Results from evoke and evoke+: Two phase 3, randomised, placebo-controlled trials of semaglutide in participants with early-stage symptomatic Alzheimer's disease

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Aim

- To confirm the superiority of once-daily oral semaglutide 14 mg versus placebo when added to standard of care with respect to the change in cognition and function in participants with mild cognitive impairment (MCI) or mild dementia due to Alzheimer's disease (AD).

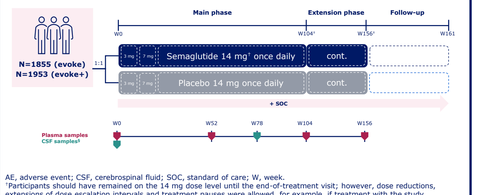
Introduction

- Evidence, including non-clinical, clinical and real-world evidence in individuals with type 2 diabetes and/or obesity, suggests a reduced risk of dementia and AD after glucagon-like peptide-1 receptor agonist (GLP-1RA) exposure.[1–7]
- Semaglutide, a GLP-1RA, was a promising candidate to slow AD progression through a multifaceted mechanism of action that could reduce neuroinflammation and neurodegeneration.
- Here, the primary results of the evoke (NCT04777396) and evoke+ (NCT04777409) trials, known collectively as evoke(+), are reported, based on all randomised participants after the last participant had the opportunity to complete 2 years in the trials; these data were recently published.[8]

Methods

- evoke and evoke+ were two multinational, multicentre, randomised, double-blind, placebo-controlled, phase 3 trials in which semaglutide versus placebo was investigated in early-stage biomarker-confirmed AD.
- The evoke(+) trial designs have been published.[9]
- Adults aged 55–85 years with amyloid positivity (assessed via positron emission tomography or cerebrospinal fluid [CSF] analysis), a Clinical Dementia Rating (CDR) global score of 0.5, with a score ≥0.5 for three activities of daily living categories, or a CDR global score of 1.0, a Mini-Mental State Examination (MMSE) score ≥22 and a Repeatable Battery for the Assessment of Neurological Status (RBANS) delayed memory index score ≤85 were included.
- Participants with evidence of a relevant neurological disorder, a clinically relevant or unstable psychiatric disorder, or a brain magnetic resonance imaging or computed tomography scan suggestive of clinically significant structural central nervous system disease or strategic infarcts were excluded.
- In evoke+ only, participants with significant small vessel pathology (defined as more than two age-related white matter changes and/or more than one lacunar infarct) were included; otherwise, the evoke(+) trials were identical.
- Continuation of stable approved AD medications was allowed.
  - Approved AD medication could be initiated throughout both trials, including anti-amyloid monoclonal antibodies.
- Participants were randomised 1:1 to receive semaglutide 14 mg (flexible dose) or placebo, plus standard of care, for up to 156 weeks (**Figure 1**).
- The primary endpoint was change in CDR–sum of boxes (CDR-SB) score from baseline to week 104.
- The secondary confirmatory endpoints were:
  - Change in AD Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment (ADCS-ADL-MCI) score from baseline to week 104 in evoke and evoke+.
  - Time to progression to dementia (CDR global score ≥1.0) among participants with MCI (CDR global score of 0.5) at baseline; assessed up to week 156 in evoke(+) (pooled).
- Other secondary endpoints included:
  - Change in AD Assessment Scale-Cognitive Subscale 13 (ADAS-Cog-13) score, Montreal Cognitive Assessment (MoCA) score, MMSE score and AD Composite Score (ADCOMS) from baseline to week 104.

Figure 1. Study design



AE, adverse event; CSF, cerebrospinal fluid; SOC, standard of care; W, week.
*Participants should have remained on the 14 mg dose level until the end-of-treatment visit; however, dose reductions, extensions of dose escalation intervals and treatment pauses were allowed, for example, if treatment with the study intervention was associated with unacceptable AEs; †Confirmatory endpoints; ‡Collected from participants in the CSF substudy (n=199).

  - Change in high-sensitivity C-reactive protein (hsCRP) levels from baseline to week 104.
  - Time to progression in disease stage (CDR global score) from baseline up to week 156.
- Safety was assessed in all participants and reported for those receiving at least one study drug dose.
- Exploratory endpoints included plasma levels (ratio to baseline at week 104) of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), phosphorylated-tau181 (p-tau181) and p-tau217.
- A CSF substudy was performed to explore the effect of oral semaglutide versus placebo on neuroinflammatory, neurodegenerative and other canonical AD CSF biomarkers from baseline to week 78.

