Supplementary Online Content

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

eAppendix 1. PIONEER 3 Investigators

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eAppendix 2. Trial Product Administration

Patients were instructed to administer trial products (regardless of assigned treatment group) in the morning, in a fasting state, with ≤120 mL of water ≥30 minutes before breakfast and ≥30 minutes before any other oral medication (including background glucose-lowering medication). Tablets were to be taken whole.

Oral semaglutide and sitagliptin are not visually identical. In order to maintain blinding, patients received two tablets daily; the active drug and a placebo. For both oral semaglutide and sitagliptin, respectively, the active drug and the corresponding placebo tablets were identical with regard to visual appearance, and all oral semaglutide tablets were visually identical to each other, irrespective of dose level.

eAppendix 3. Description of Patient-Reported Outcomes

Impact of Weight on Quality of Life-Lite questionnaire Clinical Trial Version

A 23-item version of the Impact of Weight on Quality of Life-Lite questionnaire Clinical Trial Version (IWQOL-Lite-CT) was included in the trial, and all items employ a 5-point graded response scale (never, rarely, sometimes, usually, always; or not at all true, a little true, moderately true, mostly true, completely true). The items were further grouped into the following five domains: Psychosocial, Physical, Physical Function, Pain/Discomfort, and IWQOL-Lite-CT Total. All IWQOL-Lite-CT domain scores range from 0 to 100, with higher scores reflecting better levels of functioning.

Short Form-36 Version 2 Health Survey (acute version)

Higher scores on all domains and component summary measures indicate better health-related quality of life/general health status. Scores are norm-based, using the 2009 US general population norm, presented below.[1]

Scale/measure	2009 US general population norm	
	Lowest	Highest
Physical functioning	19.03	57.60
Role limitations due to physical health (role-physical)	21.89	57.12
Bodily pain	21.39	60.87
General health perceptions (general health)	21.29	65.40
Vitality	25.60	69.15
Social functioning	17.20	56.74
Role limitations due to emotional problems (role-emotional)	9.84	55.64
Mental health	13.12	62.67
Physical component summary	10.80	75.51
Mental component summary	5.62	69.65

The individual responder threshold values are presented below.[1]

Domain	Responder threshold
Physical functioning	4.3
Role limitations due to physical health (role-physical)	4.0
Bodily pain	5.5
General health perceptions (general health)	7.0
Vitality	6.7
Social functioning	6.2
Role limitations due to emotional problems (role-emotional)	4.6
Mental health	6.7
Physical component summary	3.8
Mental component summary	4.6

Control of Eating Questionnaire

In this trial, a version of the Control of Eating Questionnaire (CoEQ) with 19 items was included. The CoEQ items are scored on an 11-point graded response scale ranging from 10 to 0.

The responder thresholds for CoEQ were defined using a distribution-based approach, half of a standard deviation of the baseline CoEQ item and domain scores per trial was used.[2] The thresholds were derived from baseline CoEQ data across the oral semaglutide groups (3, 7, and 14 mg) and sitagliptin 100 mg group.

The individual responder thresholds used in this trial calculated using the above approach are presented below.

Domain	Responder threshold for PIONEER 3
Craving control	1.2
Positive mood	0.9
Craving for sweet	1.2
Craving for savoury	1.1

eAppendix 4. Estimands

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

The attributes of the two estimands according to draft ICH E9 (R1)[3]

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, 52 and 78 in • HbA_{1c}[a] • Body weight (kg)[a] • Fasting plasma glucose • SMBG[b] • BMI • Waist circumference • IWQoL-Lite-CT score • SF-36v2 (acute version) score • CoEQ score	Mean difference between treatments
			Change from baseline to weeks 26, 52 and 78 in • Total cholesterol • Low-density lipoprotein cholesterol • Very low-density lipoprotein cholesterol • High-density lipoprotein cholesterol • Triglycerides	The geometric mean ratio between treatments
			If a patient at weeks 26, 52 and 78 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	The odds ratio between treatments in reaching target

Estimand	Population	Strategy for accounting for intercurrent events	Endpoints	Population level summary
			• Composite: HbA_{1c} reduction ≥1% and body weight loss ≥3%	
Trial product estimand	All randomized patients	Hypothetical: • Trial product discontinuation • Initiation of rescue medication	Change from baseline to weeks 26, 52 and 78 in • HbA_{1c} • Body weight (kg) • Fasting plasma glucose • SMBG[b] • BMI • Waist circumference • IWQoL-Lite-CT score • SF-36v2 (acute version) score • CoEQ score	Mean difference between treatments
			Change from baseline to weeks 26, 52 and 78 in • Total cholesterol • Low-density lipoprotein cholesterol • Very low-density lipoprotein cholesterol • High-density lipoprotein cholesterol • Triglycerides	The geometric mean ratio between treatments
			If a patient at weeks 26, 52 and 78 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

Estimand	Population	Strategy for accounting for intercurrent events	Endpoints	Population level summary
Treatment policy estimand / composite	All randomized patients	Treatment policy: • Trial product discontinuation Composite: • Initiation of additional glucose-lowering medication	• Time to additional glucose-lowering medication	The hazard ratio between treatments
Trial product estimand / composite	All exposed patients	Hypothetical: • Trial product discontinuation Composite: • Initiation of rescue medication	• Time to rescue medication	The hazard ratio between treatments

Abbreviation: BMI, body mass index; CoEQ, Control of Eating Questionnaire; 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.

[a] Confirmatory endpoint at week 26.

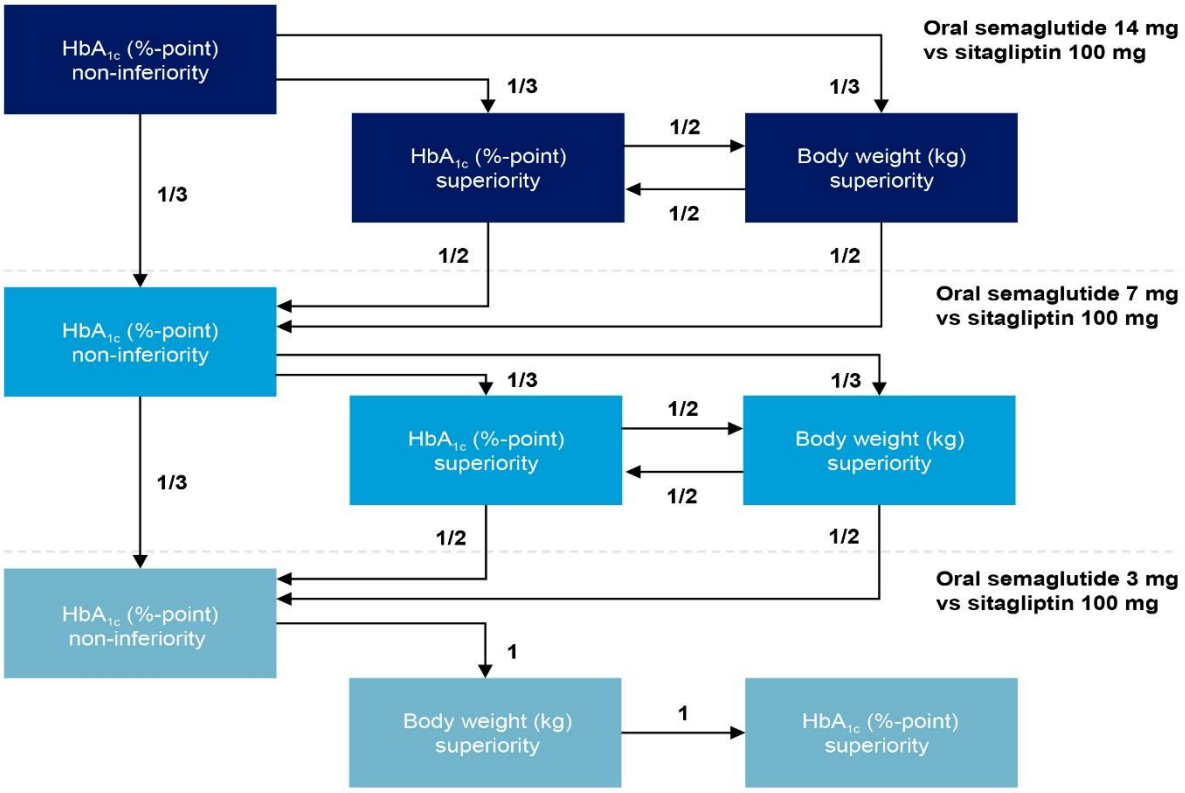
[b] Self-monitored blood glucose is reported as plasma equivalent values of capillary whole blood glucose.

eAppendix 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[4] 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, non-inferiority with respect to HbA_{1c} had to be confirmed before testing for superiority with respect to HbA_{1c} or to body weight. 2) Non-inferiority with respect to HbA_{1c} had to be confirmed on all higher dose levels before continuing testing hypotheses on lower dose levels.

A sample size of 465 patients per treatment group was calculated to provide 90% power to jointly confirm the superiority of oral semaglutide 14 and 7 mg versus sitagliptin 100 mg, and non-inferiority of oral semaglutide 3 mg versus sitagliptin in reducing HbA_{1c} at week 26. The sample size was determined assuming treatment effects of –0.5%, –0.3%, and –0.1% 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 sitagliptin and with common standard deviations of 1.1% for change from baseline in HbA_{1c} and 4.0 kg for change from baseline in body weight. 20% of patients were assumed to have discontinued trial product or initiated rescue medication, and a 75% reduced treatment effect was assumed for these patients.

Graphical illustration of the closed testing procedure.



Initially the overall two-sided significance level of α=5% was allocated to the first hypothesis of non-inferiority 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 non-inferiority of 14 mg was confirmed the full α-level of 5% was split and assigned evenly to superiority of HbA_{1c} and superiority of body weight for the 14 mg dose and non-inferiority of HbA_{1c} for the 7 mg dose allowing any of the three hypotheses to be tested at a significance level of α/3. 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 week 26 for all continuous endpoints. All data collected at week 26 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 hereby assuming that the likely values of the missing data are best described by observed responses from patients with the same randomized treatment and treatment status. Imputation of missing data at weeks 52 and 78 was done within groups defined by randomized treatment, treatment status at week 26 and at week 52 or 78. The imputation model was an analysis of covariance (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[5] to draw inference. Prior to testing for non-inferiority, a value of 0.3% (the non-inferiority margin) was added to imputed values at week 26 for the oral semaglutide treatment group. This was done to ensure imputation of missing values would not increase the likelihood of demonstrating non-inferiority.[6]

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 78 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 (8 weeks at most) to the first planned visit 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 estimand:

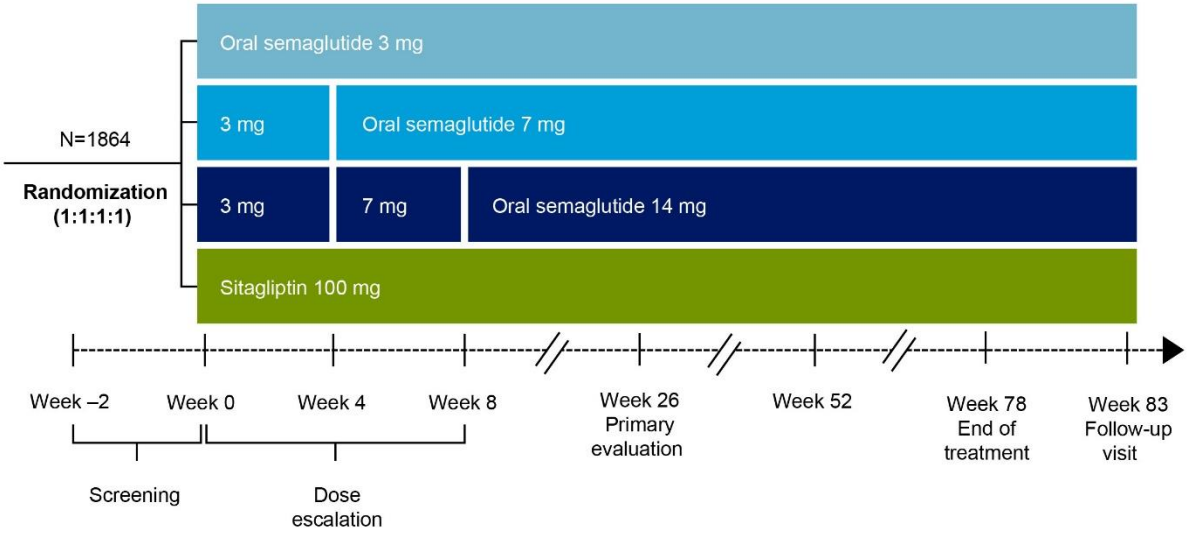
- A comparator multiple imputation analysis where missing data in the oral semaglutide groups were imputed based on the distribution of the week 26 values in the sitagliptin group.
- Adverse event determined comparator multiple imputation analysis. Missing data as a result of trial product discontinuation because of adverse events were imputed from the sitagliptin group 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 group. 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 generalized linear model with binomial distribution and identity link function. The model included treatment and background medication as factors. The model was specified post hoc. 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.[7]

The secondary endpoints time to additional glucose-lowering medication and time to rescue medication were analyzed by a Cox proportional hazards model with treatment, region and background medication as factors, and baseline HbA_{1c} as a covariate. Time to additional glucose-lowering medication was defined as the time from randomization to initiation of new glucose-lowering medication or intensification of background glucose-lowering medication, both lasting for more than 21 days and with the initiation/intensification occurring at or after randomization and before planned end-of-treatment. Intensification was defined as more than 20% increase in dose relative to baseline. Patients withdrawn or lost to follow-up were considered as having an event on the day of withdrawal, and patients without an event were censored the day before the end-of-treatment visit. Time to rescue medication was defined as the time from first dose of trial product to initiation of rescue medication. Rescue medication was defined as the subset of additional glucose-lowering medication initiated before last date on trial product, and potential events occurring between randomization and first dose of trial product were considered as events occurring on day 0. Patients without an event were censored the day before last date on trial product.

All analyses were performed using SAS Version 9.4M2.

