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Oral Semaglutide and Heart Failure Outcomes in Persons With Type 2 Diabetes

A Secondary Analysis of the SOUL Randomized Clinical Trial

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IMPORTANCE Heart failure (HF) is a common complication of type 2 diabetes (T2D). Oral semaglutide reduced the risk of major adverse cardiovascular (CV) events (MACE; comprising CV death, nonfatal myocardial infarction, or nonfatal stroke) in people with T2D in the SOUL trial, but the impact on HF outcomes in these participants is unknown.

OBJECTIVE To evaluate the effect of oral semaglutide on HF events, MACE, and safety among participants with or without HF at baseline.

DESIGN, SETTING, AND PARTICIPANTS This is a secondary analysis of the double-blind, placebo-controlled, event-driven, phase 3b SOUL randomized clinical trial, which was conducted at 444 centers in 33 countries. Participants were enrolled from June 17, 2019, to March 24, 2021, and had T2D and atherosclerotic CV disease and/or chronic kidney disease, stratified according to the presence or absence of HF history at baseline. Data were analyzed from December 2024 to August 2025.

INTERVENTION Once-daily oral semaglutide or placebo in addition to standard of care.

MAIN OUTCOMES AND MEASURES Prespecified composite HF outcome (time to first occurrence of HF hospitalization, urgent HF visit, or CV death).

RESULTS Overall, 9650 participants (median [IQR] age, 66.0 [61.0-72.0] years; 2790 [28.9%] female) were randomized, with a mean (SD) follow-up of 47.5 (10.9) months. Of these participants, 2229 (23.1%) had HF history (991 [10.3%] with preserved ejection fraction, 592 [6.1%] with reduced ejection fraction, and 646 [6.7%] with unknown subtype). For participants with HF at baseline, the hazard ratio (HR) for risk of the composite HF outcome with oral semaglutide vs placebo was 0.78 (95% CI, 0.63-0.96) and was 1.01 (95% CI, 0.84-1.20) in those without HF at baseline (*P* for interaction = .06). Among participants with HF, the HR was 0.59 (95% CI, 0.39-0.86) in those with preserved ejection fraction and 0.98 (95% CI, 0.70-1.38) in those with reduced ejection fraction. There was no heterogeneity in the risk reduction of MACE with oral semaglutide in participants with HF history (HR, 0.83; 95% CI, 0.68-1.01) or without HF history (HR, 0.86; 95% CI, 0.75-0.98) (*P* for interaction = .77). Serious adverse event occurrence among participants with HF was similar with oral semaglutide (594 [53.8%]) and placebo (642 [57.1%]).

CONCLUSIONS AND RELEVANCE In this secondary analysis of the SOUL randomized clinical trial, among individuals with T2D, atherosclerotic CV disease, and/or chronic kidney disease, a reduction of HF events was observed with use of oral semaglutide compared with placebo in those with a history of HF, without increasing the risk of serious adverse events. These data support the potential benefit of oral semaglutide in reducing HF events in people with T2D and HF.

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Supplemental content

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Heart failure (HF) is one of the most prevalent cardiac complications in people with type 2 diabetes (T2D).[1-4] Approximately 462 million individuals are affected by T2D worldwide,[5] and up to 57% of individuals with T2D also have HF.[1,6,7] People with T2D and HF have higher risk for hospitalization and mortality compared with those with T2D but no HF.[8]

Several glucagon-like peptide-1 receptor agonists (GLP-1 RAs) reduce the risk of major adverse cardiovascular (CV) events (MACE; a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke), all-cause mortality, hospital admission for HF, and worsening kidney function in people with T2D.[9] In clinical trials, the once-weekly subcutaneous formulation of semaglutide reduced the risk of HF outcomes compared with placebo in individuals with HF, including those with HF with preserved ejection fraction (HFpEF), obesity, or chronic kidney disease (CKD).[10-12] In the SOUL trial, once-daily oral semaglutide significantly reduced the risk of MACE compared with placebo in people with T2D and atherosclerotic CV disease (ASCVD) and/or CKD.[13] The aim of this secondary analysis of the SOUL trial was to evaluate the effect of oral semaglutide compared with placebo on HF and ASCVD outcomes in participants with or without a history of HF at baseline.

Key Points

Question What are the effects of oral semaglutide on heart failure (HF) and other cardiovascular outcomes according to baseline HF status in people with type 2 diabetes?

Findings In this secondary analysis of 9650 participants in the SOUL randomized clinical trial, a lower risk of composite HF outcome events was observed with oral semaglutide compared with placebo in participants with HF at baseline, while there was no effect in participants without baseline HF, with similar proportions of serious adverse events.

Meaning These data support that oral semaglutide may benefit people with type 2 diabetes and HF to reduce HF events.

Methods

Trial Design and Participants

The SOUL trial was a double-blind, randomized, placebo-controlled, event-driven, phase 3b cardiovascular outcomes trial conducted at 444 centers in 33 countries. The trial compared oral semaglutide (up to 14 mg once daily) with placebo in addition to standard of care (in accordance with local guidelines) in individuals with T2D and ASCVD and/or CKD. The trial design, population, and primary outcome have been fully reported previously.[13,14]

Participants were enrolled in SOUL from June 17, 2019, to March 24, 2021, and were eligible for inclusion if they were adults 50 years or older with T2D (glycated hemoglobin A_{1c} [HbA_{1c}], 6.5%-10.0%; to convert to proportion of total hemoglobin, multiply by 0.01) and at least 1 of the following conditions: coronary artery disease, cerebrovascular disease, symptomatic peripheral artery disease, and/or CKD (estimated glomerular filtration rate, <60 mL/min/1.73 m^2). Participants were randomized to oral semaglutide, 3 mg, or matched placebo once daily for 4 weeks, followed by 7 mg once daily for 4 weeks, then 14 mg once daily until the end of the trial, as previously described.[13,14]

The SOUL protocol (Supplement 1) was approved by the institutional review board and ethics committee for each participating center. The trial was conducted in compliance with the International Council for Harmonization's Good Clinical Practice guidelines, applicable regulatory requirements, and in accordance with the Declaration of Helsinki. All participants provided written informed consent. The trial results are reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines.

