evoke and evoke+: Two phase 3 randomised placebo-controlled trials of semaglutide in participants with early-stage Alzheimer's disease (NCT04777396 and NCT04777409)

Jeffrey Cummings, Peter Johannsen and Filip K. Knop presenting on behalf of the evoke and evoke+ study group

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evoke evaluation of oral semaglutide in early Alzheimer's disease

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Semaglutide is not approved for the treatment of Alzheimer's disease.

Cummings JL, et al. evoke and evoke+: Two phase 3 randomised placebo-controlled trials of semaglutide in participants with early-stage Alzheimer's disease (NCT04777396 and NCT04777409). Oral presentation at 18th CTAD December 1-4, 2025. San Diego, CA, USA.

evoke and evoke+ introduction

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Disclosures

- **Jeffrey L. Cummings** has provided consultation to Acadia, Actinogen, Acumen, AlphaCognition, ALZpath, Aprinoia, AriBio, Artery, Biogen, Biohaven, BioVie, BioXcel, Bristol-Myers Squib, Cassava, Cerecin, Diadem, Eisai, GAP Foundation, GemVax, Janssen, Jocasta, Karuna, Lighthouse, Lilly, Lundbeck, LSP/eqt, Merck, NervGen, New Amsterdam, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, Oxford Brain Diagnostics, Prothena, ReMYND, Roche, Sage Therapeutics, Signant Health, Simcere, sinaptica, Suven, TrueBinding, Vaxxinity, and Wren pharmaceutical, assessment, and investment companies.
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Agenda

Time (PT)	Agenda	Presenter
17:05–17:10	Introduction	Jeffrey Cummings
17:10–17:15	evoke and evoke+ trial designs	Peter Johannsen
17:15–17:20	evoke and evoke+ baseline characteristics	Peter Johannsen
17:20–17:28	evoke and evoke+ efficacy results	Jeffrey Cummings
17:28–17:32	Pooled evoke and evoke+ safety results	Filip K. Knop
17:32–17:35	Conclusions	Jeffrey Cummings
17:35–17:45	Q&A	All

evoke and evoke+ trial design

Peter Johannsen
International Medical Vice President
Novo Nordisk

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Disclosures

- **Peter Johannsen** is a full-time employee and a minor shareholder of Novo Nordisk A/S

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THANK YOU

to all **participants, care partners, families, investigators, and site staff** for their invaluable contribution to advancing the field of Alzheimer's disease research and clinical care, bringing hope to many

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Semaglutide Alzheimer's disease clinical development program

evoke
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1,855 participants[1,2]

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1,953 participants[1,3]

Safety and efficacy

CSF sub-study (199 participants)

- AD pathology, neuroinflammation, neurodegeneration and other markers in CSF

Multi-omics and immunophenotyping study investigating changes in immune-cell signatures in CSF and blood (23 participants)[4]

- Changes in gene expression (single-cell transcriptomics and proteomics) and PK
- Neuroinflammation and peripheral inflammation

Mechanism of action and pathophysiology

Semaglutide has not been approved for the treatment of Alzheimer's disease by any regulatory authority.
There are no GLP-1RAs approved for the treatment of Alzheimer's disease.

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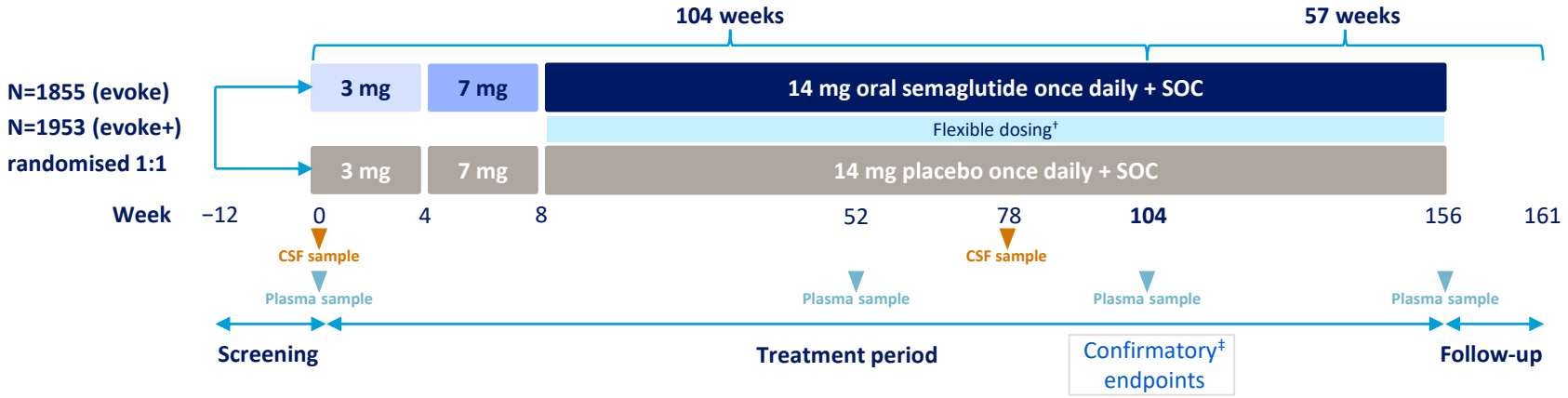
The ISAP trial research is sponsored by the University of Oxford, UK, and funded by Novo Nordisk.
CSF, cerebrospinal fluid; GLP-1RA, glucagon-like peptide-1 receptor agonist; ISAP, Impact of Semaglutide in Amyloid Positivity; MoA, mechanism of action; PK, pharmacokinetics.
1. Scheltens P et al. CTAD 2023 OO384; 2. ClinicalTrials.gov. NCT04777396. https://clinicaltrials.gov/study/NCT04777396 (accessed November 2025); 3. ClinicalTrials.gov. NCT04777409. https://clinicaltrials.gov/study/NCT04777409 (accessed November 2025); 4. ClinicalTrials.gov. NCT05891496. https://www.clinicaltrials.gov/study/NCT05891496 (accessed November 2025).

Efficacy and safety of semaglutide in early AD were assessed in evoke and evoke+



In evoke+, the study population allowed for participants with concomitant significant small-vessel pathology

1. **Treatment policy estimand**
2. Hybrid-HTC estimand

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†Participants should remain on the 14 mg dose level until the end of treatment visit; however, dose reductions, extensions of dose escalation intervals and treatment pauses are allowed e.g. if treatment with the study intervention is associated with unacceptable AEs. ‡At week 156 as well.
AD, Alzheimer's disease; ADL, activity of daily living; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CNS, central nervous system; CSF, cerebrospinal fluid; HTC, hybrid-hypothetical-treatment policy estimand; MCI, mild cognitive impairment; MMSE, Mini–Mental State Examination; RBANS-MI, Repeatable Battery for the Assessment of Neuropsychological Status Memory Index; SOC, standard of care.
Cummings JL et al. *Alzheimer Res Ther* 2025;17:14.

