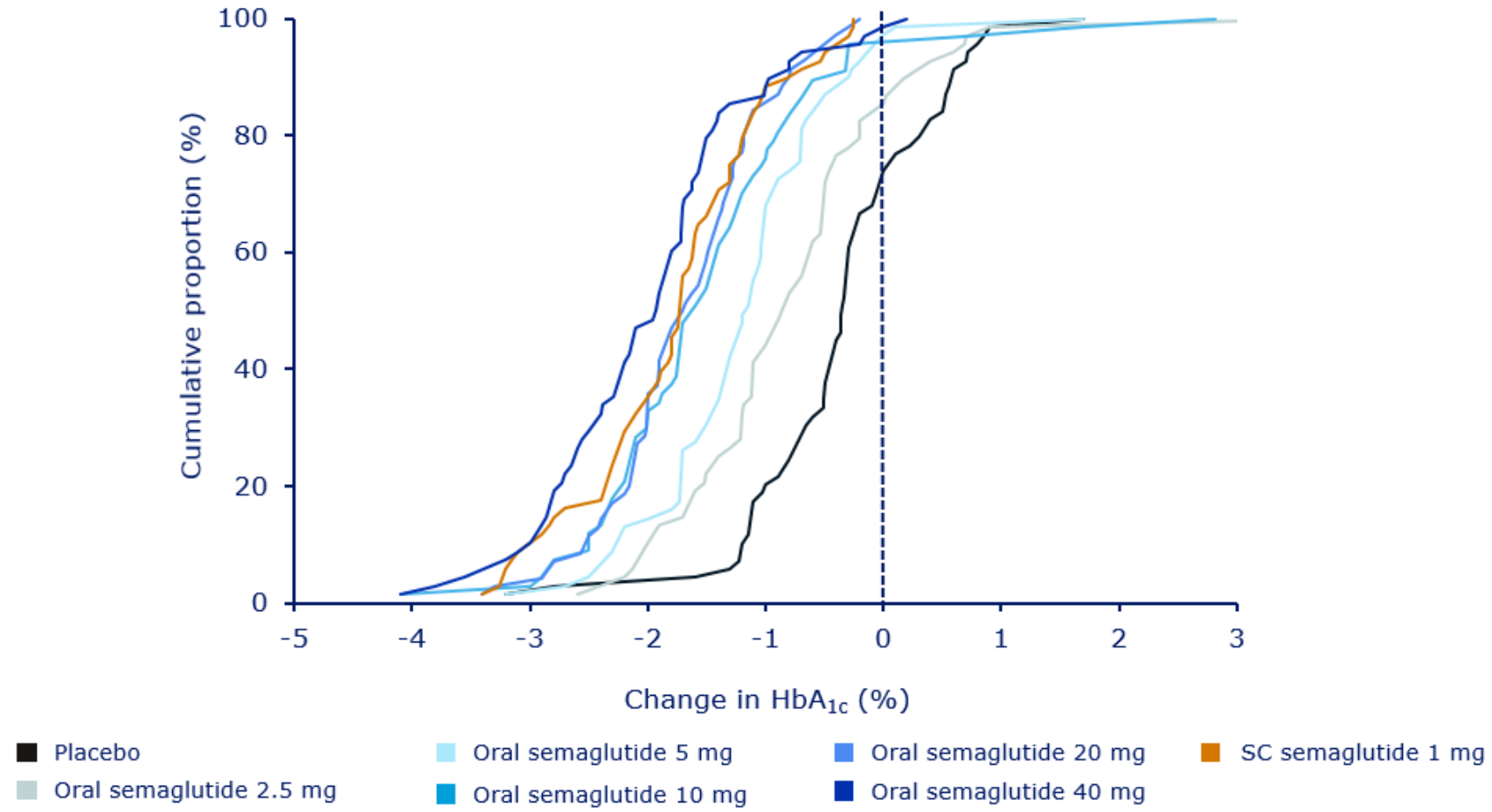
Supplementary Online Content

Davies M, Pieber TR, Hartoft-Nielsen M.-L., et al. Effect of oral semaglutide compared with placebo and subcutaneous semaglutide on glycemic control in patients with type 2 diabetes: a randomized clinical trial. *JAMA*. doi:10.1001/jama.2017.14752

