A Phase 2, Randomized, Dose-Finding Study of the Novel Once-Weekly Human GLP-1 Analog, Semaglutide, Compared With Placebo and Open-Label Liraglutide in Patients With Type 2 Diabetes

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OBJECTIVE

To investigate the dose-response relationship of semaglutide versus placebo and open-label liraglutide in terms of glycemic control in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

This was a 12-week, randomized, double-blind phase 2 trial. Patients (*n* = 415) were randomized to receive a subcutaneous injection of semaglutide once weekly without dose escalation (0.1–0.8 mg) or with dose escalation (E) (0.4 mg steps to 0.8 or 1.6 mg E over 1–2 weeks), open-label liraglutide once daily (1.2 or 1.8 mg), or placebo. The primary end point was change in HbA_{1c} level from baseline. Secondary end points included change in body weight, safety, and tolerability.

RESULTS

Semaglutide dose-dependently reduced the level of HbA_{1c} from baseline (8.1 ± 0.8%) to week 12 by up to −1.7%, and body weight by up to −4.8 kg (1.6 mg E, $P <$ 0.001 vs. placebo). Up to 81% of patients achieved an HbA_{1c} level of <7%. HbA_{1c} level and weight reductions with semaglutide 1.6 mg E were greater than those with liraglutide 1.2 and 1.8 mg (based on unadjusted CIs), but adverse events (AEs) and withdrawals occurred more frequently. The incidence of nausea, vomiting, and withdrawal due to gastrointestinal AEs increased with the semaglutide dose; most events were mild to moderate, transient, and ameliorated by dose escalation. There were no major episodes of hypoglycemia and few cases of injection site reactions.

CONCLUSIONS

After 12 weeks, semaglutide dose-dependently reduced HbA_{1c} level and weight in patients with type 2 diabetes. No unexpected safety or tolerability concerns were identified; gastrointestinal AEs typical of glucagon-like peptide 1 receptor agonists were mitigated by dose escalation. On this basis, weekly semaglutide doses of 0.5 and 1.0 mg with a 4-week dose escalation were selected for phase 3.

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Native glucagon-like peptide 1 (GLP-1) is a gut-derived incretin hormone that stimulates insulin secretion and suppresses glucagon secretion in a glucose-dependent manner. It also delays gastric emptying, and reduces appetite and energy intake (1–4). These actions improve glucose homeostasis and thereby reduce hyperglycemia, making GLP-1 a valuable therapeutic target for the management of type 2 diabetes.

Ongoing approaches to optimizing GLP-1 therapy aim to improve efficacy, tolerability, and convenience, with a focus on the frequency and ease of administration. Recent developments have focused mainly on lengthening the period between injections (5). Currently in phase 3 clinical development for the treatment of type 2 diabetes, semaglutide is a human GLP-1 analog with a long duration of action, allowing once-weekly administration.

Semaglutide is structurally similar to native human GLP-1-(7–37), with 94% homology (6). Three minor but important modifications make semaglutide suitable for once-weekly clinical use: amino acid substitutions at position 8 (alanine to α-aminoisobutyric acid) and position 34 (lysine to arginine), and acylation of the lysine in position 26 with a spacer and C-18 fatty diacid chain. The fatty diacid and the spacer mediate strong binding to albumin, thereby reducing renal clearance. The amino acid substitution at position 8 makes semaglutide less susceptible to degradation by dipeptidyl peptidase-4. The half-life of semaglutide is 165–184 h (6,7) (i.e., appropriate for once-weekly injection).

The primary objective of this phase 2 study was to explore the dose-response relationship of once-weekly semaglutide versus placebo in glycemic control therapy in patients with type 2 diabetes inadequately controlled with diet and exercise, either alone or in combination with metformin, with the aim of establishing the optimum dose and regimen to be taken forward into phase 3 clinical trials. The safety, tolerability, and efficacy/pharmacodynamics of semaglutide compared with placebo and open-label, once-daily liraglutide were also investigated.

RESEARCH DESIGN AND METHODS

This was a 12-week, randomized, nine-armed, parallel-group, phase 2, dose-finding trial, which was double-blind for semaglutide versus placebo and open-label for the active control (liraglutide). Its aim was to assess the dose-response relationship of five doses of once-weekly semaglutide compared with placebo (primary objective) and open-label liraglutide (secondary objective) in terms of glycemic control in patients with type 2 diabetes. Participants were randomized to receive semaglutide once weekly, open-label liraglutide once daily, or placebo once weekly. Patients were enrolled between June 2008 and February 2009 at 80 centers in 14 countries (Austria, Bulgaria, Finland, France, Germany, Hungary, India, Italy, Serbia, South Africa, Spain, Switzerland, Turkey, and the U.K.). Written informed consent was obtained from all participants before any study-related activities commenced. The study was registered at http://www.clinicaltrials.gov (clinical trial reg. no. NCT00696657).

Patients $\geq$18 years of age who had received a diagnosis of type 2 diabetes and had been treated with either diet and exercise alone or together with a stable regimen of metformin monotherapy ($\geq$1,500 mg) for at least 3 months were enrolled, comprising men and women categorized as not of childbearing potential (i.e., permanently sterilized or postmenopausal). Eligible patients had an HbA_{1c} level of 7.0–10.0% (inclusive 53–86 mmol/mol) and a body weight of 60–110 kg. Key exclusion criteria included treatment with antidiabetic agents other than metformin (except for short-term treatment with insulin at the discretion of the investigator) within the preceding 3 months; impaired liver and/or renal function (serum creatinine); clinically significant active cardiovascular disease (including myocardial infarction within 6 months and/or heart failure [New York Heart Association class III–IV]); uncontrolled hypertension (systolic blood pressure [SBP] $\geq$160 mmHg and/or diastolic blood pressure [DBP] $\geq$100 mmHg); proliferative retinopathy; and cancer (except basal skin cancer or squamous cell skin cancer).

The study was approved by local ethics committees and was conducted in accordance with the Declaration of Helsinki (8) and the International Conference on Harmonisation Guideline for Good Clinical Practice (9).

Drug Administration

Patients were randomly assigned using an interactive voice/web response system with equal ratio to one of nine treatment arms to receive once-weekly semaglutide (0.1, 0.2, 0.4, or 0.8 mg), once-weekly semaglutide with dose escalation (E) (0.8 or 1.6 mg E), once-daily open-label liraglutide (1.2 or 1.8 mg), or once-weekly placebo (Fig. 1). Patients were stratified according to their previous treatment (diet and exercise or metformin monotherapy). A fixed 1- to 2-week dose-escalation period was used for the two highest semaglutide doses (from 0.4 to 0.8 mg E and from 0.4 to 0.8 to 1.6 mg E, respectively), and for both open-label liraglutide active comparator arms (from 0.6 to 1.2 mg and from 0.6 to 1.2 to 1.8 mg). The 12-week treatment period was followed by a 5-week follow-up period and a follow-up visit (week 17).