Key inclusion and exclusion criteria for evoke and evoke+

Key inclusion criteria[1–3]

- Age 55-85 years
- Amyloid positivity (PET or CSF)
- CDR-G = 0.5 (≥0.5 of 3 ADLs categories), or CDR global score = 1.0
- MMSE ≥22
- RBANS delayed memory index score ≤85
- Continuation of stable approved AD treatments was allowed

Key exclusion criteria[1–3]

- Evidence of a relevant neurological disorder
- Evidence of a clinically relevant or unstable psychiatric disorder
- Brain MRI (or CT) scan suggestive of clinically-significant structural CNS disease or strategic infarcts

In evoke+, participants were allowed to have significant small vessel pathology, defined as ARWMC >2 and/or >1 lacunar infarct

In both trials, approved AD medication could be initiated throughout, including anti-amyloid MABs

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AD, Alzheimer's disease; ARWMC, age-related white matter changes; CDR, clinical dementia rating; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; iADL, instrumental activities of daily living; MAB, monoclonal antibody; MMSE, mini-mental state examination; MRI, magnetic resonance imaging; PET, positron emission tomography; RBANS, repeatable battery for the assessment of neurological status.

1. Cummings JL et al. *Alzheimer Res Ther* 2025;17:14; 2. Clinical Trials.gov. NCT04777396: A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease (EVOKE). Available at: https://clinicaltrials.gov/study/NCT04777396?term=evoke&intr=Semaglutide&rank=2 [Accessed October 2025]; 3. Clinical Trials.gov. NCT04777409: A Research Study Investigating Semaglutide in People With Early Alzheimer's Disease (EVOKE Plus). Available at: https://clinicaltrials.gov/study/NCT04777409?term=evoke&intr=Semaglutide&rank=1 [Accessed October 2025].

evoke and evoke+ primary and confirmatory secondary endpoints

Tested in:

Primary endpoint

- Change in CDR-SB score from baseline to week 104

→ evoke | evoke+

Secondary confirmatory endpoints

- Change in ADCS-ADL-MCI score from baseline to week 104

→ evoke | evoke+

- Time to progression to dementia (CDR global ≥1.0) among participants with MCI (CDR global=0.5) at baseline; assessed up to week 156

→ Pooled

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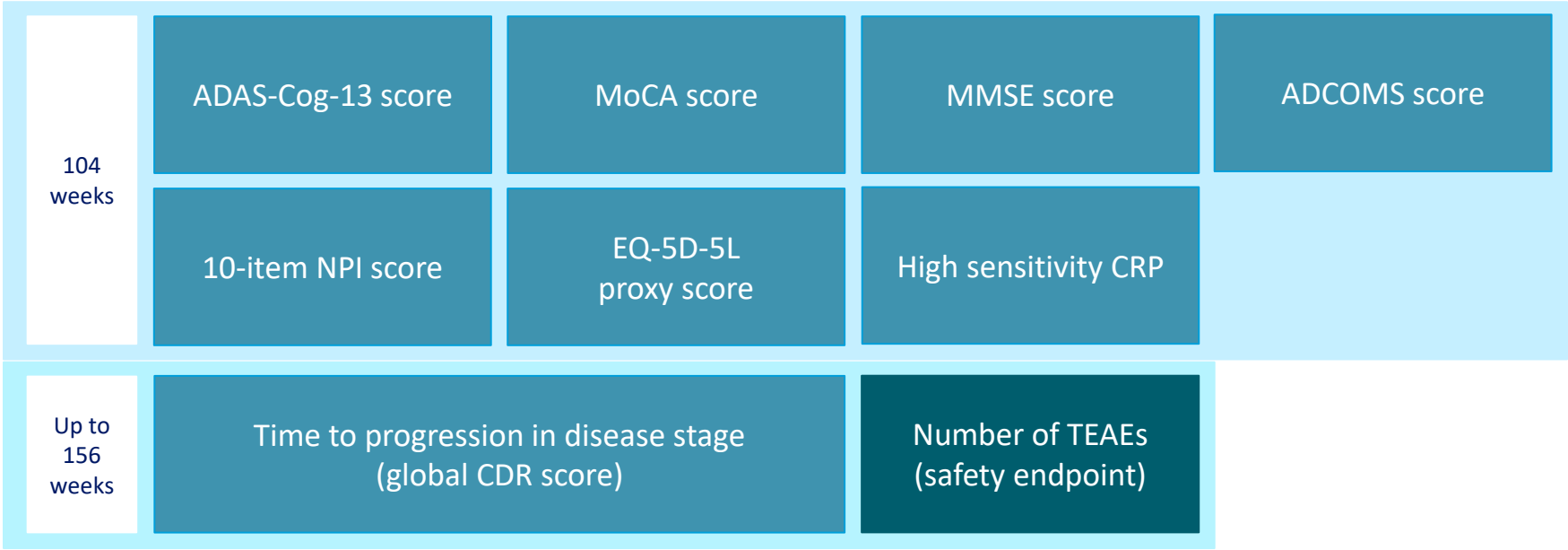
ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating – Sum of Boxes; MCI, mild cognitive impairment.

Cummings JL et al. *Alzheimers Res Ther* 2025;17:14.

evoke and evoke+ secondary endpoints



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ADAS-Cog-13, 13-item Alzheimer's Disease Assessment Scale – Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment; CDR, Clinical Dementia Rating; CRP, C-reactive Protein; EQ-5D-5L, the 5-level EQ-5D EuroQol version; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; TEAE, treatment-emergent adverse event.

Cummings JL et al. *Alzheimer Res Ther* 2025;17:14.

Blood and CSF biomarkers in evoke and evoke+

Blood-based (to week 104)

CSF-based (only in CSF sub-study; to week 78)

Amyloid-related pathology†	Tau pathology	Neuroinflammation	Neurodegeneration	BBB integrity
p-tau181 p-tau217	eMTBR-tau243	GFAP	NfL	Albumin ratio (CSF/serum)
Aβ42/40 ratio p-tau181 p-tau217	p-tau205	YKL-40 sTREM2 GFAP IL-6 MCP-1/CCL2 SMOC1 Osteopontin IL-1β IL-18 IL-8 IP-10/CXCL10 IL-1RA C3 and C4B	NfL t-tau Neurogranin	PDGFRβ

Green text = from proteomics in CSF

- Change in plasma high-sensitivity C-reactive protein levels
- Genetic sample used to measure *APOE4* variant status in both evoke and evoke+

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†Phosphorylated and secreted tau (p-tau181, p-tau217) are biomarkers more closely related to amyloid proteinopathy according to the new revised AA criteria.[1]

AA, Alzheimer's Association; Aβ, amyloid beta; BBB, blood–brain barrier; C3, complement component 3; C4B, complement component 4B; CCL2, C-C motif chemokine ligand 2; CSF, cerebrospinal fluid; CXCL10, C–X–C motif chemokine ligand 10; eMTBR, endogenously cleaved, microtubule-binding region; GFAP, glial fibrillary acidic protein; IL, interleukin; IL-1RA, IL-1 receptor antagonist; IP-10, interferon-γ inducible protein 10; MCP-1, monocyte chemoattractant protein-1; NfL, neurofilament light chain; p-tau181/205/217, tau phosphorylated at threonine 181/205/217; SMOC1, secreted modular calcium-binding protein 1; PDGFRβ, platelet-derived growth factor receptor β; sTREM2, soluble triggering receptor expressed on myeloid cells 2; t-tau, total tau; YKL-40, chitinase-3-like protein 1.