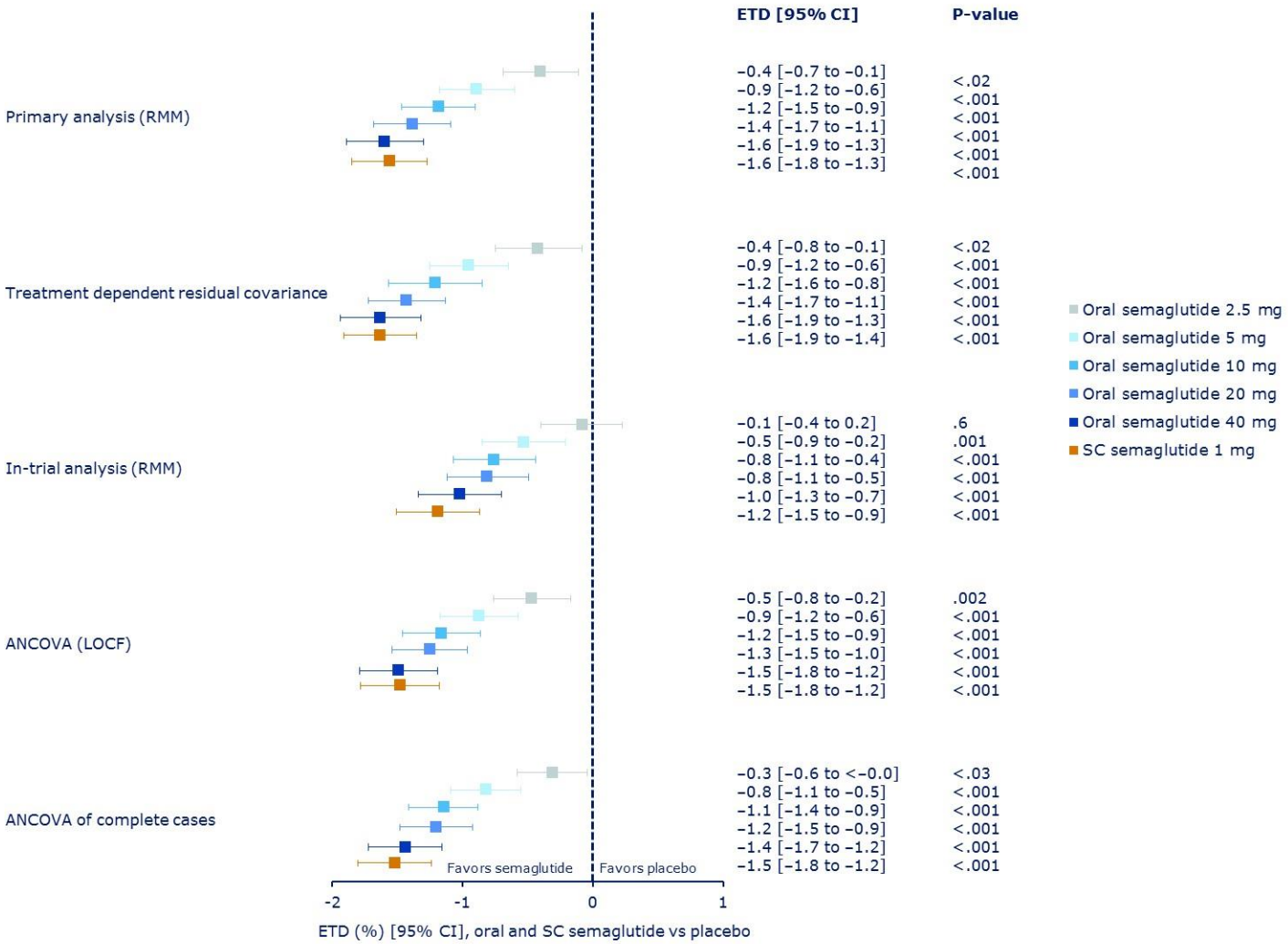
This supplementary material has been provided by the authors to give readers additional information about their work.

eFigure 1. Change in mean HbA_{1c} – cumulative distribution function at week 26



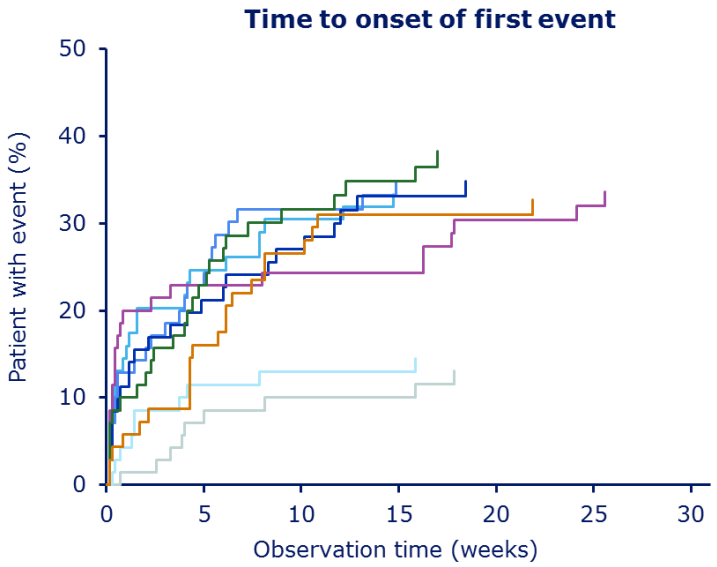
Missing HbA_{1c} values are imputed from repeated measures model analysis. SC, subcutaneous

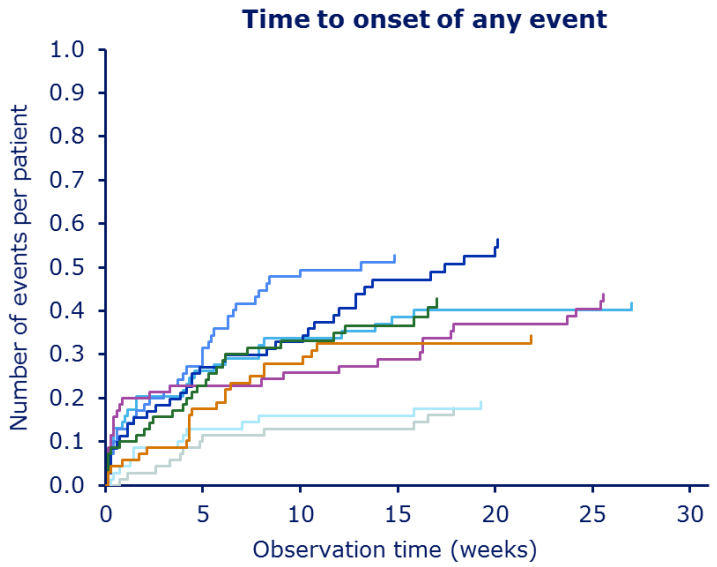
eFigure 2. Sensitivity analyses



Values are ETDs with 95% CIs (comparing oral and SC semaglutide versus placebo) from a repeated measures model analysis with treatment, stratum, country and baseline value, all nested within visit. The in-trial analysis refers to a repeated measures model based on all scheduled data recorded after randomization regardless of adherence to randomized treatment or initiation of rescue therapy.ANCOVA, analysis of covariance; LOCF, last observation carried forward; ETD, estimated treatment difference; CI, confidence interval; RMM, repeated measures model.

eFigure 3. Proportion of patients with nausea and mean number of events over time





