Oral semaglutide and cardiovascular risk factors in high-risk type 2 diabetes

Sub-title (60 characters max.): *Post hoc* analyses of a randomized clinical trial – SOUL

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Key Points (75-100 words max.):

Question:

What is the treatment effect associated with oral semaglutide on recognized cardiovascular risk factors versus placebo in SOUL?

Findings:

Oral semaglutide demonstrated sustained improvements in multiple cardiovascular risk factors in high-risk participants with type 2 diabetes and atherosclerotic cardiovascular disease and/or chronic kidney disease receiving standard of care.

Meaning:

These risk factor benefits may contribute to the overall benefit of oral semaglutide on outcomes for major adverse cardiovascular events, providing supporting evidence for the use of oral semaglutide in cardiovascular risk reduction.

Abstract (366/max 350 words)

Importance: Individuals with type 2 diabetes (T2D) are at high risk of atherosclerotic cardiovascular disease (ASCVD). In SOUL, once-daily oral semaglutide, a glucagon-like peptide-1 receptor agonist, reduced the risk of major adverse cardiovascular (CV) events by 14% versus placebo in people with T2D and ASCVD and/or chronic kidney disease (CKD), receiving standard of care (SoC). Whether and to what extent oral semaglutide modifies recognized CV risk factors in the long term is unclear.

Objective: To investigate the treatment effect of oral semaglutide versus placebo on ASCVD risk factors in SOUL.

Methods: In SOUL (double-blind, randomized, placebo-controlled), participants with T2D and ASCVD and/or CKD receiving SoC were randomized 1:1 to oral semaglutide or placebo (mean follow-up 47.5 months). These *post hoc* intention-to-treat analyses of data from SOUL assessed the treatment effect of oral semaglutide versus placebo on HbA_{1c}, body weight and blood pressure using estimated treatment differences (ETDs), and on plasma levels of high-sensitivity C-reactive protein (hsCRP) and lipids using estimated treatment ratios (ETRs).

Results: Out of all randomized participants (9650: oral semaglutide [median age 66 years; 71.5% male]; placebo [median age 66 years and 70.7% male]), 98.4% completed the trial. Early (13 weeks) improvements in HbA_{1c} (–0.87%), body weight (–2.54%), systolic blood pressure (SBP; –3.84 mmHg), pulse pressure (–3.81 mmHg), hsCRP (–18.08%), total cholesterol (TC; –7.00%), non-high-density lipoprotein cholesterol (non-HDL-c; –8.02%), high-density lipoprotein cholesterol (HDL-c; –4.49%) and triglycerides (–8.15%) were observed with oral semaglutide vs placebo and sustained over the course of the trial. Reductions in body weight were gradual across both groups. At week 156, in favor of oral semaglutide were ETDs (95% confidence interval [CI] for HbA_{1c} (–0.47%-points [–0.52; –0.42]), body weight (–3.26% [–3.55; –2.98]), SBP (–1.83 mmHg [–2.47; –1.18]), pulse pressure (–2.17 mmHg [–2.72; –1.61]), and ETRs for hsCRP (0.77 [0.74; 0.81]), TC (0.99 [0.98; 1.00], non-HDL-c (0.98 [0.97; 0.99]), HDL-c (1.01 [1.01; 1.02]) and triglycerides (0.94 [0.93; 0.96]); no significant

treatment differences were observed for low-density lipoprotein cholesterol or diastolic blood pressure.

Conclusion: Oral semaglutide demonstrated early and sustained improvements in multiple ASCVD risk factors vs placebo in high-risk participants with T2D and ASCVD and/or CKD incremental to SoC.

Introduction

Diabetes is a global health concern with an estimated prevalence among people aged 20–79 years in 2025 of 11.1% (589 million) and this figure is expected to increase to 13.0% (852.5 million) by 2050, with the overwhelming majority having type 2 diabetes (T2D).[1] Cardiovascular disease (CVD) and chronic kidney disease (CKD) are common and inter-related complications of diabetes, with around one-third of people with T2D having some type of CVD.[2,3] Atherosclerotic CVD (ASCVD) continues to be the predominant cause of morbidity and mortality in this population[4,5] and preventing CVD events is therefore a central goal in diabetes management.

The treatment paradigm for individuals with T2D has shifted from a glucose-centric approach towards a personalized approach focusing on risk mitigation for prevalent cardiovascular (CV) and kidney comorbidities, recommending newer drug classes after several CV outcome trials with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) demonstrated a reduction in CV events through mechanisms at least in part independent of their glycemic effects.[4,6-9] GLP-1 RAs may mediate these reductions through direct effects on the CV system, reducing progression of and stabilizing atherosclerotic plaques, and indirectly by improving endothelial function and by reducing inflammation, blood pressure, glycemia, body weight, and improving postprandial glucose metabolism.[10-13]

Semaglutide is a long-acting GLP-1 RA available in both an injectable and an oral formulation.[14,15] The injectable formulation has been shown to reduce the risk of CV events versus placebo in people with T2D and ASCVD or at high risk of ASCVD, and those with T2D and CKD.[16,17] The semaglutide cardiovascular outcomes trial (SOUL; NCT03914326)[18] investigated the cardiovascular efficacy of oral semaglutide, the first oral GLP-1 RA, in individuals with T2D and ASCVD and/or CKD. Treatment with oral semaglutide led to a statistically significant 14% reduction in the risk of major adverse cardiovascular events (MACE) compared with placebo.[19] Oral semaglutide also significantly reduced

glycated hemoglobin (HbA_{1c}), body weight and levels of high-sensitivity C-reactive protein (hsCRP), a marker of inflammation, compared with placebo at week 104 of SOUL.[19] However, the extent to which oral semaglutide improved other metabolic and inflammatory ASCVD risk factors in SOUL is unknown.

The aim of these *post hoc* analyses of the SOUL trial was to investigate the short term and long term treatment effects of oral semaglutide versus placebo on traditional CV risk factors (HbA_{1c}, body weight, blood pressure [BP], pulse, hsCRP and lipids), among all SOUL participants and sub-analyses among those categorized according to trial entry criteria (ASCVD only, ASCVD+CKD or CKD only).

Methods

Trial design and participant population

A detailed description of the phase 3b international, double-blind, randomized, placebo-controlled SOUL trial (NCT03914326) has been published.[19]

Eligible participants were men or women, aged ≥50 years, diagnosed with T2D, and with HbA_{1c} between 6.5% and 10.0%. Participants were also required to have at least one of the following conditions: coronary heart disease, cerebrovascular disease, symptomatic peripheral artery disease (PAD) and/or CKD. Key exclusion criteria included any of the following: myocardial infarction, stroke, hospitalization for unstable angina pectoris or transient ischemic attack within the past 60 days prior to the day of screening, planned coronary, carotid or peripheral artery revascularization known on the day of screening, heart failure presently classified as being in New York Heart Association Class IV, and/or treatment with any GLP-1 RA within 30 days before screening.

Participants, all receiving standard of care (SoC) for CV risk mitigation and for glucose management, were randomized in a 1:1 ratio to once-daily treatment with either oral semaglutide or matching placebo. Healthy lifestyle advice was not protocolized in SOUL, but recommendations for such advice in accord with regional standards were included in the SOUL SoC guidance document for

application throughout the trial period and independent of randomized treatment assignment. Full details on the trial treatments have been reported previously.[19]

The SOUL protocol (available in the additional supplementary material) was approved by the institutional review board and ethics committee for each participating center. The trial was conducted in compliance with the International Conference for Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in accordance with the Declaration of Helsinki. All the participants provided written informed consent. The trial results are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Outcomes

These *post hoc* analyses of the SOUL trial evaluated the treatment effect of oral semaglutide versus placebo on the following CV risk factors: HbA_{1c}, body weight, BP (systolic blood pressure [SBP], diastolic blood pressure [DBP], pulse pressure), pulse, plasma levels of hsCRP and lipids (total cholesterol [TC], non-high density lipoprotein cholesterol [non-HDL-c], high-density lipoprotein cholesterol [HDL-c], low-density lipoprotein cholesterol [LDL-c] and triglycerides).

Assessments were taken at baseline, and at weeks 13, 52, 104, 156 and 208 for all CV risk factors except hsCRP plasma level (done at baseline, weeks 13 and 104). Estimated treatment differences (ETDs) and/or estimated treatment ratios (ETRs) were calculated at week 13 and 156, except for hsCRP plasma level (ETR/odds ratio [OR] calculated at week 104).

Subgroup analyses

The above-mentioned CV risk factors were also assessed in subgroups by baseline presence of ASCVD, CKD or both.

Statistical methods

The analyses of CV risk factors in the overall trial population were intention-to-treat (ITT) using in-trial data and therefore included all randomized participants (full analysis set) regardless of

treatment adherence. The main ITT analysis was supplemented with analyses of the ASCVD-only, CKD-only and ASCVD+CKD subgroups based on the first on-treatment period, i.e., observation period until the first time off treatment for more than 35 days (5 times the half-life of semaglutide).[20]

ETDs/ETRs were determined using analysis of covariance (ANCOVA) models with treatment as a fixed factor and baseline value as a covariate. Before analyses, missing data were imputed as follows: the imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all participants with a measurement regardless of treatment status at week 156 (week 104 for hsCRP plasma level). The fitted models were used to impute values for participants with missing data at week 156 (week 104 for hsCRP plasma level). ORs were determined using logistic regression models with treatment and baseline category as fixed factors. Standard errors were calculated on the logarithmic scale and back-transformed to original scale using the delta-method. The complete data sets were analyzed and the results combined using Rubin's rule.[21] Mean estimates were adjusted according to observed baseline distribution. For subgroup analyses, the interaction between treatment group and subgroup was added to the models.

Results

Patient characteristics

Full details of the trial population are published.[19] In brief, 9650 individuals (**eFigure 1 in the Supplement**) were randomized (4825 in each arm) and 9495 (98.4%) participants completed the trial (attended end-of-trial visit or having died), with a mean (standard deviation [SD]) follow-up of 47.5 (10.9) months.

Most (71.1%) participants were male, and the mean (SD) age was 66.1 (7.6) years. Participant demographics and clinical characteristics including CV risk factor profile were well balanced at baseline.. The numbers of participants with ASCVD only were 2730 (56.6%) and 2748 (56.7%) in the oral semaglutide and placebo groups, respectively, while the numbers of participants with both

ASCVD and CKD was 1303 (27%) and 1317 (27.3%), and only 632 (13.1%) and 609 (12.6%) had CKD only. For the glucose-lowering and CV-related medications, the percentages of each class used at baseline were similar in both treatment groups (**Table 1**).