1. CR Jack Jr et al. *Alzheimers Dement* 2024;20:5143–5169.

evoke and evoke+ baseline characteristics

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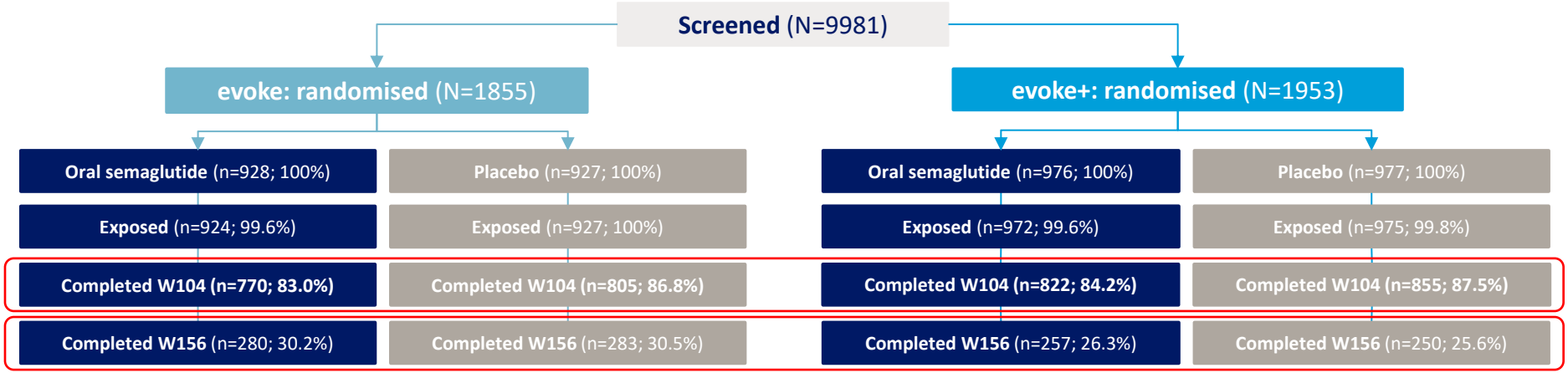
Participant disposition



Oral semaglutide (n=928; 100%)	Placebo (n=927; 100%)	Oral semaglutide (n=976; 100%)	Placebo (n=977; 100%)
Permanent discontinuation (n=298; **32.1%**) *Due to AE (n=159; 17.1%)*	**Permanent discontinuation** (n=232; **25.0%**) *Due to AE (n=76; 8.2%)*	**Permanent discontinuation** (n=307; **31.5%**) *Due to AE (n=162; 16.6%)*	**Permanent discontinuation** (n=246; **25.2%**) *Due to AE (n=84; 8.6%)*
Withdrawn from study (n=207; **22.3%**) *By participant (n=137; 14.8%)* ***Death (n=26; 2.8%)***	**Withdrawn from study** (n=172; **18.6%**) *By participant (n=118; 12.7%)* ***Death (n=22; 2.4%)***	**Withdrawn from study** (n=204; **20.9%**) *By participant (n=128; 13.1%)* ***Death (n=23; 2.4%)***	**Withdrawn from study** (n=175; **17.9%**) *By participant (n=117; 12.0%)* ***Death (n=28; 2.9%)***

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AE, adverse event; W, week.

Demographics and baseline characteristics

		evoke		evoke+		pooled
		Oral semaglutide	Placebo	Oral semaglutide	Placebo	Total
Number of participants		928	927	976	977	3808
Age, years	Mean (SD)	71.9 (7.0)	71.7 (7.1)	72.6 (7.0)	72.5 (7.2)	72.2 (7.1)
Sex	Female	489 (52.7)	496 (53.5)	515 (52.8)	498 (51.0)	1998 (52.5)
Ethnicity†	Hispanic Or Latino	114 (12.3)	130 (14.0)	117 (12.0)	85 (8.7)	446 (11.7)
Race†	American Indian or Alaska Native	3 (0.3)	1 (0.1)	1 (0.1)	0	5 (0.1)
	Asian	117 (12.6)	102 (11.0)	202 (20.7)	205 (21.0)	626 (16.4)
	Black or African American	13 (1.4)	10 (1.1)	9 (0.9)	10 (1.0)	42 (1.1)
	Native Hawaiian or Other Pacific Islander	1 (0.1)	1 (0.1)	3 (0.3)	0	5 (0.1)
	White	735 (79.2)	765 (82.5)	725 (74.3)	726 (74.3)	2951 (77.5)
	Other	24 (2.6)	25 (2.7)	4 (0.4)	2 (0.2)	55 (1.4)

evoke evaluation of oral semaglutide in early Alzheimer's disease

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†In France, the law prohibits collection of data on race and ethnicity.
Data are n (%) unless otherwise specified.
SD, standard deviation.

Demographics and baseline characteristics (cont.)

		evoke		evoke+		pooled
		Oral semaglutide	Placebo	Oral semaglutide	Placebo	Total
Number of participants		928	927	976	977	3808
BMI (kg/m^2)	<18.5	28 (3.0)	18 (1.9)	22 (2.3)	28 (2.9)	96 (2.5)
	18.5 to <25	421 (45.4)	432 (46.6)	463 (47.4)	465 (47.6)	1781 (46.8)
	25 to <30	337 (36.3)	333 (35.9)	334 (34.2)	329 (33.7)	1333 (35.0)
	≥30	142 (15.3)	139 (15.0)	156 (16.0)	154 (15.8)	591 (15.5)
	Missing	0	5 (0.5)	1 (0.1)	1 (0.1)	7 (0.2)
T2D		99 (10.7)	116 (12.5)	155 (15.9)	148 (15.1)	518 (13.6)
Concurrent significant small-vessel pathology		--	--	26 (2.7)	28 (2.9)	54 (1.4)
***APOE* genotype**	*APOE4* Carrier (Heterozygote)	451 (48.6)	448 (48.3)	443 (45.4)	437 (44.7)	1779 (46.7)
	APOE4 Carrier (Homozygote)	117 (12.6)	120 (12.9)	111 (11.4)	122 (12.5)	470 (12.3)

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Data are n (%) unless otherwise specified.

APOE, apolipoprotein E; BMI, body mass index; T2D, type 2 diabetes.

Concomitant AD medication ongoing at randomisation

	evoke		evoke+		pooled
	Oral semaglutide	Placebo	Oral semaglutide	Placebo	Total
Number of participants	928	927	976	977	3808
All medications	559 (60.2)	527 (56.9)	546 (55.9)	525 (53.7)	2157 (56.6)
Symptomatic treatments					
Donepezil	362 (39.0)	330 (35.6)	346 (35.5)	345 (35.3)	1383 (36.3)
Rivastigmine	101 (10.9)	101 (10.9)	103 (10.6)	90 (9.2)	395 (10.4)
Galantamine	31 (3.3)	38 (4.1)	31 (3.2)	35 (3.6)	135 (3.5)
Huperzine A	1 (0.1)	0	1 (0.1)	1 (0.1)	3 (0.1)
Memantine	142 (15.3)	118 (12.7)	144 (14.8)	125 (12.8)	529 (13.9)
Monoclonal antibodies					
Aducanumab	0	0	1 (0.1)	0	1 (0.0)

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AD, Alzheimer's disease.