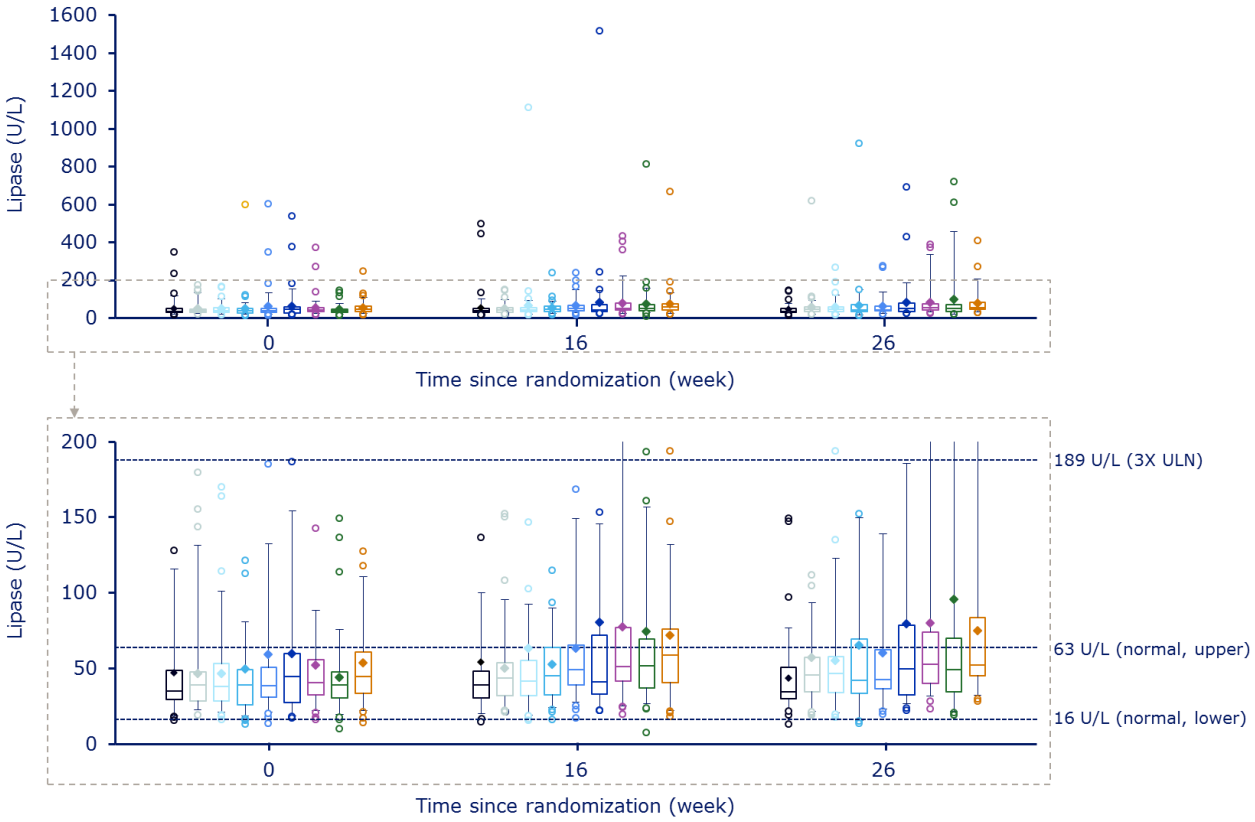
	Number of patients at risk									Number of patients at risk										Observation period
Week	0	4	8	12	16	20	24	28	31	Week	0	4	8	12	16	20	24	28	31	Days, median (Q1, Q3)
Placebo	71	70	68	67	66	66	65	64	58		71	71	69	68	67	67	66	65	59	218 (217, 219)
Oral semaglutide 2.5 mg	70	66	64	59	58	56	56	56	52		70	70	70	65	63	62	62	62	56	218 (218, 219)
Oral semaglutide 5 mg	70	62	59	57	56	56	55	52	48		70	69	67	64	64	63	62	59	55	218 (217, 220)
Oral semaglutide 10 mg	69	55	49	48	45	45	45	45	44		69	68	65	63	61	60	60	59	57	218 (218, 220)
Oral semaglutide 20 mg	70	56	45	44	41	40	38	37	35		70	70	65	59	54	52	49	48	46	218 (125, 221)
Oral semaglutide 40 mg	71	57	52	46	40	38	38	38	36		71	70	67	64	58	52	52	49	46	218 (122, 218)
Oral semaglutide 40 mg 8-week dose escalation	70	54	53	51	50	44	43	39	35		70	70	68	65	63	60	58	54	48	218 (214, 220)
Oral semaglutide 40 mg 2-week dose escalation	70	58	47	41	38	35	34	34	30		70	70	66	56	50	48	46	46	41	216 (93, 219)
SC semaglutide 1 mg	69	62	51	46	45	42	41	39	16		69	68	67	65	64	59	57	54	27	216 (213, 218)

Placebo
Oral semaglutide 2.5 mg
Oral semaglutide 5 mg
Oral semaglutide 10 mg
Oral semaglutide 20 mg
Oral semaglutide 40 mg
Oral semaglutide 40 mg 8-week dose escalation
Oral semaglutide 40 mg 2-week dose escalation
SC semaglutide 1 mg

Treatment-emergent events collected from first exposure to the follow-up visit scheduled 5 weeks (+5 day visit window) after final trial product dose. Left panel: Kaplan-Meier estimator. Right panel: mean cumulative function estimator. F, 2-week dose escalation; S, 8-week dose escalation; SC, subcutaneous.

