



# Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects With Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial\*

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## OBJECTIVE

To compare the efficacy and safety of once-weekly semaglutide 1.0 mg s.c. with exenatide extended release (ER) 2.0 mg s.c. in subjects with type 2 diabetes.

## RESEARCH DESIGN AND METHODS

In this phase 3a, open-label, parallel-group, randomized controlled trial, 813 subjects with type 2 diabetes taking oral antidiabetic drugs were randomized (1:1) to semaglutide 1.0 mg or exenatide ER 2.0 mg for 56 weeks. The primary end point was change from baseline in HbA<sub>1c</sub> at week 56.

## RESULTS

Mean HbA<sub>1c</sub> (8.3% [67.7 mmol/mol] at baseline) was reduced by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER (estimated treatment difference vs. exenatide ER [ETD] −0.62% [95% CI −0.80, −0.44] [−6.78 mmol/mol (95% CI −8.70, −4.86)];  $P < 0.0001$  for noninferiority and superiority). Mean body weight (95.8 kg at baseline) was reduced by 5.6 kg with semaglutide and 1.9 kg with exenatide ER (ETD −3.78 kg [95% CI −4.58, −2.98];  $P < 0.0001$ ). Significantly more subjects treated with semaglutide (67%) achieved HbA<sub>1c</sub> <7.0% (<53 mmol/mol) versus those taking exenatide ER (40%). Both treatments had similar safety profiles, but gastrointestinal adverse events were more common in semaglutide-treated subjects (41.8%) than in exenatide ER-treated subjects (33.3%); injection-site reactions were more frequent with exenatide ER (22.0%) than with semaglutide (1.2%).

## CONCLUSIONS

Semaglutide 1.0 mg was superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight after 56 weeks of treatment; the drugs had comparable safety profiles. These results indicate that semaglutide treatment is highly effective for subjects with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs.

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\*A full list of investigators is available in Supplementary Table 6.

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Glucagon-like peptide-1 (GLP-1) receptor agonists (RAs) are an established treatment option for type 2 diabetes (1). GLP-1 RAs stimulate insulin secretion in a glucose-dependent manner and suppress glucagon production, resulting in significant reductions in hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) levels with minimal risk of hypoglycemia (2). GLP-1 RAs also reduce body weight by inducing feelings of satiety and fullness and reducing feelings of hunger, thereby lowering energy intake (3,4). These effects are particularly beneficial given the role of obesity in the complex pathophysiology of type 2 diabetes (5–7). Recent advances in GLP-1 RA therapeutics include the development of once-weekly GLP-1 RAs, which may improve patient adherence and health-related quality of life compared with daily formulations (8), as has been demonstrated for patients with other chronic illnesses (9).

Semaglutide is a GLP-1 analog currently in development for the treatment of type 2 diabetes. It has 94% structural homology to native human GLP-1 and is structurally similar to liraglutide (10), but important structural modifications make it less susceptible to degradation by dipeptidyl peptidase-4 and increase its specific high-affinity binding to albumin (10). Its resultant half-life of approximately 1 week makes semaglutide appropriate for once-weekly subcutaneous administration (10). Exenatide, the comparator treatment in this trial, is a synthetic form of the GLP-1 RA exendin-4, which has 53% homology to native human GLP-1 (11). When encapsulated in microspheres, exenatide is released slowly from the injection site (extended release [ER]) and is therefore suitable for once-weekly dosing (12).

The Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes (SUSTAIN) 3 trial is a phase 3a comparative study that evaluated the efficacy, safety, and tolerability of once-weekly semaglutide 1.0 mg s.c. versus that of once-weekly exenatide ER 2.0 mg s.c. over 56 weeks in adults with type 2 diabetes who are inadequately controlled on oral antidiabetic drugs (OADs).

## RESEARCH DESIGN AND METHODS

### Trial Design

This 56-week, phase 3a, open-label, active-comparator, parallel-group randomized trial (SUSTAIN 3; clinicaltrials.gov identifier NCT01885208) was conducted at 141 sites

in 12 countries in Europe, South America, and the U.S. between December 2013 and July 2015, in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines (13) and the Declaration of Helsinki (14). The protocol is available in the Supplementary Data online.

### Subjects

Subjects were eligible for inclusion if they were  $\geq 18$  years of age, diagnosed with type 2 diabetes (HbA<sub>1c</sub> 7.0–10.5% [53–91 mmol/mol]), and receiving stable treatment with one or two OADs (metformin  $\geq 1500$  mg or the maximum tolerated dose, and/or thiazolidinediones, and/or sulfonylureas [at least half of the maximum dose allowed], according to the national label) for  $\geq 90$  days before screening. Key exclusion criteria included estimated glomerular filtration rate  $< 60$  mL/min/1.73 m<sup>2</sup> per the MDRD formula (four-variable version); chronic treatment with glucose-lowering agents, other than those specified by the inclusion criteria, within 90 days of screening; history of chronic or idiopathic acute pancreatitis; an acute coronary or cerebrovascular event within 90 days before randomization; and New York Heart Association class IV heart failure. Supplementary Table 1 shows all inclusion and exclusion criteria. Written informed consent was obtained from all participants.

