The effect of once-weekly semaglutide on MACE, blood pressure and lipids by race and ethnicity: a SUSTAIN 6 *post hoc* analysis

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Aim

- Semaglutide (Novo Nordisk, Denmark) is a glucagon-like peptide-1 (GLP-1) analogue approved for the once-weekly (OW) subcutaneous treatment of type 2 diabetes (T2D).[1]
- In SUSTAIN 6, semaglutide OW added to standard of care significantly reduced the risk of major adverse cardiovascular (CV) events (MACE: nonfatal myocardial infarction [MI], nonfatal stroke or CV death) vs placebo. The hazard ratio (HR) [95% confidence interval (CI)] was 0.74 [0.58;0.95]; p<0.001 for noninferiority, p=0.02 for superiority.[2]
- Fewer Caucasians are diagnosed with T2D than Black/African American, Asian or Hispanic adults.[3] There is also an increased incidence of CV disease in Black/African American patients with T2D, compared with Caucasians.[4]
- The aim of this *post hoc* analysis was to assess the effect of semaglutide OW vs placebo on MACE, blood pressure (BP) and lipid levels in race and ethnicity subgroups in SUSTAIN 6.

Methods

SUSTAIN 6 trial design

- The SUSTAIN 6 trial design has been reported previously.[2]
  - Subjects with T2D and an HbA_{1c} ≥7.0% on 0–2 oral antidiabetic drugs, basal or premixed insulin with no concomitant GLP-1 receptor agonist (GLP-1RA) therapy were eligible.
  - Subjects were randomised (1:1:1:1) to semaglutide 0.5 mg, semaglutide 1.0 mg, or volume-matched placebo for 104 weeks.
  - The primary composite outcome was time to first occurrence of MACE.

Post hoc analysis

- In this *post hoc* analysis, treatment groups (semaglutide 0.5 mg and 1.0 mg, or placebo 0.5 mg and 1.0 mg) were pooled and analysed in subgroups of race (Caucasian, Black/African American, Asian or Other) and ethnicity (Hispanic or non-Hispanic).
  - The Other race subgroup comprised all subjects in the 'American Indian or Alaska Native', 'Native Hawaiian or Other Pacific Islander' or 'Other' subgroups.
- MACE and each of its components were evaluated in race and ethnicity subgroups.
- The following secondary endpoints were also assessed in race and ethnicity subgroups:
  - Changes from baseline in systolic blood pressure (SBP) and diastolic blood pressure (DBP) at week 104.
  - Estimated treatment ratios (ETRs), defined as the relative levels of each parameter in the semaglutide vs placebo groups, of lipids (total cholesterol, low-density lipoprotein-cholesterol [LDL-C], high-density lipoprotein-cholesterol [HDL-C], free fatty acids [FFAs] and triglycerides) at week 104.
  - Adverse events (AEs) throughout the trial.

Statistical analysis

- MACE and its components were analysed using a Cox proportional hazards model, with treatment and subgroup as fixed factors.
- Changes in SBP were analysed using an analysis of covariance. Changes in DBP were analysed using a mixed model for repeated measurements (MMRM) with interaction between subgroup, randomised treatment and baseline value as covariates, all interacting with visit. ETRs were also analysed using an MMRM with treatment and stratification as fixed factors and baseline value as covariate.
- MACE, BP and lipid data were observed without imputation, irrespective of subjects' adherence to treatment (in-trial). AE data are from the period when subjects were exposed to the study drug (on-treatment).

Results

Baseline characteristics and demographics

- Overall, 3,297 subjects with T2D were randomised to semaglutide 0.5 mg or 1.0 mg, or placebo 0.5 mg or 1.0 mg.[2]
- Subject disposition and baseline characteristics by race and ethnicity are shown in Table 1.
- In general, baseline characteristics were similar across subgroups. However, mean baseline body weight was lower in the Asian subgroup than in other subgroups in both treatment groups.

