ACC.25

Oral Semaglutide Reduces Cardiovascular Events in People with Type 2 Diabetes with Atherosclerotic Cardiovascular and/or Chronic Kidney Disease: Primary Results From the SOUL Randomized Trial

Darren K. McGuire, M.D., MHSc

on behalf of the SOUL study group

University of Texas Southwestern Medical Center, and Parkland Health System, Dallas, Texas, USA

AMERICAN COLLEGE of CARDIOLOGY

SOUL
semaglutide | cardiovascular outcomes trial

Presenter disclosures

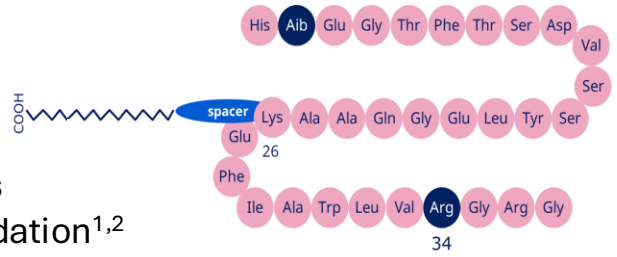
Consulting fees: Novo Nordisk, AstraZeneca, Pfizer, Altimmune, Ventyx Pharmaceuticals, Bayer, Lexicon, Applied Therapeutics, Intercept Pharmaceuticals, Esperion, Lilly USA, Boehringer Ingelheim, NewAmsterdam, CSL Behring, Amgen, Neurotronics, Metsera, Kailera and Alveus Pharma

SOUL
semaglutide | cardiovascular outcomes trial

Oral semaglutide is formulated with semaglutide and an absorption enhancer

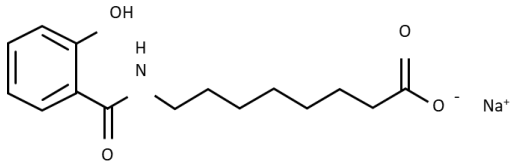
Semaglutide

- 94% homology to human GLP-1[1,2]
- Amino acid substitution protects against DPP-4 degradation[1,2]



SNAC (Sodium N-(8-(2-hydroxybenzoyl) Amino) Caprylate)

- SNAC causes a local increase of pH that protects against proteolytic degradation and facilitates absorption across the gastric epithelium[3]



- Increases bioavailability of oral administration[3]

OD oral semaglutide

Effective reductions in HbA_{1c}, body weight and CV risk factors[4–6]

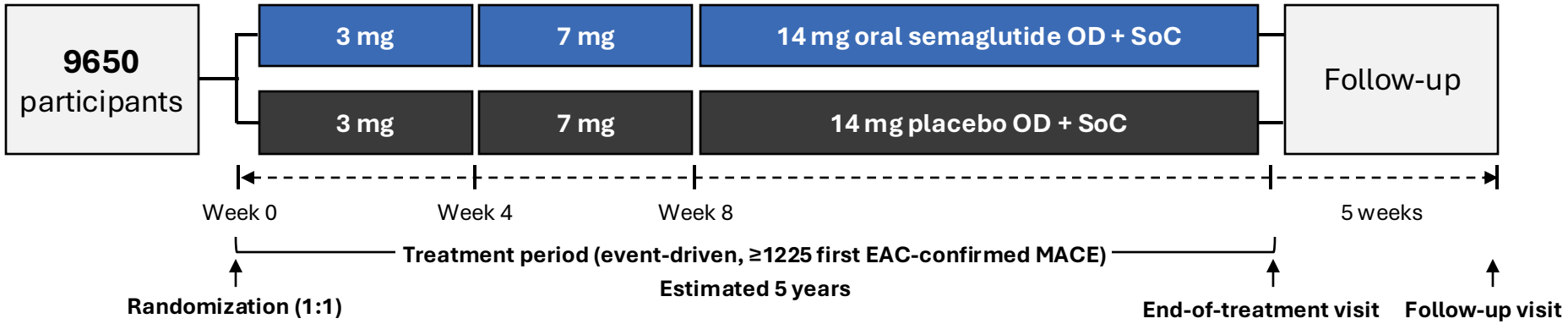
CV, cardiovascular; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; HbA_{1c}, glycated hemoglobin; OD, once-daily.

1. Lau *et al. J Med Chem* 2015;58:7370–80;
2. Kapitza *et al. J Clin Pharmacol* 2015;55:497–504;
3. Buckley *et al. Sci Transl Med* 2018;10:eaar7047;
4. Husain *et al. N Engl J Med* 2019;381:841–51;
5. Thethi *et al. Diabetes Obes Metab* 2020;22:1263–77;
6. Pratley *et al. Diabetes Ther* 2021;12:1099–116.

SOUL
semaglutide | cardiovascular outcomes trial

SOUL trial design

NCT03914326



Objective:
To assess the CV efficacy of oral semaglutide with regards to the risk of MACE compared with placebo in persons with T2D and at high risk of CV events

Key inclusion criteria*

- Age ≥50 years
- Diagnosed with T2D
- HbA_{1c} 6.5–10.0% (47–86 mmol/mol)
- History of ≥1 of the following conditions:
  - Coronary heart disease
  - Cerebrovascular disease
  - Symptomatic peripheral arterial disease
  - Chronic kidney disease†

Trial information

- Randomized, double-blind, parallel-group, placebo-controlled trial
- Group sequential design with one interim test for superiority
- Trial product added on top of SoC
- Dose reductions and treatment pauses allowed
- Selective safety reporting

*Established at screening.
†Defined as eGFR <60 mL/min/1.73 m^2 based on medical records ≤6 months old.
CV, cardiovascular; EAC, events adjudication committee; HbA_{1c}, glycated hemoglobin; MACE, major adverse cardiovascular event; OD, once daily; SoC, standard of care; T2D, type 2 diabetes.