All trial products were supplied by Novo Nordisk A/S (Søborg, Denmark). Semaglutide was supplied in 1.5-mL cartridges for once-weekly subcutaneous injection in preparations of 1 and 10 mg/mL concentrations. Semaglutide vehicle was used as a placebo. The cartridges containing semaglutide or placebo were blinded. Blinding of semaglutide treatment was maintained by administering matching volumes to patients randomized to receive semaglutide or placebo. Liraglutide was administered as open label due to differences in liraglutide (once daily) and semaglutide (once weekly) administration.

Semaglutide or placebo was administered subcutaneously in the abdomen, thigh, or upper arm by use of the NordiPen injection device. For each patient, the injection was administered on the same day of the week and, preferably, the same area for injection used throughout the trial. Liraglutide (6.0 mg/mL, open label) was available as active drug for once-daily subcutaneous injection in the abdomen, upper arm, or thigh using a 3-mL pen-injector (FlexPen).

Study End Points and Assessments

The primary efficacy end point was the change from baseline in HbA_{1c} level after 12 weeks of treatment. Secondary efficacy measures included changes from baseline in fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) area under the curve (AUC), and

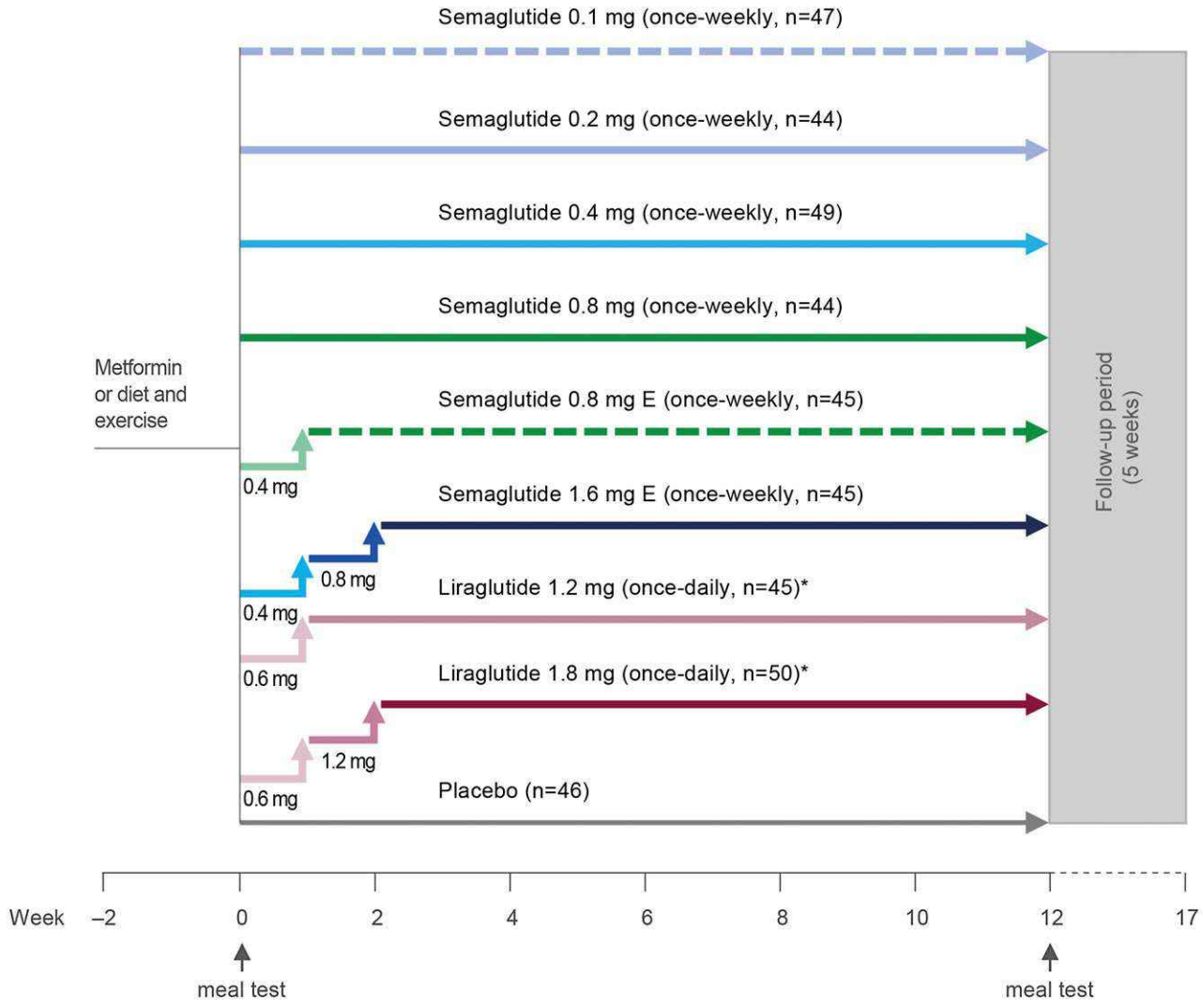

Figure 1—Study design. *Open-label.

additional glycemic control parameters (insulin, C-peptide, glucagon, HOMA index of β-cell function, and HOMA of insulin resistance), insulin/proinsulin ratio, body measurements (body weight and waist and hip circumference), and fasting lipid profile. The proportion of patients achieving predefined HbA_{1c} targets (American Diabetes Association [ADA] target <7% [53 mmol/mol] and American Association of Clinical Endocrinologists [AACE] target ≤6.5% [48 mmol/mol]) was also assessed (10,11), as was the proportion of patients achieving ≥5% and ≥10% body weight loss (12,13).

Meal tests were performed at baseline (before the initiation of treatment) and at the end of treatment (week 12). After overnight fasting, subjects were asked (but not forced) to consume within 15 min a standard breakfast meal of fixed energy content (2 MJ; further details are provided in Supplementary Table 1). Samples for the measurement of plasma glucose levels were collected 10 min before and 15, 30, 45, 60, 90, 120, 180, and 240 min after the meal test.

Safety assessments included adverse events (AEs), physical examination, vital signs (SBP, DBP, and pulse), electrocardiogram, fundoscopy, hypoglycemic episodes, and laboratory safety parameters (hematology, biochemistry, calcitonin, urinalysis, and semaglutide antibodies). The severity of AEs was defined as follows: mild (transient symptoms, no interference with a patient's daily activities); moderate (marked symptoms, moderate interference with a patient's daily activities); and severe (considerable interference with a patient's daily activities, unacceptable). Treatment-emergent AEs (TEAEs) were defined as events that had an onset on or after the first day of exposure to the study drug and no later than 5 weeks after the last date on the study drug, or that had onset before the first date, and increased in severity during the treatment period and no later than 5 weeks after the last date. All serious AEs were coded using the *Medical Dictionary for Regulatory Activities Coding*, version 11.1. The Food and Drug Administration requirement to assess amylase and lipase in clinical trials with GLP-1 receptor agonists was introduced after the semaglutide 1821 trial was initiated, and hence no such assessments were included in the protocol.

