sub>1c</sub> , %	8.2 (0.9)	8.3 (1.0)	8.2 (1.0)
Fasting plasma glucose, mmol/L	9.8 (2.3)	9.9 (2.5)	9.9 (2.4)
Diabetes duration, years	9.6 (6.1)	8.9 (5.7)	9.3 (5.9)
Body weight, kg	96.6 (21.0)	97.2 (21.7)	96.9 (21.3)
Body mass index, kg/m <sup>2</sup>	33.7 (6.6)	33.7 (7.0)	33.7 (6.8)
eGFR, mL/min/1.73 m <sup>2</sup> geometric mean (CoV)	91.3 (20.3)	89.7 (23.1)	90.5 (21.7)
Renal function, mL/min/1.73 m <sup>2a</sup>			
eGFR ≥ 90	190 (65.5%)	185 (64.5%)	375 (65.0%)
eGFR ≥ 60–< 90	86 (29.7%)	88 (30.7%)	174 (30.2%)
eGFR 30–< 60	14 (4.8%)	14 (4.9%)	28 (4.9%)
Antidiabetes medication at screening			
Biguanides	279 (96.2%)	268 (93.4%)	547 (94.8%)
Sulfonylurea	136 (46.9%)	134 (46.7%)	270 (46.8%)
SGLT-2i	73 (25.2%)	69 (24.0%)	142 (24.6%)
DPP-4i <sup>b</sup>	0	1 (0.3%)	1 (0.2%)
Other blood glucose-lowering drugs, excluding insulin <sup>b</sup>	1 (0.3%)	0	1 (0.2%)

Data are mean (SD) or n (%) for the full analysis set (FAS), unless otherwise stated. Baseline information is defined as the measurement at the latest assessment before dosing. Body mass index is calculated based on baseline measurement of body weight and height.

%: percentage of subjects; CKD-EPI: The Chronic Kidney Disease Epidemiology Collaboration; CoV: coefficient of variation; DPP-4i: dipeptidyl peptidase-4 inhibitor; eGFR: estimated glomerular filtration rate; max.: maximum; min.: minimum; n: number of subjects; N: total number of subjects; SD: standard deviation; SGLT-2i: sodium-glucose cotransporter-2 inhibitor.

<sup>a</sup> The renal function categories are based on the eGFR using CKD-EPI. No subjects had an eGFR < 30 mL/min/1.73 m<sup>2</sup>.

<sup>b</sup> The two subjects on DPP-4is and repaglinide were randomized in error and discontinued treatment.

semaglutide vs liraglutide (76% vs 37% respectively, estimated OR 6.07 [95% CI 4.02 to 9.15],  $P < 0.0001$ ; Fig. 4a).

A greater proportion of subjects treated with semaglutide vs liraglutide also achieved composite endpoints of HbA<sub>1c</sub> reduction  $\geq 1\%$  and different weight-loss responses of  $\geq 3\%$ ,  $\geq 5\%$ , and  $\geq 10\%$  body weight: 62% vs 21% (estimated OR 6.63 [95% CI 4.44 to 9.91],  $P < 0.0001$ ; Figure S4a [see supplementary materials associated with this article on line]), 50% vs 12% (estimated OR 7.55 [95% CI 4.80 to 11.88],  $P < 0.0001$ ; Figure S4b [see supplementary materials associated with this article on line]), and 17% vs 4% (estimated OR 5.26 [95% CI 2.58 to 10.73],  $P < 0.0001$ ; Fig. 4b), respectively.

The change from baseline (136.4 mmHg) to week 30 in systolic blood pressure was moderate with both semaglutide ( $-4.5$  mmHg [standard error (SE) 0.7]) and liraglutide ( $-3.5$  [0.7]), and the ETD between the treatment arms was not significant ( $-1.0$  [95% CI  $-3.0$  to 1.1] Table S5 [see supplementary materials associated with this article on line]). Similarly, there was no significant difference in diastolic blood pressure between treatments [Table S5 (see supplementary materials associated with this article on line)].

Changes from baseline to week 30 for lipid levels were modest for both treatments, but the semaglutide group showed significantly greater improvements vs the liraglutide group for total cholesterol and triglycerides [Table S6 (see supplementary materials associated with this article on line)].