SOUL
semaglutide | cardiovascular outcomes trial

SOUL trial outcomes and testing hierarchy

Primary outcome: 3-point MACE
CV death, nonfatal myocardial infarction, nonfatal stroke

↓ Superiority if $p<0.02281^{*}$

First confirmatory secondary outcome: 5-point composite kidney outcome
eGFR <15 mL/min/1.73 m^2, chronic kidney replacement therapy

↓ Superiority if $p<0.02216^{*}$

Second confirmatory outcome: CV death†

↓ Superiority if $p<0.02245^{*}$

Third confirmatory outcome: Major adverse limb events
Acute or chronic limb ischemia requiring hospitalization

Superiority if $p<0.02267^{*}$

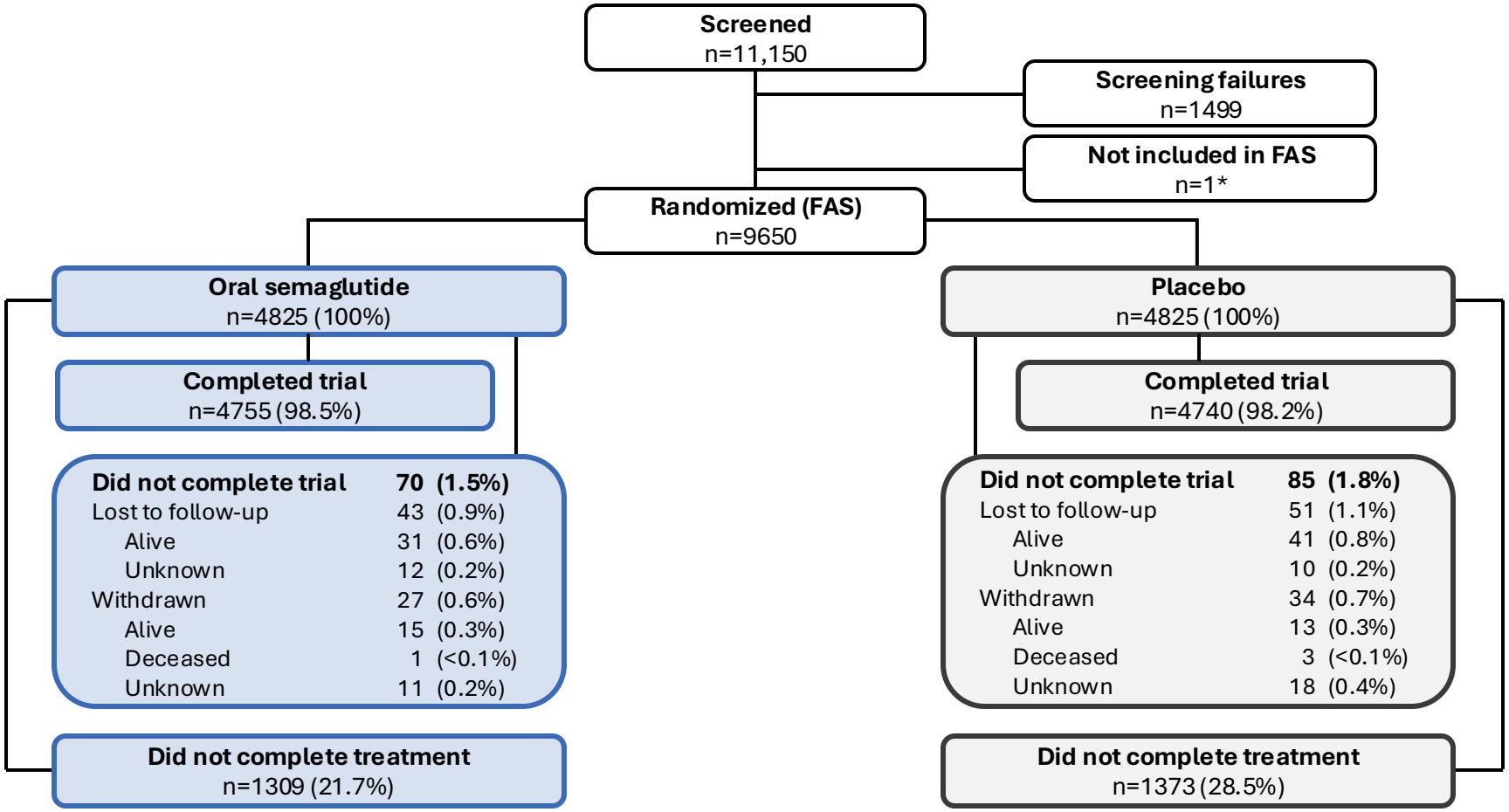
Supporting secondary outcomes included:

- Individual components of composite outcomes
- Coronary revascularization
- Hospitalization for unstable angina
- Death from non-CV causes
- Heart failure composite
- Metabolic parameters
- Inflammation markers
- Safety

*Limit determined by the Lan-DeMets alpha spending function, approximating the O'Brien-Fleming's stopping boundaries accounting for the group sequential design (interim analysis). The significance level depended on the exact number of events at interim and final analyses.
†Includes undetermined cause of death.
CV, cardiovascular; eGFR, estimated glomerular filtration rate; MACE, major adverse cardiovascular event.

SOUL
semaglutide | cardiovascular outcomes trial

Participant disposition



*Randomization was removed due to one participant being randomized more than once. Participants who completed the trial were defined as those who attended the follow-up visit or died during the trial.
FAS, full analysis set.

SOUL
semaglutide | cardiovascular outcomes trial

Baseline characteristics

	Oral semaglutide (n=4825)	Placebo (n=4825)
Age, years	66.1 (7.6)	66.1 (7.5)
Sex, n (%)		
Male	3449 (71.5)	3411 (70.7)
Female	1376 (28.5)	1414 (29.3)
HbA_{1c}, %	8.0 (1.2)	8.0 (1.1)
BMI, kg/m²	31.0 (5.7)	31.2 (5.9)
Diabetes duration, years, median (IQR)	14.7 (9.0–20.8)	14.6 (8.9–20.8)
ASCVD only	2730 (56.6)	2738 (56.7)
CKD* only	632 (13.1)	609 (12.6)
ASCVD and CKD*	1303 (27.0)	1317 (27.3)