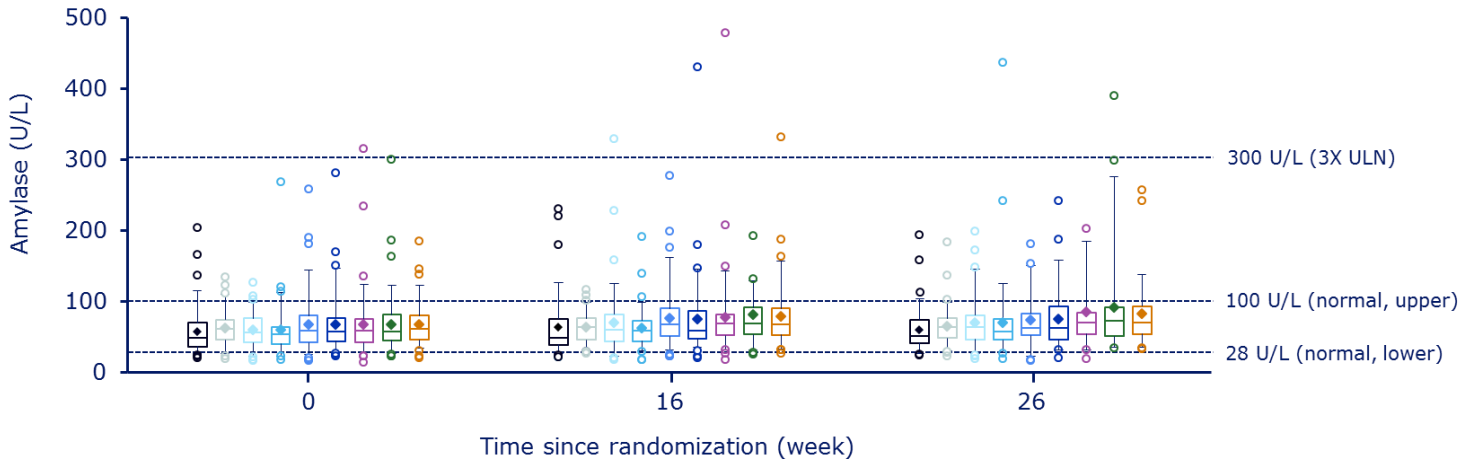
eFigure 4. Lipase and amylase

A. Lipase



	Number of patients at risk		
Placebo	70	68	64
Oral semaglutide 2.5 mg	70	65	60
Oral semaglutide 5 mg	70	64	60
Oral semaglutide 10 mg	69	64	59
Oral semaglutide 20 mg	70	66	49
Oral semaglutide 40 mg	71	60	46
Oral semaglutide 40 mg 8-week dose escalation	70	61	54
Oral semaglutide 40 mg 2-week dose escalation	69	61	42
SC semaglutide 1 mg	69	63	49

B. Amylase



	Number of patients at risk		
Placebo	71	68	64
Oral semaglutide 2.5 mg	70	65	60
Oral semaglutide 5 mg	70	64	60
Oral semaglutide 10 mg	69	64	59
Oral semaglutide 20 mg	70	66	49
Oral semaglutide 40 mg	71	61	47
Oral semaglutide 40 mg 8-week dose escalation	70	61	54
Oral semaglutide 40 mg 2-week dose escalation	70	61	42
SC semaglutide 1 mg	70	64	49

Placebo
Oral semaglutide 2.5 mg
Oral semaglutide 5 mg
Oral semaglutide 10 mg
Oral semaglutide 20 mg
Oral semaglutide 40 mg
Oral semaglutide 40 mg 8-week dose escalation
Oral semaglutide 40 mg 2-week dose escalation
SC semaglutide 1 mg

Observed values from patients in the safety analysis set. Boxes correspond to the 25th, 50th (median) and 75th percentiles, and diamond symbols correspond to the means. Whiskers correspond to the 5th and 95th percentiles and circles correspond to values beyond the 5th and 95th percentiles. Dotted lines indicate normal reference ranges and 3 times upper normal range. SC, subcutaneous; ULN, upper limit of normal range.

eBox 1. Countries involved in the trial

Austria
Bulgaria
Canada
Denmark
Germany
Israel
Italy
Malaysia
Serbia
South Africa
Spain
Sweden
United Kingdom
United States

eBox 2. Key exclusion criteria

Treatment with selected oral medications with a narrow therapeutic window
History of pancreatitis
Chronic malabsorption
History of inflammatory bowel disease
Treatment with glucose lowering agent(s) other than metformin as stated in the inclusion criteria in a period of 90 days before the screening visit
Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2

eBox 3. Pre-defined events types that were sent for blinded adjudication by an independent external committee

Fatal events
Acute coronary syndrome (myocardial infarction, hospitalization for unstable angina)
Cerebrovascular events (stroke, transient ischemic attack)
Coronary revascularization procedure
Heart failure requiring hospital admission
Pancreatitis or clinical suspicion of pancreatitis
Neoplasms
Thyroid disease (if thyroid neoplasm or resulting in thyroidectomy)