### Interventions

Subjects were randomized (1:1) to once-weekly semaglutide 1.0 mg s.c. (administered with a prefilled pen injector) or once-weekly exenatide ER 2.0 mg s.c. (administered with a vial and syringe) for 56 weeks; all subjects had a 5-week follow-up, including those who stopped treatment early. Subjects were to remain in the trial regardless of whether they received randomized treatment. Semaglutide treatment followed a fixed dose-escalation regimen: 0.25 mg for 4 weeks, then 0.5 mg for 4 weeks, then a maintenance dose of 1.0 mg for 48 weeks. Exenatide ER was dosed at 2.0 mg throughout the trial, according to standard dosing recommendations. Supplementary Fig. 1 shows the trial design. Subjects were centrally randomized to treatment groups using an interactive voice/web response system. Injections were administered in the thigh, abdomen, or upper arm, according to subject preference. Background metformin and/or thiazolidinedione

treatments were continued throughout the trial. Sulfonylurea could be titrated down, at the investigators' discretion, if a subject experienced unacceptable hypoglycemia. Subjects with unacceptable hyperglycemia despite trial medication were offered intensified treatment (rescue medication), as an add-on to the randomized treatment (excluding GLP-1 RAs, dipeptidyl peptidase-4 inhibitors, and pramlintide), at the discretion of the investigator.

### Outcomes

The primary end point was the change from baseline in HbA<sub>1c</sub> level at week 56. The confirmatory secondary end point was the change from baseline in body weight at week 56.

Other secondary efficacy end points included the proportion of subjects who achieved HbA<sub>1c</sub>  $< 7.0\%$  ( $< 53$  mmol/mol) or  $\leq 6.5\%$  ( $\leq 48$  mmol/mol) at 56 weeks; the proportion of subjects who achieved a composite outcome of HbA<sub>1c</sub>  $< 7.0\%$  ( $< 53$  mmol/mol) without severe (based on American Diabetes Association [ADA] classification [15]) or blood glucose (BG)-confirmed symptomatic hypoglycemia (plasma glucose  $\leq 3.1$  mmol/L or  $\leq 56$  mg/dL) and no weight gain; change in fasting plasma glucose (FPG) from baseline to week 56; mean self-measured plasma glucose (SMPG) at postprandial increments (over all meals) and mean seven-point profiles (before and after each main meal and at bedtime); other laboratory measurements associated with  $\beta$ -cell function and glucose metabolism (insulin, C-peptide, proinsulin, glucagon, proinsulin-to-insulin ratio, and HOMA of  $\beta$ -cell function and insulin resistance); proportion of subjects who achieved  $\geq 5\%$  and  $\geq 10\%$  weight loss; and change from baseline to week 56 in BMI, waist circumference, fasting blood lipids, and systolic and diastolic blood pressures. Additional secondary efficacy end points included biochemical markers and patient-reported outcome questionnaires (Diabetes Treatment Satisfaction Questionnaire [DTSQ] status scores and 36-item Short-Form Health Survey-V2 [SF-36v2] scores).

Safety outcomes included the incidence of adverse events (AE), severe or BG-confirmed ( $\leq 3.1$  mmol/L or 56 mg/dL) symptomatic hypoglycemic episodes, pulse rate, and anti-trial drug antibodies. An independent and blinded external

event adjudication committee (EAC) validated predefined types of events (Supplementary Table 2).

### Statistical Analysis

The trial was powered to the primary objective (change from baseline in HbA<sub>1c</sub> at week 56) of demonstrating noninferiority with 90% under the following assumptions: no treatment difference, a noninferiority margin of 0.3%, 1:1 randomization, SD of 1.1%, one-sided 0.025 significance level, and 30% of subjects discontinuing the trial product. A consequent target sample size of 798 subjects was specified to reach the required sample size of 279 subjects per group. This sample size ensures at least 90% marginal power to confirm a treatment difference of 0.3 percentage points for the primary end point and 99% marginal power to detect a 1.5-kg difference in change in body weight at 56 weeks, with an SD of 4 kg. Conservatively assuming independence between the two end points, the joint power is 89.1%. To preserve the overall type 1 error rate, hierarchical testing was used for noninferiority for the primary end point, superiority for the primary

end point, then superiority for the confirmatory end point on change in body weight. Superiority for change in either HbA<sub>1c</sub> or body weight required an upper limit of the two-sided 95% CI for the estimated difference below 0% or 0 kg, respectively.

Continuous end points were analyzed using a mixed model for repeated measurements with factors for treatment, country, and baseline value, all nested within visit, based on randomized and exposed subjects, and including only data obtained before initiating rescue therapy or discontinuing randomized treatment. An unstructured covariance matrix was assumed for measurements within the same subject. End points evaluating the secondary HbA<sub>1c</sub> targets and weight loss responses were analyzed using logistic regression.