Baseline HF Status

Effects of oral semaglutide compared with placebo on composite HF outcomes and MACE were studied in participants with or without HF history at baseline, as well as in subgroups by HF subtype and other baseline characteristics. At randomization, the presence or absence of HF and the HF subtype (HFpEF, HF with reduced ejection fraction [HFrEF], or unknown) was recorded based on existing diagnoses, as well as the New York Heart Association (NYHA) functional class. Individuals with HF in NYHA class IV were not eligible for inclusion in SOUL. Echocardiography and the collection of N-terminal pro–B-type natriuretic peptide levels were not conducted as part of the trial procedures and not required for inclusion; however, key parameters from the most recent echocardiogram, including left ventricular ejection fraction (LVEF), were recorded by the investigator if available. As the subgroup with unknown HF subtype could include participants with either HFpEF or HFrEF, a sensitivity analysis of the HF composite outcome was conducted, in which the unknown subtype was considered HFpEF in one scenario and as HFrEF in the other.

Outcomes

The main prespecified outcome of this analysis was time to the first occurrence of a centrally adjudicated composite HF outcome comprising HF events (HF hospitalization or urgent HF visit) or CV death. The primary outcome of the SOUL trial was time to first occurrence of adjudicated MACE (a composite of CV death, nonfatal myocardial infarction, or nonfatal stroke) and was also assessed herein by baseline HF status, which was a post hoc analysis.

Changes from baseline to week 104 in clinical parameters (HbA_{1c}, body weight, high-sensitivity C-reactive protein [hsCRP], and systolic/diastolic blood pressure [BP]) were also prespecified secondary outcomes assessed herein. Safety outcomes are reported as occurrence of serious adverse events (SAEs) and AEs leading to permanent treatment discontinuation. AEs of special interest based on a prespecified MedDRA search included SAEs and nonserious AEs. Predefined SOUL outcomes and event adjudication were described previously.[13]

Statistical Analysis

The analyses were based on the intention-to-treat principle based on time to the first event of composite and individual component outcomes using a Cox proportional hazards model with randomized treatment group (oral semaglutide or placebo) as a fixed factor. Hazard ratios (HRs) with 95% CIs and

Table 1. Baseline Demographics and Clinical Characteristics by Heart Failure (HF) Status at Baseline[a]

Characteristic	Participants with HF at baseline (n = 2229)			Participants without HF at baseline (n = 7418)		
	No. (%)			No. (%)		
	Oral semaglutide (n = 1105)	Placebo (n = 1124)	*P* value	Oral semaglutide (n = 3718)	Placebo (n = 3700)	*P* value
Age, median (IQR), y	66.0 (61.0-71.0)	66.0 (61.0-71.0)	.46	66.0 (61.0-72.0)	67.0 (61.0-72.0)	.91
Sex						
Female	329 (29.8)	351 (31.2)	.46	1046 (28.1)	1063 (28.7)	.57
Male	776 (70.2)	773 (68.8)		2672 (71.9)	2637 (71.3)	
Race[b]						
American Indian or Alaska Native	1 (0.1)	3 (0.3)	.51	6 (0.2)	9 (0.2)	.92
Asian	118 (10.7)	133 (11.8)		1016 (27.3)	988 (26.7)	
Black or African American	27 (2.4)	27 (2.4)		97 (2.6)	101 (2.7)	
Native Hawaiian or Pacific Islander	0	2 (0.2)		4 (0.1)	3 (0.1)	
White	924 (83.6)	933 (83.0)		2401 (64.6)	2388 (64.5)	
Other/not reported	35 (3.2)	26 (2.4)		194 (5.2)	211 (5.7)	
Ethnicity[b]						
Hispanic or Latino	118 (10.7)	132 (11.7)	.69	554 (14.9)	573 (15.5)	.77
Not Hispanic or Latino	983 (89.0)	987 (87.8)		3123 (84.0)	3085 (83.4)	
Not reported	4 (0.4)	5 (0.4)		41 (1.1)	42 (1.1)	
Body weight, median (IQR), kg	90.7 (78.7-103.0)	90.3 (79.0-105.4)	.64	84.0 (73.0-97.2)	84.8 (73.4-98.2)	.10
BMI, median (IQR)	31.8 (28.1-35.9)	31.8 (28.3-35.8)	.41	29.8 (26.6-33.8)	29.9 (26.7-34.1)	.22
HbA_{1c}, median (IQR), mmol/mol	62.8 (55.2-72.7)	62.8 (55.2-72.7)	.10	60.7 (54.1-70.5)	60.7 (54.1-70.5)	.74
HbA_{1c}, median (IQR), %	7.9 (7.2-8.8)	7.9 (7.2-8.8)	.10	7.7 (7.1-8.6)	7.7 (7.1-8.6)	.74
Duration of diabetes, median (IQR), y	13.3 (8.4-19.9)	13.8 (8.2-19.8)	.90	15.0 (9.2-20.9)	15.0 (9.0-21.0)	.78
Hypertension	1039 (94.0)	1064 (94.7)	.52	3337 (89.8)	3316 (89.6)	.85
Vital signs						
SBP, median (IQR), mm Hg	134.0 (122.0-143.0)	134.0 (123.0-144.0)	.73	135.0 (124.0-144.0)	135.0 (124.0-145.0)	.60
DBP, median (IQR), mm Hg	78.0 (70.0-84.0)	78.0 (70.0-84.0)	.29	77.0 (70.0-83.0)	77.0 (70.0-83.0)	.61
Pulse, median (IQR), beats/min	72.0 (65.0-79.0)	72.0 (66.0-78.0)	.85	72.0 (65.0-80.0)	72.0 (65.0-80.0)	.98
High-sensitivity CRP, median (IQR), mg/dL	NA	0.25 (0.12-0.54)	.15	NA	0.18 (0.08-0.41)	.90
eGFR (CKD-EPI method), median (IQR), mL/min/1.73 m^{2c}	76.0 (56.0-93.0)	76.0 (56.0-92.0)	.47	77.0 (56.0-93.0)	76.0 (56.0-92.0)	.42
eGFR, mL/min/1.73 m^{2c}						
≥60	782 (71.4)	785 (70.3)	.60	2593 (70.4)	2589 (70.6)	.88
<60	314 (28.6)	331 (29.7)		1090 (29.6)	1080 (29.4)	
History of CV event						
Prior MI or stroke						
No	342 (31.3)	375 (33.9)	.20	1889 (51.6)	1918 (52.4)	.50
Yes	750 (68.7)	732 (66.1)		1771 (48.4)	1742 (47.6)	
Atrial fibrillation	161 (14.6)	142 (12.6)	.18	171 (4.6)	188 (5.1)	.33
Coronary heart disease	983 (89.0)	980 (87.2)	.17	2421 (65.1)	2434 (65.8)	.55
Coronary revascularization	671 (60.7)	688 (61.2)	.81	1920 (51.6)	1919 (51.9)	.85
MI	627 (57.5)	618 (55.9)	.47	1316 (35.9)	1299 (35.5)	.68
Peripheral artery disease	268 (24.3)	244 (21.7)	.15	503 (13.5)	500 (13.5)	>.99
Stroke	186 (16.9)	196 (17.5)	.72	557 (15.0)	549 (14.9)	.88
ASCVD	851 (77.7)	828 (74.5)	.08	2094 (57.1)	2067 (56.4)	.59

