SUPPLEMENTARY DATA

Efficacy, Safety and Tolerability of Oral Semaglutide Versus Placebo Added to Insulin With or Without Metformin in Patients with Type 2 Diabetes: The PIONEER 8 Trial

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Supplementary Appendix 1. PIONEER 8 investigators and trial sites.

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Supplementary Appendix 2. Randomization and blinding.

Patients were randomized 1:1:1:1 to once-daily oral semaglutide 3, 7, or 14 mg, or placebo using an interactive web response system, which allocated the dispensing unit number of trial product for each patient.

All tablets containing oral semaglutide or placebo were identical with regards to visual appearance to maintain the blinding of the trial.

Supplementary Appendix 3. Insulin titration guidelines.

Insulin titration was based on the lowest of three self-measured blood glucose (SMBG) values, which were preferably measured on three consecutive days prior to each phone contact/site visit. The aim of insulin titration was to obtain a fasting plasma glucose level of 4.0–5.5 mmol/L (71–99 mg/dL) and a HbA_{1c} level below 7.0% (53 mmol/mol). Dosage was increased by 2 U for 5.6–7.0 mmol/L (100–126 mg/dL), by 4 U for 7.1–8.0 mmol/L (127–144 mg/dL), by 6 U for 8.1–9.0 mmol/L (145–162 mg/dL) and by 8 U if >9.0 mmol/L (>162 mg/dL). Dosage was decreased by 2 U for 3.1–3.9 mmol/L (56–70 mg/dL) and by 4 U for <3.1 mmol/L (<56 mg/dL). For doses >45 U, a 5% dose reduction was suggested for 3.1–3.9 mmol/L (56–70 mg/dL) and a 10% reduction was suggested for <3.1 mmol/L (<56 mg/dL). In addition, for patients on once-daily basal insulin, or once-daily premixed insulin including combinations of soluble insulin regimens, titration was based on the lowest of three fasting pre-breakfast SMBG values taken after at least 6 hours of fasting. For patients on twice-daily basal, or twice-daily premixed insulin including combinations of soluble insulins regimens, titration was performed for each dose separately: the morning dosing was titrated based on the lowest of three pre-dinner SMBG values, and the evening dosing was based on the lowest of three fasting pre-breakfast fasting SMBG values. For patients on a regimen of three times daily premixed insulin, including combinations of soluble insulins, titration was performed for each dose separately: the morning dose and the lunch dose were titrated based on the lowest of three pre-dinner SMBG values and, at the discretion of the investigator, possibly additional measurements; and the evening dose was titrated based on the lowest of three fasting pre-breakfast fasting SMBG values. For patients on a regimen of basal-bolus insulin in any combination, the basal insulin was adjusted as above and the bolus insulin dose was adjusted at the discretion of the investigator.

Supplementary Appendix 4. Estimands.

According to draft International Council of Harmonisation (ICH) E9 (R1) (1; 2) an estimand description consists of four components: 1) population; 2) endpoint; 3) intercurrent events and how they are accounted for; 4) population level summary. In the table below, the four attributes are described for the estimands in PIONEER 8. Two intercurrent events were considered: trial product discontinuation, and initiation of rescue medication/additional glucose-lowering medication.

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The attributes of the two estimands according to draft ICH E9 (R1) (1).

Estimand	Population	Strategy for accounting for intercurrent events	Endpoints	Population level summary
Treatment policy estimand	All randomized patients	Treatment policy: • Trial product discontinuation • Initiation of rescue medication	Change from baseline to weeks 26 and 52 in: • HbA_{1c}* • Body weight (kg)* • Fasting plasma glucose • SMBG† • BMI • Waist circumference • IWQoL-Lite-CT score • SF-36v2 (acute version) score • DTSQ score • Total daily insulin dosage	Mean difference between treatments
			Change from baseline to weeks 26 and 52 in: • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglycerides	The geometric mean ratio between treatments
			If a patient at weeks 26 and 52 achieves: • HbA_{1c} <7.0% • HbA_{1c} ≤6.5% • Body weight loss ≥5% • Body weight loss ≥10% • Composite: HbA_{1c} <7.0% without hypoglycemia and no weight gain • Composite: HbA_{1c} reduction ≥1% and body weight loss ≥3%	The odds ratio between treatments in reaching target
Trial product estimand	All randomized patients	Hypothetical: • Trial product discontinuation • Initiation of rescue medication	Change from baseline to weeks 26 and 52 in: • HbA_{1c} • Body weight (kg) • Fasting plasma glucose • SMBG† • BMI • Waist circumference • IWQoL-Lite-CT score • SF-36v2 (acute version) score • DTSQ score • Total daily insulin dosage	Mean difference between treatments
			Change from baseline to weeks 26 and 52 in: • Total cholesterol • LDL cholesterol • HDL cholesterol • Triglycerides	The geometric mean ratio between treatments

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Estimand	Population	Strategy for accounting for intercurrent events	Endpoints	Population level summary
			If a patient at weeks 26 and 52 achieves: • HbA_{1c} <7.0% • HbA_{1c} ≤6.5% • Body weight loss ≥5% • Body weight loss ≥10% • Composite: HbA_{1c} <7.0% without hypoglycemia and no weight gain • Composite: HbA_{1c} reduction ≥1% and body weight loss ≥3%	The odds ratio between treatments in reaching target

BMI, body mass index; DTSQ, Diabetes Treatment Satisfaction Questionnaire; ICH, International Council of Harmonisation; IWQoL-Lite-CT, Impact of Weight on Quality of Life-Lite questionnaire Clinical Trial Version; SF-36v2, Short Form-36 version 2 health survey; SMBG, self-monitored blood glucose.
*Confirmatory endpoint at week 26.
†Self-monitored blood glucose is reported as plasma equivalent values of capillary whole blood glucose.

Supplementary Appendix 5. Statistical considerations.

The confirmation of efficacy of oral semaglutide on change in HbA_{1c} and in body weight, both from baseline to week 26, was based on a weighted Bonferroni closed testing strategy (3) to control the overall type 1 error for the hypotheses evaluated by the treatment policy estimand. The testing strategy was based on two principles: 1) within a dose level, glycemic effect must be established in terms of HbA_{1c} superiority before testing for added benefits in terms of body weight superiority; 2) glycemic effect in terms of HbA_{1c} superiority must be established on all higher dose levels before continuing testing hypotheses on lower dose levels.

A sample size of 180 patients per treatment arm was calculated to provide 90% power to confirm the superiority of oral semaglutide at all dose levels versus placebo in reducing HbA_{1c} at week 26. The sample size was determined assuming treatment effects of –0.80%, –0.60%, and –0.45% for HbA_{1c} and –3.0 kg, –2.0 kg, and –1.0 kg for body weight for the 14, 7, and 3 mg dose, respectively, all versus placebo and with common standard deviations of 1.1% for HbA_{1c} and 4.0 kg for body weight. 10% of patients were assumed to have discontinued trial product or initiated rescue medication, and a 75% reduced treatment effect was assumed for these patients.

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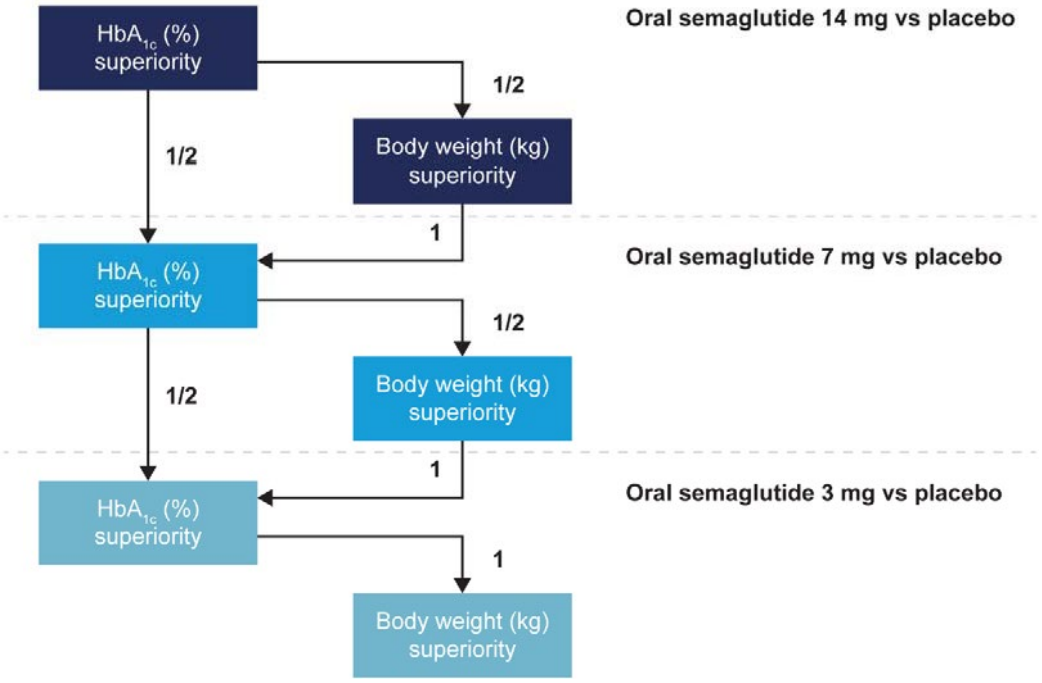
Graphical illustration of the closed testing procedure.



Initially, the overall two-sided significance level of α=0.05 was allocated to the first hypothesis of superiority with respect to HbA_{1c} for the 14 mg dose. If confirmed, the α-level was split and propagated to the next hypotheses according to the weights and direction given at the edges between the hypotheses. E.g. if superiority of 14 mg was confirmed, the full α-level of 0.05 was split evenly to superiority of body weight for the 14 mg dose, and superiority of HbA_{1c} for the 7 mg dose, allowing either of these two hypotheses to be tested at a significance level of α/2. The procedure continued until no more hypotheses could be confirmed. A hypothesis was considered confirmed if the two-sided *P* value was below the significance level and the point estimate favored oral semaglutide (the alternative hypothesis); equivalent to a one-sided test at half the significance level.

The treatment policy estimand was estimated by a pattern mixture model using multiple imputation to handle missing data at weeks 26 and 52 for all continuous endpoints. All data collected at weeks 26 and 52 irrespective of discontinuation of trial product or initiation of rescue medication were included in the statistical analysis. Imputation of missing data at week 26 was done within groups defined by randomized treatment and treatment status at week 26. Imputation of missing data at week 52 was done within groups defined by randomized treatment and treatment status at weeks 26 and 52. The imputation model was an ANCOVA, with region and background medication as factors, and baseline value as covariate. One thousand complete data sets were generated and analyzed separately by an ANCOVA with treatment, region, and background medication as factors, and baseline value as covariate. The estimated means and variances were combined by use of Rubin's rule (4) to draw inference.

The trial product estimand was estimated by a mixed model for repeated measurements. A restricted maximum likelihood was used. The model included all post-baseline measurements collected at scheduled visits, up to and including week 52, from the on-treatment without rescue observation period for all randomized patients as dependent variable. The independent effects included in the model were treatment, region, and background medication as categorical fixed effects and baseline value as a covariate, all nested within visit. An unstructured covariance matrix for endpoint measurements within the same patient was employed. For patients who did not have post-baseline assessments for planned visits available in the on-treatment without rescue medication period, the baseline value was carried forward to the first planned visit (8 weeks at most) to ensure that all randomized patients contributed to the statistical analysis. For the analyses of change in HbA_{1c} and body weight at week 26 the model included all post-baseline measurements collected at scheduled visits up to and including week 26 only. Three sensitivity analyses were pre-specified for the main analysis of the treatment policy

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estimand:

- A comparator multiple imputation analysis where missing data in the oral semaglutide groups were imputed based on the distribution of the week 26 values in the placebo arm.
- Adverse event determined comparator multiple imputation analysis. Missing data as a result of trial product discontinuation because of adverse events were imputed from the placebo as described above, and the remaining missing data were imputed as in the main analysis.
- A tipping point analysis where a penalty was added to the imputed values in the oral semaglutide arms. The penalty was increased until the conclusions from the main analyses were reversed. The specific value of the penalty that reversed the conclusion was used to evaluate the robustness of the main analysis results.