The robustness of the conclusions from the primary and confirmatory secondary analyses was evaluated in several statistical sensitivity analyses, including a comparator-based multiple imputation analysis (Supplementary Fig. 3 and Supplementary Table 3). All analyses were performed using SAS version 9.3.

Treatment-emergent AEs, defined as AEs with an onset or increase in severity at any time from the first day of treatment with the trial product to the follow-up visit scheduled 5 weeks (plus a 7-day visit window) after the last dose, were evaluated by descriptive statistics.

## RESULTS

### Subject Disposition and Baseline Characteristics

Subjects were recruited between December 2013 and April 2014. Of the 813 subjects randomized, 809 were exposed to treatment; 82 semaglutide-treated subjects (20.3%) and 85 exenatide ER-treated subjects (21.0%) discontinued treatment early (Supplementary Fig. 2). Rescue medication was administered to 29 subjects (7.2%) in the semaglutide group and 48 subjects (11.9%) in the exenatide ER group. Baseline characteristics were similar between groups (Table 1).

### Primary Outcome

Mean HbA<sub>1c</sub> decreased over time (Fig. 1A) by 1.5% (16.8 mmol/mol) with semaglutide and 0.9% (10.0 mmol/mol) with exenatide ER at 56 weeks (estimated treatment difference vs. exenatide ER [ETD] −0.62%; 95% CI

**Table 1—Baseline characteristics of trial populations**

	Semaglutide 1.0 mg (n = 404)	Exenatide ER 2.0 mg (n = 405)	Total (n = 809)
Age, years (min.–max.)	56.4 (20–82)	56.7 (21–83)	56.6 (20–83)
HbA <sub>1c</sub>			
% (min.–max.)*	8.4 (6.7–11.1)	8.3 (6.5–11.2)	8.3 (6.5–11.2)
mmol/mol (min.–max.)	67.9 (49.7–97.8)	67.6 (47.5–98.9)	67.7 (47.5–98.9)
Diabetes duration, years (min.–max.)	9.0 (0.4–37.1)	9.4 (0.3–54.0)	9.2 (0.3–54.0)
Body weight, kg (min.–max.)	96.2 (49.9–198.3)	95.4 (53.2–171.9)	95.8 (49.9–198.3)
BMI, (kg/m <sup>2</sup> ) (min.–max.)	34.0 (21.0–72.8)	33.6 (21.2–55.8)	33.8 (21.1–72.8)
eGFR (MDRD), mL/min/1.73 m <sup>2</sup> (min.–max.)	100.5 (60.0–208.0)	100.5 (60.0–194.0)	100.5 (60.0–208.0)
Sex, n (%)			
Female	185 (45.8)	177 (43.7)	362 (44.7)
Male	219 (54.2)	228 (56.3)	447 (55.3)
Ethnicity, n (%)			
Hispanic or Latino	91 (22.5)	106 (26.2)	197 (24.4)
Not Hispanic or Latino	313 (77.5)	299 (73.8)	612 (75.6)
Race, n (%)			
White	341 (84.4)	338 (83.5)	679 (83.9)
Black or African American	28 (6.9)	30 (7.4)	58 (7.2)
Asian	8 (2.0)	6 (1.5)	14 (1.7)
Other	27 (6.6)	31 (7.6)	58 (7.2)
Diabetes medications at screening, n (%)			
Biguanides	391 (96.8)	390 (96.3)	781 (96.5)
Sulfonylureas	181 (44.8)	208 (51.4)	389 (48.1)
Thiazolidinediones	13 (3.2)	6 (1.5)	19 (2.3)
Other BG-lowering drugs (excluding insulin)†	1 (0.2)	2 (0.5)	3 (0.4)
Long-acting insulins and analogs for injection†	0 (0)	1 (0.2)	1 (0.1)