(continued)

2-sided *P* values are presented. Participants who withdrew from the trial, died of causes not included in the outcome, or were lost to follow-up were censored at the time of these events. Subgroup analyses for time-to-event outcomes were based on a similar Cox proportional hazards model by adding the specific subgroup as a factor and an interaction term between treatment group (oral semaglutide and placebo) and the subgroup. Similarly, time-to-event outcomes were plotted by treatment group and subgroup using the Aalen-Johansen estimator and presented as cumulative incidences, considering non-CV death or all-cause death as a competing event dependent on the outcome.

Table 1. Baseline Demographics and Clinical Characteristics by Heart Failure (HF) Status at Baseline[a] (continued)

Characteristic	Participants with HF at baseline (n = 2229)			Participants without HF at baseline (n = 7418)		
	No. (%)			No. (%)		
	Oral semaglutide (n = 1105)	Placebo (n = 1124)	*P* value	Oral semaglutide (n = 3718)	Placebo (n = 3700)	*P* value
NYHA class						
I	392 (35.5)	405 (36.0)	.45	NA	NA	NA
II	635 (57.5)	626 (55.7)		NA	NA	
III	77 (7.0)	93 (8.3)		NA	NA	
Missing	1 (0.1)	0		NA	NA	
LVEF group						
<40%	150 (13.6)	175 (15.6)	.35	49 (1.3)	66 (1.8)	.22
40% to <50%[d]	207 (18.7)	196 (17.4)		165 (4.4)	182 (4.9)	
≥50%	507 (45.9)	530 (47.2)		1561 (42.0)	1574 (42.5)	
Missing	241 (21.8)	223 (19.8)		1943 (52.3)	1878 (50.8)	
HF subtype						
HFpEF	494 (44.7)	497 (44.2)	.89	NA	NA	NA
HFrEF	296 (26.8)	296 (26.3)		NA	NA	
Unknown	315 (28.5)	331 (29.4)		NA	NA	
CV-related medication						
Lipid-lowering medication	956 (86.5)	978 (87.0)	.73	3317 (89.2)	3318 (89.8)	.52
Antiplatelet medication	895 (81.0)	904 (80.4)	.73	2822 (75.9)	2823 (76.3)	.69
β-Blocker	903 (81.7)	885 (78.7)	.08	2201 (59.2)	2211 (59.8)	.62
Diuretic	670 (60.6)	695 (61.8)	.56	1334 (35.9)	1362 (36.8)	.40
Loop diuretic	373 (33.8)	382 (34.0)	.91	392 (10.5)	400 (10.8)	.71
MRA	261 (23.6)	258 (23.0)	.71	173 (4.7)	200 (5.4)	.14
ACE inhibitor/ARB (ARNI)	927 (83.9)	946 (84.2)	.86	2848 (76.6)	2894 (78.3)	.10
ARNI	12 (1.1)	14 (1.2)	.73	5 (0.1)	4 (0.1)	.74
Glucose-lowering medication						
Metformin	800 (72.4)	820 (73.0)	.77	2850 (76.7)	2854 (77.1)	.62
Insulin	589 (53.3)	599 (53.3)	>.99	1885 (50.7)	1814 (49.0)	.15
Sulfonylureas	317 (28.7)	337 (30.0)	.50	1068 (28.7)	1097 (29.7)	.38
SGLT2 inhibitors	290 (26.2)	272 (24.2)	.27	1006 (27.1)	1028 (27.8)	.48
DPP-4 inhibitors	184 (16.7)	211 (18.8)	.19	910 (24.5)	930 (25.1)	.51
Thiazides	123 (11.1)	121 (10.8)	.78	679 (18.3)	651 (17.6)	.45

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor-neprilysin inhibitor; ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CRP, C-reactive protein; CV, cardiovascular; DBP, diastolic blood pressure; DPP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin A_{1c}; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; LVEF, left ventricular ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist, NA, not applicable; NYHA, New York Heart Association; SBP, systolic blood pressure; SGLT2, sodium-glucose co-transporter-2.

SI conversion factors: To convert HbA_{1c} to proportion of total hemoglobin, multiply by 0.01; to convert CRP to mg/L, multiply by 10.

[a] Concomitant therapies could be adjusted during the trial. Initiation of open-label treatment with a glucagon-like peptide-1 receptor agonist was prohibited. For 3 participants, HF at baseline could not be determined.

[b] Race and ethnicity data were self-reported by participants, including the other category. The not reported category reflects participants in France, where collecting data on race and ethnicity is prohibited by law.

[c] Measured at randomization.