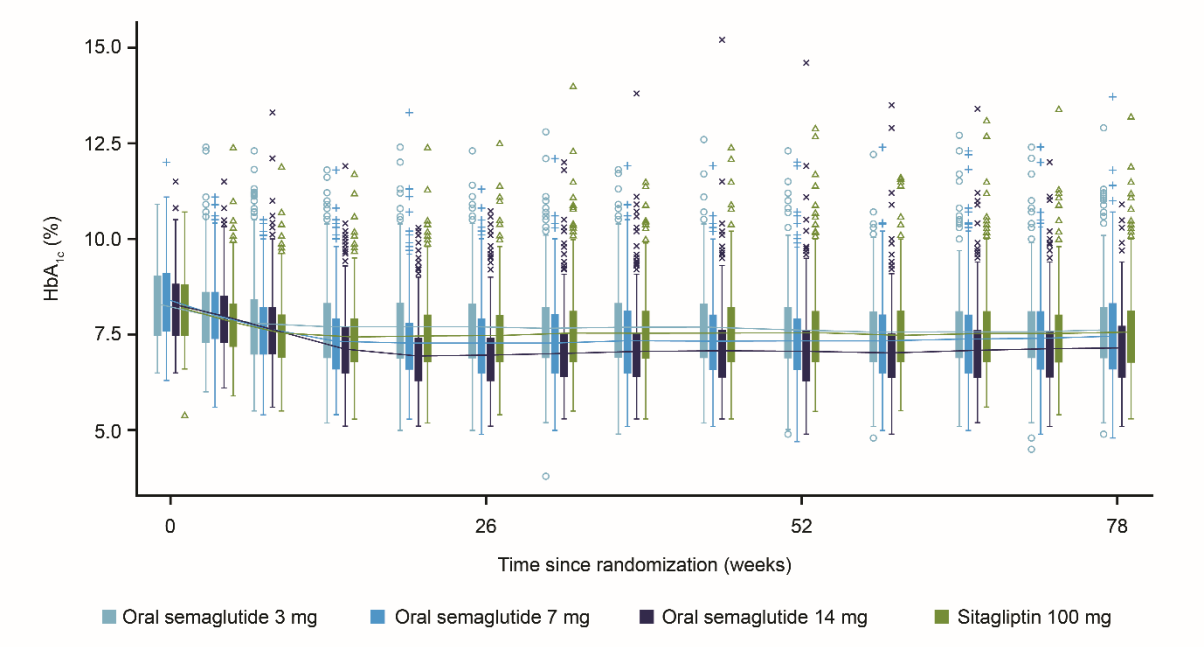
eFigure 1. Trial Design



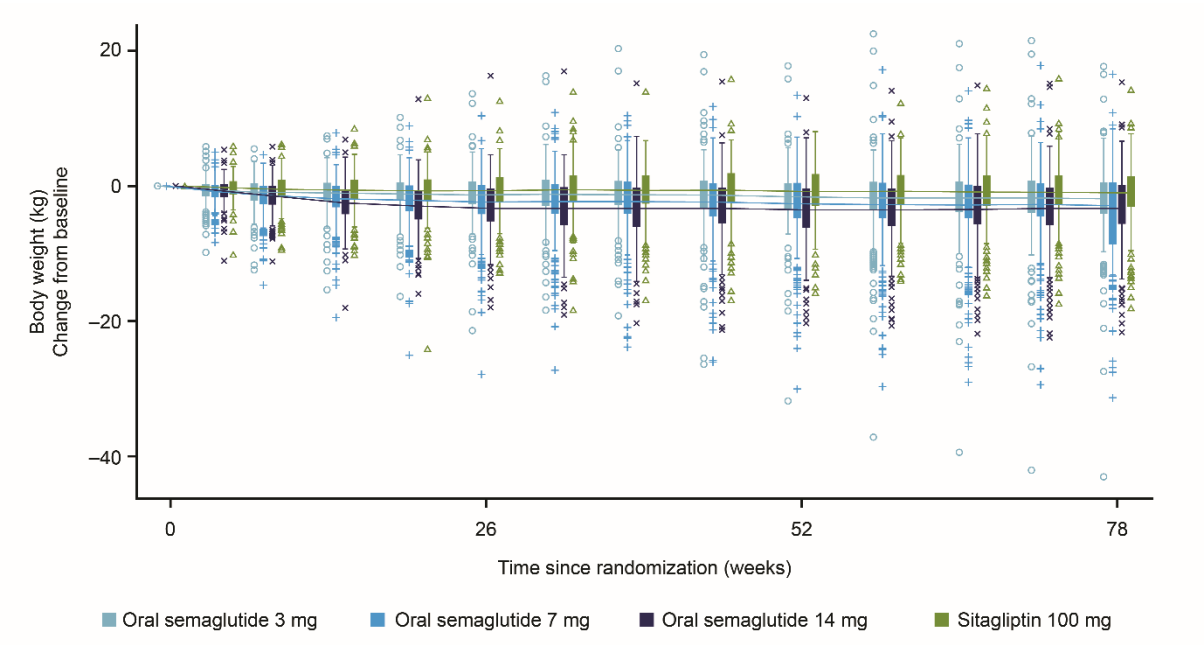
All patients randomized to oral semaglutide initiated treatment with 3 mg once daily and followed a fixed 4-week dose-escalation regimen until reaching the randomized dose.

eFigure 2. Boxplots of Observed HbA_{1c} and Body Weight Over Time

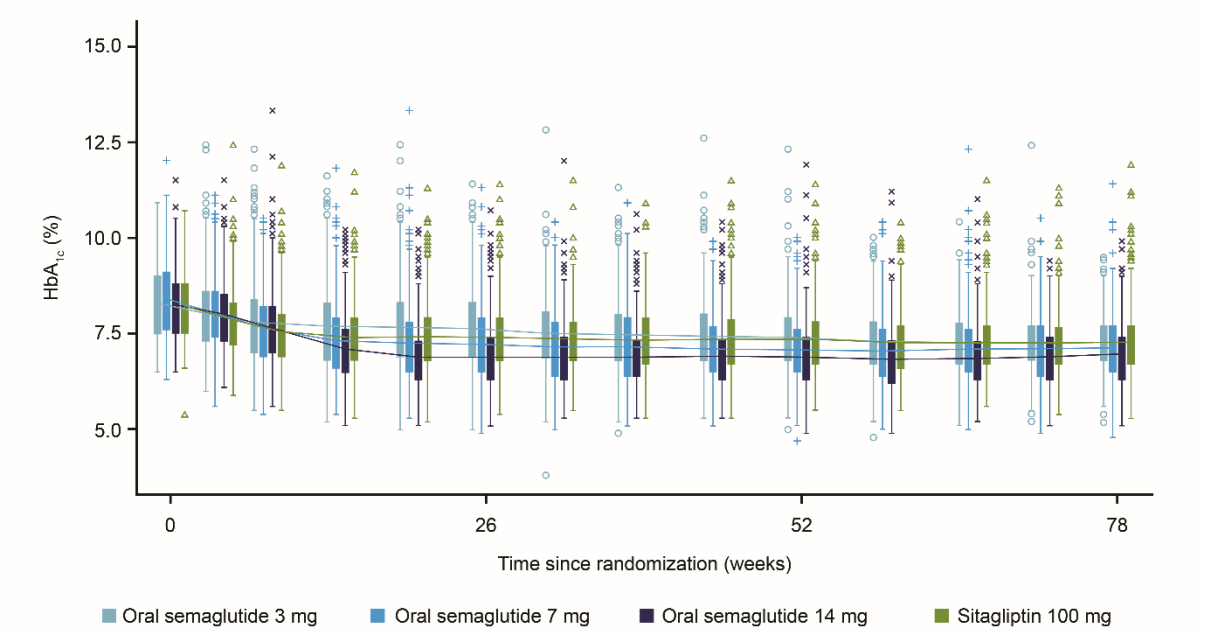
A1. HbA_{1c} – treatment policy estimand



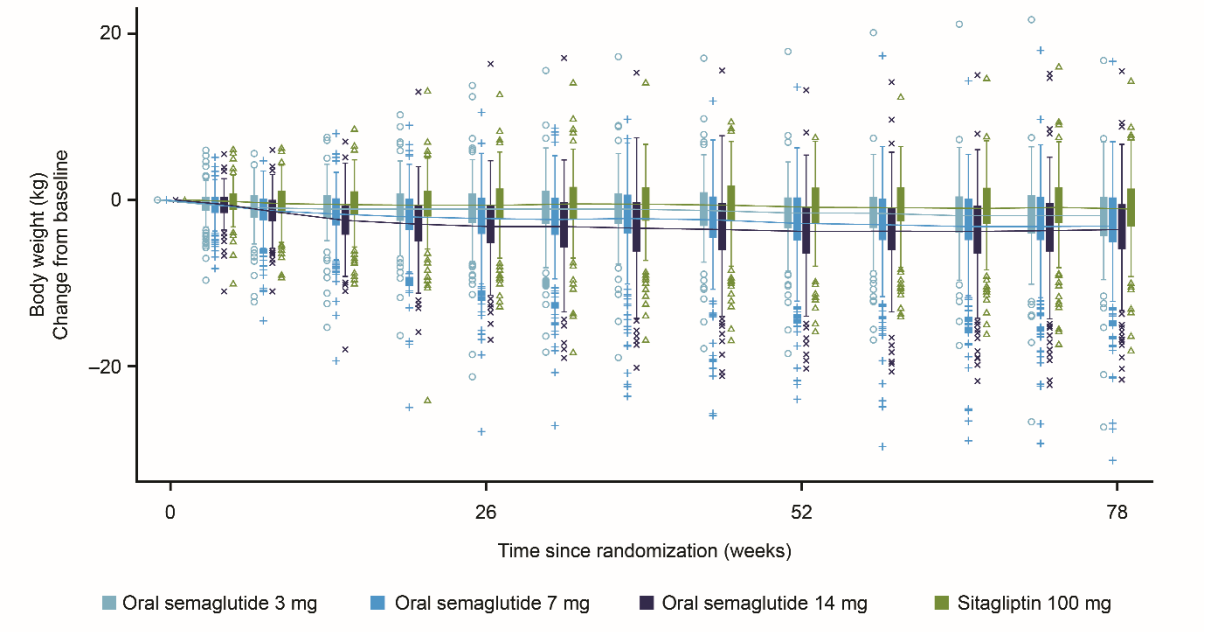
A2. Body weight – treatment policy estimand



B1. HbA_{1c} – trial product estimand



B2. Body weight – trial product estimand

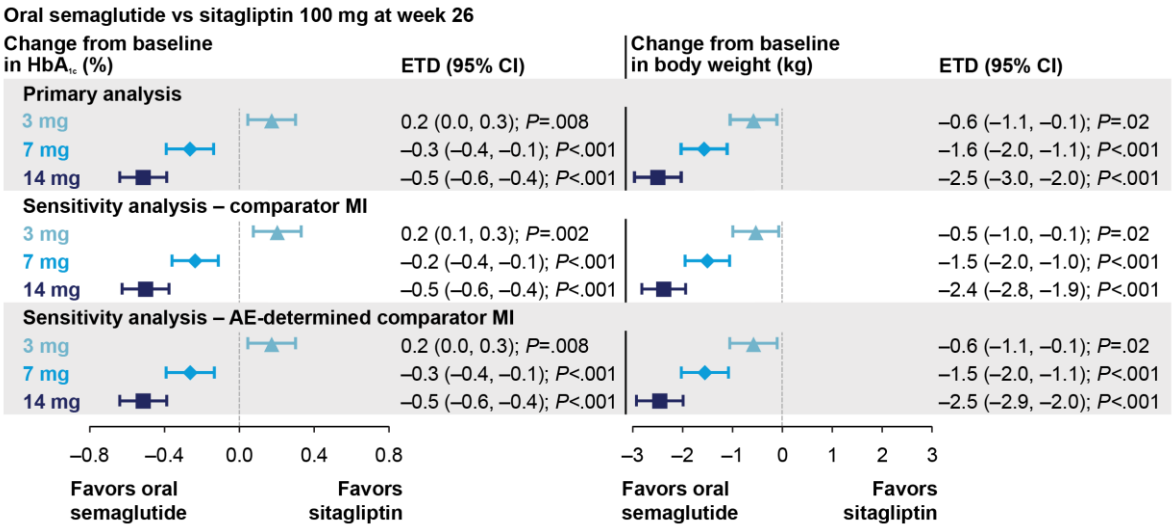


Observed mean over time overlaid with boxplot. The bottom and top edges of the box indicate the intra-quartile range (IQR). The whiskers that extend from each box indicate the range of values that are outside of the IQR but less than 1.5*IQR. Any points that are a distance of more than 1.5*IQR from the box are indicated by markers.

Treatment policy estimand: Observed data irrespective of discontinuation of trial product or initiation of rescue medication.

Trial product estimand: Observed data collected prior to discontinuation of trial product or initiation of rescue medication.

eFigure 3. Sensitivity Analyses for Changes From Baseline in HbA_{1c} and Body Weight at Week 26 for the Treatment Policy Estimand

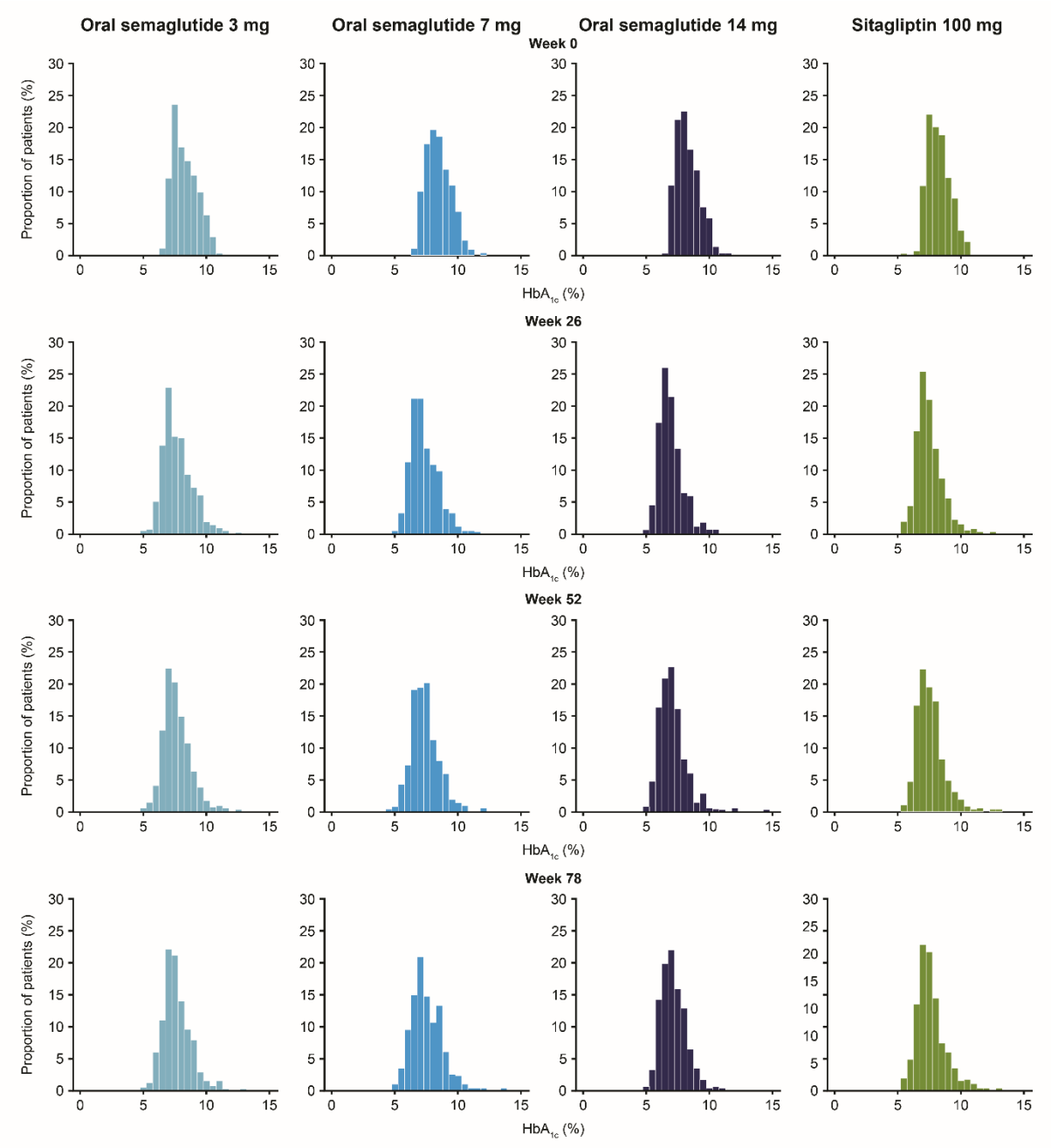


Abbreviation: AE, adverse event; CI, confidence interval; ETD, estimated treatment difference; MI, multiple imputation.

