Semaglutide effects on cardiovascular outcomes in people with overweight or obesity

SELECT Cardiovascular Outcomes Trial

Semaglutide 2.4 mg

SELECT is a Phase 3b, multinational, randomized, double-blind, placebo controlled, event-driven superiority trial that evaluated the effect of semaglutide 2.4 mg vs placebo, both in addition to SoC for CVD, in patients with established CVD and overweight or obesity on CV outcomes.[1]

Key Eligibility Criteria[2]

- Adults (age ≥45 years) with a BMI ≥27 kg/m²
- A1C <6.5%, and no history of type 1 or 2 diabetes
- Established CVD, defined as prior MI, prior stroke (ischemic or hemorrhagic) or symptomatic PAD (as evidenced by ≥1 of the following; intermittent claudication with ABI <0.85 at rest, history of peripheral arterial revascularization or amputation due to atherosclerotic disease
- Key exclusion criteria: history of either type 1 or type 2 diabetes, A1C ≥6.5% at screening or treatment with glucose-lowering agents or GLP-1 RAs within previous 90 days, NYHA Class IV HF, a CV or neurological event within previous 60 days, or ESRD or hemodialysis (chronic or intermittent) or peritoneal dialysis.

Study Design[2]

Patients were randomized (1:1) to semaglutide 2.4 mg or placebo, both in addition to SoC for CVD.

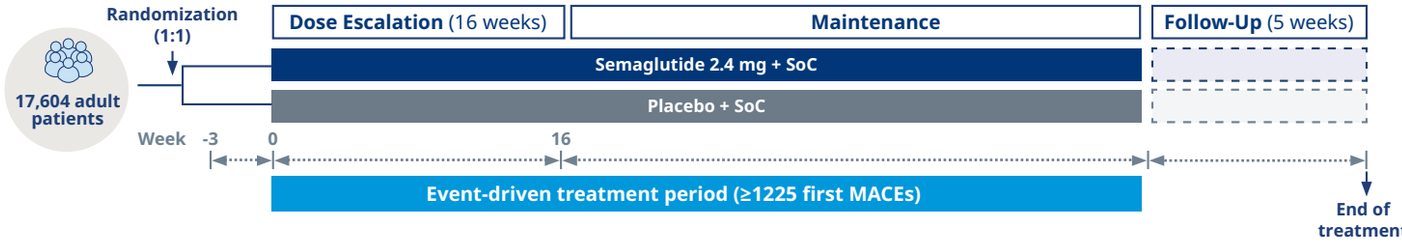


Figure 1: SELECT Trial Design[2]
Note: once-weekly semaglutide 2.4 mg and placebo are given as an adjunct to SoC (guideline-directed medical treatment, individualized healthy lifestyle guidance) for CVD.

Cardiovascular Endpoints[a]

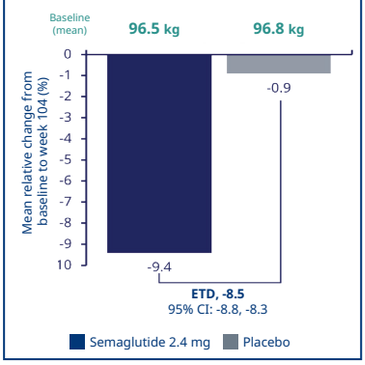
	Semaglutide 2.4 mg (n=8803)	Placebo (n=8801)	HR (95% CI); *p*-value[d]
Primary CV composite endpoints, n (%)[b]	569 (6.5)	701 (8.0)	0.80 (0.72 to 0.90); *P*<.001[d]
Confirmatory secondary endpoints, n (%)[c]			
CV death	223 (2.5)	262 (3.0)	0.85 (0.71 to 1.01); *P*=.07[d]
HF composite[e]	300 (3.4)	361 (4.1)	0.82 (0.71 to 0.96)
All-cause death	375 (4.3)	458 (5.2)	0.81 (0.71 to 0.93)
Supportive secondary endpoints, n (%)[f,g]			
CV expanded composite[h]	873 (9.9)	1074 (12.2)	0.80 (0.73 to 0.87)
CV composite with all-cause death[i]	710 (8.1)	877 (10.0)	0.80 (0.72 to 0.8)
Nonfatal MI	234 (2.7)	322 (3.7)	0.72 (0.61 to 0.85)
Nonfatal stroke	154 (1.7)	165 (1.9)	0.93 (0.74 to 1.15)
HF-related hospitalization or urgent medical visit	97 (1.1)	122 (1.4)	0.79 (0.60 to 1.03)
Nephropathy composite[j]	155 (1.8)	198 (2.2)	0.78 (0.63 to 0.96)