[d] Includes HF with mildly reduced ejection fraction (41%-49%).

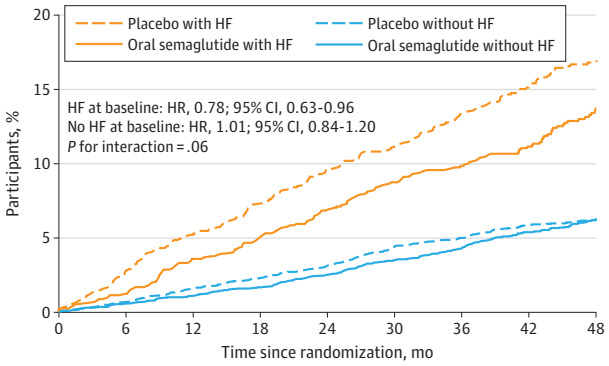
Continuous outcomes from baseline to week 104 were analyzed using linear regression with randomized treatment group, baseline HF subgroup, and an interaction term between treatment group and HF subgroups at baseline, adjusted for baseline values of the outcome. Multiple imputations (n = 500) were used for missing values under a missing-at-random assumption. An imputation model (linear regression) is estimated separately for each treatment group, including baseline value as a covariate and fitted to participants having an observed data point at week 104. Results were combined using the Rubin rule.[15]

Interaction *P* values were derived from an *F* test of equality between the treatment differences across the baseline HF subgroups. Log transformation was applied before analyses for parameters specified in the statistical analysis plan (Supplement 1), and treatment differences were expressed as a treatment mean ratio.

A 2-sided *P* value of .05 was considered statistically significant, and no adjustment for multiplicity was made. Statistical analyses were performed with SAS software, version 9.4 (SAS Institute), and data were analyzed from December 2024 to

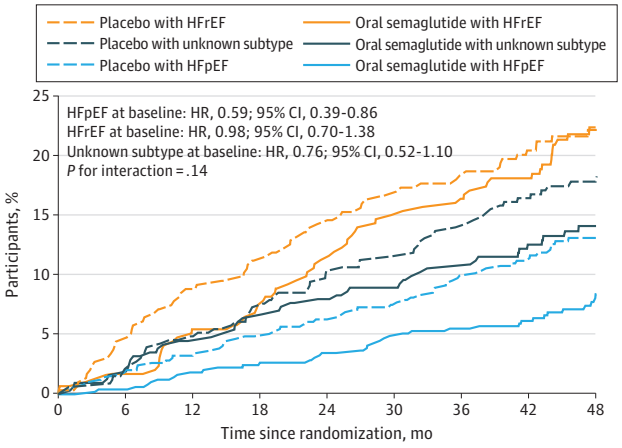
Figure 1. Time to First Composite Heart Failure (HF) Outcome by Treatment and Baseline HF Status and Subtype

A HF composite outcome by HF at baseline



No. at risk									
Oral semaglutide with HF	1105	1084	1045	1020	989	962	941	841	543
Oral semaglutide without HF	3718	3684	3641	3595	3549	3488	3434	3136	2123
Placebo with HF	1124	1088	1047	1011	971	941	909	814	558
Placebo without HF	3700	3651	3591	3527	3473	3406	3363	3087	2098

B HF composite outcome by HF subtype in participants with HF at baseline



No. at risk									
Oral semaglutide with HFpEF	494	491	476	467	456	447	439	389	261
Oral semaglutide with HFrEF	296	287	275	265	252	241	237	212	119
Oral semaglutide with unknown subtype	315	306	294	288	281	274	265	240	163
Placebo with HFpEF	497	484	469	459	446	433	419	368	265
Placebo with HFrEF	296	281	266	254	242	233	223	202	120
Placebo with unknown subtype	331	323	312	298	283	275	267	244	173

Data are from the in-trial full-analysis set. The HF composite outcome comprised HF events (HF hospitalization or urgent HF visit) or cardiovascular death. For 3 participants, HF at baseline could not be determined. Missing data were defined as data planned to be collected according to protocol but not present in the database. Hence, data that are absent in the database due to death or administrative censoring were not considered missing and, therefore, not imputed. The *P* for interaction across HF subtypes (HF with preserved ejection fraction [HFpEF], HF with reduced ejection fraction [HFrEF], and unknown) and no HF at baseline in all randomized participants was .06. HR indicates hazard ratio.

August 2025. Novo Nordisk A/S (Copenhagen, Denmark) maintained the clinical database and performed the statistical analyses.