Improvements in PRO scores were reported with both treatment arms. The DTSQs showed a significant difference between treatment groups in 'Feeling of unacceptably high blood sugars', with this aspect of treatment satisfaction favouring semaglutide (ETD  $-0.55$  [95% CI  $-0.83$  to  $-0.27$ ],  $P = 0.0001$ ; Table S7 [see supplementary materials associated with this article on line]). The SF-36v2<sup>®</sup> questionnaire showed significant differences between the two treatment groups in two components of health-related quality of life, with the results favouring semaglutide: vitality (ETD 1.68 [95% CI 0.45 to 2.92],  $P = 0.0076$ ) and mental health (ETD 1.30 [95% CI 0.06; 2.53],  $P = 0.0396$ ; Table S7 [see supplementary materials associated with this article on line]).

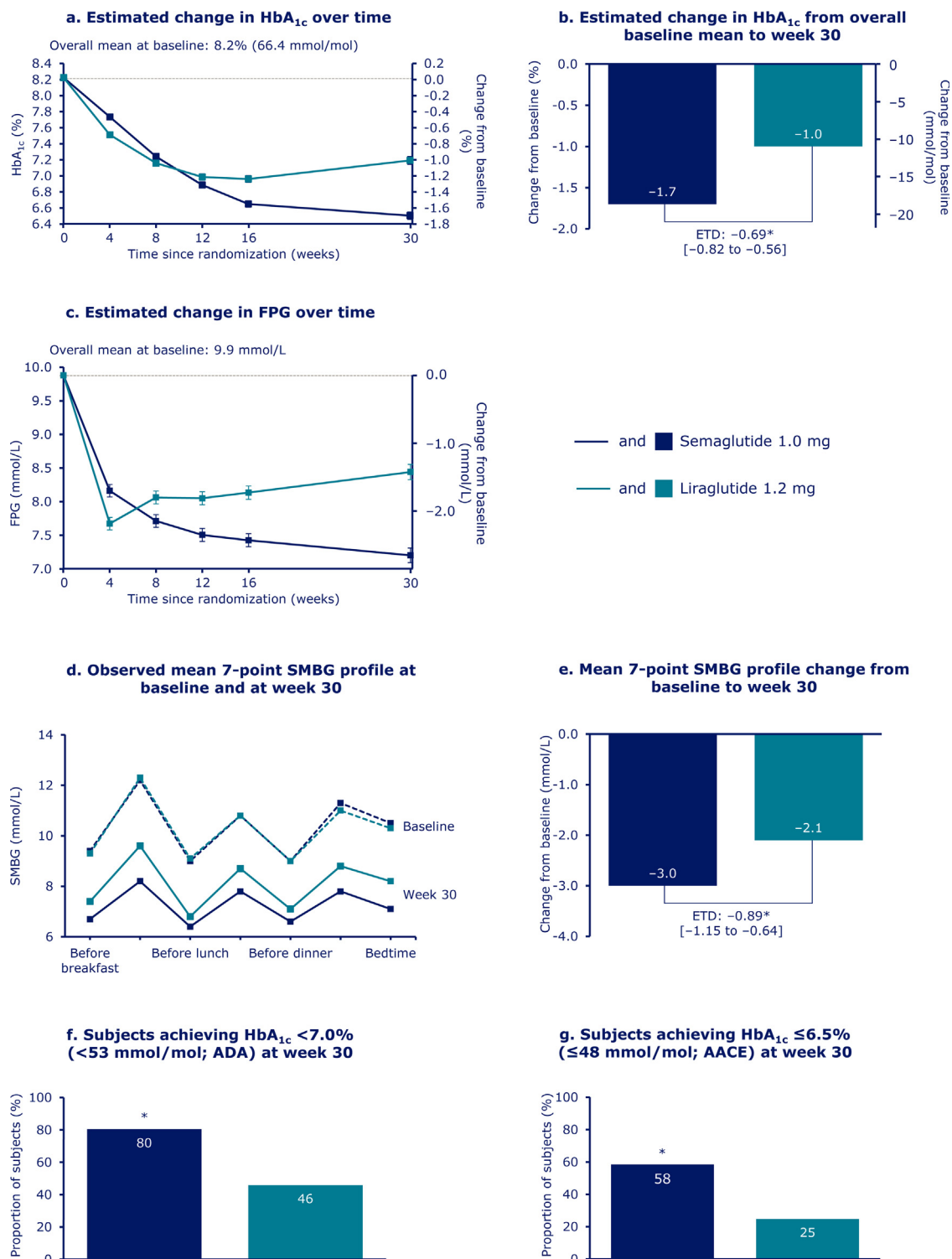
There were no significant differences in any other DTSQs scales or SF-36v2<sup>®</sup> domains [Table S7 (see supplementary materials associated with this article on line)].