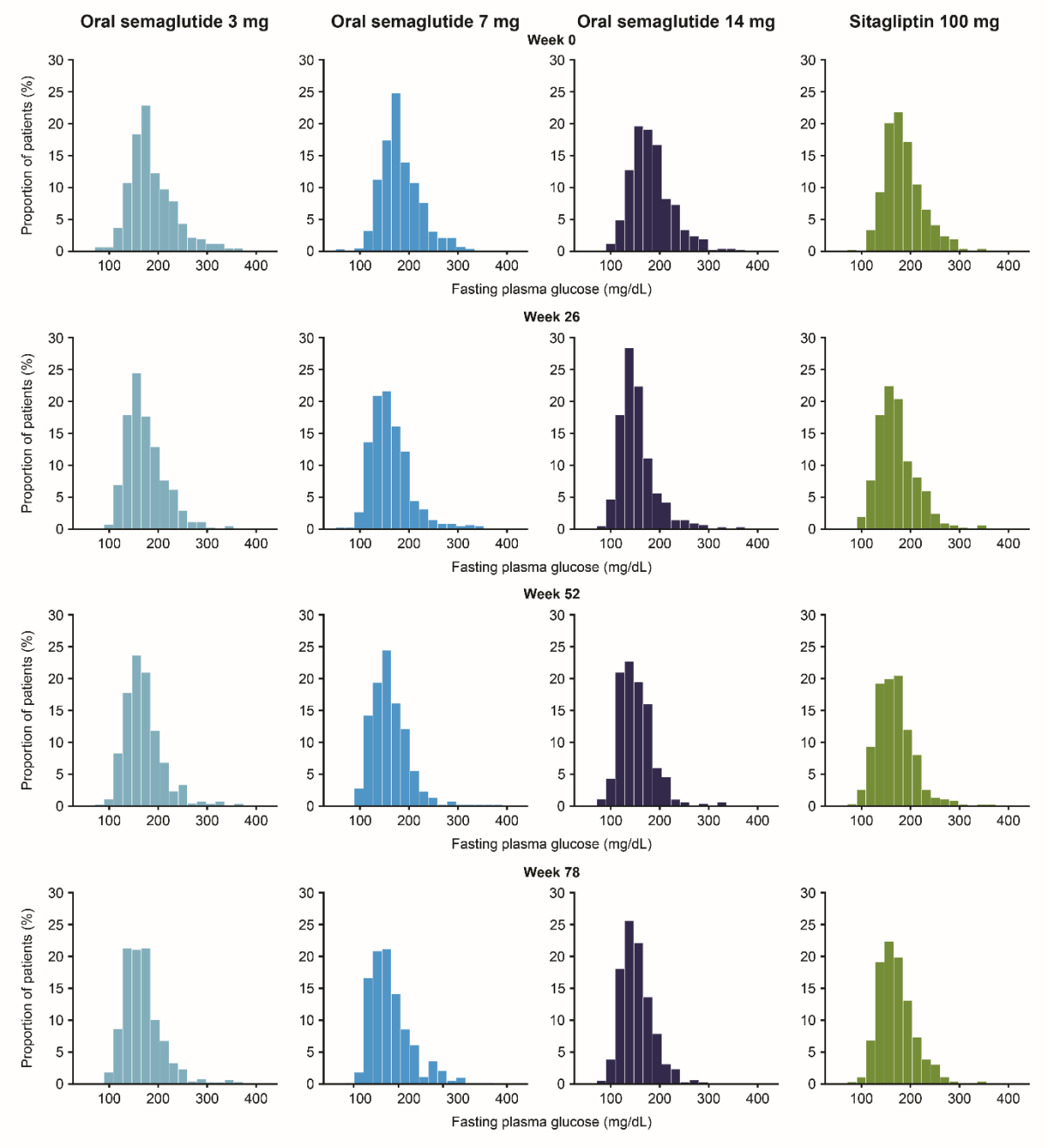
P values are unadjusted two-sided *P* values for the test of no difference.

eFigure 4. Distributions of HbA_{1c} and Fasting Plasma Glucose Values at Baseline and Weeks, 26, 52 and 78

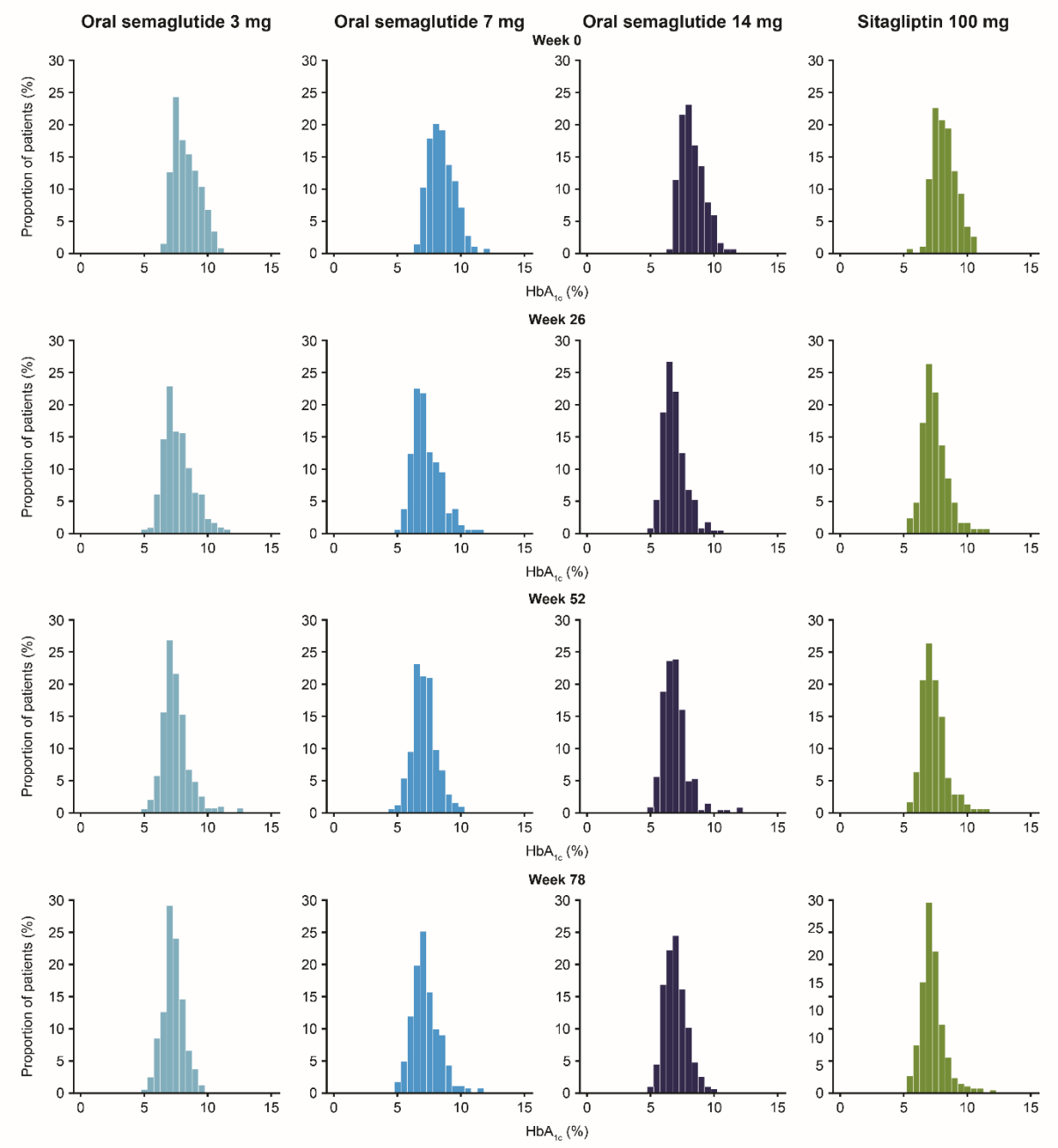
A1. HbA_{1c} – treatment policy estimand



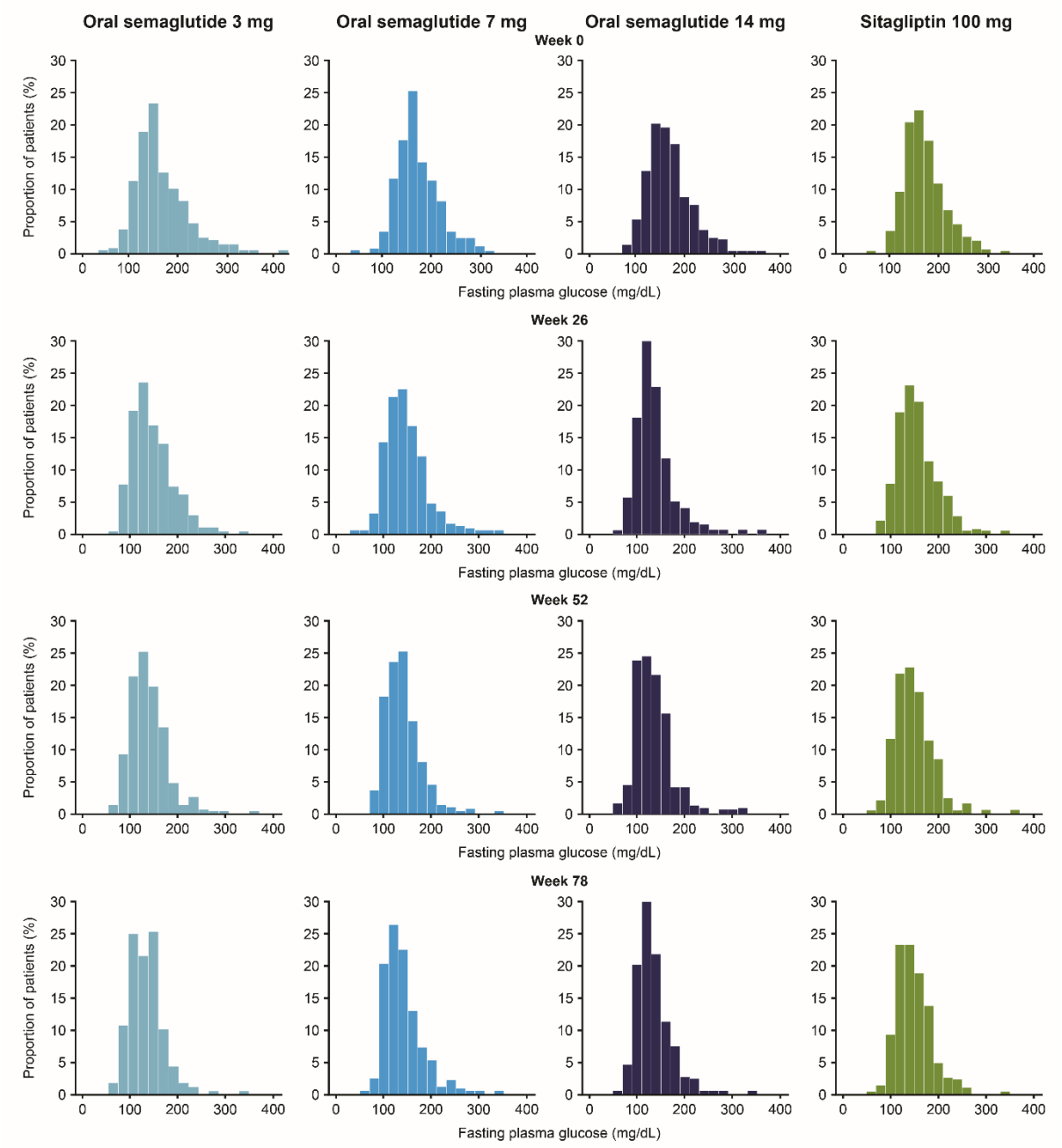
A2. Fasting plasma glucose – treatment policy estimand



B1, HbA_{1c} – trial product estimand



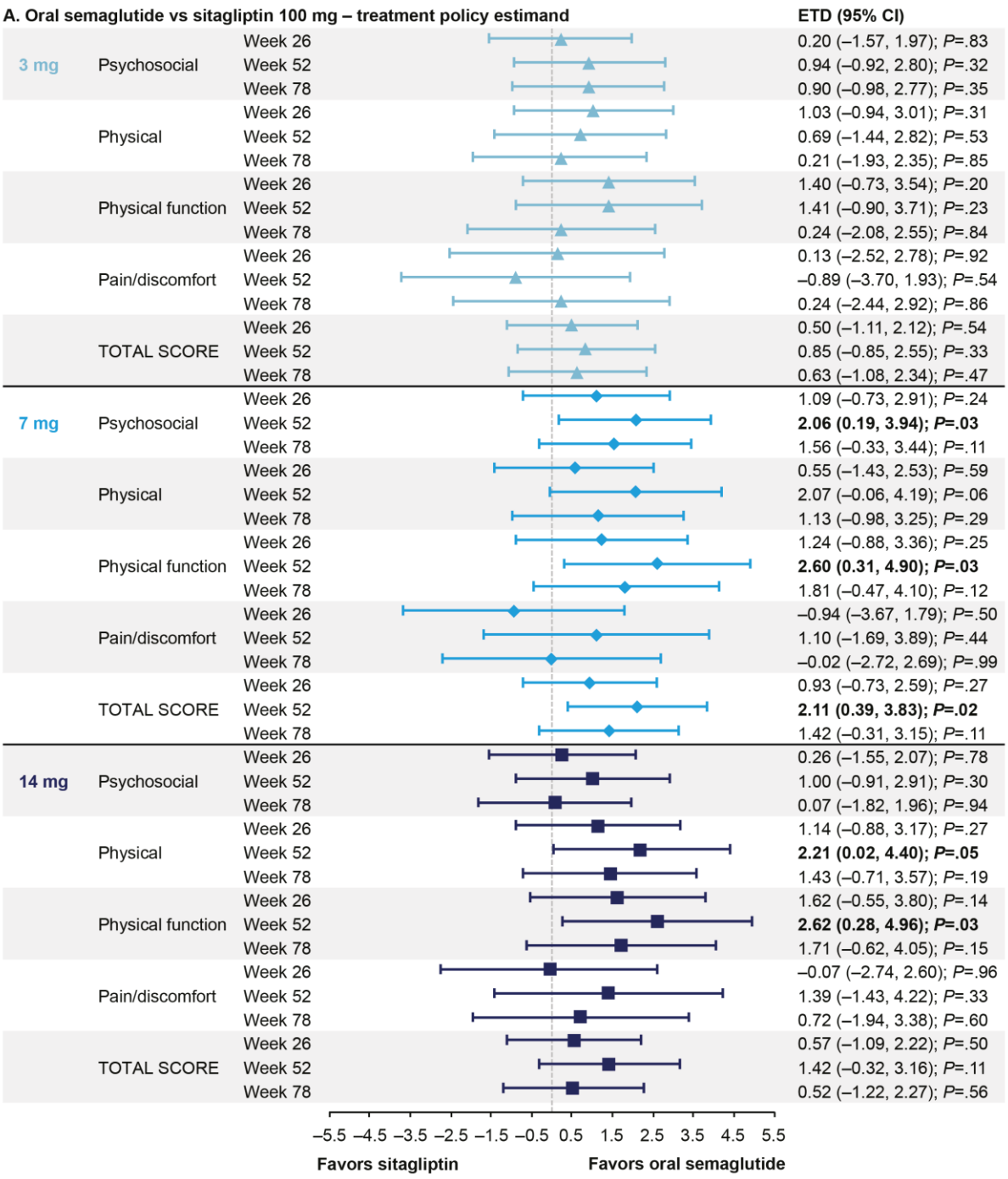
B2. Fasting plasma glucose – trial product estimand