Results

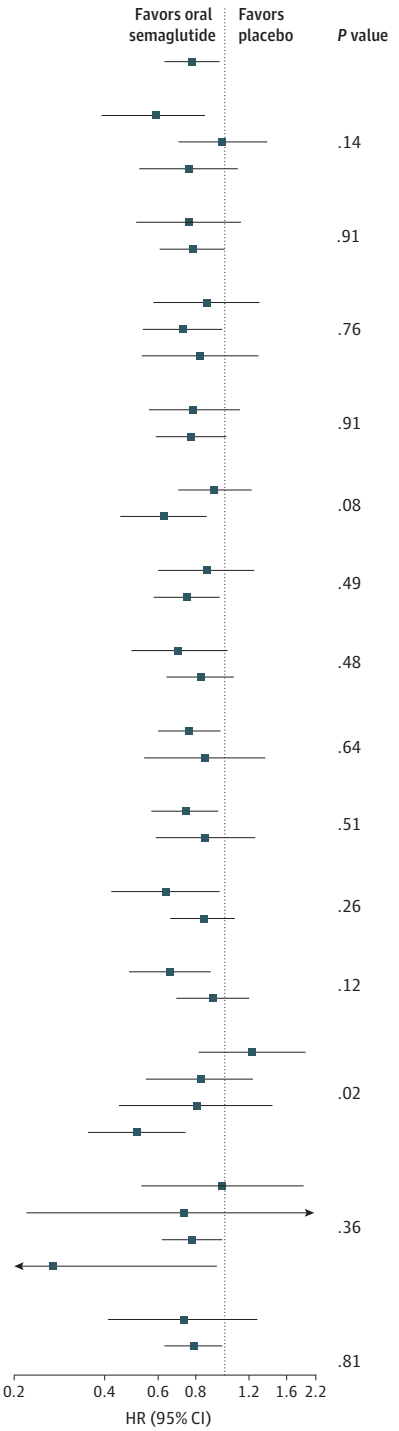
Trial Population

The baseline characteristics of the SOUL participants were previously reported.[13,14] Briefly, 9650 participants (median [IQR] age, 66.0 [61.0-72.0] years; 2790 [28.9%] female) were randomized and followed up for a mean (SD) of 47.5 (10.9) months.[13] Among these, 2229 participants (23.1%) had a history of HF at baseline (991 [10.3%] with HFpEF, 592 [6.1%] with HFrEF, and 646 [6.7%] with unknown subtype): 1105 in the oral semaglutide group and 1124 in the placebo group (eFigure 1 in Supplement 2). Echocardiogram data were available for 5902 (61.2%) of all participants and 1869 (83.8%) of those with reported HF at baseline. Data on LVEF for the different HF subtypes are provided in eTable 1 in Supplement 2.

The baseline characteristics were balanced between treatment arms within the groups by HF at baseline (**Table 1**). Participants with history of HF at baseline had higher body mass index (BMI), HbA_{1c}, diastolic BP, and hsCRP levels than participants without baseline HF history; concomitant sodium-glucose cotransporter 2 (SGLT2) inhibitor use was similar (Table 1). Among participants with HF, those with HFpEF had a higher BMI, BP, hsCRP, and concomitant use of SGLT2 inhibitors than those with HFrEF (eTable 2 in Supplement 2).

Figure 2. Time to First Composite Heart Failure (HF) Outcome in Subgroups Among Participants With HF at Baseline

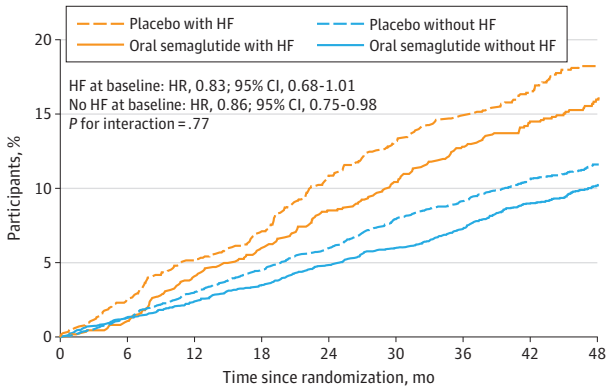
Subgroup	Participants with events, No./participants included in analysis, No.		HR (95% CI)	P value
	Oral semaglutide	Placebo		
Overall analysis	157/1105	200/1124	0.78 (0.63-0.96)	
HF subtype				
HFpEF	40/494	67/497	0.59 (0.39-0.86)	
HFrEF	68/296	67/296	0.98 (0.70-1.38)	.14
Unknown	49/315	66/331	0.76 (0.52-1.10)	
Sex				
Female	41/329	58/351	0.76 (0.51-1.13)	.91
Male	116/776	142/773	0.78 (0.61-1.00)	
Age, y				
<65	46/480	52/476	0.87 (0.58-1.30)	
≥65 to <75	78/490	100/490	0.73 (0.54-0.98)	.76
≥75	33/135	48/158	0.83 (0.53-1.29)	
BMI				
≤30	58/410	71/413	0.79 (0.56-1.12)	.91
>30	99/695	128/709	0.77 (0.59-1.01)	
HbA_{1c}, %				
≤8.0	97/607	104/608	0.92 (0.70-1.22)	.08
>8.0	60/487	94/502	0.63 (0.45-0.87)	
High-sensitivity CRP ratio to baseline				
<2	56/502	61/484	0.87 (0.60-1.25)	.49
≥2	101/603	139/640	0.75 (0.58-0.96)	
CV disease				
No prior MI or stroke	48/342	69/375	0.70 (0.49-1.02)	.48
Prior MI or stroke	108/750	127/732	0.83 (0.64-1.07)	
SGLT2 inhibitor				
No	121/815	162/852	0.76 (0.60-0.96)	.64
Yes	36/290	38/272	0.86 (0.54-1.36)	
MRA				
No	106/844	143/866	0.74 (0.57-0.95)	.51
Yes	51/261	57/258	0.86 (0.59-1.26)	
Diuretic				
No	38/435	46/429	0.64 (0.42-0.96)	.26
Yes	119/670	144/695	0.85 (0.66-1.08)	
Loop diuretic				
No	66/732	98/742	0.66 (0.48-0.89)	.12
Yes	91/373	102/382	0.91 (0.69-1.21)	
Region				
North America	53/177	44/173	1.23 (0.82-1.84)	.02
Europe	43/307	52/318	0.83 (0.55-1.24)	
Asia	19/132	30/171	0.81 (0.45-1.43)	
Other	42/489	74/462	0.51 (0.35-0.74)	
Race				
Asian	19/118	22/133	0.98 (0.53-1.82)	.36
Black or African American	5/27	7/27	0.73 (0.22-2.29)	
White	129/924	162/933	0.78 (0.62-0.98)	
Other	3/32	8/27	0.27 (0.06-0.94)	
Ethnicity				
Hispanic or Latino	20/118	30/132	0.73 (0.41-1.28)	.81
Not Hispanic or Latino	136/983	169/987	0.79 (0.63-0.99)	



Data are from the in-trial period in participants with HF at baseline. The composite HF outcome consists of HF hospitalization, urgent HF visit, or cardiovascular (CV) death. Time from randomization to relevant end point was analyzed using a Cox proportional hazards model with treatment as a fixed factor. Participants without events of interest were censored at the end of their in-trial period. For the subgroup analyses, estimated hazard ratios (HRs) and corresponding 95% CIs were calculated using a Cox proportional hazards model with interaction between treatment group and subgroup as a fixed factor. *P* values are for the test of no interaction effect. Race and ethnicity data were self-reported by participants, including the other category. BMI indicates body mass index (calculated as weight in kilograms divided by height in meters squared); CRP, C-reactive protein; HbA_{1c}, glycated hemoglobin A_{1c}; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium-glucose cotransporter 2.