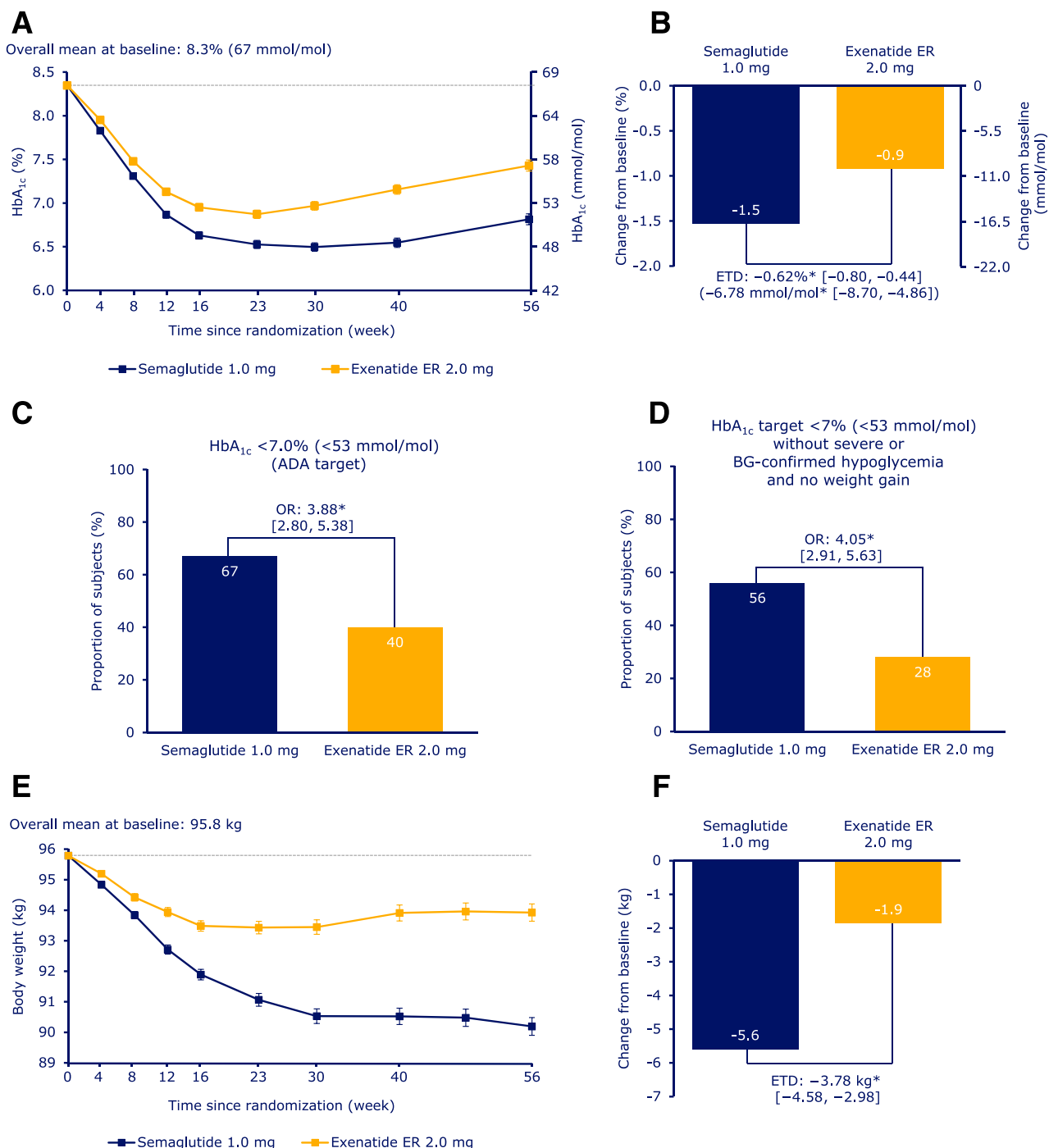
Values are arithmetic means (minimum–maximum) or n (%). eGFR, estimated glomerular filtration rate. \*Min./max. HbA<sub>1c</sub> may be outside the range specified in the inclusion criteria because measurements were taken at the randomization visit. †Subjects receiving other BG-lowering drugs, insulins, and analogs for injection were randomized in error.

−0.80, −0.44 [−6.78 mmol/mol; 95% CI −8.70, −4.86];  $P < 0.0001$  for noninferiority and superiority; Fig. 1B, Table 2 and Supplementary Fig. 4A). This result was supported by all six sensitivity analyses (Supplementary Fig. 3).

### Secondary Efficacy Outcomes

The ADA target of  $\text{HbA}_{1c} < 7.0\%$  ( $< 53$  mmol/mol) was achieved by 67% of semaglutide-treated subjects and 40% of exenatide ER-treated subjects ( $P < 0.0001$ ; Fig. 1C). Overall, 56% of semaglutide-treated

subjects and 28% of exenatide ER-treated subjects achieved the composite outcome of  $\text{HbA}_{1c} < 7.0\%$  ( $< 53$  mmol/mol) without severe or BG-confirmed symptomatic hypoglycemia and without weight gain ( $P < 0.0001$ ; Fig. 1D). The target of  $\text{HbA}_{1c}$



**Figure 1**—Efficacy parameters when comparing semaglutide 1.0 mg once weekly with exenatide ER: mean  $\text{HbA}_{1c}$  by week (A), change in mean  $\text{HbA}_{1c}$  after 56 weeks (B), the proportion of subjects achieving  $\text{HbA}_{1c} < 7.0\%$  ( $< 53$  mmol/mol) (C), the proportion of subjects achieving  $\text{HbA}_{1c} < 7.0\%$  ( $< 53$  mmol/mol) without severe or BG-confirmed hypoglycemia (BG  $< 3.1$  mmol/L [ $< 56$  mg/dL]) and no weight gain at week 56 (D), mean body weight by week (E), and change in mean body weight after 56 weeks (F). \*Significant at  $P < 0.0001$ . Values are estimated mean  $\pm$  SE from a mixed model for repeated measurements analysis (A, B, E, and F) or observed proportions (C and D) using “on treatment without rescue medication” data from subjects in the full analysis set. The dotted lines in A and E indicate the overall mean values at baseline. Missing data were imputed from a mixed model for repeated measurements analysis and subsequently classified.