Statistical Analysis

The enrollment of 40 patients in the semaglutide 1.6 mg E arm and 42 patients in the combined placebo arm provided 90% power of detecting a 1.0%

HbA_{1c} difference between treatments, with a two-sided test at a 5% significance level, a common SD of 1.2%, and a dropout rate of 20%. The placebo arm of 42 patients consisted of six groups with seven patients in each group, corresponding to the six semaglutide regimens (doses and/or dose-escalation regimens). In line with the sample size calculation, data for all patients randomized to receive placebo were pooled, analyzed, and reported as one placebo group.

All efficacy end points were assessed for all randomized patients who were exposed to at least one dose of investigational drug, and patients were analyzed as randomized (full analysis set). The safety analysis set included all patients who were exposed to at least one dose of trial drug, and patients were analyzed by the actual treatment received, regardless of the treatment to which they were randomized. The primary efficacy analysis was assessed by ANOVA, with treatment, previous antidiabetic treatment (diet and exercise or metformin), and country as fixed factors, and baseline value as the covariate. Missing values were imputed using the last-observation-carried-forward approach using post-baseline values.

Data for continuous secondary efficacy end points prespecified for statistical analysis and the post hoc analyses of fasting lipid parameters and three safety end points (SBP, DBP, and pulse) were analyzed by a similar ANOVA, with the corresponding baseline value as the covariate. The AUC and maximum concentration (C_{max}) derived from meal test profiles were log-transformed and analyzed. The categorical variable of patients attaining the ADA HbA_{1c} target of $<$7% (53 mmol/mol) and the AACE HbA_{1c} target of $\leq$6.5% (48 mmol/mol) was analyzed separately using a logistic regression model based on the last observation carried forward and with the same covariates that were used for the primary end point. To adjust for multiplicity within an end point, the results for the primary pairwise comparisons of the semaglutide doses (0.1, 0.2, 0.4, 0.8, and 0.8 mg E, and 1.6 mg E) versus those for the placebo arm were reported as prespecified using the Dunnett method with adjusted 95% CIs and *P* values for two-sided testing of the null hypothesis (no difference at α = 0.05). As prespecified, the estimated treatment differences (ETDs) for the semaglutide-liraglutide and liraglutide-placebo comparisons were presented with unadjusted 95% CIs and without *P* values.

RESULTS

Patient Disposition

Overall, 711 patients were screened; a total of 415 patients were randomized to receive treatment, and 411 patients were exposed to an investigational drug. Two patients randomized to receive semaglutide 0.8 mg were mistakenly allocated to dose escalation, so their actual treatment was semaglutide 0.8 mg E. In two patients who were randomized to semaglutide 0.8 mg E, a 1.6 mg E was erroneously used. Of all patients randomized, 341 (82.2%) completed the 12-week treatment period (Supplementary Fig. 1). The nine treatment arms were generally well matched in terms of demographic and baseline characteristics (Table 1). The mean age of patients was 55 years, and baseline HbA_{1c} values were comparable across treatment arms (mean 8.1 $\pm$ 0.8% [65 mmol/mol]). The mean duration of diabetes was 2.6 $\pm$ 3.1 years, with marked variation, ranging from 0.2 to 30.7 years. The mean weight was 87.5 kg, with a mean BMI of 30.9 kg/m^2. The majority of patients were white (75.7%) and male (65.0%).

Efficacy

Glycemic Control

HbA_{1c} decreased dose dependently with semaglutide 0.1–1.6 mg E from baseline to week 12 (range $-$0.6 to $-$1.7%; Fig. 2*A*); the mean change in HbA_{1c} by week is also shown in Fig. 2*A*. The mean change from baseline in HbA_{1c} was significantly greater for semaglutide 0.2–1.6 mg E vs. placebo ($P < 0.05$), and was greater for semaglutide 1.6 mg E vs. liraglutide 1.2 and 1.8 mg (Fig. 2*A* and Table 2).

Dose-dependent increases in the proportion of patients reaching the predefined ADA target (HbA_{1c} $<$7% [53 mmol/mol]) and AACE target (HbA_{1c} $\leq$6.5% [48 mmol/mol]) for glycemic control were observed for semaglutide (Fig. 2*B*). Up to 81% of patients reached an HbA_{1c} level of $<$7% with semaglutide (0.1–1.6 mg E) vs. 57% with 1.8 mg liraglutide and 15% with placebo. Up to 63% of patients achieved an HbA_{1c} level of $\leq$6.5% with semaglutide (0.1–1.6 mg E) vs. 36% with 1.8 mg liraglutide and 4% with placebo.

FPG levels decreased dose dependently with semaglutide 0.1–1.6 mg E from baseline to week 12 (range $-$0.5 to $-$2.6 mmol/L; Fig. 2*C*); the mean change in FPG levels by week is also shown in Fig. 2*C*. The reduction in FPG levels at week 12 was significantly greater for semaglutide 0.4–1.6 mg E vs. placebo ($P < 0.01$), and was greater for semaglutide 0.8–1.6 mg E vs. liraglutide 1.2 mg (Fig. 2*C* and Table 2).

Reductions in FPG levels were apparent in all treatment groups as early as week 1 and had stabilized within the first 3 weeks of treatment (Fig. 2*C*). In the remaining treatment period, the mean FPG level remained stable in all groups.

Fasting plasma glucagon levels decreased dose dependently with semaglutide 0.1–1.6 mg E (the change from baseline ranged from 4.9 to $-$15.0 ng/L); this reached statistical significance for semaglutide 1.6 mg E vs. placebo at week 12 ($P < 0.05$; Supplementary Table 1). No treatment differences were apparent between lower doses of semaglutide and placebo, or between semaglutide and liraglutide.

Data on fasting insulin levels, fasting C-peptide levels, HOMA index of β-cell function, HOMA of insulin resistance, and meal-related responses, including food consumption, PPG, gastric emptying, and sensation of appetite, thirst, well-being, and nausea, are included in the data supplement.

Although identical standardized meals of 2 MJ in energy content were served, there was a reduction in food consumption of up to 39.8 g (203.5 kJ) in the semaglutide and liraglutide groups (12.2 g [62.5 kJ] with placebo) at week 12 compared with baseline.

