# A 26-Week Randomized Controlled Trial of Semaglutide Once Daily Versus Liraglutide and Placebo in Patients With Type 2 Diabetes Suboptimally Controlled on Diet and Exercise With or Without Metformin

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*Diabetes Care 2018;41:1926–1937 | https://doi.org/10.2337/dc17-2381*

**OBJECTIVE**

**To investigate the efficacy and safety of once-daily semaglutide in comparison with once-daily liraglutide and placebo in patients with type 2 diabetes.**

**RESEARCH DESIGN AND METHODS**

**This 26-week, multicenter, double-blind trial involved patients diagnosed with type 2 diabetes with $HbA_{1c}$ 7.0–10.0% (53–86 mmol/mol) and treated with diet and exercise with or without metformin. Patients were randomized 2:2:1 to once-daily semaglutide, liraglutide, or placebo in one of four volume-matched doses (semaglutide 0.05, 0.1, 0.2, or 0.3 mg and liraglutide 0.3, 0.6, 1.2, or 1.8 mg, with both compared within each volume-matched dose group). Primary end point was change in $HbA_{1c}$ from baseline to week 26.**

**RESULTS**

**In total, 705 randomized patients were exposed to trial products. At week 26, a dose-dependent change in $HbA_{1c}$ was observed with semaglutide from −1.1% (0.05 mg) to −1.9% (0.3 mg) and with liraglutide from −0.5% (0.3 mg) to −1.3% (1.8 mg) (all $P < 0.001$ in favor of volume-matched semaglutide dose). Change with pooled placebo was −0.02% ($P < 0.0001$ vs. semaglutide). Gastrointestinal (GI) disorders were the most common adverse events (AEs) with semaglutide and liraglutide, occurring in 32.8–54.0% and 21.9–41.5% of patients, respectively.**

**CONCLUSIONS**

**Once-daily semaglutide at doses up to 0.3 mg/day resulted in greater reductions in $HbA_{1c}$ compared with liraglutide or placebo but with a higher frequency of GI AEs.**

Glucagon-like peptide 1 (GLP-1) is a gut-derived peptide and a potent blood glucose (BG)-lowering hormone (1). It functions in a glucose-dependent manner and is therefore associated with a low risk of hypoglycemia (2). GLP-1 inhibits gastric emptying and reduces body weight by lowering energy intake and inducing feelings

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*Received 13 November 2017 and accepted 18 June 2018.*

*Clinical trial reg. no. NCT02461589, clinicaltrials.gov.*

*This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc17-2381/-/DC1.*

*This article is featured in a podcast available at http://www.diabetesjournals.org/content/diabetes-core-update-podcasts.*

of satiety, a mechanism thought to involve GLP-1 receptors expressed in the hypothalamus, the region of the brain that regulates satiety and appetite (3–5). For these reasons, alongside evidence that some GLP-1 receptor agonists can improve cardiovascular outcomes (6,7), these therapies have become integral in the treatment of type 2 diabetes and are recommended early in the treatment guidelines (8,9).

Semaglutide is a new human GLP-1 analog for the treatment of patients with type 2 diabetes. It has 94% amino acid sequence homology to native GLP-1; amino acid substitutions in the semaglutide molecule confer increased albumin affinity while also making it resistant to degradation by dipeptidyl peptidase 4 (DPP-4). Consequently, semaglutide has a half-life of ~1 week (10).

In the Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) phase 3a global clinical trial program in patients with type 2 diabetes, once-weekly subcutaneous semaglutide 0.5 mg and 1.0 mg showed superior and clinically meaningful reductions in $HbA_{1c}$ and body weight versus a range of comparators (sitagliptin, exenatide extended release, insulin glargine, and placebo) (11–15). The most common adverse events (AEs) with semaglutide were gastrointestinal (GI) in nature (11–15). The effect of semaglutide on gastric emptying was investigated in a separate trial and showed that although overall gastric emptying was similar to that of placebo, the observed first-hour delay with semaglutide may contribute to a slower entry of glucose into the circulation (16).

This trial aimed to investigate the efficacy and safety of a wider dose range of semaglutide administered once daily in comparison with liraglutide and placebo in patients with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

### Trial Design

This was a 26-week, multicenter, randomized, double-blind (within dose level), dose-finding trial comparing semaglutide with liraglutide and placebo, all administered subcutaneously once daily, in patients diagnosed with type 2 diabetes and treated with diet and exercise with or without metformin. There were 138 participating sites in 10 countries (Austria, Canada, Czech Republic, Germany, Malaysia, Russia, Serbia, South Africa, U.K., and U.S.).

Patients were randomized in a 2:2:1 ratio to semaglutide:liraglutide:placebo in one of four volume-matched doses (described below and in Supplementary Fig. 1). The trial included an additional open-label treatment arm to explore whether a more flexible semaglutide titration scheme could improve tolerability.

The trial was conducted in compliance with the International Conference on Harmonization Good Clinical Practice guidelines (17) and the Declaration of Helsinki (18). Written informed consent was obtained from all patients before any trial-related activities commenced, in line with institutional review board–approved detailed informed consent procedures: subjects were provided verbal and written information about the trial and the procedures involved in a form that they could read and understand. Subjects were fully informed of their rights and responsibilities while participating in the trial, as well as the risks and benefits of being exposed to the trial products (19).

### Trial Patients

Patients of either sex were eligible for inclusion if they were at least 18 years of age at the time of informed consent, diagnosed with type 2 diabetes at least 90 days prior to screening, and on stable diabetes treatment consisting of diet and exercise ± metformin (≥1,500 mg daily or maximum tolerated dose documented in the patient medical record) for at least 90 days prior to screening, with a $HbA_{1c}$ 7.0–10.0% (53–86 mmol/mol) and a BMI 25.0–40.0 kg/$m^2$.

Key exclusion criteria were a history of chronic or idiopathic acute pancreatitis and moderate-to-severe renal impairment (estimated glomerular filtration rate <60 mL/min/1.73 $m^2$). Full details of inclusion and exclusion criteria can be found in Supplementary Table 1.

### Randomization and Masking

Eligible patients enrolled by the study investigators were randomly assigned into 1 of 12 treatment arms in a 2:2:1 ratio (semaglutide:liraglutide:placebo) within each of the four dosing levels (50, 100, 200, and 300 μL) or to an additional 13th semaglutide treatment arm with the same number of patients as the active treatment arms (Supplementary Fig. 1). This corresponds to the following daily doses: semaglutide 0.05, 0.1, 0.2, and 0.3 mg, respectively, and liraglutide 0.3, 0.6, 1.2, and 1.8 mg, respectively. The last treatment arm represents the semaglutide exploratory flexible escalation arm based on tolerability to GI AEs (Supplementary Fig. 1).

The randomization session was performed in the interactive voice/web-response system, which would allocate the dispensing unit number of trial product to be dispensed to the patient. Patients were assigned to the lowest available number allocated to the trial site. The patient number was a six-digit number. Randomization was performed by the study sponsor.

A portion of the trial was double blinded to the study sponsor, investigators, and patients. Semaglutide, liraglutide, and placebo were visually identical to fulfill the requirements for double-blind procedures, and equal volumes of semaglutide, liraglutide, and placebo were administered during treatment, ensuring blinding within dose level.

The treatment code for a particular patient could be broken in a medical emergency; however, the treatment code was not broken for any patient during this trial.

### Trial Drug Administration

After a 2-week screening period, patients received trial medication for 26 weeks, followed by a 7-week follow-up period (Supplementary Fig. 1). For the 12 blinded treatment arms, patients were initiated on treatment with 0.05 mg semaglutide, 0.3 mg liraglutide, or 50 μL placebo, all administered subcutaneously once daily, titrated every 4 weeks up to their final randomized dose. This similar titration algorithm was used in all patients to ensure blinding across the products, and thus liraglutide was initiated at a lower dose and escalated at a slower pace than recommended in the label (20). The fixed dose escalation in groups 1–13 is described as follows: 1) semaglutide 0.05 mg/day, 2) liraglutide 0.3 mg/day, 3) placebo 50 μL/day, 4) semaglutide 0.05/0.1 mg/day, 5) liraglutide 0.3/0.6 mg/day, 6) placebo 50/100 μL/day, 7) semaglutide 0.05/0.1/0.2 mg/day, 8) liraglutide 0.3/0.6/1.2 mg/day, 9) placebo 50/100/200 μL/day, 10) semaglutide 0.05/0.1/0.2/0.3 mg/day, 11) liraglutide 0.3/0.6/1.2/1.8 mg/day, 12) placebo 50/100/200/300 μL/day, and 13) semaglutide flexible dose escalation from 0.05

to 0.3 mg/day (Supplementary Fig. 1) (randomized in the same ratio as for the other semaglutide arms).