**Table 2—Key outcomes by treatment group**

	Overall value at baseline, mean (SD)*	Change from baseline at week 56, LSM (SE)		Estimated treatment difference [95% CI]	P value†
		Semaglutide 1.0 mg	Exenatide ER 2.0 mg		
HbA <sub>1c</sub> , %	8.3 (0.95)	−1.5 (0.06)	−0.9 (0.06)	−0.62 [−0.80, −0.44]	<0.0001
HbA <sub>1c</sub> , mmol/mol	67.7 (10.4)	−16.8 (0.68)	−10.0 (0.70)	−6.78 [−8.70, −4.86]	<0.0001
FPG, mmol/L	10.5 (2.7)	−2.8 (0.13)	−2.0 (0.14)	−0.84 [−1.21, −0.47]	<0.0001
7-Point SMPG, mmol/L					
Mean	10.9 (2.5)	−2.2 (0.10)	−1.5 (0.10)	−0.73 [−1.02, −0.44]	<0.0001
Increment	2.2 (1.9)	−0.6 (0.07)	−0.3 (0.07)	−0.24 [−0.44, −0.04]	0.0189
Body weight, kg	95.8 (21.5)	−5.6 (0.29)	−1.9 (0.29)	−3.78 [−4.58, −2.98]	<0.0001
BMI, kg/m <sup>2</sup>	33.8 (6.7)	−2.0 (0.10)	−0.6 (0.10)	−1.36 [−1.64, −1.07]	<0.0001
Waist circumference, cm	111.2 (14.5)	−5.1 (0.31)	−2.3 (0.32)	−2.76 [−3.63, −1.89]	<0.0001
Blood pressure, mmHg					
Systolic	133.5 (14.5)	−4.6 (0.68)	−2.2 (0.70)	−2.37 [−4.29, −0.45]	0.0158
Diastolic	79.9 (8.7)	−1.0 (0.45)	−0.1 (0.46)	−0.90 [−2.16, 0.36]	0.1616
Pulse rate, bpm	75.1 (10.5)	2.1 (0.44)	1.1 (0.44)	1.03 [−0.19, 2.25]	0.0973
Subjects achieving target at week 56, ‡ n (%)					
HbA <sub>1c</sub> targets					
<7.0% (<53 mmol/mol)		270 (67)	161 (40)		<0.0001
≤6.5% (≤48 mmol/mol)		190 (47)	89 (22)		<0.0001
HbA <sub>1c</sub> target <7.0% (<53 mmol/mol) without severe or BG-confirmed hypoglycemia and no weight gain at week 56		226 (56)	113 (28)		<0.0001
Body weight reduction					
≥5%		212 (52)	70 (17)		<0.0001
≥10%		86 (21)	18 (4)		<0.0001

Values are observed means, or observed proportions, based on “on treatment without rescue medication” data from subjects in the full analysis set, with the exception of pulse rate values, which are based on “on-treatment” data from subjects in the safety analysis set. LSM, least squares mean. \*Baseline values are for the entire trial population. †P values are two-sided, testing the null hypothesis of no treatment difference. ‡For the proportions of subjects achieving targets at week 56, missing data were imputed from a mixed model for repeated measurements and subsequently classified. Severe hypoglycemia was based on the ADA classification. BG-confirmed hypoglycemia was defined as plasma glucose <3.1 mmol/L (56 mg/dL).

≤6.5% (≤48 mmol/mol), specified by the American Association of Clinical Endocrinologists, was achieved by 47% of semaglutide-treated subjects and 22% of exenatide ER-treated subjects ( $P < 0.0001$ ; Table 2).

Mean FPG was reduced by 2.8 mmol/L with semaglutide and 2.0 mmol/L with exenatide ER (ETD −0.84 mmol/L; 95% CI −1.21, −0.47;  $P < 0.0001$ ) (Table 2). The mean postprandial increment in BG across all meals, calculated using the seven-point SMPG profile, was reduced by 0.6 mmol/L with semaglutide and 0.3 mmol/L with exenatide ER (ETD −0.24; 95% CI −0.44, −0.04;  $P = 0.0189$ ) (Table 2). The mean of all glucose values from the seven-point SMPG profile was reduced by 2.2 mmol/L with semaglutide and 1.5 mmol/L with exenatide ER (ETD −0.73; 95% CI −1.02, −0.44;  $P < 0.0001$ ).

Fasting insulin, plasma glucagon, proinsulin, proinsulin-to-insulin ratio, and HOMA-insulin resistance were significantly lower at week 56 with semaglutide than with

exenatide ER. The change in HOMA- $\beta$ -cell function was similar between groups. The increase in fasting C-peptide was significantly smaller at week 56 with semaglutide than with exenatide ER (Supplementary Table 4).