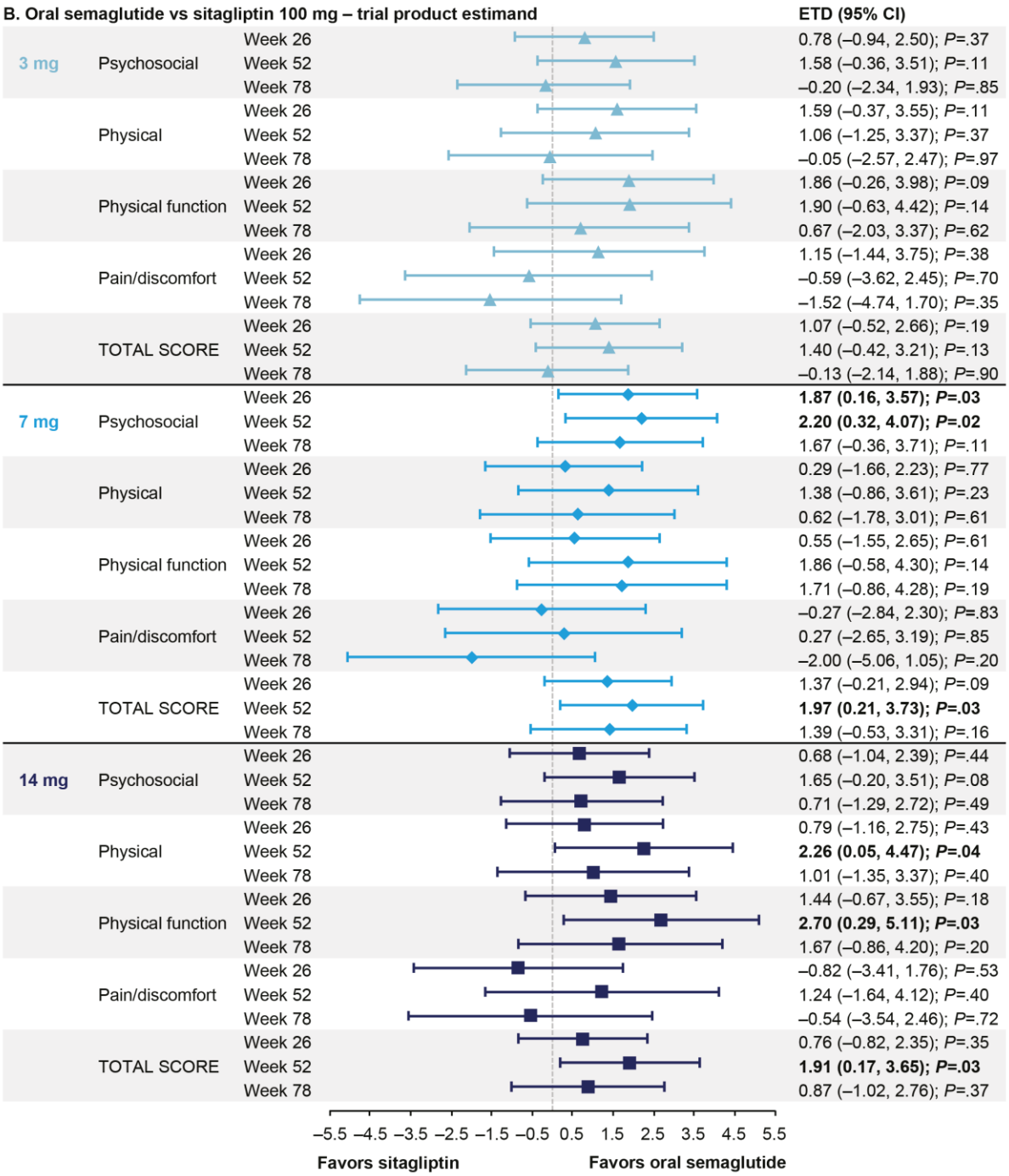


Treatment policy estimand: Observed data irrespective of discontinuation of trial product or initiation of rescue medication.

Trial product estimand: Observed data collected prior to discontinuation of trial product or initiation of rescue medication.

eFigure 5. Change From Baseline in Impact of Weight on Quality of Life-Lite Clinical Trial Version Questionnaire Scores





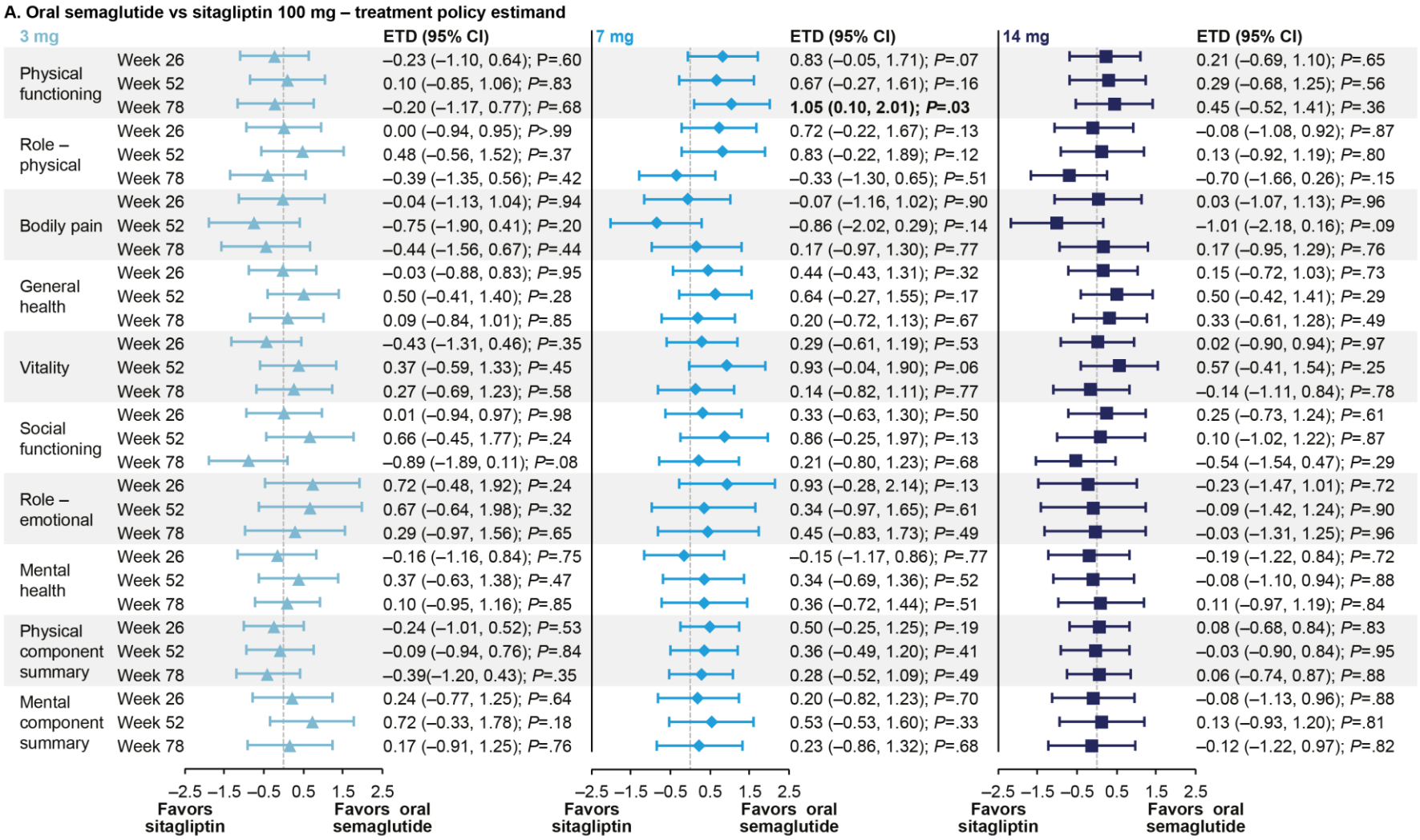
Abbreviation: CI, confidence interval; ETD, estimated treatment difference.

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

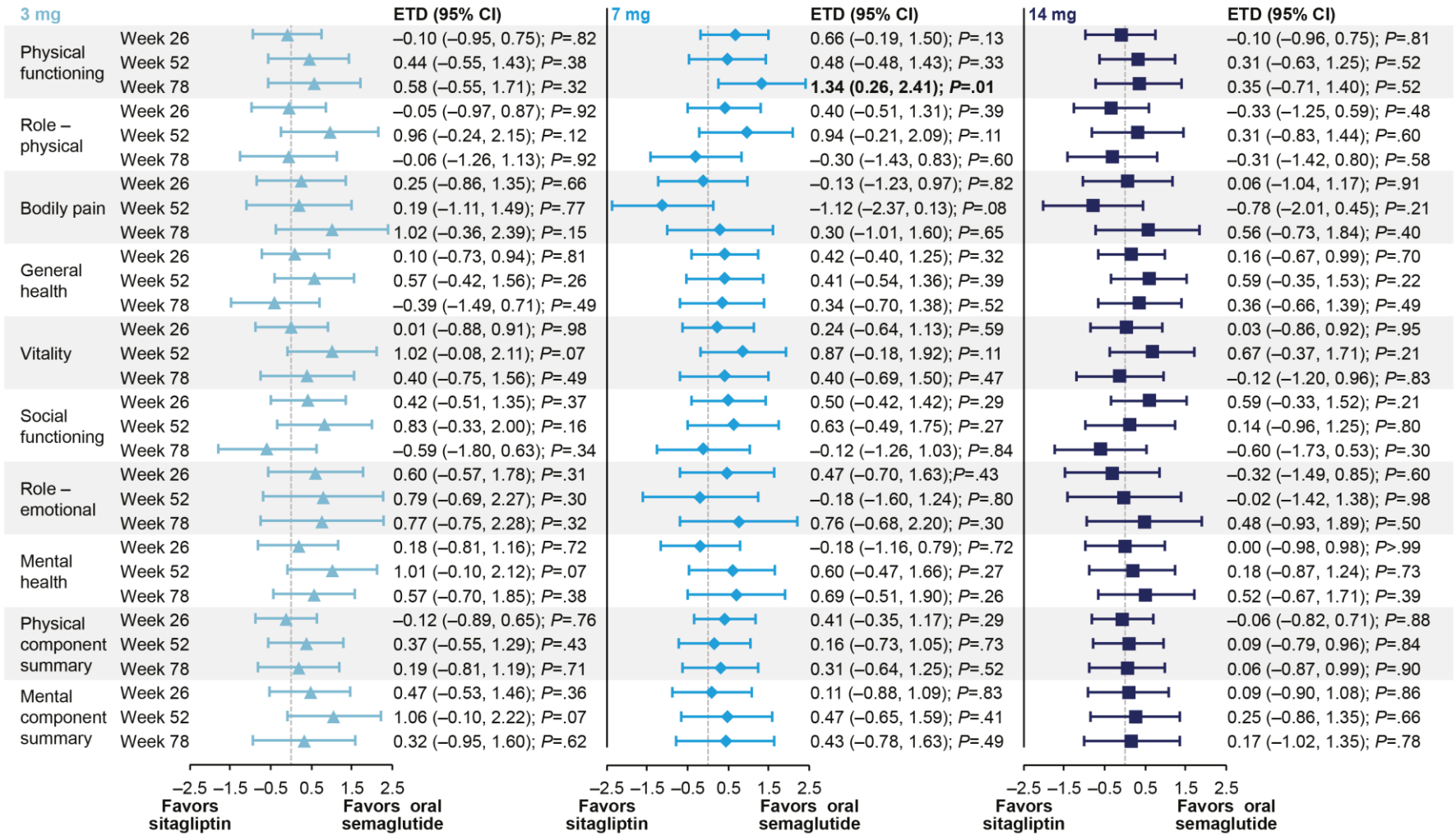
Treatment policy estimand: Analysis of covariance using data irrespective of discontinuation of trial product or initiation of rescue medication. Missing values were imputed by a pattern mixture model using multiple imputation. Pattern was defined by randomized trial product and treatment status (premature trial product discontinuation and/or initiation of rescue medication).

Trial product estimand: Mixed model for repeated measurements. Data collected after discontinuation of trial product or initiation of rescue medication were excluded.

eFigure 6. Change From Baseline in Short Form-36 Version 2 (Acute Version) Health Survey Summary Scores



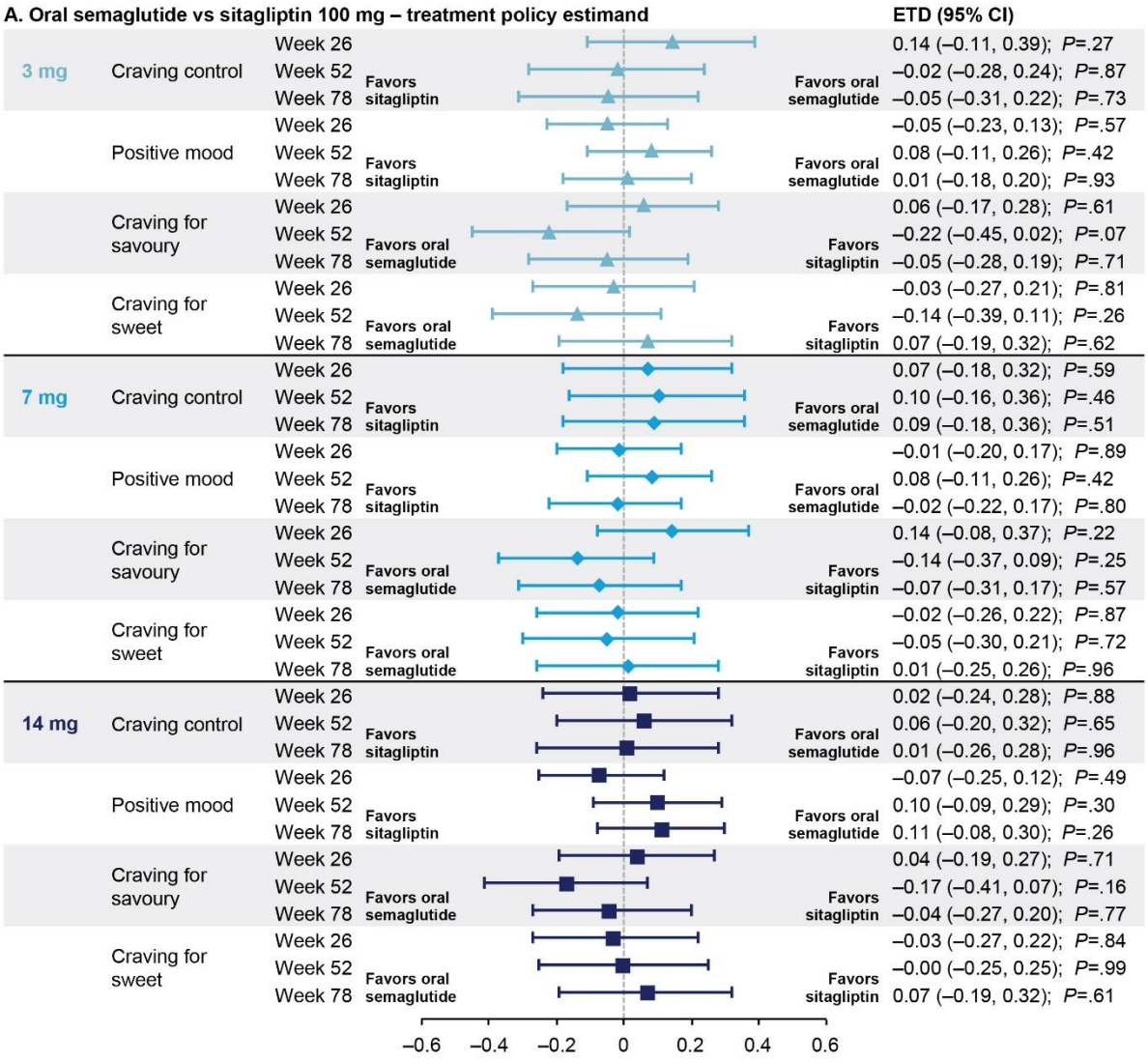
B. Oral semaglutide vs sitagliptin 100 mg – trial product estimand