The trial was double blinded within (but not between) each dose level of semaglutide, liraglutide, and placebo, as treatment was volume matched. Thus, within each dose level, patients could be treated with either semaglutide, liraglutide, or placebo. An open-label design was chosen for the flexible-dosing arm to explore tolerability in a flexible escalation regimen for semaglutide. Patients in this arm were initiated on 0.05 mg semaglutide, but dose escalation could be modified and final dose reduced in patients with poor GI tolerability, based on investigator's assessment.

Once-daily trial product could be administered at any time of day (preferably at the same time each day), irrespective of meals.

If fasting plasma glucose (FPG) values exceeded the limits of 15.0 mmol/L (270 mg/dL) from randomization to end of week 5, 13.3 mmol/L (240 mg/dL) from week 6 to 11, or 11.1 mmol/L (200 mg/dL) from week 12 to end of trial, randomized treatment was discontinued and the patients were offered rescue medication at the investigator's discretion (preferably excluding GLP-1 receptor agonists, DPP-4 inhibitors, and amylin analogs) and at the same time offered to discontinue randomized treatment.

### Trial End Points

The primary end point was change from baseline to week 26 in $HbA_{1c}$ with semaglutide versus placebo. The secondary end point was change from baseline to week 26 in $HbA_{1c}$ with semaglutide versus liraglutide.

Key supportive secondary efficacy end points were change from baseline to week 26 in FPG, body weight, and systolic (SBP) and diastolic (DBP) blood pressure. Patient-reported outcomes were assessed using the Diabetes Treatment Satisfaction Questionnaire. Full details of the secondary efficacy end points are provided in Supplementary Table 2.

Supportive secondary safety end points included number of treatment-emergent AEs and number of and occurrence of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes (defined as an episode that was severe according to the American Diabetes Association classification [21] or BG confirmed by a plasma glucose value $<3.1$ mmol/L [56 mg/dL] with symptoms consistent with hypoglycemia) (Supplementary Table 2).

The above noted end points were compared between each dose of semaglutide and volume-matched placebo, as well as each dose of semaglutide and the corresponding dose of liraglutide as follows: 0.05 vs. 0.3, 0.1 vs. 0.6, 0.2 vs. 1.2, and 0.3 vs. 1.8 mg/day.

Additional end points in the open-label arm were dose level at end of trial, time to last dose change, and average dose during the trial.

### Adjudication of AEs

An external event adjudication committee (EAC) comprising independent external medical experts within specialized areas was established to perform blinded validation of safety focus areas according to predefined diagnostic criteria.

### Collection and Analysis of the Data

For assessment of efficacy and safety and data collection, each patient attended a screening visit (visit 1) at the study site, 10 site visits (visits 2, 4, 6, and 8–14), three phone visits (visits 3, 5, and 7), and a study site follow-up visit (visit 15). Patients randomized to the open-label flexible dose arm had one additional visit (visit 12S).

A central laboratory was responsible for analyzing all clinical safety laboratory tests, except for anti-semaglutide antibodies, pharmacokinetic samples, and IgE antibodies. A special laboratory was responsible for analyzing serum antibodies to semaglutide and plasma concentrations of semaglutide for pharmacokinetic assessments. Characterization of the in vitro neutralizing effect of antibodies against semaglutide and native GLP-1 was performed by the study sponsor.

### Statistical Analysis

Sample size was calculated based on a comparison of change from baseline to end of treatment (week 26) in $HbA_{1c}$ between the highest dose of semaglutide once daily (0.3 mg) and the four pooled placebo arms. A placebo-adjusted treatment effect of 0.55% was used in the sample size calculation, and the SD was assumed to be 1.1%. A sample size of 704 was calculated to yield 90% power to detect a difference between semaglutide and placebo at a type I error rate of 5% (two sided). Two-sided *P* values testing the null hypothesis of no difference are presented, with *P* values $<5\%$ deemed significant. There was no control for multiple testing.

All analyses were based on the full analysis set (FAS), which consisted of data from all randomized patients exposed to trial product.

Categorical and binary efficacy and safety end points were summarized using counts and relative frequencies at all planned visits. Continuous efficacy end points including the primary $HbA_{1c}$ end point were analyzed using a mixed model for repeated measurements (MMRM) including treatment, stratification factor (metformin use at baseline [yes/no]) and region as fixed factors and the corresponding baseline $HbA_{1c}$ value as covariate. The MMRM was based on data obtained before treatment cessation and before any rescue medication and did not include data from the semaglutide flexible-dosing arm. Data on lipids and on lipase and amylase activity were log-transformed prior to statistical analysis.

The number of severe or BG-confirmed symptomatic hypoglycemic episodes was analyzed using a negative binomial regression model that included factors for treatment and strata as fixed factors and baseline $HbA_{1c}$ as the covariate. Data from the four placebo groups were pooled.

Prespecified sensitivity analyses were performed to ascertain the robustness of analyses of $HbA_{1c}$ and body weight. The analyses included *1*) an MMRM based on all "in-trial" observed data between baseline and the week 26 landmark visit, regardless of treatment adherence; *2*) a multiple-imputation ANCOVA where data from patients with missing records were imputed as if they had been switched from whichever randomized treatment they had received to placebo; and *3*) a multiple-imputation ANCOVA where data from patients with missing records were imputed as if they had been switched from whichever randomized treatment/dosing volume they had received to the matching liraglutide-dosing volume.

For comparison of semaglutide and liraglutide in terms of efficacy and tolerability, the ratio between semaglutide and liraglutide doses that achieved equal responses based on dose-response modeling was evaluated to determine the

potency of semaglutide relative to liraglutide. Dose-response modeling was performed on change from baseline in $HbA_{1c}$ and body weight, using a three-parameter $E_{max}$ (maximum effect) model, and performed on incidence of AEs leading to premature treatment discontinuation and GI AEs using a logistic regression model.

## RESULTS

### Patient Disposition and Baseline Characteristics

The trial was initiated on 21 September 2015 and completed on 13 October 2016 per protocol. A total of 706 patients were randomized, of whom 705 were exposed to trial products and were included in the efficacy and safety analyses (Supplementary Fig. 2). Treatment groups were well balanced in demographic and baseline characteristics (Table 1). Mean (SD) age was 56.7 (9.9) years, 46.2% of patients were women, and mean (SD) $HbA_{1c}$ was 8.1% (0.8) (64.6 [9.2] mmol/mol), FPG 9.5 (2.6) mmol/L (170.4 [46.6] mg/dL), BMI 32.8 (4.4) kg/m$^2$, and duration of diabetes 7.2 (5.6) years (Table 1). Details of on-treatment administration of rescue medication are shown in Supplementary Table 3.

### $HbA_{1c}$ (Primary Efficacy End Point)

Between baseline and week 26, mean $HbA_{1c}$ decreased in the semaglutide and liraglutide groups but not in the pooled placebo group (Fig. 1*A*). At week 26, a dose-dependent estimated mean change in $HbA_{1c}$ was observed with semaglutide treatment ranging from −1.1% (0.05 mg dose group) to −1.9% (0.3 mg). Changes in $HbA_{1c}$ with liraglutide treatment ranged from −0.5% (0.3 mg dose group) to −1.3% (1.8 mg) (Fig. 1*B* and Supplementary Table 4). Change in $HbA_{1c}$ with pooled placebo was −0.02% (Fig. 1*B*). The estimated change in $HbA_{1c}$ was significant for all semaglutide doses versus pooled placebo ($P < 0.0001$ for all) and for each volume-matched dose of semaglutide versus liraglutide ($P < 0.001$ for all) (Fig. 1*C*). The results of the primary analysis were supported by all sensitivity analyses (data not shown).