Figure 3. Time to First Occurrence of Major Adverse Cardiovascular Event (MACE) by Treatment and Baseline Heart Failure (HF) Status

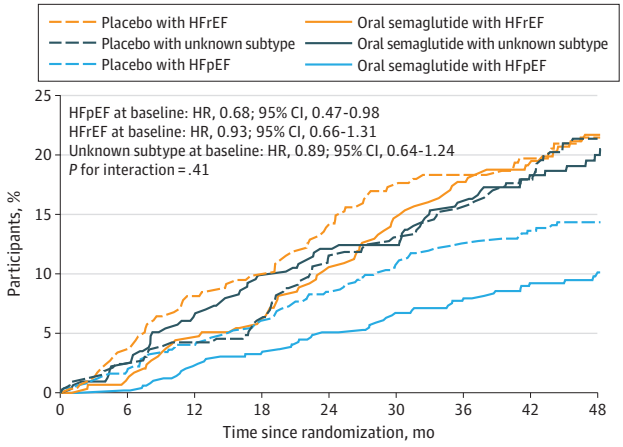
A MACE by HF status at baseline



No. at risk

Oral semaglutide with HF	1105	1085	1039	1010	972	944	909	810	526
Oral semaglutide without HF	3718	3656	3594	3530	3464	3400	3328	3019	2028
Placebo with HF	1124	1088	1047	1011	971	941	909	814	558
Placebo without HF	3700	3628	3538	3445	3368	3278	3211	2927	1975

B MACE by HF subtype in participants with HF at baseline



No. at risk

Oral semaglutide with HFpEF	494	492	474	465	451	441	430	379	254
Oral semaglutide with HFrEF	296	289	278	269	254	241	232	209	121
Oral semaglutide with unknown subtype	315	304	287	276	267	262	247	222	151
Placebo with HFpEF	497	483	464	452	434	416	405	357	256
Placebo with HFrEF	296	284	266	256	241	229	222	202	122
Placebo with unknown subtype	331	322	314	301	278	270	262	240	164

Data are from the in-trial full-analysis set. The MACE composite outcome comprised cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. For 3 participants, HF at baseline could not be determined. Missing data were defined as data planned to be collected according to protocol but not present in the database. Hence, data that are absent in the database due to death or administrative censoring were not considered missing and, therefore, not imputed. The *P* for interaction across HF subtypes (HF with preserved ejection fraction [HFpEF], HF with reduced ejection fraction [HFrEF], and unknown) and no HF at baseline in all randomized participants was .61. HR indicates hazard ratio.

Outcomes

HF Composite Outcome by Baseline HF Status

In the overall SOUL population, the HR with oral semaglutide compared with placebo for the time to first composite HF outcome event was 0.90 (95% CI, 0.79-1.03).[13] Among 2229 participants with HF at baseline, the composite HF outcome occurred in 157 of 1105 (14.2%; incidence rate, 3.81 per 100 person-years) receiving oral semaglutide and in 200 of 1124 (17.8%; incidence rate, 4.90 per 100 person-years) receiving placebo (HR, 0.78; 95% CI, 0.63-0.96); in 7418 participants without baseline HF, it occurred in 248 of 3718 (6.7%; incidence rate, 1.67 per 100 person-years) and 243 of 3700 (6.6%; incidence rate, 1.66 per 100 person-years), respectively (HR, 1.01; 95% CI, 0.84-1.20) (*P* for interaction = .06; **Figure 1**A). Individual components of the HF composite outcome (HF events or CV death) are shown in eFigure 3 in Supplement 2. Among participants with HF at baseline, HF events (HF hospitalization or urgent HF visit) occurred in 72 participants (6.5%) in the oral semaglutide group and 91 (8.1%) in the placebo group, while in participants without baseline HF, it was 74 (2.0%) and 76 (2.1%), respectively. CV death occurred in 112 participants (10.1%) in the oral semaglutide group and 131 (11.7%) in the placebo group among participants with HF at baseline; in the participants without baseline HF, it occurred in 189 participants (5.1%) in each treatment group.

In an analysis of HF composite outcome events occurring through week 156 (3 years) among participants with HF at baseline, 108 events occurred with oral semaglutide and 149 with placebo. The absolute risk reduction was 3.5 percentage points (95%

Table 2. Safety Outcomes by Heart Failure (HF) at Baseline and HF Subtypes[a]

Outcome	Participants with no HF at baseline, No. (%)		Participants with HF at baseline, No. (%)		HF subtype, participants, No. (%)					
					HFpEF		HFrEF		Unknown	
	Oral semaglutide (n = 3718)	Placebo (n = 3700)	Oral semaglutide (n = 1105)	Placebo (n = 1124)	Oral semaglutide (n = 494)	Placebo (n = 497)	Oral semaglutide (n = 296)	Placebo (n = 296)	Oral semaglutide (n = 315)	Placebo (n = 331)
SAE	1718 (46.2)	1785 (48.2)	594 (53.8)	642 (57.1)	227 (46.0)	261 (52.5)	173 (58.4)	187 (63.2)	194 (61.6)	194 (58.6)
AE leading to permanent discontinuation	577 (15.5)	399 (10.8)	172 (15.6)	160 (14.2)	61 (12.3)	51 (10.3)	58 (19.6)	52 (17.6)	53 (16.8)	57 (17.2)

Abbreviations: AE, adverse event; HFpEF, HF with preserved ejection fraction; HFrEF, HF with reduced ejection fraction; SAE, serious adverse event.

[a] Data are from the in-trial full-analysis set. For 3 participants, HF at baseline could not be determined.

CI, 0.8-6.1 percentage points; $P = .01$), and the number needed to treat to prevent 1 event was 29 persons.

