Efficacy and safety of oral semaglutide 14 mg (flexible dose) in early-stage symptomatic Alzheimer's disease (evoke and evoke+): two phase 3, randomised, placebo-controlled trials

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Summary

Background Evidence, including animal, clinical, and real-world studies in individuals with type 2 diabetes and/or obesity, suggests reduced risk of dementia and Alzheimer's disease after GLP-1 receptor agonist exposure. The evoke and evoke+ trials aimed to investigate the efficacy and safety of oral semaglutide in individuals with early Alzheimer's disease.

Methods evoke and evoke+ were multicentre, randomised, double-blind, placebo-controlled phase 3 trials conducted across 566 sites in 40 countries. The trials assessed the efficacy and safety of oral semaglutide up to 14 mg once daily in participants with amyloid-confirmed Alzheimer's disease, aged 55–85 years, with mild cognitive impairment or mild dementia due to Alzheimer's disease. In evoke+, participants with significant small vessel pathology were included. Participants were randomly assigned (1:1) to once-daily semaglutide 14 mg (flexible dose) or placebo for up to 156 weeks. The primary endpoint was change in Clinical Dementia Rating—Sum of Boxes (CDR-SB) score from baseline to week 104, assessed in all randomised participants. Safety was assessed in all randomised participants and reported for those receiving at least one dose of study drug. These trials were registered at ClinicalTrials.gov (NCT04777396 and NCT04777409); both trials have been discontinued due to negative clinical outcome.

Findings Between May 18, 2021, and Sept 8, 2023, 9981 participants were screened, of whom 3808 were randomly assigned; 1855 in evoke (semaglutide, n=928; placebo, n=927) and 1953 in evoke+ (semaglutide, n=976; placebo, n=977). Mean age was 72·2 years (SD 7·1), and mean CDR-SB score was 3·7 (SD 1·6) at baseline. In evoke+, 54 (2·8%) participants had small vessel pathology. In evoke and evoke+, mean changes in CDR-SB score from baseline to week 104 were 2·3 (SE 0·1) and 2·2 (0·1) with semaglutide, compared with 2·3 (0·1) and 2·1 (0·1) with placebo (estimated difference –0·08 [95% CI –0·35 to 0·20], p=0·57 in evoke and 0·10 [–0·17 to 0·38], p=0·46 in evoke+). Treatment-emergent adverse events were reported in 1729 (91·2%) of 1896 participants receiving semaglutide versus 1613 (84·8%) of 1902 receiving placebo. There were five fatalities considered treatment-related by the investigators (one in the semaglutide group and four in the placebo group).

Interpretation Oral semaglutide was not efficacious in slowing clinical progression in participants with early Alzheimer's disease. Safety and tolerability of semaglutide in early Alzheimer's disease is consistent with studies in other indications.

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Introduction

Alzheimer's disease is a progressive neurodegenerative disease characterised by gradual cognitive and functional decline and is the leading cause of dementia worldwide.[1] Therapeutic interventions targeting the early stages of cognitive impairment due to Alzheimer's disease could have substantial clinical, economic, and socioeconomic consequences for patients, care partners, and society in delaying progression of disease and forestalling disability.[2] Neuroinflammation and neuroimmune dysfunction have been identified as key factors in the pathophysiology of Alzheimer's disease and occur at early disease stages with microglial and astrocytic activation and activation of the innate and adaptive immune systems with cytokine release.[3–5] Neurovascular dysfunction resulting from cerebral amyloid angiopathy and vessel inflammation can compromise blood–brain barrier integrity in early Alzheimer's disease and might contribute to disease progression.[6] Microvascular dysfunction has also been associated with Alzheimer's disease progression in mouse models.[7]

GLP-1 is a multifaceted peptide hormone that potentiates glucose-dependent insulin secretion.[8] Semaglutide, a GLP-1 receptor agonist, is approved for the treatment of type 2 diabetes, weight management, and cardiovascular risk reduction in individuals with

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Research in context

Evidence before this study

We searched PubMed on May 15, 2025, with no date or language restrictions, using the search terms "glucagon-like peptide-1 receptor agonist", "GLP-1RA", "Alzheimer's disease", "MCI", "AD", "small vessel pathology", and "cognitive function". In observational, longitudinal cohort studies in patients with type 2 diabetes and/or obesity, a reduced risk of dementia and clinical diagnosis of Alzheimer's disease was reported after GLP-1 receptor agonist exposure. Animal studies demonstrate that GLP-1 receptor agonist exposure reduces systemic and CNS inflammation, improves memory function, and preserves blood–brain barrier integrity. In humans, two small investigator-sponsored studies suggested GLP-1 receptor agonist treatment might prevent cognitive decline or slow disease progression in Alzheimer's disease. These studies provided the basis for the mechanistic hypotheses of the current study relating to anti-inflammatory, neuroprotective, vascular, and blood–brain barrier effects in Alzheimer's disease. The evoke(+) trials were initiated to assess the safety and efficacy of a GLP-1 receptor agonist (once-daily semaglutide up to 14 mg) on top of standard of care for slowing disease progression in individuals with early Alzheimer's disease.

Added value of this study

The evoke(+) trials were the first large-scale, multi-country, randomised clinical trials investigating the clinical efficacy and safety of semaglutide in early-stage Alzheimer's disease. Neither trial demonstrated superiority of oral semaglutide 14 mg to placebo in slowing cognitive or global decline in people with early-stage Alzheimer's disease from baseline to week 104. Prespecified pooled trial analyses did not demonstrate a delay in time to progression to dementia in participants with mild cognitive impairment (MCI) due to Alzheimer's disease from baseline up to week 156. In the cerebrospinal fluid (CSF) substudy, semaglutide led to significant reductions of up to 10% in CSF-based core biomarkers associated with Alzheimer's disease (phosphorylated-tau181 [p-tau181], p-tau217, non-phosphorylated-tau181 [np-tau181], and np-tau205) and CSF biomarkers of neuroinflammation, neurodegeneration, and synaptic function (YKL-40, total tau, and neurogranin). Semaglutide treatment was also associated with significantly reduced plasma high-sensitivity C-reactive protein concentrations.

Implications of all the available evidence

The results of the large evoke(+) trials do not support the efficacy of 14 mg/day of semaglutide given for up to 156 weeks in participants with biomarker-confirmed Alzheimer's disease in the MCI or mild dementia stage.

established cardiovascular disease and overweight or obesity. Studies in mice have shown GLP-1 receptor agonists impact multiple inflammatory, vascular, and metabolic processes that are implicated in the pathogenesis of Alzheimer's disease.[9–12] Real-world and observational studies have demonstrated that patients with type 2 diabetes and obesity treated with GLP-1 receptor agonists have a reduced risk of all-cause dementia and Alzheimer's disease.[13–19] In a case–control study of 176 250 patients with type 2 diabetes, GLP-1 receptor agonists were associated with lower odds of dementia (odds ratio [OR] 0·58; 95% CI 0·50–0·67).[16] A pooled post-hoc analysis of three randomised cardiovascular outcome trials including 15 280 patients with type 2 diabetes showed a risk reduction of dementia in those receiving GLP-1 receptor agonists versus placebo (hazard ratio [HR] 0·47; 95% CI 0·25–0·86).[17] In a real-world target trial emulation study including 1 710 995 patients with type 2 diabetes without a previous diagnosis of Alzheimer's disease, semaglutide was associated with a significantly lower risk of dementia due to Alzheimer's disease versus other GLP-1 receptor agonists (HR 0·80; 95% CI 0·72–0·89).[18] A meta-analysis including 819 511 individuals with type 2 diabetes reported a lower incidence of dementia in GLP-1 receptor agonist users versus non-users (relative risk [RR] 0·72; 95% CI 0·54–0·97).[19]