In total, 70.6% ( $n = 204$ ) subjects experienced TEAEs in the semaglutide group, and 66.2% ( $n = 190$ ) in the liraglutide group (Table 2). TEAEs were mainly mild to moderate in severity. A slightly higher number of subjects experienced serious TEAEs with liraglutide ( $n = 22$ , 7.7%) than with semaglutide ( $n = 17$ , 5.9%). There were no deaths in either treatment group. A higher proportion of subjects reported TEAEs leading to premature treatment discontinuation with semaglutide ( $n = 33$ , 11.4%) vs liraglutide ( $n = 19$ , 6.6%); this was primarily driven by GI AEs (7.6% with semaglutide vs 3.8% with liraglutide).

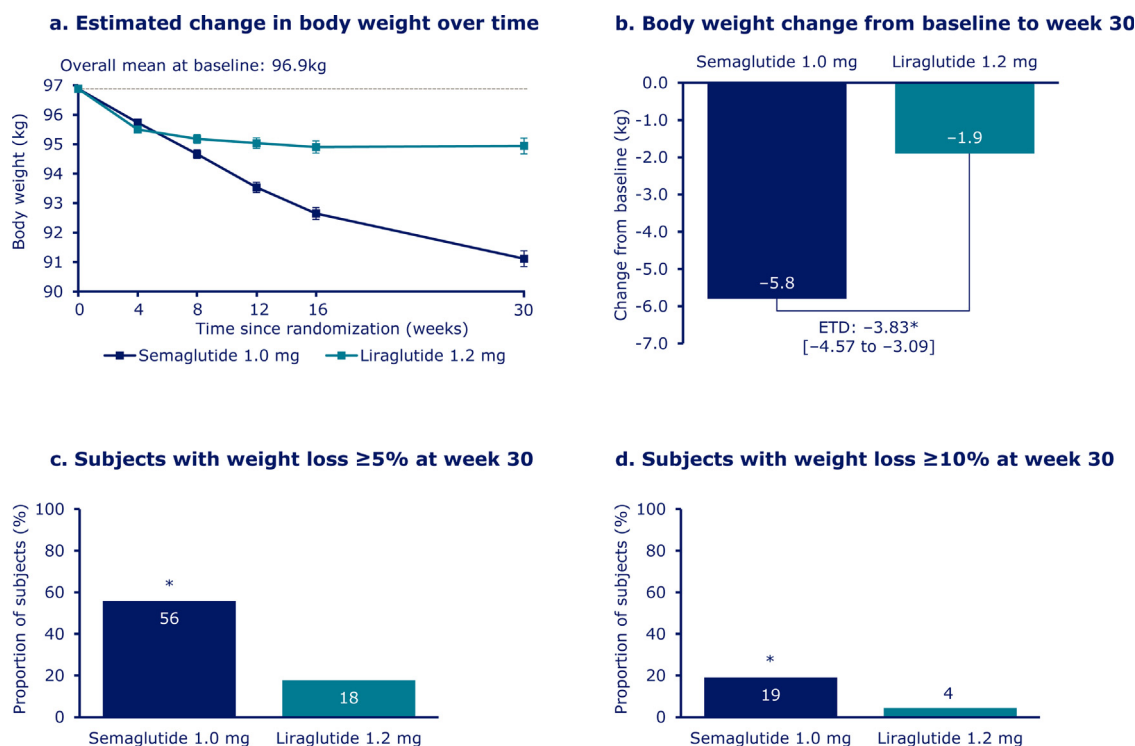
The most commonly reported AEs were GI disorders, reported in 127 (43.9%) subjects with semaglutide and 110 (38.3%) subjects with liraglutide. The onset of GI AEs was typically during the initial 12 weeks of the trial. GI AEs were most prevalent during the dose-escalation period (liraglutide) or within the first 12 weeks of treatment (semaglutide); events were generally mild in severity. Nausea was the most frequently reported GI AE, reported by 63 (21.8%) vs 45 (15.7%) subjects with semaglutide vs liraglutide (Table 2). Other frequently reported GI AEs with semaglutide and liraglutide were: diarrhea (15.6% and 12.2%), vomiting (10.4% and 8.0%), constipation (5.9% and 3.5%), and abdominal pain (5.2% and 2.1%). A list of the AEs reported in  $\geq 5\%$  of subjects in either treatment arm is shown in Table S8 (see supplementary materials associated with this article on line).