Data were collected from most patients for most endpoints at most timepoints, although during the COVID-19 pandemic, some site visits were converted to telephone visits or missed, accounting for majority of the missing data. As an example, 10.1% of data for body weight at week 156 were missing for the oral semaglutide arm, with 11.5% missing for the placebo arm. Similar proportions of data were missing for the other risk factors at either week 156 or week 104.

Treatment effect on CV risk factors

Blood pressure decreased over time in all participants (**Figure 1 [ITT mean values over time]; eFigure 2 [ITT and first on-treatment changes over time]**). A substantial reduction in SBP was observed by week 13 in the oral semaglutide group (–3.84 mmHg) and this was sustained throughout the trial (–3.63 mmHg at week 156) compared with a smaller and more gradual reduction in SBP with placebo. Pulse pressure also reduced substantially in the oral semaglutide group by week 13 (–3.81 mmHg), with gradual attenuation thereafter (–2.04 mmHg at week 156) and no change observed at any time point in the placebo group (**Figure 1; eFigure 2**). At week 13, there were reductions in favor of semaglutide for SBP (ETD: –3.19 mmHg [–3.76, –2.62], $P < .001$] and pulse pressure (ETD: –3.70 mmHg [–4.19, –3.21], $P < .001$). Similar reductions in favor of semaglutide were observed at week 156 for both SBP (ETD: –1.83 mmHg [–2.47; –1.18], $P < .001$) and pulse pressure (ETD: (–2.17 mmHg [–2.72; –1.61], $P < .001$), but not for DBP (ETD: 0.33 mmHg [–0.06; 0.73], $P = .10$) (**Figure 1; eFigure 2**). Similar reductions over time in pulse were observed in all participants (**eFigure 3 [ITT mean values over time, ITT and first on-treatment changes over time]**).

For plasma levels of lipids, at week 13, reductions in TC, non-HDL-c and HDL-c, were observed in all participants but were of greater magnitude in semaglutide-treated participants (**Figure 2 [ITT mean values over time]; eFigure 4 [ITT and first on-treatment changes over time]**). TC and non-HDL-c

were reduced substantially by week 13 in semaglutide-treated participants (–7.00% and –8.02%, respectively). Thereafter placebo-adjusted differences were attenuated whereas HDL-c only increased after week 13 in semaglutide-treated patients only and differences were sustained thereafter. Compared with placebo, differences were apparent at week 13 in LDL-c (oral sema: –7.53%; placebo: –1.66%) and triglycerides (oral sema: –8.15%; placebo: –1.20%). However, while these differences in triglycerides were maintained throughout the follow-ups, no differences were apparent in LDL-c from week 104 onwards (**Figure 2; eFigure 4**).

Statistically significant improvements were observed at week 13 in TC, (ETR: 0.94 [0.94; 0.95], *P* < .001), non-HDL-c (ETR: 0.93 [0.92; 0.94], *P* < .001), HDL-c (ETR: 0.97 [0.96; 0.98], *P* < .001) and triglycerides (ETR: 0.93 [0.92; 0.94], *P* < .001). Similarly at week 156, semaglutide affected statistically significant relative improvements in TC, (–4.21% from baseline; ETR: 0.99 [0.98; 1.00], *P* = .03), non-HDL-c (–6.70% from baseline; ETR: 0.98 [0.97; 0.99], *P* < .01), HDL-c (0.94% from baseline; ETR: 1.01 [1.01; 1.02], *P* < .001) and triglycerides (–11.70% from baseline; ETR: 0.94 [0.93; 0.96], *P* < .001) (**Figure 2; eFigure 4**). At week 13, there was a significant difference between treatment groups in LDL-c (ETR: 0.94 [0.93; 0.95], *P* < .001), but no difference at week 156 (ETR: 1.00 [0.98; 1.02], *P* = .87) (–7.53% and –4.22% from baseline for semaglutide at weeks 13 and 156, respectively; **Figure 2; eFigure 4**).

Mean values for $HbA_{1c,}$ hsCRP and body weight over time have been published previously.[19] Reductions from baseline in HbA_{1c} and hsCRP were observed in semaglutide-treated participants only (**eFigure 5A–5B [ITT and first on-treatment]**). For both variables, a notable reduction was observed by week 13 (–0.87%-points for HbA_{1c} and –18.08% for hsCRP) and these improvements were sustained throughout the trial (–0.61%-points for HbA_{1c} at week 156 and –21.03% for hsCRP at week 104). Body weight decreased over time in both treatment arms, with a greater reduction (–2.54% at week 13 and –5.26% at week 156) in the semaglutide arm (**eFigure 5C [ITT and first on-treatment]**). The reduction in body weight was more gradual than that of HbA_{1c} and hsCRP. At week

13, the ETD in HbA_{1c} was –0.82%-points (95% CI: –0.85; –0.79), $P < .001$; for body weight ETD was –2.28% (95% CI –2.41, –2.15), $P < .001$, with oral semaglutide versus placebo. At week 156, the ETD in HbA_{1c} was –0.47%-points (95% CI: –0.52; –0.42), $P < .001$; for body weight ETD was –3.26% (–3.55; –2.98), $P < .001$. The ETR for hsCRP at week 13 was 0.81 (0.78; 0.84), $P < .001$, and at week 104 was 0.77 (0.74; 0.81), $P < .001$, with oral semaglutide versus placebo (**eFigure 5A–5C**).

Subgroup analyses by CV risk history subgroups

For BP, there was no significant interaction between treatment and CV risk history ($P_{interaction}$ = .53 for SBP, .79 for DBP and .70 for pulse pressure; **Figure 3A**). Findings on pulse (**eFigure 6**) and lipids (**Figure 3B**) were broadly similar across the subgroups.

Among the ASCVD-only, CKD-only and ASCVD+CKD subgroups, the ETDs (95% CI) for HbA_{1c} at week 156 with oral semaglutide versus placebo were –0.54%-points (–0.60; –0.47), –0.68%-points (–0.82; –0.53) and –0.54%-points (–0.64; –0.44), respectively (**eFigure 7**). There was no significant interaction between treatment and change in HbA_{1c} ($P_{interaction}$ = .20). For hsCRP at week 104, the ETRs (95% CI) with oral semaglutide versus placebo were 0.38 (0.23; 0.61), 0.75 (0.28; 2.05), and 0.71 (0.35; 1.43), respectively (**eFigure 7**). There was no significant interaction between treatment and hsCRP ($P_{interaction}$ = .49). For body weight at week 156, the ETDs (95% CI) with oral semaglutide versus placebo were –3.17% (–3.57; –2.77), –4.76% (–5.58; –3.93) and –4.26% (–4.85; –3.67), respectively (**eFigure 7**). There was a significant interaction between treatment and body weight ($P_{interaction} < .001$).

Discussion

The results from these *post hoc* analyses of SOUL demonstrate that treatment with oral semaglutide compared with placebo in participants already receiving SoC for CV risk and glucose control resulted

in sustained improvements in recognized CV risk factors, including HbA_{1c}, body weight, hsCRP, SBP, plasma levels of TC, non-HDL-c, HDL-c and triglycerides. Importantly, site investigators were instructed to ensure that all participants' CV risk factors were managed according to local guidelines in collaboration with the participants' usual care clinicians. Such treatment effects were observed soon after initiation, except for HDL-c, sustained for at least 2 and up to 4 years (median trial duration), and were consistent across all entry criteria subgroups.

Improvements in HbA_{1c}, SBP, hsCRP, non-HDL-c and triglycerides with oral semaglutide were greatest at week 13 and sustained thereafter, whereas the decline in body weight was maximized at 52 weeks and maintained thereafter. The overall effect associated with oral semaglutide on lipid plasma levels was favorable. TC, non-HDL-c and triglyceride levels fell significantly more in the oral semaglutide group versus placebo while HDL-c levels rose, and LDL-c levels were not significantly changed. A potential concern might be that differences between the treatment groups in these risk factors could be confounded by between-group differences in the use of concomitant CV or glucose-lowering therapies, i.e. any greater glucose-, BP- or lipid-lowering effects with semaglutide might be offset, respectively, by a relatively greater use of anti-hyperglycemic, antihypertensive or lipid-lowering therapies in the placebo group. However, this does not appear to be the case, as the baseline and incident use of such drugs were remarkably consistent between the treatment groups (**Table 1**). For example, statins were used in >80% of enrolled participants, and renin-angiotensin system inhibitors in almost all. Thus, the observed differences in risk factors between groups likely represent the true treatment effects of oral semaglutide in the context of SoC. It is known that a sustained reduction of 10 mmHg in SBP is associated with an approximately 30% reduction in the 4-year risk of stroke [22] and a 20% reduction in the 4-year risk of MACE. [23] Similarly, in a meta-analysis of randomised controlled trials to determine whether intensive control of glucose reduces macrovascular events and all-cause mortality in individuals with T2D, a reduction of 0.9% in HbA_{1c} was associated with a 17% reduction in non-fatal myocardial infarction but had no significant effect on events of stroke. [24] These observations are broadly consistent with those concerning MACE in the

semaglutide CVOTs, [16,19,25] and suggest that the observed CV outcome benefits of GLP-1 RAs may derive from their effects on multiple risk factors beyond glycemia.