See Online for appendix 1

These cumulative data suggested semaglutide was a promising candidate to slow Alzheimer's disease progression through a multifaceted mechanism of action that could reduce neuroinflammation and neurodegeneration. Two small trials showed potential benefits of GLP-1 receptor agonist treatment in mild-to-moderate Alzheimer's disease dementia, but no definitive clinical conclusions could be drawn due to small sample sizes and trial designs.[20,21]

The evoke and evoke+ trials, referred to here as "evoke(+)", investigated the efficacy and safety of oral semaglutide in participants with biomarker-positive Alzheimer's disease in the mild cognitive impairment (MCI) or mild dementia stage with up to 3 years of treatment.[22] Here, we report the primary results of evoke(+) based on all randomised participants after the last participant had the opportunity to complete 2 years in the trials.

Methods

Study design

The evoke(+) trial designs have been published (appendix 1 p 30).[22] evoke and evoke+ were two multicentre, randomised, double-blind, parallel-group, placebo-controlled phase 3 trials in participants with Alzheimer's disease in the MCI or mild dementia stage with confirmed amyloid positivity (by PET or

cerebrospinal fluid [CSF] testing). Participants were recruited from 566 sites across 40 countries.[22] The trials were conducted in accordance with the consensus ethical principles from international guidelines including the Declaration of Helsinki and applicable ICH Good Clinical Practice Guideline and local laws and regulations. The trials were approved by local ethics committees and institutional review boards. The trial protocols and statistical analysis plans are available in appendix 2. The trials were registered at ClinicalTrials.gov (NCT04777396 and NCT04777409) and EudraCT (2020-004848-29 and 2020-004864-25); both trials have been discontinued due to negative clinical outcome.

Both trials included a 12-week screening phase before randomisation (1:1) to receive oral semaglutide titrated to 14 mg (flexible dosing) or placebo for 104 weeks (main phase) and up to 156 weeks (inclusive of the 52-week extension phase). Results reported here are from data collected after all participants had the opportunity to complete week 104 (at the time of the main phase database lock); for some participants, safety and efficacy data were available for up to week 156 and have been included for specific analyses, as described below with the results. All data reported here are for the hybrid hypothetical–treatment policy–composite (HTC) estimand (see statistical analysis section and trial protocol in appendix 2 for further information). Initiation of approved Alzheimer's disease treatments was permitted during the trial if deemed medically necessary by investigators, including anti-amyloid therapies. If participants at baseline were receiving Alzheimer's disease treatment (such as acetylcholinesterase inhibitors, memantine, or aducanumab), the dose must have been stable for at least 3 months before screening and should not have been expected to change during the trial unless deemed medically necessary. All participants and study partners provided written informed consent.

Participants

Full inclusion and exclusion criteria have been published.[22] In both trials, adults aged 55–85 years (inclusive) at the time of signing informed consent with MCI or mild dementia due to Alzheimer's disease according to the National Institute on Aging and the Alzheimer's Association (NIA-AA) 2018 criteria were included. Participants had a Clinical Dementia Rating (CDR) global score of 0·5 and CDR of 0·5 or higher in at least one of the three instrumental activities of daily living categories (personal care, home and hobbies, community affairs), or a CDR global score of 1·0; Repeated Battery for the Assessment of Neuropsychological Status (RBANS) delayed memory index score of 85 or lower; Mini-Mental State Exam (MMSE) score of 22 or higher; and amyloid positivity established with either amyloid PET (determined by visual read) or CSF $A\beta_{1\text{-}42}$ or CSF $A\beta_{1\text{-}42}$/$A\beta_{1\text{-}40}$. More details on criteria for amyloid positivity for both PET and CSF are available in appendix 1 (p 21).

In evoke+ only, participants with significant small vessel pathology (defined as more than one lacunar infarct and/or Age-Related White Matter Changes [ARWMC] scale score >2 [white matter >20 mm]) were allowed (these participants were excluded in the evoke trial). Otherwise, the evoke(+) trials were identical.

Randomisation and masking

In each trial, participants were randomly assigned 1:1 to receive flexible doses of once-daily oral semaglutide 14 mg or placebo for 156 weeks, both added to standard of care. All participants were screened and centrally randomised using an interactive web response system and assigned to the next available treatment according to the randomisation schedule. Participants, care providers, investigators, and outcome assessors were masked to investigational intervention allocation.

See Online for appendix 2

Further information on randomisation and masking can be found in the trial protocols (appendix 2).

Procedures

Randomised participants initiated once-daily oral semaglutide 3 mg or placebo followed by a 4-week dose escalation regimen (3 mg to 7 mg to 14 mg) until the treatment dose of 14 mg was reached. Participants were intended to remain on the 14-mg dose level until week 156; however, flexible dosing was allowed; dose reductions, extensions of dose escalation intervals, and treatment pauses were permitted if treatment was associated with unacceptable adverse events. All cognition and function efficacy assessments described were performed by a minimum of two independently trained and certified raters at each site. The CDR rater remained masked to adverse events and other information that had the potential to reveal the treatment assignment. Blood samples for plasma biomarker evaluation were collected at weeks 0, 52, 104, and 156.

In 15 countries, with sites experienced in CSF collection, randomised participants were eligible to participate in the CSF substudy that explored the effect of oral semaglutide versus placebo on neuroinflammatory, neurodegenerative, and other canonical Alzheimer's disease CSF biomarkers. This substudy also measured semaglutide concentration in the CSF of participants. In total, 199 participants enrolled in the CSF substudy. Participants in each trial were stratified by CSF substudy participation to ensure 1:1 randomisation in the substudy population. CSF samples were collected for these biomarkers at weeks 0 and 78. The concentration of semaglutide in CSF samples was measured at week 78.

Outcomes

Full details on the evoke(+) trial outcome instruments have been published.[22] The primary endpoint in both trials was change in the CDR—Sum of Boxes (CDR-SB) score from baseline to week 104. Confirmatory secondary endpoints were change from baseline in Alzheimer's

disease Cooperative Study Activities of Daily Living—MCI (ADCS-ADL-MCI) score from baseline to week 104 in each trial, and time to progression to a CDR global score of 1·0 or higher among participants with a baseline CDR global score of 0·5 from baseline to week 156 in a pooled analysis of both trials.

Secondary clinical endpoints included change in the following cognitive assessments: Alzheimer's Disease Assessment Scale—Cognitive Subscale 13 (ADAS-Cog-13) score, Montreal Cognitive Assessment (MoCA) score, Alzheimer's Disease Composite Score (ADCOMS), MMSE score, and composite Z score (based on the three outcome measures CDR-SB, ADCS-ADL-MCI, and ADAS-Cog-13 from baseline to week 104). Further details can be found in appendix 1 (pp 22–24).