a. Data from the in-trial period (uninterrupted time from randomization to last contact with trial site) in time-to-event analyses.
b. Primary CV composite endpoints consisted of time from randomization to the first occurence of CV death, no-fatal MI or non-fatal stroke.
c. Confirmatory secondary endpoints were assessed in the following hierarchial order: CV death, HF composite endpoints or all-cause death. Stagewise hierarchial testing was used for multipliity control, in which statistical significance at each step was required to test the next hypothesis. Following the non-significant *P*-value for first confirmatory secondary endpoints. Statistical testing was not performed for the remaining confirmatory secondary endpoints.
d. For the primary and confirmatory secondary endpoints, a *P*-value below the nominal limit demonstrated superiority. The nominal two-sided significance level was 0.046 for the primary composite endpoints and 0.023 for CV death.
e. HF composite endpoints consisted of the first occurence of CV death or HF-related hospitalization or urgent medical visit for HF.
f. Supportive secondary endpoints were not controlled for multiplicity.
g. Please note, this is not an all-inclusive list of supportive secondary endpoints.
h. CV expanded composite endpoints consisted of the first occurence of CV death, non-fatal MI, non-fatal stroke, coronary revascularization or hospitalization for unstable angina.
i. CV composite endpoints with all-cause death consisted of the first occurence of all-cause death, non-fatal MI or non-fatal stroke.
j. Nephropathy composite endpoints consisted of the first occurence of renal death, initiation of chronic RRT (dialysis or transplantation), onset of persistent eGFR <1 mL/min/1.73 m², persistent 50% eGFR reduction from baseline or onset of persistent macroalbuminuria (uACR >300 mg/g).

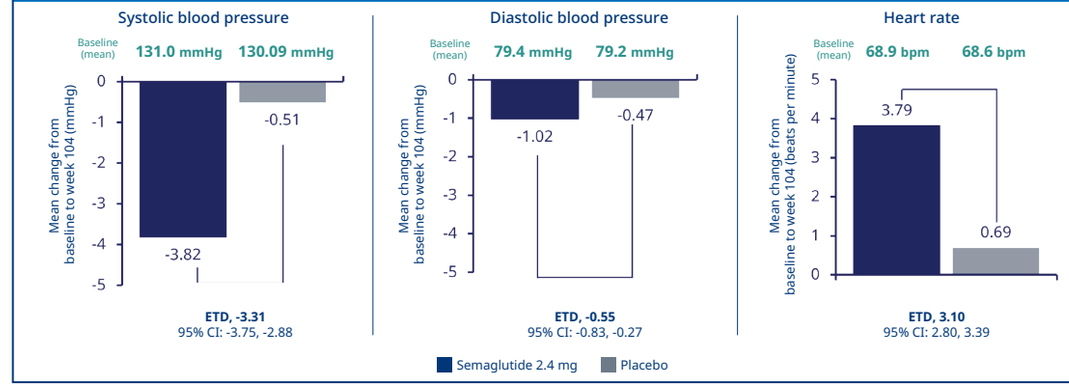
Per the intention-to-treat analysis, which assesses the treatment effect regardless of rescue intervention or adherence to trial product, semaglutide 2.4 mg significantly reduced the relative risk of the primary composite endpoint of time to first occurence of CV death, non-fatal MI or non-fatal stroke by 20%.[1]

Additional Supportive Secondary Endpoints[1]