Treatment with semaglutide 0.2–1.6 mg E was associated with a significant and dose-dependent reduction in PPG AUC, $AUC_{0–240min}$, compared with placebo (up to 35% reduction vs. placebo; $P < 0.05$); this effect appeared to be of a magnitude that was similar to the effect of liraglutide 1.8 mg (27% reduction vs. placebo; Supplementary Table 1). In addition, C_{max} and incremental AUCs (iAUCs) for glucose during a standard breakfast meal were reduced in the semaglutide 0.4–1.6 mg E dose range vs. placebo (by up to 30% and 56%, respectively, for C_{max} and iAUC). There

Table 1—Demographics and baseline characteristics (safety analysis set)

	Placebo	Semaglutide					Liraglutide	
		0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg E	1.6 mg E	1.2 mg	1.8 mg
Exposed patients, *n*	46	47	43	48	42	43	47	45	50
Diet and exercise/metformin, %	22/78	23/77	14/86	23/77	19/81	16/84	19/81	18/82	24/76
Age, years	55.3 ± 10.6	55.2 ± 10.1	54.7 ± 10.0	53.8 ± 10.2	55.0 ± 9.7	55.9 ± 7.9	56.4 ± 10.5	54.8 ± 9.2	54.3 ± 10.1
Women/men, %	39/61	34/66	30/70	23/77	48/52	37/63	45/55	31/69	30/70
Diabetes duration, years	2.4 ± 3.3	3.6 ± 5.0	2.3 ± 2.7	2.0 ± 2.3	3.0 ± 3.0	2.6 ± 2.1	1.8 ± 2.0	3.3 ± 3.4	2.5 ± 2.6
HbA_{1c}, % (mmol/mol)	8.1 ± 0.8 (65)	8.2 ± 0.9 (66)	8.2 ± 0.9 (66)	8.1 ± 0.9 (65)	8.2 ± 0.9 (66)	8.0 ± 0.8 (64)	8.0 ± 0.7 (64)	8.0 ± 0.8 (64)	8.1 ± 0.7 (65)
FPG, mmol/L	8.9 ± 1.5	9.8 ± 2.7	9.5 ± 2.5	9.3 ± 2.1	9.5 ± 2.4	9.6 ± 2.1	9.0 ± 1.9	9.0 ± 2.3	9.3 ± 2.0
Body weight, kg	90.5 ± 13.0	89.5 ± 14.2	86.3 ± 15.1	87.0 ± 14.0	85.9 ± 15.1	85.7 ± 12.6	84.5 ± 14.0	90.5 ± 13.5	87.2 ± 13.1
BMI, kg/m^2	31.7 ± 3.8	31.5 ± 4.6	30.4 ± 3.9	29.7 ± 4.5	30.7 ± 4.5	31.2 ± 4.2	30.9 ± 4.7	31.0 ± 4.6	30.9 ± 4.6
Waist circumference, cm	106 ± 11	106 ± 11	104 ± 9	105 ± 12	101 ± 11	104 ± 11	103 ± 11	106 ± 11	102 ± 12
Hip circumference, cm	111 ± 10	111 ± 11	107 ± 8	106 ± 10	107 ± 10	108 ± 11	108 ± 10	110 ± 11	106 ± 13

Data are reported as the mean ± SD, unless otherwise stated.

was a more pronounced effect on the AUC for glucose and a trend for a more pronounced effect on iAUC for glucose with semaglutide 1.6 mg E vs. liraglutide 1.8 mg (Supplementary Table 1).

Body Weight

Body weight decreased dose dependently from baseline to week 12 with semaglutide 0.1–1.6 mg E (Fig. 2*D*); the mean change in body weight by week is also shown in Fig. 2*D*. The reduction in body weight at week 12 was significantly greater for semaglutide 0.8–1.6 mg E (range −3.4 to −4.8 kg; $P < 0.001$) vs. placebo (−1.2 kg). The mean change in body weight from baseline to week 12 was greater for semaglutide 0.8 and 1.6 mg E vs. liraglutide 1.8 mg (−2.6 kg), and for semaglutide 0.8 mg, 0.8 mg E, and 1.6 mg E vs. liraglutide 1.2 mg (−1.9 kg) based on unadjusted CIs (Fig. 2*D* and Table 2).

The proportion of patients achieving a ≥5% weight reduction increased dose dependently after 12 weeks of treatment (2.1%, 7.0%, 13.0%, 37.5%, 51.2%, and 63.6% with semaglutide 0.1–1.6 mg E). With liraglutide 1.2 and 1.8 mg, 17.8% and 14.3% of patients, respectively, achieved a ≥5% weight reduction, compared with 13% of patients in the placebo group. The proportion of patients achieving a ≥10% weight reduction was 2.1%, 0%, 0%, 2.5%, 4.7%, and 9.1% with semaglutide treatment (0.1–1.6 mg E), while no patients achieved a 10% weight loss in the liraglutide and placebo groups. Weight loss occurred independently of whether or not patients reported nausea or vomiting during the trial (data not shown). Both hip and waist circumference were reduced between baseline and the end of treatment for all treatment groups (data not shown), in accordance with the observed weight loss.

Safety and Tolerability

In total, 74 of the 415 randomized patients (17.8%) withdrew from the trial, of whom 46 patients withdrew due to AEs (11% of total patients; 62% of all withdrawals). Across all treatment groups, the majority of AE withdrawals were due to gastrointestinal (GI) disorders (86.7%) in the first month of randomized treatment. The proportion of patients withdrawing from the study due to TEAEs increased dose dependently up to 29.8% in the semaglutide 1.6 mg E group, compared with 4.4% and 10.0% in the liraglutide groups (1.2 and 1.8 mg). The proportion of patients