Other secondary endpoints were time to progression in disease stage based on CDR global score from baseline up to week 156 and time to progression to a CDR global score of 1·0 or higher among participants with a baseline CDR global score of 0·5 from baseline to week 156 in each trial; change in neuropsychiatric symptoms, as assessed by the Neuropsychiatric Inventory (NPI) score; change in peripheral inflammation, assessed by high-sensitivity C-reactive protein (hsCRP) concentrations; and change in quality of life, assessed by the EuroQol 5-Dimension 5-Level (EQ-5D-5L; proxy version) index score from baseline to week 104.

Safety endpoints included number of treatment-emergent adverse events (TEAEs) from baseline up to week 156; time to first occurrence of major adverse cardiovascular event (MACE), comprising non-fatal myocardial infarction, non-fatal stroke, and all-cause death, from baseline to week 104 (non-adjudicated); and time to first occurrence of stroke from baseline to week 104. Data were collected on serious adverse events, including death and TEAEs leading to treatment discontinuation. Adverse events were described according to preferred term (MedDRA version 28.0 classification) and data reported for the on-treatment period unless otherwise stated.

Exploratory endpoints included plasma concentrations (ratio to baseline at week 104) of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), phosphorylated-tau181 (p-tau181), and p-tau217. In the CSF substudy, exploratory endpoints were changes in canonical Alzheimer's disease biomarkers, as well as neuroinflammation, neurodegeneration, blood–brain barrier integrity, oxidative stress, synaptic integrity, and vascular biomarkers from baseline to week 78. All CSF biomarker endpoints are described in appendix 1 (pp 28–29).

Statistical analysis

In each trial, a sample size of 1840 was required to provide 95% power for confirming superiority of oral semaglutide 14 mg over placebo (assumed mean difference of –0·44 points; 20% benefit; SD 2·6) for the primary endpoint of change in CDR-SB score from baseline to week 104, and 76% power for confirming superiority for the confirmatory secondary endpoint of change in ADCS-ADL-MCI score from baseline to week 104. The confirmatory statistical tests were performed hierarchically using a one-sided significance level of α=2·5% in each trial. To achieve 83% power for confirming superiority for the confirmatory secondary time-to-progression endpoint, analysis was based on the pooled evoke(+) dataset.

Efficacy outcomes are presented for all randomised participants (the full analysis set), and safety outcomes are presented for all randomised participants who received at least one dose of trial product (safety analysis set). A post-hoc analysis assessed CDR-SB change from baseline to week 104 in age, sex, and type 2 diabetes subgroups.

To address the primary and secondary endpoints, and as recommended by regulatory authorities, the hybrid-HTC was the primary estimand and addressed the treatment difference at week 104 for all randomised patients on the assumption that the participants had not discontinued treatment (hypothetical strategy), regardless of initiation of additional Alzheimer's disease medication, while the intercurrent event of death was handled by a composite strategy. In addition, a treatment policy estimand was defined as an additional estimand. Further information on the hybrid-HTC and treatment policy estimands is available in the trial protocols.

The primary endpoint was analysed according to the hybrid-HTC estimand using a restricted maximum likelihood-based mixed models for repeated measures (MMRM) test, with treatment, visit, apolipoprotein E ε4 (*APOE*-ε4) gene carrier status (carrier or non-carrier), sex, region, and use of Alzheimer's disease medication at baseline as factors, and baseline age as a continuous covariate, with two-way interaction between each covariate or factor and visit. Non-ascertainable data due to death were imputed by assuming a worst-case scenario, with imputations done on the CDR-SB scale. From the MMRM model, the mean treatment differences between oral semaglutide and placebo at week 104 were estimated and the corresponding two-sided 95% CI and two-sided p value were calculated. Further details on confirmatory secondary endpoint analyses are in the trial protocols. Pharmacokinetic analyses were prespecified in a modelling analysis plan finalised before database lock.

The Data Monitoring Committee (DMC) had oversight of the data during the trial. The DMC was an independent, external committee composed of members with relevant expertise including statistics. The protocols were approved by the Ethics Committee at each participating centre.

Role of the funding source

Novo Nordisk was responsible for data collection and analysis. In collaboration with all authors, Novo Nordisk was involved in data interpretation, writing of the report, and the decision to submit.

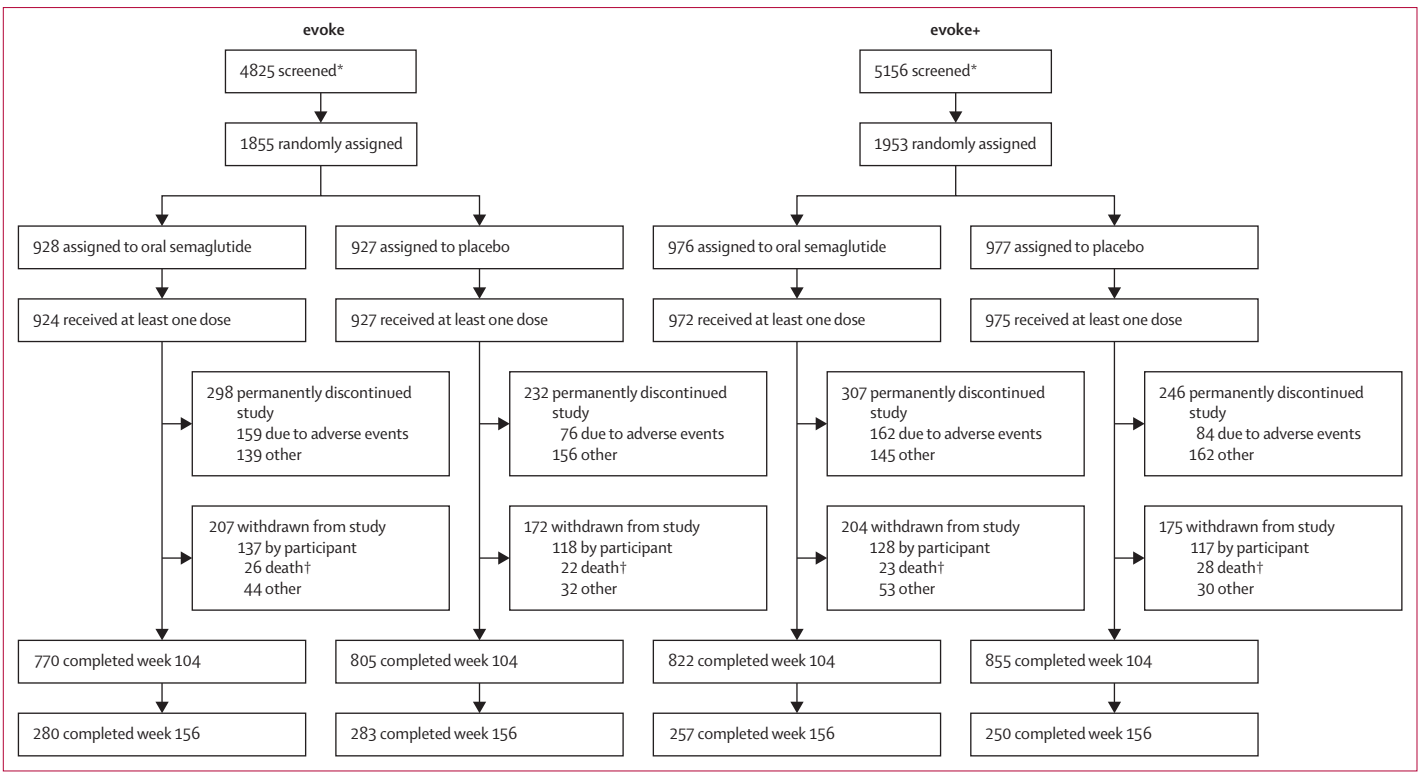


Figure 1: **Trial profiles**
*See the appendix (pp 46–47) for details on screening failures. †Includes fatalities reported for participants during trial participation.