Mean body weight was reduced by 5.6 kg with semaglutide and by 1.9 kg with exenatide ER (ETD −3.78 kg; 95% CI −4.58 to −2.98;  $P < 0.0001$ ; Fig. 1E and F and Supplementary Fig. 4B), showing the superiority of semaglutide over exenatide ER in weight loss. The results were supported by the statistical sensitivity analyses. A weight loss response of ≥5% was achieved by 52% of semaglutide-treated subjects and 17% of exenatide ER-treated subjects ( $P < 0.0001$ ; Table 2). A weight loss response of ≥10% was achieved by 21% of semaglutide-treated subjects and 4% of exenatide ER-treated subjects ( $P < 0.0001$ ; Table 2). BMI and waist circumference were also reduced to a greater extent with semaglutide than with exenatide ER (both  $P < 0.0001$ ; Table 2).

Free fatty acid, VLDL cholesterol, and triglycerides were improved with semaglutide compared with exenatide ER ( $P = 0.0342$  for free fatty acid;  $P < 0.0001$  for both VLDL cholesterol and triglycerides; Supplementary Table 4). Systolic blood pressure was reduced by 4.6 mmHg with semaglutide and 2.2 mmHg with exenatide ER (ETD −2.37 mmHg;  $P = 0.0158$ ). No statistically significant difference was found between treatments for change in diastolic blood pressure (Table 2).

Compared with subjects treated with exenatide ER, those treated with semaglutide experienced a significantly greater improvement in overall treatment satisfaction ( $P = 0.0068$ ) and self-perceived hyperglycemia ( $P = 0.0200$ ), as measured by DTSQ scores. No significant differences were found between the treatment groups for domains of health status assessed by the SF-36v2 health survey (Supplementary Fig. 5).

### Safety Outcomes

AEs were reported by similar proportions of subjects in each treatment group: 75.0% (semaglutide) and 76.3% (exenatide ER). Serious AEs were reported in 9.4% of subjects treated with semaglutide and 5.9% of those treated with exenatide ER (Table 3 and Supplementary Table 5). AEs leading to premature treatment discontinuation were reported in 9.4% of subjects treated with semaglutide and 7.2% of subjects treated with exenatide ER (Table 3 and Supplementary Fig. 6). Of these, 5.7% of semaglutide-treated subjects discontinued treatment because of gastrointestinal (GI) AEs—2.5% for nausea, 1.2% for vomiting, and 0.7% for diarrhea—whereas 2.7% of exenatide ER-treated subjects discontinued treatment for the same AEs: 1.5% for nausea, 0.5% for vomiting, and 0.2% for diarrhea.

Nine subjects, all in the exenatide ER group, stopped treatment prematurely because of injection-site nodules (1.2%), mass (0.5%), or reaction (0.5%). Two fatal events occurred in the semaglutide group (one from hepatocellular carcinoma and the other from invasive lobular breast carcinoma) and were judged by the investigator to be unrelated to treatment with the trial product. Both subjects had a short duration of exposure before the onset of the events (65 and 11 days, respectively).

The most common AEs in both treatment groups were GI (semaglutide 41.8%, exenatide ER 33.3%). Nausea was reported in 22.3% and 11.9% of semaglutide- and exenatide ER-treated subjects, respectively

(Table 3). Diarrhea was reported in 11.4% and 8.4% of semaglutide- and exenatide ER-treated subjects, while vomiting occurred in 7.2% and 6.2%, respectively (Table 3). The proportions of subjects with nausea, diarrhea, or vomiting tended to diminish over time (Supplementary Fig. 7).

Overall, 15 EAC-confirmed (treatment-emergent) neoplasms (8 malignant and 7 benign) were reported with semaglutide and 8 (2 malignant and 6 benign) with exenatide ER; we found no evident pattern to the organ distribution of malignant neoplasms. Two instances of EAC-confirmed mild acute pancreatitis occurred with semaglutide and three with exenatide ER. Mean lipase and amylase levels increased similarly at 56 weeks in the two groups (by 19% and 29% with semaglutide and by 15% and 32% with exenatide ER, respectively) (Supplementary Fig. 8). Six cases of cholelithiasis were reported in the semaglutide group and two in the exenatide ER group.

Two episodes of severe hypoglycemia were reported in two semaglutide-treated subjects. One subject was taking sulfonylureas and metformin, and a BG level of 2.33 mmol/L was recorded during the episode; the other subject was taking metformin only, and a BG level of 3.66 mmol/L was recorded during this episode. In total, 33 subjects (8.2%) treated with semaglutide reported severe or BG-confirmed symptomatic episodes, compared with 33 subjects (8.1%) receiving exenatide ER. Rates of severe or BG-confirmed hypoglycemia were 13.0 and 14.0 events

per 100 observation years for semaglutide and exenatide ER, respectively. The majority of events were reported in subjects concomitantly receiving sulfonylureas in both the semaglutide 1.0 mg and exenatide ER 2.0 mg groups.