Among 991 participants with the HFpEF subtype at baseline, the risk of an HF composite outcome was lower among those with HFpEF than those with HFrEF (2.84 and 6.56 events per 100 person-years, respectively; HR, 2.31; 95% CI, 1.80-2.99; $P < .001$). Compared with participants with no HF at baseline, the HR for risk of HF composite event was 1.72 (95% CI, 1.39-2.11) for those with HFpEF, 3.99 (95% CI, 3.28-4.81) for those with HFrEF, and 2.91 (95% CI, 2.37-3.56) for participants with unknown HF subtype ($P < .001$ for all). Comparing oral semaglutide and placebo, the composite HF outcome occurred in 40 of 494 participants (8.1%; incidence rate, 2.10 per 100 person-years) receiving oral semaglutide compared with 67 of 497 (13.5%; incidence rate, 3.60 per 100 person-years) in the placebo group (HR, 0.59; 95% CI, 0.39-0.86). In 592 participants with HFrEF, 68 of 296 events (23.0%; incidence rate, 6.50 per 100 person-years) occurred in participants receiving oral semaglutide and 67 of 296 (22.6%; incidence rate, 6.62 per 100 person-years) in those receiving placebo (HR, 0.98; 95% CI, 0.70-1.38). For 646 participants with unknown HF subtype, events occurred in 49 of 315 (15.6%; incidence rate, 4.17 per 100 person-years) receiving oral semaglutide and 66 of 331 (19.9%; incidence rate, 5.47 per 100 person-years) receiving placebo (HR, 0.76; 95% CI, 0.52-1.10). The P for interaction among the 3 HF subtype groups was .14 (Figure 1B). In the sensitivity analysis in which participants with unknown HF subtype were assumed to have either subtype, the updated HR was 0.67 (95% CI, 0.51-0.87) for HFpEF and 0.88 (95% CI, 0.69-1.13) for HFrEF. The overall risk of the HF composite outcome by HF baseline status independent of randomized treatment is shown in eTable 3 in Supplement 2.

Subgroup Analyses of HF Composite Outcome

Among participants with HF at baseline, no statistically significant interaction was observed for the benefit of oral semaglutide compared with placebo on the composite HF outcome with respect to HF subtype, CV disease history, demographics (age, sex, and race and ethnicity), or clinical characteristics at baseline (BMI, HbA_{1c}, and hsCRP) (**Figure 2**). Likewise, no statistically significant interaction was observed with other concomitant treatment at baseline, such as SGLT2 inhibitors, mineralocorticoid receptor antagonists (MRAs), or loop diuretics (Figure 2). Subgroup analyses among participants without HF at baseline are shown in eFigure 2 in Supplement 2.

MACE Composite Outcome by Baseline HF Status

In the overall population, oral semaglutide lowered the risk of MACE when compared with placebo (HR, 0.86; 95% CI, 0.77-0.96).[13] In participants with HF at baseline, MACE occurred in 180 (16.3%; incidence rate, 4.43 per 100 person-years) receiving oral semaglutide and 215 (19.1%; incidence rate, 5.34 per 100 person-years) receiving placebo (HR, 0.83; 95% CI, 0.68-1.01), and in participants without baseline HF, it was 399 (10.7%; incidence rate, 2.75 per 100 person-years) and 453 (12.2%; incidence rate, 3.20 per 100 person-years), respectively (HR, 0.86; 95% CI, 0.75-0.98) (P for interaction = .77; **Figure 3**A). Among participants with HF at baseline, the HR for risk of MACE with oral semaglutide compared with placebo was 0.68 (95% CI, 0.47-0.98) in participants with HFpEF (50 events [10.1%; incidence rate, 2.66 per 100 person-years] with oral semaglutide and 71 events [14.3%; incidence rate, 3.89 per 100 person-years] with placebo), 0.93 (95% CI, 0.66-1.31) with HFrEF (65 events [22.0%; incidence rate, 6.19 per 100 person-years] with oral semaglutide and 67 events [22.6%; incidence rate, 6.63 per 100 person-years] with placebo), and 0.89 (95% CI, 0.64-1.24) with unknown HF subtype (65 events [20.6%; incidence rate, 5.76 per 100 person-years] with oral semaglutide and 77 events [23.3%; incidence rate, 6.45 per 100 person-years] with placebo) (P for interaction = .41; Figure 3B). The overall risk of MACE by HF baseline status independent of randomized treatment is shown in eTable 3 in Supplement 2.

Clinical Efficacy Parameters During Trial by Baseline HF Status

There was no evidence of heterogeneity in the treatment effect of oral semaglutide based on HF status at baseline across the efficacy parameters of HbA_{1c}, body weight, hsCRP, and systolic/diastolic BP assessed as change from baseline to week 104 (eTable 4 in Supplement 2).

Safety

Among participants with HF at baseline, the proportions of participants with at least 1 SAE did not differ between oral semaglutide (594 [53.8%]) and placebo (642 [57.1%]) (**Table 2**). In participants with HFpEF, a smaller proportion of participants experienced at least 1 SAE with oral semaglutide (227 [46.0%]) than with placebo (261 [52.5%]) (Table 2). There were no major differences in the occurrence of AEs of special interest (pancreatitis and gastrointestinal or gallbladder disorders) among the groups by HF at baseline (eTable 5 in Supplement 2). The full list of safety outcomes for the oral semaglutide and placebo groups has been reported previously.[13]

Discussion

In this secondary analysis of the SOUL trial among individuals with T2D and ASCVD and/or CKD, we observed a reduction in the risk of the composite HF outcome (HF hospitalization, urgent HF visit, or CV death) with oral semaglutide compared with placebo in participants with HF history at baseline, with a notable, not statistically significant difference compared to the group without HF history at baseline (*P* for interaction = .06). The relative contributions of the individual components to the HF composite outcome appeared to be balanced. The treatment effect of oral semaglutide on HF-related outcomes appeared numerically greater in participants with HFpEF compared with those with HFrEF. Importantly, these benefits were seen with no differences in safety outcomes according to HF status at baseline.