Results

Between May 18, 2021, and Sept 8, 2023, 9981 participants were screened across 566 sites in 40 countries, and 3808 participants were randomly assigned (1855 and 1953 in evoke and evoke+, respectively; figure 1). In evoke, 928 (50·0%) participants were assigned to receive semaglutide and 927 (50·0%) were assigned to receive placebo. In evoke+, 976 (50·0%) and 977 (50·0%) participants were assigned to receive semaglutide and placebo, respectively. At baseline, 2746 (72·1%) of 3808 participants had MCI (CDR global score 0·5) and 1034 (27·2%) had mild Alzheimer's disease dementia (CDR global score 1; table 1). The proportions of participants who withdrew from the study were similar between treatment groups in both trials (figure 1). At week 104, 456 (59·8%) of 763 participants in the semaglutide group in evoke and 477 (58·4%) of 817 in evoke+ were receiving semaglutide 14 mg (appendix 1 p 40).

Baseline characteristics were generally similar between treatment groups (table 1).[23] Most participants were White (2951 [77·5%]) and female (1998 [52·5%]), mean age was 72·2 years (SD 7·1), and most were *APOE*-ε4 carriers. Mean CDR-SB score was 3·7 (SD 1·6) and mean ADCS-ADL-MCI score was 39·2 (SD 7·4). Geometric mean hsCRP was 0·8 mg/L (coefficient of variation 170·3%). At randomisation, 2157 (56·6%) participants were receiving Alzheimer's disease concomitant medications; one participant was on aducanumab. During the trials, 512 (26·9%) and 598 (31·4%) participants in the semaglutide and placebo groups, respectively, initiated concomitant Alzheimer's disease medication; 78 (2·1%) participants initiated lecanemab or donanemab. In evoke+, 54 (2·8%) participants had small vessel pathology and the proportion of Asian participants was numerically higher than in evoke (table 1).

Of 98 and 101 participants randomly assigned to semaglutide and placebo, 69 and 73 participants completed the CSF substudy, respectively, at week 78. Baseline characteristics were similar between treatment groups and generally representative of the full evoke(+) population. Most participants were male (103 [51·8%]), mean age was 71·7 years (SD 6·8), and most were *APOE*-ε4 carriers (129 [64·8%]).

In both trials, no change in slowing of cognitive and functional decline on the CDR-SB was observed with semaglutide versus placebo. In evoke and evoke+, mean changes in CDR-SB score from baseline to week 104 were 2·3 (SE 0·1) and 2·2 (0·1) with semaglutide, compared with 2·3 (0·1) and 2·1 (0·1) with placebo. The estimated difference in the change from baseline to 104 weeks for CDR-SB between semaglutide and placebo was –0·08 (95% CI –0·35 to 0·20; p=0·57) in evoke. In

	evoke		evoke+		Pooled evoke(+)
	Semaglutide 14 mg (n=928)	Placebo (n=927)	Semaglutide 14 mg (n=976)	Placebo (n=977)	Total (N=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%)
Male	439 (47·3%)	431 (46·5%)	461 (47·2%)	479 (49·0%)	1810 (47·5%)
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%)
BMI, kg/m²					
<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%)
Type 2 diabetes	99 (10·7%)	116 (12·5%)	155 (15·9%)	148 (15·1%)	518 (13·6%)
Concurrent significant small vessel pathology	NA	NA	26 (2·7%)	28 (2·9%)	54 (1·4%)
hsCRP, mg/L; geometric mean (CV)†	0·8 (160·2)	0·9 (174·5)	0·9 (178·1)	0·8 (167·9)	0·8 (170·3)
APOE-ε4 gene carrier status					
APOE-ε4 carrier (heterozygote)	451 (48·6%)	448 (48·3%)	443 (45·4%)	437 (44·7%)	1779 (46·7%)
APOE-ε4 carrier (homozygote)	117 (12·6%)	120 (12·9%)	111 (11·4%)	122 (12·5%)	470 (12·3%)
Any concomitant Alzheimer's disease medications ongoing at randomisation	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%)
CDR-SB‡					
Mean (SD)	3·8 (1·6)	3·7 (1·5)	3·7 (1·5)	3·7 (1·7)	3·7 (1·6)
Range	0·5–11·0	1·0–11·0	0·5–10·0	0·5–12·0	0·5–12·0
CDR-G					
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)
Range	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)
Range	15·0–30·0	15·0–30·0	13·0–30·0	13·0–30·0	13·0–30·0

Data are n (%) unless otherwise stated. ADCS-ADL-MCI=Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment. *APOE*-ε4=apolipoprotein E ε4 variant. CDR-G=Clinical Dementia Rating—Global. CDR-SB=Clinical Dementia Rating—Sum of Boxes. CV=coefficient of variation in %. hsCRP=high-sensitivity C-reactive protein. MMSE=Mini-Mental State Examination. NA=not applicable. *In France, the law prohibits collection of data on race and ethnicity. †In evoke, oral semaglutide, n=911; placebo, n=916; in evoke+, oral semaglutide, n=964; placebo, n=967. ‡In evoke, oral semaglutide, n=927; placebo, n=927.

Table 1: **Demographic and clinical characteristics of the participants at baseline for evoke(+)**