Supportive binary endpoints were analyzed by a logistic regression model with treatment, region, and background medication as factors, and baseline variable as a covariate. For the treatment policy estimand, missing data were imputed similarly as for the continuous endpoints, whereas missing data for the trial product estimand were imputed from patients randomized to same trial product using a sequential multiple imputation method. Missing data for the hypoglycemia component of the composite endpoint, HbA_{1c} <7.0% without hypoglycemia and no weight gain, was imputed based on a Bayesian log-linear negative binomial model fitted to the observed data (5).

All analyses were performed using SAS Version 9.4 M2.

Supplementary Results 1. Patient-reported outcomes.

There were some statistically significant improvements from baseline favoring oral semaglutide at weeks 26 and 52 in domains of the patient-reported outcomes (Supplementary Figures 4–6).

For the treatment policy estimand, oral semaglutide significantly improved general health (3 mg, week 26; 3, 7, and 14 mg, week 52), role-emotional (3 mg, week 52), and mental health (14 mg, week 26) of the Short Form (SF)-36v2 (Acute Version) compared with placebo. For the trial product estimand, oral semaglutide significantly improved the mental component summary (14 mg, week 26) and the domains bodily pain (7 mg, week 26), general health (14 mg, week 26; 7 and 14 mg, week 52), role-emotional (3 and 14 mg, week 52), and mental health (14 mg, week 26) of the SF-36v2 (acute version) compared with placebo.

Statistically significant improvements in the psychosocial domain and total score of the Impact of Weight on Quality of Life-Lite Clinical Trial Version (IWQOL-Lite CT) were observed with oral semaglutide 14 mg versus placebo at weeks 26 and 52 for both estimands. For the trial product estimand, there were significant improvements over placebo in the physical (14 mg, week 26; 3 mg, week 52), physical function (14 mg, week 26) and pain/discomfort (3 mg, week 52) domains.

Oral semaglutide (7 and 14 mg) significantly improved total treatment satisfaction (measured by the Diabetes Treatment Satisfaction Questionnaire [DTSQs]) compared with placebo at weeks 26 and 52 for both estimands; improvements with the 3 mg dose were significant at week 52 for the trial product estimand. In addition, there was a significant reduction in feelings of unacceptably high blood sugars measured with the DTSQs compared with placebo at weeks 26 and 52 with the 7 and 14 mg doses for both estimands.

There was no statistically significant worsening of any domain of the patient-reported outcomes with oral semaglutide compared with placebo.

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Supplementary Table 1. Inclusion and exclusion criteria.

Inclusion criteria	
1.	Informed consent obtained before any trial-related activities. Trial-related activities are defined as any procedures that are carried out as part of the trial, including activities to determine suitability for the trial.
2.	Male or female, age ≥18 years at the time of signing informed consent. *For Japan only: Male or female, age ≥20 years at the time of signing informed consent.*
3.	Diagnosed with type 2 diabetes ≥90 days prior to day of screening.
4.	HbA_{1c} 7.0–9.5% (53–80 mmol/mol) (both inclusive).
5.	Stable treatment with one of the following insulin regimens (minimum 10 U/day) ≥90 days prior to the day of screening: basal insulin alone, basal-bolus insulin in any combination, premixed insulin including combinations of soluble insulins. Maximum 20% change in total daily dose was acceptable. Concomitant treatment with stable daily dose of metformin (≥1500 mg or maximum tolerated dose as documented in the patient medical record) ≥90 days prior to the day of screening was allowed. *For Japan only: Concomitant treatment with metformin is only was allowed in combination with basal insulin alone (not in combination with basal-bolus or premixed insulin including combinations of soluble insulins).*
Exclusion criteria	
1.	Known or suspected hypersensitivity to trial products or related products.
2.	Previous participation in this trial. Participation is defined as signed informed consent.
3.	Female who is pregnant, breast-feeding, intends to become pregnant, or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice). *For Greece and Canada only: Adequate contraceptive measures are defined as combined hormonal contraception (containing estrogen and progesterone), which suppress ovulation (oral, intravaginal, percutaneous), progesterone-only hormonal contraception which suppress ovulation (oral, injectable, implantable), intrauterine device, hormone-releasing intrauterine system, bilateral tubal occlusion, partner with vasectomy, sexual abstinence.* *For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide, or oral contraceptives.*
4.	Receipt of any investigational medicinal product within 90 days before screening.
5.	Any disorder, which in the investigator's opinion might jeopardize patient's safety or compliance with the protocol.
6.	Family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma.
7.	History of pancreatitis (acute or chronic).
8.	History of major surgical procedures involving the stomach potentially affecting absorption of trial product (e.g. subtotal and total gastrectomy, sleeve gastrectomy, gastric bypass surgery).
9.	Any of the following: myocardial infarction, stroke, or hospitalization for unstable angina and/or transient ischemic attack within the past 180 days prior to the day of screening.
10.	Patients presently classified as being in New York Heart Association Class IV.
11.	Planned coronary, carotid, or peripheral artery revascularization known on the day of screening.
12.	Renal impairment defined as estimated glomerular filtration rate <60 mL/min/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration.
13.	Treatment with any medication for the indication of diabetes or obesity, other than stated in the inclusion criteria, in a period of 90 days before the day of screening. An exception is short-term insulin treatment for acute illness for a total of ≤14 days.
14.	Known hypoglycemic unawareness according to Clarke's questionnaire.
15.	Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomization.
16.	History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, and in-situ carcinomas).
17.	Patients with alanine aminotransferase >2.5 times the upper normal limit.

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Supplementary Table 2. Baseline demographics and clinical characteristics.

	Oral semaglutide			Placebo (N=184)	Total (N=731)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		
Male, n (%)	102 (55.4)	103 (56.6)	85 (47.0)	105 (57.1)	395 (54.0)
Age, mean (SD), y	61 (9)	60 (10)	61 (10)	60 (10)	61 (10)
Race, n (%)					
White	89 (48.4)	95 (52.2)	94 (51.9)	98 (53.3)	376 (51.4)
Black or African American	15 (8.2)	10 (5.5)	11 (6.1)	13 (7.1)	49 (6.7)
Asian	66 (35.9)	66 (36.3)	66 (36.5)	65 (35.3)	263 (36.0)
Other*	14 (7.6)	11 (6.0)	10 (5.5)	8 (4.3)	43 (5.9)
Ethnicity,† n (%)					
Hispanic or Latino	18 (9.8)	24 (13.2)	30 (16.6)	25 (13.6)	97 (13.3)
Duration of diabetes, mean (SD), y	15.1 (7.9)	16.2 (8.6)	14.1 (8.0)	14.8 (7.9)	15.0 (8.1)
Body weight, mean (SD), kg	85.9 (21.5)	87.1 (23.6)	84.6 (21.0)	86.0 (21.4)	85.9 (21.8)
BMI, mean (SD), kg/m^2	31.0 (6.8)	31.1 (7.0)	30.8 (6.3)	31.0 (6.5)	31.0 (6.7)
HbA_{1c}, mean (SD), %	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)	8.2 (0.7)
FPG, mean (SD), mmol/L	8.8 (3.2)	8.5 (2.7)	8.3 (2.6)	8.3 (2.6)	8.5 (2.8)
eGFR,‡ mean (SD), mL/min/1.73 m^2	92 (16)	92 (16)	91 (14)	91 (15)	92 (15)
Total daily insulin dosage at baseline, mean (SD), U	61 (54)	63 (77)	53 (43)	55 (48)	58 (57)
Insulin regimen at screening, n (%)					
Basal	76 (41.3)	76 (41.8)	75 (41.4)	79 (42.9)	306 (41.9)
Basal-bolus	71 (38.6)	72 (39.6)	70 (38.7)	71 (38.6)	284 (38.9)
Premixed	35 (19.0)	28 (15.4)	34 (18.8)	32 (17.4)	129 (17.6)
Bolus§	1 (0.5)	2 (1.1)	1 (0.6)	1 (0.5)	5 (0.7)
Basal and premixed§	0	2 (1.1)	0	1 (0.5)	3 (0.4)
Bolus and premixed§	1 (0.5)	2 (1.1)	1 (0.6)	0	4 (0.5)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SD, standard deviation.

*Includes 'American Indian or Alaska Native', 'Native Hawaiian or other Pacific Islander', 'Other', and 'Not Applicable', as race was not recorded for France as per local regulation.

†Ethnicity was not recorded for France as per local regulation.

‡Glomerular filtration rate was estimated by the CKD-EPI formula.

§Regimen not defined in protocol.

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Supplementary Table 3. Rescue medication and additional glucose-lowering medication use.

	Week 26				Week 52			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (n=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
Patients on rescue medication,* n (%)								
Total	5 (2.7)	2 (1.1)	4 (2.2)	9 (4.9)	54 (29.3)	33 (18.1)	31 (17.1)	67 (36.4)
Intensification of insulin	5 (2.7)	2 (1.1)	3 (1.7)	8 (4.3)	50 (27.2)	32 (17.6)	25 (13.8)	60 (32.6)
Sulfonylurea	1 (0.5)	0	0	1 (0.5)	3 (1.6)	3 (1.6)	2 (1.1)	3 (1.6)
Biguanides	0	0	1 (0.6)	0	2 (1.1)	0	4 (2.2)	3 (1.6)
SGLT2 inhibitors	0	0	0	1 (0.5)	2 (1.1)	1 (0.5)	2 (1.1)	7 (3.8)
Repaglinide	0	0	0	1 (0.5)	0	0	0	1 (0.5)
DPP-4 inhibitors	0	0	0	0	0	0	1 (0.6)	0
Patients on additional glucose-lowering medication,† n (%)								
Total	9 (4.9)	8 (4.4)	8 (4.4)	11 (6.0)	61 (33.2)	45 (24.7)	44 (24.3)	75 (40.8)
Intensification of insulin	8 (4.3)	4 (2.2)	6 (3.3)	10 (5.4)	57 (31.0)	39 (21.4)	34 (18.8)	69 (37.5)
Sulfonylureas	1 (0.5)	1 (0.5)	0	1 (0.5)	3 (1.6)	4 (2.2)	2 (1.1)	4 (2.2)
Biguanides	0	0	2 (1.1)	0	2 (1.1)	0	7 (3.9)	3 (1.6)
SGLT2 inhibitors	1 (0.5)	0	0	1 (0.5)	3 (1.6)	1 (0.5)	3 (1.7)	7 (3.8)
Repaglinide	0	0	0	1 (0.5)	0	0	0	1 (0.5)
GLP-1RAs	0	1 (0.5)	0	0	0	2 (1.1)	1 (0.6)	0
DPP-4 inhibitors	0	3 (1.6)	1 (0.6)	0	0	4 (2.2)	2 (1.1)	0
Oral drug combination	0	0	0	0	1 (0.5)	0	0	0
Alpha glucosidase inhibitors	0	0	0	0	0	0	1 (0.6)	0

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2.
*Antidiabetic medication initiated only while patients received trial product, between week 0 and the actual end of treatment, and could be classified as either new medication or intensification of existing medication. To be considered as intensification of an existing medication, total daily insulin dosage and other glucose-lowering medications needed to have been increased by >20% of the dose at baseline and maintained over ≥2 visits for insulin, or ≥21 days for other

medications. Criteria for initiation of rescue medication were two measures (the second, confirmatory measure conducted at the central laboratory) of fasting plasma glucose >11.1 mmol/L from week 16 onwards, and/or HbA_{1c} (measured at the central laboratory) >8.5% from week 26 onwards.

†As described for rescue medication, but initiated between weeks 0 and 52 (i.e. up to the planned end of treatment), regardless of premature trial product discontinuation.

SUPPLEMENTARY DATA

Supplementary Table 4. Tipping point analyses for changes from baseline in HbA_{1c} and body weight at week 26 for the treatment policy estimand.