Dose-response modeling was performed for semaglutide and liraglutide on $HbA_{1c}$. Liraglutide 1.8 mg was equipotent to semaglutide 0.062 mg; thus, the potency of semaglutide versus liraglutide (i.e., the ratio between the median effective dose of semaglutide and liraglutide, representing the conversion factor between equipotent doses of semaglutide and liraglutide) was ∼28 ($P < 0.0001$) (Supplementary Fig. 3*A* and *C*).

At week 26, the $HbA_{1c}$ target of ≤6.5% was achieved by 43–73% of patients treated with semaglutide, 14–42% treated with liraglutide, and 6% treated with pooled placebo. The $HbA_{1c}$ target of <7.0% was achieved by 58–89% of patients on semaglutide, 33–62% on liraglutide, and 13% on pooled placebo (Fig. 1*D*).

### FPG

Between baseline and week 26, mean FPG levels decreased in the semaglutide and liraglutide groups but not in the pooled placebo group (Fig. 1*E*). At week 26, the estimated mean change in FPG with semaglutide ranged from −2.2 mmol/L (−39.3 mg/dL) for the 0.05 mg dose group to −3.35 mmol/L (−60.4 mg/dL) for the 0.3 mg group and with liraglutide ranged from −1.4 mmol/L (−25.1 mg/dL) for the 0.3 mg group to −2.0 mmol/L (−36.6 mg/dL) for the 1.8 mg group. The change in FPG was −0.4 mmol/L (−6.9 mg/dL) with pooled placebo. The estimated change in FPG was significant for each dose of semaglutide compared with pooled placebo ($P < 0.0001$ for all) and between each volume-matched dose of semaglutide and liraglutide ($P < 0.03$ for all).

### Body Weight and Waist Circumference

Between baseline and week 26, mean body weight (overall mean at baseline 94.3 kg) declined with semaglutide, liraglutide, and pooled placebo treatment (Fig. 2*A*). At week 26, a dose-dependent estimated mean change in body weight was observed with semaglutide treatment ranging from −2.8 kg (0.05 mg dose group) to −8.2 kg (0.3 mg). Change in body weight for the liraglutide groups at week 26 ranged from −1.5 kg (0.3 mg dose group) to −3.7 kg (1.8 mg). The change in body weight was −1.2 kg with pooled placebo (Fig. 2*B*). The estimated change in body weight was significant for all semaglutide doses versus pooled placebo ($P < 0.02$ for all) and between each volume-matched dose of semaglutide and liraglutide ($P \leq 0.0003$ for all) except for semaglutide 0.05 mg vs. liraglutide 0.3 mg ($P = 0.077$) (Fig. 2*C*). The results of these analyses were supported by all sensitivity analyses (data not shown).

Dose-response modeling was performed between semaglutide and liraglutide for body weight. Liraglutide 1.8 mg was equipotent to semaglutide 0.06 mg; thus, the potency of semaglutide versus liraglutide (representing the conversion factor between equipotent doses of semaglutide and liraglutide) was ∼30 ($P < 0.0001$) (Supplementary Fig. 3*B* and *C*).

At week 26, the 5% weight loss response was achieved by 22–76% and 16–42% of patients treated with semaglutide and liraglutide, respectively, both in a dose-dependent manner (Fig. 2*D*). The 10% weight loss response was achieved by 5–38% and 0–8% of patients in the semaglutide and liraglutide groups, respectively, both in a dose-dependent manner. In comparison, 11 and 2% of placebo-treated patients achieved the 5% and 10% weight loss responses, respectively.

At week 26, significant reductions in waist circumference were observed in all groups (Fig. 2*E* and Supplementary Data).

### Blood Pressure

SBP levels decreased from baseline until week 26 in all treatment groups (Supplementary Fig. 4*A*). At week 26, estimated mean change in SBP with semaglutide ranged from −3.4 mmHg (0.1 mg dose group) to −10.0 mmHg (0.3 mg), with liraglutide ranged from −3.1 mmHg (0.6 mg) to −3.6 mmHg (1.8 mg), and with placebo was −2.4 mmHg.

DBP levels from baseline until week 26 are shown in Supplementary Fig. 4*B*. At week 26, estimated mean change in DBP with semaglutide ranged from −0.1 mmHg (0.1 mg dose group) to −3.9 mmHg (0.3 mg), with liraglutide ranged from 0.4 mmHg (1.2 and 1.8 mg) to −1.7 mmHg (0.6 mg), and with placebo was −0.6 mmHg.

Estimated treatment differences between semaglutide and placebo/liraglutide are shown in Supplementary Fig. 4*C*.

### Other Secondary Efficacy End Points

Results for seven-point self-measured BG, BMI, lipids, and the Diabetes Treatment Satisfaction Questionnaire are described in Supplementary Data.

**Table 1—Baseline characteristics of the FAS**

| | Semaglutide | | | | | Liraglutide | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0.05 mg | 0.1 mg | 0.2 mg | 0.3 mg | Flexible dose | 0.3 mg | 0.6 mg | 1.2 mg | 1.8 mg | Pooled placebo | Total |
| *n* | 64 | 63 | 65 | 63 | 64 | 64 | 64 | 64 | 65 | 129 | 705 |
| Age (years) | 57.5 (9.8) | 57.5 (10.0) | 58.4 (9.6) | 54.8 (9.7) | 54.8 (9.7) | 57.2 (10.8) | 59.5 (9.8) | 53.7 (11.4) | 55.8 (9.2) | 57.1 (9.2) | 56.7 (9.9) |
| $HbA_{1c}$ (%) | 7.9 (0.7) | 7.9 (0.8) | 8.0 (0.8) | 8.2 (0.8) | 8.1 (0.9) | 8.1 (0.9) | 8.1 (0.8) | 8.1 (0.9) | 8.1 (0.8) | 8.1 (0.9) | 8.1 (0.8) |
| FPG (mmol/L, mg/dL) | 9.3 (2.6), 166.9 (46.9) | 9.0 (2.2), 161.6 (40.0) | 9.2 (2.3), 165.7 (41.1) | 9.7 (2.6), 174.2 (46.2) | 9.8 (2.7), 177.0 (47.9) | 9.3 (2.5), 168.0 (45.8) | 9.3 (2.3), 168.3 (41.9) | 9.9 (2.7), 178.5 (48.7) | 9.2 (2.4), 165.5 (44.1) | 9.7 (3.0), 174.3 (53.8) | 9.5 (2.6), 170.4 (46.6) |
| Diabetes duration (years) | 6.5 (4.6) | 8.1 (7.3) | 7.2 (5.7) | 6.5 (4.4) | 8.0 (7.1) | 8.1 (7.1) | 6.8 (4.6) | 6.9 (4.9) | 6.6 (5.2) | 7.1 (4.5) | 7.2 (5.6) |
| Body weight (kg) | 93.4 (18.3) | 92.4 (17.2) | 98.1 (17.9) | 94.8 (17.8) | 95.3 (15.4) | 92.3 (17.5) | 92.7 (16.5) | 96.7 (18.3) | 93.4 (19.3) | 94.0 (17.8) | 94.3 (17.6) |
| BMI ($kg/m^2$) | 32.3 (4.6) | 32.4 (4.5) | 32.8 (4.5) | 33.1 (4.7) | 33.2 (4.4) | 32.9 (3.9) | 33.0 (4.3) | 33.3 (4.3) | 32.1 (4.5) | 32.8 (4.2) | 32.8 (4.4) |
| Female sex | 31 (48.4) | 28 (44.4) | 22 (33.9) | 31 (49.2) | 28 (43.8) | 35 (54.7) | 32 (50.0) | 30 (46.9) | 32 (49.2) | 57 (44.2) | 326 (46.2) |
| Race, *n* (%) | | | | | | | | | | | |
| Asian | 6 (9.4) | 9 (14.3) | 5 (7.7) | 7 (11.1) | 4 (6.3) | 4 (6.3) | 2 (3.1) | 4 (6.3) | 11 (16.9) | 14 (10.9) | 66 (9.4) |
| Black or African American | 9 (14.1) | 4 (6.3) | 6 (9.2) | 11 (17.5) | 4 (6.3) | 4 (6.3) | 4 (6.3) | 6 (9.4) | 4 (6.2) | 11 (8.5) | 63 (8.9) |
| White | 49 (76.6) | 50 (79.4) | 51 (78.5) | 44 (69.8) | 52 (81.3) | 53 (82.8) | 56 (87.5) | 54 (84.4) | 48 (73.8) | 103 (79.8) | 560 (79.4) |
| Other | — | — | 3 (4.6) | 1 (1.6) | 4 (6.3) | 3 (4.7) | 2 (3.1) | — | 2 (3.1) | 1 (0.8) | 16 (2.3) |
| Ethnicity, *n* (%) | | | | | | | | | | | |
| Hispanic or Latino | 9 (14.1) | 7 (11.1) | 6 (9.2) | 4 (6.4) | 7 (10.9) | 7 (10.9) | 6 (9.4) | 6 (9.4) | 8 (12.3) | 16 (12.4) | 76 (10.8) |
| Not Hispanic or Latino | 55 (85.9) | 56 (88.9) | 59 (90.8) | 59 (93.7) | 57 (89.1) | 57 (89.1) | 58 (90.6) | 58 (90.6) | 57 (87.7) | 113 (87.6) | 629 (89.2) |
| Renal function,* *n* (%) | | | | | | | | | | | |
| Normal (eGFR ≥90 mL/min/1.73 $m^2$) | 36 (56.3) | 34 (54.0) | 34 (52.3) | 43 (68.3) | 46 (71.9) | 39 (60.9) | 33 (51.6) | 44 (68.8) | 45 (69.2) | 78 (60.5) | 432 (61.3) |
| Mild dysfunction (eGFR 60 to <90 mL/min/1.73 $m^2$) | 28 (43.8) | 28 (44.4) | 31 (47.7) | 20 (31.7) | 18 (28.1) | 24 (37.5) | 31 (48.4) | 19 (29.7) | 20 (30.8) | 51 (39.5) | 270 (38.3) |
| Moderate dysfunction (eGFR 30 to <60 mL/min/1.73 $m^2$) | — | 1 (1.6) | — | — | — | 1 (1.6) | — | 1 (1.6) | — | — | 3 (0.4) |