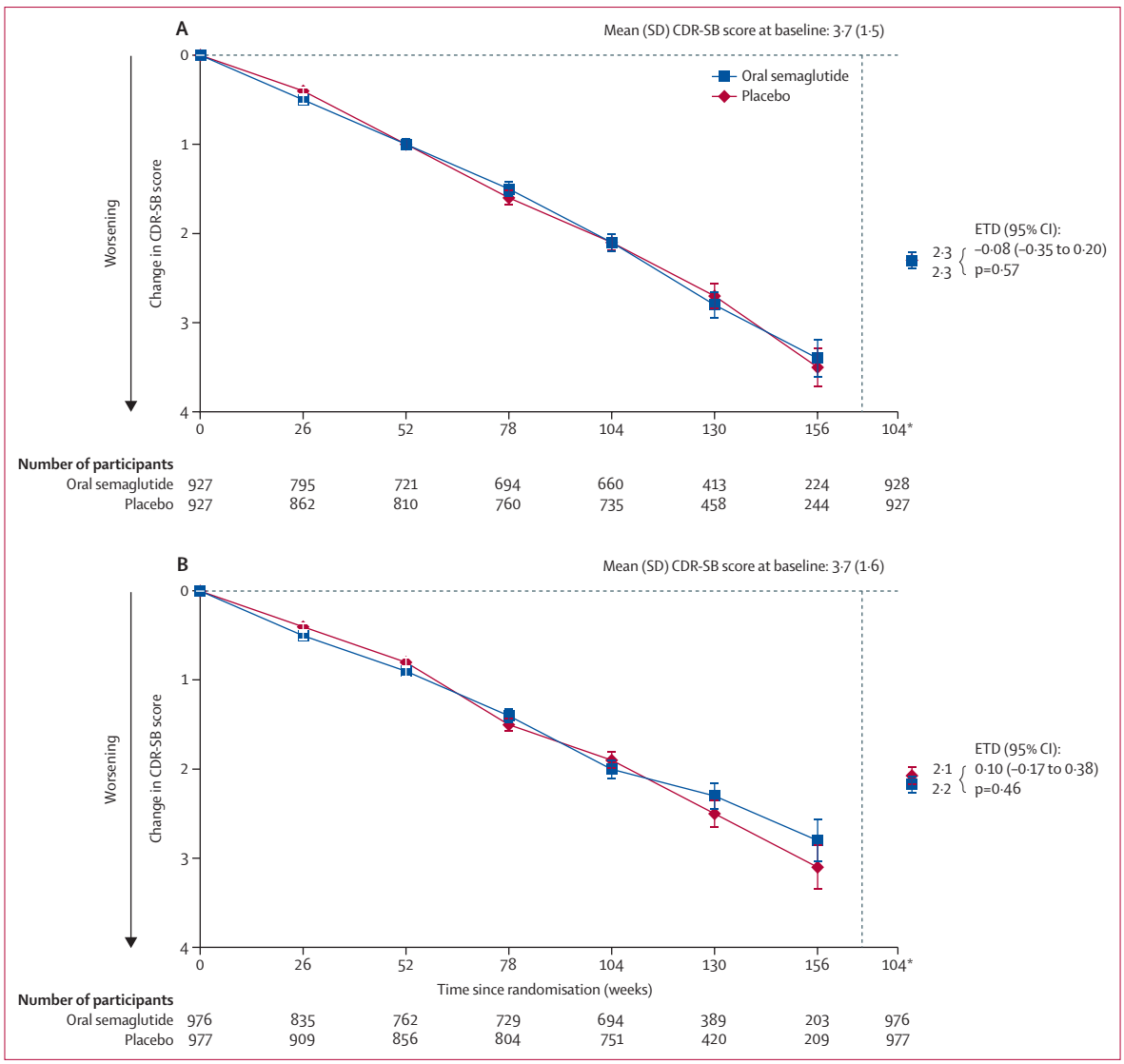


Figure 2: **Change in CDR-SB score from baseline up to week 104 for evoke (A) and evoke+ (B)**
Observed data from the on-treatment dataset. One participant in the oral semaglutide group had a missing baseline value and did not contribute to observed mean at week 0; however, they did contribute to the analyses for estimated mean as participants were assessed post randomisation. Error bars show mean (SE). CDR-SB=Clinical Dementia Rating—Square of Boxes. ETD=estimated treatment difference. HTC=hypothetical–treatment policy–composite. *Estimated mean and corresponding SE at week 104 based on the on-treatment dataset, using the hybrid-HTC estimand.

evoke+, the estimated difference between semaglutide and placebo was 0·10 (–0·17 to 0·38; p=0·46; figure 2). Subgroup analyses supported the main results (appendix 1 pp 42–43). As superiority of the primary endpoint was not confirmed, the testing hierarchy was stopped after the primary analysis, and no p values were calculated for the confirmatory endpoints.

The estimated difference in the change from baseline to 104 weeks for ADCS-ADL-MCI between semaglutide and placebo was –0·25 (95% CI –1·22 to 0·72) in evoke and –0·03 (–0·97 to 0·91) in evoke+ (figure 3). For time to progression to a CDR global score of 1·0 or higher among participants with a baseline CDR global score of 0·5, no difference was observed between semaglutide and placebo in the pooled analysis (appendix 1 p 31). Time to progression in disease stage based on CDR global score at baseline did not differ between treatment groups when evaluated separately for each trial (appendix 1 p 36). Time to progression to a CDR global score of 1·0 or higher among participants with a baseline CDR global score of 0·5 did not differ between treatment groups (evoke, HR 0·98; 95% CI 0·85–1·14; evoke+, 0·96; 0·83–1·12).

No differences between treatment groups were observed for any secondary supportive endpoints. ADAS-Cog-13 score, MoCA, ADCOMS, MMSE, and NPI results are reported in appendix 1 (pp 32–35, 37). Change in the composite Z score (based on the three outcome measures