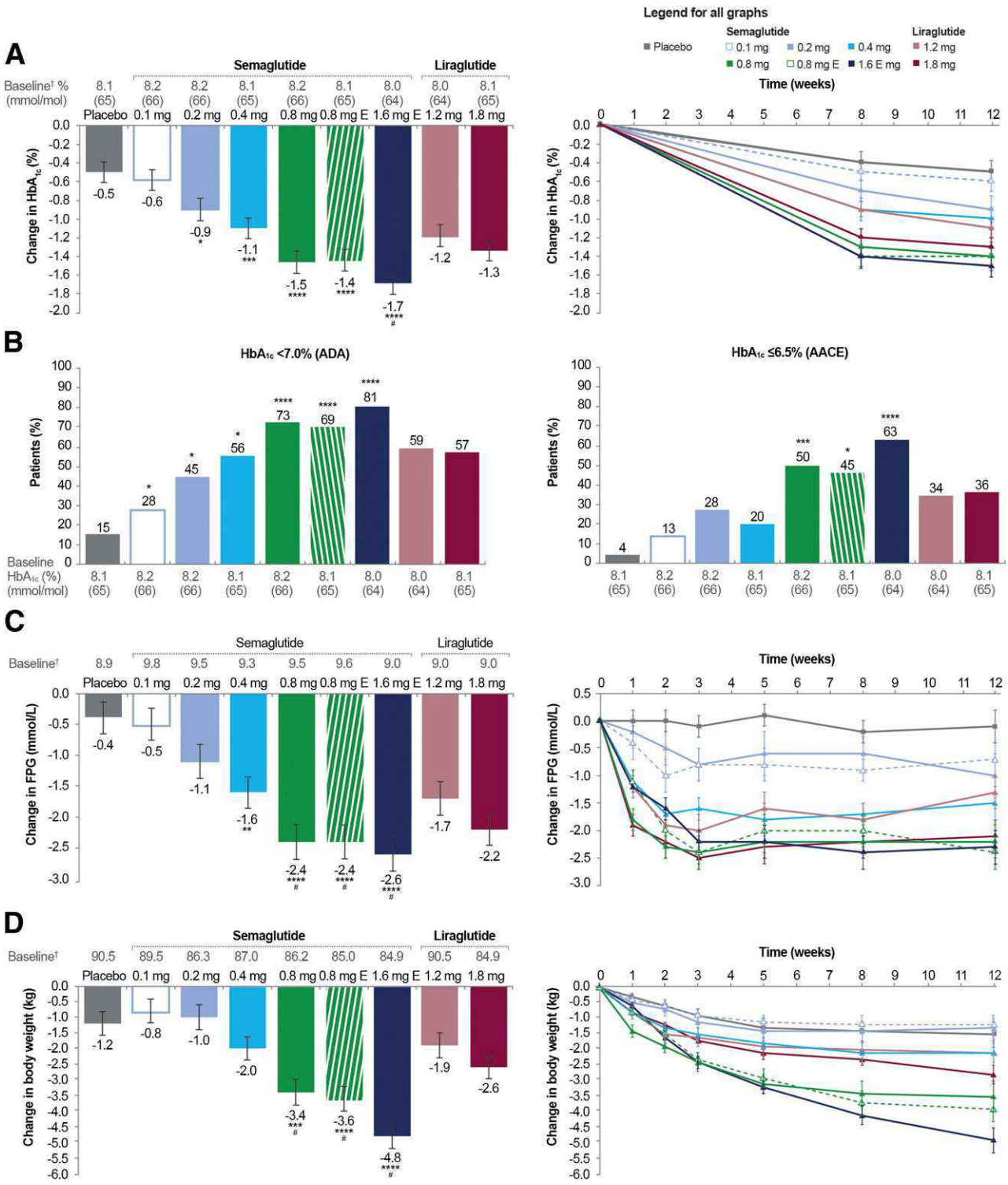

Figure 2—Glycemic control and change in body weight. *A*: Mean change in HbA_{1c} (%) from baseline at week 12 and by week. *B*: Patients reaching ADA and AACE criteria for glycemic control. *C*: Mean change in FPG level (mmol/L) from baseline at week 12 and by week. *D*: Mean change in body weight (kg) from baseline at week 12 and by week. All data are full analysis sets, last observation carried forward. Change from baseline data are reported as the least squares mean ± SEM. Time-course data are reported as the raw mean ± SEM. †Mean baseline value. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$, $****P < 0.0001$ vs. placebo (*P* values adjusted for multiple testing using the Dunnett method). #Mean change greater for semaglutide vs. liraglutide based on the unadjusted CI—for specific comparison between treatment arms, see ETDs and 95% CIs in Table 2.

withdrawing from the study due to GI AEs was similar for semaglutide 0.8 mg with dose escalation and without dose escalation (18.6% for 0.8 mg E vs. 14.3% for 0.8 mg). No patients withdrew due to an AE in the placebo group.

A summary of TEAEs with a frequency of ≥5% in one or more treatment arm is provided in Table 3. The majority of TEAEs in the semaglutide and liraglutide treatment groups were mild or moderate in severity (Supplementary Table 2).

Table 2—ETDs for semaglutide vs. placebo and liraglutide at week 12 (HbA_{1c}, FPG, and body weight)

	Semaglutide					Liraglutide	
ETDs	0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg E	1.6 mg E	1.2 mg	1.8 mg
HbA_{1c}, % (95% CI)								
vs. placebo	−0.1 (−0.5, 0.3)	−0.4* (−0.8, −0.0)	−0.6*** (−1.0, −0.2)	−1.0**** (−1.4, −0.6)	−1.0**** (−1.3, −0.6)	−1.2**** (−1.6, −0.8)	−0.7 (−1.0, −0.4)	−0.8 (−1.1, −0.6)
vs. liraglutide 1.2 mg	0.6 (0.3, 0.9)	0.3 (−0.0, 0.6)	0.1 (−0.2, 0.4)	−0.3 (−0.6, 0.0)	−0.3 (−0.6, 0.0)	−0.5 (−0.8, −0.2)		
vs. liraglutide 1.8 mg	0.8 (0.5, 1.0)	0.4 (0.2, 0.7)	0.2 (−0.1, 0.5)	−0.1 (−0.4, 0.2)	−0.1 (−0.4, 0.2)	−0.4 (−0.6, −0.1)		
FPG, mmol/L (95% CI)								
vs. placebo	−0.1 (−1.0, −0.8)	−0.6 (−1.5, −0.3)	−1.2** (−2.1, −0.3)	−2.0**** (−2.9, −1.0)	−2.0**** (−2.9, −1.1)	−2.1**** (−3.0, −1.2)	−1.2 (−1.9, −0.5)	−1.8 (−2.4, −1.1)
vs. liraglutide 1.2 mg	1.1 (0.5, 1.8)	0.6 (−0.1, 1.3)	0.0 (−0.7, 0.7)	−0.8 (−1.5, −0.1)	−0.8 (−1.5, −0.1)	−0.9 (−1.6, −0.2)		
vs. liraglutide 1.8 mg	1.7 (1.1, 2.4)	1.1 (0.5, 1.8)	0.6 (−0.1, 1.2)	−0.2 (−0.9, 0.5)	−0.2 (−0.9, 0.5)	−0.3 (−1.0, 0.3)		
Body weight, kg (95% CI)								
vs. placebo	0.4 (−0.9, 1.7)	0.1 (−1.2, 1.5)	−0.8 (−2.1, 0.5)	−2.2**** (−3.5, −0.9)	−2.4**** (−3.7, −1.1)	−3.6**** (−5.0, −2.3)	−0.7 (−1.7, 0.3)	−1.4 (−2.4, −0.4)
vs. liraglutide 1.2 mg	1.1 (0.1, 2.0)	0.8 (−0.2, 1.8)	−0.2 (−1.2, 0.8)	−1.5 (−2.6, −0.5)	−1.7 (−2.8, −0.7)	−3.0 (−4.0, −2.0)		
vs. liraglutide 1.8 mg	1.8 (0.8, 2.8)	1.6 (0.6, 2.5)	0.6 (−0.4, 1.5)	−0.8 (−1.8, 0.2)	−1.0 (−2.0, −0.0)	−2.2 (−3.2, −1.3)		

Estimates are from an ANOVA model with treatment, country, and previous treatment as fixed effects, and baseline value as the covariate; CIs for treatment differences vs. placebo are based on the Dunnett method (with 6 comparisons); CIs for treatment differences vs. liraglutide are not corrected for multiple testing. *$P < 0.05$. **$P < 0.01$. ***$P < 0.001$. ****$P < 0.0001$.