Tipping point	Hypothesis	alpha	Penalty
HbA_{1c} change from baseline, %			
Oral semaglutide 14 mg vs placebo	Superiority	0.050	17.0
Oral semaglutide 7 mg vs placebo	Superiority	0.050	12.2
Oral semaglutide 3 mg vs placebo	Superiority	0.050	5.9
Body weight change from baseline, kg			
Oral semaglutide 14 mg vs placebo	Superiority	0.025	41.2
Oral semaglutide 7 mg vs placebo	Superiority	0.025	16.7
Oral semaglutide 3 mg vs placebo	Superiority	0.050	1.2

'alpha', local significance level according to the testing strategy where the conclusion for the hypothesis in question was no longer confirmed; 'Penalty', penalty that had to be added to imputed values for the oral semaglutide group in question in order for the conclusion to change.

SUPPLEMENTARY DATA

Supplementary Table 5. Additional secondary endpoints not included in the main text.

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
HbA_{1c} ≤6.5%								
Week 26								
Patients meeting endpoint, n (%)	24 (13.6)	45 (25.9)	74 (42.8)	6 (3.4)	24 (14.8)	43 (27.4)	72 (49.3)	6 (3.7)
EOR vs placebo	4.55	12.05	25.92	–	4.76	12.84	33.01	–
[95% CI]	[1.75, 11.84]	[4.77, 30.45]	[10.34, 64.95]	–	[1.86, 12.23]	[5.14, 32.08]	[13.28, 82.06]	–
P value	0.0019	<0.0001	<0.0001	–	0.0012	<0.0001	<0.0001	–
Week 52								
Patients meeting endpoint, n (%)	20 (11.6)	33 (19.5)	65 (38.7)	4 (2.3)	15 (14.4)	29 (25.7)	55 (49.1)	2 (2.0)
EOR vs placebo	5.07	10.34	28.27	–	6.50	13.79	36.69	–
[95% CI]	[1.68, 15.26]	[3.53, 30.30]	[9.82, 81.36]	–	[1.70, 24.86]	[3.72, 51.04]	[9.96, 135.10]	–
P value	0.0039	<0.0001	<0.0001	–	0.0062	<0.0001	<0.0001	–
7-point SMBG* post-prandial increment, mmol/L								
Week 26								
Estimated mean	2.0	1.8	1.6	2.4	2.1	1.7	1.5	2.4
Estimated change from baseline	–0.5	–0.7	–0.9	–0.1	–0.4	–0.8	–0.9	–0.1
ETD vs placebo	–0.4	–0.6	–0.8	–	–0.3	–0.7	–0.9	–
[95% CI]	[–0.8, 0.0]	[–1.1, –0.2]	[–1.3, –0.4]	–	[–0.7, 0.1]	[–1.1, –0.3]	[–1.3, –0.4]	–
P value	0.0803	0.0046	0.0001	–	0.1206	0.0011	<0.0001	–
Week 52								
Estimated mean	2.0	1.9	2.0	2.3	2.0	1.7	2.1	2.4
Estimated change from baseline	–0.5	–0.6	–0.4	–0.2	–0.5	–0.7	–0.4	–0.1
ETD vs placebo	–0.2	–0.4	–0.2	–	–0.4	–0.6	–0.3	–
[95% CI]	[–0.7, 0.2]	[–0.8, 0.1]	[–0.7, 0.2]	–	[–0.8, 0.1]	[–1.1, –0.2]	[–0.7, 0.1]	–
P value	0.2487	0.0901	0.2692	–	0.1102	0.0083	0.1941	–

SUPPLEMENTARY DATA

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
Body weight loss ≥10%								
Week 26								
Patients meeting endpoint, n (%)	2 (1.1)	12 (6.9)	19 (11.0)	1 (0.6)	2 (1.2)	10 (6.4)	16 (11.0)	1 (0.6)
EOR vs placebo	1.41	8.68	12.92	–	1.87	9.83	18.27	–
[95% CI]	[0.20, 9.88]	[1.70, 44.35]	[2.59, 64.39]	–	[0.27, 12.89]	[1.91, 50.53]	[3.67, 90.88]	–
P value	0.7301	0.0094	0.0018	–	0.5264	0.0062	0.0004	–
Week 52								
Patients meeting endpoint, n (%)	4 (2.3)	17 (9.9)	21 (12.4)	1 (0.6)	3 (2.8)	16 (13.9)	20 (17.4)	0
EOR vs placebo	2.85	13.48	17.71	–	8.34	41.03	65.58	–
[95% CI]	[0.48, 17.04]	[2.67, 68.08]	[3.55, 88.25]	–	[0.51, 137.4]	[2.77, 607.6]	[4.47, 962.4]	–
P value	0.2514	0.0016	0.0005	–	0.1378	0.0069	0.0023	–
Body weight change, %								
Week 26								
Estimated change from baseline	–1.7	–2.9	–4.3	–0.4	–1.7	–3.5	–4.8	–0.4
ETD vs placebo	–1.3	–2.5	–3.9	–	–1.3	–3.1	–4.4	–
[95% CI]	[–2.3, –0.3]	[–3.7, –1.4]	[–4.9, –2.8]	–	[–2.0, –0.5]	[–3.9, –2.3]	[–5.2, –3.6]	–
P value	0.0104	<0.0001	<0.0001	–	0.0019	<0.0001	<0.0001	–
Week 52								
Estimated change from baseline	–1.0	–2.3	–4.3	0.7	–1.4	–3.5	–5.2	0.8
ETD vs placebo	–1.8	–3.1	–5.0	–	–2.1	–4.3	–5.9	–
[95% CI]	[–2.8, –0.7]	[–4.2, –1.9]	[–6.1, –3.9]	–	[–3.2, –1.0]	[–5.4, –3.2]	[–7.0, –4.8]	–
P value	0.0014	<0.0001	<0.0001	–	0.0002	<0.0001	<0.0001	–

SUPPLEMENTARY DATA

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
BMI, kg/m^2								
Week 26								
Estimated mean	30.5	30.1	29.6	30.8	30.5	29.9	29.5	30.8
Estimated change from baseline	–0.5	–0.9	–1.4	–0.1	–0.5	–1.1	–1.5	–0.1
ETD vs placebo	–0.4	–0.8	–1.2	–	–0.3	–0.9	–1.4	–
[95% CI]	[–0.7, –0.0]	[–1.1, –0.4]	[–1.5, –0.9]	–	[–0.6, –0.1]	[–1.2, –0.7]	[–1.6, –1.1]	–
P value	0.0241	<0.0001	<0.0001	–	0.0070	<0.0001	<0.0001	–
Week 52								
Estimated mean	30.7	30.2	29.6	31.2	30.6	29.9	29.4	31.2
Estimated change from baseline	–0.3	–0.7	–1.4	0.2	–0.4	–1.1	–1.6	0.2
ETD vs placebo	–0.5	–1.0	–1.6	–	–0.6	–1.3	–1.8	–
[95% CI]	[–0.9, –0.1]	[–1.3, –0.6]	[–2.0, –1.3]	–	[–1.0, –0.3]	[–1.7, –0.9]	[–2.2, –1.5]	–
P value	0.0055	<0.0001	<0.0001	–	0.0007	<0.0001	<0.0001	–
Waist circumference, cm								
Week 26								
Estimated mean	103.2	102.0	100.5	103.4	103.1	101.3	100.6	103.6
Estimated change from baseline	–0.9	–2.2	–3.6	–0.7	–1.0	–2.8	–3.4	–0.5
ETD vs placebo	–0.2	–1.5	–2.9	–	–0.5	–2.3	–3.0	–
[95% CI]	[–1.2, 0.8]	[–2.5, –0.4]	[–3.9, –1.9]	–	[–1.4, 0.4]	[–3.2, –1.4]	[–3.9, –2.1]	–
P value	0.6654	0.0065	<0.0001	–	0.2447	<0.0001	<0.0001	–
Week 52								
Estimated mean	103.3	101.9	100.1	104.5	103.0	101.3	99.8	104.5
Estimated change from baseline	–0.8	–2.2	–4.0	0.4	–1.1	–2.8	–4.2	0.5
ETD vs placebo	–1.2	–2.6	–4.4	–	–1.6	–3.2	–4.7	–
[95% CI]	[–2.3, –0.0]	[–3.7, –1.4]	[–5.6, –3.2]	–	[–2.7, –0.4]	[–4.4, –2.1]	[–5.8, –3.6]	–
P value	0.0450	<0.0001	<0.0001	–	0.0077	<0.0001	<0.0001	–

SUPPLEMENTARY DATA

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
HbA_{1c} reduction ≥1% and body weight loss ≥3%								
Week 26								
Patients meeting endpoint, n (%)	28 (15.9)	51 (29.3)	76 (43.9)	7 (4.0)	28 (17.3)	49 (31.2)	71 (48.6)	7 (4.3)
EOR vs placebo	4.57	9.90	18.56	–	4.67	10.66	23.06	–
[95% CI]	[1.93, 10.81]	[4.33, 22.64]	[8.19, 42.03]	–	[1.98, 11.04]	[4.66, 24.37]	[10.14, 52.47]	–
P value	0.0005	<0.0001	<0.0001	–	0.0004	<0.0001	<0.0001	–
Week 52								
Patients meeting endpoint, n (%)	20 (11.6)	37 (21.9)	64 (38.1)	5 (2.9)	14 (13.5)	33 (29.2)	50 (44.6)	2 (2.0)
EOR vs placebo	4.23	9.11	20.10	–	7.07	17.80	38.44	–
[95% CI]	[1.54, 11.58]	[3.47, 23.90]	[7.80, 51.81]	–	[1.78, 28.15]	[4.66, 67.99]	[10.13, 145.9]	–
P value	0.0050	<0.0001	<0.0001	–	0.0055	<0.0001	<0.0001	–
Total cholesterol, mmol/L								
Week 26								
Estimated mean	4.33	4.17	4.17	4.52	4.27	4.15	4.18	4.49
Estimated ratio to baseline	0.99	0.95	0.95	1.03	0.97	0.95	0.95	1.02
ETR vs placebo	0.96	0.92	0.92	–	0.95	0.92	0.93	–
[95% CI]	[0.92, 0.99]	[0.89, 0.95]	[0.89, 0.96]	–	[0.92, 0.98]	[0.89, 0.96]	[0.90, 0.96]	–
P value	0.0138	<0.0001	<0.0001	–	0.0028	<0.0001	<0.0001	–
Week 52								
Estimated mean	4.26	4.26	4.18	4.42	4.29	4.23	4.19	4.46
Estimated ratio to baseline	0.97	0.97	0.95	1.01	0.98	0.96	0.96	1.02
ETR vs placebo	0.96	0.96	0.95	–	0.96	0.95	0.94	–
[95% CI]	[0.93, 1.00]	[0.93, 1.00]	[0.91, 0.98]	–	[0.92, 1.01]	[0.91, 0.99]	[0.90, 0.98]	–
P value	0.0460	0.0480	0.0034	–	0.0918	0.0165	0.0053	–