This study has several limitations. Firstly, the analyses were *post hoc*, not adjusted for multiplicity, and thus should be used as a prompt for further validation studies. Secondly, the demographic characteristics of this trial population are not representative of the global population, since only 28.9% of enrolled participants were women and 2.6% were Black/African American.[26] Thirdly, the impact of improved individual CV risk factors (as part of SoC) over the course of the study on MACE remains unclear. For example, if patients with higher baseline HbA_{1c} also had a higher overall baseline CV risk (such as higher LDL-c, higher blood pressure) then the differences reported herein may not be due to baseline glycemic control or glycemic improvement over the trial, but rather to a potential improvement of suboptimally controlled baseline CV risk factors. Further analyses are warranted to determine the influence of glycemic control and other individual baseline CV risk factors on MACE. Additionally, owing to the trial design, there is limited insight into treatment effects prior to week 13, and there were no measurements of waist circumference or post-baseline liver parameters. Lastly, due to the eligibility criteria, all participants had ASCVD and/or CKD, whereas in the real world, around a third of people with T2D are estimated to have ASCVD, and CKD is reported to affect approximately 40% of people with diabetes. Further investigation is needed to confirm the impact on people with T2D with less advanced disease.[2,3]

In conclusion, oral semaglutide showed early and sustained improvements up to 4 years (median trial duration) in multiple CV risk factors (HbA_{1c}, body weight, SBP, pulse, hsCRP, TC, non-HDL-c, HDL-c and triglycerides) in a large sample of high-risk patients with T2D and ASCVD and/or CKD receiving SoC. Although when assessed individually, the observed beneficial changes were relatively small in magnitude, collectively, these risk factor benefits may contribute to the overall benefit of oral semaglutide on MACE outcomes. These findings thus substantiate the evolving evidence for the use of oral semaglutide in CV risk reduction.

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Sharon L. Mulvagh, M.D.: has served as a consultant or on advisory boards for Novo Nordisk and Merck.

Silvio E. Inzucchi, M.D.: has served as a consultant or on advisory boards for Novo Nordisk, AstraZeneca, Boehringer Ingelheim, Merck, Pfizer and Bayer. He has given lectures sponsored by AstraZeneca and Boehringer Ingelheim/Lilly. He declares royalties from McGraw Hill and Wolters Kluwer Health and support for attending meetings and/or travel from Novo Nordisk, AstraZeneca, Boehringer Ingelheim/Lilly and Bayer.

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Data sharing statement

De-identified participant-level data will be made available on a specialized data platform following completion of the research and approval of the product and product use in both the EU and the USA. The clinical study report will be made available following completion of the research and approval of the product and product use in both the EU and the USA. Data will be shared with bona fide researchers submitting a research proposal requesting access to data for research use, as approved

by the Institutional Review Board. The access request proposal form and full detail of access criteria can be found at www.novonordisk-trials.com.

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Table 1. Participant demographics and characteristics at baseline.

	Oral semaglutide				Placebo			
	FAS (n = 4825)	**ASCVD-only (n = 2730)**	**CKD-only (n = 632)**	**ASCVD+CKD (n = 1303)**	**FAS (n = 4825)**	**ASCVD-only (n = 2739)**	**CKD-only (n = 609)**	**ASCVD+CKD (n = 1317)**
Age, years	66 (61; 72)	64 (59; 70)	69 (63; 74)	69 (63; 73)	66 (61; 72)	65 (59; 70)	69 (63; 74)	68 (63; 73)
Sex, n (%)								
Male	3449 (71.5)	2107 (77.2)	340 (53.8)	911 (69.9)	3411 (70.7)	2059 (75.2)	306 (50.2)	957 (72.7)
Female	1376 (28.5)	623 (22.8)	292 (46.2)	392 (30.1)	1414 (29.3)	680 (24.8)	303 (49.8)	360 (27.3)
Race, n (%)								
African American/Black	124 (2.6)	53 (1.9)	32 (5.1)	33 (2.5)	128 (2.7)	53 (1.9)	40 (6.6)	34 (2.6)
American Indian or Alaska Native	7 (0.1)	5 (0.2)	2 (0.3)	0 (0.0)	12 (0.2)	4 (0.1)	3 (0.5)	4 (0.3)
Asian	1134 (23.5)	659 (24.1)	183 (29.0)	260 (20.0)	1121 (23.2)	642 (23.4)	173 (28.4)	266 (20.2)
Native Hawaiian/ Pacific Islander	4 (<0.1)	2 (<0.1)	0 (0.0)	1 (<0.1)	5 (0.1)	1 (<0.1)	2 (0.3)	1 (<0.1)
Not reported	44 (0.9)	23 (0.8)	10 (1.6)	11 (0.8)	46 (1.0)	32 (1.2)	6 (1.0)	7 (0.5)
White	3327 (69.0)	1886 (69.1)	376 (59.5)	955 (73.3)	3321 (68.8)	1908 (69.7)	350 (57.5)	965 (73.3)

Other*	185 (3.8)	102 (3.7)	29 (4.6)	43 (3.3)	192 (4.0)	99 (3.6)	35 (5.7)	40 (3.0)
Ethnicity, n (%)								
Hispanic/Latino	674 (14.0)	347 (12.7)	109 (17.2)	171 (13.1)	706 (14.6)	364 (13.3)	117 (19.2)	186 (14.1)
Body weight, kg	85.7 (74.0; 98.9)	85.5 (74.2; 98.5)	82.8 (71.2; 96.5)	88.1 (75.2; 100.0)	86.3 (74.4; 100.0)	86.4 (74.5; 99.3)	83.9 (73.5; 97.9)	87.0 (75.2; 102.4)
BMI, kg/m^2	30.3 (26.9; 34.2)	29.8 (26.7; 33.7)	30.4 (26.8; 35.1)	31.3 (27.3; 35.3)	30.4 (27.0; 34.5)	30.0 (26.8; 34.0)	31.2 (27.5; 35.5)	30.9 (27.3; 35.4)
HbA_{1c}, mmol/mol	61.8 (54.1; 71.6)	60.7 (54.1; 71.6)	60.7 (54.1; 69.4)	61.8 (55.2; 71.6)	61.8 (54.1; 70.5)	60.7 (54.1; 71.6)	61.8 (54.1; 69.4)	61.8 (55.2; 70.5)
HbA_{1c}, %	7.8 (7.1; 8.7)	7.7 (7.1; 8.7)	7.7 (7.1; 8.5)	7.8 (7.2; 8.7)	7.8 (7.1; 8.6)	7.7 (7.1; 8.7)	7.8 (7.1; 8.5)	7.8 (7.2; 8.6)
Duration of diabetes, years	14.7 (9.0; 20.8)	13.1 (7.9; 19.8)	16.0 (10.7; 21.8)	16.0 (10.9; 22.5)	14.6 (8.9; 20.8)	13.1 (7.7; 19.8)	16.6 (10.9; 22.8)	15.9 (10.8; 22.0)
History of CVD, n (%)								
Coronary artery disease	3406 (70.6)	2288 (83.8)	-	1074 (82.4)	3415 (70.8)	2304 (84.1)	-	1085 (82.4)
Cerebrovascular disease	1026 (21.3)	649 (23.8)	-	363 (27.9)	1016 (21.1)	664 (24.2)	-	342 (26.0)
Prior MI or stroke	2522 (52.3)	1707 (62.5)	-	780 (59.9)	2474 (51.3)	1714 (62.6)	-	738 (56.0)
Peripheral arterial disease	771 (16.0)	438 (16.0)	-	326 (25.0)	744 (15.4)	394 (14.4)	-	346 (26.3)
Heart failure	1105 (22.9)	568 (20.8)	41 (6.5)	475 (36.5)	1124 (23.3)	581 (21.2)	56 (9.2)	470 (35.7)

CKD, n (%)[†]	2041 (42.3)	-	632 (100)	1303 (100)	2051 (42.5)	-	609 (100)	1317 (100)
Hypertension, n (%)	4378 (90.7)	-	-	-	4381 (90.8)	-	-	-
Current smoking, n (%)	545 (11.3)	373 (13.7)	58 (9.2)	100 (7.7)	584 (12.1)	369 (13.5)	52 (8.5)	147 (11.2)
Vital signs								
	Oral semaglutide				**Placebo**			
	FAS (n = 4825)	**ASCVD-only (n = 2730)**	**CKD-only (n = 632)**	**ASCVD+CKD (n = 1303)**	**FAS (n = 4825)**	**ASCVD-only (n = 2739)**	**CKD-only (n = 609)**	**ASCVD+CKD (n = 1317)**
Systolic blood pressure, mmHg	134 (124; 144)	134 (123; 143)	136 (125; 147)	135 (124; 145)	135 (124; 144)	133 (123; 143)	137 (126; 147)	136 (125; 146)
Diastolic blood pressure, mmHg	77 (70; 83)	78 (70; 84)	76 (70; 82)	76 (68; 82)	78 (70; 83)	78 (70; 83)	77 (70; 83)	76 (69; 83)
Pulse — beats/min	72 (65; 80)	72 (65; 80)	75 (66; 83)	72 (64; 78)	72 (65; 80)	72 (65; 80)	74 (66; 82)	72 (64; 79)
Lipids, mmol/l								
Total cholesterol	3.9 (3.3; 4.6)	3.8 (3.2; 4.5)	4.1 (3.5; 4.9)	3.9 (3.3; 4.6)	3.8 (3.3; 4.6)	3.8 (3.2; 4.5)	4.0 (3.5; 4.8)	3.8 (3.3; 4.6)
Non-HDL-c	2.7 (2.2; 3.5)	2.7 (2.2; 3.4)	2.9 (2.4; 3.6)	2.8 (2.3; 3.5)	2.7 (2.2; 3.5)	2.7 (2.2; 3.4)	2.9 (2.4; 3.6)	2.7 (2.2; 3.6)
HDL-c	1.1 (0.9; 1.3)	1.1 (0.9; 1.3)	1.1 (0.9; 1.3)	1.1 (0.9; 1.2)	1.1 (0.9; 1.3)	1.1 (0.9; 1.2)	1.1 (0.9; 1.3)	1.0 (0.9; 1.2)
LDL-c	1.9 (1.4; 2.5)	1.8 (1.4; 2.4)	2.0 (1.6; 2.6)	1.9 (1.4; 2.5)	1.9 (1.4; 2.4)	1.8 (1.4; 2.4)	2.0 (1.5; 2.5)	1.8 (1.4; 2.5)
Triglycerides	1.8 (1.3; 2.5)	1.7 (1.2; 2.4)	1.9 (1.4; 2.7)	1.8 (1.3; 2.5)	1.8 (1.3; 2.5)	1.7 (1.2; 2.4)	1.9 (1.3; 2.6)	1.9 (1.3; 2.7)