Table 1: Subject disposition and baseline characteristics by race and ethnicity

	Semaglutide (pooled)						Placebo (pooled)					
	Race				Ethnicity		Race				Ethnicity	
	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic
Subject disposition												
Full analysis set, n	1,384	108	121	35	256	1,392	1,352	113	152	32	254	1,395
Trial completers, n (%)	1,364 (82.8)	105 (6.4)	120 (7.3)	34 (2.1)	253 (15.4)	1,370 (83.1)	1,321 (80.1)	104 (6.3)	152 (9.2)	32 (1.9)	251 (15.2)	1,358 (82.4)
Treatment completers, n (%)	1,091 (66.2)	72 (4.4)	109 (6.6)	25 (1.5)	215 (13.0)	1,082 (65.7)	1,100 (66.7)	75 (4.5)	138 (8.4)	26 (1.6)	211 (12.8)	1,128 (68.4)
Baseline characteristics*												
Male, n (%)	871 (62.9)	46 (42.6)	73 (60.3)	23 (65.7)	151 (59.0)	862 (61.9)	811 (60.0)	55 (48.7)	105 (69.1)	18 (56.3)	137 (53.9)	852 (61.1)
Age, years	64.9 (7.2)	63.3 (7.3)	63.5 (7.2)	63.0 (7.4)	64.3 (7.3)	64.7 (7.2)	65.2 (7.5)	61.9 (7.6)	61.8 (6.8)	63.7 (6.5)	63.8 (7.6)	64.8 (7.5)
Diabetes duration, years	13.8 (8.2)	16.2 (9.4)	15.7 (7.1)	15.6 (7.0)	15.7 (8.7)	13.9 (8.1)	13.4 (7.9)	14.3 (8.4)	15.0 (8.4)	14.1 (8.3)	16.0 (8.5)	13.2 (7.9)
HbA_{1c}, %	8.7 (1.4)	9.0 (1.5)	8.9 (1.4)	9.4 (2.3)	8.9 (1.7)	8.7 (1.4)	8.6 (1.4)	9.1 (1.8)	9.2 (1.6)	8.9 (1.8)	8.9 (1.6)	8.7 (1.5)
FPG, mmol/L	10.4 (3.7)	9.6 (4.0)	9.4 (3.4)	9.2 (2.8)	9.7 (4.2)	10.3 (3.6)	10.4 (3.6)	10.4 (3.9)	9.5 (3.9)	9.9 (3.4)	9.9 (3.6)	10.3 (3.7)
Body weight, kg	93.8 (20.1)	97.5 (23.9)	74.3 (14.7)	82.2 (15.2)	84.0 (18.4)	93.9 (20.7)	93.4 (20.1)	97.4 (22.7)	74.5 (13.1)	89.6 (19.8)	82.5 (16.2)	93.6 (20.8)

*Values are mean (SD) unless otherwise indicated. Data were pooled for both the semaglutide groups and for the placebo groups. Trial completers were subjects who either attended the last follow-up visit or died while considered an active trial participant. Treatment completers were subjects who were exposed and did not discontinue treatment prematurely, did not withdraw from trial and were not lost to follow-up before the last treatment visit. FPG, fasting plasma glucose; n, number of subjects; SD, standard deviation.

Time to first occurrence of MACE

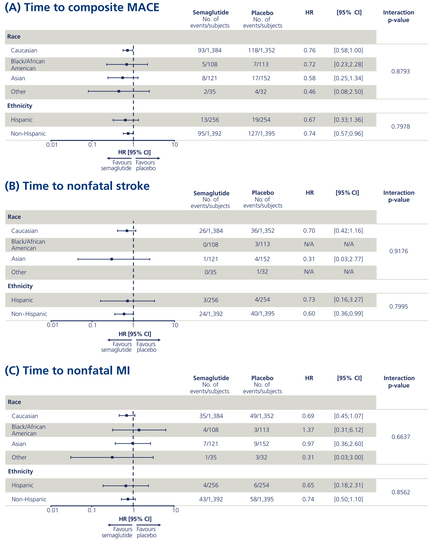
- The HRs for the time to composite MACE were <1 in each race and ethnicity subgroup (Figure 1A).
- The HRs for the individual components of MACE were <1 in each race and ethnicity subgroup, except in Black/African American subjects for nonfatal MI and CV death, and in non-Hispanics for CV death (Figure 1B–D).
- All interaction p-values were nonsignificant (p>0.05).