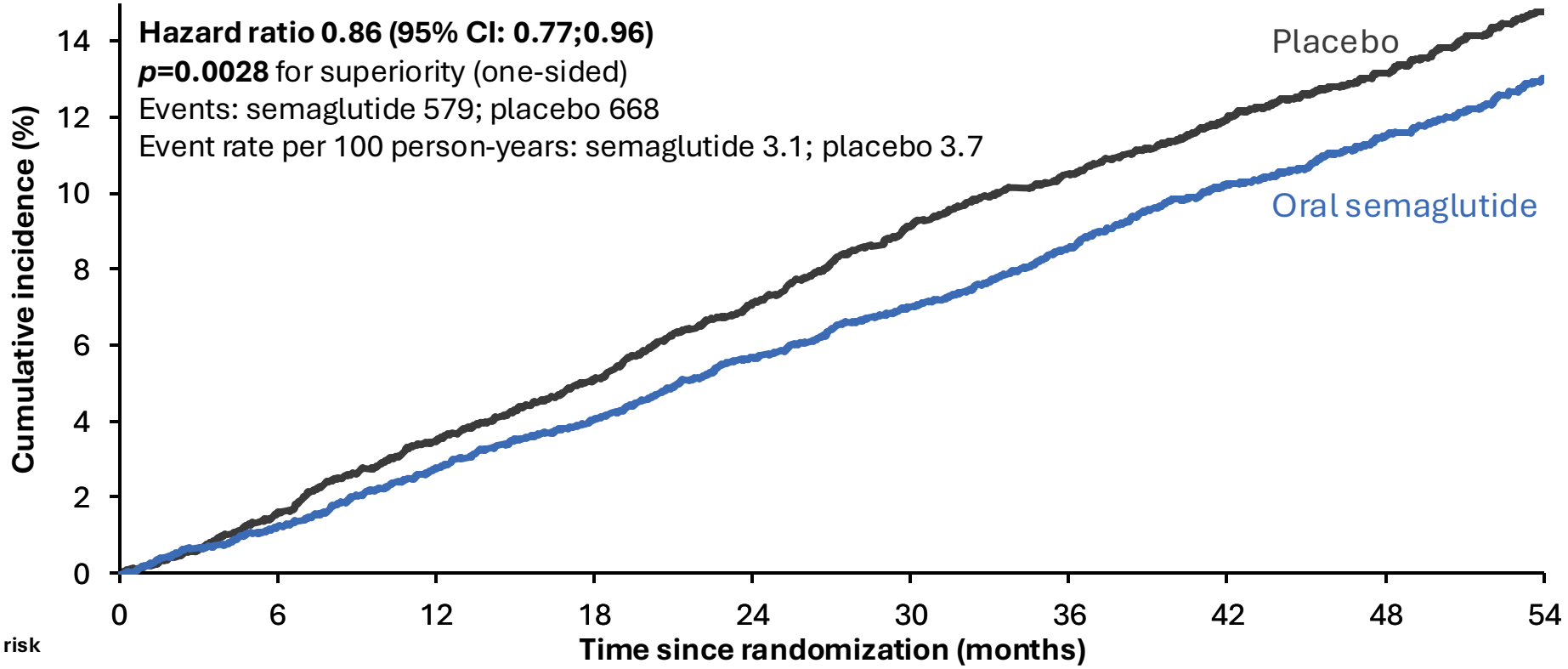
	Oral semaglutide (n=4825)	Placebo (n=4825)
eGFR†, mL/min/1.73 m²	74.0 (22.6)	73.6 (22.6)
eGFR subgroups, n (%)		
<15	7 (0.1)	4 (<0.1)
≥15 to <30	113 (2.3)	114 (2.4)
≥30 to <45	474 (9.8)	475 (9.8)
≥45 to <60	811 (16.8)	818 (17.0)
≥60 to <90	1845 (38.2)	1903 (39.4)
≥90	1531 (31.7)	1472 (30.5)
hsCRP, mg/L, median (IQR)	2.0 (0.9–4.3)	2.0 (0.9–4.5)
SGLT2i use, n (%)	1296 (26.9)	1300 (26.9)

Data are mean (SD) except where stated.
*Defined as eGFR <60 mL/min/1.73 m².
†Calculated with the CKD-EPI method.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD-EPI, chronic kidney disease epidemiology collaboration; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein; IQR, interquartile range; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

SOUL
semaglutide | cardiovascular outcomes trial

3-point MACE composite

Primary outcome



No. at risk										
Placebo	4825	4718	4583	4455	4322	4194	4101	3727	2517	1346
Semaglutide	4825	4743	4835	4542	4438	4346	4239	3831	2555	1346

Components:

- CV death
- Nonfatal MI
- Nonfatal stroke

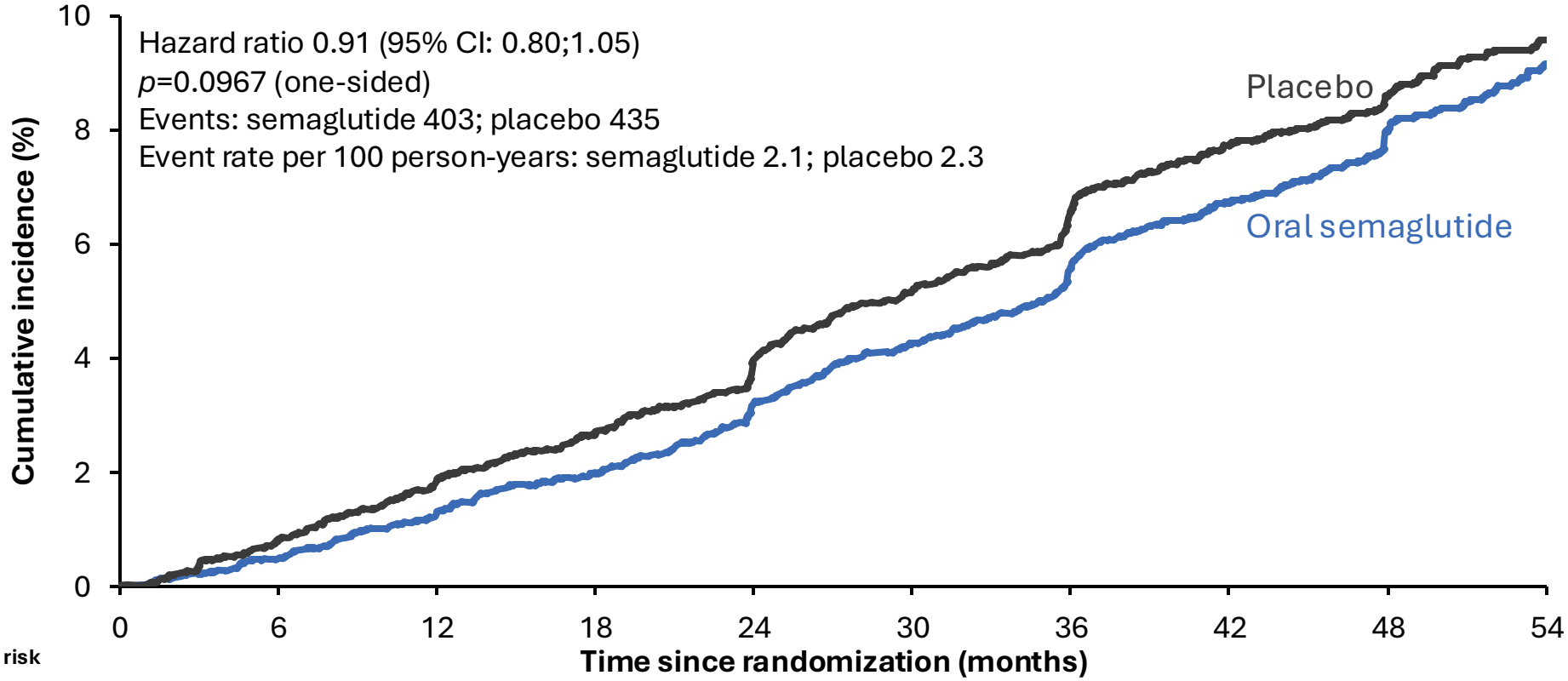
- Results consistent across pre-specified sensitivity analyses
- Absolute risk reduction 2% over 3 years
- NNT = 50

Cumulative incidence estimates are based on time from randomization to first MACE with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Time from randomization to first MACE was analysed using a Cox proportional hazards model with treatment as categorical fixed factor. Adjustment for group sequential design was done using likelihood ratio ordering.
CI, confidence interval; CV, cardiovascular; MACE, major adverse cardiovascular event; MI, myocardial infarction; NNT, number needed to treat.