Severe or BG-confirmed symptomatic hypoglycaemia was experienced by 1.7% of subjects ( $n = 5$ ; 8 events) in the semaglutide group and 2.4% of subjects ( $n = 7$ ; 8 events) in the liraglutide group; no subject in either group experienced severe hypoglycaemic episodes (ADA definition; data not shown). Of the 16 episodes of severe or BG-confirmed symptomatic hypoglycaemia, 15 were in subjects receiving background SU.

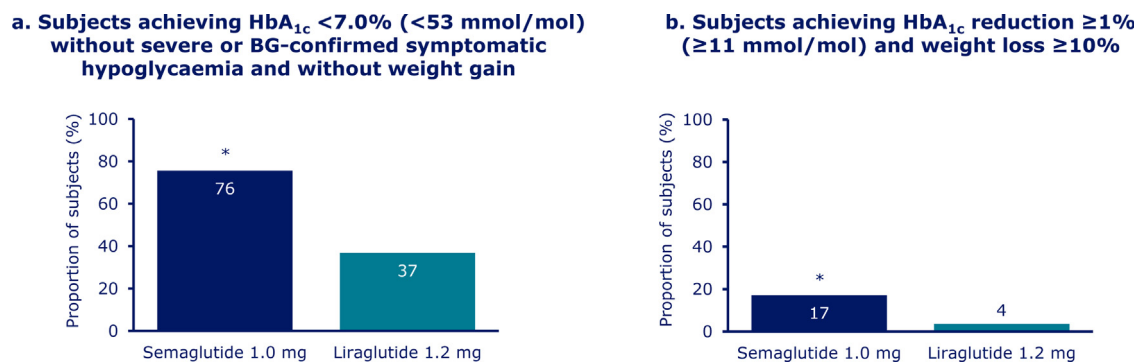
Pancreatitis TEAEs (pre-defined MedDRA search) were reported in two (0.7%) subjects receiving liraglutide and no subjects. Neoplasms (benign, malignant, and unspecified) were reported in



**Fig. 2.** Glycaemic endpoints with semaglutide 1.0 mg and liraglutide 1.2 mg. Estimated change in HbA<sub>1c</sub> by week (a); estimated change in HbA<sub>1c</sub> from overall baseline mean to week 30 (b); estimated change in FPG over time (c); observed mean 7-point SMBG profile at baseline and at week 30 (d); mean 7-point SMBG profile change from baseline to week 30 (e); proportion of subjects achieving HbA<sub>1c</sub> < 7.0% (f) and ≤ 6.5% (g) at week 30. \**P* < 0.0001 vs liraglutide 1.2 mg. All figures based on the full analysis set, using 'on-treatment without rescue medication' data. Figures a–c and e: mean estimates are from an analysis of covariance, where missing data were accounted for using multiple imputation (data from subjects within the same group defined by randomized treatment) using a regression model including stratification factor as categorical effect and data from baseline and all previous post-baseline visits as covariates. Error bars are ± standard errors of the means. Dashed grey lines indicate the overall mean values at baseline. Values in square brackets are 95% CIs. Figure d: dashed lines indicate baseline values; solid lines indicate week 30 data. SMBG assessed with glucose meter as plasma equivalent values of capillary whole blood glucose. Figures f, g: missing HbA<sub>1c</sub> data were accounted for using multiple imputation (data from subjects within the same group defined by randomized treatment) using a regression model including stratification factor as categorical effect and data from baseline and all previous post-baseline visits as covariates. After imputation, continuous data were dichotomized. AACE: American Association of Clinical Endocrinologists; ADA: American Diabetes Association; CI: confidence interval; ETD: estimated treatment difference; FPG: fasting plasma glucose; SMBG: self-measured blood glucose.