eTable 1. Additional efficacy and safety endpoints

	Overall mean at baseline	Placebo	Oral semaglutide 2.5 mg	Oral semaglutide 5 mg	Oral semaglutide 10 mg	Oral semaglutide 20 mg	Oral semaglutide 40 mg	SC semaglutide 1 mg
Glycemic parameters								
Fasting insulin, pmol/L[a]	110.0	0.9 [0.8 to 1.0]	0.9 [0.8 to 1.1]	0.9 [0.8 to 1.0]	0.9 [0.8 to 1.0]	0.9 [0.8 to 1.1]	0.8 [0.7 to 0.9]	0.7* [0.6 to 0.8]
Fasting glucagon, pg/mL[a]	98.9	1.0 [0.9 to 1.1]	0.9 [0.9 to 1.0]	0.9 [0.8 to 1.0]	0.9 [0.9 to 1.0]	0.9* [0.8 to 0.9]	0.8** [0.8 to 0.9]	0.8** 0.8 to 0.9]
Fasting C-peptide nmol/L[a]	1.0	1.0 [0.9 to 1.1]	1.0 [1.0 to 1.1]	1.1 [1.0 to 1.2]	1.0 [1.0 to 1.1]	1.1 [1.0 to 1.2]	1.0 [0.9 to 1.1]	0.9 [0.9 to 1.0]
HOMA-IR, %[a]	6.2	0.9 [0.8 to 1.0]	0.8 [0.7 to 1.0]	0.8 [0.7 to 0.9]	0.7* [0.6 to 0.8]	0.7* [0.6 to 0.8]	0.6** [0.5 to 0.6]	0.5** [0.4 to 0.6]
HOMA-B, %[a]	55.5	0.9 [0.8 to 1.1]	1.2* [1.0 to 1.3]	1.3** [1.1 to 1.5]	1.6** [1.4 to 1.8]	1.6** [1.4 to 1.8]	1.6** [1.4 to 1.8]	1.6** [1.4 to 1.9]
Body measurements								
Body weight, % change[a]		–1.4 [–2.5 to –0.2]	–2.4 [–3.5 to –1.2]	–2.9 [–4.1 to –1.8]	–5.2** [–6.4 to –4.1]	–6.6** [–7.9 to –5.4]	–7.6** [–8.7 to –6.4]	–7.3** [–8.5 to –6.1]
Body weight, ETD % change[a]			–1.0 [–2.7 to 0.6]	–1.5 [–3.2 to 0.1]	–3.9** [–5.5 to –2.2]	–5.28** [–7.0 to –3.6]	–6.2** [–7.9 to –4.5]	–5.9** [–7.6 to –4.3]
Waist circumference, cm[b]	107.4	–1.7 [–2.9 to –0.4]	–1.8 [–3.0 to –0.7]	–2.2 [–3.4 to –1.0]	–4.5** [–5.7 to –3.3]	–4.5* [–5.7 to –3.2]	–5.8** [–7.0 to –4.5]	–6.2** [–7.4 to –5.0]
Patients achieving ≥5% weight loss at week 26, n (%)		9 (13)	15 (21)	15 (21)	38 (56)**	45 (64)**	50 (71)**	45 (66)**
Patients achieving ≥10% weight loss, n (%)		1 (1)	3 (4)	3 (4)	10 (15)	11 (16)	19 (27)	18 (26)
Fasting blood lipids								
Total cholesterol, mg/dL[a]	178.6	1.0 [0.9 to 1.0]	1.0 [1.0 to 1.0]	0.9 [0.9 to 1.0]	1.0 [1.0 to 1.0]	1.0 [0.9 to 1.0]	0.9 [0.9 to 1.0]	0.9 [0.9 to 1.0]
LDL, mg/dL[a]	101.7	0.9 [0.9 to 1.0]	1.0 [0.92 to 1.1]	0.9 [0.8 to 0.9]	1.0 [0.9 to 1.0]	0.9 [0.9 to 1.0]	0.9 [0.8 to 1.0]	0.9 [0.8 to 1.0]
VLDL, mg/dL[a]	30.4	1.0 [0.9 to 1.1]	0.9 [0.8 to 1.0]	1.1 [1.0 to 1.2]	1.0 [0.9 to 1.1]	0.9 [0.8 to 1.0]	0.8* [0.7 to 0.9]	0.8* [0.8 to 0.9]
HDL, mg/dL[a]	46.2	1.0 [1.0 to 1.1]	1.1 [1.0 to 1.1]	1.0* [0.9 to 1.0]	1.0 [1.0 to 1.0]	1.0 [1.0 to 1.0]	1.0 [1.0 to 1.1]	1.0 [1.0 to 1.1]
TG, mg/dL[a]	158.8	1.0 [0.9 to 1.1]	0.9 [0.8 to 1.0]	1.0 [0.9 to 1.1]	1.0 [0.9 to 1.1]	0.9 [0.8 to 1.0]	0.8* [0.7 to 0.9]	0.8* [0.7 to 0.9]
FFA, mmol/L[a]	0.8	1.0 [0.9 to 1.1]	1.0 [0.9 to 1.1]	1.0 [0.9 to 1.1]	1.0 [0.9 to 1.1]	0.9 [0.8 to 1.0]	1.0 [0.9 to 1.1]	0.9* [0.8 to 1.0]

	Overall mean at baseline	Placebo	Oral semaglutide 2.5 mg	Oral semaglutide 5 mg	Oral semaglutide 10 mg	Oral semaglutide 20 mg	Oral semaglutide 40 mg	SC semaglutide 1 mg
Patient-reported outcomes								
SF-36 score, physical component summary[b]	49.1	0.5 [–1.1 to 2.1]	0.3 [–1.2 to 1.8]	0.7 [–0.7 to 2.2]	1.3 [–0.1 to 2.7]	–0.1 [–1.6 to 1.3]	–0.2 [–1.6 to 1.3]	0.4 [–1.1 to 1.8]
SF-36 score, mental component summary[b]	51.1	0.5 [–1.7 to 2.8]	–0.0 [–2.1 to 2.1]	0.5 [–1.6 to 2.7]	–0.0 [–2.1 to 2.0]	–0.9 [–3.0 to 1.1]	–0.2 [–2.3 to 1.8]	–0.6 [–2.7 to 1.5]
Safety								
Heart rate, bpm[b]	73.5	–4.0 [–5.9 to –2.1]	–1.7 [–3.7 to 0.2]	0.6** [–1.4 to 2.6]	2.9** [0.9 to 4.8]	3.0** [0.8 to 5.1]	1.9** [–0.2 to 4.1]	2.6** [0.5 to 4.8]
Systolic blood pressure, mmHg[b]	134.0	–2.7 [–5.7 to 0.4]	–5.4 [–8.5 to –2.3]	–6.6 [–9.8 to –3.5]	–7.8* [–10.9 to –4.6]	–6.2 [–9.6 to –2.7]	–6.1 [–9.5 to –2.6]	–5.7 [–9.2 to –2.2]
Diastolic blood pressure, mmHg[b]	81.1	–2.4 [–4.3 to –0.5]	–2.5 [–4.4 to –0.5]	–2.2 [–4.1 to –0.2]	–3.1 [–5.1 to –1.2]	–2.8 [–4.9 to –0.6]	–0.3 [–2.4 to 1.9]	–0.4 [–2.6 to 1.7]