SUPPLEMENTARY DATA

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
LDL cholesterol, mmol/L								
Week 26								
Estimated mean	2.29	2.22	2.22	2.45	2.26	2.22	2.24	2.42
Estimated ratio to baseline	0.97	0.94	0.94	1.04	0.96	0.94	0.95	1.02
ETR vs placebo	0.94	0.91	0.90	–	0.93	0.92	0.93	–
[95% CI]	[0.88, 0.99]	[0.85, 0.96]	[0.85, 0.96]	–	[0.88, 0.99]	[0.87, 0.97]	[0.88, 0.98]	–
P value	0.0230	0.0009	0.0006	–	0.0148	0.0023	0.0083	–
Week 52								
Estimated mean	2.26	2.30	2.26	2.37	2.30	2.27	2.26	2.41
Estimated ratio to baseline	0.96	0.97	0.96	1.00	0.98	0.96	0.96	1.02
ETR vs placebo	0.95	0.97	0.96	–	0.96	0.94	0.94	–
[95% CI]	[0.90, 1.01]	[0.91, 1.03]	[0.90, 1.01]	–	[0.89, 1.02]	[0.88, 1.01]	[0.88, 1.00]	–
P value	0.1023	0.3307	0.1404	–	0.1809	0.0876	0.0609	–
HDL cholesterol, mmol/L								
Week 26								
Estimated mean	1.19	1.17	1.18	1.22	1.20	1.17	1.18	1.21
Estimated ratio to baseline	1.00	0.98	0.98	1.02	1.00	0.98	0.99	1.01
ETR vs placebo	0.98	0.96	0.97	–	0.99	0.96	0.97	–
[95% CI]	[0.95, 1.01]	[0.94, 0.99]	[0.94, 1.00]	–	[0.96, 1.02]	[0.94, 0.99]	[0.95, 1.00]	–
P value	0.2282	0.0145	0.0373	–	0.5122	0.0164	0.0872	–
Week 52								
Estimated mean	1.21	1.17	1.21	1.20	1.21	1.17	1.21	1.20
Estimated ratio to baseline	1.01	0.98	1.01	1.00	1.01	0.98	1.01	1.00
ETR vs placebo	1.01	0.97	1.00	–	1.01	0.97	1.01	–
[95% CI]	[0.98, 1.04]	[0.94, 1.01]	[0.97, 1.04]	–	[0.97, 1.04]	[0.94, 1.01]	[0.98, 1.04]	–
P value	0.5880	0.1213	0.8091	–	0.7578	0.1093	0.6040	–

SUPPLEMENTARY DATA

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=182)	14 mg (N=181)		3 mg (N=184)	7 mg (N=182)	14 mg (N=181)	
Triglycerides, mmol/L								
Week 26								
Estimated mean	1.47	1.37	1.37	1.47	1.43	1.36	1.36	1.47
Estimated ratio to baseline	0.98	0.91	0.92	0.98	0.95	0.91	0.91	0.98
ETR vs placebo	1.00	0.93	0.93	–	0.97	0.92	0.92	–
[95% CI]	[0.92, 1.08]	[0.86, 1.01]	[0.86, 1.01]	–	[0.90, 1.04]	[0.86, 0.99]	[0.85, 0.99]	–
P value	0.9179	0.0833	0.1010	–	0.3860	0.0339	0.0361	–
Week 52								
Estimated mean	1.39	1.40	1.29	1.45	1.39	1.37	1.30	1.44
Estimated ratio to baseline	0.93	0.93	0.86	0.97	0.93	0.91	0.87	0.96
ETR vs placebo	0.96	0.96	0.89	–	0.97	0.95	0.91	–
[95% CI]	[0.88, 1.04]	[0.88, 1.04]	[0.82, 0.97]	–	[0.88, 1.07]	[0.86, 1.05]	[0.82, 1.00]	–
P value	0.2992	0.3329	0.0059	–	0.4940	0.3242	0.0528	–

CI, confidence interval; EOR, estimated odds ratio; ETD, estimated treatment difference; ETR, estimated treatment ratio; SMBG, self-measured blood glucose.
*SMBG is reported as plasma equivalent values of capillary whole blood glucose.
Proportions are observed proportions of patients with non-missing information. *P* values are unadjusted two-sided *P* values for the test of no difference. Fasting lipid profile endpoints were log-transformed prior to analysis, with the associated log-transformed baseline value as a covariate.
Treatment policy estimand: ANCOVA for continuous endpoints and logistic regression for binary endpoints, using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by randomized trial product and treatment status.
Trial product estimand: Mixed model for repeated measurements for continuous endpoints and logistic regression for binary endpoints. Data collected after discontinuation of trial product or initiation of rescue medication were excluded. For binary endpoints, missing values were imputed from patients randomized to the same trial product using sequential multiple imputation.

SUPPLEMENTARY DATA

Supplementary Table 6. On-treatment adverse events leading to premature discontinuation by system organ class and preferred term.

MedDRA system organ class and preferred term	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=181)	14 mg (N=181)	
Number of patients with at least one event leading to premature trial product discontinuation,* n (%)				
Any AE	13 (7.1)	16 (8.8)	24 (13.3)	5 (2.7)
Gastrointestinal disorders	9 (4.9)	12 (6.6)	19 (10.5)	1 (0.5)
Nausea	3 (1.6)	5 (2.8)	11 (6.1)	0
Vomiting	2 (1.1)	2 (1.1)	5 (2.8)	0
Abdominal discomfort	0	3 (1.7)	4 (2.2)	0
Diarrhea	2 (1.1)	5 (2.8)	3 (1.7)	1 (0.5)
Abdominal distension	0	2 (1.1)	2 (1.1)	0
Abdominal pain upper	0	1 (0.6)	2 (1.1)	0
Constipation	0	1 (0.6)	2 (1.1)	0
Eructation	0	0	2 (1.1)	0
Flatulence	0	1 (0.6)	1 (0.6)	0
Gastrointestinal pain	1 (0.5)	0	1 (0.6)	0
Abdominal pain	0	1 (0.6)	0	0
Abnormal feces	0	1 (0.6)	0	0
Duodenitis	1 (0.5)	0	0	0
Dyspepsia	0	1 (0.6)	0	0
Feces soft	1 (0.5)	0	0	0
Gastritis	1 (0.5)	0	0	0
Gingival swelling	1 (0.5)	0	0	0
Lower gastrointestinal hemorrhage	1 (0.5)	0	0	0
Metabolism and nutrition disorders	1 (0.5)	2 (1.1)	4 (2.2)	0
Decreased appetite	0	2 (1.1)	4 (2.2)	0
Dehydration	1 (0.5)	0	0	0
Nervous system disorders	4 (2.2)	0	3 (1.7)	0
Dizziness	0	0	1 (0.6)	0
Headache	0	0	1 (0.6)	0
Ischemic cerebral infarction	0	0	1 (0.6)	0
Dysgeusia	1 (0.5)	0	0	0
Ischemic stroke	1 (0.5)	0	0	0
Lethargy	1 (0.5)	0	0	0
Migraine	1 (0.5)	0	0	0
General disorders and administration site conditions	0	0	2 (1.1)	0
Asthenia	0	0	2 (1.1)	0
Investigations	0	2 (1.1)	2 (1.1)	1 (0.5)
Alanine aminotransferase increased	0	0	1 (0.6)	0
Aspartate aminotransferase increased	0	0	1 (0.6)	0
Weight decreased	0	1 (0.6)	1 (0.6)	0
Lipase increased	0	1 (0.6)	0	0
Liver function test increased	0	0	0	1 (0.5)
Ear and labyrinth disorders	0	0	1 (0.6)	0
Vertigo	0	0	1 (0.6)	0

Eye disorders	0	0	1 (0.6)	0
Retinopathy proliferative	0	0	1 (0.6)	0
Musculoskeletal and connective tissue disorders	1 (0.5)	0	1 (0.6)	0
Muscle spasms	0	0	1 (0.6)	0
Rhabdomyolysis	1 (0.5)	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (0.5)	0	1 (0.6)	0
Dyspnea	0	0	1 (0.6)	0
Oropharyngeal pain	1 (0.5)	0	0	0
Social circumstances	0	0	1 (0.6)	0
Family stress	0	0	1 (0.6)	0
Blood and lymphatic system disorders	1 (0.5)	0	0	0
Normocytic anemia	1 (0.5)	0	0	0
Cardiac disorders	0	1 (0.6)	0	1 (0.5)
Acute myocardial infarction	0	1 (0.6)	0	0
Cardiac failure	0	0	0	1 (0.5)
Hepatobiliary disorders	1 (0.5)	0	0	0
Liver injury	1 (0.5)	0	0	0
Infections and infestations	3 (1.6)	0	0	0
Gastroenteritis	1 (0.5)	0	0	0
Gastroenteritis viral	1 (0.5)	0	0	0
Gingivitis	1 (0.5)	0	0	0
Psychiatric disorders	0	0	0	1 (0.5)
Depression suicidal	0	0	0	1 (0.5)
Renal and urinary disorders	1 (0.5)	2 (1.1)	0	0
Acute kidney injury	1 (0.5)	1 (0.6)	0	0
Ureterolithiasis	0	1 (0.6)	0	0
Skin and subcutaneous tissue disorders	0	0	0	1 (0.5)
Skin discoloration	0	0	0	1 (0.5)
Vascular disorders	1 (0.5)	0	0	0
Peripheral artery thrombosis	1 (0.5)	0	0	0
Peripheral vascular disorder	1 (0.5)	0	0	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities (version 20.1).
*Patients could experience multiple events.
On-treatment: The period where the patient is considered treated with trial product.

SUPPLEMENTARY DATA

Supplementary Table 7. In-trial adverse events related to diabetic retinopathy.

MedDRA preferred term	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=181)	14 mg (N=181)	
Number of patients with at least one AE, n (%)				
Eye disorders*	11 (6.0)	14 (7.7)	13 (7.2)	11 (6.0)
Diabetic retinopathy	7 (3.8)	8 (4.4)	9 (5.0)	8 (4.3)
Diabetic retinal edema	1 (0.5)	1 (0.6)	1 (0.6)	0
Macular edema	0	1 (0.6)	1 (0.6)	0
Maculopathy	1 (0.5)	2 (1.1)	1 (0.6)	1 (0.5)
Retinopathy	1 (0.5)	1 (0.6)	1 (0.6)	2 (1.1)
Retinopathy proliferative	0	0	1 (0.6)	0
Retinal detachment	1 (0.5)	1 (0.6)	0	0
Retinal hemorrhage	0	2 (1.1)	0	0
Retinal edema	1 (0.5)	0	0	0

AE, adverse event; MedDRA, Medical Dictionary for Regulatory Activities (version 20.1).

*Most adverse events related to diabetic retinopathy were identified by routine examination (40/49) and did not require treatment (41/49). Exceptions were:

- Diabetic retinopathy was identified in four patients based on symptoms (oral semaglutide 7 mg, n=2; oral semaglutide 14 mg, n=1; placebo, n=1), and one of these patients received focal laser therapy (oral semaglutide 14 mg). Two patients with diabetic retinopathy identified in a routine examination were referred to a specialist (oral semaglutide 7 mg, n=1; placebo, n=1). One patient (oral semaglutide 3 mg) with diabetic retinopathy identified in a routine examination was treated with intravitreal agents.
- In three patients, diabetic retinal edema was identified in a routine examination (oral semaglutide 3 mg, n=1; oral semaglutide 7 mg, n=1; oral semaglutide 14 mg, n=1), which was treated with intravitreal agents in two patients (oral semaglutide 7 mg, n=1; oral semaglutide 14 mg, n=1); treatment was recommended, but declined by the third patient (oral semaglutide 3 mg).
- Retinopathy proliferative was identified in one patient in the oral semaglutide 14 mg arm based on symptoms and was treated with pan-retinal photocoagulation.
- Retinal detachment was identified in one patient in the oral semaglutide 3 mg arm based on symptoms and was treated with vitrectomy.
- Macular edema was identified in one patient in the oral semaglutide 7 mg arm during a routine eye examination and was treated with eye drops containing a non-steroidal anti-inflammatory drug.

In-trial: The period where the patient is considered to be in the trial regardless of trial product discontinuation.

SUPPLEMENTARY DATA

Supplementary Table 8. External event adjudication committee–confirmed in-trial events.