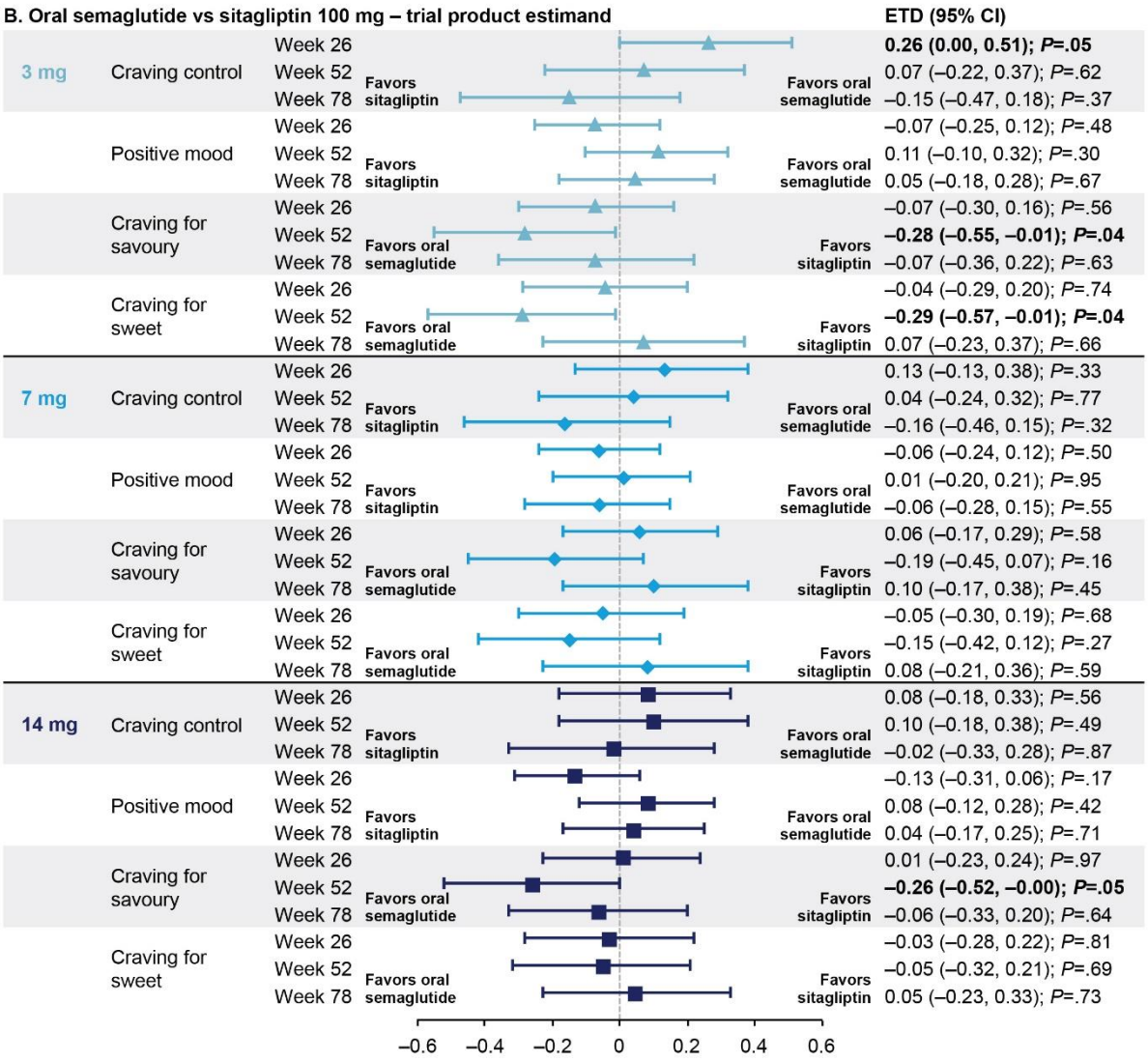


Abbreviation: CI, confidence interval; ETD, estimated treatment difference. *P* values are unadjusted two-sided *P* values for the test of no difference.

Treatment policy estimand: Analysis of covariance 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 (premature trial product discontinuation and/or initiation of rescue medication).
Trial product estimand: Mixed model for repeated measurements. Data collected after discontinuation of trial product or initiation of rescue medication were excluded.

eFigure 7. Change From Baseline in Control of Eating Questionnaire Domain Scores





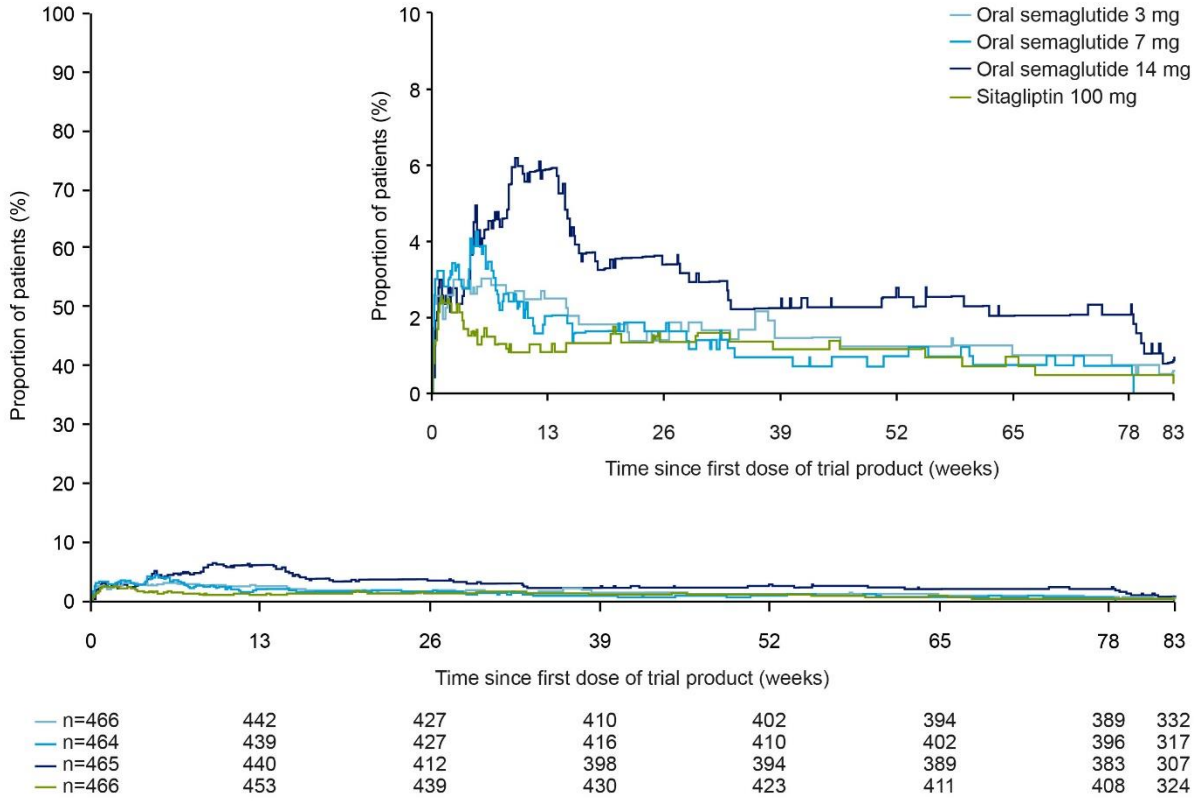
Abbreviation: CI, confidence interval; ETD, estimated treatment difference.

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

Treatment policy estimand: Analysis of covariance 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 (premature trial product discontinuation and/or initiation of rescue medication).

Trial product estimand: Mixed model for repeated measurements. Data collected after discontinuation of trial product or initiation of rescue medication were excluded.

eFigure 8. 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 are the same data but with the axis truncated to allow better visualization.

eTable 1. List of 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} 7.0–10.5% (53–91 mmol/mol) (both inclusive).
5.	Stable daily dose of metformin (≥1500 mg or maximum tolerated dose as documented in the patient medical record) alone, or in combination with sulfonylurea (≥half of the maximum approved dose according to local label or maximum tolerated dose as documented in the patient medical record), within 90 days prior to the day of screening.
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 or 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 Germany only: Only highly effective methods of birth control are accepted (i.e. one that results in ≤1% per year failure rate when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intrauterine device), or sexual abstinence or vasectomized partner.* *For United Kingdom only: Adequate contraceptive measures are defined as established use of oral, intravaginal, transdermal combined estrogen and progestogen hormonal methods of contraception; oral, injected or implanted progestogen only hormonal methods of contraception; placement of an intrauterine device or intrauterine hormone releasing system, bilateral tubal occlusion, barrier methods of contraception (condom or occlusive cap with spermicidal foam/gel/film/cream/suppository), female sterilization, vasectomized partner (where partner is sole partner of patient), or true abstinence (when in line with preferred and usual lifestyle).* *For Brazil only: For women who expressly declare free of the risk of pregnancy, either by not engaging in sexual activity or by having sexual activity with no birth potential risk, use of contraceptive method will not be mandatory.* *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. *For Brazil only: Participation in other trials within one year prior to screening visit (visit 1) unless there is a direct benefit to the research patient at the investigator's discretion.*
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 MEN2 or MTC.
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 NYHA Class IV.
11.	Planned coronary, carotid or peripheral artery revascularization known on the day of screening.

12.	Renal impairment defined as eGFR <60 mL/min/1.73 m^2 as per CKD-EPI.
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.	Proliferative retinopathy or maculopathy requiring acute treatment. Verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomization.
15.	History or presence of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer and in-situ carcinomas).

Abbreviation: CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration fate; MEN2, multiple endocrine neoplasia type 2; MTC, medullary thyroid carcinoma; NYHA, New York Heart Association.

eTable 2. Rescue Medication and Additional Glucose-Lowering Medication Use

	Week 26				Week 52				Week 78			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Patients on rescue medication[a], n (%)	**25 (5.4)**	**11 (2.4)**	**5 (1.1)**	**13 (2.8)**	**121 (26.0)**	**73 (15.7)**	**31 (6.7)**	**94 (20.1)**	**160 (34.3)**	**103 (22.2)**	**47 (10.1)**	**129 (27.6)**
Sulfonylureas	13 (2.8)	5 (1.1)	3 (0.6)	8 (1.7)	54 (11.6)	40 (8.6)	22 (4.7)	54 (11.6)	75 (16.1)	56 (12.0)	28 (6.0)	76 (16.3)
SGLT2 inhibitors	1 (0.2)	4 (0.9)	0 (0.0)	1 (0.2)	25 (5.4)	15 (3.2)	6 (1.3)	22 (4.7)	41 (8.8)	24 (5.2)	9 (1.9)	31 (6.6)
Biguanides	3 (0.6)	1 (0.2)	1 (0.2)	5 (1.1)	29 (6.2)	13 (2.8)	3 (0.6)	24 (5.1)	36 (7.7)	20 (4.3)	4 (0.9)	31 (6.6)
Insulins, long-acting	5 (1.1)	1 (0.2)	1 (0.2)	2 (0.4)	17 (3.6)	10 (2.2)	6 (1.3)	10 (2.1)	28 (6.0)	17 (3.7)	14 (3.0)	16 (3.4)
Thiazolidinediones	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	7 (1.5)	2 (0.4)	0 (0.0)	6 (1.3)	9 (1.9)	4 (0.9)	1 (0.2)	9 (1.9)
Insulins, intermediate-acting	2 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	4 (0.9)	2 (0.4)	1 (0.2)	2 (0.4)	9 (1.9)	5 (1.1)	3 (0.6)	3 (0.6)
Alpha glucosidase inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	3 (0.6)	0 (0.0)	0 (0.0)	6 (1.3)	3 (0.6)	1 (0.2)	1 (0.2)
Insulins, fast-acting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
Insulins, intermediate- or long-acting combined with fast-acting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	1 (0.2)	0 (0.0)	0 (0.0)	2 (0.4)	3 (0.6)	0 (0.0)	1 (0.2)

	Week 26				Week 52				Week 78			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Glinides	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
DPP-4 inhibitors	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)
Patients on additional glucose-lowering medication[b], n(%)	**33 (7.1)**	**20 (4.3)**	**15 (3.2)**	**20 (4.3)**	**137 (29.4)**	**86 (18.5)**	**51 (11.0)**	**111 (23.8)**	**179 (38.4)**	**119 (25.6)**	**75 (16.1)**	**148 (31.7)**
Sulfonylureas	16 (3.4)	6 (1.3)	7 (1.5)	11 (2.4)	59 (12.7)	44 (9.5)	32 (6.9)	61 (13.1)	82 (17.6)	61 (13.1)	43 (9.2)	83 (17.8)
SGLT2 inhibitors	2 (0.4)	6 (1.3)	2 (0.4)	1 (0.2)	27 (5.8)	18 (3.9)	10 (2.2)	23 (4.9)	45 (9.7)	28 (6.0)	16 (3.4)	34 (7.3)
Biguanides	5 (1.1)	1 (0.2)	2 (0.4)	6 (1.3)	32 (6.9)	13 (2.8)	7 (1.5)	27 (5.8)	39 (8.4)	20 (4.3)	10 (2.2)	35 (7.5)
Insulins, long-acting	5 (1.1)	2 (0.4)	2 (0.4)	3 (0.6)	18 (3.9)	14 (3.0)	10 (2.2)	13 (2.8)	31 (6.7)	22 (4.7)	18 (3.9)	22 (4.7)
DPP-4 inhibitors	1 (0.2)	5 (1.1)	4 (0.9)	4 (0.9)	2 (0.4)	7 (1.5)	7 (1.5)	5 (1.1)	4 (0.9)	7 (1.5)	11 (2.4)	6 (1.3)
Thiazolidinediones	2 (0.4)	0 (0.0)	0 (0.0)	1 (0.2)	7 (1.5)	2 (0.4)	0 (0.0)	7 (1.5)	9 (1.9)	4 (0.9)	1 (0.2)	10 (2.1)
Insulins, intermediate-acting	3 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.1)	2 (0.4)	1 (0.2)	2 (0.4)	10 (2.1)	5 (1.1)	4 (0.9)	3 (0.6)
Insulins, fast-acting	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.9)	2 (0.4)	3 (0.6)	4 (0.9)	6 (1.3)	4 (0.9)	5 (1.1)	4 (0.9)
Alpha glucosidase inhibitors	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	5 (1.1)	4 (0.9)	0 (0.0)	0 (0.0)	8 (1.7)	4 (0.9)	1 (0.2)	3 (0.6)
GLP-1RAs	1 (0.2)	1 (0.2)	0 (0.0)	1 (0.2)	4 (0.9)	1 (0.2)	0 (0.0)	3 (0.6)	5 (1.1)	1 (0.2)	1 (0.2)	3 (0.6)

	Week 26				Week 52				Week 78			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Insulins, intermediate- or long-acting combined with fast-acting	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)	0 (0.0)	0 (0.0)	3 (0.6)	4 (0.9)	0 (0.0)	1 (0.2)
Glinides	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	1 (0.2)	0 (0.0)
Oral drug combination	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)

Abbreviation: DPP, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose cotransporter 2.