Data are means (SD) unless otherwise indicated. eGFR, estimated glomerular filtration rate. *Based on estimated glomerular filtration rate using the MDRD formula.

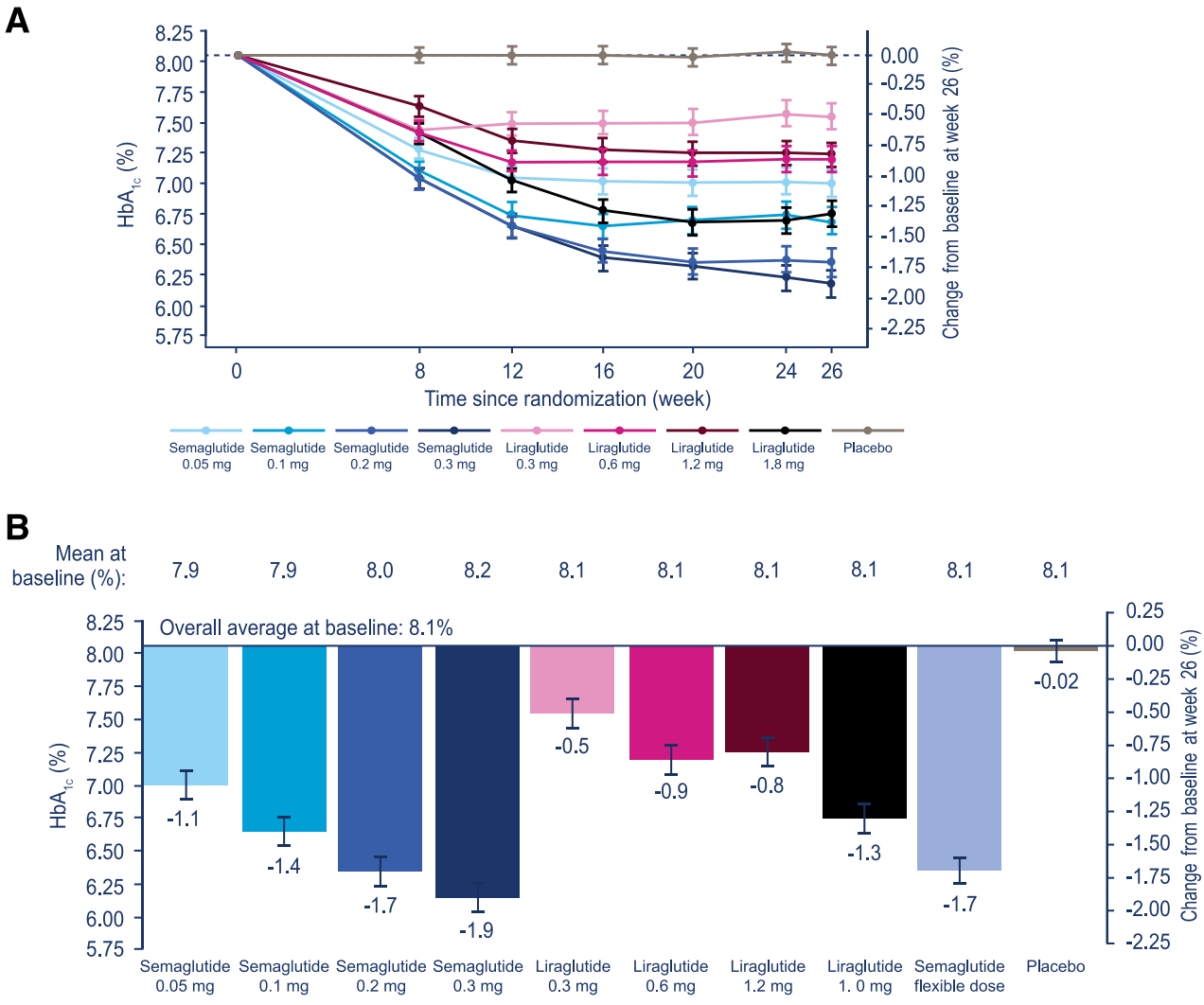


**Figure 1**—Mean change in $HbA_{1c}$ from baseline over time (*A*) and at week 26 (*B*), estimated treatment difference for the percentage change in $HbA_{1c}$ (*C*) and patients achieving <7.0% $HbA_{1c}$ target at week 26 (*D*), and mean change in FPG (mmol/L) from baseline over time (*E*). *A*: Observed "on treatment until rescue medication" data. Mean estimates are from an MMRM analysis with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM; dashed line is the total average value at baseline. *B*: Observed "on treatment until rescue medication" data. Mean estimates are from an MMRM analysis with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM; solid line is the total average value at baseline. *C*: Summary of ETDs and associated CIs from statistical analyses of the parameters at week 26 using the "on treatment until rescue medication" data. The MMRM used for analysis included treatment, region, stratum, and baseline value, all nested within visit. *D*: Analyses of "on treatment until rescue medication" data. The binary end point was analyzed using a logistic regression model with treatment, stratum, and region as fixed factors and the baseline weight value as covariate. Before analysis, missing data were imputed from an MMRM with treatment and region and baseline value, all nested within visit. *E*: Observed "on treatment until rescue medication" data. Mean estimates are from an MMRM analysis with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM; dashed line is the total average value at baseline. According to the protocol, only the fixed treatment arms were analyzed statistically. ADA, American Diabetes Association; ETD, estimated treatment difference.

### Safety

The proportion of patients reporting AEs with semaglutide was dose dependent and comparable with that of the liraglutide groups (Supplementary Table 5). The most common AEs in the semaglutide and liraglutide arms were GI disorders, and the incidence was higher with semaglutide than liraglutide (32.8–54.0% with semaglutide and 21.9–41.5% with liraglutide). Nausea was reported in 17.2–25.4% of patients receiving semaglutide vs. 9.4–20.0% receiving liraglutide, diarrhea in 10.9–25.4 vs. 7.8–10.8%, and vomiting in 6.3–9.5 vs. 1.6–10.9% (Table 2 and Supplementary Table 6). The majority of these GI events occurred during the first 12 weeks of treatment (Supplementary Fig. 5). Liraglutide 1.8 mg was equivalent to semaglutide 0.14 mg for patients reporting at least one GI AE; thus, the dose ratio for semaglutide versus liraglutide was 12.8 ($P < 0.0001$) (Supplementary Fig. 3*C*).