Results

Table 1. Baseline demographics and characteristics[10]

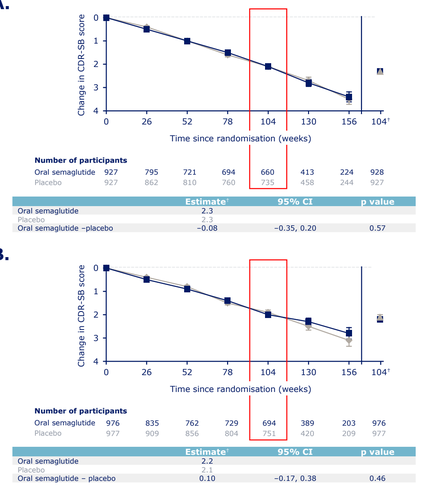
		evoke		evoke+		evoke(+)
		Semaglutide	Placebo	Semaglutide	Placebo	Total
Number of participants		928	927	976	977	3808
Age, years	Mean (SD)	71.9 (7.0)	71.7 (7.1)	72.6 (7.0)	72.5 (7.2)	72.2 (7.1)
Sex	Female	489 (52.7)	496 (53.5)	515 (52.8)	498 (51.0)	1998 (52.5)
Race	White	735 (79.2)	765 (82.5)	725 (74.3)	726 (74.3)	2951 (77.5)
	Asian	117 (12.6)	102 (11.0)	202 (20.7)	205 (21.0)	626 (16.4)
BMI, kg/m²	Mean (SD)	25.7 (4.5)	25.8 (4.4)	25.7 (4.5)	25.7 (4.6)	25.7 (4.5)
T2D		99 (10.7)	116 (12.5)	155 (15.9)	148 (15.1)	518 (13.6)
Concurrent SSVP		--	--	26 (2.7)	28 (2.9)	54 (1.4)
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)
Concomitant AD medication		559 (60.2)	527 (56.9)	546 (55.9)	525 (53.7)	2157 (56.6)
CDR-SB	Mean (SD)	3.8 (1.6)	3.7 (1.5)	3.7 (1.5)	3.7 (1.7)	3.7 (1.6)
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)

Data are n (%) unless otherwise specified.
AD, Alzheimer's disease; ADCS-ADL-MCI, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment; BMI, body mass index; CDR-SB, Clinical Dementia Rating–sum of boxes; SD, standard deviation; SSVP, significant small vessel pathology; T2D, type 2 diabetes.

- Between 18 May 2021 and 8 September 2023, 9981 participants were screened across 566 sites in 40 countries, and 3808 participants were randomised (1855 and 1953 in evoke and evoke+, respectively).[10]
- Baseline demographics were similar between treatment groups (**Table 1**).
- Oral semaglutide did not slow cognitive and functional decline in participants with early AD versus placebo in either trial, as measured by change in CDR-SB score (evoke, estimated treatment difference [ETD] −0.08, 95% confidence interval [CI] −0.35, 0.20; p=0.57; evoke+, ETD 0.10, 95% CI −0.17, 0.38; p=0.46) (**Figure 2**).
- Oral semaglutide did not slow functional decline as measured by change in ADCS-ADL-MCI score (evoke, ETD −0.25, 95% CI −1.22, 0.72; evoke+, ETD −0.03, 95% CI −0.97, 0.91) (**Figure 3**).
- Oral semaglutide did not delay time to progression to dementia (CDR global ≥1.0) among participants with MCI (CDR global=0.5) at baseline (hazard ratio 0.97, 95% CI 0.87, 1.08; pooled for evoke and evoke+).
- Oral semaglutide was not associated with significant changes in MoCA, ADAS-Cog-13, MMSE or ADCOMS scores versus placebo.
- Exploratory plasma biomarker data showed a significant increase of ~5% in NfL levels in evoke+ (estimated treatment ratio [ETR] 1.05, 95% CI 1.01, 1.08; unadjusted p<0.05), a significant increase of ~4% in GFAP levels in both evoke and evoke+ (ETR 1.05, 95% CI 1.02, 1.08, and ETR 1.07, 95% CI 1.04, 1.10, respectively; unadjusted p<0.05) and no significant changes in p-tau217 or p-tau181 levels.

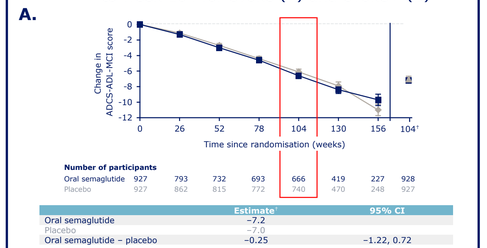
Figure 2. Change in CDR-SB score from baseline up to week 104 for evoke (A) and evoke+ (B)

Key result



†Data are for the hybrid-Hypothetical-Treatment Policy-Composite (HTC) estimand. Error bars are mean ± standard error of the mean. CDR-SB, Clinical Dementia Rating–sum of boxes; CI, confidence interval.

Figure 3. Change in ADCS-ADL-MCI score from baseline to week 104 for evoke (A) and evoke+ (B)



†Data are for the hybrid-Hypothetical-Treatment Policy-Composite (HTC) estimand. Error bars are mean ± standard error of the mean. ADCS-ADL-MCI, AD Cooperative Study Activities of Daily Living Scale for Mild Cognitive Impairment; CI, confidence interval.