MedDRA preferred term	Oral semaglutide						Placebo (N=184)	
	3 mg (N=184)		7 mg (N=181)		14 mg (N=181)			
	n (%)	E	n (%)	E	n (%)	E	n (%)	E
Death	0	0	0	0	3 (1.7)	3	0	0
Undetermined	0	0	0	0	2 (1.1)	2	0	0
Infection	0	0	0	0	1 (0.6)	1	0	0
Acute kidney injury	2 (1.1)	2	1 (0.6)	1	0	0	0	0
Acute pancreatitis	0	0	0	0	0	0	0	0
Cardiovascular events	4 (2.2)	5	5 (2.8)	6	5 (2.8)	5	5 (2.7)	5
Acute myocardial infarction	2 (1.1)	2	1 (0.6)	1	1 (0.6)	1	1 (0.5)	1
Silent myocardial infarction	0	0	0	0	1 (0.6)	1	1 (0.5)	1
Stroke	2 (1.1)	2	2 (1.1)	2	1 (0.6)	1	3 (1.6)	3
Transient ischemic attack	0	0	1 (0.6)	1	0	0	0	0
Heart failure	1 (0.5)	1	2 (1.1)	2	0	0	0	0
Malignant neoplasm*	4 (2.2)	5	2 (1.1)	2	2 (1.1)	2	0	0
Skin cancer	2 (1.1)	3	0	0	1 (0.6)	1	0	0
Colorectal cancer	1 (0.5)	1	0	0	1 (0.6)	1	0	0
Breast cancer	0	0	1 (0.6)	1	0	0	0	0
Gynecologic cancer	0	0	1 (0.6)	1	0	0	0	0
Prostate cancer	1 (0.5)	1	0	0	0	0	0	0
Lactic acidosis	0	0	0	0	0	0	0	0

E, total number of events; MedDRA, Medical Dictionary for Regulatory Activities (version 20.1); n, number of patients with at least one event.
*Excludes malignant thyroid neoplasms.
In-trial: The period where the patient is considered to be in the trial regardless of trial product discontinuation.

SUPPLEMENTARY DATA

Supplementary Table 9. Additional safety parameters.

	In-trial				On-treatment			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=181)	14 mg (N=181)		3 mg (N=184)	7 mg (N=181)	14 mg (N=181)	
Systolic blood pressure, mmHg								
Week 26								
Estimated mean	132	130	130	134	131	130	129	134
Estimated change from baseline	–1	–3	–3	1	–2	–3	–4	1
ETD vs placebo	–3	–4	–4	–	–2	–4	–5	–
[95% CI]	[–6, 0]	[–7, –1]	[–7, –1]		[–5, 0]	[–7, –1]	[–8, –2]	
P value	0.0698	0.0055	0.0054	–	0.0858	0.0056	0.0002	–
Week 52								
Estimated mean	132	131	129	133	132	131	128	133
Estimated change from baseline	–1	–2	–4	–0	–1	–2	–5	–0
ETD vs placebo	–0	–2	–4	–	–1	–2	–5	–
[95% CI]	[–3, 2]	[–4, 1]	[–7, –1]		[–4, 2]	[–5, 1]	[–8, –2]	
P value	0.8411	0.2070	0.0036	–	0.5239	0.1296	0.0005	–
Diastolic blood pressure, mmHg								
Week 26								
Estimated mean	78	77	76	78	78	77	76	78
Estimated change from baseline	0	–1	–1	0	–0	–1	–1	0
ETD vs placebo	–0	–1	–2	–	–0	–1	–1	–
[95% CI]	[–2, 1]	[–3, 0]	[–3, 0]		[–2, 2]	[–3, 0]	[–3, 0]	
P value	0.8054	0.1492	0.0678	–	0.9472	0.1631	0.1360	–

SUPPLEMENTARY DATA

	In-trial				On-treatment			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=181)	14 mg (N=181)		3 mg (N=184)	7 mg (N=181)	14 mg (N=181)	
Week 52								
Estimated mean	76	76	75	77	77	76	76	77
Estimated change from baseline	–1	–2	–2	–1	–1	–2	–2	–1
ETD vs placebo	–1	–1	–1	–	–0	–1	–1	–
[95% CI]	[–2, 1]	[–3, 1]	[–3, 0]	–	[–2, 1]	[–3, 1]	[–3, 1]	–
P value	0.4954	0.3230	0.0799	–	0.6562	0.2688	0.2321	–
Pulse rate, beats per minute								
Week 26								
Estimated mean	75	76	77	74	75	76	77	73
Estimated change from baseline	1	2	3	–0	1	2	3	–1
ETD vs placebo	1	2	3	–	2	3	4	–
[95% CI]	[–0, 3]	[0, 4]	[1, 4]	–	[0, 4]	[1, 5]	[2, 6]	–
P value	0.1092	0.0175	0.0024	–	0.0228	0.0006	<0.0001	–
Week 52								
Estimated mean	75	75	76	74	75	75	76	74
Estimated change from baseline	0	1	1	–0	0	1	2	–0
ETD vs placebo	1	1	2	–	1	2	2	–
[95% CI]	[–1, 2]	[–0, 3]	[–0, 4]	–	[–1, 3]	[–0, 3]	[1, 4]	–
P value	0.5415	0.1221	0.0528	–	0.4118	0.0895	0.0107	–
Lipase, U/L								
Week 26								
Estimated mean	31	36	35	27	31	37	36	28
Estimated ratio to baseline	1.14	1.32	1.27	1.01	1.13	1.37	1.34	1.01
ETR vs placebo	1.14	1.31	1.27	–	1.12	1.35	1.32	–
[95% CI]	[1.02, 1.27]	[1.17, 1.46]	[1.14, 1.41]	–	[1.01, 1.24]	[1.21, 1.50]	[1.19, 1.47]	–
P value	0.0219	<0.0001	<0.0001	–	0.0375	<0.0001	<0.0001	–

SUPPLEMENTARY DATA

	In-trial				On-treatment			
	Oral semaglutide			Placebo (N=184)	Oral semaglutide			Placebo (N=184)
	3 mg (N=184)	7 mg (N=181)	14 mg (N=181)		3 mg (N=184)	7 mg (N=181)	14 mg (N=181)	
Week 52								
Estimated mean	29	33	34	27	29	34	37	27
Estimated ratio to baseline	1.05	1.22	1.25	1.00	1.07	1.25	1.34	1.00
ETR vs placebo	1.05	1.22	1.25	–	1.07	1.25	1.34	–
[95% CI]	[0.95, 1.17]	[1.10,1.36]	[1.12, 1.39]	–	[0.97, 1.19]	[1.12, 1.39]	[1.21, 1.49]	–
P value	0.3531	0.0003	<0.0001	–	0.1719	<0.0001	<0.0001	–
Amylase, U/L								
Week 26								
Estimated mean	55	58	58	53	55	58	59	53
Estimated ratio to baseline	1.06	1.11	1.12	1.02	1.07	1.12	1.13	1.02
ETR vs placebo	1.05	1.09	1.10	–	1.05	1.09	1.11	–
[95% CI]	[1.00, 1.10]	[1.04, 1.14]	[1.05, 1.15]	–	[1.00, 1.10]	[1.04, 1.15]	[1.05, 1.16]	–
P value	0.0776	0.0008	0.0002	–	0.0677	0.0005	0.0001	–
Week 52								
Estimated mean	55	57	59	52	55	57	60	52
Estimated ratio to baseline	1.05	1.10	1.14	1.00	1.06	1.10	1.16	0.99
ETR vs placebo	1.05	1.09	1.13	–	1.07	1.11	1.17	–
[95% CI]	[0.99, 1.10]	[1.04, 1.15]	[1.08, 1.19]	–	[1.01, 1.12]	[1.05, 1.17]	[1.11, 1.23]	–
P value	0.0810	0.0007	<0.0001	–	0.0118	<0.0001	<0.0001	–
Estimated glomerular filtration rate* ratio to baseline, mL/min/1.73 m^2								
Week 26								
Geometric mean (CV)	0.99 (11.0)	0.99 (8.6)	0.99 (10.0)	1.01 (10.1)	0.99 (11.1)	0.99 (8.8)	0.99 (10.0)	1.01 (10.1)
Week 52								
Geometric mean (CV)	1.00 (10.7)	1.00 (10.4)	0.98 (9.1)	0.99 (11.9)	0.99 (10.0)	0.99 (10.7)	0.98 (9.3)	0.99 (12.2)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, coefficient of variation; ETD, estimated treatment difference; ETR, estimated treatment ratio.
*Glomerular filtration rate was estimated by the CKD-EPI formula.

SUPPLEMENTARY DATA

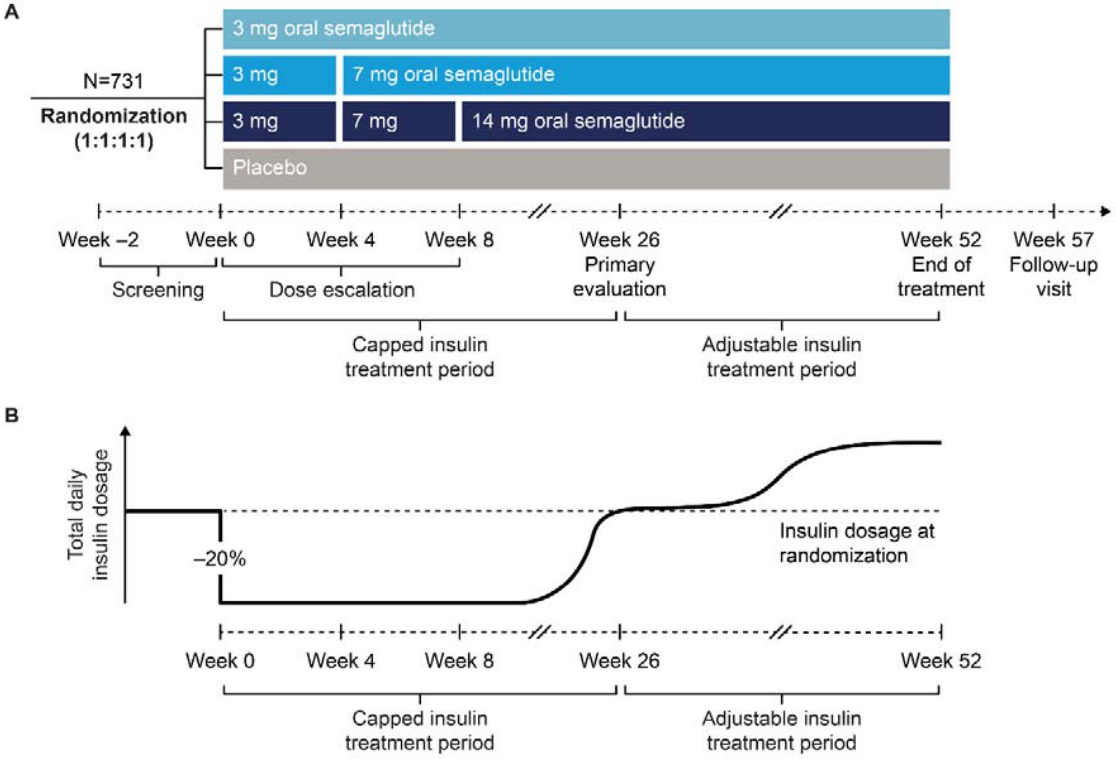
P values are unadjusted two-sided *P* values for the test of no difference. Lipase and amylase were log-transformed prior to analysis with the associated log-transformed baseline value as a covariate.

In-trial: ANCOVA using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by randomized trial product and treatment status.

On-treatment: Mixed model for repeated measurements. Data collected after discontinuation of trial product were excluded.