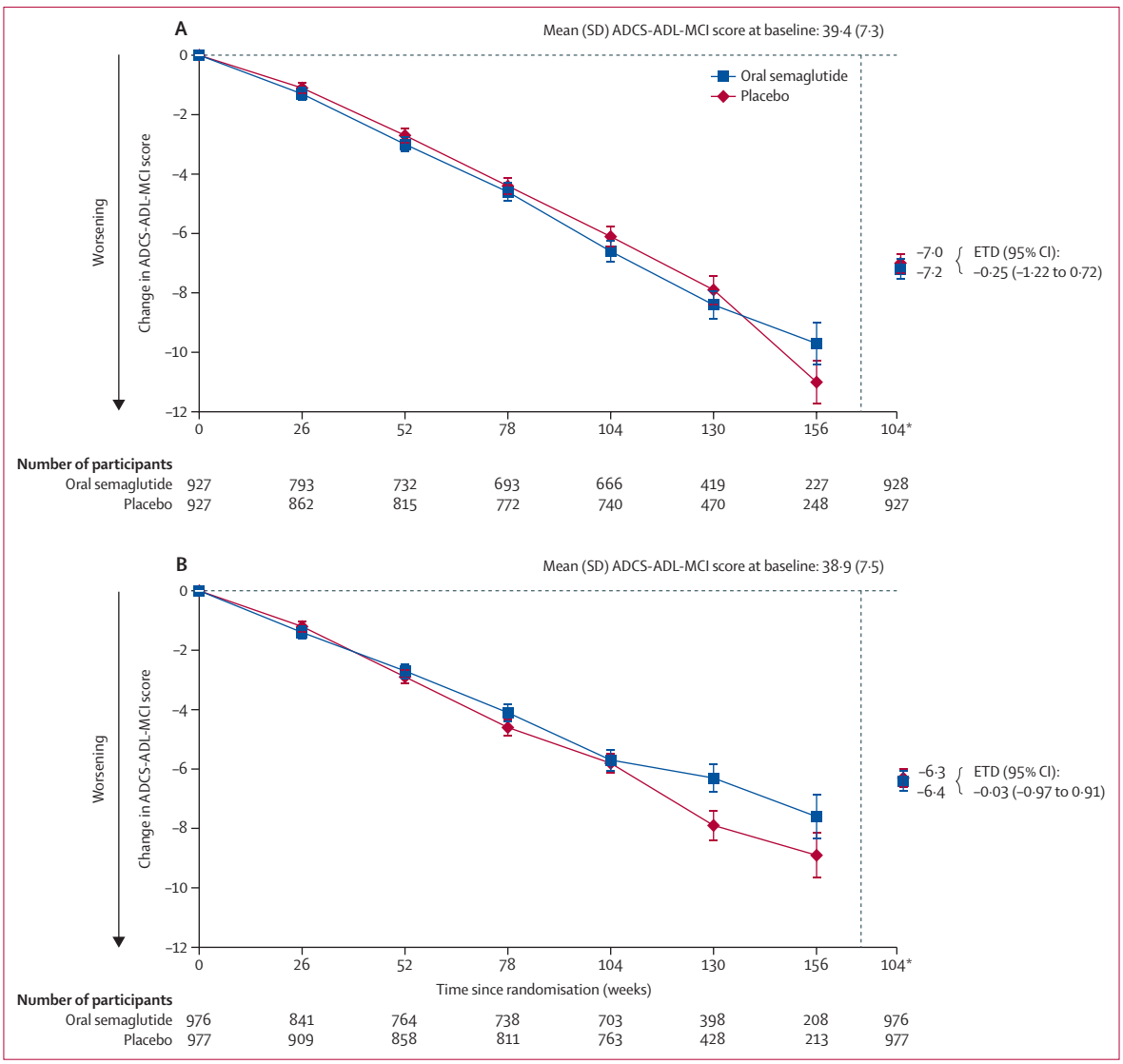


Figure 3: **Change in ADCS-ADL-MCI score from baseline up to week 104 for evoke (A) and evoke+ (B)**
Observed data from the on-treatment dataset. One participant in the oral semaglutide group had a missing baseline value and did not contribute to observed mean at week 0; however, they did contribute to the analyses for estimated mean as participants were assessed post randomisation. Error bars show mean (SE). ADCS-ADL-MCI=Alzheimer's Disease Cooperative Study Activities of Daily Living Scale for mild cognitive impairment. ETD=estimated treatment difference. HTC=hypothetical–treatment policy–composite. *Estimated mean and corresponding SE at week 104 based on the on-treatment dataset, using the hybrid-HTC estimand.

CDR-SB, ADCS-ADL-MCI, and ADAS-Cog-13) did not differ with semaglutide compared with placebo in evoke (estimated difference 0·04 [95% CI −0·04 to 0·11]), nor in evoke+ (estimated difference 0·01 [−0·07 to 0·08]).

At week 104, hsCRP concentrations (ratio to baseline) decreased significantly with semaglutide in both trials compared with placebo, which remained relatively unchanged (appendix 1 p 38). Changes from baseline in EQ-5D-5L index score did not differ between treatment groups in both trials (appendix 1 p 39).

The proportions of participants reporting adverse events were similar across the trials (table 2). In the pooled analysis, the proportion of participants reporting any adverse event was 1729 (91·2%) of 1896 with semaglutide versus 1613 (84·8%) of 1902 with placebo (appendix 1 pp 44–45). The most common adverse events reported with semaglutide were weight decreased (692 [36·5%] of 1896), decreased appetite (627 [33·1%]), and nausea (460 [24·3%]). In evoke, falls were reported by 55 (6·0%) of 924 participants in the semaglutide group and 85 (9·2%) of 927 in the placebo group. In evoke+, falls were reported by 72 (7·4%) of 972 participants in the semaglutide group and 88 (9·0%) of 975 in the placebo group. In evoke, bone and joint injuries (mainly various types of fractures) were reported by 46 (5·0%) of 924 participants in the semaglutide group and 82 (8·8%) of 927 in the placebo group. In evoke+, bone injuries were reported by 61 (6·3%) of 972 participants in the semaglutide group and 73 (7·5%)

	evoke						evoke+					
	Semaglutide 14 mg (n=924)			Placebo (n=927)			Semaglutide 14 mg (n=972)			Placebo (n=975)		
	Participants	Events	Events per 100 patient-years	Participants	Events	Events per 100 patient-years	Participants	Events	Events per 100 patient-years	Participants	Events	Events per 100 patient-years
Any TEAE	837 (90·6%)	4895	246·2	793 (85·5%)	4248	195·6	892 (91·8%)	5770	278·9	820 (84·1%)	4667	209·2
SAEs	176 (19·0%)	267	13·4	232 (25·0%)	403	18·6	210 (21·6%)	186	17·3	221 (22·7%)	353	15·8
AEs leading to permanent trial product discontinuation	159 (17·2%)	159	8·0	75 (8·1%)	75	3·5	162 (16·7%)	162	7·8	84 (8·6%)	84	3·8
Fatal events*	28 (3·0%)	31	1·4	23 (2·5%)	28	1·2	23 (2·4%)	29	1·3	28 (2·9%)	30	1·3
AEs occurring in ≥10% of participants												
Weight decreased	335 (36·3%)	403	20·3	60 (6·5%)	72	3·3	357 (36·7%)	427	20·6	81 (8·3%)	87	3·9
Decreased appetite	293 (31·7%)	351	17·7	53 (5·7%)	58	2·7	334 (34·4%)	406	19·6	61 (6·3%)	76	3·4
Nausea	233 (25·2%)	344	17·3	64 (6·9%)	77	3·6	227 (23·4%)	323	15·6	66 (6·8%)	81	3·6
Diarrhoea	136 (14·7%)	183	9·2	104 (11·2%)	143	6·6	139 (14·3%)	210	10·2	81 (8·3%)	103	4·6
Vomiting	114 (12·3%)	180	9·1	38 (4·1%)	55	2·5	120 (12·3%)	189	9·1	31 (3·2%)	35	1·6
COVID-19	97 (10·5%)	103	5·2	103 (11·1%)	109	5·0	109 (11·2%)	116	5·6	111 (11·4%)	122	5·5

Data are n (%) or n. Data from baseline up to week 156 for all participants randomly assigned to study drug and who took at least one dose of study drug were included. AE=adverse event. SAE=serious adverse event. TEAE=treatment-emergent adverse event. *Data are for the in-study period and include fatalities reported for participants who withdrew from the trials. Participants could have several ongoing AEs that the investigator reported as having a fatal outcome.