SOUL
semaglutide | cardiovascular outcomes trial

5-point major kidney disease events composite

Confirmatory secondary outcome



No. at risk										
Placebo	4825	4753	4661	4570	4469	4378	4282	3911	2658	1429
Semaglutide	4825	4778	4704	4636	4551	4469	4372	3973	2681	1430

Components:

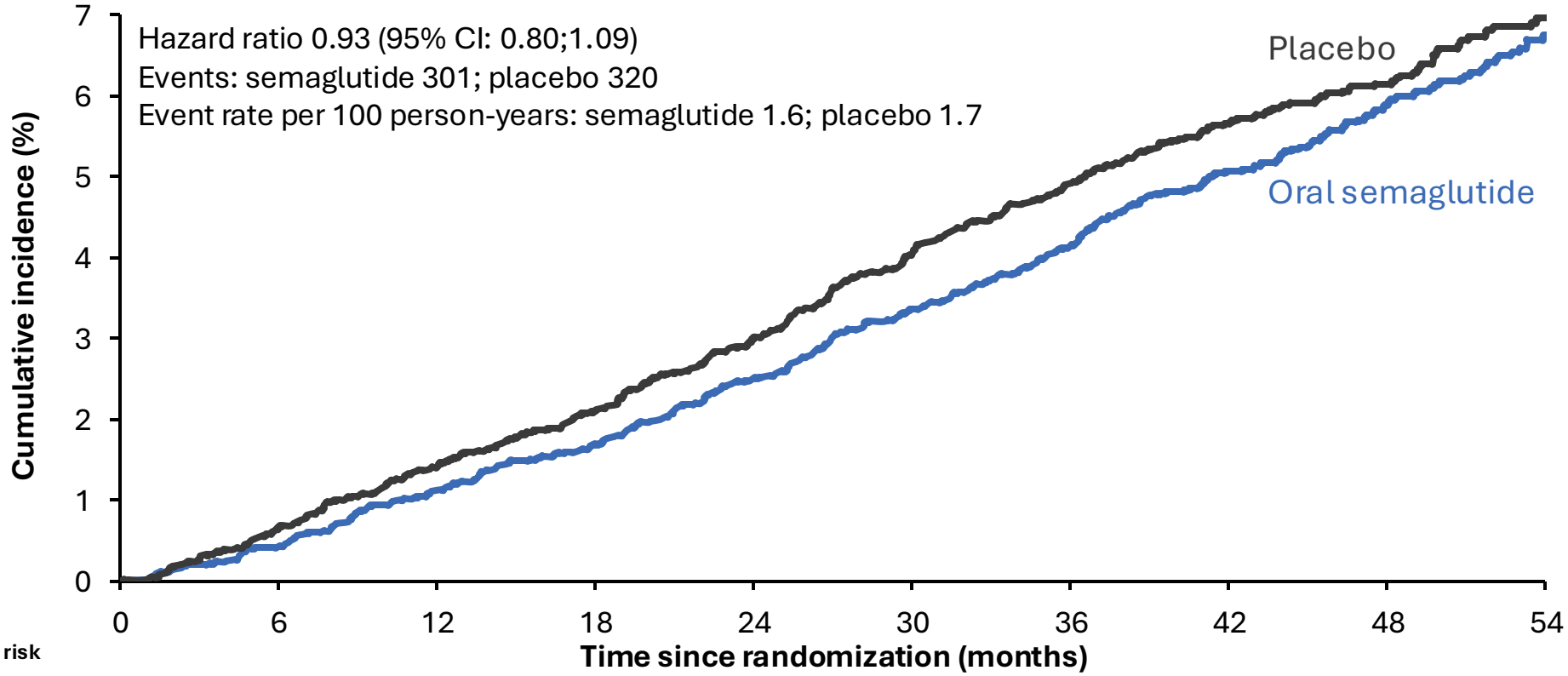
- CV-related death
- Kidney-related death
- Persistent ≥50% eGFR reduction
- Persistent eGFR <15 mL/min/1.73 m^2
- Chronic kidney replacement therapy

eGFR values were assessed at Week 0, 13, 52, and annually thereafter.
Cumulative incidence estimates are based on time from randomization to first major kidney disease event, with non-CV death modelled as competing risk using the Aalen-Johansen estimator.
Time from randomization to first composite major kidney disease outcome was analysed using a Cox proportional hazards model with treatment as categorical fixed factor.
CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; eGFR, estimated glomerular filtration rate.