Comparable proportions of patients across all treatment groups reported serious AEs (Supplementary Table 5); no clustering was identified within organ systems. There was one fatality in the trial in the liraglutide arm (1.8 mg group); this was due to sudden cardiac death in a patient with a history of ischemic heart disease.

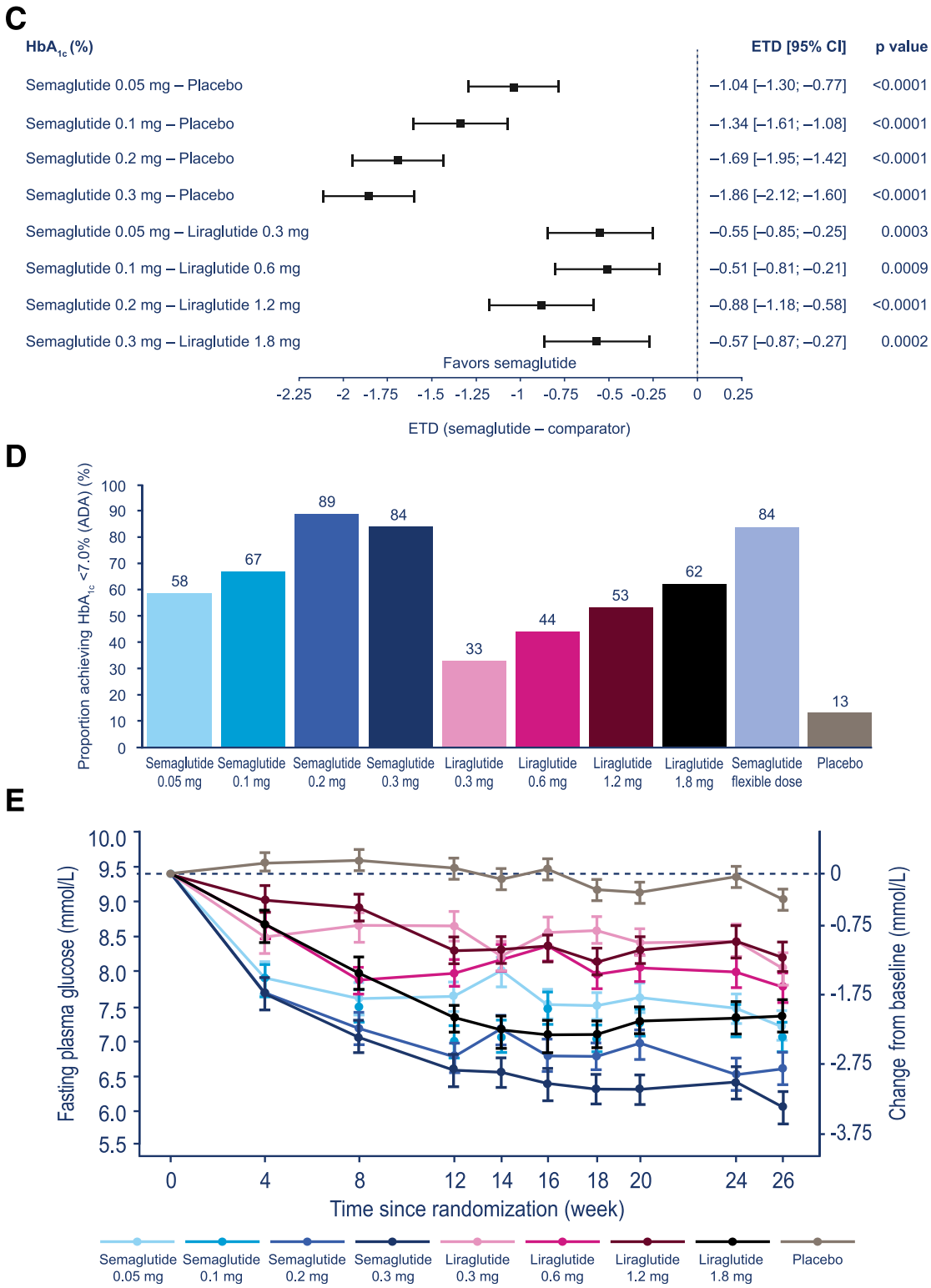


**Figure 1**—*Continued*.

The proportion of patients with AEs leading to premature treatment discontinuation was higher with pooled placebo (10.9%) than with semaglutide (6.3–7.9%) and liraglutide (3.1–7.8%) (Supplementary Table 5). The majority of AEs leading to premature treatment discontinuation in the semaglutide and liraglutide groups were GI AEs (1.6–4.7 and 1.6–3.1%, respectively)—mainly nausea, vomiting, and diarrhea—whereas in the pooled placebo group were mainly hyperglycemia events (6.2%). Liraglutide 1.8 mg was equivalent to semaglutide 0.24 mg for patients discontinuing treatment due to AEs; thus, the dose ratio for semaglutide versus liraglutide was 7.4 ($P$ = 0.0006) (Supplementary Fig. 3*C*).