*P<.05; **P<.001, all versus placebo. Full analysis set. Overall mean at baseline includes the dose escalation arms. [a]Values are geometric mean at baseline and ratio-to-baseline at week 26 [95% CI]; [b]Values are mean at baseline and mean change from baseline at week 26 [95% CI]. Ratios-to-baseline and changes from baseline are estimated means from a repeated measures model analysis with treatment, stratum, country and baseline value all nested within visit. With SF-36, a higher score (0–100) was related to a better self-perceived quality of life.

bpm, beats per minute; ETD, estimated treatment difference; FFA, free fatty acids; HDL, high-density lipoprotein cholesterol; HOMA-IR/B, homeostasis model assessment-insulin resistance/beta-cell function; LDL, low-density lipoprotein cholesterol; SF-36, 36-item short-form health survey; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol. SI conversion factors: to convert insulin values to pmol/L, multiply by 6.945; glucagon values = ng/L; total cholesterol, HDL cholesterol, and LDL cholesterol values to mmol/L, multiply by 0.0259; triglycerides to mmol/L, multiply by 0.0113; free fatty acids to mmol/L, multiply by 0.0355.

eTable 2. Efficacy and safety endpoints for oral semaglutide dose escalation arms at week 26

	Overall mean at baseline	Placebo	Oral semaglutide 40 mg (Standard 4-week dose escalation)	Oral semaglutide 40 mg (8-week dose escalation)	Oral semaglutide 40 mg (2-week dose escalation)	SC semaglutide 1 mg
Glycemic parameters						
HbA_{1c}, %[a]	7.9	–0.3 [–0.5 to –0.1]	–1.9** [–2.2 to –1.7]	–1.7** [–1.9 to –1.5]	–1.7** [–1.9 to –1.4]	–1.9** [–2.1 to –1.7]
HbA_{1c}, ETD %[a]	-		–1.6** [–1.9 to –1.3]	–1.4** [–1.7 to –1.1]	–1.3** [–1.6 to –1.0]	–1.6** [–1.8 to –1.3]
Patients achieving HbA_{1c} target <7%, N (%)	-	19 (28)	61 (90)**	58 (87)**	57 (88)**	63 (93)**
FPG, mg/dL[a,b]	170.2	–1 [–9.6 to 7.5]	–51** [–60.0 to –42.4]	–54** [–62.2 to –45.4]	–46** [–54.8 to –36.4]	–56** [–65.3 to –47.4]
Fasting insulin, pmol/[c]	110.0	0.9 [0.8 to 1.0]	0.8 [0.7 to 0.9]	0.9 [0.8 to 1.0]	0.8 [0.7 to 0.9]	0.7* [0.6 to 0.8]
Fasting glucagon, pg/mL[c]	98.9	1.0 [0.9 to 1.1]	0.8** [0.8 to 0.9]	0.9 [0.9 to 1.0]	0.9* [0.8 to 1.0]	0.8** [0.8 to 0.9]
Fasting C-peptide nmol/L[c]	1.0	1.0 [0.9 to 1.1]	1.0 [0.9 to 1.1]	1.1 [1.0 to 1.2]	1.0 [0.9 to 1.1]	0.9 [0.9 to 1.0]
HOMA-IR, %[c]	6.2	0.9 [0.8 to 1.0]	0.6** [0.5 to 0.6]	0.6** [0.5 to 0.7]	0.6** [0.5 to 0.7]	0.5** [0.4 to 0.6]
HOMA-B, %[c]	55.5	0.9 [0.8 to 1.1]	1.6** [1.4 to 1.8]	1.9** [1.6 to 2.2]	1.4** [1.2 to 1.7]	1.6** [1.4 to 1.9]
Body measurements						
Body weight, kg[a]	92.3	–1.2 [–2.3 to –0.1]	–6.9** [–8.0 to –5.8]	–6.1** [–7.1 to –5.0]	–8.2** [–9.3 to –7.0]	–6.4** [–7.5 to –5.3]
Body weight, % change[a]	-	–1.4 [–2.5 to –0.2]	–7.6** [–8.7 to –6.4]	–6.7** [–7.8 to –5.5]	–9.2** [–10.4 to –7.9]	–7.3** [–8.5 to –6.1]
Body weight, ETD % change[a]	-		–6.2** [–7.9 to –4.5]	–5.3** [–7.0 to –3.7]	–7.8** [–9.5 to –6.1]	–5.9** [–7.6 to –4.3]
Waist circumference, cm[a]	107.4	–1.7 [–2.9 to –0.4]	–5.8** [–7.0 to –4.5]	–5.1** [–6.3 to –3.9]	–6.3** [–7.5 to –5.0]	–6.2** [–7.4 to –5.0]
Patients achieving ≥5% weight loss, n (%)	-	9 (13)	50 (71)**	41 (59)**	55 (82)**	45 (66)**
Patients achieving ≥10% weight loss, n (%)	-	1 (1)	19 (27)	12 (17)	27 (40)	18 (26)