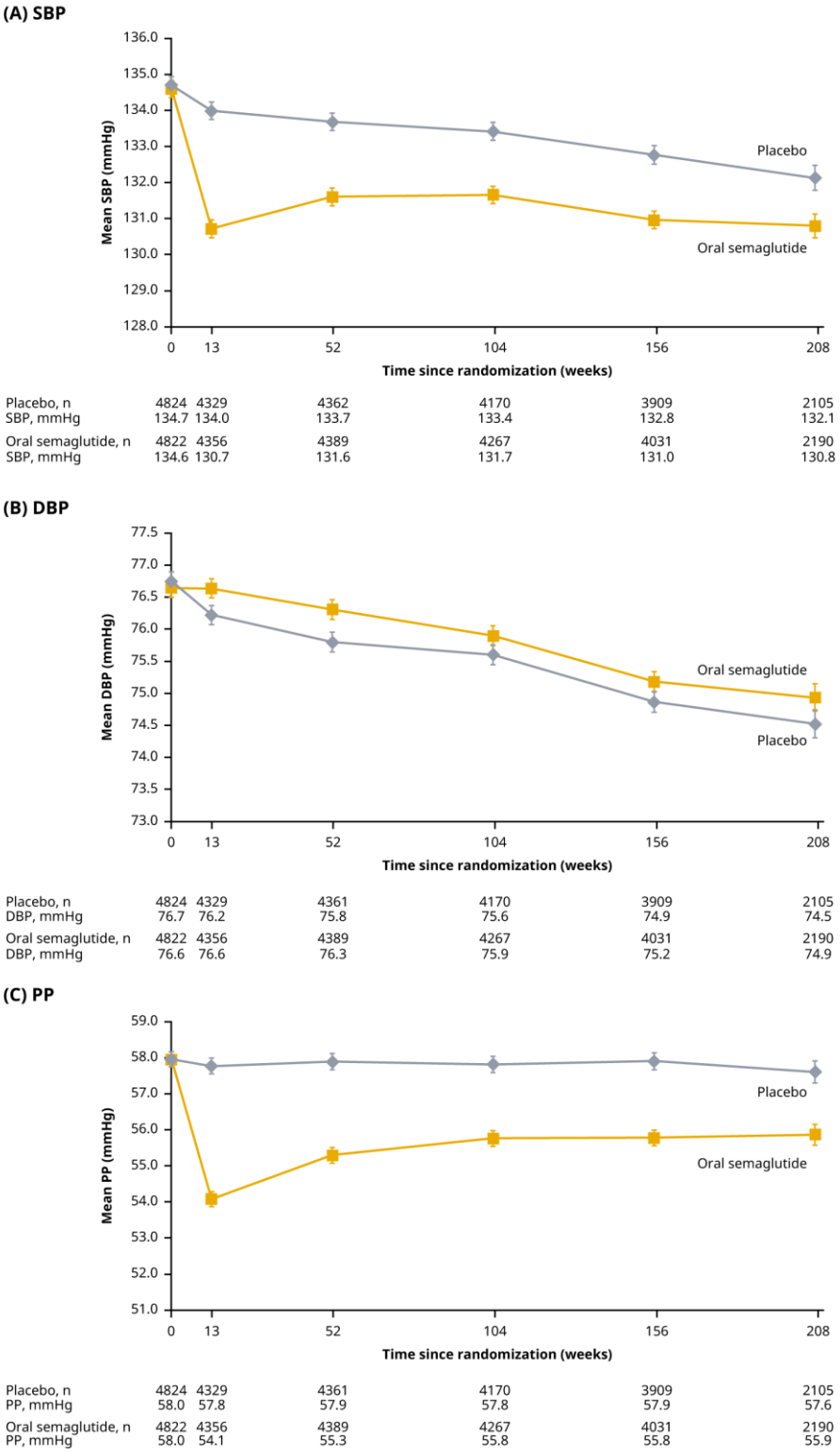
hsCRP, mg/l	2.0 (0.9; 4.3	1.8 (0.8; 3.9)	2.3 (1.1; 4.9)	2.2 (1.0; 4.9)	2.0 (0.9; 4.5)	1.7 (0.8; 3.8)	2.6 (1.2; 4.9)	2.3 (1.0; 5.4)
eGFR, ml/min/1.73 m^2 (CKD-EPI method[1])[†]	77.0 (56.0; 93.0)	90.0 (77.0; 98.0)	52.0 (42.0; 61.0)	57.5 (44.0; 73.5)	76.0 (56.0; 92.0)	89.0 (76.0; 97.0)	51.0 (41.0; 62.0)	57.0 (44.0; 73.0)
eGFR, ml/min/1.73 m^2, n (%)[‡]								
End-stage kidney disease (<15)	7 (0.1)	0 (0.0)	3 (0.5)	4 (0.3)	4 (<0.1)	0 (0.0)	1 (0.2)	3 (0.2)
≥15 to <30	113 (2.3)	6 (0.2)	39 (6.2)	54 (4.1)	114 (2.4)	6 (0.2)	38 (6.2)	63 (4.8)
≥30 to <45	474 (9.8)	21 (0.8)	151 (23.9)	269 (20.6)	475 (9.8)	17 (0.6)	154 (25.3)	265 (20.1)
≥45 to <60	811 (16.8)	132 (4.8)	256 (40.5)	380 (29.2)	818 (17.0)	138 (5.0)	243 (39.9)	381 (28.9)
≥60 to <90	1845 (38.2)	1190 (43.6)	163 (25.8)	446 (34.2)	1903 (39.4)	1246 (45.5)	157 (25.8)	459 (34.9)
≥90	1531 (31.7)	1357 (49.7)	12 (1.9)	139 (10.7)	1472 (30.5)	1310 (47.8)	12 (2.0)	134 (10.2)
Cardiovascular-related medications at baseline, n (%)								
Lipid-lowering medications	4275 (88.6)	2481 (90.9)	513 (81.2)	1148 (88.1)	4297 (89.1)	2504 (91.5)	485 (79.6)	1184 (89.9)
Antiplatelet medications	3718 (77.1)	2374 (87.0)	223 (35.3)	1051 (80.7)	3727 (77.2)	2397 (87.5)	204 (33.5)	1055 (80.1)
Beta-blockers	3104 (64.3)	1858 (68.1)	212 (33.5)	951 (73.0)	3097 (64.2)	1889 (69.0)	214 (35.1)	922 (70.0)
Diuretics	2006 (41.6)	935 (34.2)	296 (46.8)	691 (53.0)	2058 (42.7)	987 (36.0)	303 (49.8)	697 (52.9)
ACE inhibitors	1990 (41.2)	1228 (45.0)	189 (29.9)	507 (38.9)	1992 (41.3)	1269 (46.3)	186 (30.5)	478 (36.3)
ARBs	1814 (37.6)	887 (32.5)	315 (49.8)	544 (41.7)	1883 (39.0)	905 (33.1)	293 (48.1)	609 (46.2)

Calcium channel blockers	1762 (36.5)	870 (31.9)	282 (44.6)	537 (41.2)	1810 (37.5)	921 (33.6)	249 (40.9)	564 (42.8)
	Oral semaglutide				**Placebo**			
	FAS (n = 4825)	**ASCVD-only (n = 2730)**	**CKD-only (n = 632)**	**ASCVD+CKD (n = 1303)**	**FAS (n = 4825)**	**ASCVD-only (n = 2739)**	**CKD-only (n = 609)**	**ASCVD+CKD (n = 1317)**
Antithrombotic medications	458 (9.5)	228 (8.4)	38 (6.0)	179 (13.7)	464 (9.6)	233 (8.5)	39 (6.4)	183 (13.9)
ARNIs	17 (0.4)	11 (0.4)	2 (0.3)	4 (0.3)	18 (0.4)	8 (0.3)	1 (0.2)	9 (0.7)
Glucose-lowering medication at baseline, n (%)								
Metformin	3651 (75.7)	2304 (84.4)	395 (62.5)	837 (64.2)	3675 (76.2)	2303 (84.1)	397 (65.2)	860 (65.3)
Insulins	2476 (51.3)	1262 (46.2)	337 (53.3)	799 (61.3)	2413 (50.0)	1240 (45.3)	331 (54.4)	760 (57.7)
Sulfonylureas	1386 (28.7)	805 (29.5)	182 (28.8)	352 (27.0)	1434 (29.7)	829 (30.3)	183 (30.0)	367 (27.9)
SGLT2 inhibitors	1296 (26.9)	838 (30.7)	125 (19.8)	308 (23.6)	1300 (26.9)	813 (29.7)	130 (21.3)	334 (25.4)
DPP-4 inhibitors	1094 (22.7)	554 (20.3)	215 (34.0)	295 (22.6)	1141 (23.6)	589 (21.5)	194 (31.9)	330 (25.1)
Thiazolidinediones	225 (4.7)	103 (3.8)	52 (8.2)	59 (4.5)	188 (3.9)	105 (3.8)	39 (6.4)	36 (2.7)
α-glucosidase inhibitors	87 (1.8)	41 (1.5)	20 (3.2)	24 (1.8)	114 (2.4)	58 (2.1)	20 (3.3)	29 (2.2)
GLP-1 RAs and GIP GLP-1 RAs	0 (0.0)	0 (0.0)	-	0 (0.0)	2 (<0.1)	1 (<0.1)	-	1 (<0.1)
Other	70 (1.5)	30 (1.1)	14 (2.2)	22 (1.7)	53 (1.1)	22 (0.8)	9 (1.5)	21 (1.6)

Data are median (interquatile range) unless otherwise stated. CKD was defined as eGFR <60 ml/min/1.73 m^2. *Reflects participants in France, where collecting data on race and ethnicity is prohibited by law.†Reported by the investigators at screening. ‡Measured at randomization.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DDP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; FAS, full analysis set; GIP, gastric inhibitory polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated hemoglobin; HDL-c, high-density lipoprotein cholesterol; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; LDL-c, low-density lipoprotein cholesterol; MI, myocardial infarction; SGLT2, sodium-glucose co-transporter-2

Figure 1. Mean blood pressure values over time (full analysis set)



Data were analyzed according to the intention-to-treat principle. Error bars are standard error of the mean.