**Fig. 3.** Body weight outcomes with semaglutide 1.0 mg and liraglutide 1.2 mg. Estimated change in body weight over time (a); body weight change from baseline to week 30 (b); proportion of subjects achieving weight loss  $\geq 5\%$  (c) and  $\geq 10\%$  (d) at week 30. \*  $P < 0.0001$  vs liraglutide 1.2 mg. All figures based on the full analysis set, using 'on-treatment without rescue medication' data. Figure a, b: mean estimates are from an analysis of covariance, where missing data were accounted for using multiple imputation (data from subjects within the same group defined by randomized treatment) using a regression model including stratification factor as categorical effect and data from baseline and all previous post-baseline visits as covariates. Error bars are  $\pm$  standard errors of the means. Dashed grey line indicates the overall mean value at baseline. Values in square brackets are 95% CIs. Figure c, d: missing body weight (kg) data were accounted for using multiple imputation (data from subjects within the same group defined by randomized treatment) using a regression model including stratification factor as categorical effect and data from baseline and all previous post-baseline visits as covariates. After imputation, continuous data were dichotomized. All site visits, except screening visits, were to be completed in a fasting state. CI: confidence interval; ETD: estimated treatment difference.



**Fig. 4.** Composite endpoints with semaglutide 1.0 mg and liraglutide 1.2 mg at week 30. Proportion of subjects achieving HbA<sub>1c</sub> <7.0% without severe or BG-confirmed symptomatic hypoglycaemia and without weight gain (a); and proportion of subjects achieving HbA<sub>1c</sub> reduction  $\geq 1\%$  and weight loss  $\geq 10\%$  (b). \*  $P < 0.0001$  vs liraglutide 1.2 mg. Full analysis set and 'on-treatment without rescue medication' data with missing HbA<sub>1c</sub> (%) and body weight (kg) data accounted for using multiple imputation (individual components imputed separately for composite endpoints; data from subjects within the same group defined by randomized treatment) using a regression model including stratification factor as categorical effect and data from baseline and all previous post-baseline visits as covariates. After imputation continuous data were dichotomized. All site visits, except screening visit, were completed in the fasting state. BG: blood glucose.

nine (3.1%) subjects receiving semaglutide and four (1.4%) subjects receiving liraglutide during the 'in-trial' period; no clustering of neoplasms was reported. 'In-trial' AEs related to diabetic retinopathy (pre-defined MedDRA search) were reported in three (1.0%) subjects receiving semaglutide and four (1.4%) subjects receiving liraglutide. All seven events were non-serious, and all but one were mild in severity (one event with liraglutide was recorded as moderate severity).

There was no change in eGFR (geometric mean) from baseline to week 30 with semaglutide or liraglutide (ratios to baseline at week 30 were 0.99 and 1.00, respectively). Mean pulse rate increased from baseline (74.3 bpm) to week 30 with both semaglutide (2.5 bpm [SE 0.5]) and liraglutide (3.9 bpm [0.5]); the difference was not significantly different (ETD-1.36 [95% CI - 2.75 to 0.03],  $P = 0.0556$ ; Table S5 [see supplementary materials associated with this article on line]). There were no



**Table 2**  
Treatment-emergent adverse events.

	Semaglutide 1.0 mg (n = 289)			Liraglutide 1.2 mg (n = 287)		
	n (%)	E	R	n (%)	E	R
All TEAEs	204 (70.6)	758	418.5	190 (66.2)	691	377.6
Severity of TEAEs						
Mild	175 (60.6)	564	311.4	168 (58.5)	512	279.8
Moderate	84 (29.1)	168	92.8	83 (28.9)	152	83.1
Severe	17 (5.9)	26	14.4	15 (5.2)	27	14.8
Serious TEAEs	17 (5.9)	22	12.1	22 (7.7)	31	16.9
TEAEs leading to premature treatment discontinuation	33 (11.4)	54	29.8	19 (6.6)	26	14.2
Gastrointestinal AEs leading to premature treatment discontinuation	22 (7.6)	34	18.8	11 (3.8)	13	7.1
Gastrointestinal disorders	127 (43.9)	315	173.9	110 (38.3)	219	119.7
Nausea <sup>a</sup>	63 (21.8)	89	49.1	45 (15.7)	54	29.5
Diarrhea <sup>a</sup>	45 (15.6)	56	30.9	35 (12.2)	44	24.0
Vomiting <sup>a</sup>	30 (10.4)	44	24.3	23 (8.0)	33	18.0
Constipation <sup>a</sup>	17 (5.9)	17	9.4	10 (3.5)	13	7.1
Abdominal pain <sup>a</sup>	15 (5.2)	18	9.9	6 (2.1)	6	3.3