Concomitant AD medication initiated at or after at randomisation

	evoke		evoke+		pooled
	Oral semaglutide	Placebo	Oral semaglutide	Placebo	Total
Number of participants	928	927	976	977	3808
All medications	246 (26.5)	290 (31.3)	266 (27.2)	308 (31.5)	1110 (29.1)
Symptomatic treatments					
Donepezil	109 (11.8)	134 (14.5)	135 (13.8)	153 (15.7)	531 (13.9)
Rivastigmine	76 (8.2)	71 (7.7)	57 (5.8)	75 (7.7)	279 (7.3)
Galantamine	13 (1.4)	15 (1.6)	15 (1.5)	11 (1.1)	54 (1.4)
Huperzine A	0	0	0	2 (0.2)	2 (0.1)
Memantine	104 (11.2)	125 (13.5)	99 (10.1)	127 (13.0)	455 (11.9)
Monoclonal antibodies					
Lecanemab	9 (1.0)	21 (2.3)	20 (2.0)	17 (1.7)	67 (1.8)
Donanemab	3 (0.3)	1 (0.1)	4 (0.4)	3 (0.3)	11 (0.3)

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AD, Alzheimer's disease.

Demographics and baseline characteristics (cont.)

		evoke		evoke+		pooled
		Oral semaglutide	Placebo	Oral semaglutide	Placebo	Total
Number of participants		928	927	976	977	3808
CDR-Sum of Boxes[†]	Mean (SD)	3.8 (1.6)	3.7 (1.5)	3.7 (1.5)	3.7 (1.7)	3.7 (1.6)
	Min ; Max	0.5 ; 11.0	1.0 ; 11.0	0.5 ; 10.0	0.5 ; 12.0	0.5 ; 12.0
CDR global score, n (%)	0.5	670 (72.2)	680 (73.4)	699 (71.6)	697 (71.3)	2746 (72.1)
	1	252 (27.2)	240 (25.9)	273 (28.0)	269 (27.5)	1034 (27.2)
ADCS-ADL-MCI[†]	Mean (SD)	39.2 (7.3)	39.7 (7.4)	38.7 (7.5)	39.2 (7.5)	39.2 (7.4)
	Min ; Max	12.0 ; 53.0	10.0 ; 53.0	12.0 ; 53.0	10.0 ; 52.0	10.0 ; 53.0
MMSE[†]	Mean (SD)	24.1 (2.9)	24.0 (3.1)	24.0 (3.1)	24.1 (3.1)	24.0 (3.0)
	Min ; Max	15.0 ; 30.0	15.0 ; 30.0	13.0 ; 30.0	13.0 ; 30.0	13.0 ; 30.0

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[†]In evoke, oral semaglutide, N=927; placebo, N=927.
ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment; CDR, Clinical Dementia Rating; MMSE, Mini-Mental State Examination; SD, standard deviation.

evoke and evoke+ efficacy results

Jeffrey Cummings
Professor
University of Nevada, Las Vegas

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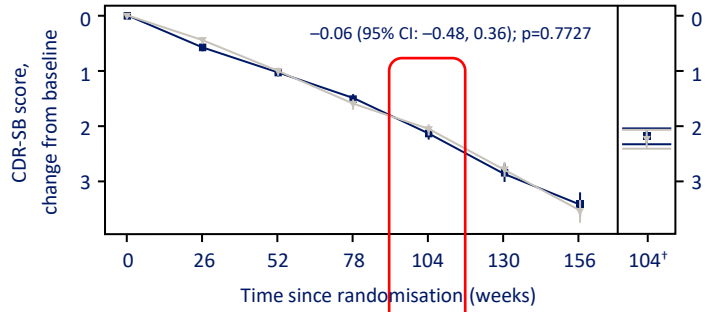
Oral semaglutide did not slow cognitive and functional decline in participants with early AD versus placebo in either trial

Change in CDR–SB score from baseline to week 104

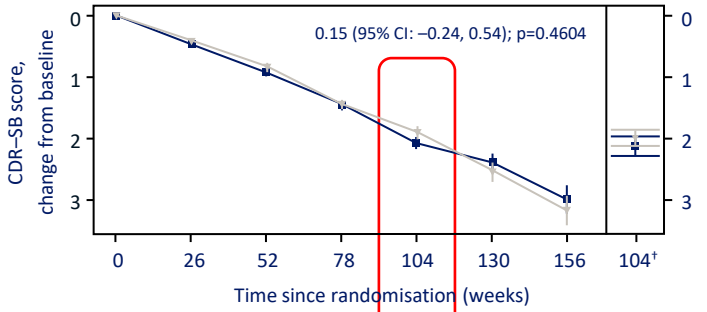
evoke



Oral semaglutide	927	847	777	750	709	452	251	928
Placebo	927	868	822	777	755	477	261	927

	Estimate†	95% CI	P-value
Oral semaglutide	2.2		
Placebo	2.2		
Oral semaglutide – Placebo	–0.06	–0.48 ; 0.36	0.7727

evoke+



Oral semaglutide	967	885	814	781	748	423	226	976
Placebo	977	919	873	823	776	439	223	977

	Estimate†	95% CI	P-value
Oral semaglutide	2.1		
Placebo	2.0		
Oral semaglutide – Placebo	0.15	–0.24 ; 0.54	0.4604

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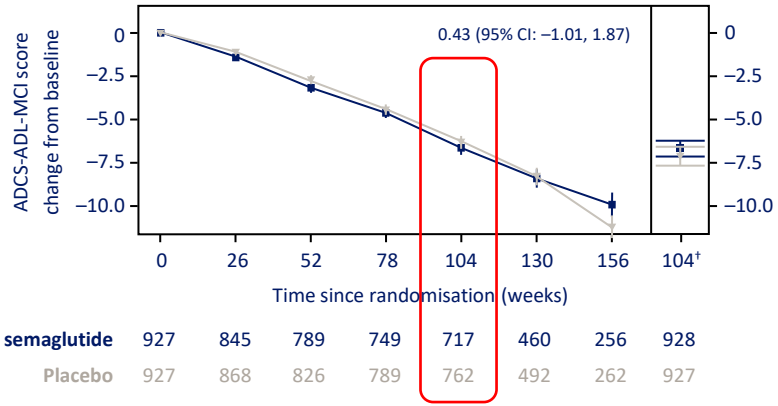
†Data are for the treatment policy estimand. Error bars are mean +/- standard error of the mean.
AD, Alzheimer's disease; CDR–SB, Clinical Dementia Rating–Sum of Boxes; CI, Confidence interval.