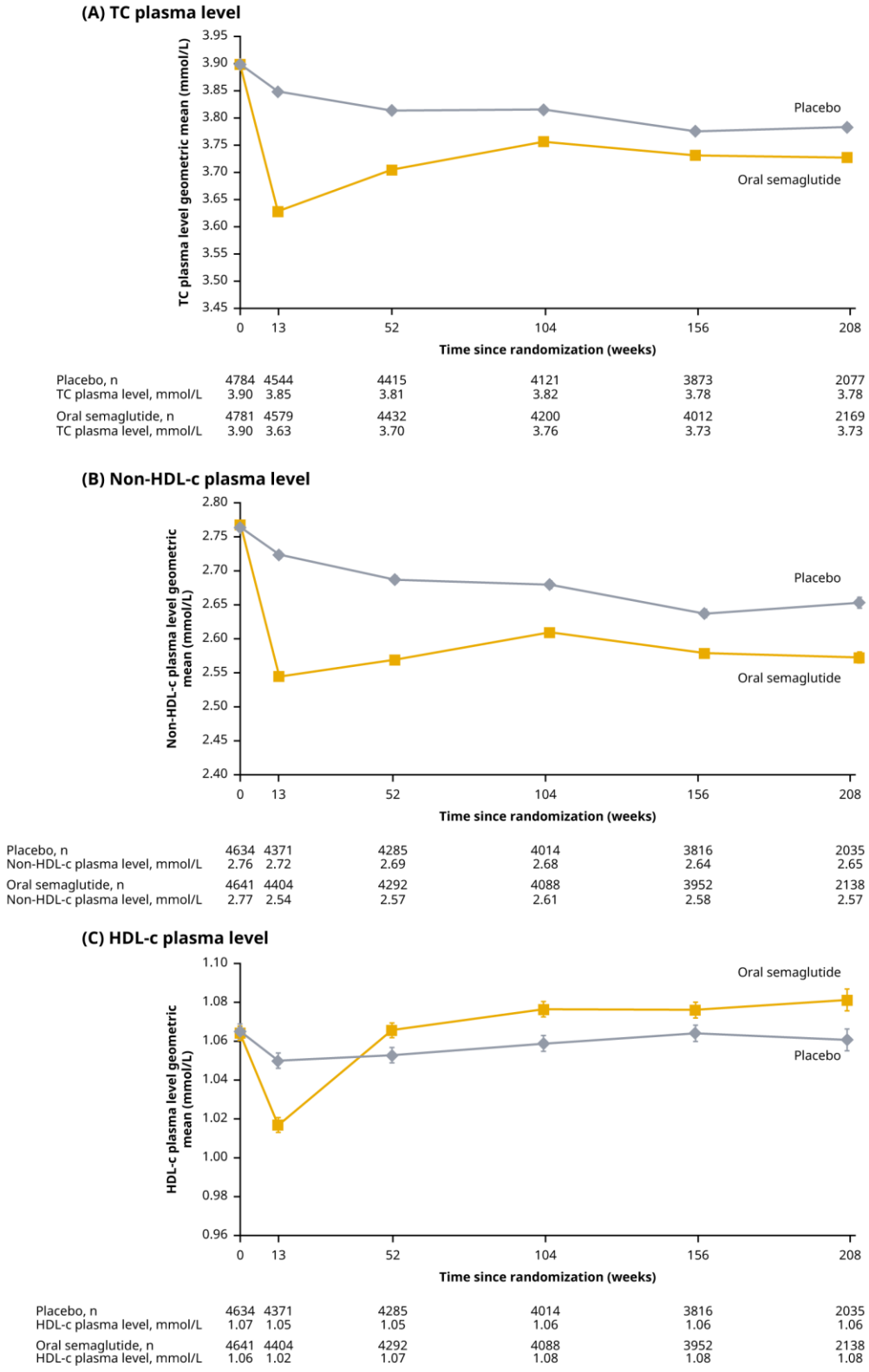
The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate.

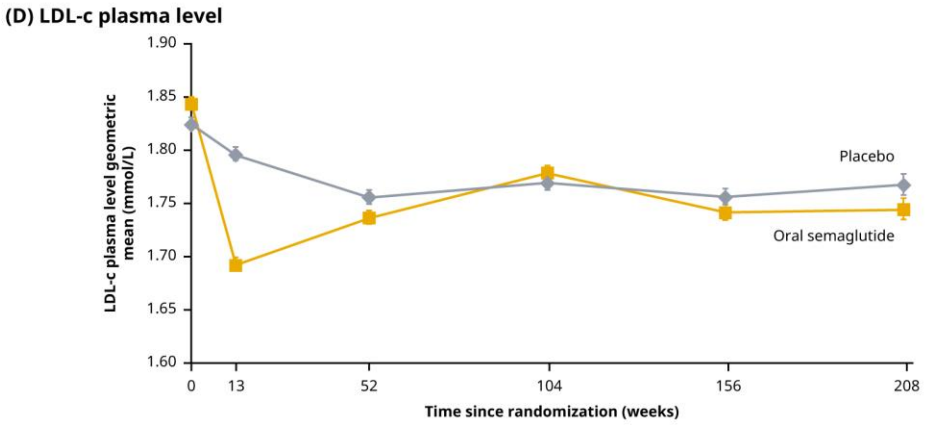
Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done

separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Mean estimates were adjusted according to observed baseline distribution.

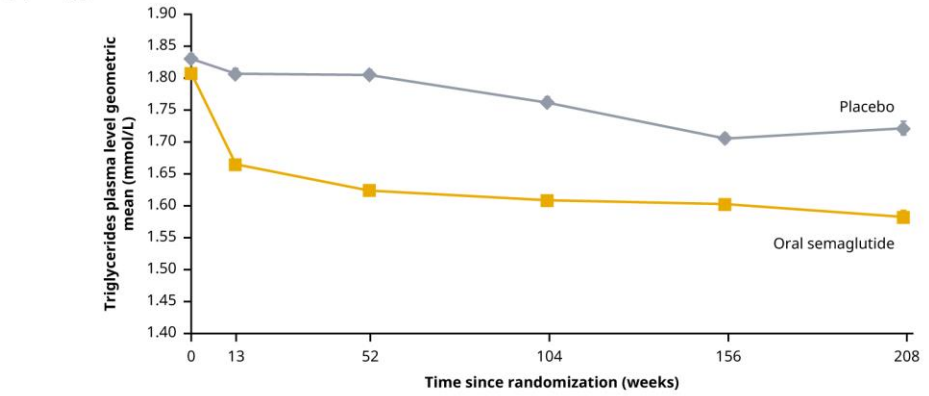
ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; PP, pulse pressure; SBP, systolic blood pressure.

Figure 2. Geometric mean plasma levels of lipids over time (full analysis set)





Placebo, n	4404	4152	4077	3837	3662	1949
LDL-c plasma level, mmol/L	1.82	1.80	1.76	1.77	1.76	1.77
Oral semaglutide, n	4395	4246	4147	3956	3840	2074
LDL-c plasma level, mmol/L	1.84	1.69	1.74	1.78	1.74	1.74



Placebo, n	4756	4532	4397	4111	3869	2071
Triglycerides plasma level, mmol/L	1.83	1.81	1.80	1.76	1.71	1.72
Oral semaglutide, n	4758	4563	4417	4187	4009	2167
Triglycerides plasma level, mmol/L	1.81	1.66	1.62	1.61	1.60	1.58

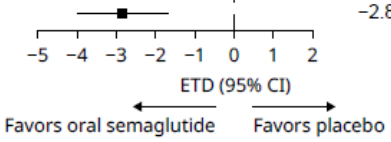
Observed data from the in-trial period. Error bars are standard error of the mean. The effects were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed 500 times. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Mean estimates were adjusted according to observed baseline distribution.

ANCOVA, analysis of covariance; CI, confidence interval; ETR, estimated treatment ratio; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol.

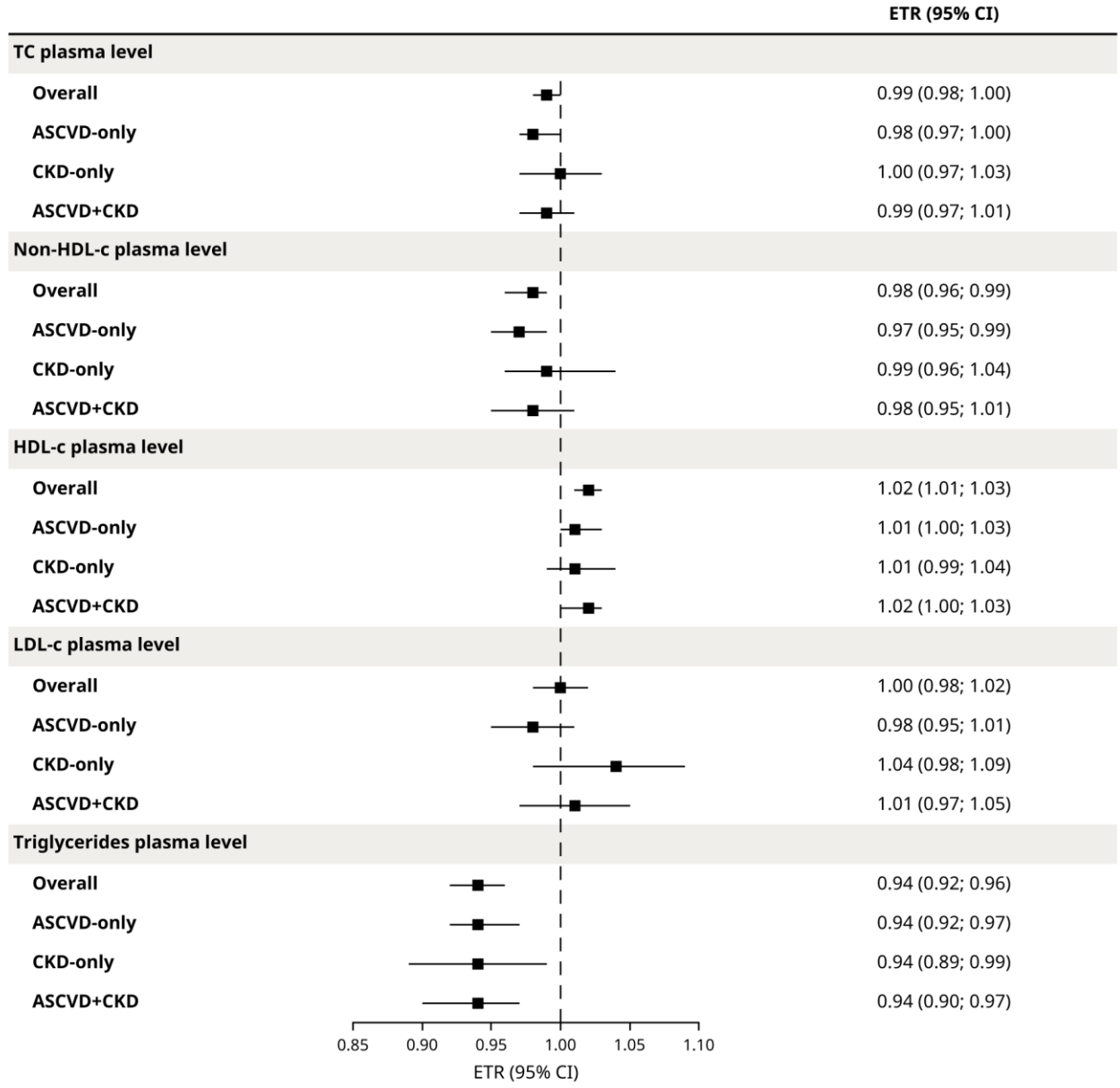
Figure 3. Treatment difference in change in blood pressure and lipid plasma level ratio (first on-treatment)