Pulse rate increased by 2.1 bpm with semaglutide and by 1.1 bpm with exenatide ER ( $P = 0.0973$ ). Injection-site reactions (defined by prespecified *Medical Dictionary for Regulatory Activities*—preferred terms) occurred in 1.2% of semaglutide-treated and 22.0% of exenatide ER-treated subjects. Anti-semaglutide antibodies developed in 13 subjects; none were neutralizing to semaglutide or endogenous GLP-1. Anti-exenatide antibodies developed in 355 subjects; in 39 subjects these were neutralizing to exenatide, but none were neutralizing to endogenous GLP-1.

### CONCLUSIONS

#### Main Findings and Interpretations

Treatment with once-weekly semaglutide 1.0 mg s.c. showed superior glycemic control compared with once-weekly exenatide ER 2.0 mg s.c. in adults with type 2 diabetes inadequately controlled on one or two OADs. The conclusion of superiority was supported by all sensitivity analyses. Despite subjects having a mean diabetes duration >9 years, 67% of the subjects achieved an HbA<sub>1c</sub> target <7.0% (<53 mmol/mol) with semaglutide treatment. Mean baseline HbA<sub>1c</sub> was reduced by 0.9% (10.0 mmol/mol) with exenatide ER in this trial, which is lower than the

**Table 3—Treatment-emergent adverse events\***

	Semaglutide 1.0 mg			Exenatide ER 2.0 mg		
	Subjects experiencing ≥1 event, n (%) (n = 404)	Events, n	Event rate†	Subjects experiencing ≥1 event, n (%) (n = 405)	Events, n	Event rate†
AEs	303 (75.0)	1551	374.7	309 (76.3)	1511	370.4
Serious AEs	38 (9.4)	52	12.6	24 (5.9)	27	6.6
AEs leading to treatment discontinuation	38 (9.4)	48	11.6	29 (7.2)	47	11.5
AEs occurring in ≥5% of subjects‡						
Nausea	90 (22.3)	159	38.4	48 (11.9)	70	17.2
Diarrhea	46 (11.4)	86	20.8	34 (8.4)	58	14.2
Lipase increased	41 (10.1)	51	12.3	49 (12.1)	64	15.7
Nasopharyngitis	39 (9.7)	46	11.1	38 (9.4)	51	12.5
Headache	38 (9.4)	81	19.6	39 (9.6)	65	15.9
Decreased appetite	32 (7.9)	34	8.2	21 (5.2)	24	5.9
Vomiting	29 (7.2)	37	8.9	25 (6.2)	40	9.8
Dyspepsia	27 (6.7)	33	8.0	19 (4.7)	23	5.6
Constipation	26 (6.4)	28	6.8	21 (5.2)	26	6.4
Injection-site nodule	0 (0.0)	0	0	49 (12.1)	55	13.5

\*Treatment-emergent AE (by preferred term) include events with onset at or after the date of the first trial product dose and before or at the date of the last trial medication dose plus 5 weeks plus the 7-day visit window for the end-of-treatment follow-up visit (42 days). †Event rate per 100 years of treatment exposure. ‡By preferred term.



1.0–2.0% (11–22 mmol/mol) mean change from baseline to the end of treatment reported in the Diabetes Therapy Utilization: Researching Changes in A1C, Weight and Other Factors Through Intervention with Exenatide Once Weekly (DURATION) clinical trial program that investigated exenatide ER against a range of comparators (16–21). While trials should be indirectly compared with caution, we cannot exclude the possibility that the open-label design of the trial and the more complex device system used to administer exenatide ER contributed to the lower performance of this treatment. Mean HbA<sub>1c</sub> gradually increased in the exenatide ER group from week 23, and a less pronounced analogous increase occurred in the semaglutide group from week 30; HbA<sub>1c</sub> levels in both groups stayed well below baseline by week 56. These findings are consistent with HbA<sub>1c</sub> trajectory reported in trials of other GLP-1 RAs (22,23).

At the start of treatment, 182 of 404 subjects treated with semaglutide received a concomitant sulfonylurea compared with 209 of 405 subjects receiving exenatide ER; by the end of the observation period, these numbers rose to 193 semaglutide-treated subjects and 213 exenatide ER-treated subjects. We believe that the influence of this differential use of a concomitant sulfonylurea on HbA<sub>1c</sub> level by the end of treatment would be small.