Oral semaglutide did not slow functional decline in participants with early AD versus placebo in either trial

Change in ADCS-ADL-MCI score from baseline to week 104

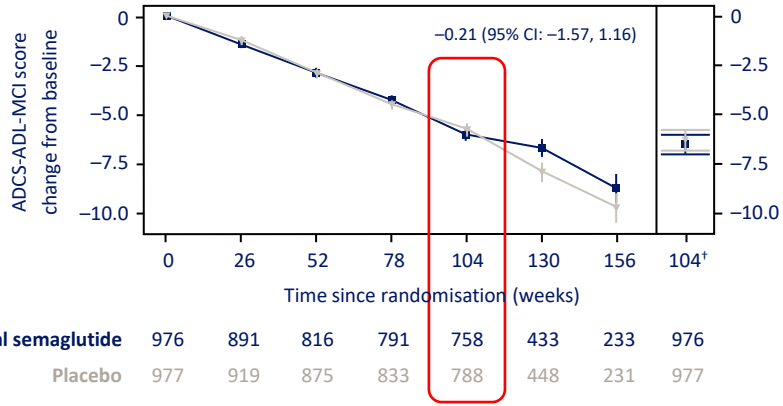
evoke



Oral semaglutide	927	845	789	749	717	460	256	928
Placebo	927	868	826	789	762	492	262	927

	Estimate†	95% CI
Oral semaglutide	−6.6	
Placebo	−7.1	
Oral semaglutide – Placebo	0.43	−1.01; 1.87

evoke+



Oral semaglutide	976	891	816	791	758	433	233	976
Placebo	977	919	875	833	788	448	231	977

	Estimate†	95% CI
Oral semaglutide	−6.5	
Placebo	−6.3	
Oral semaglutide – Placebo	−0.21	−1.57; 1.16

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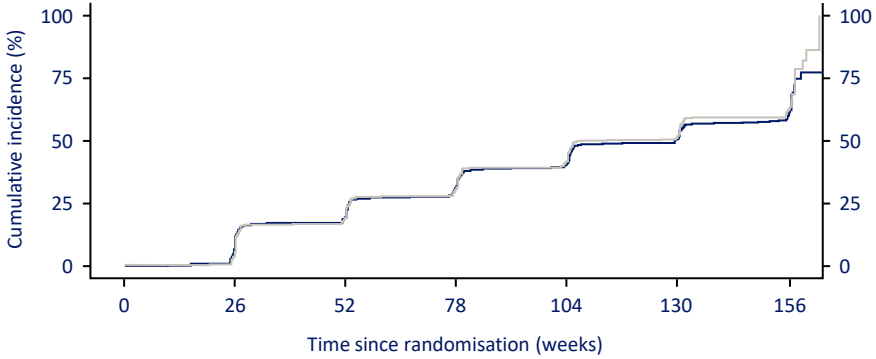
†Data are for the treatment policy estimand. Error bars are mean +/- standard error of the mean.

AD, Alzheimer's disease; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment; CI, confidence interval.

Oral semaglutide did not delay time to progression to dementia in participants with MCI across both trials

Time to progression to CDR global ≥1.0 among patients with CDR global = 0.5 at baseline (pooled evoke and evoke+)



Oral semaglutide	1369	1237	1001	831	697	381	134
Placebo	1377	1287	1050	873	716	374	115

	N	Events	HR	95% CI
Oral semaglutide	1369	717		
Placebo	1377	757		
Oral semaglutide – Placebo			0.96	0.86 ; 1.06

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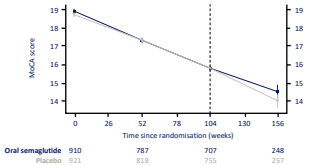
CDR, Clinical Dementia Rating; HR, hazard ratio; CI, confidence interval; MCI, mild cognitive impairment.

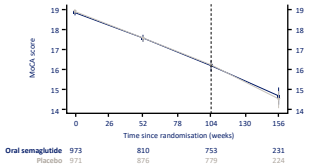
Oral semaglutide did not show beneficial effects on cognition and function in participants with early AD

MoCA

evoke

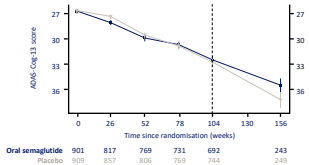


evoke+

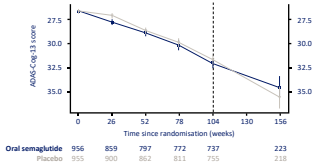


ADAS-Cog-13

evoke

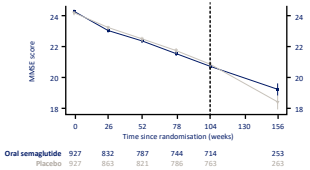


evoke+

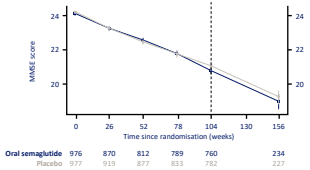


MMSE

evoke

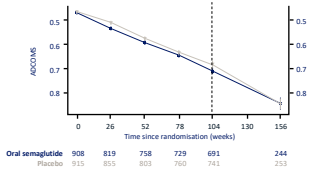


evoke+

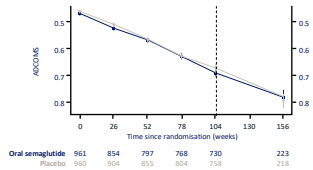


ADCOMS

evoke



evoke+



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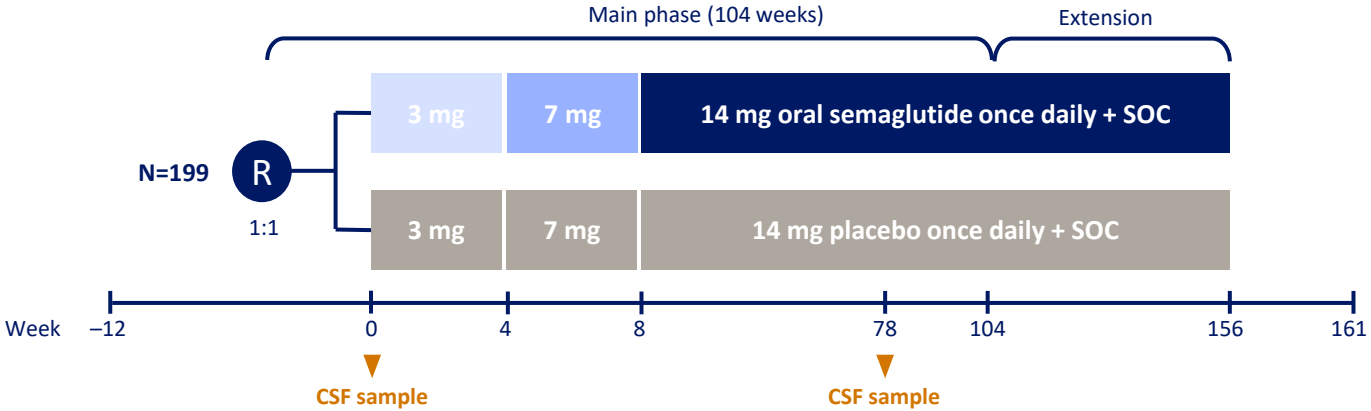
Error bars are mean +/- standard error of the mean.
AD, Alzheimer's disease; ADAS-Cog-13, Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCOMS, Alzheimer's Disease Composite Score; MoCA, Montreal Cognitive Assessment Score; MMSE, Mini-Mental Status Exam.