SOUL
semaglutide | cardiovascular outcomes trial

CV death

Confirmatory secondary outcome



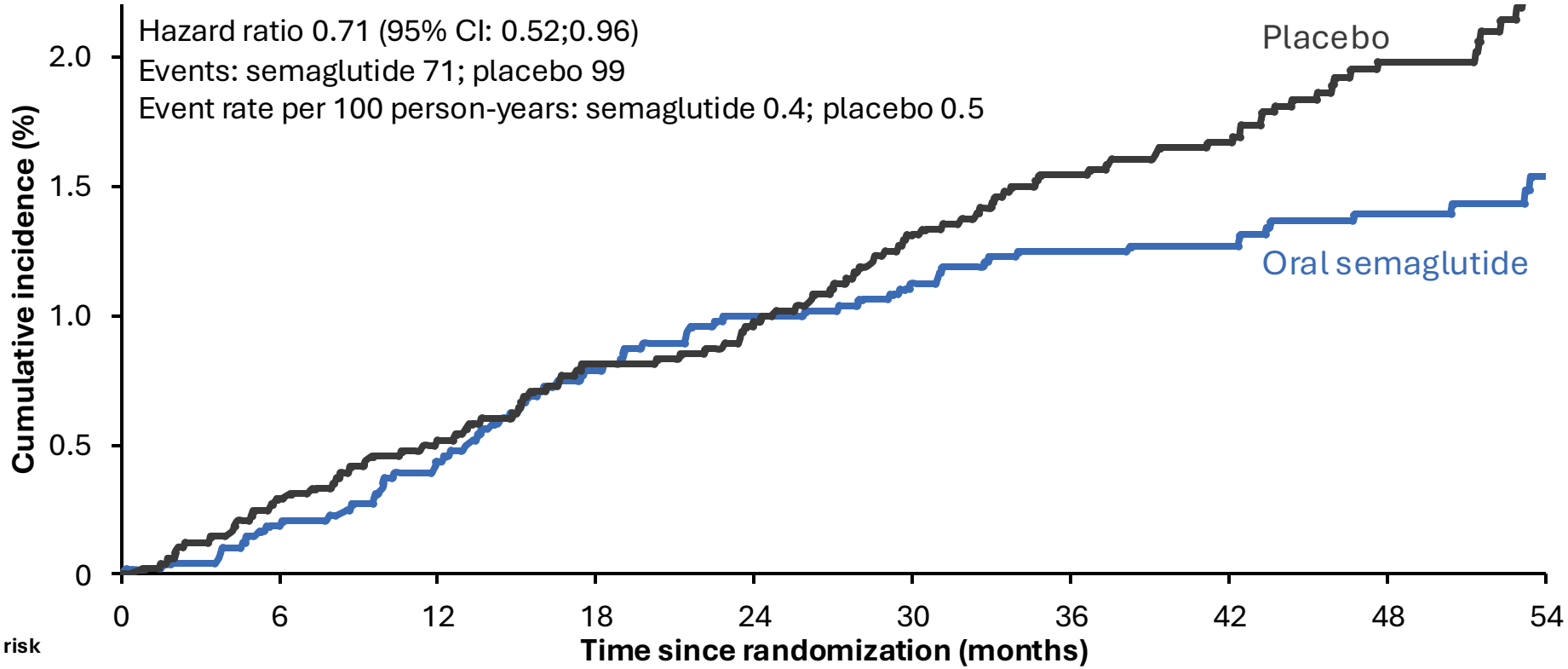
No. at risk										
Placebo	4825	4760	4680	4594	4511	4427	4355	3991	2721	1460
Semaglutide	4825	4781	4712	4648	4583	4509	4436	4040	2727	1460

Cumulative incidence estimates are based on time from randomization to CV death with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Time from randomization to CV death was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor.
CI, confidence interval; CV, cardiovascular.

SOUL
semaglutide | cardiovascular outcomes trial

Major adverse limb event composite

Confirmatory secondary outcome



Components:

- Hospitalization for acute limb ischemia
- Hospitalization for chronic limb ischemia

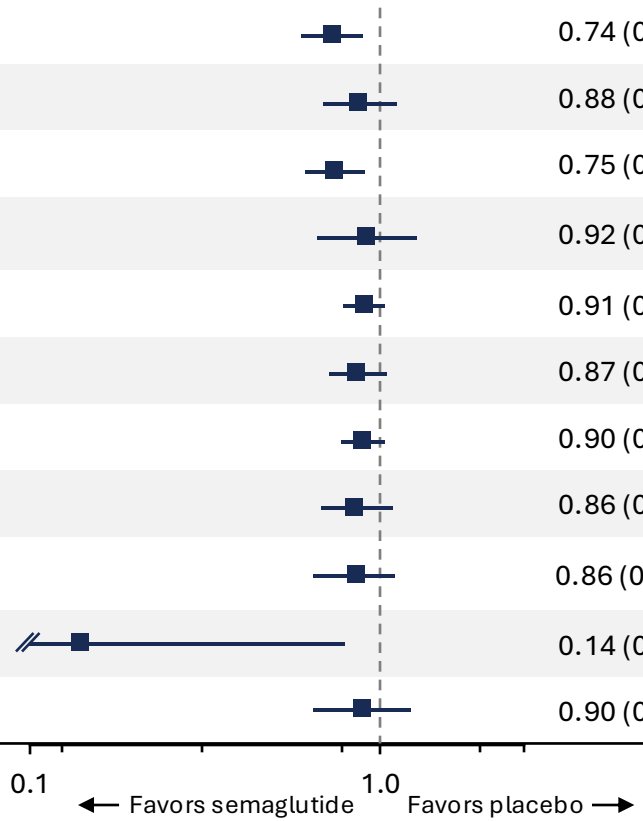
No. at risk										
Placebo	4825	4746	4655	4559	4470	4376	4296	3940	2678	1436
Semaglutide	4825	4772	4691	4612	4540	4463	4388	3999	2696	1439

Cumulative incidence estimates are based on time from randomization to CV death with non-CV death modelled as competing risk using the Aalen-Johansen estimator. Time from randomization to CV death was analyzed using a Cox proportional hazards model with treatment as categorical fixed factor.
CI, confidence interval

SOUL
semaglutide | cardiovascular outcomes trial

Supportive secondary outcomes

Event	Oral semaglutide (n=4825)		Placebo (n=4825)		Hazard ratio (95% CI)
	n (%)	*Rate*	*n (%)*	*Rate*	
Nonfatal MI	191 (4.0)	1.0	253 (5.2)	1.4	0.74 (0.61;0.89)
Nonfatal stroke	144 (3.0)	0.8	161 (3.3)	0.9	0.88 (0.70;1.11)
Coronary revascularization*	200 (4.1)	1.1	263 (5.5)	1.4	0.75 (0.62;0.90)
Hospitalization for unstable angina	74 (1.5)	0.4	80 (1.7)	0.4	0.92 (0.67;1.26)
All-cause death	528 (10.9)	2.8	577 (12.0)	3.0	0.91 (0.80;1.02)
Non-CV death	227 (4.7)	1.2	257 (5.3)	1.4	0.87 (0.73;1.04)
Heart failure composite†	405 (8.4)	2.1	443 (9.2)	2.4	0.90 (0.79;1.03)
Heart failure‡	146 (3.0)	0.8	167 (3.5)	0.9	0.86 (0.69;1.08)
4-point major kidney disease events composite§	112 (2.3)	0.6	129 (2.7)	0.7	0.86 (0.66;1.10)
Death from kidney cause¶	1 (<0.1)	(<0.1)	7 (0.1)	(<0.1)	0.14 (0.01;0.79)
Severe hypoglycemic episode	76 (1.6)	0.5	84 (1.7)	0.6	0.90 (0.66;1.22)

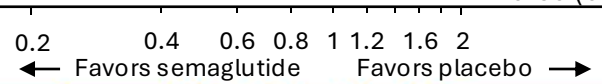


*Included only coronary revascularization for ACS.
†Death from CV cause, heart failure requiring hospitalization or urgent outpatient heart failure visit.
‡Hospitalization for heart failure and urgent outpatient heart failure visits.
§Death from kidney cause, onset of persistent ≥50% reduction in eGFR from baseline, onset of persistent eGFR <15 mL/min/1.73 m² or initiation of chronic kidney replacement therapy.
¶Lower CI limit not graphically shown.
ACS, acute coronary syndrome; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; Rate, incidence rate per 100 person-years.