[a] Initiated after randomization and before last day on trial product. Criteria for initiation of rescue medication were fasting plasma glucose (at central laboratory) >260 mg/dL (14.4 mmol/L) for weeks 8–13, >240 mg/dL (13.3 mmol/L) for weeks 14–25, and >200 mg/dL (11.1 mmol/L) or HbA_{1c} >8.5% (at central laboratory) for week 26 onwards.

[b] Initiated after randomization and before planned end of treatment. Additional glucose-lowering medication includes 1) the use of rescue medication, and/or 2) the use of glucose-lowering medication for patients who discontinued the trial product but remained in the trial.

eTable 3. 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 sitagliptin 100 mg	Non-inferiority Superiority	0.050 0.025	9.6 5.5
Oral semaglutide 7 mg vs sitagliptin 100 mg	Non-inferiority Superiority	0.050 0.025	6.6 2.0
Body weight change from baseline, kg			
Oral semaglutide 14 mg vs sitagliptin 100 mg	Superiority	0.025	31.3
Oral semaglutide 7 mg vs sitagliptin 100 mg	Superiority	0.025	17.7

'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. For the non-inferiority analysis, the penalty does not include the fixed non-inferiority margin penalty added on imputed values in any oral semaglutide group.

eTable 4. Time to Rescue Medication and Additional Glucose-Lowering Medication

	Hazard ratio (95% CI)	*P* value
Time from first dose to rescue medication with oral semaglutide vs sitagliptin 100 mg[a]		
3 mg	1.33 (1.05, 1.68)	.02
7 mg	0.66 (0.51, 0.86)	.002
14 mg	0.31 (0.22, 0.43)	<.001
Time from randomization to additional glucose-lowering medication with oral semaglutide vs sitagliptin 100 mg[b]		
3 mg	1.34 (1.09, 1.65)	.006
7 mg	0.77 (0.61, 0.96)	.02
14 mg	0.53 (0.41, 0.68)	<.001

Abbreviation: CI, confidence interval.

[a] Initiated after randomization and before last day on trial product. Data from the on-treatment without rescue medication period. Time to initiation of rescue medication was analyzed using a Cox proportional hazards model with treatment, background medication, and region as factors and baseline HbA_{1c} as covariate. Censoring time was one day before last day on trial product.

[b] Initiated after randomization and before planned end of treatment. Additional glucose-lowering medication includes 1) the use of rescue medication, and/or 2) the use of glucose-lowering medication for patients who discontinued the trial product but remained in the trial. Data from the in-trial observation period. Time to initiation of additional glucose-lowering medication was analyzed using a Cox proportional hazards model with treatment, background medication, and region as factors and baseline HbA_{1c} as covariate. Withdrawal for any reason or lost to follow-up contributed to the analysis as events (initiation of additional glucose-lowering medication). Censoring time was one day before planned end of treatment.

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

eTable 5. Additional Secondary Endpoints Not Included in the Main Text

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Change from baseline in body weight, %								
Week 26								
Estimated mean change from baseline	–1.2	–2.3	–3.4	–0.6	–1.3	–2.4	–3.6	–0.7
ETD vs sitagliptin (95% CI)	–0.6 (–1.1, –0.1)	–1.7 (–2.2, –1.2)	–2.8 (–3.3, –2.3)	–	–0.6 (–1.1, –0.0)	–1.7 (–2.2, –1.2)	–2.9 (–3.4, –2.4)	–
P value	.02	<.001	<.001	–	.03	<.001	<.001	–
Week 52								
Estimated mean change from baseline	–1.7	–2.5	–3.7	–0.8	–1.7	–2.5	–4.2	–0.9
ETD vs sitagliptin (95% CI)	–0.9 (–1.6, –0.3)	–1.8 (–2.4, –1.1)	–3.0 (–3.6, –2.3)	–	–0.8 (–1.4, –0.1)	–1.6 (–2.2, –1.0)	–3.2 (–3.9, –2.6)	–
P value	.006	<.001	<.001	–	.02	<.001	<.001	–
Week 78								
Estimated mean change from baseline	–1.9	–2.8	–3.4	–1.0	–1.9	–2.9	–3.9	–1.2
ETD vs sitagliptin (95% CI)	–0.9 (–1.6, –0.1)	–1.8 (–2.5, –1.1)	–2.4 (–3.1, –1.7)	–	–0.7 (–1.5, –0.0)	–1.7 (–2.4, –1.0)	–2.7 (–3.4, –2.0)	–
P value	.02	<.001	<.001	–	.05	<.001	<.001	–
7-point self-measured blood glucose[a] post-prandial increment, mg/dL								
Week 26								
Estimated mean	34.6	33.0	32.3	31.5	35.5	33.3	31.1	30.7

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Estimated mean change from baseline	–6.2	–7.9	–8.6	–9.4	–6.2	–8.4	–10.5	–10.9
ETD vs sitagliptin (95% CI)	3.2 (–1.0, 7.3)	1.5 (–2.6, 5.6)	0.8 (–3.6, 5.2)	–	4.7 (0.8, 8.7)	2.6 (–1.4, 6.5)	0.4 (–3.5, 4.3)	–
P value	.14	.48	.72	–	.02	.20	.84	–
Week 52								
Estimated mean	34.8	32.5	31.7	33.9	34.8	30.9	30.9	33.4
Estimated mean change from baseline	–6.1	–8.4	–9.2	–7.0	–6.9	–10.8	–10.8	–8.3
ETD vs sitagliptin (95% CI)	0.8 (–3.2, 4.9)	–1.4 (–5.4, 2.6)	–2.3 (–6.4, 1.9)	–	1.4 (–3.0, 5.8)	–2.5 (–6.7, 1.7)	–2.6 (–6.7, 1.6)	–
P value	.69	.49	.28	–	.54	.24	.23	–
Week 78								
Estimated mean	34.9	32.3	31.9	31.1	34.0	32.6	32.6	29.6
Estimated mean change from baseline	–6.0	–8.6	–9.0	–9.8	–7.7)	–9.1)	–9.1	–12.1
ETD vs sitagliptin (95% CI)	3.8 (–0.4, 8.0)	1.2 (–3.0, 5.4)	0.7 (–3.6, 5.0)	–	4.3 (–0.6, 9.3)	2.9 (–1.7, 7.6)	3.0 (–1.6, 7.6)	–
P value	.08	.58	.75	–	.08	.22	.20	–
HbA_{1c} ≤6.5%								
Week 26								
Estimated proportion of patients, %	13	26	36	14	13	27	39	14

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
ETD vs sitagliptin (95% CI)	–1 (–5, 3)	12 (7, 17)	22 (16, 27)	–	–1 (–5, 3)	13 (8, 18)	25 (20, 31)	–
P value	.60	<.001	<.001	–	.62	<.001	<.001	–
Week 52								
Estimated proportion of patients, %	14	22	32	14	12	23	35	14
ETD vs sitagliptin (95% CI)	–0 (–5, 4)	8 (3, 13)	18 (13, 24)	–	–2 (–6, 2)	9 (4, 14)	21 (16, 27)	–
P value	.90	.001	<.001	–	.42	<.001	<.001	–
Week 78								
Estimated proportion of patients, %	13	23	29	14	12	21	32	13
ETD vs sitagliptin (95% CI)	–1 (–5, 3)	9 (4, 14)	15 (10, 20)	–	–2 (–6, 3)	8 (3, 13)	18 (13, 24)	–
P value	.63	<.001	<.001	–	.44	.002	<.001	–
Body weight loss ≥10%								
Week 26								
Estimated proportion of patients, %	1	5	7	2	1	6	8	2
ETD vs sitagliptin (95% CI)	–0 (–2, 1)	4 (1, 6)	5 (2, 8)	–	–1 (–2, 1)	4 (1, 6)	6 (3, 9)	–
P value	.70	.005	<.001	–	.43	.005	<.001	–
Week 52								
Estimated proportion of patients, %	4	7	11	3	2	7	12	3
ETD vs sitagliptin (95% CI)	1 (–1, 3)	4 (2, 7)	8 (5, 12)	–	–0 (–3, 2)	5 (2, 8)	10 (6, 13)	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
P value	.43	.003	<.001	–	.74	.003	<.001	–
Week 78								
Estimated proportion of patients, %	4	10	11	4	3	10	12	3
ETD vs sitagliptin (95% CI)	–0 (–3, 3)	6 (3, 10)	7 (3, 10)	–	–0 (–3, 2)	6 (3, 10)	9 (5, 13)	–
P value	.89	<.001	<.001	–	.74	<.001	<.001	–
Body mass index, kg/m^2								
Week 26								
Estimated mean	32.1	31.7	31.4	32.3	32.1	31.7	31.3	32.2
Estimated mean change from baseline	–0.4	–0.8	–1.1	–0.2	–0.4	–0.8	–1.2	–0.2
ETD vs sitagliptin (95% CI)	–0.2 (–0.4, –0.0)	–0.6 (–0.7, –0.4)	–0.9 (–1.1, –0.7)	–	–0.2 (–0.4, –0.0)	–0.5 (–0.7, –0.4)	–0.9 (–1.1, –0.8)	–
P value	.02	<.001	<.001	–	.02	<.001	<.001	–
Week 52								
Estimated mean	31.9	31.6	31.3	32.2	31.9	31.6	31.1	32.2
Estimated mean change from baseline	–0.6	–0.9	–1.2	–0.3	–0.6	–0.9	–1.4	–0.3
ETD vs sitagliptin (95% CI)	–0.3 (–0.5, –0.1)	–0.6 (–0.8, –0.4)	–1.0 (–1.2, –0.7)	–	–0.3 (–0.5, –0.0)	–0.5 (–0.7, –0.3)	–1.0 (–1.2, –0.8)	–
P value	.005	<.001	<.001	–	.02	<.001	<.001	–
Week 78								
Estimated mean	31.8	31.5	31.4	32.1	31.8	31.5	31.2	32.1

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Estimated mean change from baseline	–0.7	–1.0	–1.1	–0.4	–0.7	–1.0	–1.3	–0.4
ETD vs sitagliptin (95% CI)	–0.3 (–0.6, –0.1)	–0.6 (–0.8, –0.4)	–0.8 (–1.0, –0.5)	–	–0.3 (–0.5, –0.0)	–0.6 (–0.8, –0.3)	–0.8 (–1.1, –0.6)	–
P value	.01	<.001	<.001	–	.03	<.001	<.001	–
Waist circumference (cm)								
Week 26								
Estimated mean	106.7	105.8	105.2	106.8	106.8	105.8	105.1	106.9
Estimated mean change from baseline	–0.7	–1.7	–2.3	–0.6	–0.7	–1.7	–2.4	–0.6
ETD vs sitagliptin (95% CI)	–0.1 (–0.7, 0.6)	–1.1 (–1.7, –0.4)	–1.6 (–2.3, –1.0)	–	–0.1 (–0.7, 0.6)	–1.1 (–1.7, –0.4)	–1.8 (–2.4, –1.1)	–
P value	.83	.002	<.001	–	.84	.002	<.001	–
Week 52								
Estimated mean	106.2	105.4	104.8	107.0	106.0	105.2	104.7	106.8
Estimated mean change from baseline	–1.3	–2.1	–2.6	–0.4	–1.5	–2.4	–2.8	–0.7
ETD vs sitagliptin (95% CI)	–0.9 (–1.7, –0.1)	–1.7 (–2.5, –0.9)	–2.2 (–3.0, –1.4)	–	–0.8 (–1.6, 0.0)	–1.7 (–2.5, –0.8)	–2.1 (–2.9, –1.3)	–
P value	.03	<.001	<.001	–	.06	<.001	<.001	–
Week 78								
Estimated mean	106.2	105.2	105.1	106.8	106.1	105.2	104.9	106.7

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Estimated mean change from baseline	–1.3	–2.2	–2.4	–0.7	–1.4	–2.3	–2.6	–0.8
ETD vs sitagliptin (95% CI)	–0.6 (–1.4, 0.3)	–1.6 (–2.4, –0.7)	–1.7 (–2.5, –0.9)	–	–0.6 (–1.6, 0.4)	–1.5 (–2.4, –0.6)	–1.8 (–2.8, –0.9)	–
P value	.19	<.001	<.001	–	.22	.001	<.001	–
Total cholesterol (mg/dL)								
Week 26								
Estimated mean	173	170	168	174	171	170	167	174
Estimated ratio to baseline	1.00	0.98	0.97	1.00	0.99	0.98	0.96	1.00
ETR vs sitagliptin (95% CI)	1.00 (0.97, 1.02)	0.98 (0.96, 1.00)	0.97 (0.94, 0.99)	–	0.99 (0.97, 1.01)	0.98 (0.96, 1.00)	0.96 (0.94, 0.98)	–
P value	.67	.05	.001	–	.25	.04	<.001	–
Week 52								
Estimated mean	174	174	171	175	173	172	170	175
Estimated ratio to baseline	1.00	1.00	0.99	1.01	1.00	0.99	0.98	1.01
ETR vs sitagliptin (95% CI)	0.99 (0.97, 1.02)	0.99 (0.97, 1.02)	0.98 (0.96, 1.00)	–	0.99 (0.97, 1.02)	0.99 (0.96, 1.01)	0.97 (0.95, 0.99)	–
P value	.62	.52	.06	–	.51	.22	.01	–
Week 78								
Estimated mean	173	172	171	174	171	172	171	173
Estimated ratio to baseline	1.00	0.99	0.99	1.00	0.99	0.99	0.98	1.00
ETR vs sitagliptin (95% CI)	0.99 (0.97, 1.02)	0.99 (0.96, 1.01)	0.99 (0.96, 1.01)	–	0.99 (0.96, 1.02)	0.99 (0.97, 1.02)	0.99 (0.96, 1.01)	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
P value	.67	.37	.28	–	.45	.64	.32	–
Low-density lipoprotein cholesterol (mg/dL)								
Week 26								
Estimated mean	94	91	90	95	93	91	90	94
Estimated ratio to baseline	1.02	0.99	0.98	1.02	1.00	0.98	0.98	1.02
ETR vs sitagliptin (95% CI)	0.99 (0.96, 1.03)	0.96 (0.93, 1.00)	0.95 (0.92, 0.99)	–	0.98 (0.95, 1.02)	0.96 (0.93, 1.00)	0.96 (0.92, 0.99)	–
P value	.74	.04	.008	–	.36	.04	.01	–
Week 52								
Estimated mean	94	93	92	95	93	92	91	94
Estimated ratio to baseline	1.01	1.00	1.00	1.03	1.01	0.99	0.98	1.03
ETR vs sitagliptin (95% CI)	0.99 (0.95, 1.02)	0.98 (0.94, 1.01)	0.97 (0.94, 1.00)	–	0.98 (0.95, 1.02)	0.97 (0.93, 1.01)	0.96 (0.92, 0.99)	–
P value	.47	.20	.09	–	.44	.11	.03	–
Week 78								
Estimated mean	95	92	93	95	93	93	92	94
Estimated ratio to baseline	1.02	1.00	1.00	1.03	1.01	1.01	1.00	1.02
ETR vs sitagliptin (95% CI)	1.00 (0.96, 1.04)	0.98 (0.94, 1.02)	0.98 (0.94, 1.02)	–	1.00 (0.95, 1.04)	0.99 (0.95, 1.03)	0.99 (0.95, 1.03)	–
P value	.99	.23	.31	–	.87	.70	.52	–
Very low-density lipoprotein cholesterol (mg/dL)								
Week 26								