Long-acting GLP-1 RAs such as semaglutide and exenatide ER are known to reduce both fasting and postprandial BG levels (24). In this study, semaglutide led to greater improvements in FPG and postprandial glucose (seven-point SMPG) than did exenatide ER, as well as improvements in a range of glycemic parameters, including insulin, glucagon, C-peptide, proinsulin, and the proinsulin-to-insulin ratio. A significant decrease was found in insulin resistance (as measured by HOMA–insulin resistance) in semaglutide-treated subjects compared with that in exenatide ER-treated subjects—particularly notable when comparing two GLP-1 RAs—whereas  $\beta$ -cell function increased similarly in both groups. Semaglutide treatment also resulted in a pronounced mean change in body weight—a reduction of 5.6 kg over the 1-year treatment period—which was almost three times larger than that occurring with exenatide ER (1.9 kg). In addition,

markedly more subjects receiving semaglutide than exenatide ER achieved a clinically meaningful weight loss response of  $\geq 5\%$  (52% vs. 17%). This sustained weight loss is particularly encouraging because of the high proportion of patients with type 2 diabetes who are overweight or obese and the propensity of some antihyperglycemic medications to lead to further weight gain in these individuals (25). While weight gain can lead to frustration, reduced motivation, and decreased adherence to treatment (26), a weight loss of 5% or more is associated with improvements in metabolic and cardiovascular risk factors in patients with type 2 diabetes (27).

Overall, diabetes treatment satisfaction and self-perceived hyperglycemia improved more with semaglutide than with exenatide ER, consistent with the differences observed in glycemic control, without a significant difference in overall health-related quality of life, as measured by the SF-36v2 questionnaire.

A higher proportion of GI-related AEs were reported with semaglutide (41.8%) than with exenatide ER (33.3%). In both groups, the majority of GI AEs were transient and largely mild or moderate in severity. The prevalence of nausea diminished over time in both treatment groups. Injection-site reactions occurred more frequently with exenatide ER (22.0% of subjects) than with semaglutide (1.2% of subjects).

The increased pulse rate observed with semaglutide is consistent with that reported for other once-weekly GLP-1 RAs and should be considered in the context of the full cardiovascular risk profile for semaglutide-treated subjects, which is characterized by a reduction in systolic blood pressure. The long-term cardiovascular safety of semaglutide was investigated in the SUSTAIN 6 trial, which demonstrated that semaglutide significantly reduced the risk of a major adverse cardiovascular event (defined as a composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) compared with placebo, both as add-ons to standard of care (28).

A higher proportion of subjects reported neoplasms as treatment-related AEs with semaglutide compared with exenatide ER; this was driven predominantly by differences across multiple single events (based on preferred terms), and malignant neoplasms were not clustered in

relation to organ distribution. No imbalances in malignant neoplasms were observed in the larger SUSTAIN 6 over 2 years (28).

Antiexenatide antibody formation and injection-site reactions are relatively frequent in patients treated with exenatide and exenatide ER (29), whereas they are less frequent with semaglutide. This is likely due to a lower homology to native GLP-1 with exenatide than semaglutide.

Because a potential association has been suggested between GLP-1 treatment and acute pancreatitis (30), although this was not confirmed in a recent large cohort study (31), mean lipase and amylase values were determined and suspected cases of pancreatitis were adjudicated. Mean lipase and amylase levels increased similarly in the two groups. Two cases of mild acute pancreatitis were found in the semaglutide group and three in the exenatide ER group. Ongoing safety evaluation of GLP-1 RAs, including evaluation of pancreatitis, cardiovascular safety, and neoplasms, will be important in understanding the long-term benefits and safety of treatments within this class.

In terms of overall effect, composite outcomes were also evaluated, showing that the proportion of subjects achieving HbA<sub>1c</sub> <7.0% (<53 mmol/mol) without severe or BG-confirmed symptomatic hypoglycemia and without weight gain was significantly higher with semaglutide than exenatide ER treatment.

### **Trial Strengths and Limitations**

The proven efficacy of once-weekly exenatide ER in glycemic control and weight loss underpins its validity as a treatment comparator for semaglutide, although this trial did not investigate the use of an exenatide ER prefilled pen that has since become available. The trial population represented a wide range of ages, body weights, BMIs, diabetes durations, and HbA<sub>1c</sub> levels, and was therefore representative of different type 2 diabetes phenotypes. The treatment duration of 56 weeks was longer than the 6-month duration typically used in other GLP-1 RA phase 3 trials, but longer studies are still required. The open-label design, necessitated because the investigators and participants could not be blinded to the different devices used, is also a limitation. Because subjects and physicians were aware of how the drugs were allocated, we cannot discount that this may have

influenced motivation of participants to adhere to treatments. In addition, we cannot exclude that differences in the adherence to and quality of administration of the two treatments had a potential impact on the lower performance of exenatide ER compared with semaglutide. However, this would also be reflected in a real-life setting.

In this head-to-head trial, once-weekly semaglutide 1.0 mg was shown to be superior to exenatide ER 2.0 mg in improving glycemic control and reducing body weight over 56 weeks of treatment in adults with type 2 diabetes inadequately controlled with one or two OADs. The overall safety profile was similar between the two agents, although semaglutide was associated with a higher incidence of GI-related AEs, whereas exenatide ER-treated subjects experienced comparatively more injection-site reactions. While several GLP-1 RAs are available and/or in development, this trial demonstrates both the similarities and differences in efficacy, safety, and tolerability of drugs within the class. Comparison with other soluble weekly GLP-1 RAs is also underway (clinicaltrials.gov identifier NCT02648204), which may help to inform treatment choices further.

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