SOUL
semaglutide | cardiovascular outcomes trial

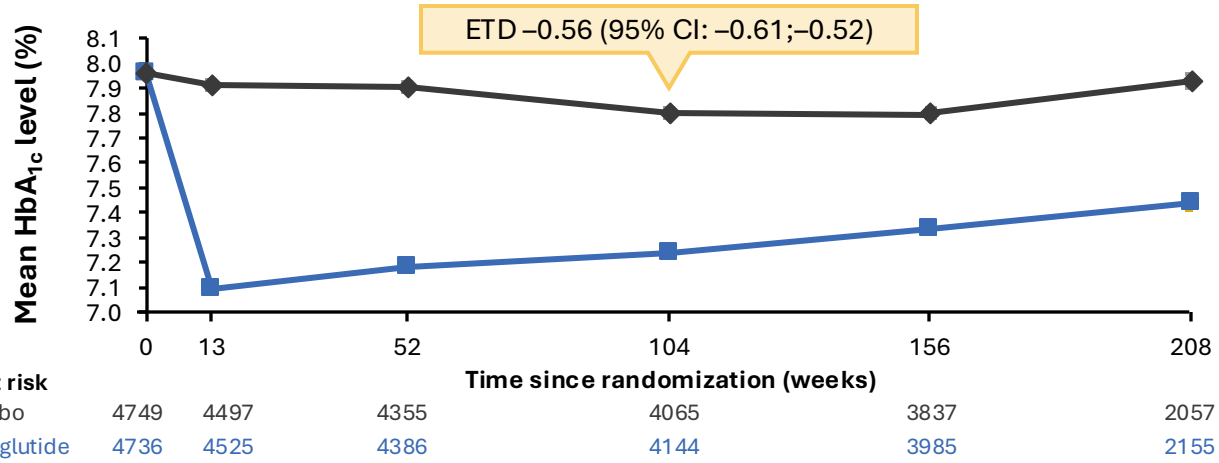
Subgroup analyses of the primary outcome

Subgroup		Oral semaglutide	Placebo	Hazard ratio (95% CI)
		No. with event/no. in analysis		
	All participants	579/4825	668/4825	0.86 (0.77;0.96)
Sex	Female	131/1376	160/1414	0.83 (0.66;1.05)
	Male	448/3449	508/3411	0.85 (0.75;0.97)
Age (years)	<65	200/2058	234/1976	0.80 (0.66;0.97)
	≥65 to <75	259/2085	296/2164	0.89 (0.76;1.05)
	≥75	120/682	138/685	0.86 (0.67;1.09)
BMI (kg/m^2)	≤30	285/2318	323/2284	0.85 (0.72;1.00)
	>30	291/2499	344/2536	0.84 (0.72;0.98)
HbA_{1c} (%)	≤8.0	331/2855	336/2798	0.96 (0.82;1.12)
	>8.0	237/1881	323/1951	0.73 (0.62;0.86)
eGFR (mL/min/1.73 m^2)	≥60	370/3376	416/3375	0.88 (0.76;1.01)
	≥45 to <60	105/811	128/818	0.80 (0.62;1.04)
	≥30 to <45	65/474	84/475	0.74 (0.53;1.02)
	<30	34/120	32/118	0.95 (0.58;1.54)
Region	North America	147/956	145/956	1.01 (0.80;1.27)
	Europe	177/1449	173/1438	1.01 (0.82;1.24)
	Asia	118/1230	161/1248	0.73 (0.57;0.93)
	Other	137/1190	189/1183	0.68 (0.55;0.85)
SGLT2i at baseline	No	436/3529	510/3525	0.84 (0.74;0.95)
	Yes	143/1296	158/1300	0.89 (0.71;1.11)

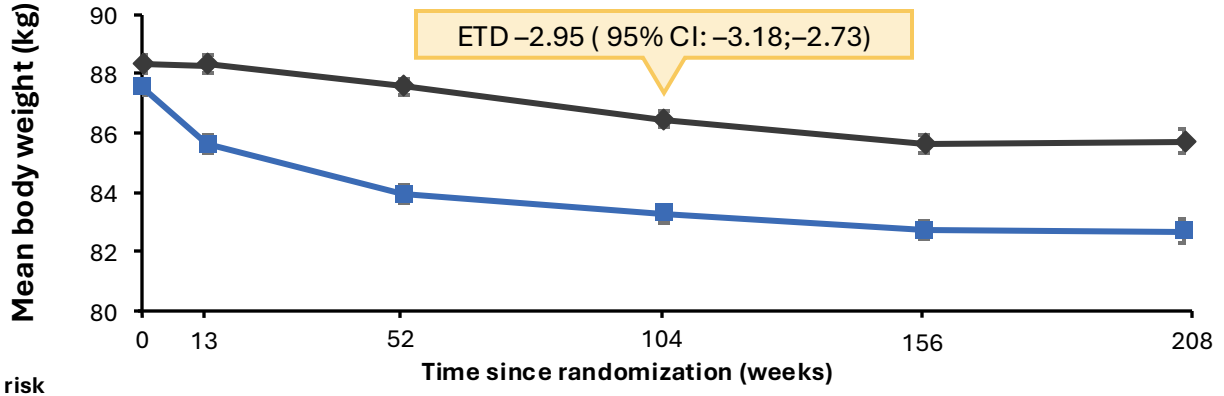


For subgroup analyses, estimated hazard ratios and corresponding CIs were calculated in a Cox proportional hazards model with interaction between treatment group and the relevant subgroup as fixed factor.
BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycated hemoglobin; SGLT2i, sodium-glucose co-transporter-2 inhibitor.

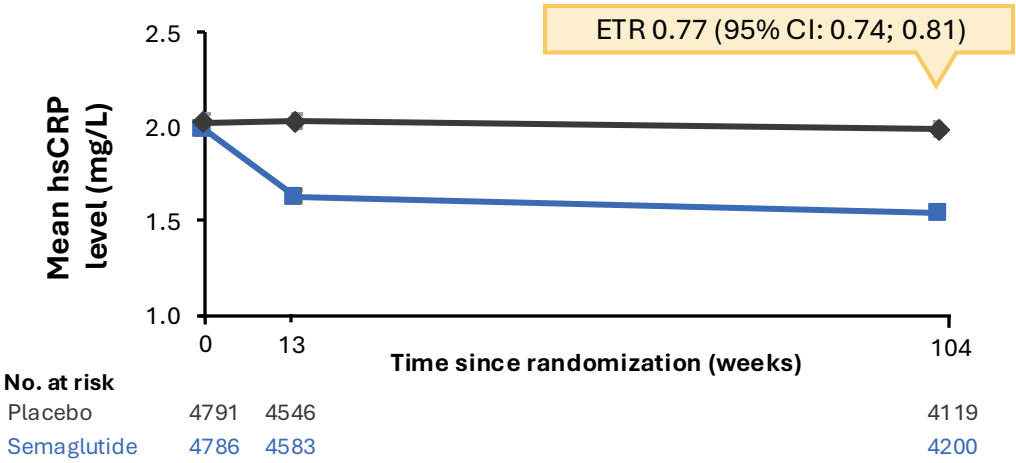
Measures of metabolism and inflammation



No. at risk						
Placebo	4749	4497	4355	4065	3837	2057
Semaglutide	4736	4525	4386	4144	3985	2155