Change in SBP and DBP from baseline

- Reductions in SBP with semaglutide were consistent across most subgroups (Figure 2A), except in Black/African American subjects.
  - In Black/African American subjects, the increase was driven by a 1.9 mmHg increase with semaglutide 0.5 mg (n=54; data not shown).
  - SBP decreased by 2.0 mmHg in Black/African American subjects with semaglutide 1.0 mg (n=54; data not shown).
  - In SUSTAIN 1–5 and 7, SBP was reduced in Black/African American subjects (data not shown).
- Changes in DBP with semaglutide were consistent across all subgroups (Figure 2B).

Figure 1: Time to composite MACE and its individual components by race and ethnicity

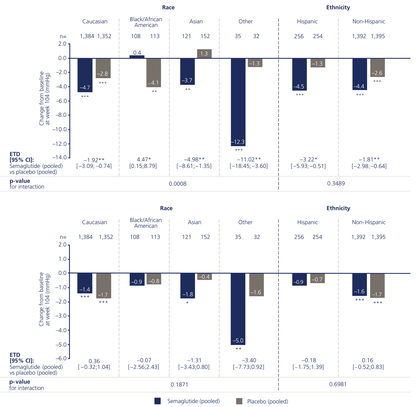
Key result



Data are from the in-trial observation period from the full analysis set, and were pooled for both the semaglutide groups and for the placebo groups. CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MACE, major adverse cardiovascular events; MI, myocardial infarction; N/A, not available.

- The greatest reductions in SBP and DBP were observed in the Other subgroup. It should be noted that the subject numbers in this group were low.
- All interaction p-values were nonsignificant (p>0.05), with the exception of the treatment effect of semaglutide on SBP by race (p=0.0008).

Figure 2: Change in (A) SBP and (B) DBP from baseline by race and ethnicity



*p<0.05, **p<0.01, ***p<0.001. Data are estimated mean changes from baseline or ETD [95% CI] from the in-trial observation period from the full analysis set, and were pooled for the semaglutide groups and for the placebo groups. CI, confidence interval; DBP, diastolic blood pressure; ETD, estimated treatment difference; SBP, systolic blood pressure.

ETRs for total cholesterol, LDL-C, HDL-C, FFAs and triglycerides

- Most ETRs were <1 for total cholesterol, LDL-C, FFAs and triglycerides in all race and ethnicity subgroups (data not shown).
  - Exceptions were ETRs for LDL-C and total cholesterol in Black/African Americans (1.08 and 1.02, respectively); and total cholesterol, FFAs and triglycerides in Asians (1.01, 1.02 and 1.01, respectively) (data not shown).
- Most ETRs were >1 for HDL-C in all race and ethnicity subgroups, except for the Other subgroup (ETR: 0.98).
- All interaction p-values were nonsignificant (p>0.05).

Safety

- Semaglutide was well tolerated in all race and ethnicity subgroups (Table 2), and had a safety profile similar to that of other GLP-1RAs.[5,6]
- A greater proportion of Caucasian and Black/African American subjects discontinued treatment due to AEs with semaglutide, compared with subjects in other race subgroups.
- A slightly lower proportion of Asian subjects reported gastrointestinal AEs with semaglutide compared with subjects in other race and ethnicity subgroups.
- The overall incidence of severe hypoglycaemia with semaglutide was low.