	Overall mean at baseline	Placebo	Oral semaglutide 40 mg (Standard 4-week dose escalation)	Oral semaglutide 40 mg (8-week dose escalation)	Oral semaglutide 40 mg (2-week dose escalation)	SC semaglutide 1 mg
Lipid parameters						
Total cholesterol, mg/dL[c]	178.6	1.0 [0.9 to 1.0]	0.9 [0.9 to 1.0]	1.0 [0.9 to 1.0]	0.9 [0.9 to 1.0]	0.9 [0.9 to 1.0]
LDL, mg/dL[c]	101.7	0.9 [0.9 to 1.0]	0.9 [0.8 to 1.0]	0.9 [0.9 to 1.0]	0.9 [0.9 to 1.0]	0.9 [0.8 to 1.0]
VLDL, mg/dL[c]	30.4	1.0 [0.9 to 1.1]	0.8* [0.7 to 0.9]	0.9 [0.8 to 0.9]	0.8 [0.8 to 0.9]	0.8* [0.8 to 0.9]
HDL, mg/dL[c]	46.2	1.0 [1.0 to 1.1]	1.0 [1.0 to 1.1]	1.0 [1.0 to 1.1]	1.0 [1.0 to 1.1]	1.0 [1.0 to 1.1]
TG, mg/dL[c]	158.8	1.0 [0.9 to 1.1]	0.8* [0.7 to 0.9]	0.8 [0.8 to 0.9]	0.8 [0.7 to 0.9]	0.8* [0.7 to 0.9]
FFA, mmol/L[c]	0.8	1.0 [0.9 to 1.1]	1.0 [0.9 to 1.1]	0.9* [0.8 to 1.0]	0.9* [0.8 to 1.0]	0.9* [0.8 to 1.0]
Patient–reported outcomes						
SF-36 score, overall physical score[a]	49.1	0.5 [–1.1 to 2.1]	–0.2 [–1.6 to 1.3]	–0.3 [–1.8 to 1.1]	–0.4 [–1.8 to 1.1]	0.4 [–1.1 to 1.8]
SF-36 score, overall mental score[a]	51.1	0.5 [–1.7 to 2.8]	–0.2 [–2.3 to 1.8]	0.5 [–1.6 to 2.6]	–1.1 [–3.2 to 1.0]	–0.6 [–2.7 to 1.5]
Safety						
Heart rate, bpm[a]	73.5	–4.0 [–5.9 to –2.1]	1.9** [–0.2 to 4.1]	2.3** [0.2 to 4.3]	1.6** [–0.6 to 3.8]	2.6** [0.5 to 4.8]
Systolic blood pressure, mmHg[a]	134.0	–2.7 [–5.7 to 0.4]	–6.1 [–9.5 to –2.6]	–7.1 [–10.3 to –3.8]	–7.2 [–10.8 to –3.6]	–5.7 [–9.2 to –2.2]
Diastolic blood pressure, mmHg[a]	81.1	–2.4 [–4.3 to –0.5]	–0.3 [–2.4 to 1.9]	–2.7 [–4.8 to –0.7]	–1.9 [–4.1 to 0.3]	–0.4 [–2.6 to 1.7]

*P<.05; **P<.001, all versus placebo. Full analysis set. Overall mean at baseline includes the dose escalation arms. [a]Values are mean at baseline and mean change from baseline at week 26 [95% CI]; [b]mmol/L = mg/dL/18; [c]Values are geometric mean at baseline and ratio-to-baseline at week 26 [95% CI]. Ratios-to-baseline and changes from baseline are estimated means from a repeated measures model analysis with treatment, stratum, country and baseline value all nested within visit. With SF-36, a higher score (0–100) was indicative of a better self-perceived quality of life.

bpm, beats per minute; ETD, estimated treatment difference; FFA, free fatty acids; FPG, fasting plasma glucose; HbA_{1c}, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HOMA-IR/B, homeostasis model assessment-insulin resistance/beta-cell function; LDL, low-density lipoprotein cholesterol; SF-36, 36-item short-form health survey; TG, triglycerides; VLDL, very low-density lipoprotein cholesterol.

eTable 3. Serious adverse events by system organ class

	Placebo N (%) E	Oral semaglutide 2.5 mg N (%) E	Oral semaglutide 5 mg N (%) E	Oral semaglutide 10 mg N (%) E	Oral semaglutide 20 mg N (%) E	Oral semaglutide 40 mg N (%) E	Oral semaglutide 40 mg (8-week dose escalation) N (%) E	Oral semaglutide 40 mg (2-week dose escalation) N (%) E	SC semaglutide 1 mg N (%) E
Number of patients	71	70	70	69	70	71	70	70	69
Observation time (patient-years)	40.5	38.9	38.4	37.8	34.5	35.5	37.8	32.9	37.0
Events	5 (7) 8	1 (1) 1	2 (3) 2	2 (3) 5	-	1 (1) 1	3 (4) 3	5 (7) 9	2 (3) 2
Infections and infestations	1 (1) 1	1 (1) 1	-	-	-	1 (1) 1	1 (1) 1	1 (1) 1	-
Gastrointestinal disorders	-	-	-	1 (1) 2	-	-	-	1 (1) 3	1 (1) 1
Renal and urinary disorders	1 (1) 1	-	-	1 (1) 1	-	-	-	1 (1) 1	-
Injury, poisoning and procedural complications	1 (1) 1	-	-	1 (1) 2	-	-	-	-	-
Metabolism and nutrition disorders	-	-	-	-	-	-	-	2 (3) 2	-
Musculoskeletal and connective tissue disorders	1 (1) 1	-	-	-	-	-	-	1 (1) 1	-
Nervous system disorders	1 (1) 1	-	-	-	-	-	1 (1) 1	-	-
Cardiac disorders	1 (1) 2	-	-	-	-	-	-	-	-
Eye disorders	-	-	-	-	-	-	-	1 (1) 1	-
General disorders and administration site conditions	-	-	-	-	-	-	1 (1) 1	-	-
Hepatobiliary disorders	-	-	1 (1) 1	-	-	-	-	-	-
Investigations	-	-	1 (1) 1	-	-	-	-	-	-
Neoplasms[a]	1 (1) 1	-	-	-	-	-	-	-	-
Skin + subcutaneous disorders	-	-	-	-	-	-	-	-	1 (1) 1

Safety analysis set; [a]benign, malignant and unspecified (including cysts and polyps). A serious adverse event (SAE) was defined as an experience that at any dose results in any of the following: death; a life-threatening experience, in-patient hospitalisation or prolongation of existing hospitalisation; a persistent or significant disability or incapacity; a congenital anomaly or birth defect; or where medical judgement deems that medical or surgical intervention is necessary to prevent one of the outcomes listed in this definition of SAE. -, no events reported; E, number of events; SC, subcutaneous.