The most commonly reported AEs were GI disorders, mainly nausea, vomiting, diarrhea, and dyspepsia. Rates of nausea, vomiting, and diarrhea appeared to be dose dependent (Table 3). The proportion of patients reporting nausea, vomiting, and diarrhea was numerically lower for semaglutide 0.8 mg with dose escalation than without dose escalation (nausea 39.5% for 0.8 mg E vs. 59.5% for 0.8 mg; vomiting 30.2% for 0.8 mg E vs. 40.5% for 0.8 mg; diarrhea 16.3% for 0.8 mg E vs. 19.0% for 0.8 mg; Table 3).

The majority of GI AEs were reported as mild or moderate in severity (Supplementary Table 3). The proportion of patients reporting GI AEs was numerically lower for semaglutide 0.8 mg with E than without E (62.8% for 0.8 mg E vs. 78.6% for 0.8 mg; Table 3). Rates for abdominal pain were low across treatment groups; in no case was there a suspicion of pancreatitis based on local laboratory monitoring.

Most GI AEs occurred within the first 2 weeks after the first dose, and nausea and vomiting were transient in nature, decreasing over time, for both the semaglutide and liraglutide treatment groups. The proportion of patients with nausea and vomiting by day is shown in Supplementary Fig. 2.

Overall, 10 treatment-emergent serious AEs (TESAEs) and 2 non-TESAEs were reported by 10 patients (8 patients received treatment with semaglutide: 0.1 mg [*n* = 2], 0.2 mg [*n* = 1], 0.4 mg [*n* = 2], 0.8 mg E [*n* = 1], and 1.6 mg E [*n* = 2]; 1 patient received treatment with liraglutide 1.8 mg; and 1 patient received treatment with placebo). TESAEs included cardiac disorders (four events reported by three patients: acute left ventricular failure [semaglutide 0.2 mg], acute myocardial infarction [semaglutide 0.8 mg], coronary artery disease [semaglutide 0.8 mg], and myocardial infarction [semaglutide 0.4 mg]) and vascular disorders (two events reported by two patients: arterial occlusive disease [semaglutide 0.1 mg] and hypertension [semaglutide 0.4 mg]). No apparent dose or time dependency was observed. All TESAEs in semaglutide-treated patients were judged by the investigator as being unlikely to be related to the trial product; one TESAE in the liraglutide 1.8 mg group was judged as being possibly/unlikely related to the trial product.

There were no clinically relevant differences among the treatment groups in

Table 3—TEAEs by system organ class and preferred term, with frequency ≥5% in one or more treatment arms (safety analysis set)

		Semaglutide						Liraglutide	
	Placebo (*n* = 46)	0.1 mg (*n* = 47)	0.2 mg (*n* = 43)	0.4 mg (*n* = 48)	0.8 mg (*n* = 42)	0.8 mg E (*n* = 43)	1.6 mg E (*n* = 47)	1.2 mg (*n* = 45)	1.8 mg (*n* = 50)
TEAEs, *n* (%)	20 (43.5)	28 (59.6)	24 (55.8)	35 (72.9)	36 (85.7)	31 (72.1)	44 (93.6)	25 (55.6)	31 (62.0)
GI disorders	5 (10.9)	16 (34.0)	9 (20.9)	22 (45.8)	33 (78.6)	27 (62.8)	35 (74.5)	15 (33.3)	15 (30.0)
Nausea	2 (4.3)	4 (8.5)	5 (11.6)	13 (27.1)	25 (59.5)	17 (39.5)	27 (57.4)	11 (24.4)	4 (8.0)
Vomiting	1 (2.2)	0 (0.0)	3 (7.0)	7 (14.6)	17 (40.5)	13 (30.2)	13 (27.7)	4 (8.9)	6 (12.0)
Diarrhea	0 (0.0)	5 (10.6)	2 (4.7)	7 (14.6)	8 (19.0)	7 (16.3)	11 (23.4)	2 (4.4)	7 (14.0)
Dyspepsia	1 (2.2)	5 (10.6)	0 (0.0)	4 (8.3)	4 (9.5)	4 (9.3)	6 (12.8)	5 (11.1)	4 (8.0)
Constipation	0 (0.0)	0 (0.0)	2 (4.7)	2 (4.2)	1 (2.4)	3 (7.0)	3 (6.4)	3 (6.7)	1 (2.0)
Nervous system disorders	7 (15.2)	11 (23.4)	4 (9.3)	11 (22.9)	8 (19.0)	3 (7.0)	5 (10.6)	10 (22.2)	6 (12.0)
Headache	3 (6.5)	7 (14.9)	3 (7.0)	4 (8.3)	5 (11.9)	1 (2.3)	3 (6.4)	4 (8.9)	2 (4.0)
Dizziness	1 (2.2)	3 (6.4)	0 (0.0)	2 (4.2)	1 (2.4)	0 (0.0)	0 (0.0)	2 (4.4)	0 (0.0)
Lethargy	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	1 (2.3)	0 (0.0)	3 (6.7)	0 (0.0)
Infections/infestations	6 (13.0)	9 (19.1)	7 (16.3)	10 (20.8)	4 (9.5)	6 (14.0)	10 (21.3)	2 (4.4)	9 (18.0)
Nasopharyngitis	4 (8.7)	6 (12.8)	0 (0.0)	4 (8.3)	2 (4.8)	2 (4.7)	3 (6.4)	1 (2.2)	2 (4.0)
Gastroenteritis	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)	2 (4.3)	0 (0.0)	3 (6.0)
Urinary tract infection	0 (0.0)	0 (0.0)	3 (7.0)	0 (0.0)	1 (2.4)	1 (2.3)	2 (4.3)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (2.2)	1 (2.1)	2 (4.7)	7 (14.6)	4 (9.5)	4 (9.3)	11 (23.4)	3 (6.7)	5 (10.0)
Fatigue	1 (2.2)	1 (2.1)	0 (0.0)	3 (6.3)	0 (0.0)	0 (0.0)	6 (12.8)	0 (0.0)	2 (4.0)
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	2 (4.2)	3 (7.1)	3 (7.0)	5 (10.6)	0 (0.0)	0 (0.0)
Metabolism/nutrition disorders	1 (2.2)	2 (4.3)	3 (7.0)	4 (8.3)	10 (23.8)	10 (23.3)	23 (48.9)	6 (13.3)	6 (12.0)
Anorexia	1 (2.2)	2 (4.3)	2 (4.7)	3 (6.3)	10 (23.8)	7 (16.3)	15 (31.9)	3 (6.7)	5 (10.0)
Decreased appetite	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	2 (4.7)	8 (17.0)	1 (2.2)	1 (2.0)
Musculoskeletal/connective tissue disorders	2 (4.3)	5 (10.6)	2 (4.7)	3 (6.3)	2 (4.8)	3 (7.0)	4 (8.5)	2 (4.4)	2 (4.0)
Investigations	1 (2.2)	1 (2.1)	1 (2.3)	1 (2.1)	0 (0.0)	3 (7.0)	2 (4.3)	1 (2.2)	3 (6.0)
Vascular disorders	4 (8.7)	2 (4.3)	0 (0.0)	2 (4.2)	1 (2.4)	1 (2.3)	2 (4.3)	2 (4.4)	3 (6.0)
Hypertension	4 (8.7)	1 (2.1)	0 (0.0)	2 (4.2)	1 (2.4)	1 (2.3)	1 (2.1)	1 (2.2)	2 (4.0)
Injury/poisoning/procedural complications	4 (8.7)	1 (2.1)	2 (4.7)	2 (4.2)	0 (0.0)	1 (2.3)	4 (8.5)	1 (2.2)	0 (0.0)
Skin and subcutaneous disorders	0 (0.0)	3 (6.4)	1 (2.3)	3 (6.3)	1 (2.4)	0 (0.0)	1 (2.1)	2 (4.4)	2 (4.0)
Respiratory, thoracic, and mediastinal disorders	3 (6.5)	1 (2.1)	1 (2.3)	1 (2.1)	2 (4.8)	1 (2.3)	1 (2.1)	2 (4.4)	2 (4.0)
Eye disorders	3 (6.5)	1 (2.1)	0 (0.0)	1 (2.1)	1 (2.4)	0 (0.0)	1 (2.1)	3 (6.7)	4 (8.0)
Diabetic retinopathy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.0)
Cardiac disorders	2 (4.3)	1 (2.1)	4 (9.3)	2 (4.2)	0 (0.0)	1 (2.3)	1 (2.1)	1 (2.2)	0 (0.0)
Psychiatric disorders	1 (2.2)	3 (6.4)	0 (0.0)	2 (4.2)	0 (0.0)	0 (0.0)	1 (2.1)	0 (0.0)	0 (0.0)
Blood/lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	3 (6.3)	1 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Data are reported as the number (*n*) of randomized patients exposed to at least one dose of trial product and the percentage (%) of patients experiencing at least one AE.