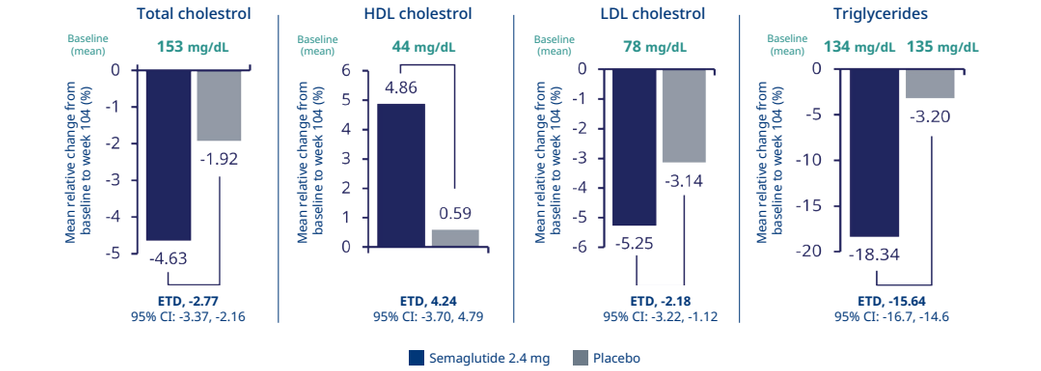
Body Weight



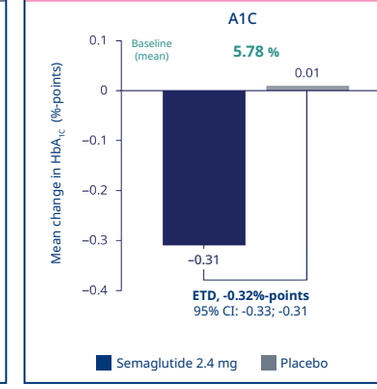
Blood Pressure and Heart rate



Lipids



A1C



Safety

- During the trial, more placebo-treated patients reported serious adverse events (SAEs) than patients treated with semaglutide 2.4 mg.[1]
- Trial product discontinuation due to AEs occured in more patients treated with semaglutide 2.4 mg than placebo-treated patients, with the largest between-group difference in gastrointestinal events.

Table 2. Safety Overview [1,a]

Investigator-Reported AEs, n (%)	Semaglutide 2.4 mg (n=8803)	Placebo (n=8801)	*P*-value
SAE[b]	2941 (33.4)	3204 (36.4)	<.001
Cardiac disorders	1008 (11.5)	1184 (13.5)	<.001
Infections and infestations	624 (7.1)	738 (8.4)	.001
Nervous system disorders	444 (5.0)	496 (5.6)	.08
Surgical and medical procedures	433 (4.9)	548 (6.2)	<.001
Neoplasms benign, malignant, and unspecified	405 (4.6)	402 (4.6)	.94
GI disorders	342 (3.9)	323 (3.7)	.48
AEs leading to trial product discontinuation[b]	1461 (16.6)	718 (8.2)	<.001
GI disorders	880 (10.0)	172 (2.0)	<.001
Nervous system disorders	124 (1.4)	92 (1.0)	.03
Metabolism and nutrition disorders	108 (1.2)	27 (0.3)	<.001
General disorders and administration site conditions	105 (1.2)	47 (0.5)	<.001
Neoplasms benign, malignant, and unspecified	80 (0.9)	105 (1.2)	.07
Infections and infestations	75 (0.9)	84 (1.0)	.47
Prespecified AEs of special interest, irrespective of seriousness[c]			
COVID-19 related events	2108 (23.9)	2150 (24.4)	.46
Malignant neoplasms	422 (4.8)	418 (4.7)	.92
Gallbladder-related disorders	246 (2.8)	203 (2.3)	.04
Acute renal failure	171 (1.9)	200 (2.3)	.13
Acute pancreatitis[d]	17 (0.2)	24 (0.3)	.28

a. Targeted safety data collection was utilized: only SAEs, AEs leading to trial product discontinuation irrespective of seriousness, and prespecified AEs of special interest irrespective of seriousness were systematically collected and reported.
b. Classified by system organ class.
c. Based on prespecified MedDRA queries
d. EAC-confirmed acute pancreatitis events.

Abbreviations: A1C: glycated hemoglobin; ABI: ankle-brachial index; AE: adverse event; BMI: body mass index; BPM: beats per minute; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; CVOT: cardiovascular outcomes trial; eGFR: estimated glomerular filtration rate; ETD: estimated treatment difference; GI: gastrointestinal; HDL: high-density lipoprotein; HF: heart failure; HR: hazard ratio; LDL: low-density lipoprotein; MACE: major adverse cardiovascular events; MedDRA: Medical Dictionary for Regulatory Activities; MI: myocardial infarction; n: number of patients; RRT: renal replacement therapy; PAD: peripheral arterial disease; SAE: serious adverse event; SOC: standard of care; uACR: urinary albumin-to-creatinine ratio.

Wegovy® (semaglutide 2.4 mg) prescribing information. Last revised Mar 2024. Available https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/215256s011lbl.pdf
References: 1. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and Cardiovascular Outcomes in Obesity without Diabetes. *New England Journal of Medicine*. 2023. 2. Ryan DH, Lingvay I, Colhoun HM, et al. Semaglutide Effects on Cardiovascular Outcomes in People With Overweight or Obesity (SELECT) rationale and design. *Am Heart J.* 2020;229:61-69.