(A) Change in blood pressure with oral semaglutide versus placebo

	Number of participants		ETD, mmHg (95% CI)	*p*-value	$p_{interaction}$
	Oral semaglutide (N=4825)	Placebo (N=4825)			
SBP					
Overall	4438	4369	−2.16 (−2.86; −1.47)	<.001	0.53
ASCVD-only	2535	2528	−1.89 (−2.78; −0.99)	<.001	
CKD-only	596	563	−2.68 (−4.54; −0.82)	.005	
ASCVD+CKD	1161	1134	−2.68 (−4.00; −1.36)	<.001	
DBP					
Overall	4438	4369	0.38 (−0.06; 0.81)	.09	0.79
ASCVD-only	2535	2528	0.51 (−0.05; 1.06)	.07	
CKD-only	596	563	0.34 (−0.81; 1.49)	.56	
ASCVD+CKD	1161	1134	0.17 (−0.65; 0.99)	.69	
PP					
Overall	4438	4369	−2.55 (−3.15; −1.95)	<.001	0.70
ASCVD-only	2535	2528	−2.41 (−3.18; −1.64)	<.001	
CKD-only	596	563	−3.06 (−4.66; −1.45)	<.001	
ASCVD+CKD	1161	1134	−2.84 (−3.98; −1.69)	<.001	



(B) Lipid plasma levels ratio to baseline with oral semaglutide versus placebo



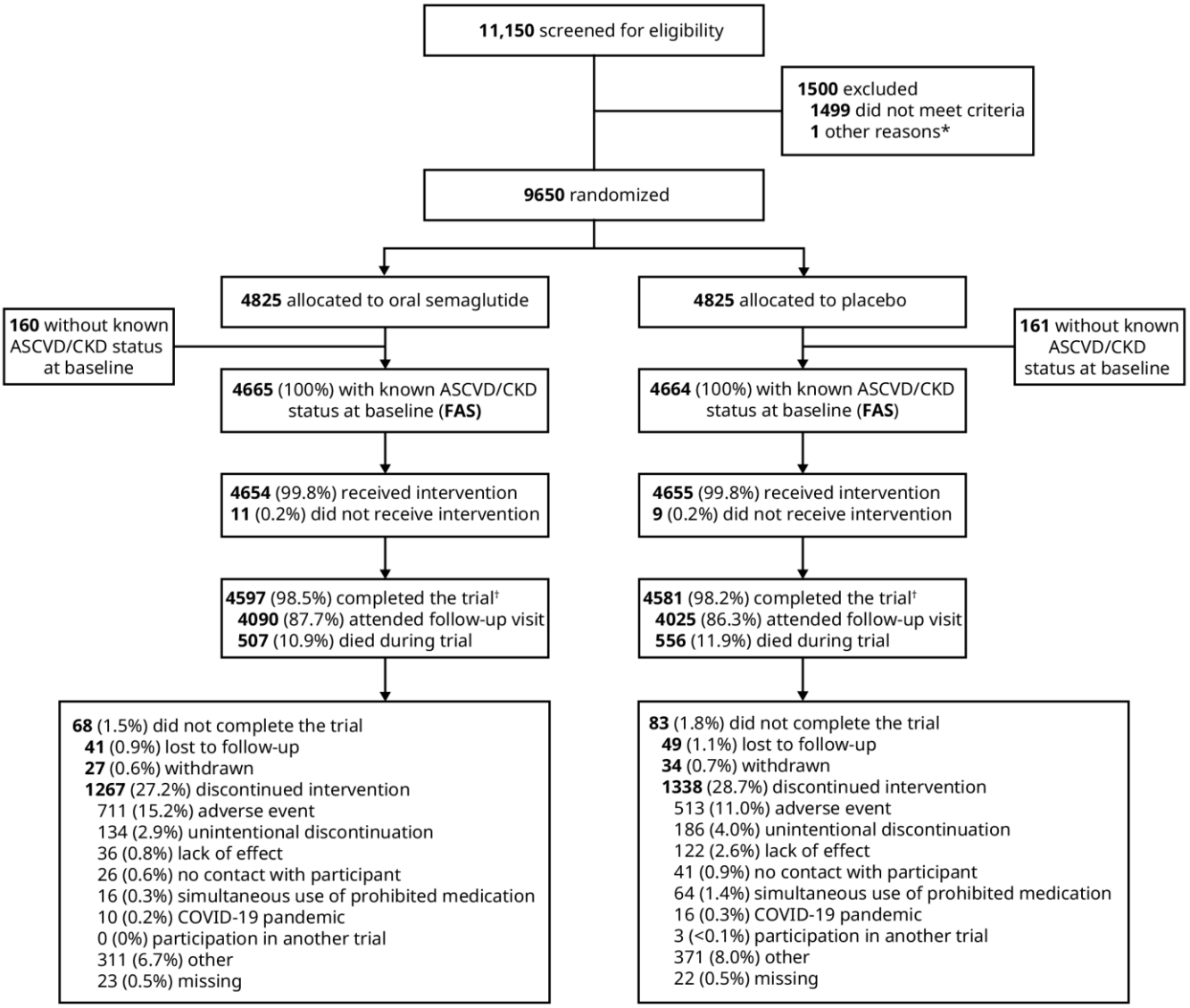
The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Decreases in plasma levels of TC, non-HDL-c, LDL-c, and triglycerides and increases in plasma levels of HDL-c favored oral semaglutide.

ANCOVA, analysis of covariance; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; ETD, estimated treatment difference; ETR, estimated treatment ratio; HDL-c, high-density lipoprotein cholesterol; LDL-c, low density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.

SUPPLEMENTARY MATERIAL

Contents:

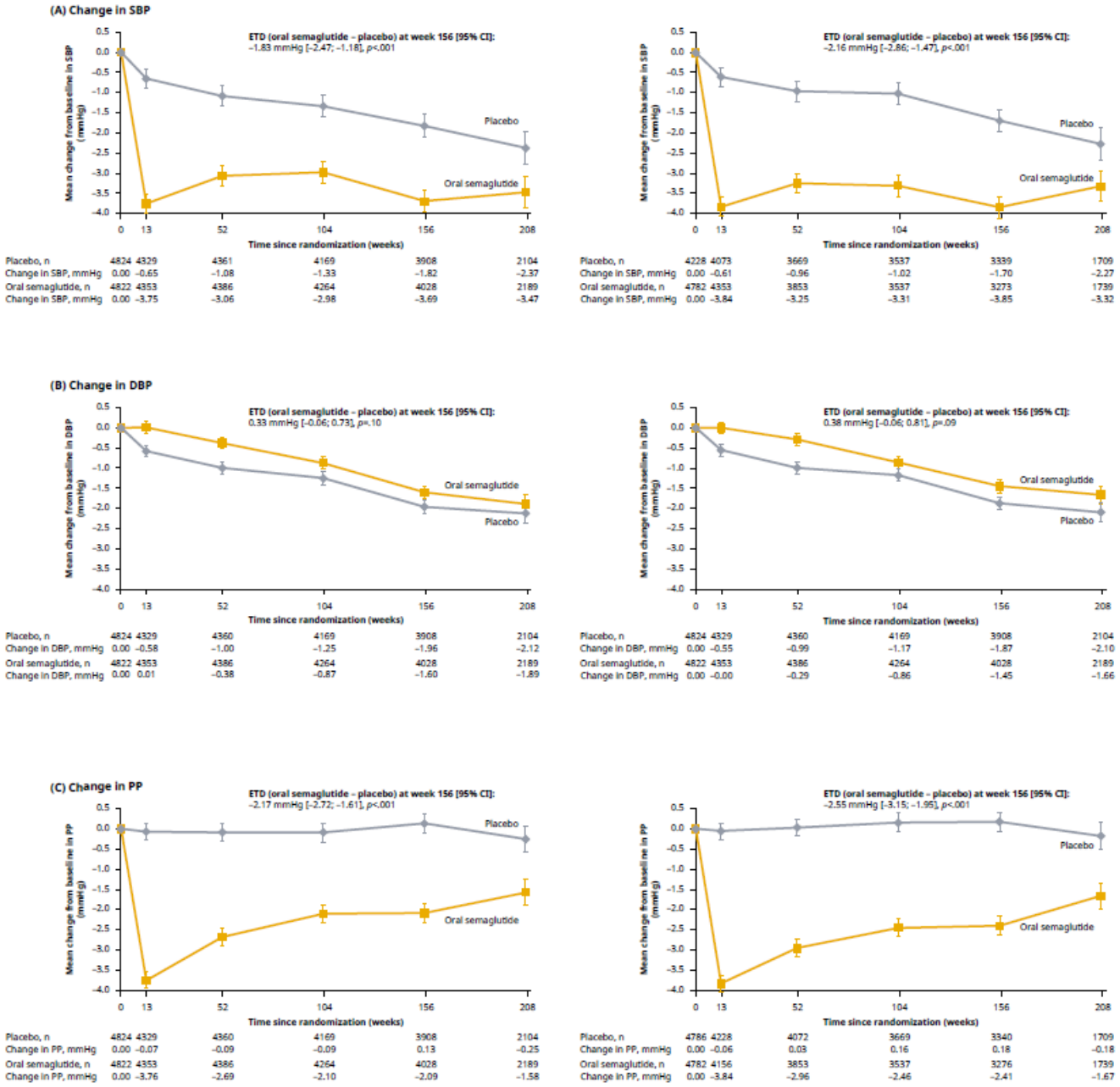
eFigure 1. Disposition of participants in SOUL and the current study subgroup analyses