Trial design of the CSF sub-study



n	Oral semaglutide	Placebo
At randomisation (week 0)	98	101
At end of the CSF sub study (week 78)	63	61

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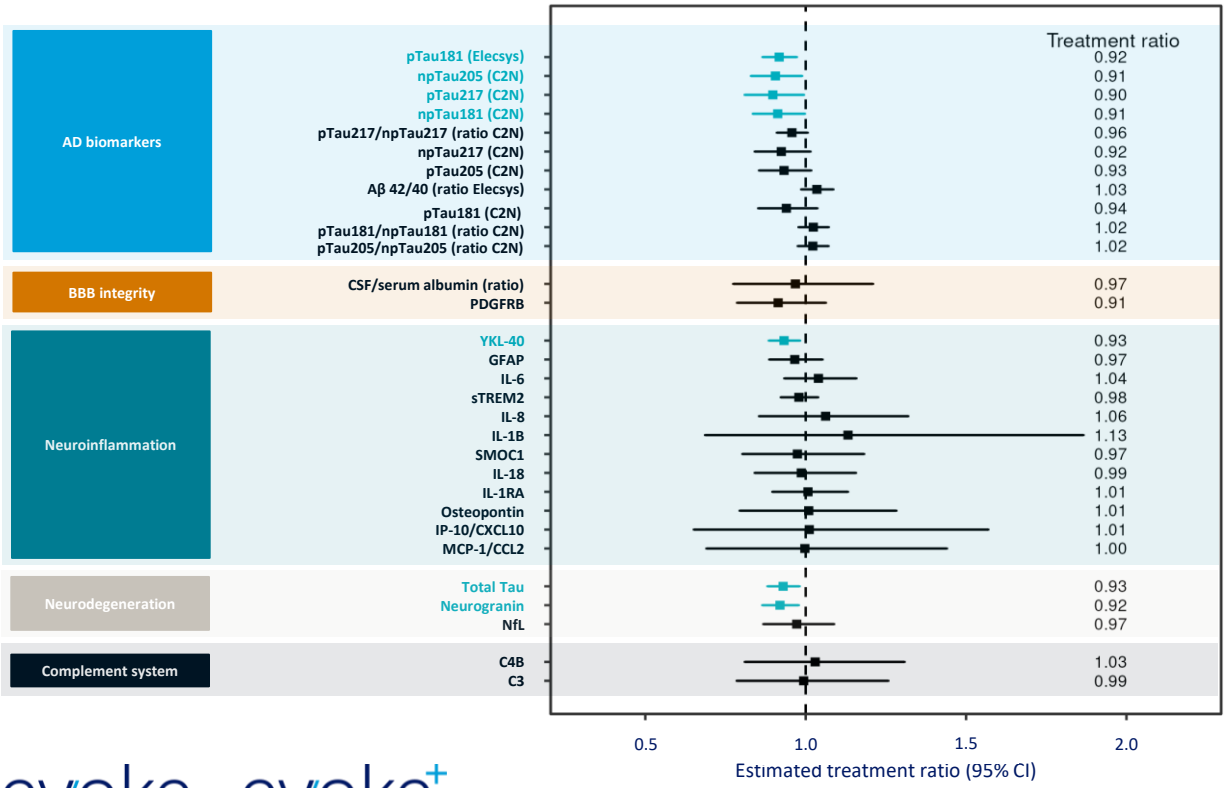
CSF, cerebrospinal fluid; R, randomisation; SOC, standard of care.

CSF biomarkers – ratio to baseline at week 78



Significant reductions of up to 10%† with semaglutide treatment versus placebo in:

AD biomarkers	• pTau181 • pTau217 • npTau181 • npTau205
Neuroinflammation	• YKL-40
Neurodegeneration	• Total tau • Neurogranin

- Unadjusted p-value <0.05
- Unadjusted p-value ≥0.05

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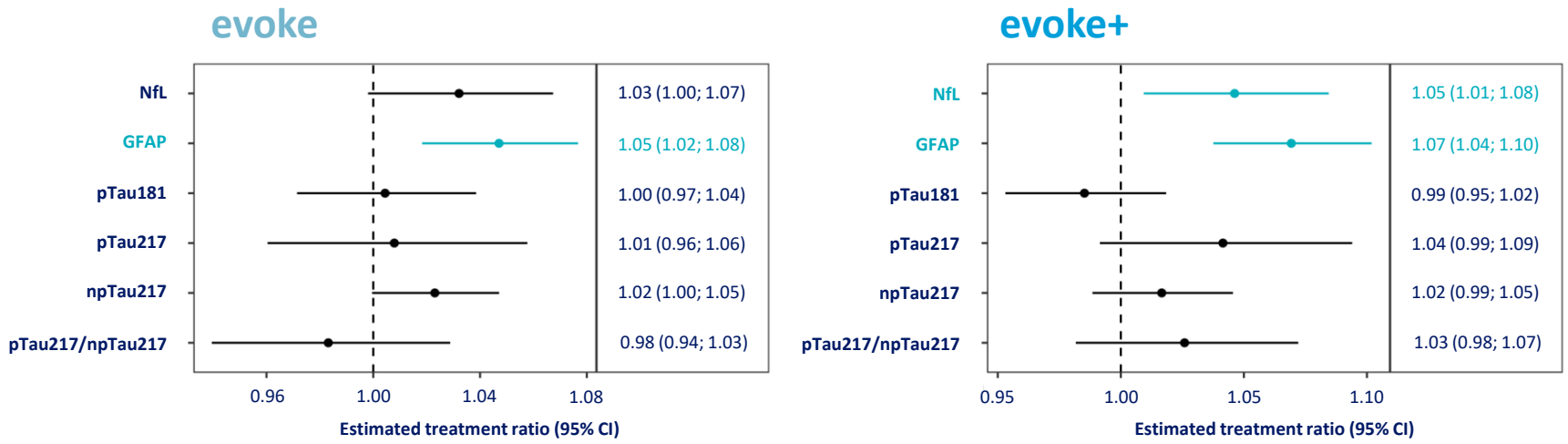
†Data were not adjusted for multiplicity.

AD, Alzheimer's disease; CSF, cerebrospinal fluid; GFAP, glial fibrillary acidic protein; IL, interleukin; NfL, neurofilament light chain; sTREM2, Triggering receptor expressed on myeloid cells 2.

Exploratory blood-based biomarkers - ratio to baseline at week 104



n	Oral semaglutide	Placebo
At randomisation (week 0)	1677	1695
At end of main study phase (week 104)	1427	1500

- A significant increase of ~5% in NfL in evoke+
- A significant increase of ~4% in GFAP in both trials
- No significant changes for pTau217 and pTau181

Unadjusted p-value <0.05
Unadjusted p-value ≥0.05

- Approx 2/3 participants had eMTBR-tau243 below lower limit of quantification
- **Significant decrease in hsCRP**, estimated treatment ratio in
  - evoke: 0.76 [0.64 ; 0.90]$_{95\%\ CI}$ and evoke+: 0.71 [0.62 ; 0.82]$_{95\%\ CI}$

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CI, confidence interval; eMTBR, endogenously cleaved, microtubule-binding region; GFAP, glial fibrillary acidic protein; hsCRP, high sensitivity C-reactive protein; NfL, neurofilament light chain.