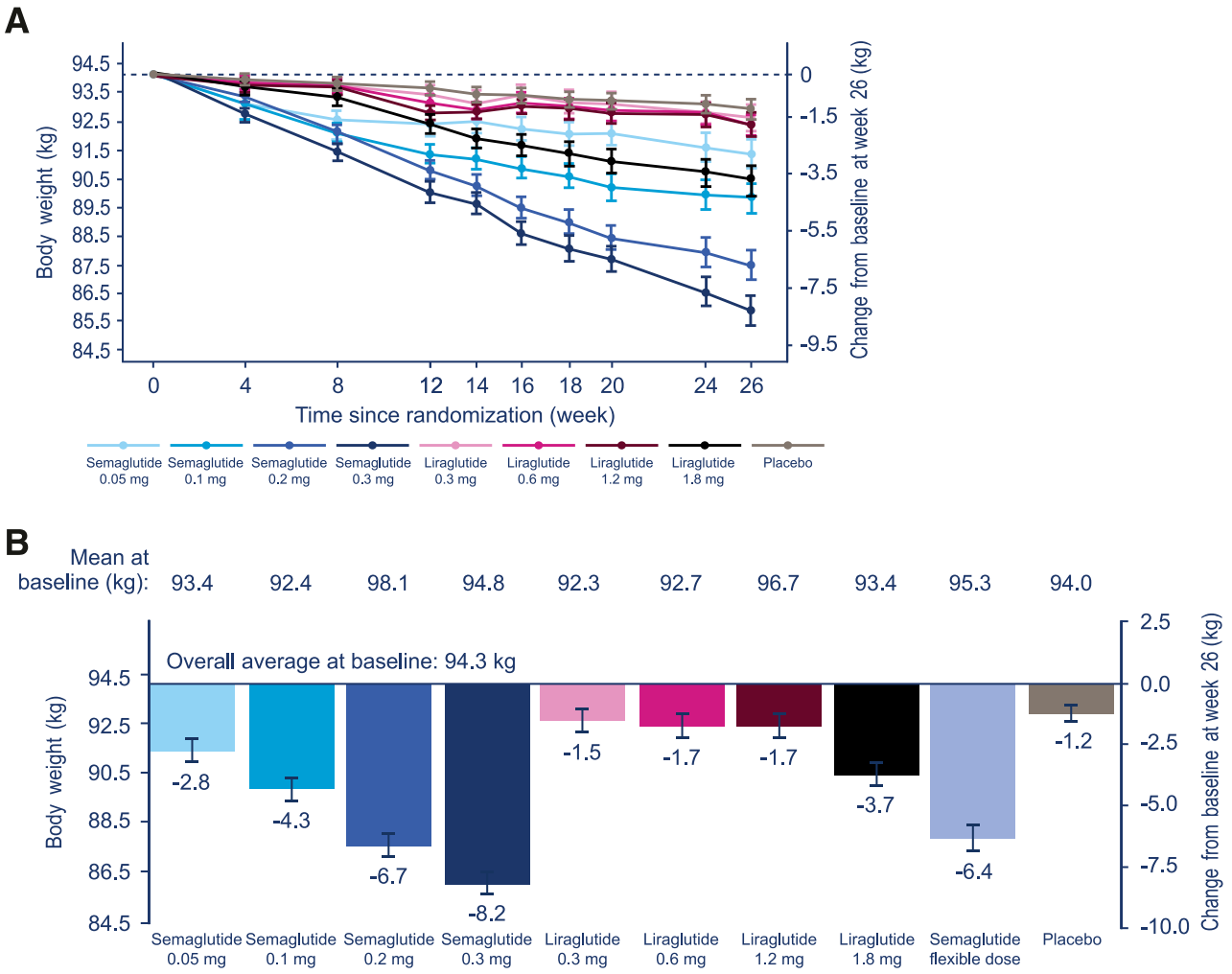


**Figure 2**—Mean change in body weight (kg) from baseline over time (*A*) and at week 26 (*B*), estimated treatment difference for mean change in body weight (*C*) and patients achieving ≥5% weight loss response at week 26 (*D*), and mean change in waist circumference from baseline over time (*E*). *A*: Observed "on treatment until rescue medication" data. Mean estimates are from an MMRM analysis with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM; dashed line is the total average value at baseline. *B*: Observed "on treatment until rescue medication" data. Mean estimates are from an MMRM analysis with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM; solid line is the total average value at baseline. *C*: Summary of estimated treatment differences and associated CIs from statistical analyses of the parameters at week 26 using the "on treatment until rescue medication" data. The MMRM used for analysis included treatment, region, stratum, and baseline value, all nested within visit. *D* and *E*: Analyses of "on treatment until rescue medication" data. The binary end point was analyzed using a logistic regression model with treatment, stratum, and region as fixed factors and the baseline weight value as covariate. Before analysis, missing data were imputed from an MMRM with treatment and region and baseline value, all nested within visit. Observed "on treatment until rescue medication" data. Mean estimates are from an MMRM analysis with treatment, region, and stratum as fixed factors and baseline value as covariate, all nested within visit, and are adjusted according to observed baseline distribution. Error bars are ±1*SEM; dashed line is the total average value at baseline. According to the protocol, only the fixed treatment arms were analyzed statistically. ETD, estimated treatment difference.

The incidence of severe or BG-confirmed symptomatic hypoglycemia was similar among all groups (3.1–4.6% with semaglutide, 0–4.6% with liraglutide, and 3.1% with pooled placebo) (Supplementary Table 7).

Two AEs of pancreatitis (semaglutide 0.2 mg and semaglutide 0.05 mg groups) were sent for event adjudication by the EAC; neither event was confirmed. Mean lipase and amylase values from baseline to week 26 were significantly increased for all semaglutide and liraglutide doses compared with pooled placebo (ratio to baseline for lipase 1.18–1.52 and 1.32–1.44 vs. 0.93 and for amylase 1.13–1.23 and 1.13–1.15 vs. 0.99), with no difference between semaglutide and liraglutide groups (except semaglutide 0.2 mg vs. liraglutide 1.2 mg, where a higher increase in amylase activity was observed in the semaglutide arm [$P$ = 0.0060]) (Supplementary Table 8). At week 26, the proportion of patients with a more than twofold increase in lipase from baseline was 1.6–6.3% with semaglutide and 1.6–7.8% with liraglutide vs. 0.8–2.8% with placebo; a more than threefold increase was reported in 1.6–3.1 and 3.1 vs. 0.9% of patients, respectively. There were no patients with a more than twofold increase in amylase levels in any of the treatment groups.

EAC-confirmed cardiovascular events were reported in two patients (four events) on semaglutide 0.05 mg, three

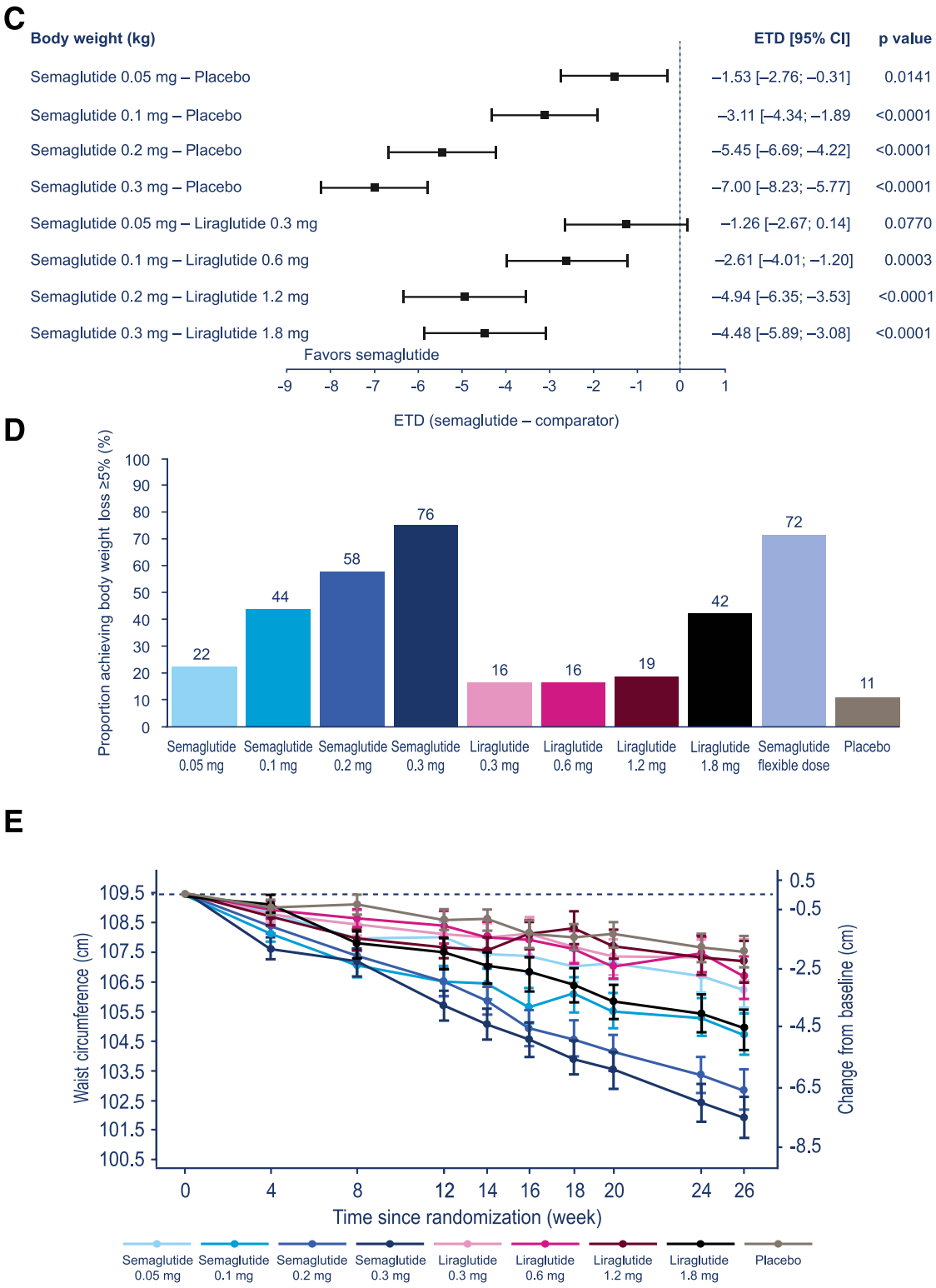


**Figure 2**—*Continued.*

patients (six events) on liraglutide 1.8 mg, and one patient (one event) on pooled placebo during the on-treatment observation period.

There were four EAC-confirmed neoplasms, three of which were malignant: one pancreatic carcinoma with semaglutide 0.05 mg, one basal cell skin cell carcinoma with liraglutide 0.6 mg, and one prostate adenocarcinoma with liraglutide 1.8 mg.

Pulse rate (baseline 74 beats per minute [bpm]) increased in all treatment groups: by 0.7–2.8 bpm with semaglutide, by 2.4–5.4 bpm with liraglutide, and by 0.8 bpm with pooled placebo.