Table 2. Pooled evoke(+) safety summary

	Semaglutide	Placebo
Number of participants	1896	1902
Any AE	1729 (91.2)	1613 (84.8)
Serious AEs	386 (20.4)	453 (23.8)
AEs leading to permanent discontinuation	321 (16.9)	159 (8.4)
Fatal AEs	51 (2.7)	51 (2.7)
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)

Data are n (%) unless otherwise specified.
AE, adverse event.

Table 3. Change in CSF biomarkers from baseline to week 78 (ratio to baseline)

	Biomarker	ETR (95% CI)†	Unadjusted p value
AD biomarkers	**p-tau181 (Elecsys)**	**0.92 (0.87, 0.97)**	**0.0035**
	p-tau217 (C2N)	**0.90 (0.81, 0.99)**	**0.038**
	p-tau217/np-tau217 (ratio; C2N)	0.96 (0.91, 1.01)	0.085
	p-tau205 (C2N)	0.93 (0.85, 1.02)	0.11
	Aβ42/40 (ratio; Elecsys)	1.03 (0.99, 1.09)	0.16
	p-tau181 (C2N)	0.94 (0.85, 1.04)	0.21
	p-tau181/np-tau181 (ratio; C2N)	1.02 (0.98, 1.07)	0.32
	p-tau205/np-tau205 (ratio; C2N)	1.02 (0.98, 1.07)	0.36
BBB integrity	CSF/serum albumin (ratio)	0.97 (0.77, 1.21)	0.77
	PDGFRβ	0.91 (0.79, 1.06)	0.24
Neuroinflammation	**YKL-40**	**0.93 (0.89, 0.98)**	**0.0082**
	GFAP	0.97 (0.89, 1.05)	0.43
	IL-6	1.04 (0.93, 1.16)	0.48
	sTREM2	0.98 (0.92, 1.04)	0.48
	IL-8	1.06 (0.85, 1.32)	0.59
	IL-1β	1.13 (0.69, 1.87)	0.63
	SMOC1	0.97 (0.80, 1.18)	0.79
	IL-18	0.99 (0.84, 1.16)	0.87
	IL-1RA	1.01 (0.90, 1.13)	0.91
	Osteopontin	1.01 (0.79, 1.28)	0.94
	IP-10/CXCL10	1.01 (0.65, 1.57)	0.96
	MCP-1/CCL2	1.00 (0.69, 1.44)	0.99
Neurodegeneration	**Total tau**	**0.93 (0.88, 0.98)**	**0.0075**
	Neurogranin	**0.92 (0.87, 0.98)**	**0.0076**
	NfL	0.97 (0.87, 1.09)	0.62
	C4B	1.03 (0.81, 1.31)	0.81
Complement system	C3	0.99 (0.79, 1.26)	0.96

Rows highlighted in green are statistically significant (unadjusted p<0.05). †Data are for the hypothetical biomarker estimand. AD, Alzheimer's disease; BBB, blood–brain barrier; C3, complement component 3; C4B, complement component 4B; CCL2, C-C motif ligand 2; CI, confidence interval; CSF, cerebrospinal fluid; CXCL10, C-X-C motif chemokine ligand 10; ETR, estimated treatment ratio; GFAP, glial fibrillary acidic protein; IL, interleukin; IL-1RA, IL-1 receptor antagonist; IP-10, interferon γ-induced protein 10; mAb, monoclonal antibody; MCP-1 monocyte chemoattractant protein 1; NfL, neurofilament light chain; np, non-phosphorylated; p, phosphorylated; PDGFRβ, platelet-derived growth factor receptor β; SMOC1, SPARC-related modular calcium-binding protein 1; sTREM2, soluble triggering receptor expressed on myeloid cells 2.

- A significant decrease in plasma hsCRP was observed in evoke (ETR 0.74, 95% CI 0.66, 0.83) and evoke+ (ETR 0.67, 95% CI 0.61, 0.75).
- More AEs were reported with oral semaglutide compared with placebo, but rates of AEs with a fatal outcome or serious AEs were similar across treatment groups (**Table 2**).
- AE types reported were as expected, with more gastrointestinal disorders and a higher incidence of decreased appetite and weight reported with oral semaglutide compared with placebo; all consistent with the known tolerability profile and mode of action of semaglutide.
- AEs leading to study drug withdrawal or dose reduction were driven by gastrointestinal disorders, weight decrease and decreased appetite.
- In the CSF substudy (n=199), significant reductions of up to 10% were reported with semaglutide versus placebo for AD biomarkers (p-tau181 and p-tau217), neuroinflammatory biomarkers (YKL-40) and neurodegeneration biomarkers (total tau and neurogranin) from baseline to week 78 (unadjusted p<0.05 for all comparisons) (**Table 3**).

Conclusion

- Superiority of semaglutide 14 mg versus placebo in slowing cognitive and functional decline was not demonstrated in participants with early AD.
- Plasma hsCRP and AD-relevant CSF biomarkers were significantly impacted, but this did not translate into clinical efficacy.
- Safety and tolerability of semaglutide in early AD were consistent with studies in other indications.

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