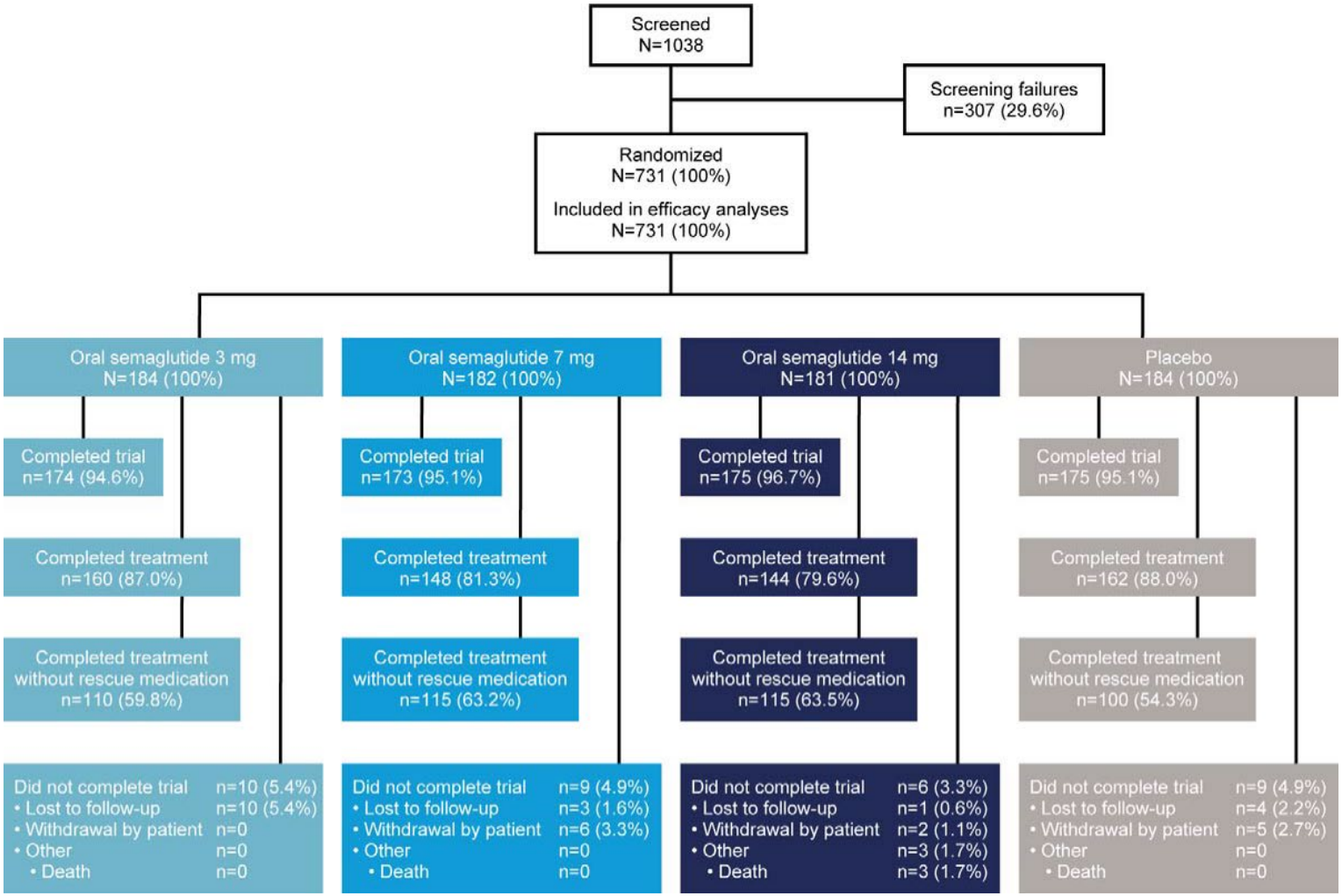
SUPPLEMENTARY DATA

Supplementary Figure 1. A: Trial design; B: Insulin dosing periods.



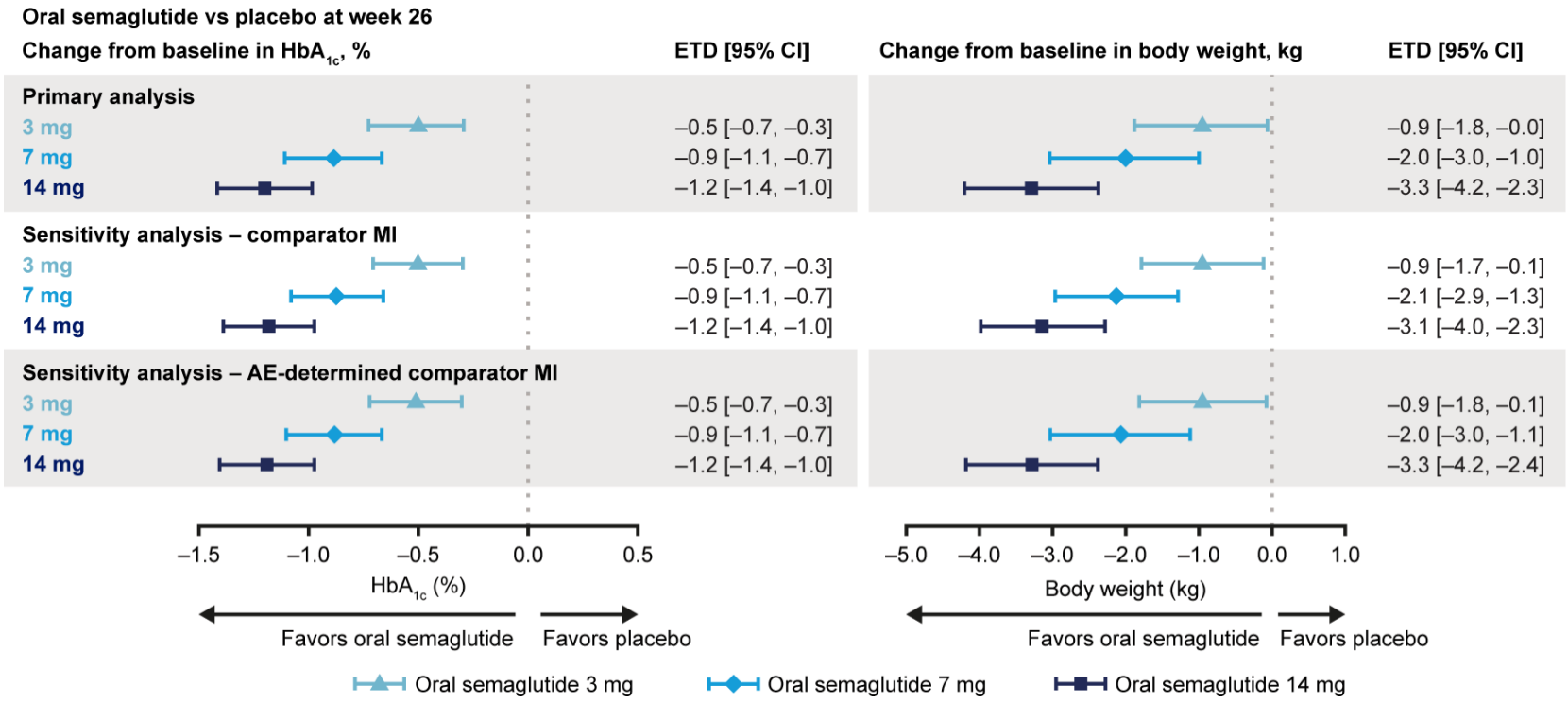
SUPPLEMENTARY DATA

Supplementary Figure 2. Patient disposition.



SUPPLEMENTARY DATA

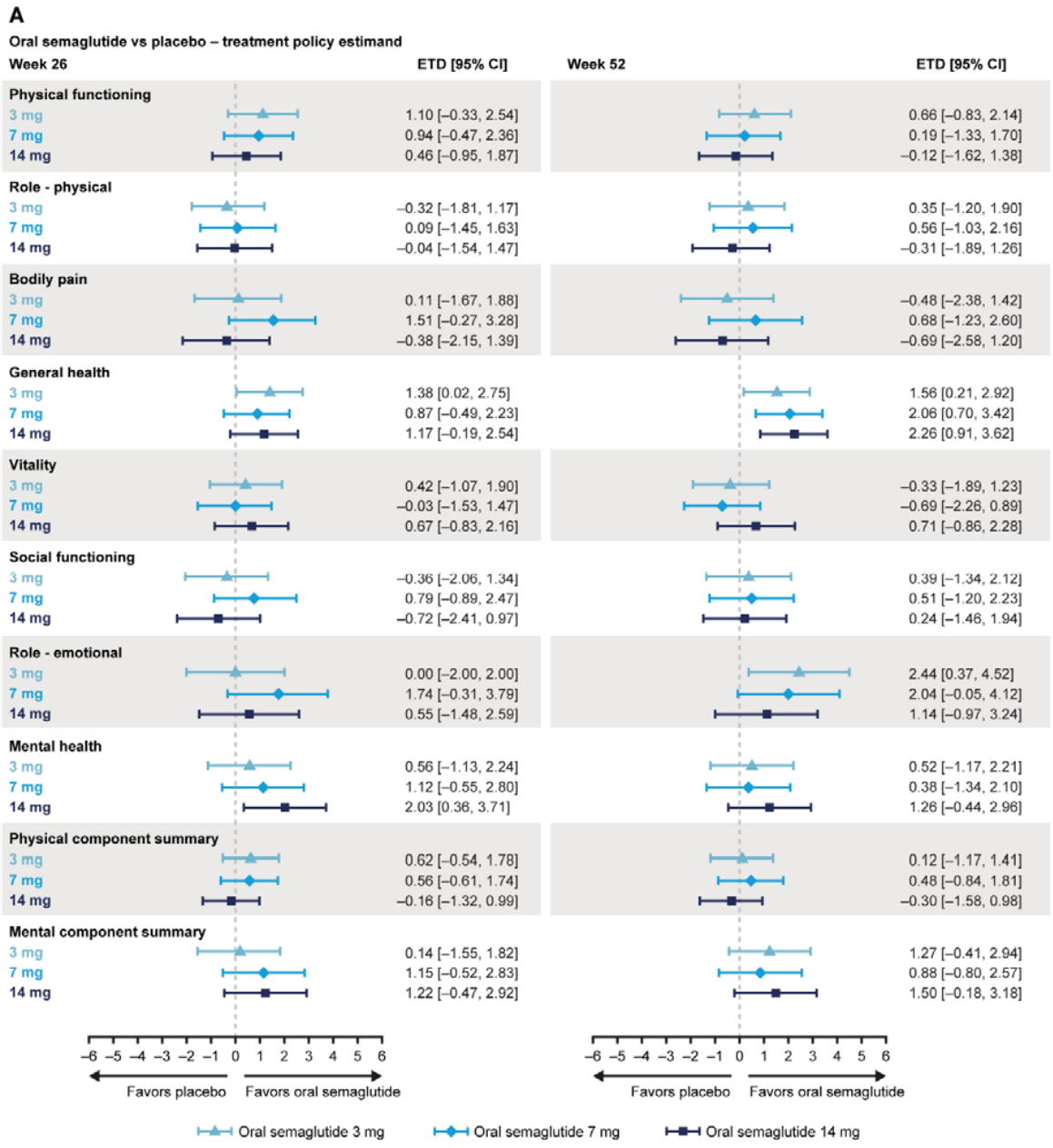
Supplementary Figure 3. Sensitivity analyses for changes from baseline in HbA_{1c} and body weight at week 26 for the treatment policy estimand.