Table 2: **Adverse events for evoke and evoke+**

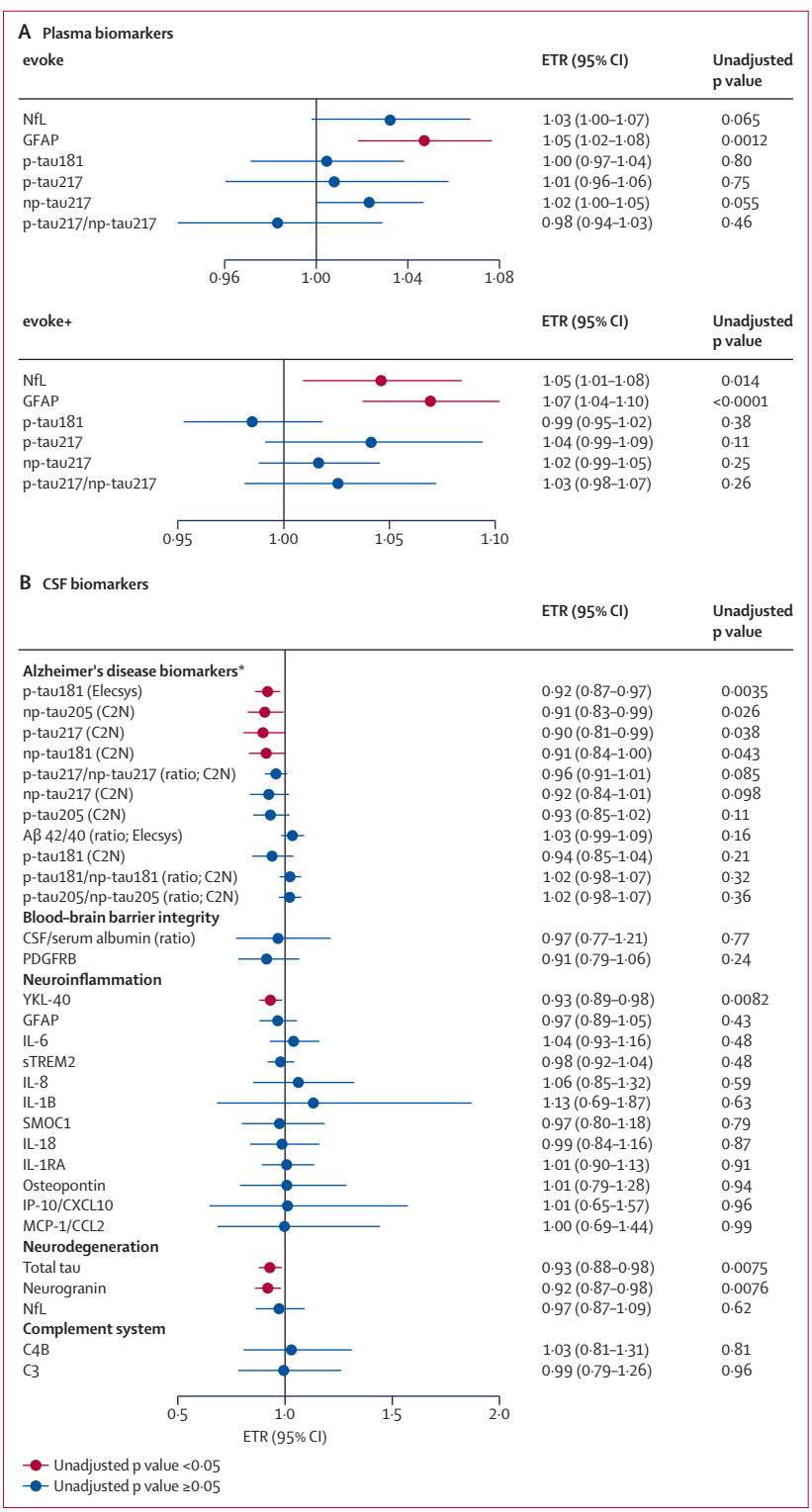
of 975 in the placebo group. Adverse events leading to treatment discontinuation were higher with semaglutide versus placebo (table 2; appendix 1 pp 44–45). Serious adverse events were reported by 386 (20·4%) of 1896 participants in the semaglutide group and 453 (23·8%) of 1902 in the placebo group. Adverse events with fatal outcomes were reported for 51 (2·7%) of 1896 participants in the semaglutide group and 51 (2·7%) of 1902 in the placebo group during the in-study period. There were five fatalities considered treatment-related by the investigators (one in the semaglutide group [haemorrhagic stroke] and four in the placebo group [congestive cardiac failure, metabolic acidosis, intestinal ischaemia, and undetermined]). The participant who died in the semaglutide group had medical histories of hypertension, arteriosclerotic coronary disease with heart failure, and a carotid artery stenosis. Across both trials, the mean bodyweight change from baseline at week 104 was –5·8% (–4·3 kg) and 0·6% (0·2 kg) in the oral semaglutide and placebo groups, respectively. Bodyweight reductions were reported across all BMI categories, with greater mean weight reductions reported in those with higher baseline BMI in the semaglutide group (appendix 1 p 41). The cumulative incidence of non-adjudicated MACE (probability range 0–1) at week 104 was 0·03 (95% CI 0·03–0·04) and 0·03 (0·02–0·04) in the semaglutide and placebo groups, respectively. The cumulative incidence of stroke at week 104 was 0·01 (95% CI 0·01–0·01) and 0·01 (0·01–0·02) in the semaglutide and placebo groups, respectively. Evaluation of the safety data revealed no unexpected findings, and no new safety concerns were identified in these participants with early Alzheimer's disease.

Measures of plasma biomarkers revealed no significant changes in NfL concentrations between treatment groups in evoke (estimated treatment ratio [ETR] 1·03; 95% CI 1·00–1·07), and a significant increase was observed in participants receiving semaglutide in evoke+ (1·05; 1·01–1·08; unadjusted p=0·0137). In both trials, a significant increase in GFAP in participants receiving semaglutide was observed (evoke, ETR 1·05; 95% CI 1·02–1·08; unadjusted p=0·0012; evoke+, 1·07; 1·04–1·10; unadjusted p<0·0001). For plasma p-tau181 and p-tau217, no significant changes between treatment groups were observed (figure 4A).

In the CSF substudy, significant reductions of up to 10% were observed in CSF biomarkers with semaglutide versus placebo in canonical Alzheimer's disease biomarkers (p-tau181, p-tau217, non-phosphorylated-tau181 [np-tau181], and np-tau 205) and biomarkers of neuroinflammation, neurodegeneration (YKL-40, total tau), and synaptic function (neurogranin; figure 4B). The geometric mean of semaglutide concentration in CSF was 0·08 nmol/L (coefficient of variation 109·7%; n=98).

When using population pharmacokinetic modelling to determine the average semaglutide concentration at steady state over a dosing interval of 24 h in evoke(+) (n=1863), the geometric mean was 17·21 nmol/L (geometric SD 2·36), and 95% of the exposure values fell

within the interval 2·87 nmol/L to 70·12 nmol/L. The median steady state average pharmacokinetic concentration over a dosing interval of 24 h was 19·06 nmol/L (IQR 22·46).



Discussion

In these two large and robustly designed clinical trials, oral semaglutide up to 14 mg once daily was not efficacious in slowing clinical progression in participants with early Alzheimer's disease across a range of global, cognitive, and functional measures.

TEAEs included gastrointestinal events, and bodyweight reduction was reported; these observations are consistent with the GLP-1 receptor agonist class,[24] recognising that bodyweight reduction is a goal in type 2 diabetes and weight management and thus is not usually reported as a TEAE in semaglutide studies. Adverse events leading to treatment discontinuation or dose reduction were driven by gastrointestinal disorders (including appetite decrease) and weight decrease.

The current evoke(+) trial results do not support hypothesis-generating literature that showed a reduced risk of dementia or Alzheimer's disease after GLP-1 receptor agonist exposure.[13–21] Possible explanations for this divergence from the real-world evidence are the inclusion of participants with biologically defined Alzheimer's disease rather than all-cause dementia; investigating the slowing of decline in a symptomatic Alzheimer's disease population rather than reduced Alzheimer's disease incidence in a type 2 diabetes population without symptoms at the time of treatment initiation; evaluating an Alzheimer's disease population with low levels of peripheral inflammation rather than high levels observed in type 2 diabetes populations; and limiting exposure to 24 months compared with longer exposures evaluated in type 2 diabetes populations (eg, those observed in registries). The distinct populations in evoke(+) (eg, prespecified, regulator-recommended global clinical outcomes in biomarker-confirmed amyloid-positive, early Alzheimer's disease *vs* incident dementia diagnoses derived from routine coding, composite cognitive measures, or surrogate markers in type 2 diabetes or obesity cohorts) might account for the differences observed between evoke(+) and existing real-world evidence. The evoke(+) trials were carried out in an early-stage symptomatic Alzheimer's disease population. It might be that the same intervention at an earlier stage of Alzheimer's disease with lesser pathology in those individuals who are asymptomatic might have potential