Table 2: Adverse events by race and ethnicity

	Semaglutide (pooled)						Placebo (pooled)					
	Race				Ethnicity		Race				Ethnicity	
	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic	Caucasian	Black/ African American	Asian	Other	Hispanic	Non-Hispanic
All AEs	1,230 (89.3)	98 (90.7)	95 (78.5)	31 (88.6)	231 (90.9)	1,223 (88.1)	1,196 (88.8)	101 (89.4)	127 (83.6)	29 (90.6)	229 (90.9)	1,224 (87.9)
Serious AEs	420 (30.5)	34 (31.5)	40 (33.1)	10 (28.6)	54 (21.3)	450 (32.4)	478 (35.5)	42 (37.2)	43 (28.3)	11 (34.4)	66 (26.2)	508 (36.5)
AEs leading to premature treatment discontinuation	189 (13.7)	15 (13.9)	7 (5.8)	3 (8.6)	20 (7.9)	194 (14.0)	94 (7.0)	8 (7.1)	4 (2.6)	4 (12.5)	13 (5.2)	97 (7.0)
GI AEs	718 (52.1)	55 (50.9)	52 (43.0)	16 (45.7)	118 (46.5)	723 (52.1)	482 (35.8)	34 (30.1)	36 (23.7)	12 (37.5)	77 (30.6)	487 (35.0)
Severe hypoglycaemia*	14 (1.0)	2 (1.9)	6 (5.0)	1 (2.9)	5 (2.0)	18 (1.3)	23 (1.7)	3 (2.7)	0 (0.0)	0 (0.0)	3 (1.2)	23 (1.7)
Severe or BG-confirmed symptomatic hypoglycaemia†	300 (21.8)	25 (23.1)	23 (19.0)	9 (25.7)	71 (28.0)	286 (20.6)	277 (20.6)	21 (18.6)	32 (21.1)	3 (9.4)	65 (25.8)	268 (19.3)

*Defined as an episode that is severe according to the ADA classification. †Defined as an episode that is severe (according to the ADA classification) or BG-confirmed (plasma glucose value <3.1 mmol/L [56 mg/dL] with symptoms consistent with hypoglycaemia). Data are number (percentage) of subjects experiencing ≥1 event, for the on-treatment observation period and from the safety analysis set, and were pooled for both the semaglutide groups and for the placebo groups. ADA, American Diabetes Association; AE, adverse event; BG, blood glucose; GI, gastrointestinal.

Discussion

- This *post hoc* analysis assessed the effects of semaglutide vs placebo on MACE and its components, BP and lipid levels in race and ethnicity subgroups.
- The effect of semaglutide vs placebo on MACE and its individual components was largely consistent across all race and ethnicity subgroups.
- The effects of semaglutide on MACE shown here align with analyses from the LEADER and REWIND CV outcomes trials, which showed that the respective effects of liraglutide and dulaglutide vs placebo on MACE were consistent, irrespective of race or ethnicity.[7,8]
- SBP was reduced with semaglutide in all subgroups except in Black/African American subjects, although this was unlikely to be clinically meaningful.
  - Only the interaction p-value for the effect of semaglutide on SBP by race was statistically significant. This could be due to the large decrease and the heterogeneity observed in the Other subgroup in which the 95% CI was broad.
- Despite minor variations in all subgroups, the absence of significant interaction p-values suggests there was no differential effect of semaglutide on lipids across race and ethnicity subgroups.
- An association between the occurrence of severe hypoglycaemia and risk of MACE was demonstrated in the LEADER trial.[9]
  - In this study, HRs for nonfatal MI and CV death in Black/African American subjects slightly favoured placebo; however, the variation was large and there did not appear to be an imbalance in severe hypoglycaemia across race and ethnicity subgroups.

Conclusion

- In this *post hoc* analysis of the SUSTAIN 6 trial, there appeared to be no heterogeneity in the effect of semaglutide vs placebo on MACE, BP and lipid levels in race and ethnicity subgroups.
- The safety profile in each subgroup was similar to that of all subjects in the SUSTAIN clinical trial programme.[10]

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