In SOUL trial participants with HF history at baseline, the benefit of oral semaglutide on the composite HF outcome was generally consistent across subgroups by demographic and clinical characteristics at baseline, except for geographic region. It should be noted that the trial was not powered to compare the treatment effect across subgroups. Importantly, there were no meaningful interactions between the effects of oral semaglutide on HF outcomes and concomitant treatment with loop diuretics, MRAs, or SGLT2 inhibitors at baseline. Of note, 27% of SOUL participants were receiving SGLT2 inhibitors at baseline.[13] Use of SGLT2 inhibitors at the point of care in individuals with T2D is a potential proxy for more severe CV disease, as clinical guidelines prioritize these and similar agents for individuals with established ASCVD, HF, and CKD. Therefore, the findings of the benefits of oral semaglutide regardless of SGLT2 inhibitor or MRA use among SOUL participants are clinically meaningful, highlighting the potential benefit for adding a GLP-1 RA to these therapies in people with T2D, ASCVD and/or CKD, and HF.

The risk for both HF and MACE was consistently higher in participants with than without baseline HF. However, the treatment effect of oral semaglutide on both outcomes was observed only in participants with HFpEF, not in those with HFrEF. This larger treatment effect observed in participants with HFpEF could potentially be related to mechanistic differences between the subtypes. In diabetes, HFpEF is predominantly driven by coronary microvascular dysfunction and compromised nitric oxide–cGMP signaling, systemic inflammation, autonomic dysfunction and impaired myocardial oxidative metabolism, and enhanced advanced glycation end products/collagen crosslinks leading to remodeling and stiffness (particularly in those with T2D), while HFrEF is predominantly driven by adverse remodeling secondary to accelerated ASCVD/myocardial infarction.[16-20] The present findings suggest that, in individuals with HFpEF, the most prevalent HF subtype in T2D, oral semaglutide reduces the risk of both MACE and HF outcomes.

The benefits of oral semaglutide in reducing the risk of a composite HF outcome in participants with HF at baseline were not associated with increased SAEs when compared with placebo. In the subgroup with HFpEF, the incidence of SAEs was numerically lower in those randomized to oral semaglutide than to placebo. The safety of oral semaglutide in people with HF, including those with HFrEF, is clinically relevant, reassuring clinicians who provide daily care for such patients, who are often treated with multiple pharmaceutical therapies.

Given the high prevalence of HF (and particularly HFpEF) in people with T2D and in those with obesity, these data provide additional information for clinicians when considering therapy choices and impact on HF outcomes in people with or without known HF. Compared with those without T2D, individuals with HFpEF and T2D exhibit worse prognosis, likely driven by higher burden of comorbidities, underlying microvascular dysfunction, insulin resistance, autonomic imbalance, and mitochondrial abnormalities.[1]

Several other trials have previously evaluated HF outcomes with subcutaneous semaglutide in people with T2D with HFpEF,[10] among people with T2D and CKD,[11] or in individuals with overweight/obesity and ASCVD but without T2D.[12] Although there were differences in the phenotypes of participants included, these prior trials reported more or less similar results to the results described herein with oral semaglutide in participants with T2D and ASCVD and/or CKD. It should also be noted that similar benefits have been reported with the long-acting GLP-1 and gastric inhibitory polypeptide receptor agonist tirzepatide.[21]

Strengths and Limitations

Strengths of these analyses include standardized data collection and centrally adjudicated HF outcomes, minimizing bias and providing a deeper understanding of the effects of oral semaglutide across specific T2D individual phenotypes. Limitations include those intrinsic to a secondary analysis, such as the small number of participants in some of the subgroups, which restricts the power to detect meaningful treatment differences within or between subgroups. The analysis of HF outcomes was also not adjusted for multiple comparisons. Another limitation of the analyses is that HF subtype classification relied on investigator-reported data rather than standardized clinical assessments (eg, by N-terminal pro–B-type natriuretic peptide), which may have led to some participants being misclassified. HFrEF was generally defined as LVEF less than 40% and HFpEF as 40% or higher, but systematic assessment of LVEF was not collected at baseline. Given the variability of LVEF over time, some participants may have changed subtype between diagnosis and trial inclusion. Finally, a substantial proportion of participants with HF in SOUL (nearly 30%) could not be further subtyped. As participants were clinically stable at baseline, the results may not apply to patients recently hospitalized, with unstable HF, or with NYHA class IV HF, as they were excluded from the SOUL trial.

Conclusions

In this secondary analysis of the SOUL randomized clinical trial among individuals with T2D and ASCVD and/or CKD, we observed a reduction in the composite risk of HF hospitalization, urgent HF visit, or CV death in those with a history of HF receiving oral semaglutide compared with placebo, despite a high base-

line use of SGLT2 inhibitors and MRAs, and without increasing the risk of SAEs. These benefits were attributed mostly to those with HFpEF, with no indication of compromised safety in HFrEF. These data therefore support the potential role of oral semaglutide in reducing HF events in people with T2D, ASCVD and/or CKD, and HF, particularly in those with HFpEF.

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Acquisition, analysis, or interpretation of data: Pop-Busui, Rasmussen, Deanfield, Buse, Marx, Mulvagh, Inzucchi, Mann, Emerson, Engelmann, Bayer Tanggaard, Birkenfeld, Connelly, Haluzik, Kellerer, Jhund, Gregersen, Nielsen, Lam, McGuire.
Drafting of the manuscript: Pop-Busui, Deanfield, Nielsen.
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director of Us2.ai; and a patent for PCT/SG2016/050217 pending and US Patent Nos. 10,631,828 B1; US 10,702,247 B2; US 11,301,996 B2; US 11,446,009 B2; US 11,931,207 B2; US 12,001,939; and US 12,400,762 B2 issued. Prof McGuire reported personal fees from Novo Nordisk, Lilly, Boehringer Ingelheim, Lexicon, Amgen, Neurotronic, Kailera, Alveus, Regor, F. Hoffmann-La Roche, New Amsterdam, Metsera, and Novartis during the conduct of the study. No other disclosures were reported.

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SOUL Study Group: The members of the SOUL Study Group appear in Supplement 3.

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