<sup>a</sup>On-treatment<sup>a</sup> data based on the safety analysis set.

%: percentage of subjects experiencing at least one event; AE: adverse event; E: number of events; n: number of subjects experiencing at least one event; R: event rate per 100 exposure-years; TEAE: treatment-emergent adverse event.

<sup>a</sup> The gastrointestinal AEs listed here are those experienced by  $\geq 5\%$  of subjects in at least one of the treatment arms.

clinically relevant changes in other safety laboratory assessments, physical examinations category, or electrocardiogram category (data not shown).

## Discussion

The SUSTAIN 10 trial showed that OW semaglutide 1.0 mg was superior to OD liraglutide 1.2 mg in reducing HbA<sub>1c</sub> and body weight after 30 weeks of treatment in subjects with T2D uncontrolled on 1–3 OADs, few of whom received rescue medication. A greater proportion of subjects achieved HbA<sub>1c</sub> targets of  $< 7.0\%$  and  $\leq 6.5\%$  and weight-loss responses of  $\geq 5\%$  and  $\geq 10\%$  with semaglutide vs liraglutide. The observed differences in efficacy between the two medications could be due to minor but clinically relevant differences in their molecular structure: compared with liraglutide, which has an alanine at position 8 and a C-16 fatty acid chain with a gamma glutamate ( $\gamma$ Glu) linker at position 26, semaglutide has an alanine to alpha-aminoisobutyric acid amino acid substitution at position 8 and a C-18 fatty diacid side chain with a  $\gamma$ Glu-2xOEG linker at position 26 [30].

Both semaglutide 1.0 mg and liraglutide 1.2 mg were generally well tolerated. As expected, GI events were the most commonly reported, with a higher proportion of subjects experiencing them with semaglutide vs liraglutide. GI AEs, which generally occurred in the first 12 weeks of treatment, were typically mild in severity and transient in duration. Conversely, a slightly higher proportion of subjects reported serious TEAEs with liraglutide vs semaglutide.

While it may be anticipated that patient preference and treatment satisfaction could be influenced by dosing frequency, SUSTAIN 10 showed similar improvements in patient-reported treatment satisfaction with both the OW (semaglutide) and OD (liraglutide) treatments. This may be a result of the already good glycaemic and body weight control observed with liraglutide, and/or other factors affecting treatment satisfaction. It should be noted, however, that SUSTAIN 10 was not powered to reveal differences in treatment satisfaction and/or effect of dosing frequency.

The results from SUSTAIN 10 are consistent with those from the SUSTAIN 3 and 7 trials, which also compared OW semaglutide with other GLP-1RAs (exenatide ER and dulaglutide, both OW), and with those from a systematic literature review and network meta-analysis comparing OW semaglutide with other GLP-1RAs

(OD liraglutide, OW dulaglutide, twice-daily exenatide, OW exenatide, OD lixisenatide, and OW albiglutide) in subjects with T2D previously receiving basal insulin or 1–2 OADs [31,32]. In these analyses, OW semaglutide 1.0 mg was associated with greater reductions in HbA<sub>1c</sub> and body weight vs all GLP-1RA comparators and was generally well tolerated.

Other clinical trials have studied the effects of OW GLP-1RAs (dulaglutide 1.5 mg [AWARD-6] [33], exenatide ER 2.0 mg [DURATION-6] [34]) vs OD liraglutide 1.85 mg (a higher dose than in SUSTAIN 10) in subjects with T2D. Whereas in AWARD-6 dulaglutide was non-inferior to liraglutide in reducing HbA<sub>1c</sub>, in DURATION-6 liraglutide demonstrated superiority vs exenatide ER.