regard to electrocardiogram changes from baseline to the end of treatment. The change in SBP, DBP, and pulse rate from baseline to the end of treatment is shown in Table 4. A modest reduction in SBP from baseline to week 12 was observed with treatment with semaglutide 0.2–1.6 mg E, although the reduction was not significantly different from that with placebo. No consistent change in DBP was observed. Pulse rate increased from baseline in all groups after 12 weeks (Table 4). The increase in pulse appeared to be dose dependent in the semaglutide group. The ETDs were not statistically significantly different for semaglutide versus placebo. No apparent differences were observed for the semaglutide and liraglutide comparisons for SBP, DBP, or pulse rate.

There were no major episodes of hypoglycemia (classified as patients being unable to treat the episode themselves), and the incidence of minor hypoglycemia (a plasma glucose level <3.1 mmol/L) was low: eight patients reported 11 minor hypoglycemia events; 11 patients reported 16 events of symptoms-only hypoglycemia. The frequency of minor hypoglycemia was comparable across all nine treatment arms, and no dose-dependent trends were observed (range 0–4.4% corresponding to 0–0.205 episodes/patient-year). No new development of proliferative retinopathy was observed over the duration of the study.

There were few cases of injection site reactions, as follows: two patients receiving semaglutide (0.2 mg, one event of edema; 0.4 mg, two events of irritation); three patients receiving liraglutide 1.2 mg (two events of hematoma, one event of pruritus); and two patients receiving liraglutide 1.8 mg (one event of erythema, one event of site reaction), with no differences among treatment groups. A single patient in the semaglutide 1.6 mg E treatment group developed low-titer anti-semaglutide antibodies, which did not cross-react with native GLP-1 and had no neutralizing effect in vitro. No treatment-related changes in hematology or biochemistry, including blood calcitonin levels, were observed; pancreatic

enzymes were not routinely monitored. There were no reports of pancreatitis or clinical thyroid AEs.

CONCLUSIONS

This 12-week dose-finding study evaluated a wide range of semaglutide doses versus placebo and open-label liraglutide in patients with type 2 diabetes. The effect of a 1-week dose escalation was explored with semaglutide 0.8 mg in order to establish whether this regimen would mitigate the known GI side effects associated with this class of agents, and thus provide insight into appropriate dosing for phase 3 trials.

Once-weekly semaglutide treatment provided clinically meaningful, dose-dependent improvements in HbA_{1c} level (up to −1.7% vs. −0.5% with placebo) and weight loss (up to −4.8 kg vs. −1.2 kg with placebo), without any major episodes of hypoglycemia. Weight loss seemed to occur independently of nausea or vomiting. Weight loss with liraglutide (up to −2.6 kg) was consistent with previous clinical trials (at doses up to 1.8 mg added to metformin) (14). Based on this relatively short study, HbA_{1c} and body weight reductions with semaglutide 1.6 mg were numerically greater than with liraglutide 1.8 mg. Nevertheless, the relatively short dose-escalation period of 1–2 weeks resulted in an unacceptable tolerability profile, certainly for semaglutide 1.6 mg. The similarity of responses in FPG levels between liraglutide and semaglutide and differences in HbA_{1c} levels suggest that semaglutide may have a preferential impact on PPG levels, perhaps mediated by differences in gastric emptying.

No pancreatitis, thyroid AEs, or treatment-related effects on blood calcitonin levels were observed. A similar increase in pulse rate from baseline was seen with semaglutide and liraglutide, although these findings were not significantly different from placebo in this small study, and modest decreases in mean SBP were observed. Four serious cardiovascular events were reported in three semaglutide-treated patients; however, no dose- or time-dependency could be established. Very few cases of injection site reactions were reported, and although low-titer anti-semaglutide antibodies developed in one patient, no in vitro neutralizing effect or cross-reactivity to native GLP-1 was observed.