AEs related to diabetic retinopathy were reported during study follow-up in five patients: one in each of the

**Table 2—Most frequent (≥5%) GI disorders on treatment by preferred term (predefined MedDRA search)**

| | Semaglutide 0.05 mg, *n* = 64 | | | | Semaglutide 0.1 mg, *n* = 63 | | | | Semaglutide 0.2 mg, *n* = 65 | | | | Semaglutide 0.3 mg, *n* = 63 | | | | Semaglutide flexible dose, *n* = 64 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | % | E | R | *N* | % | E | R | *N* | % | E | R | *N* | % | E | R | *N* | % | E | R |
| GI AEs | 21 | 32.8 | 61 | 162 | 28 | 44.4 | 90 | 236 | 30 | 46.2 | 106 | 283 | 34 | 54.0 | 101 | 268 | 36 | 56.3 | 128 | 322 |
| Nausea | 11 | 17.2 | 16 | 42 | 12 | 19.0 | 20 | 52 | 14 | 21.5 | 22 | 59 | 16 | 25.4 | 22 | 58 | 25 | 39.1 | 34 | 85 |
| Diarrhea | 7 | 10.9 | 10 | 26 | 10 | 15.9 | 13 | 34 | 10 | 15.4 | 15 | 40 | 16 | 25.4 | 29 | 77 | 11 | 17.2 | 22 | 55 |
| Vomiting | 6 | 9.4 | 10 | 26 | 4 | 6.3 | 13 | 34 | 6 | 9.2 | 9 | 24 | 6 | 9.5 | 8 | 21 | 6 | 9.4 | 8 | 20 |
| Constipation | 2 | 3.1 | 2 | 5 | 4 | 6.3 | 4 | 10 | 6 | 9.2 | 11 | 29 | 5 | 7.9 | 7 | 19 | 4 | 6.3 | 6 | 15 |
| Dyspepsia | 1 | 1.6 | 6 | 16 | 5 | 7.9 | 7 | 18 | 5 | 7.7 | 8 | 21 | 6 | 9.5 | 6 | 16 | 4 | 6.3 | 4 | 10 |
| Abdominal discomfort | 2 | 3.1 | 2 | 5 | 3 | 4.8 | 4 | 10 | 1 | 1.5 | 1 | 3 | 2 | 3.2 | 3 | 8 | 4 | 6.3 | 4 | 10 |
| Abdominal pain | 2 | 3.1 | 4 | 11 | 2 | 3.2 | 4 | 10 | 3 | 4.6 | 7 | 19 | 5 | 7.9 | 6 | 16 | 4 | 6.3 | 7 | 18 |
| Flatulence | 2 | 3.1 | 2 | 5 | 1 | 1.6 | 5 | 13 | 4 | 6.2 | 6 | 16 | 1 | 1.6 | 1 | 3 | 6 | 9.4 | 9 | 23 |
| Abdominal pain, upper | 0 | — | — | — | 1 | 1.6 | 1 | 3 | 4 | 6.2 | 5 | 13 | 4 | 6.3 | 4 | 11 | 6 | 9.4 | 8 | 20 |
| Gastroesophageal reflux disease | 0 | — | — | — | 4 | 6.3 | 8 | 21 | 3 | 4.6 | 3 | 8 | 3 | 4.8 | 3 | 8 | 4 | 6.3 | 5 | 13 |
| | Liraglutide 0.3 mg, *n* = 64 | | | | Liraglutide 0.6 mg, *n* = 64 | | | | Liraglutide 1.2 mg, *n* = 64 | | | | Liraglutide 1.8 mg, *n* = 65 | | | | Pooled placebo, *n* = 129 | | | |
| | *N* | % | E | R | *N* | % | E | R | *N* | % | E | R | *N* | % | E | R | *N* | % | E | R |
| GI AEs | 14 | 21.9 | 25 | 65 | 19 | 29.7 | 62 | 161 | 20 | 31.3 | 40 | 106 | 27 | 41.5 | 81 | 207 | 29 | 22.5 | 54 | 73 |
| Nausea | 6 | 9.4 | 7 | 18 | 7 | 10.9 | 11 | 29 | 7 | 10.9 | 11 | 29 | 13 | 20.0 | 18 | 46 | 6 | 4.7 | 7 | 9 |
| Diarrhea | 5 | 7.8 | 5 | 13 | 5 | 7.8 | 9 | 23 | 5 | 7.8 | 8 | 21 | 7 | 10.8 | 15 | 38 | 14 | 10.9 | 18 | 24 |
| Vomiting | 1 | 1.6 | 1 | 3 | 7 | 10.9 | 10 | 26 | 1 | 1.6 | 1 | 3 | 5 | 7.7 | 8 | 20 | 3 | 2.3 | 3 | 4 |
| Constipation | 0 | — | — | — | 3 | 4.7 | 3 | 8 | 1 | 1.6 | 2 | 5 | 7 | 10.8 | 7 | 18 | 4 | 3.1 | 4 | 5 |
| Dyspepsia | 2 | 3.1 | 2 | 5 | 3 | 4.7 | 3 | 8 | 1 | 1.6 | 1 | 3 | 3 | 4.6 | 3 | 8 | 1 | 0.8 | 1 | 1 |
| Abdominal discomfort | 1 | 1.6 | 1 | 3 | 3 | 4.7 | 5 | 13 | 2 | 3.1 | 2 | 5 | 4 | 6.2 | 13 | 33 | 3 | 2.3 | 4 | 5 |
| Abdominal pain | 3 | 4.7 | 3 | 8 | 0 | — | — | — | 4 | 6.3 | 4 | 11 | 0 | — | — | — | 0 | — | — | — |

E, number of events; MedDRA, Medical Dictionary for Regulatory Activities; *N*, number of patients experiencing at least one event; R, event rate per 100 years of exposure; %, percentage of patients experiencing at least one event. GI AEs were defined as any of the AEs listed in the table. All AEs, either observed by the investigator or subject, were reported by the investigator and evaluated. The "on treatment" overview includes treatment-emergent AEs with onset at or after the date of the first trial product dose and before or at the date of the last trial product dose plus 7 weeks plus the 7 days' visit window for the end-of-treatment follow-up visit (56 days). The observation time is the duration of this period.

semaglutide 0.1 and 0.3 mg and liraglutide 0.3, 0.6, and 1.2 mg groups.

There were no reported clinically relevant effects on biochemistry, hematology, urinalysis, electrocardiogram, or physical examination. No anti-semaglutide antibodies were detected in any of the fixed-dose treatment groups during the trial or at week 26. Additional safety results are shown in Supplementary Data and Supplementary Table 9.

## Semaglutide Flexible-Dosing Arm

### *Patient Disposition and Dosing*

A total of 65 patients were randomized to the semaglutide flexible-dosing arm. Sixty-four patients were exposed to treatment; of these, 90.6% completed treatment (Supplementary Fig. 2).

Patient characteristics at baseline are shown in Table 1.

The dose history of the 64 exposed patients is shown in Supplementary Fig. 6*A*. Overall, dose escalation was delayed by 2 weeks for most patients compared with the 4-week default planned time points (dotted lines).

After week 12, approximately one-third of patients were receiving the 0.3 mg dose, and an additional one-third of patients were by week 14. At week 26, 80% of patients were receiving semaglutide 0.3 mg. The median time to reach specific doses was 5.7 weeks for the 0.1 mg dose, 9.9 weeks for 0.2 mg, and 13.7 weeks for 0.3 mg. Mean dose at 26 weeks for patients in the open-label flexible-dosing group is shown in Supplementary Fig. 6*B*.

### *Efficacy*

Mean change in $HbA_{1c}$ at week 26 in the semaglutide flexible-dosing arm was −1.7% (Fig. 1*B*). A total of 67% and 84% of patients achieved the $HbA_{1c}$ treatment targets of ≤6.5% (48 mmol/mol) and <7.0% (53 mmol/mol) (Fig. 1*D*), respectively.

Mean change in body weight at week 26 in the semaglutide flexible-dosing arm was −6.4 kg (Fig. 2*B*). A total of 72% and 19% of patients achieved weight loss responses of ≥5% (Fig. 2*D*) and ≥10%, respectively.