The SUSTAIN 10 trial was the first Europe-based head-to-head trial to compare s.c. OW semaglutide vs s.c. OD liraglutide, and had relatively broad inclusion criteria in terms of the range of background medications and baseline characteristics. SUSTAIN 10 is, thus, both representative of patients that physicians are likely to consider for treatment with a GLP-1RA and reflective of discussions that physicians may have with patients regarding dosing regimen preferences. These factors make the findings of SUSTAIN 10 particularly relevant for real-world clinical practice. The trial design also aimed to reflect real-world clinical practice, as it compared the most commonly prescribed dose for OD liraglutide (1.2 mg) with the anticipated most frequent dose for OW semaglutide (1.0 mg) in Europe. These features of the trial increase the relevance of the results for physicians and also for medicine management teams, who are responsible for planning formularies in a crowded diabetes treatment arena.

The limitations of the SUSTAIN 10 trial include its open-label design, which was necessitated by the different dosing frequencies of semaglutide and liraglutide. The relatively short trial duration is also a limitation; the change over time curves for HbA<sub>1c</sub> and body weight indicate that the effects, at least with semaglutide, had not yet plateaued – a longer trial duration would have enabled the full extent of any treatment differences to be revealed. Furthermore, the trial only included two of the four potential treatment doses, as semaglutide 0.5 mg and liraglutide 1.8 mg were not investigated, although this was based on the rationale to assess the most commonly prescribed and anticipated most commonly prescribed doses of the two GLP-1RAs, and provide a basis for clinical decision-making when choosing treatment.



Overall, the results from the SUSTAIN 10 trial provide useful information for physicians, medicine management teams, and patients, in their joint decision-making process to optimize T2D management.

## Conclusions

Semaglutide 1.0 mg OW was superior to liraglutide 1.2 mg OD in improving glycaemic control and reducing body weight in subjects with T2D uncontrolled on 1–3 OADs. The safety profile of both GLP-1RAs was similar, although a higher proportion of subjects prematurely discontinued treatment with semaglutide vs liraglutide, primarily due to GI AEs.

The efficacy and safety profile of semaglutide 1.0 mg was consistent with that observed in the other phase 3 SUSTAIN trials. Thus, the SUSTAIN 10 results support the favourable benefit–risk profile of semaglutide, as established in the SUSTAIN phase 3a clinical trial program.

## Disclosure of interest

MC reports being an unpaid board member of the Association for the Study of Obesity (ASO) and the Primary Care Academy of Diabetes Specialists (PCADS), an expert advisor to The National Institute for Health and Care Excellence (NICE), a part-time Medical Director at LighterLife (a commercial weight-loss company), a partner at Clifton Medical Centre, and director at RIO Weight Management, Ltd; he also reports research income/support from Novo Nordisk, Novartis, BI/Lilly, GSK, Leo, and Abbott; advisory board support from Novo Nordisk, BI/Lilly, Janssen, and MSD; and speaker fees from Novo Nordisk, BI/Lilly and Janssen. AMC is a Novo Nordisk employee, and his wife is an employee of Novo Nordisk Region Europe Pharmaceuticals A/S. JKF is a Novo Nordisk employee and shareholder. ST is a Novo Nordisk employee. AJ and BV declare that they have no competing interest. HP reports that her institute was a trial site for the SUSTAIN 10 clinical trial (funded by Novo Nordisk); she also reports grants and personal fees from Novo Nordisk; and personal fees from Sanofi, Boehringer Ingelheim, MSD, Lilly, and AstraZeneca. MM reports personal fees from Novo Nordisk, Servier, and Merck Sharp & Dohme; and grants from Sanofi and Bayer; he also reports being the president of a not-for-profit institution named Fondation Francophone pour la Recherche sur le Diabète (supported by grants from Novo Nordisk, Sanofi, Merck Sharp & Dohme, AstraZeneca, Abbott, and Roche).

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## Appendix A. Supplementary data

Supplementary data (Figures S1, S2, S3, S4, Tables S1, S2, S3, S4, S5, S6, S7, S8 and the Appendix) associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2019.101117>.

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