Table 4—Mean change in SBP, DBP, and pulse rate from baseline to week 12

		Semaglutide						Liraglutide	
	Placebo	0.1 mg	0.2 mg	0.4 mg	0.8 mg	0.8 mg E	1.6 mg E	1.2 mg	1.8 mg
SBP, mmHg									
Estimated LS mean change from baseline	−3.8	2.4	−3.8	−1.8	−6.2	−8.4	−6.2	−4.9	−5.7
ETD vs. placebo (95% CI)		6.1* (0.1, 12.1)	−0.1 (−6.2, 6.0)	2.0 (−4.0, 7.9)	−2.4 (−8.6, 3.8)	−4.6 (−10.7, 1.5)	−2.5 (−8.5, 3.6)	−1.1 (−5.8, 3.5)	−2.0 (−6.4, 2.5)
ETD vs. liraglutide 1.2 mg (95% CI)		7.2 (2.7, 11.8)	1.1 (−3.6, 5.8)	3.1 (−1.6, 7.8)	−1.3 (−6.0, 3.5)	−3.5 (−8.2, 1.2)	−1.3 (−5.9, 3.3)		
ETD vs. liraglutide 1.8 mg (95% CI)		8.1 (3.6, 12.5)	1.9 (−2.7, 6.5)	3.9 (−0.5, 8.4)	−0.5 (−5.1, 4.2)	−2.7 (−7.3, 1.9)	−0.5 (−5.0, 3.9)		
DBP, mmHg									
Estimated LS mean change from baseline	−1.9	1.9	0.3	0.4	0.0	−1.6	−1.9	−1.0	0.1
ETD vs. placebo (95% CI)		3.8 (−0.3, 7.9)	2.1 (−2.1, 6.3)	2.3 (−1.9, 6.4)	1.9 (−2.4, 6.2)	0.2 (−4.0, 4.5)	−0.1 (−4.3, 4.1)	0.8 (−2.4, 4.0)	1.9 (−1.2, 5.0)
ETD vs. liraglutide 1.2 mg (95% CI)		3.0 (−0.2, 6.1)	1.3 (−2.0, 4.5)	1.4 (−1.8, 4.6)	1.1 (−2.2, 4.4)	−0.6 (−3.8, 2.6)	−0.9 (−4.1, 2.3)		
ETD vs. liraglutide 1.8 mg (95% CI)		1.9 (−1.2, 4.9)	0.2 (−3.0, 3.4)	0.3 (−2.7, 3.4)	−0.0 (−3.3, 3.2)	−1.7 (−4.9, 1.5)	−2.0 (−5.1, 1.1)		
Pulse rate, bpm									
Estimated LS mean change from baseline	0.4	0.9	1.2	2.7	2.6	4.1	4.2	4.8	3.3
ETD vs. placebo (95% CI)		0.6 (−4.5, 5.6)	0.8 (−4.3, 6.0)	2.4 (−2.6, 7.4)	2.2 (−3.0, 7.5)	3.7 (−1.4, 8.9)	3.9 (−1.3, 9.0)	4.5 (0.6, 8.3)	2.9 (−0.9, 6.7)
ETD vs. liraglutide 1.2 mg (95% CI)		−3.9 (−7.8, −0.0)	−3.6 (−7.6, 0.3)	−2.1 (−6.0, 1.8)	−2.2 (−6.2, 1.8)	−0.7 (−4.7, 3.2)	−0.6 (−4.5, 3.3)		
ETD vs. liraglutide 1.8 mg (95% CI)		−2.4 (−6.1, 1.4)	−2.1 (−5.9, 1.8)	−0.6 (−4.3, 3.2)	−0.7 (−4.6, 3.2)	0.8 (−3.0, 4.7)	0.9 (−2.8, 4.7)		

LS mean, least squares mean. Estimates are from an ANOVA model with treatment, country, and previous treatment as fixed effects and baseline value as the covariate; CIs for treatment differences vs. placebo are based on the Dunnett method (with 6 comparisons); CIs for treatment differences vs. liraglutide are not corrected for multiple testing. All values for SBP, DBP, and pulse rate are means, safety analysis set, last observation carried forward. *$P <$ 0.05.

A dose-dependent increase in GI AEs (mainly nausea and vomiting) and in study withdrawals due to GI AEs was observed with semaglutide, which is consistent with the known side effects of the GLP-1 drug class (15). Most GI AEs occurred within the first 2 weeks of the first dose. Nausea and vomiting were transient, decreasing gradually over time with both semaglutide and liraglutide, indicating the development of tolerance. The observed dose-dependent increase in the proportion of patients with GI AEs, and the proportion of patients reporting nausea and vomiting, was ameliorated by including a 1-week dose escalation of semaglutide from 0.4 to 0.8 mg (the second-highest semaglutide dose). This phase 2 dose-finding study was designed to explore the dose-response relationship of once-weekly semaglutide treatment. While the overall GI side effects were not unexpected, the incidence of GI side effects observed with the highest dose of semaglutide were not considered acceptable. Semaglutide 1.6 mg has not, therefore, been taken forward into phase 3. There was a notable reduction in GI AEs with semaglutide 0.8 mg following a 1-week dose-escalation step. This, together with the mild/moderate and transient nature of the GI AEs, indicates that unwanted side effects may be ameliorated with slower dose escalation without compromising efficacy—this strategy is being further explored in phase 3 studies, using semaglutide 0.5 and 1.0 mg with a 4-week dose-escalation step from 0.25 to 0.5 mg and from 0.5 to 1.0 mg.

Indeed, findings from a recent phase 1 study of semaglutide (6) have provided further insight into the most appropriate dose and regimen. This study used a more gradual dose-escalation regimen involving once-weekly semaglutide treatment at 0.25 mg for 4 weeks, followed by 0.5 mg for 4 weeks, before increasing the dose to 1.0 mg for 5 weeks (6). This regimen was well tolerated, and substantially reduced the severity of nausea and the incidence of vomiting and study withdrawals due to GI AEs. However, this was a small phase 1 study, and phase 3 trials are needed to confirm the appropriate use of semaglutide in clinical practice. The ongoing comprehensive semaglutide phase 3a clinical trial program, SUSTAIN, comprises eight clinical trials and is expected to include >8,000 patients with type 2 diabetes. The program includes a long-term, global cardiovascular outcomes study, SUSTAIN-6 (clinical trial reg. no. NCT01720446, clinicaltrials.gov), involving >3,000 patients, which was initiated preapproval to address the requirements outlined in the Food and Drug Administration and European Medicines Agency guidance on cardiovascular safety studies for new antidiabetic drugs. It is estimated that the SUSTAIN-6 study will be completed in early 2016.

This phase 2 study has some limitations, including its relatively short duration (12 weeks), which is too short to evaluate fully the impact of the highest semaglutide doses on HbA_{1c} and body weight. There are statistical limitations to the efficacy and safety comparisons with liraglutide, as this treatment arm was open-label and not blinded, and there was no specific hypothesis testing for semaglutide versus liraglutide comparisons. A further limitation relates to the paracetamol method for measuring gastric emptying, which is not ideal for obtaining details regarding GI motility, but rather provides an approximation (16). In addition, this study did not control for or standardize what patients consumed during the meal test. As such, the reduction in food consumption in the semaglutide and liraglutide groups compared with baseline may confound interpretation of the treatment effects on postprandial responses.

In summary, semaglutide administered once weekly provides clinically meaningful, dose-dependent reductions in HbA_{1c} and body weight, with a low risk of hypoglycemia and injection-site reactions, in patients with type 2 diabetes. Semaglutide potentially offers potent glucose-lowering efficacy with a similar overall safety profile compared with other available GLP-1 receptor agonists, providing a robust basis for further investigation. Glucose-lowering medications administered once weekly have the potential to improve patient adherence and, therefore, may impact treatment outcomes and quality of life (17). However, the relatively high incidence of GI side effects seen in this study supports the adoption of slower dose escalation, with a view to optimizing the potent clinical efficacy of semaglutide in the phase 3 setting. The results of the ongoing SUSTAIN phase 3 clinical trial program will provide further information on the potential of semaglutide to improve the management of type 2 diabetes.

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