Throughout the trial, the overall trend in $HbA_{1c}$ and body weight decrease was comparable with the semaglutide 0.2 mg group.

### *Safety*

AEs were reported in 82.8% of patients in the semaglutide flexible-dosing arm and serious AEs in 6.3% of patients. No fatalities were reported. The proportion of patients with AEs leading to premature treatment discontinuation was 4.7% (three patients reported four events, three of which were GI in nature).

In total, 56.3% of patients experienced GI disorders. The most common GI events were nausea (39.1%), diarrhea (17.2%), and vomiting, flatulence, and upper-abdominal pain (9.4% each) (Table 2). The proportion of patients across the fixed-dose semaglutide arms reporting nausea, diarrhea, and vomiting was 17.2–25.4, 10.9–25.4, and 6.3–9.5%, respectively (Table 2). The majority of these GI events occurred during the first 12 weeks of treatment (Supplementary Fig. 5).

Further details of AEs in the semaglutide flexible-dosing arm are detailed in Supplementary Data.

## CONCLUSIONS

In this phase 2, 26-week, randomized, double-blind (within dose level), dose-

finding trial in patients with type 2 diabetes, semaglutide administered subcutaneously once daily led to significantly greater glycemic control compared with placebo or liraglutide. The weekly sum of the semaglutide doses tested in this trial was equivalent to 0.35–2.1 mg/week. In the SUSTAIN program, only the semaglutide dose of 0.5 and 1 mg once weekly was evaluated, while the current analysis evaluated the efficacy and tolerability of semaglutide at higher doses than previously studied.

Treatment with semaglutide also led to significantly greater weight loss compared with pooled placebo or liraglutide. This effect was dose dependent, with observed weight reductions of up to 8.2 kg, approximately seven times greater than with pooled placebo (1.2 kg) and more than double the maximum weight reduction observed with liraglutide (3.7 kg).

The reductions in $HbA_{1c}$ and body weight were generally dose dependent across all fixed-dose groups, with greater and linear reductions from semaglutide 0.05 mg to semaglutide 0.3 mg vs. liraglutide 0.3 mg to liraglutide 1.8 mg.

GI AEs were the most frequently reported AEs with semaglutide once daily and liraglutide once daily. These AEs mainly occurred in the initial 12 weeks of treatment, and the majority were mild to moderate. A dose response was seen, with a higher number of GI AEs reported with higher doses of semaglutide.

The potency of semaglutide (based on the ratio between liraglutide's and semaglutide's equipotent doses) was 28 times higher than liraglutide for $HbA_{1c}$ reduction and 30 times higher for weight loss. In contrast, the equivalent dose ratio between semaglutide and liraglutide was only 12.8 for GI AEs and 7.4 for treatment discontinuation owing to AEs. This suggests that greater reductions in $HbA_{1c}$ and body weight might be achieved with semaglutide without an increase in the risk of GI AEs compared with liraglutide. Nevertheless, discontinuation owing to GI AEs occurred more frequently with semaglutide than liraglutide; therefore, the greater efficacy of semaglutide was not sufficient to maintain adherence to treatment. The reasons for this difference in potency are speculative. However, the properties of semaglutide, such as greater free drug concentrations in the plasma and stronger albumin binding compared with liraglutide, or greater affinity for the GLP-1 receptor (10), may be a contributing factor.

Notably, semaglutide doses were initiated at 0.05 mg and patients dosed to a maximum of 0.3 mg, while liraglutide doses were initiated using a subtherapeutic dose (0.3 mg) and increased to a maximum of 1.8 mg (slower titration compared with label) (20). Therefore, it is possible that the lower rate of GI AEs observed with liraglutide may also be due to the slower titration of liraglutide, which was employed to preserve the blinded nature of the study.

Interestingly, the GI AE rate in the open-label, flexible-dosing group was similar to that in the semaglutide 0.3 mg group despite a delay in titration (median time to reach the 0.3 mg dose was 13.7 weeks vs. 12 weeks in the fixed-titration group). This may be due to the open-label nature of the dosing, and therefore patient anticipation of GI AEs, or to chance, owing to variability and the small group size. Conversely, the proportion of patients with AEs leading to premature treatment discontinuation was the lowest in this group at 4.7%, suggesting good patient adherence and tolerability despite the occurrence of GI AEs.

The efficacy of semaglutide with respect to $HbA_{1c}$ and body weight in the open-label, flexible-dosing group was similar to that in the semaglutide 0.2 mg arm. This is possibly due to the combination of delayed titration and relatively short trial duration, which resulted in only 12 weeks of follow-up on the final dose in this group, leading to a shorter semaglutide maintenance period at the given dose compared with the other groups.

The trial was robust in terms of patients being randomized and controlled within each dosing volume—both with placebo and liraglutide—for each semaglutide dose. However, the trial had a number of limitations. First, the trial duration was relatively short (the highest fixed-dose arm had only 14 weeks of dose maintenance after the titration period) and the maximum effects were not reached, especially in the higher-dose semaglutide arms. Second, the investigated treatment arms were relatively small. Third, liraglutide was titrated at a slower rate than label, thus potentially affecting its efficacy and tolerability profile. In addition, a major limitation was that GI AEs were assessed by patient self-reporting, a method whereby accuracy and consistency are known to be low because it relies on the patient's awareness and perception of their symptoms. Self-reporting can be particularly inaccurate if the symptoms are embarrassing (e.g., fecal incontinence) (22). In addition, reporting may have been influenced by an expectation of experiencing GI AEs, as patients had been advised of this risk in the informed consent form prior to commencing the trial. A validated measure for GI AEs that asks patients specifically about their symptoms, such as the Gastrointestinal System Rating Scale (23), would have been more appropriate. Also, this trial only enrolled individuals who were either treatment naïve or treated with metformin; therefore, results should not be extrapolated to patients with more advanced disease.

Based on the clinical results of this study, including the GI AE profile, paired with the general changing focus toward weekly injections of GLP-1 receptor agonists for type 2 diabetes, there are no current plans for further development of semaglutide once daily.

In conclusion, in this 26-week phase 2 trial in patients with type 2 diabetes, treatment with semaglutide once daily at doses up to 0.3 mg/day resulted in greater reductions in $HbA_{1c}$ compared with once-daily liraglutide and pooled placebo. Based on dose-response modeling, the liraglutide 1.8 mg dose is equivalent to semaglutide 0.06 mg at lowering $HbA_{1c}$ as well as body weight. The incidence of GI AEs was higher with the semaglutide doses than the liraglutide doses, although no new safety concerns were identified with semaglutide once daily.

**Acknowledgments**. The authors thank all the participants, investigators, and trial site staff who were involved in the conduct of the trial. The authors also thank Gurudutt Nayak (Novo Nordisk) for review of and input into the manuscript and Saroshi Amirthalingam and Sola Neunie (both AXON Communications, London, U.K.) for medical writing and editorial assistance, who received compensation from Novo Nordisk.
**Duality of Interest**. This trial was funded by Novo Nordisk. I.L. has received research grants from Novo Nordisk, Merck, Pfizer, GI Dynamics, Novartis; consulting fees from Novo Nordisk, Lilly, Sanofi, and AstraZeneca; and other services (travel/editorial support) from Sanofi, Boehringer

Ingelheim, AstraZeneca, and Novo Nordisk. C.V.D. has a consulting agreement with Novo Nordisk and has received research support from Janssen and Theracos. T.H. is an employee of Novo Nordisk. J.Z. is an employee and stock owner of Novo Nordisk. T.R.P. has received research grants from AstraZeneca and Novo Nordisk; has received consulting fees from Adocia, AstraZeneca, Eli Lilly, Novo Nordisk, and Roche Diabetes Care; and is Chief Scientific Officer of CBmed (Center for Biomarker Research in Medicine), a public-owned research company. No other potential conflicts of interest relevant to this article were reported.

**Author Contributions.** I.L., T.H., J.Z., and T.R.P. researched data, reviewed and edited the manuscript, and contributed to the discussion. C.V.D. reviewed and edited the manuscript and contributed to the discussion. K.S.L. researched data and reviewed and edited the manuscript. L.R. researched data and reviewed and edited the manuscript. T.R.P. 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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