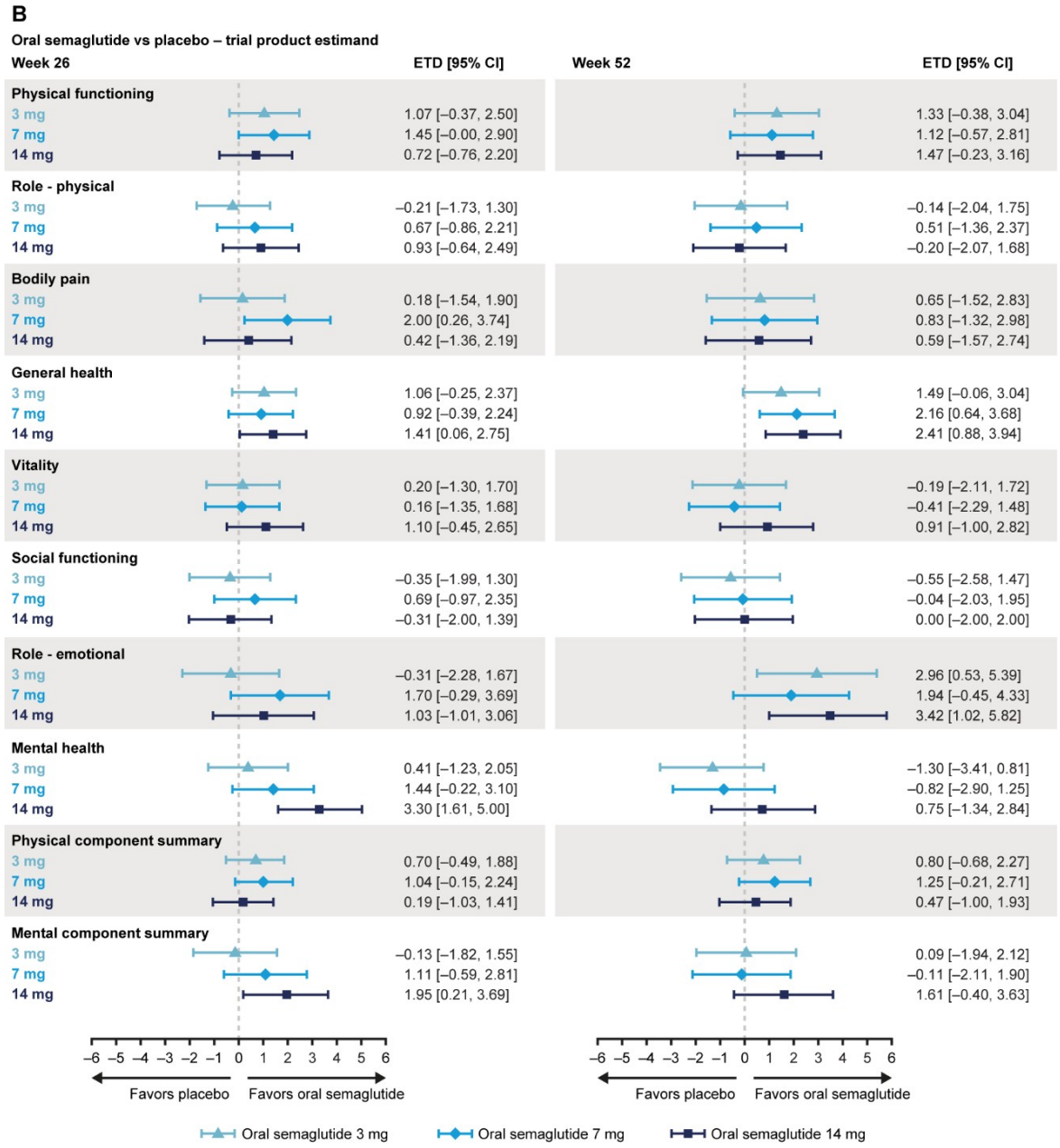
AE, adverse event; ETD, estimated treatment difference; MI, multiple imputation.
P values are unadjusted two-sided *P* values for the test of no difference.
Pale blue triangles = oral semaglutide 3 mg; blue diamonds = oral semaglutide 7 mg; dark blue squares = oral semaglutide 14 mg.

SUPPLEMENTARY DATA

Supplementary Figure 4. Change from baseline in Short Form-36 Version 2 (Acute Version) Health Survey summary scores.
A: Treatment policy estimand; B: Trial product estimand.



SUPPLEMENTARY DATA

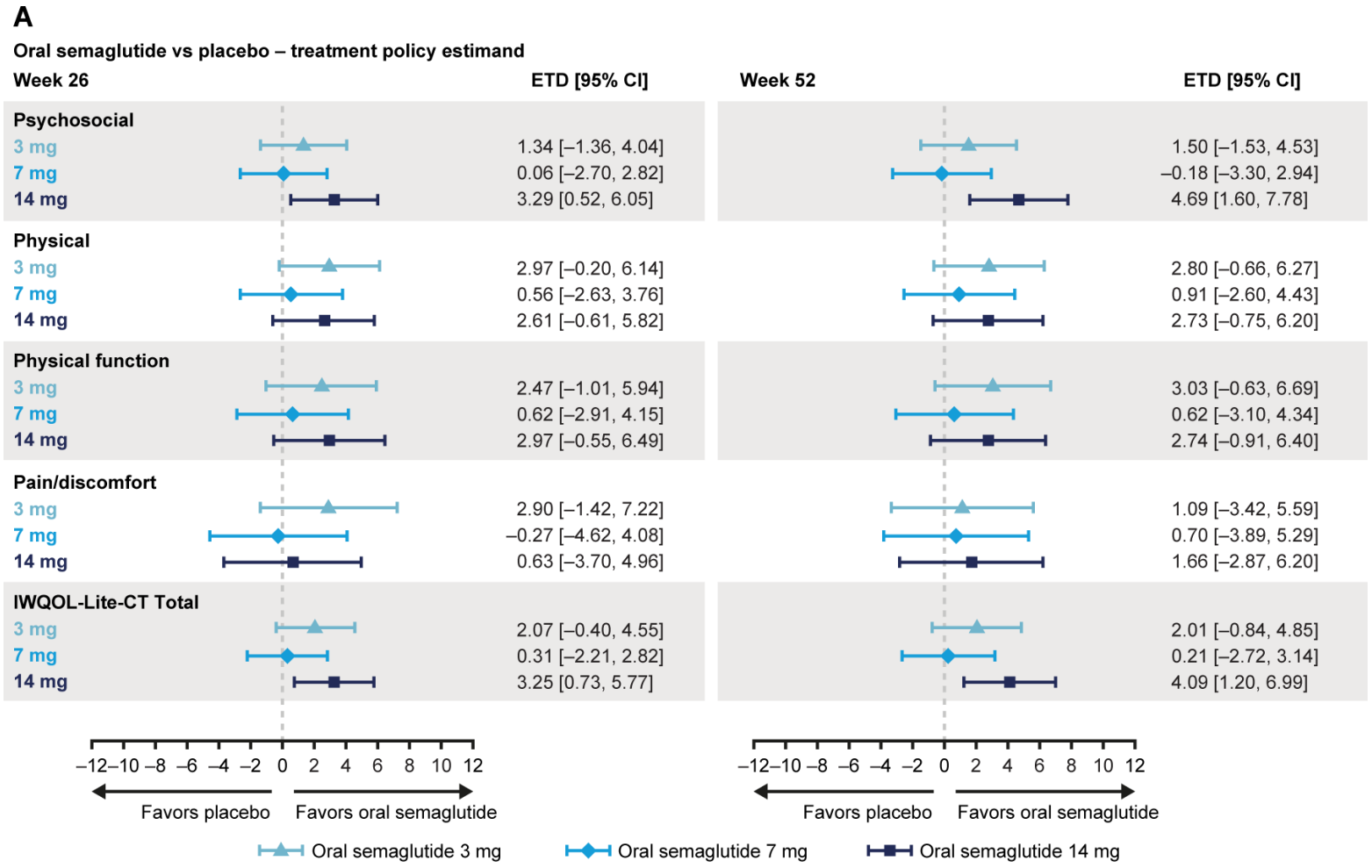


ETD, estimated treatment difference.
P values are unadjusted two-sided *P* values for the test of no difference.
Treatment policy estimand: ANCOVA using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by randomized trial product and treatment status.
Trial product estimand: Mixed model for repeated measurements. Data collected after discontinuation of trial product or initiation of rescue medication were excluded.
Pale blue triangles = oral semaglutide 3 mg; blue diamonds = oral semaglutide 7 mg; dark blue squares = oral semaglutide 14 mg.

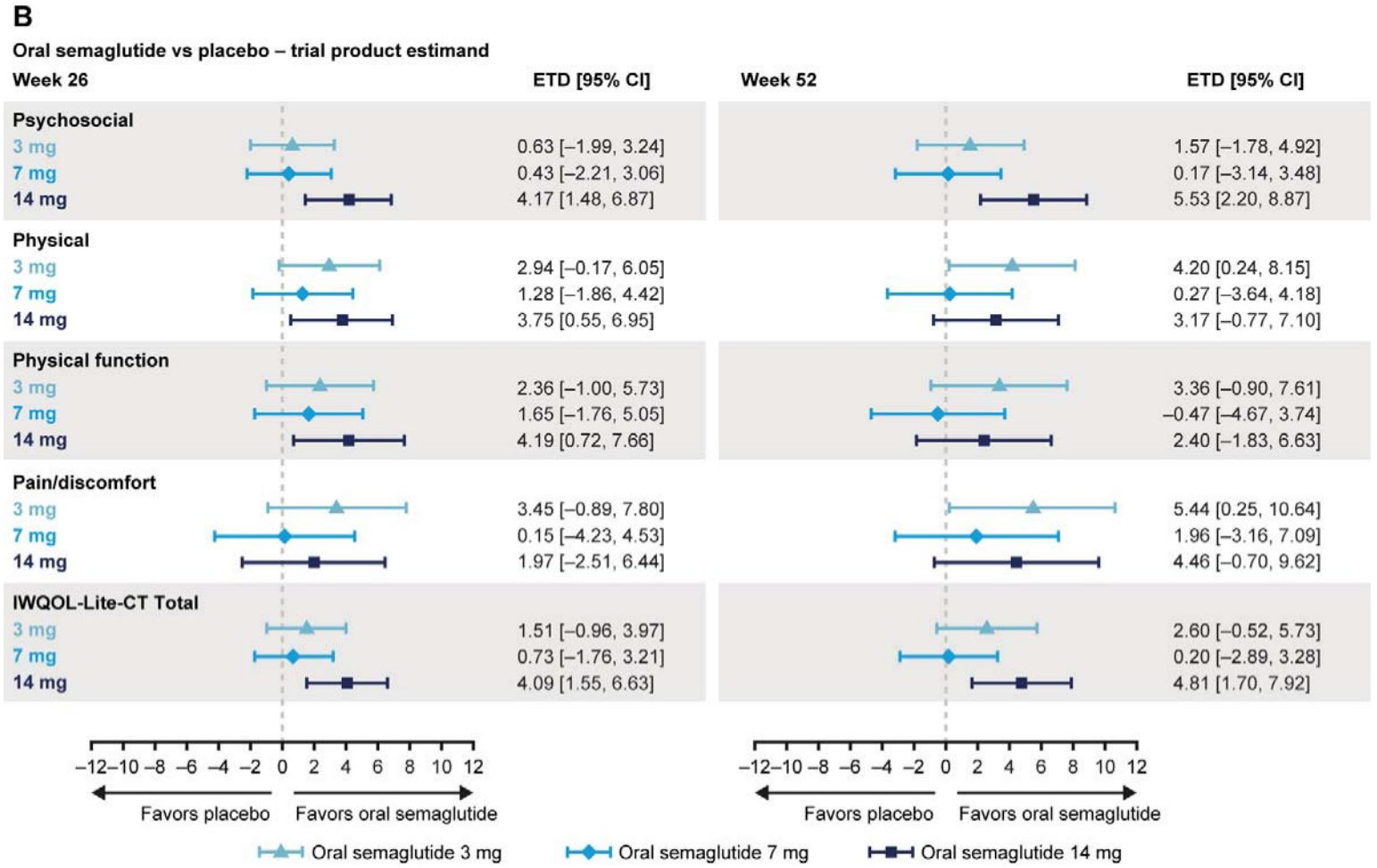
SUPPLEMENTARY DATA

Supplementary Figure 5. Change from baseline in Impact of Weight on Quality of Life-Lite Clinical Trial Version Questionnaire scores.

A: Treatment policy estimand; B: Trial product estimand.