Pooled evoke and evoke+ safety results

Filip K. Knop
Senior Vice President & Chief Medical Officer
Novo Nordisk

evoke evaluation of oral semaglutide in early Alzheimer's disease

evoke+ evaluation of oral semaglutide in early Alzheimer's disease

Semaglutide is not approved for the treatment of Alzheimer's disease.

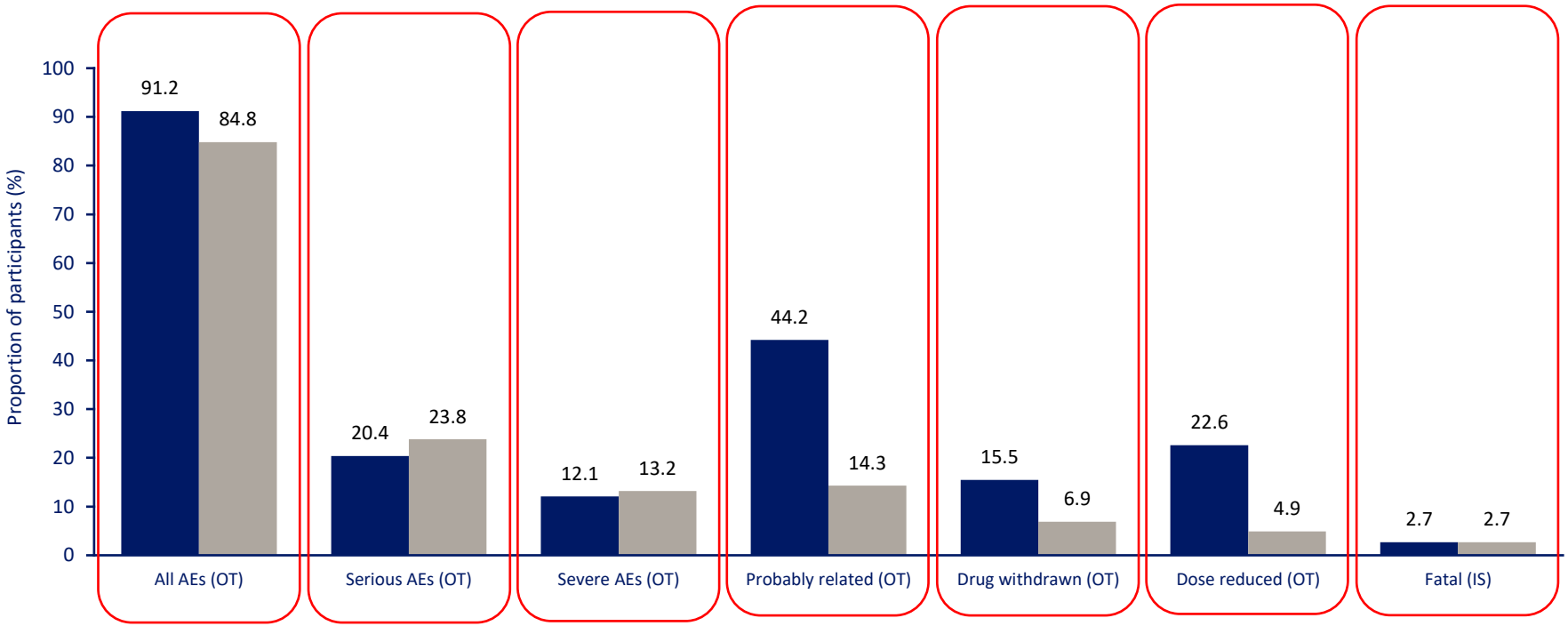
Cummings JL, et al. evoke and evoke+: Two phase 3 randomised placebo-controlled trials of semaglutide in participants with early-stage Alzheimer's disease (NCT04777396 and NCT04777409). Oral presentation at 18th CTAD December 1-4, 2025. San Diego, CA, USA.

Disclosures

- **Filip K. Knop** is a full-time employee and a minor shareholder of Novo Nordisk A/S

Adverse events overview

Pooled evoke and evoke+



evoke evaluation of oral semaglutide in early Alzheimer's disease

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AE, adverse event; IS, in study; OT, on treatment

Safety summary

Safety analysis set

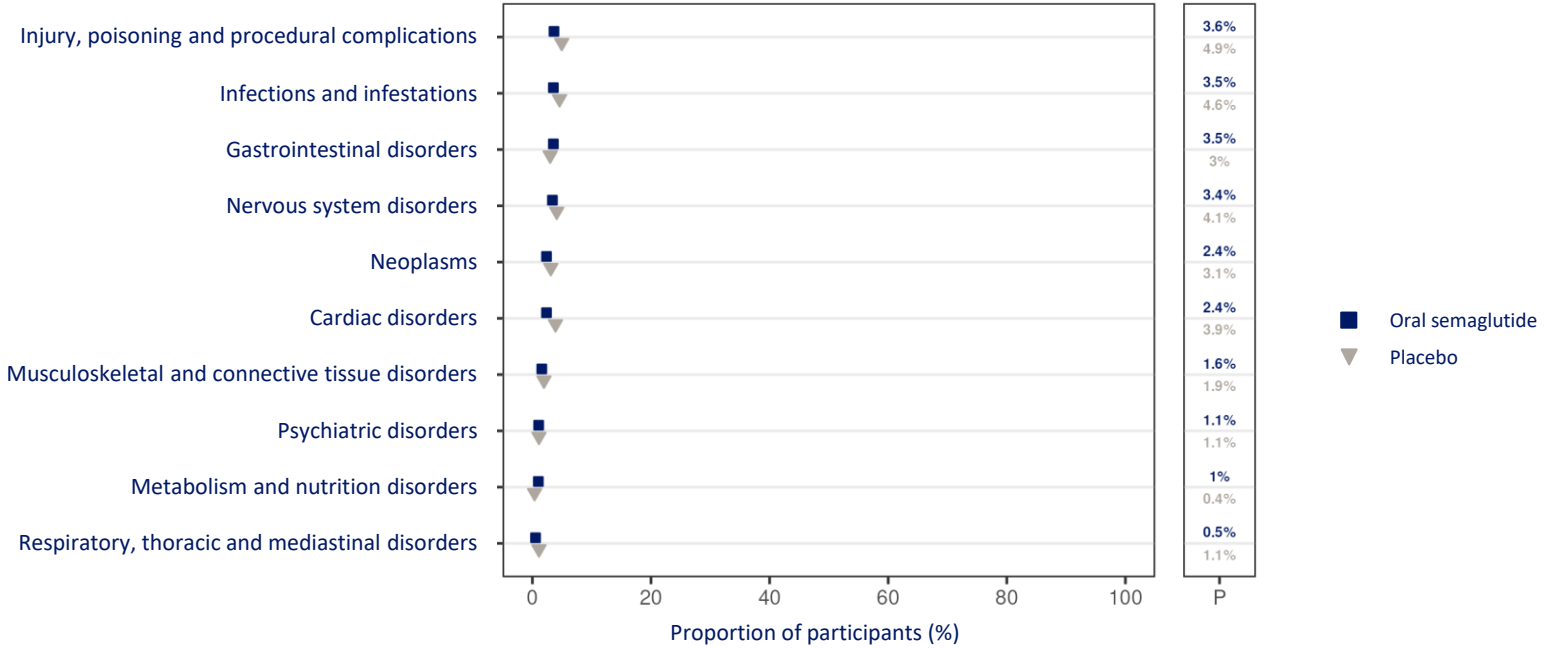
	Oral semaglutide 14 mg (n=1896)	Placebo (n=1902)
AEs affecting ≥10% of participants		
Body weight decreased	692 (36.5)	141 (7.4)
Decreased appetite	627 (33.1)	114 (6.0)
Nausea	460 (24.3)	130 (6.8)
Diarrhoea	275 (14.5)	185 (9.7)
Vomiting	234 (12.3)	69 (3.6)
COVID-19	206 (10.9)	214 (11.3)

AE, adverse event; COVID-19, corona virus disease caused by SARS-CoV-2 virus.