No. at risk						
Placebo	4820	4322	4350	4159	3897	2100
Semaglutide	4819	4336	4371	4255	4022	2183



No. at risk			
Placebo	4791	4546	4119
Semaglutide	4786	4583	4200

HbA_{1c} and body weight reductions with oral semaglutide were consistent with previous clinical trial findings[1,2]

Data are for the full analysis set during the in-trial observation period. Bars indicate standard errors.
ETD, estimated treatment difference; ETR, estimated treatment ratio; HbA_{1c}, glycated hemoglobin; hsCRP, high-sensitivity C-reactive protein.

1. Pratley *et al. Diabetes Ther* 2021;12:1099–116;
2. Aroda *et al. Diabetes Obes Metab* 2023;25:1385–97.

SOUL
semaglutide | cardiovascular outcomes trial

Conclusions

- Oral semaglutide was superior to placebo in reducing the incidence of 3-point MACE in people with T2D and ASCVD and/or CKD
- There was consistent CV efficacy of oral semaglutide across subgroups by sex, age, BMI, eGFR and concomitant medication

- The overall safety profile of oral semaglutide in SOUL was similar to that observed in previous clinical trials with semaglutide,[1] and no new safety signals were found
- The trial results add to the favorable benefit–risk profile of oral semaglutide in this population

- Oral semaglutide is the first and only oral GLP-1 RA with proven CV benefits

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; T2D, type 2 diabetes.

1. Aroda *et al. Diabetes Obes Metab* 2023;25:1385–97.

SOUL
semaglutide | cardiovascular outcomes trial

Publication announcements (1/2)

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Oral Semaglutide and Cardiovascular Outcomes in High-Risk Type 2 Diabetes

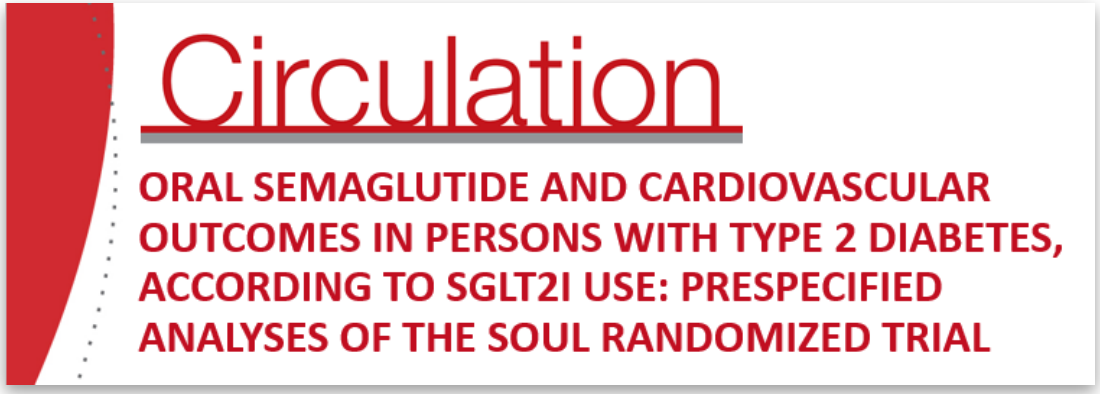
D.K. McGuire,[1] N. Marx,[2] S.L. Mulvagh,[3] J.E. Deanfield,[4] S.E. Inzucchi,[5] R. Pop-Busui,[6] J.F.E. Mann,[7,8] S.S. Emerson,[9] N.R. Poulter,[10] M.D.M. Engelmann,[11] M.S. Ripa,[11] G.K. Hovingh,[11] K. Brown-Frandsen,[11] S.C. Bain,[12] M.A. Cavender,[13] M. Gislum,[11] J.-P. David,[11] and J.B. Buse,[13] for the SOUL Study Group*

Published online:

ACC.25

SOUL
semaglutide | cardiovascular outcomes trial

Publication announcements (2/2)



Circulation 2025, 10.1161/CIRCULATIONAHA.125.074545

Diabetes Care 2025;48(5):1–14, doi.org/10.2337/dc25-0241

You can come talk to us at
Meet the Trialist session (#502)
Saturday, March 29
2:45 – 3:15 pm
Meet-Up Zone 1
Lounge and Learn