eTable 4. Nausea by time and severity

		Nausea AEs, N (%)			
	N	Mild	Moderate	Severe	Total
Placebo	71	1 (1.4)	0 (0)	0 (0)	1 (1.4)
Oral semaglutide 2.5 mg	70	8 (11.4)	(0)	1 (1.4)	9 (12.9)
Oral semaglutide 5 mg	70	10 (14.3)	(0)	0 (0)	10 (14.3)
Oral semaglutide 10 mg	69	17 (24.6)	7 (10.1)	2 (2.9)	23 (33.3)
Oral semaglutide 20 mg	70	16 (22.9)	11 (15.7)	3 (4.3)	24 (34.3)
Oral semaglutide 40 mg	71	12 (22.5)	11 (15.5)	2 (2.8)	24 (33.8)
Oral semaglutide 40 mg 8-week dose escalation	70	16 (22.9)	6 (8.6)	2 (2.9)	23 (32.9)
Oral semaglutide 40 mg 2-week dose escalation	70	16 (22.9)	9 (12.9)	1 (1.4)	26 (37.1)
SC semaglutide 1 mg	69	15 (21.7)	6 (8.7)	1 (1.4)	22 (31.9)

Treatment-emergent events collected from first exposure to the follow-up visit scheduled 5 weeks (+5 day visit window) after final trial product dose. For each treatment, the total incidence at a given day is grouped by adverse event severity. The highest severity experienced by each patient is shown. SC, subcutaneous.

eTable 5. Hypoglycemic events

	Placebo		Oral semaglutide 2.5 mg		Oral semaglutide 5 mg		Oral semaglutide 10 mg		Oral semaglutide 20 mg		Oral semaglutide 40 mg		Oral semaglutide 40 mg (8-week dose escalation)		Oral semaglutide 40 mg (2-week dose escalation)		SC semaglutide 1 mg	
	N	E	N	E	N	E	N	E	N	E	N	E	N	E	N	E	N	E
Number of patients	71		70		70		69		70		71		70		70		69	
Severe or BG-confirmed[a]	2	3	2	4	1	3	3	6	1	1	1	1	3	3	1	1	4	4
ADA classified[b]	8	20	8	14	6	18	6	32	16	26	6	8	12	26	9	14	12	16
Severe[c]	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	1	1	1

[a]'Severe or BG-confirmed' hypoglycemic episodes are defined as severe by ADA classification[c] or BG-confirmed with a plasma glucose value of <56 mg/dL (<3.1 mmol/L) with/without symptoms consistent with hypoglycemia; [b]ADA classified, ≤70 mg/dL (≤3.9 mmol/L); [c]ADA-classified 'severe' hypoglycemia is an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other corrective actions.

ADA, American Diabetes Association; BG, blood glucose; E, number of events; SC, subcutaneous.

eTable 6. Event adjudication committee-confirmed cardiovascular events

Treatment	Patient characteristics (Sex/age [years]/ BMI [kg/m^2])	Confirmed diagnosis	Treatment-emergent (Yes/No)	Trial day of event	Serious adverse event (Yes/No)	Outcome
Placebo	Male/46/39.7	Ischemic stroke	Yes	104	Yes	Recovered with sequelae
	Male/64/35.3	Silent MI	Yes	183	No	Recovered
Oral semaglutide 10 mg	Female/58/31.8	Silent MI	Yes	Not available[a]	Not available[a]	
Oral semaglutide 40 mg (8-week dose escalation)	Female/64/31.4	Transient ischemic attack	Yes	133	Yes	Recovered
	Female/29/35.6	Acute MI	No	270	Yes	Recovered
		Coronary revascularization	No	271	Yes	Recovered

In-trial adverse events from the safety analysis set. Treatment-emergent adverse events include events that are collected from first exposure to the follow-up visit scheduled 5 weeks (+5 day visit window) after final trial product dose. [a]Not reported as an adverse event by the trial site. A serious adverse event (SAE) was defined as an experience that at any dose results in any of the following: death; a life-threatening experience, in-patient hospitalisation or prolongation of existing hospitalisation; a persistent or significant disability or incapacity; a congenital anomaly or birth defect; or where medical judgement deems that medical or surgical intervention is necessary to prevent one of the outcomes listed in this definition of SAE. The non-serious CV event reported in the placebo arm was a silent MI based on an ECG recording only and therefore not considered a serious adverse event using the classification described above. BMI, body-mass index; MI, myocardial infarction.

eTable 7. Event adjudication committee-confirmed pancreatitis events

Treatment	Patient characteristics (Sex/age [years]/BMI [kg/m^2])	Trial day of event	Severity[a]	Serious adverse event (Yes/No)	Diagnostic criteria fulfilled	Imaging	Gallstones (Yes/No)	Elevated ALT (Yes/No)
Oral semaglutide 20 mg	Female/58/36.7	66	Mild to moderate	No	Abdominal pain, elevated amylase and/or lipase	Unknown	No	Yes (both ALT and AST already at baseline)
Oral semaglutide 40 mg	Male/47/39.7	184	Moderate	No	Abdominal pain, elevated amylase and/or lipase	No abnormal findings; pancreas normal	No	No
Subcutaneous semaglutide 1 mg	Male/58/30.0	180	Mild to moderate	No	Abdominal pain, elevated amylase and/or lipase	No abnormal findings; pancreas normal	No	No

[a]Based on investigator assessment. A serious adverse event (SAE) was defined as an experience that at any dose results in any of the following: death; a life-threatening experience, in-patient hospitalisation or prolongation of existing hospitalisation; a persistent or significant disability or incapacity; a congenital anomaly or birth defect; or where medical judgement deems that medical or surgical intervention is necessary to prevent one of the outcomes listed in this definition of SAE. None of the pancreatitis events fulfilled this criteria and are therefore not considered to be serious adverse events. ALT, alanine transaminase; AST, aspartate aminotransferase; BMI, body-mass index.

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