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Estimated mean	30	29	28	29	29	29	27	29
Estimated ratio to baseline	0.99	0.96	0.92	0.98	0.98	0.96	0.91	0.97
ETR vs sitagliptin (95% CI)	1.02 (0.97, 1.06)	0.98 (0.94, 1.03)	0.94 (0.90, 0.99)	–	1.01 (0.97, 1.05)	0.99 (0.94, 1.03)	0.93 (0.89, 0.97)	–
P value	.48	.43	.009	–	.66	.50	.001	–
Week 52								
Estimated mean	30	29	28	30	29	29	28	29
Estimated ratio to baseline	1.00	0.98	0.93	0.99	0.98	0.96	0.92	0.98
ETR vs sitagliptin (95% CI)	1.01 (0.97, 1.06)	0.99 (0.95, 1.04)	0.95 (0.90, 0.99)	–	1.00 (0.95, 1.05)	0.98 (0.93, 1.03)	0.94 (0.89, 0.98)	–
P value	.58	.76	.02	–	.95	.41	.007	–
Week 78								
Estimated mean	29	28	27	28	28	27	27	28
Estimated ratio to baseline	0.95	0.95	0.92	0.95	0.92	0.91	0.90	0.93
ETR vs sitagliptin (95% CI)	1.01 (0.96, 1.06)	1.00 (0.95, 1.05)	0.97 (0.92, 1.02)	–	0.99 (0.93, 1.05)	0.97 (0.92, 1.03)	0.97 (0.91, 1.02)	–
P value	.82	.98	.21	–	.73	.35	.21	–
High-density lipoprotein cholesterol (mg/dL)								
Week 26								
Estimated mean	43	44	44	44	43	44	44	44
Estimated ratio to baseline	0.97	0.99	0.98	0.99	0.97	0.99	0.98	0.99

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
ETR vs sitagliptin (95% CI)	0.98 (0.96, 1.00)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	–	0.98 (0.97, 1.00)	1.00 (0.98, 1.02)	0.99 (0.97, 1.01)	–
P value	.05	.98	.46	–	.07	.82	.36	–
Week 52								
Estimated mean	44	45	45	44	45	46	45	45
Estimated ratio to baseline	0.99	1.01	1.01	1.00	1.00	1.02	1.01	1.00
ETR vs sitagliptin (95% CI)	0.99 (0.97, 1.01)	1.01 (0.99, 1.03)	1.01 (1.00, 1.03)	–	1.00 (0.98, 1.02)	1.02 (1.00, 1.04)	1.02 (0.99, 1.04)	–
P value	.40	.27	.13	–	.89	.07	.14	–
Week 78								
Estimated mean	43	44	45	44	44	45	45	44
Estimated ratio to baseline	0.97	0.99	1.00	0.99	0.98	1.01	1.00	0.99
ETR vs sitagliptin (95% CI)	0.98 (0.96, 1.00)	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)	–	0.99 (0.97, 1.02)	1.02 (1.00, 1.05)	1.01 (0.99, 1.04)	–
P value	.09	.85	.32	–	.55	.03	.22	–
Triglycerides (mg/dL)								
Week 26								
Estimated mean	154	150	144	152	152	150	141	151
Estimated ratio to baseline	0.99	0.96	0.92	0.97	0.98	0.97	0.91	0.97
ETR vs sitagliptin (95% CI)	1.02 (0.97, 1.06)	0.99 (0.94, 1.04)	0.95 (0.91, 0.99)	–	1.01 (0.96, 1.06)	0.99 (0.95, 1.04)	0.93 (0.89, 0.98)	–
P value	.52	.63	.03	–	.71	.74	.003	–

	Treatment policy estimand				Trial product estimand			
	Oral semaglutide			Sitagliptin 100 mg (N=467)	Oral semaglutide			Sitagliptin 100 mg (N=467)
	3 mg (N=466)	7 mg (N=465)	14 mg (N=465)		3 mg (N=466)	7 mg (N=465)	14 mg (N=465)	
Week 52								
Estimated mean	155	152	145	154	151	149	142	153
Estimated ratio to baseline	1.00	0.98	0.93	0.99	0.98	0.96	0.92	0.99
ETR vs sitagliptin (95% CI)	1.01 (0.96, 1.06)	0.99 (0.94, 1.04)	0.94 (0.90, 0.99)	–	0.99 (0.94, 1.04)	0.97 (0.93, 1.02)	0.93 (0.89, 0.98)	–
P value	.72	.64	.01	–	.69	.30	.004	–
Week 78								
Estimated mean	149	148	143	147	144	141	140	145
Estimated ratio to baseline	0.96	0.95	0.92	0.94	0.93	0.91	0.90	0.94
ETR vs sitagliptin (95% CI)	1.01 (0.96, 1.07)	1.01 (0.96, 1.06)	0.97 (0.92, 1.03)	–	0.99 (0.93, 1.06)	0.97 (0.92, 1.03)	0.97 (0.91, 1.02)	–
P value	.60	.79	.32	–	.80	.39	.25	–

Abbreviation: CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio.

[a] Self-monitored blood glucose is reported as plasma equivalent values of capillary whole blood glucose.

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: Analysis of covariance for continuous endpoints and generalized linear model with binomial distribution and identity link 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 (premature trial product discontinuation and/or initiation of rescue medication).

Trial product estimand: Mixed model for repeated measurements for continuous endpoints and generalized linear model with binomial distribution and identity link 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.

eTable 6. On-Treatment Adverse Events Leading to Discontinuation by System Organ Class/Preferred Term

	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Adverse events leading to premature trial product discontinuation[a], n (%)	26 (5.6)	27 (5.8)	54 (11.6)	24 (5.2)
Gastrointestinal disorders	11 (2.4)	16 (3.4)	32 (6.9)	12 (2.6)
Nausea	2 (0.4)	7 (1.5)	13 (2.8)	5 (1.1)
Diarrhea	3 (0.6)	2 (0.4)	8 (1.7)	1 (0.2)
Vomiting	0	7 (1.5)	8 (1.7)	2 (0.4)
Abdominal pain upper	1 (0.2)	2 (0.4)	3 (0.6)	0
Pancreatitis acute	1 (0.2)	1 (0.2)	3 (0.6)	1 (0.2)
Abdominal pain	1 (0.2)	0	2 (0.4)	2 (0.4)
Flatulence	0	0	2 (0.4)	0
Gastroesophageal reflux disease	0	1 (0.2)	2 (0.4)	0
Abdominal discomfort	0	1 (0.2)	1 (0.2)	1 (0.2)
Abdominal distension	1 (0.2)	0	1 (0.2)	0
Abdominal tenderness	0	0	1 (0.2)	0
Dry mouth	0	0	1 (0.2)	0
Eructation	0	0	1 (0.2)	0
Gastritis	0	1 (0.2)	1 (0.2)	1 (0.2)
Dyspepsia	3 (0.6)	1 (0.2)	0	0
Epigastric discomfort	0	1 (0.2)	0	0
Ileus paralytic	1 (0.2)	0	0	0
Mallory-Weiss syndrome	0	1 (0.2)	0	0
Pancreatic cyst	0	0	0	1 (0.2)
Metabolism and nutrition disorders	1 (0.2)	2 (0.4)	6 (1.3)	1 (0.2)
Decreased appetite	1 (0.2)	2 (0.4)	6 (1.3)	0
Diabetes mellitus inadequate control	0	0	0	1 (0.2)
General disorders and administration site conditions	2 (0.4)	3 (0.6)	4 (0.9)	1 (0.2)
Fatigue	0	1 (0.2)	2 (0.4)	0
Malaise	0	0	1 (0.2)	0
Pain	0	0	1 (0.2)	0
Asthenia	1 (0.2)	1 (0.2)	0	0
Chest discomfort	0	1 (0.2)	0	0
Chest pain	0	0	0	1 (0.2)
Pyrexia	1 (0.2)	0	0	0
Investigations	2 (0.4)	2 (0.4)	4 (0.9)	2 (0.4)
Weight decreased	1 (0.2)	0	2 (0.4)	0
Lipase increased	1 (0.2)	0	1 (0.2)	2 (0.4)
Pancreatic enzymes increased	0	0	1 (0.2)	0
Hepatic enzyme increased	0	1 (0.2)	0	0
Renal function test abnormal	0	1 (0.2)	0	0
Nervous system disorders	1 (0.2)	0	4 (0.9)	1 (0.2)

	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Chronic inflammatory demyelinating polyradiculoneuropathy	0	0	1 (0.2)	0
Dizziness	0	0	1 (0.2)	0
Headache	0	0	1 (0.2)	1 (0.2)
Ischemic stroke	1 (0.2)	0	1 (0.2)	0
Skin and subcutaneous tissue disorders	2 (0.4)	1 (0.2)	3 (0.6)	1 (0.2)
Dermatosis	0	0	1 (0.2)	0
Pruritus	0	0	1 (0.2)	0
Rash	0	0	1 (0.2)	0
Alopecia	0	1 (0.2)	0	0
Angioedema	1 (0.2)	0	0	0
Dermatitis allergic	0	0	0	1 (0.2)
Hyperhidrosis	1 (0.2)	0	0	0
Cardiac disorders	2 (0.4)	1 (0.2)	2 (0.4)	1 (0.2)
Cardiac failure congestive	0	1 (0.2)	2 (0.4)	0
Acute coronary syndrome	0	0	0	1 (0.2)
Atrial fibrillation	2 (0.4)	0	0	0
Cardiac failure chronic	1 (0.2)	0	0	0
Ear and labyrinth disorders	1 (0.2)	0	2 (0.4)	0
Vertigo	0	0	2 (0.4)	0
Acute vestibular syndrome	1 (0.2)	0	0	0
Neurosensory hypoacusis	1 (0.2)	0	0	0
Tinnitus	1 (0.2)	0	0	0
Injury, poisoning and procedural complications	1 (0.2)	0	2 (0.4)	0
Clavicle fracture	0	0	1 (0.2)	0
Medication error	0	0	1 (0.2)	0
Scapular fracture	0	0	1 (0.2)	0
Subarachnoid hemorrhage	1 (0.2)	0	0	0
Neoplasms benign, malignant and unspecified	0	1 (0.2)	2 (0.4)	2 (0.4)
Colon cancer	0	0	1 (0.2)	0
Plasma cell myeloma	0	0	1 (0.2)	0
Brain neoplasm malignant	0	0	0	1 (0.2)
Breast cancer	0	0	0	1 (0.2)
Rectal adenocarcinoma	0	1 (0.2)	0	0
Infections and infestations	5 (1.1)	1 (0.2)	1 (0.2)	0
Helicobacter gastritis	0	0	1 (0.2)	0
Gastroenteritis	1 (0.2)	0	0	0
Influenza	1 (0.2)	0	0	0
Peritonitis bacterial	1 (0.2)	0	0	0
Pyelonephritis acute	1 (0.2)	0	0	0
Subcutaneous abscess	0	1 (0.2)	0	0

	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Urinary tract infection	1 (0.2)	0	0	0
Musculoskeletal and connective tissue disorders	0	0	1 (0.2)	2 (0.4)
Myalgia	0	0	1 (0.2)	0
Arthralgia	0	0	0	1 (0.2)
Osteoarthritis	0	0	0	1 (0.2)
Psychiatric disorders	0	1 (0.2)	1 (0.2)	0
Libido decreased	0	1 (0.2)	1 (0.2)	0
Renal and urinary disorders	1 (0.2)	0	1 (0.2)	1 (0.2)
Urinary retention	0	0	1 (0.2)	0
Acute kidney injury	1 (0.2)	0	0	0
End stage renal disease	0	0	0	1 (0.2)
Reproductive system and breast disorders	0	0	1 (0.2)	0
Prostatitis	0	0	1 (0.2)	0
Blood and lymphatic system disorders	1 (0.2)	0	0	0
Thrombocytopenia	1 (0.2)	0	0	0
Endocrine disorders	0	0	0	1 (0.2)
Goitre	0	0	0	1 (0.2)
Eye disorders	1 (0.2)	0	0	0
Vision blurred	1 (0.2)	0	0	0
Hepatobiliary disorders	1 (0.2)	1 (0.2)	0	1 (0.2)
Chronic hepatic failure	0	0	0	1 (0.2)
Hepatic cirrhosis	1 (0.2)	0	0	0
Hepatitis	0	1 (0.2)	0	0
Immune system disorders	0	2 (0.4)	0	0
Hypersensitivity	0	1 (0.2)	0	0
Sarcoidosis	0	1 (0.2)	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (0.2)	0	0
Hemoptysis	0	1 (0.2)	0	0
Vascular disorders	1 (0.2)	0	0	0
Hypertension	1 (0.2)	0	0	0

[a] Patients could experience multiple events.

System organ class and preferred terms defined using Medical Dictionary for Regulatory Activities (version 20.1).

On-treatment: The period where the patient is considered treated with trial product.

eTable 7. On-Treatment Hypoglycemic Episodes

	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
All patients, n (%)				
Severe or BG-confirmed symptomatic hypoglycemia[a]	23 (4.9)	24 (5.2)	36 (7.7)	39 (8.4)
Nocturnal[b] severe or BG-confirmed symptomatic hypoglycemia[a]	9 (1.9)	2 (0.4)	6 (1.3)	5 (1.1)
ADA classification	102 (21.9)	108 (23.3)	131 (28.2)	112 (24.0)
Severe	0 (0.0)	0 (0.0)	1 (0.2)	4 (0.9)
Patients on metformin alone, n (%)	246	247	245	248
Severe or BG-confirmed symptomatic hypoglycemia[a]	1 (0.4)	5 (2.0)	6 (2.4)	4 (1.6)
Nocturnal[b] severe or BG-confirmed symptomatic hypoglycemia[a]	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)
ADA classification	29 (11.8)	35 (14.2)	38 (15.5)	28 (11.3)
Severe	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.4)
Patients on metformin and sulfonylurea, n (%)	220	217	220	218
Severe or BG-confirmed symptomatic hypoglycemia[a]	22 (10.0)	19 (8.8)	30 (13.6)	35 (16.1)
Nocturnal[b] severe or BG-confirmed symptomatic hypoglycemia[a]	9 (4.1)	1 (0.5)	6 (2.7)	5 (2.3)
ADA classification	73 (33.2)	73 (33.6)	93 (42.3)	84 (38.5)
Severe	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.4)

Abbreviation: ADA, American Diabetes Association; BG, blood glucose.