Serious AEs by System Organ Class (reported by ≥1%)

Pooled evoke and evoke+

No unexpected findings or safety concerns were identified



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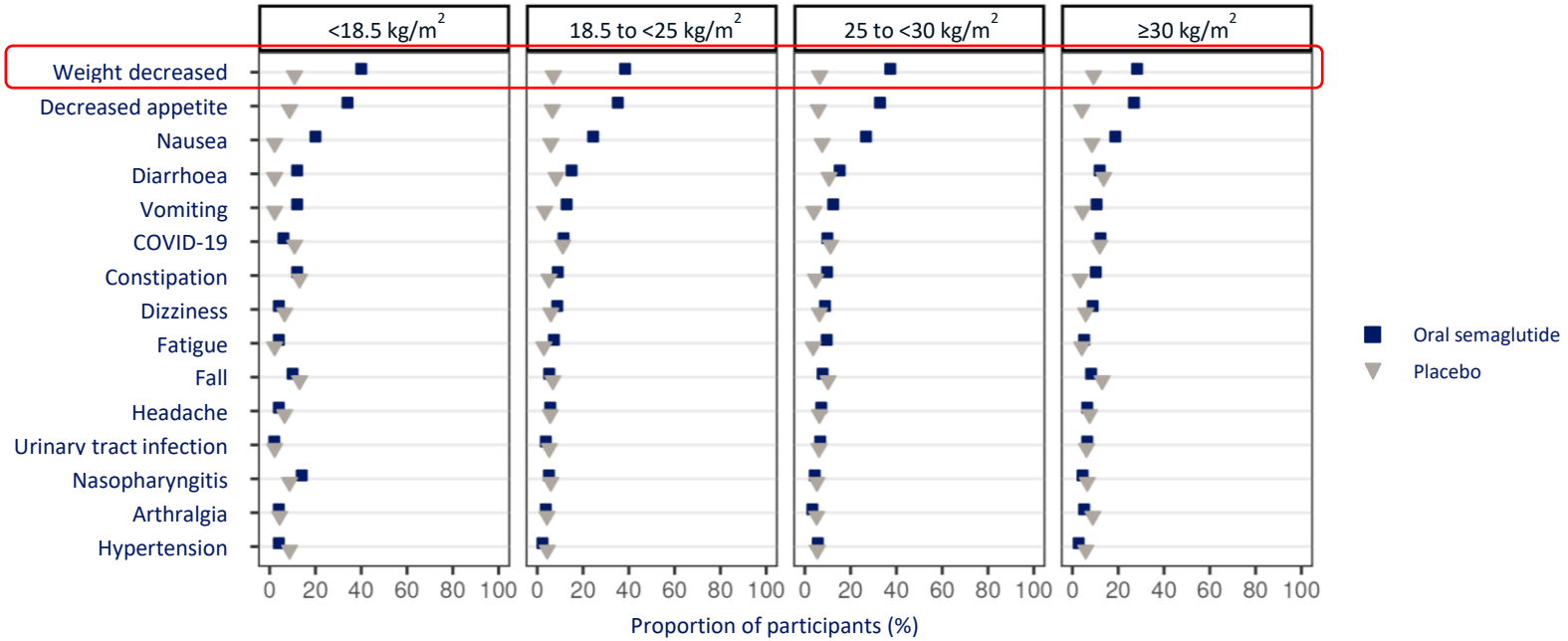
AE, adverse event.
On-treatment data presented.

Weight loss AEs by baseline BMI subgroup

Pooled evoke and evoke+



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AE, adverse event; BMI, body mass index.
Sorted in descending order by preferred term based on the proportion of participants in the oral semaglutide treatment group experiencing at least one event.

Body weight change (%) by baseline BMI subgroup

Change from baseline to week 104

Across both trials, the mean body weight change from baseline at week 104:

–5.8% (–4.3 kg) for oral semaglutide
+0.6% (+0.2 kg) for placebo

	Oral semaglutide 14 mg		Placebo	
BMI category (kg/m^2)	n	Body weight change (%) from baseline	n	Body weight change (%) from baseline
<18.5	34	**–1.0**	36	**+4.9**
18.5 to <25	628	**–4.5**	722	**+1.4**
25 to <30	486	**–6.5**	514	**–0.1**
≥30	231	**–8.6**	237	**–1.4**

BMI, body mass index.

Safety and tolerability for oral semaglutide in early AD was consistent with the known safety profile of semaglutide

1. More AEs were reported with oral semaglutide compared with placebo, but **no treatment differences were observed for AEs with a fatal outcome, severe AEs or serious AEs**
2. **Event types reported were as expected**, with more GI disorders and decreased appetite and weight reported with oral semaglutide compared with placebo; all consistent with the known tolerability profile and mode of action of semaglutide
3. AEs leading to study drug **withdrawal or dose-reduction** were driven by GI disorders, weight decrease and decreased appetite
4. Evaluation of the safety focus areas as well as other safety parameters revealed **no unexpected findings**, and **no safety concerns were identified** in this early AD population

evoke evaluation of oral semaglutide in early Alzheimer's disease

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AD, Alzheimer's Disease; AE, adverse event; GI, gastrointestinal

Conclusions

Jeffrey Cummings
Professor
University of Nevada, Las Vegas

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Conclusions

1. **evoke and evoke+** are two large multinational, randomised, placebo-controlled trials that enrolled **3,808 participants** with biomarker-positive early AD in **40 countries**
2. **Superiority** of oral semaglutide 14 mg once-daily versus placebo was **not confirmed** in change in cognition and function after 104 weeks, as measured by the CDR-SB
3. Plasma hs-CRP and AD-relevant **CSF biomarkers were significantly impacted** but this did not translate into clinical efficacy
4. **Safety and tolerability** for oral semaglutide in participants with early AD was **consistent** with studies in other indications

evoke evaluation of oral semaglutide in early Alzheimer's disease

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AD, Alzheimer's disease; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CSF, cerebrospinal fluid; hs-CRP, high sensitivuty C-reactive protein; MCI, mild cognitive impairment.

Visit sciencehub.novonordisk.com for these slides and more meeting materials:

https://sciencehub.novonordisk.com/CTAD25/johannsen1.html?cid=qr-rnmv70fs9o&source=ctad-2025

Thank you!
Any questions?

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