SUPPLEMENTARY DATA

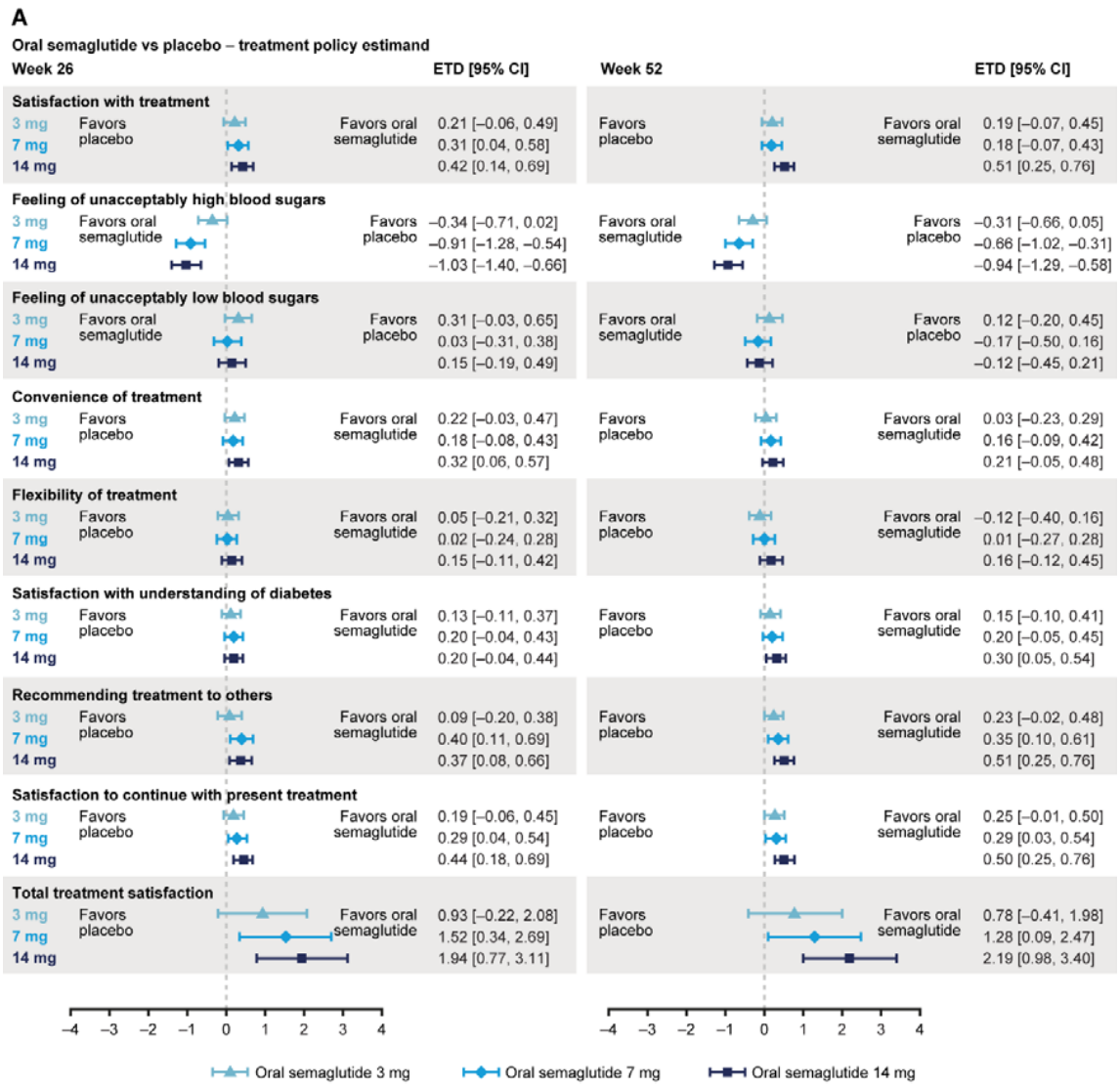


ETD, estimated treatment difference.
P values are unadjusted two-sided *P* values for the test of no difference.
Treatment policy estimand: ANCOVA for continuous endpoints using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by randomized trial product and treatment status.
Trial product estimand: Mixed model for repeated measurements for continuous endpoints and logistic regression for binary endpoints. Data collected after discontinuation of trial product or initiation of rescue medication were excluded.
Pale blue triangles = oral semaglutide 3 mg; blue diamonds = oral semaglutide 7 mg; dark blue squares = oral semaglutide 14 mg.

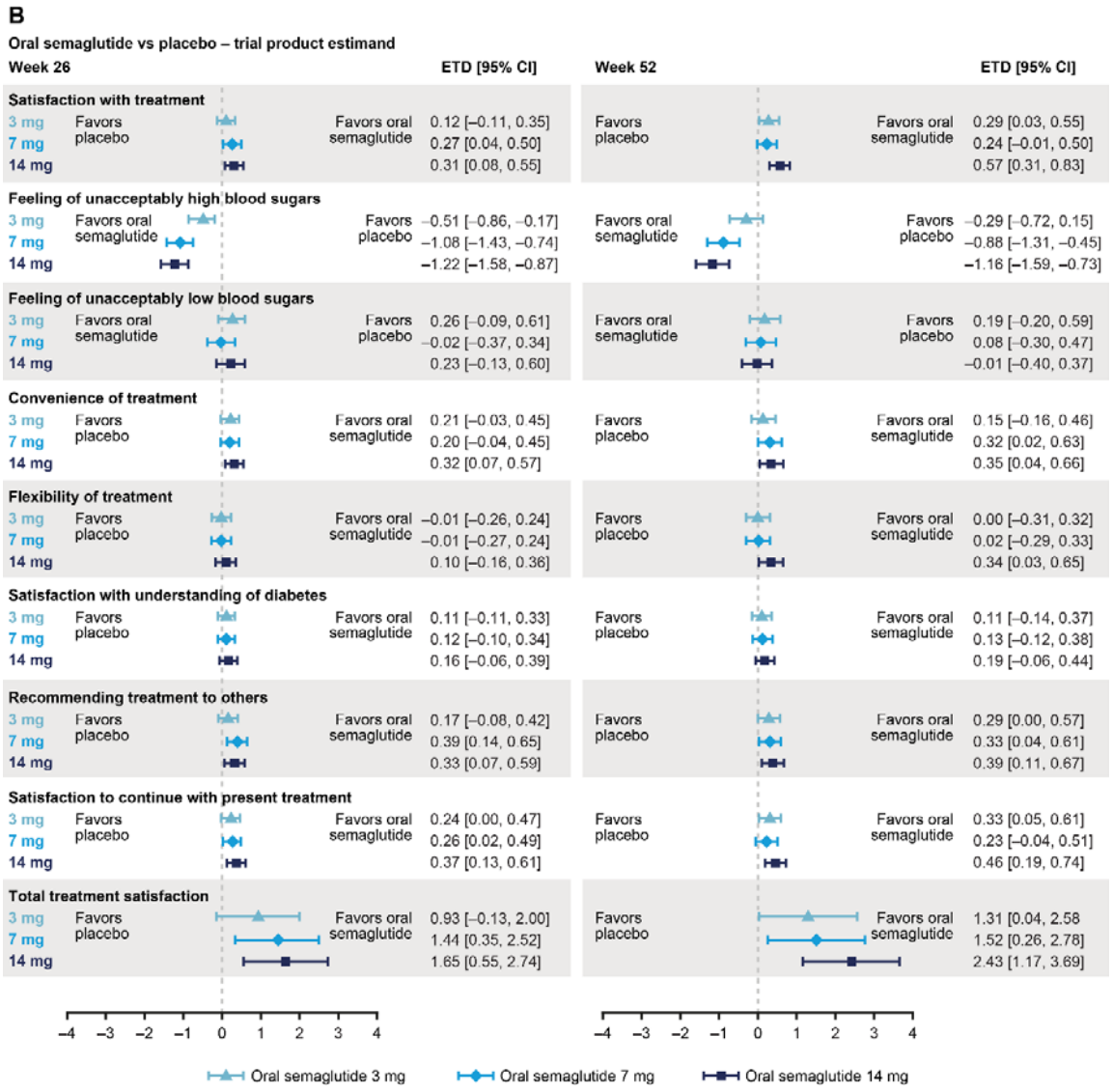
SUPPLEMENTARY DATA

Supplementary Figure 6. Change from baseline in Diabetes Treatment Satisfaction Questionnaire scores.

A: Treatment policy estimand; B: Trial product estimand.



SUPPLEMENTARY DATA



ETD, estimated treatment difference.

P values are unadjusted two-sided *P* values for the test of no difference.

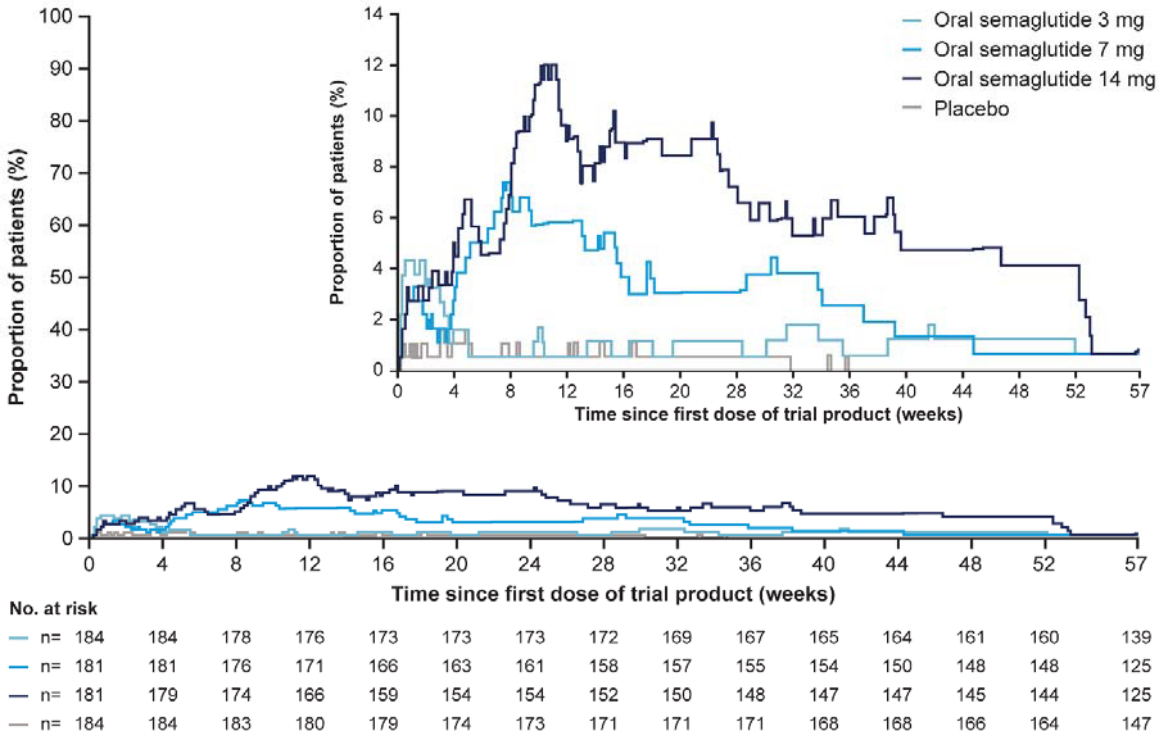
Treatment policy estimand: ANCOVA for continuous endpoints using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by randomized trial product and treatment status.

Trial product estimand: Mixed model for repeated measurements for continuous endpoints and logistic regression for binary endpoints. Data collected after discontinuation of trial product or initiation of rescue medication were excluded.

Pale blue triangles = oral semaglutide 3 mg; blue diamonds = oral semaglutide 7 mg; dark blue squares = oral semaglutide 14 mg.

SUPPLEMENTARY DATA

Supplementary Figure 7. Overview of on-treatment nausea events.



On-treatment: The period where the patient is considered treated with trial product. The figure shows the proportion of patients with nausea events during the course of the trial. The inset figure shows the same data but with the axis truncated to allow better visualization.

SUPPLEMENTARY DATA

Supplementary references

1. ICH harmonised tripartite guideline. Estimands and sensitivity analysis in clinical trials E9 (R1) [article online], 2017. Available from https://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html. Accessed 27 March 2019

2. Aroda VR, Saugstrup T, Buse JB, Donsmark M, Zacho J, Davies MJ. Incorporating and interpreting regulatory guidance on estimands in diabetes clinical trials: The PIONEER 1 randomized clinical trial as an example. Diabetes Obes Metab 2019;21:2203–2210

3. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biom J 2011;53:894–913

4. Little RJA, Rubin DB. *Statistical Analysis With Missing Data*. New York, NY, John Wiley & Sons, 1987

5. Keene ON, Roger JH, Hartley BF, Kenward MG. Missing data sensitivity analysis for recurrent event data using controlled imputation. Pharmaceutical statistics 2014;13:258–264