[a] Reported episodes were either severe (defined according to the American Diabetes Association classification) or confirmed by a blood glucose value <56 mg/dL (3.1 mmol/L), with symptoms consistent with hypoglycemia.

[b] Episodes with onset between 00:01 and 05:59 (inclusive).

SI conversion factor: To convert glucose to mmol/L, multiply by 0.055494.

On treatment: The period where the patient is considered treated with trial product.

eTable 8. In-Trial Adverse Events Related to Diabetic Retinopathy

Preferred term	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Number of patients with at least one event, n (%)				
Eye disorders	31 (6.7)	28 (6.0)	26 (5.6)	36 (7.7)
Diabetic retinopathy	28 (6.0)	24 (5.2)	17 (3.7)	29 (6.2)
Retinopathy	1 (0.2)	2 (0.4)	4 (0.9)	0
Retinal hemorrhage	1 (0.2)	0 (0.0)	3 (0.6)	2 (0.4)
Macular edema	0	2 (0.4)	2 (0.4)	1 (0.2)
Maculopathy	0	1 (0.2)	1 (0.2)	1 (0.2)
Diabetic retinal edema	3 (0.6)	0	0	1 (0.2)
Retinal detachment	0	1 (0.2)	0	1 (0.2)
Retinopathy proliferative	0	0	0	1 (0.2)
Vitreous detachment	1 (0.2)	0	0	2 (0.4)
Vitreous hemorrhage	0	1 (0.2)	0	1 (0.2)

Events identified using Medical Dictionary for Regulatory Activities (version 20.1) terms.

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

eTable 9. External Event Adjudication Committee–Confirmed Events and Selected In-Trial Adverse Events

Preferred term	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Number of patients with at least one event, n (%)				
Death	5 (1.1)	3 (0.6)	1 (0.2)	3 (0.6)
Sudden cardiac death	0	0	1 (0.2)	0
Stroke	2 (0.4)	0	0	0
Renal causes	1 (0.2)	0	0	0
Malignancy	0	0	0	1 (0.2)
Pancreatic causes	1 (0.2)	0	0	0
Neurological	0	1 (0.2)	0	0
Infection	1 (0.2)	0	0	0
Hepatobiliary causes	0	0	0	1 (0.2)
Undetermined cause	0	2 (0.4)	0	1 (0.2)
Acute kidney injury	3 (0.6)	2 (0.4)	5 (1.1)	3 (0.6)
Acute pancreatitis	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.2)
Cardiovascular events	15 (3.2)	7 (1.5)	5 (1.1)	10 (2.1)
Acute coronary syndrome	4 (0.9)	4 (0.9)	1 (0.2)	4 (0.9)
Acute myocardial infarction	3 (0.6)	1 (0.2)	0	2 (0.4)
Unstable angina pectoris	2 (0.4)	3 (0.6)	1 (0.2)	1 (0.2)
Cerebrovascular events	7 (1.5)	1 (0.2)	2 (0.4)	2 (0.4)
Stroke	6 (1.3)	1 (0.2)	2 (0.4)	1 (0.2)
Transient ischemic attack	1 (0.2)	0	0	1 (0.2)
Cardiovascular and undetermined cause of death	2 (0.4)	2 (0.4)	1 (0.2)	1 (0.2)
Cardiovascular death	2 (0.4)	0	1 (0.2)	0
Undetermined cause of death	0	2 (0.4)	0	1 (0.2)
Heart failure	4 (0.9)	0	1 (0.2)	3 (0.6)
Malignant neoplasm[a]	5 (1.1)	9 (1.9)	3 (0.6)	7 (1.5)
Skin cancer	2 (0.4)	4 (0.9)	0	1 (0.2)
Breast cancer	0	2 (0.4)	0	2 (0.4)
Colorectal cancer	0	1 (0.2)	1 (0.2)	2 (0.4)
Gastrointestinal cancer	0	0	1 (0.2)	2 (0.4)
Pancreas	0	0	1 (0.2)	1 (0.2)
Stomach	0	0	0	1 (0.2)
Prostate	2 (0.4)	1 (0.2)	0	0
Lymphoid neoplasm	0	1 (0.2)	1 (0.2)	0
Lung cancer	0	0	0	1 (0.2)
Unknown primary site	1 (0.2)	0	0	0
Lactic acidosis	0	1 (0.2)	0	0

[a] Excludes malignant thyroid neoplasms.

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

eTable 10. Additional Safety Parameters

	In-trial observation period				On-treatment observation period			
	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)		3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Systolic blood pressure, mmHg								
Week 26								
Estimated mean	133	131	131	132	132	131	131	132
Estimated mean change from baseline	–1	–3	–3	–2	–1	–3	–3	–2
ETD vs sitagliptin (95% CI)	1 (–1, 2)	–1 (–3, 1)	–1 (–3, 1)	–	0 (–1, 2)	–1 (–2, 1)	–1 (–3, 1)	–
P value	.40	.32	.25	–	.60	.46	.19	–
Week 52								
Estimated mean	132	129	131	133	132	129	131	133
Estimated mean change from baseline	–2	–5	–3	–1	–2	–4	–3	–1
ETD vs sitagliptin (95% CI)	–1 (–3, 0)	–4 (–6, –2)	–2 (–4, –1)	–	–1 (–3, 0)	–4 (–5, –2)	–2 (–4, –1)	–
P value	.15	<.001	.01	–	.16	<.001	.009	–
Week 78								
Estimated mean	133	130	131	133	132	131	131	134
Estimated mean change from baseline	–1	–3	–3	0	–2	–3	–3	0
ETD vs sitagliptin (95% CI)	–1 (–3, 1)	–3 (–5, –1)	–2 (–4, –0)	–	–1 (–3, 0)	–3 (–5, –1)	–2 (–4, –0)	–
P value	.33	.001	.02	–	.12	.002	.01	–

	In-trial observation period				On-treatment observation period			
	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)		3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Diastolic blood pressure, mmHg								
Week 26								
Estimated mean	79	80	80	80	79	80	80	80
Estimated mean change from baseline	–1	–1	–1	–0	–1	–0	–0	–0
ETD vs sitagliptin (95% CI)	–1 (–2, 1)	–0 (–1, 1)	–0 (–1, 1)	–	–1 (–2, 0)	–0 (–1, 1)	–1 (–1, 1)	–
P value	.31	.69	.63	–	.17	.73	.64	–
Week 52								
Estimated mean	78	79	79	79	78	79	79	79
Estimated mean change from baseline	–2	–1	–2	–1	–2	–1	–1	–1
ETD vs sitagliptin (95% CI)	–1 (–2, –0)	–0 (–1, 1)	–1 (–2, 0)	–	–1 (–2, 0)	–0 (–1, 1)	–0 (–1, 1)	–
P value	.03	.53	.28	–	.09	.75	.77	–
Week 78								
Estimated mean	79	79	79	79	79	79	79	79
Estimated mean change from baseline	–1	–1	–1	–1	–1	–1	–1	–1
ETD vs sitagliptin (95% CI)	–0 (–2, 1)	–0 (–2, 1)	–0 (–1, 1)	–	–0 (–1, 1)	0 (–1, 1)	0 (–1, 1)	–
P value	.56	.63	.64	–	.69	.84	.96	–
Pulse rate, beats per minute								
Week 26								
Estimated mean	75	76	77	75	75	76	77	75
Estimated mean change from baseline	1	2	2	0	1	2	2	0
ETD vs sitagliptin (95% CI)	0 (–1, 1)	1 (0, 3)	2 (1, 3)	–	1 (–0, 2)	2 (1, 3)	2 (1, 3)	–

	In-trial observation period				On-treatment observation period			
	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)		3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
P value	.52	.01	<.001	–	.23	.001	<.001	–
Week 52								
Estimated mean	75	76	76	74	75	76	76	74
Estimated mean change from baseline	0	1	1	–0	1	2	2	–0
ETD vs sitagliptin (95% CI)	1 (–1, 2)	1 (0, 3)	1 (0, 2)	–	1 (–0, 2)	2 (1, 3)	2 (1, 3)	–
P value	.36	.01	.02	–	.12	.003	<.001	–
Week 78								
Estimated mean	75	76	76	75	76	76	76	75
Estimated mean change from baseline	1	1	1	0	1	1	2	0
ETD vs sitagliptin (95% CI)	1 (–1, 2)	1 (–0, 2)	1 (–0, 2)	–	1 (–0, 2)	1 (0, 2)	2 (1, 3)	–
P value	.34	.17	.11	–	.12	.05	.003	–
Lipase, U/L								
Week 26								
Estimated mean	36	39	42	39	36	39	43	39
Estimated ratio to baseline	1.05	1.13	1.22	1.13	1.06	1.14	1.26	1.13
ETR vs sitagliptin (95% CI)	0.93 (0.87, 0.99)	1.00 (0.94, 1.07)	1.08 (1.01, 1.15)	–	0.94 (0.88, 1.00)	1.01 (0.94, 1.07)	1.11 (1.04, 1.18)	–
P value	.02	.99	.03	–	.05	.84	.002	–
Week 52								
Estimated mean	35	40	41	39	36	40	43	39
Estimated ratio to baseline	1.04	1.16	1.21	1.14	1.05	1.16	1.25	1.15

	In-trial observation period				On-treatment observation period			
	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)		3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
ETR vs sitagliptin (95% CI)	0.91 (0.85, 0.97)	1.02 (0.95, 1.08)	1.05 (0.99, 1.12)	–	0.92 (0.86, 0.98)	1.01 (0.95, 1.08)	1.08 (1.02, 1.15)	–
P value	.002	.61	.10	–	.007	.75	.02	–
Week 78								
Estimated mean	35	40	40	37	35	40	41	38
Estimated ratio to baseline	1.03	1.17	1.16	1.09	1.03	1.16	1.19	1.11
ETR vs sitagliptin (95% CI)	0.94 (0.88, 1.01)	1.07 (1.00, 1.14)	1.06 (0.99, 1.13)	–	0.93 (0.87, 0.99)	1.04 (0.98, 1.11)	1.07 (1.00, 1.14)	–
P value	.07	.05	.08	–	.03	.22	.05	–

	In-trial observation period				On-treatment observation period			
	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)		3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Amylase, U/L								
Week 26								
Estimated mean	54	57	59	57	55	57	60	57
Estimated ratio to baseline	1.03	1.07	1.13	1.07	1.03	1.07	1.14	1.07
ETR vs sitagliptin (95% CI)	0.96 (0.93, 0.99)	1.00 (0.97, 1.03)	1.05 (1.01, 1.08)	–	0.96 (0.93, 0.99)	1.00 (0.97, 1.03)	1.06 (1.03, 1.10)	–
P value	.01	.95	.005	–	.02	.96	<.001	–
Week 52								
Estimated mean	54	58	58	56	54	58	59	57
Estimated ratio to baseline	1.02	1.09	1.11	1.07	1.03	1.09	1.12	1.07
ETR vs sitagliptin (95% CI)	0.96 (0.93, 0.99)	1.02 (0.99, 1.06)	1.04 (1.00, 1.07)	–	0.96 (0.93, 0.99)	1.02 (0.98, 1.05)	1.04 (1.01, 1.08)	–
P value	.01	.21	.03	–	.02	.32	.01	–
Week 78								
Estimated mean	54	58	57	56	54	58	58	57
Estimated ratio to baseline	1.02	1.10	1.09	1.07	1.03	1.09	1.10	1.08
ETR vs sitagliptin (95% CI)	0.96 (0.92, 0.99)	1.03 (0.99, 1.07)	1.02 (0.98, 1.06)	–	0.95 (0.92, 0.99)	1.02 (0.98, 1.05)	1.02 (0.99, 1.06)	–
P value	.02	.11	.31	–	.007	.35	.26	–
Estimated glomerular filtration rate[a] ratio to baseline								
Week 26								
Geometric mean (CV)	0.99 (10.9)	0.98 (10.0)	0.98 (10.3)	0.97 (9.5)	0.99 (10.9)	0.98 (10.1)	0.98 (10.5)	0.97 (9.3)

	In-trial observation period				On-treatment observation period			
	Oral semaglutide			Sitagliptin 100 mg (N=466)	Oral semaglutide			Sitagliptin 100 mg (N=466)
	3 mg (N=466)	7 mg (N=464)	14 mg (N=465)		3 mg (N=466)	7 mg (N=464)	14 mg (N=465)	
Week 52								
Geometric mean (CV)	0.99 (12.5)	0.98 (11.2)	0.98 (12.0)	0.98 (11.6)	0.99 (12.9)	0.98 (11.3)	0.98 (11.7)	0.98 (11.5)
Week 78								
Geometric mean (CV)	0.99 (14.6)	0.98 (10.7)	0.98 (12.7)	0.98 (10.8)	0.99 (13.5)	0.98 (10.8)	0.98 (11.8)	0.98 (10.9)

Abbreviation: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CV, coefficient of variation; ETD, estimated treatment difference; ETR, estimated treatment ratio.

[a] Glomerular filtration rate was estimated by the CKD-EPI formula.

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: Analysis of covariance 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 (premature trial product discontinuation and/or initiation of rescue medication).

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

eTable 11. In-Trial Anti-Semaglutide Antibodies

	Oral semaglutide		
	3 mg (N=466)	**7 mg (N=464)**	**14 mg (N=465)**
Week 0			
Patients with positive result, n (%)	0 (0.0)	1 (0.2)	0 (0.0)
Mean (SD) concentration, %B/T	–	2.84 (0.00)	–
Week 4			
Patients with positive result, n (%)	0 (0.0)	0 (0.0)	1 (0.2)
Mean (SD) concentration, %B/T	–	–	9.82 (0.00)
Week 8			
Patients with positive result, n (%)	1 (0.2)	0 (0.0)	0 (0.0)
Mean (SD) concentration, %B/T	1.93 (0.00)	–	–
Week 14			
Patients with positive result, n (%)	0 (0.0)	1 (0.2)	0 (0.0)
Mean (SD) concentration, %B/T	–	3.28 (0.00)	–
Week 26			
Patients with positive result, n (%)	0 (0.0)	1 (0.2)	1 (0.2)
Mean (SD) concentration, %B/T	–	2.39 (0.00)	2.05 (0.00)
Week 38			
Patients with positive result, n (%)	0 (0.0)	0 (0.0)	1 (0.2)
Mean (SD) concentration, %B/T	–	–	2.24 (0.00)
Week 52			
Patients with positive result, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD) concentration, %B/T	–	–	–
Week 78			
Patients with positive result, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD) concentration, %B/T	–	–	–
Week 83			
Patients with positive result, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Mean (SD) concentration, %B/T	–	–	–

Abbreviation: B/T, bound/total; SD, standard deviation.

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

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