Visit the Novo Nordisk Science Hub for a copy of this presentation

ACC.25

ACC.25

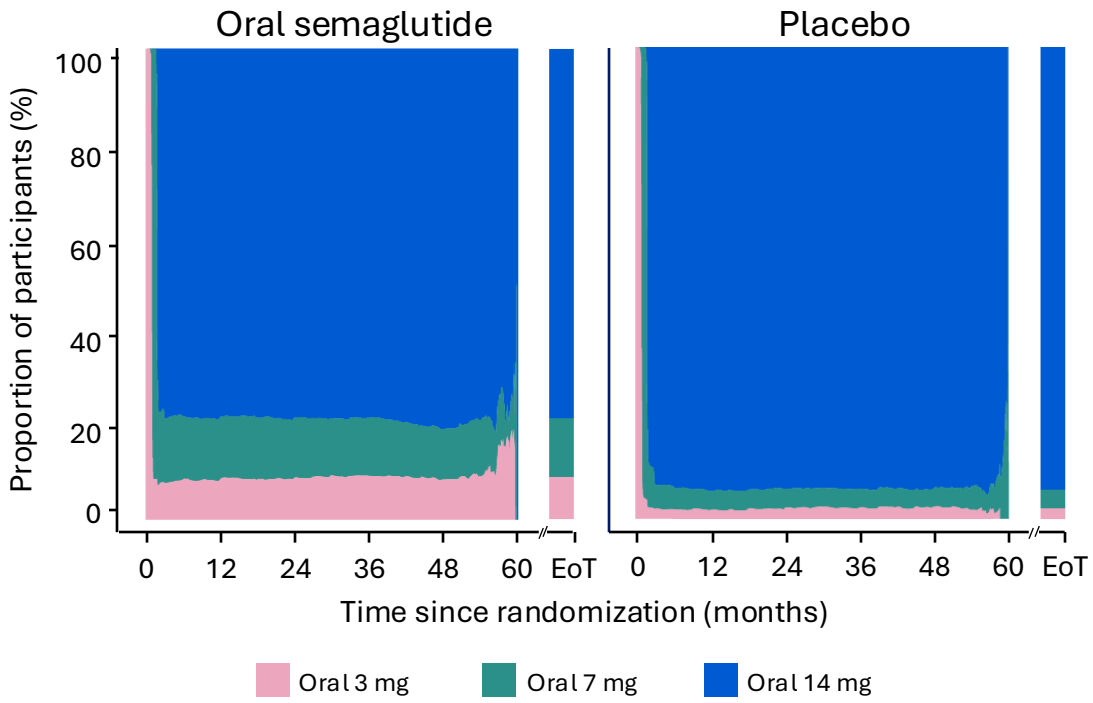
Back-up slides

AMERICAN COLLEGE of CARDIOLOGY

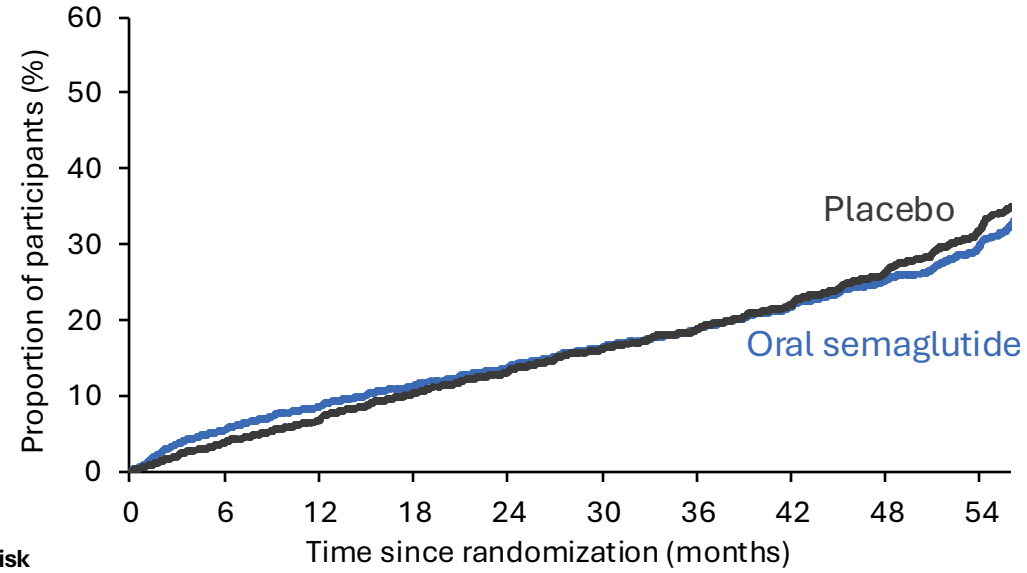
SOUL
semaglutide | cardiovascular outcomes trial

Dose distribution and participant discontinuations

Dose distribution over time*



Permanent treatment discontinuation for any reason†



No. at risk

Placebo	4825	4609	4438	4245	4073	3903	3753	3166	2011	751
Semaglutide	4825	4534	4364	4212	4070	3935	3792	3209	2058	789

*Proportions are based on number of participants receiving trial product. †Cumulative incidence estimates are based on the time from randomization to permanent treatment discontinuation, with death modelled as a competing risk. Participants who did not permanently discontinue treatment are censored at the time of their last dose. Permanent treatment discontinuations do not include treatment discontinuations starting the day before either completion, withdrawal, being lost to follow-up or the end of treatment visit. Participants never exposed to treatment are censored at day 1. The x-axis is truncated at 54 months due to the limited number of participants after 54 months.

SOUL
semaglutide | cardiovascular outcomes trial

Safety (1/2)

	Oral semaglutide (n=4825)	Placebo (n=4825)
Serious adverse events		
Cardiac disorders	861 (17.8)	954 (19.8)
Infections and infestations	726 (15.0)	797 (16.5)
Nervous system disorders	382 (7.9)	387 (8.0)
Neoplasms benign, malignant, and unspecified	330 (6.8)	274 (5.7)
Renal and urinary disorders	249 (5.2)	287 (5.9)
Gastrointestinal disorders	239 (5.0)	210 (4.4)
Vascular disorders	237 (4.9)	222 (4.6)
Injury, poisoning and procedural complications	218 (4.5)	304 (6.3)
General disorders and administration-site conditions	206 (4.3)	184 (3.8)
Respiratory, thoracic, and mediastinal disorders	185 (3.8)	217 (4.5)
Metabolism and nutrition disorders	182 (3.8)	219 (4.5)
Musculoskeletal and connective tissue disorders	161 (3.3)	169 (3.5)
Hepatobiliary disorders	115 (2.4)	101 (2.1)
Eye disorders	102 (2.1)	97 (2.0)

	Oral semaglutide (n=4825)	Placebo (n=4825)
Adverse events leading to treatment discontinuation		
Gastrointestinal disorders	310 (6.4)	98 (2.0)
Neoplasms benign, malignant, and unspecified	79 (1.6)	61 (1.3)
Infections and infestations	63 (1.3)	96 (2.0)
Nervous system disorders	63 (1.3)	61 (1.3)
Cardiac disorders	59 (1.2)	74 (1.5)
Renal and urinary disorders	29 (0.6)	31 (0.6)
Metabolism and nutrition disorders	23 (0.5)	20 (0.4)
General disorders and administration-site conditions	22 (0.5)	20 (0.4)
Hepatobiliary disorders	17 (0.4)	19 (0.4)
Respiratory, thoracic and mediastinal disorders	16 (0.3)	16 (0.3)
Investigations	12 (0.2)	8 (0.2)
Vascular disorders	11 (0.2)	13 (0.3)
Injury, poisoning, and procedural complications	11 (0.2)	13 (0.3)
Psychiatric disorders	10 (0.2)	5 (0.1)

SOUL
semaglutide | cardiovascular outcomes trial

Safety (2/2)

	Oral semaglutide (n=4825)	Placebo (n=4825)
Prespecified safety focus areas		
Acute gallbladder disease	136 (2.8)	104 (2.2)
Acute pancreatitis	18 (0.4)	21 (0.4)
Retinal disorders	1102 (22.8)	1080 (22.4)
Malignant neoplasms	332 (6.9)	294 (6.1)
Severe hypoglycemia	76 (1.6)	84 (1.7)
Medication errors	27 (0.6)	34 (0.7)
COVID-19		
All events	1076 (22.3)	1131 (23.4)
Serious events	255 (5.3)	317 (6.6)

	Oral semaglutide (n=4825)	Placebo (n=4825)
Additional safety areas		
Acute kidney failure	148 (3.1)	168 (3.5)
Hepatic disorders	43 (0.9)	41 (0.8)
Allergic reaction	17 (0.4)	18 (0.4)
Abuse and misuse	5 (0.1)	4 (<0.1)