*Removed due to participant randomized more than once. †Participants who attended the follow-up visit or died during trial

ASCVD, atherosclerotic cardiovascular disease; CKD, chronic kidney disease; FAS, full analysis set

eFigure 2. Change from baseline in blood pressure over time, in-trial, and first on-treatment analysis

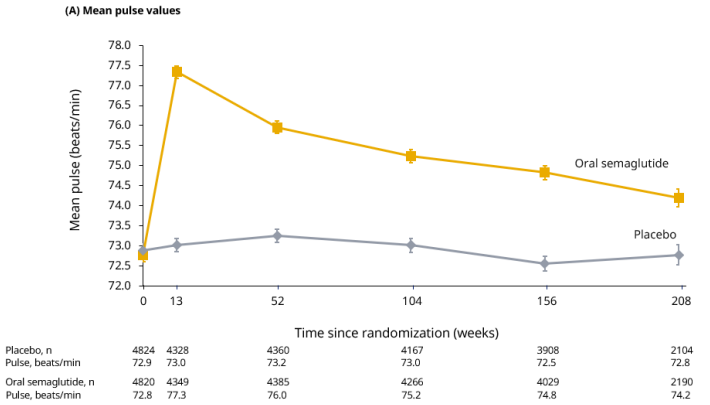


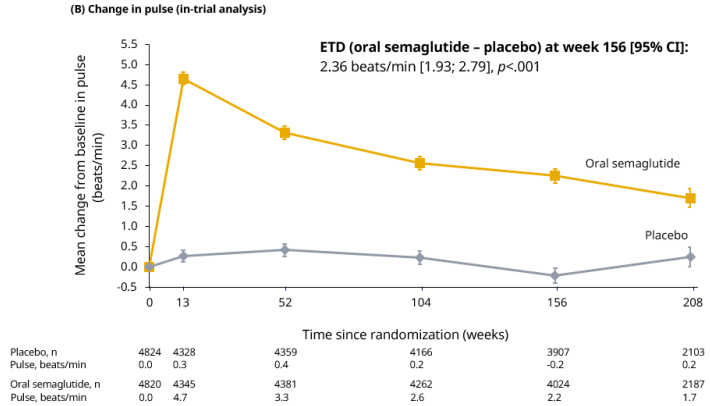
Left panel: in-trial analysis (ITT). Right panel: first on-treatment analysis (Per Protocol).

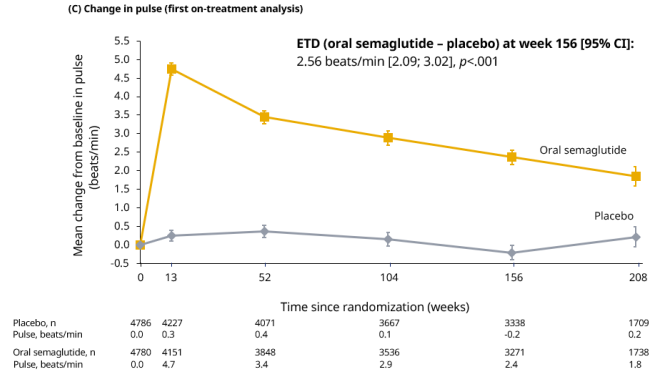
Error bars are standard error of the mean. The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Mean estimates were adjusted according to observed baseline distribution.

ANCOVA, analysis of covariance; CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; ITT, intention to treat; PP, pulse pressure; SBP, systolic blood pressure.

eFigure 3. Mean pulse values over time (FAS) and change from baseline in pulse over time (in-trial [ITT] and first on-treatment [per protocol] analysis)





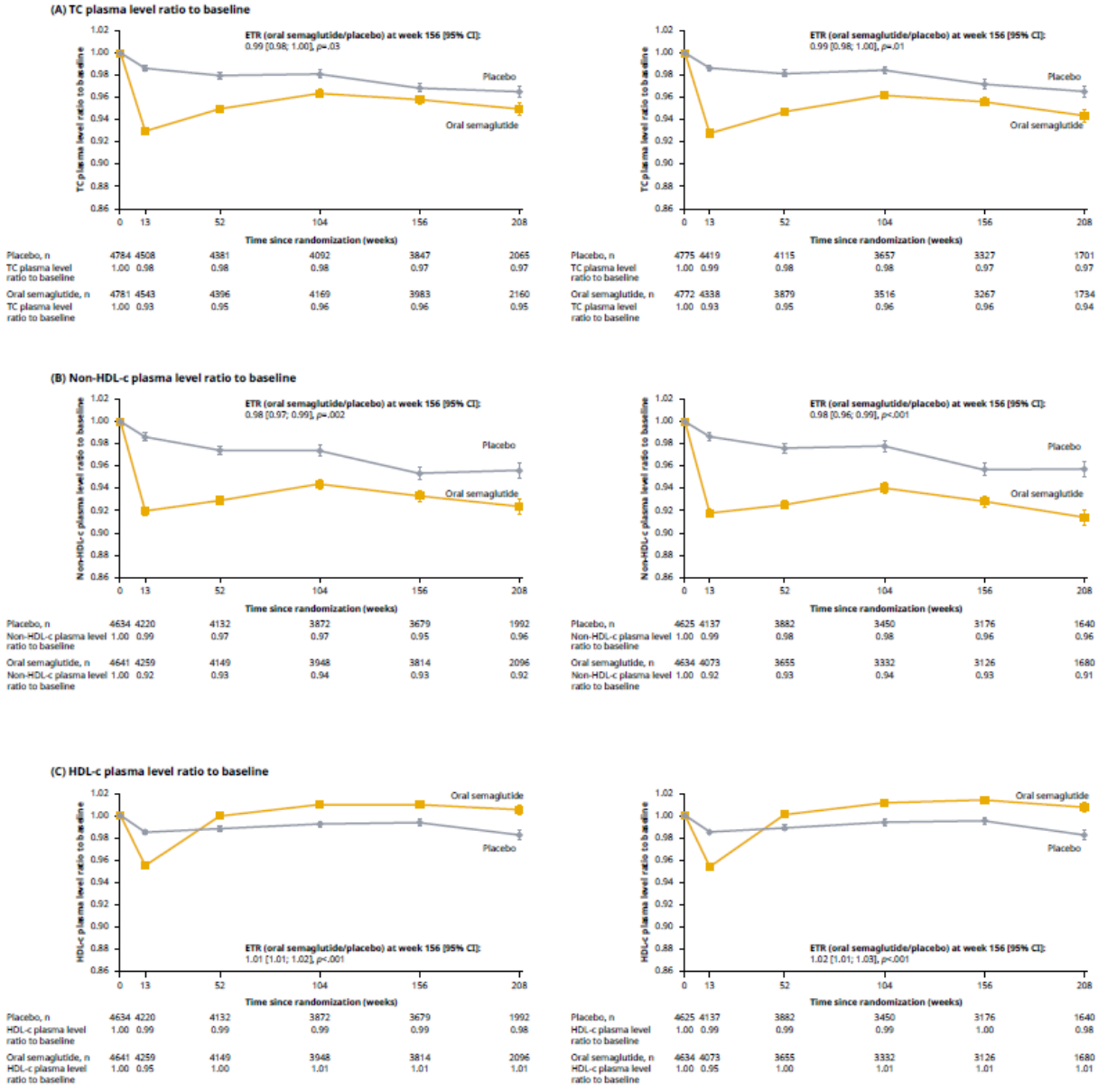


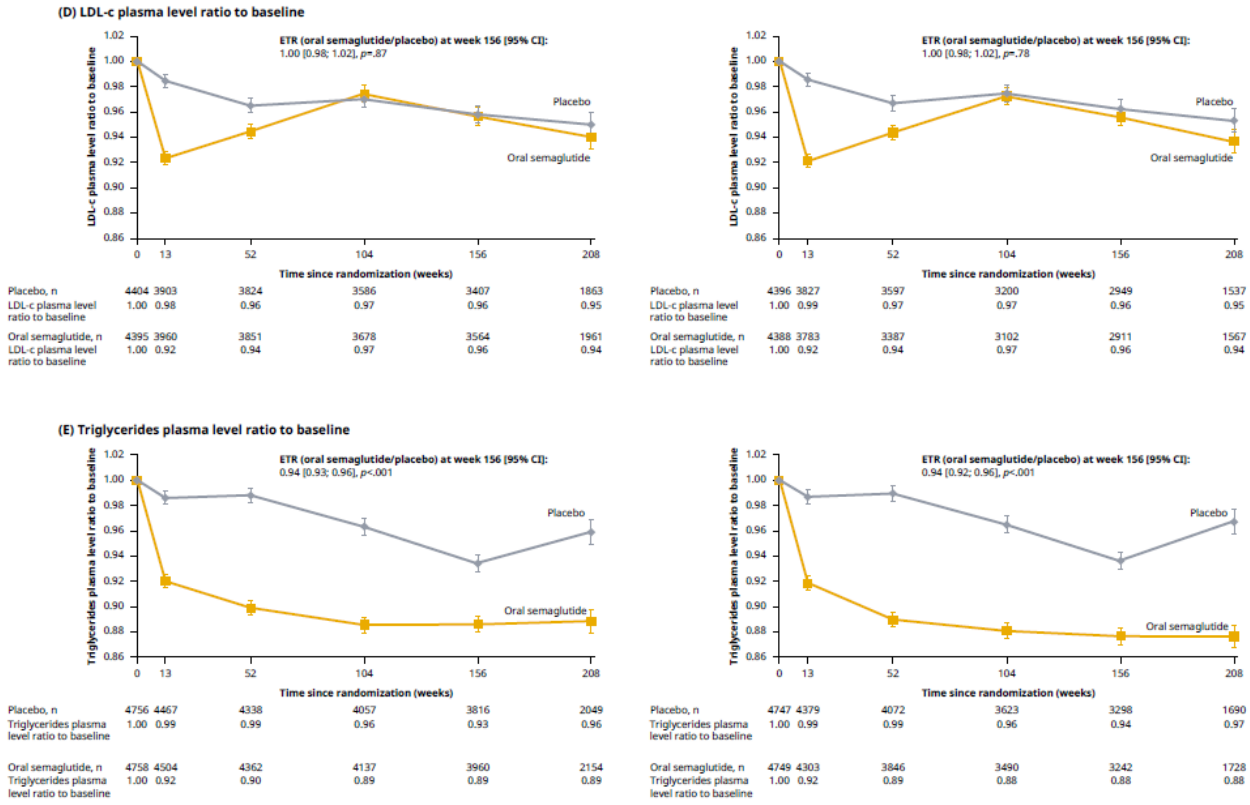
Error bars are standard error of the mean. The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Mean estimates were

adjusted according to observed baseline distribution.

ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; ITT, intention to treat; FAS, full analysis set.

eFigure 4. Change in lipids ratio to baseline over time, in-trial, and first on-treatment analysis

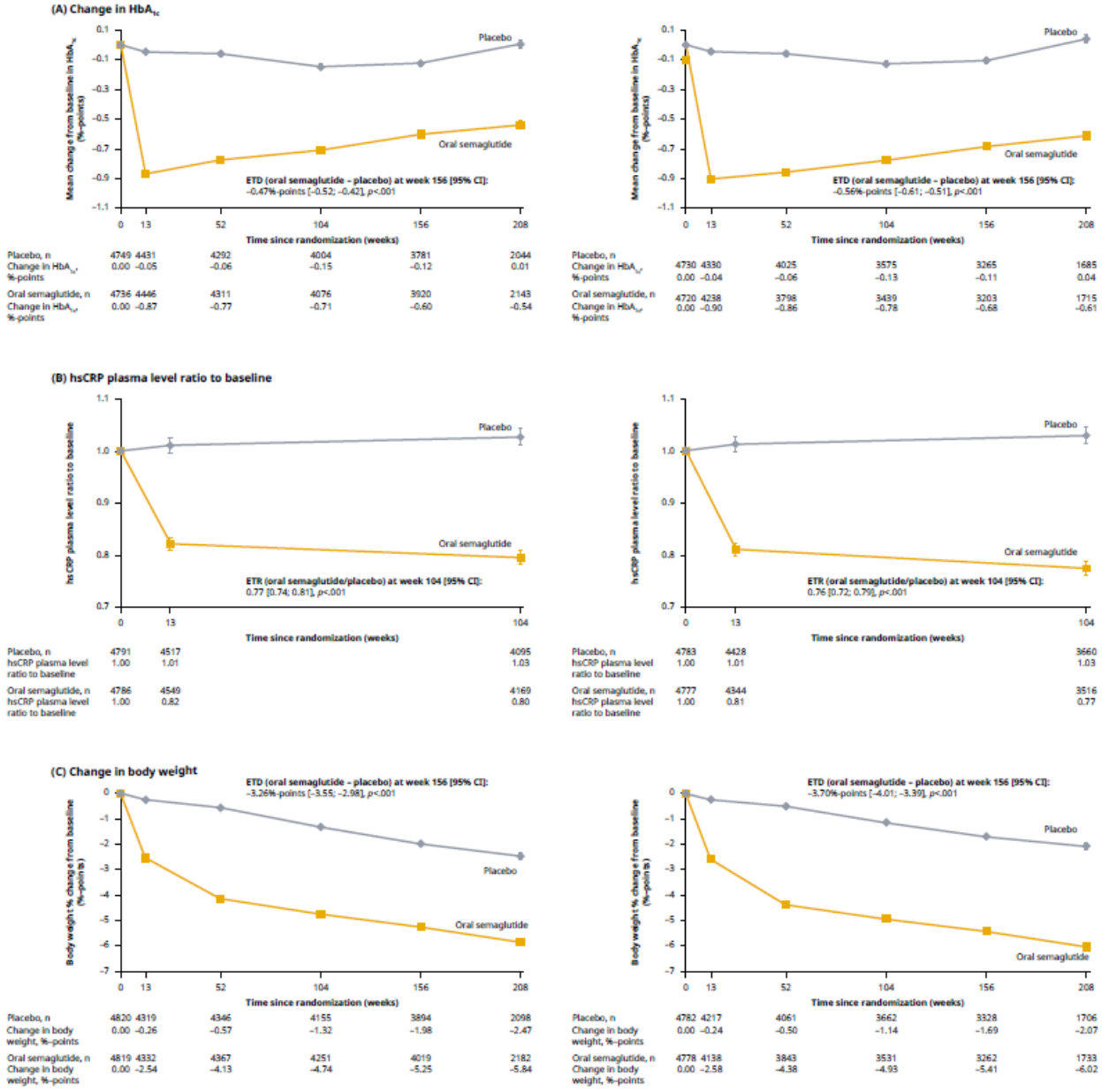




Left panel: in-trial analysis (ITT). Right panel: first on-treatment analysis (Per Protocol).Changes from baseline in plasma levels of lipids are reported on the log-scale and given as a ratio to baseline. Error bars are standard error of the mean. The effects were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed 500 times. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Mean estimates were adjusted according to observed baseline distribution.

ANCOVA, analysis of covariance; CI, confidence interval; ETR, estimated treatment ratio; HDL-c, high-density lipoprotein cholesterol; ITT, intention to treat; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol.

eFigure 5. Changes in the key measures of metabolism and inflammation over time, in-trial, and first on-treatment analysis



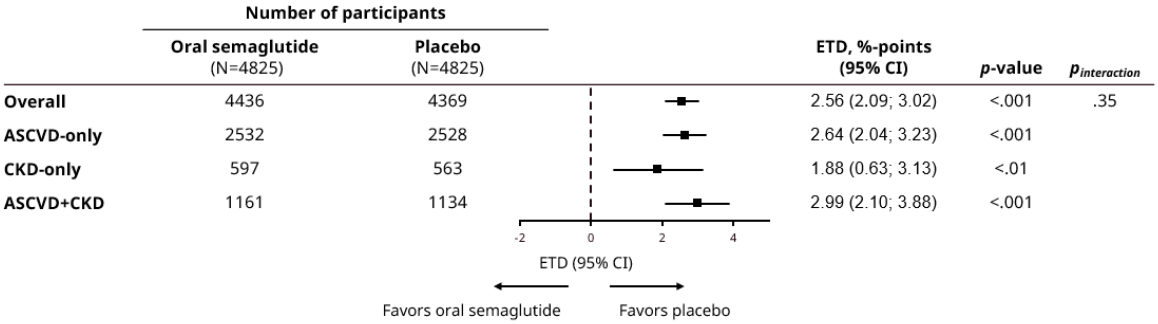
Left panel: in-trial analysis (ITT). Right panel: first on-treatment analysis (Per Protocol).

Error bars are ± standard error of the mean. The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed 500 times. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all

patients with a measurement regardless of treatment status at week 156 (or week 104 for hsCRP). The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule. Mean estimates were adjusted according to observed baseline distribution.

ANCOVA, analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated hemoglobin, hsCRP, high-sensitivity C-reactive protein; ITT, intention to treat.

eFigure 6. Treatment differences in pulse (first on-treatment) at week 156



The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156. The fitted model was used to impute values for patients with missing data at week 156. The complete data sets were analyzed and the results combined using Rubin's rule.

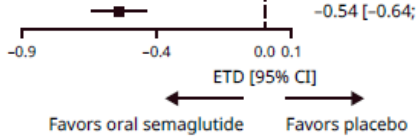
ANCOVA, analysis of covariance; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; ETD, estimated treatment difference.

eFigure 7.

Treatment differences in the key measures of metabolism and inflammation (first on-treatment) at week 156

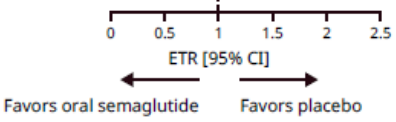
(A) Change in HbA_{1c} with oral semaglutide versus placebo

	Number of participants: Oral semaglutide (N=4825)	Number of participants: Placebo (N=4825)	ETD, %-points [95% CI]	*p*-value	$p_{interaction}$
Overall	4381	4317	−0.56 [−0.61; −0.51]	<.001	.20
ASCVD-only	2501	2499	−0.54 [−0.60; −0.47]	<.001	
CKD-only	588	551	−0.68 [−0.82; −0.53]	<.001	
ASCVD+CKD	1149	1129	−0.54 [−0.64; −0.44]	<.001	



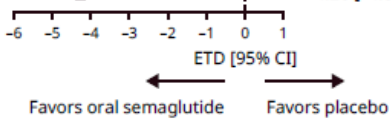
(B) hsCRP plasma level ratio to baseline with oral semaglutide versus placebo

	Number of participants: Oral semaglutide (N=4825)	Number of participants: Placebo (N=4825)	ETR [95% CI]	*p*-value	$p_{interaction}$
Overall	4556	4507	0.76 [0.72; 0.79]	<.001	0.23
ASCVD-only	2587	2597	0.38 [0.23; 0.61]	<.001	
CKD-only	608	573	0.75 [0.28; 2.05]	.58	
ASCVD+CKD	1212	1188	0.71 [0.35; 1.43]	.34	



(C) Percentage change in body weight with oral semaglutide versus placebo

	Number of participants: Oral semaglutide (N=4825)	Number of participants: Placebo (N=4825)	ETD, %-points [95% CI]	*p*-value	$p_{interaction}$
Overall	4434	4366	−3.70 [−4.01; −3.39]	<.001	<.001
ASCVD-only	2531	2528	−3.17 [−3.57; −2.77]	<.001	
CKD-only	596	562	−4.76 [−5.58; −3.93]	<.001	
ASCVD+CKD	1161	1132	−4.26 [−4.85; −3.67]	<.001	



The responses were analyzed using an ANCOVA with treatment as fixed factor and baseline value as covariate. Before analysis, missing data were multiple imputed. The imputation model (linear regression) was done separately for each treatment arm and included baseline value as a covariate and was fitted to all patients with a measurement regardless of treatment status at week 156 (HbA_{1c} and body weight) or 104 (hsCRP). The fitted model was used to impute values for patients with missing data at week 156 (HbA_{1c} and body weight) or 104 (hsCRP). The complete data sets were analyzed and the results combined using Rubin's rule.

ANCOVA, analysis of covariance; ASCVD, atherosclerotic cardiovascular disease; CI, confidence interval; CKD, chronic kidney disease; ETD, estimated treatment difference; ETR, estimated treatment ratio; hsCRP, high-sensitivity C-reactive protein.

Reference

1. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150(9):604-612.