Figure 4: **Changes in plasma biomarkers in evoke and evoke+ (A), and changes in CSF biomarkers in the CSF substudy (B)**
CSF biomarker data are not adjusted for multiplicity. Aβ=amyloid β. CCL2=C-C motif chemokine ligand 2. CSF=cerebrospinal fluid. CXCL10=C-X-C motif chemokine ligand 10. ETR=estimated treatment ratio. GFAP=glial fibrillary acidic protein. IL=interleukin. IL-1RA=interleukin 1 receptor antagonist. IP=interferon gamma-induced protein. MCP-1=monocyte chemoattractant protein-1. NfL=neurofilament light chain. np-tau=non-phosphorylated tau. PDGFRB=platelet-derived growth factor receptor beta. p-tau=phosphorylated tau. SMOC1=SPARC-related modular calcium-binding protein 1. sTREM2=soluble triggering receptor expressed on myeloid cells 2. *Different assays were used by different diagnostics companies (Elecsys and C2N) to measure the Alzheimer's disease biomarkers.

for treatment efficacy. Given the safety profile from the current trials, such future investigation might be warranted in specified trial populations.

The changes in canonical CSF biomarkers (p-tau181, p-tau217) and markers of neurodegeneration (total tau, neurogranin) in a proportion of participants suggest that semaglutide might have an effect on Alzheimer's disease pathophysiology. While the mode of action of semaglutide on the Alzheimer's disease-related CSF biomarkers remains unclear, the biomarker changes in the CSF substudy are consistent with a randomised, placebo-controlled, exploratory trial of biofluid biomarkers and multiomics immunophenotyping in early-stage Alzheimer's disease that showed similar significant effects on biomarkers with semaglutide.[25]

In the evoke(+) trials, the effect size of semaglutide on CSF biomarkers ranged from 5% to 10%; these are smaller than the corresponding effects of up to 25% in some studies with monoclonal antibodies (mAbs) against amyloid.[26] This smaller effect size might indicate that the distribution of semaglutide in affected Alzheimer's disease regions is lower than needed for Alzheimer's disease treatment. Semaglutide appeared to have limited CSF or CNS bioavailability but can achieve low sustained concentrations.[25] Its delivery is not optimised for treating CNS diseases (including Alzheimer's disease), which could require higher CNS concentrations and more region-specific drug distribution. It is also possible that the observed effects on biomarkers do not require a GLP-1 receptor agonist to cross the blood–brain barrier and could instead be mediated via a cross talk between the peripheral and central immune system.

Semaglutide treatment led to significant reductions in hsCRP, indicating a potential role in reducing peripheral inflammation, although the concentrations at baseline were normal and the mean change was within the clinically normal range. This supports data from participants with overweight or obesity or type 2 diabetes that show a consistent effect of semaglutide in reducing hsCRP and other markers of systemic inflammation.[27] These reductions in hsCRP did not meaningfully alter the clinical course of early Alzheimer's disease in evoke(+), which suggests the disease inflammatory effects are more central than peripheral. In plasma, semaglutide also led to small but significant increases in GFAP (a biomarker of astrocyte activation[28]) in both trials. In studies of amyloid-lowering mAbs in early Alzheimer's disease, a significant decrease in GFAP has been reported and this could be specifically linked to the strong effect of amyloid lowering, an effect not seen with semaglutide. The interpretation of the plasma-based biomarker findings and their divergence from the CSF directional changes is not yet understood.

The established efficacy of semaglutide in MACE and stroke in type 2 diabetes and obesity underscored an interest to include participants with a larger cerebrovascular burden than is usually permitted in early-stage Alzheimer's disease trials, although it was not intended to confirm cerebrovascular disease efficacy in a mixed dementia population. In evoke+, a lower than expected proportion of participants had concomitant significant small vessel pathology, which was defined as having more than one lacunar infarct and/or ARWMC score of more than 2 (white matter >20 mm). The clinical scale inclusion criteria with a focus on memory impairment, combined with amyloid positivity, might have inadvertently excluded participants with concomitant significant small vessel pathology who often lack the amnestic phenotype of Alzheimer's disease.[23] evoke+ is one of the first randomised clinical trials in Alzheimer's disease that has required participants to have confirmed amyloid positivity and allowed for cerebrovascular contribution, and can serve to inform the design of future trials where mixed Alzheimer's disease and cerebrovascular disease pathology is desired.

The trials had several strengths, including the recruitment of a diverse global population from 40 countries. The use of concomitant approved Alzheimer's disease medications allowed flexibility in an evolving treatment landscape and provided reassurance to participants who might have otherwise withdrawn due to concerns regarding randomisation to placebo. As the tolerability profile and mode of action of semaglutide are well described in other populations,[24] several strategies were implemented throughout the trials to mitigate attrition due to gastrointestinal events or weight loss, including close monitoring and use of a flexible dosing regimen. Attrition rates were low, indicating high site, participant, and family engagement with the study. Change in CDR-SB score was selected as the primary endpoint as this is considered a clinically meaningful measure of disease progression, and the trials were powered accordingly. The CSF substudy was included to improve knowledge around GLP-1 receptor agonists in relation to neurodegeneration.

There were several limitations. While efforts were made to avoid potential unblinding effects of semaglutide, including bodyweight reduction and gastrointestinal intolerance, participants and site staff might have been aware of these side-effects and potentially made associations with treatment. Safety and tolerability data quantified the difference in bodyweight reductions, which were reported as adverse events in 36·5% and 7·4% of participants with semaglutide and placebo, respectively, across the two trials. The occurrence of similar symptoms in both the semaglutide and placebo groups would mitigate some of the risk of unblinding. The 14 mg dose was based on previous clinical data where either up to 14 mg oral semaglutide or up to 1 mg subcutaneous semaglutide was used; this included efficacy results from randomised clinical trials and real-world evidence combined with the safety profile of semaglutide in type 2 diabetes.[22] Semaglutide exposure rates and median plasma concentrations were, as expected, comparable with those

reported for semaglutide in type 2 diabetes studies where a decreased incidence of dementia was observed.[29]

In conclusion, oral semaglutide up to 14 mg did not slow progression of cognition and function versus placebo at 104 weeks in participants with MCI or mild dementia due to Alzheimer's disease. Concentrations of hsCRP and several CSF biomarkers were significantly reduced with semaglutide, but this did not translate into slowing of clinical decline. No new safety signals were observed in this population. These results provide important knowledge for future trials and a large dataset for this clinical population.

Contributors

JLC, AA, MS, HZ, PS, FKK, PJ, and HHF were involved in the study design. RMA conducted the statistical analysis and was responsible for data curation. JLC, AA, MS, HZ, PS, FKK, PJ, CAW, RMA, and HHF were involved in the data analysis, and all authors were involved in the interpretation. JLC, FKK, PJ, CW, RMA, TL, and HHF wrote the first draft of the manuscript; JLC, PJ, CWA, RMA, and HHF edited the manuscript; and all authors reviewed the manuscript. All authors had full access to all the data in the study and have directly accessed and verified the underlying data. All authors have contributed to the development of the manuscript and had final responsibility for the decision to submit for publication.

Declaration of interests

JLC has provided consultation to Acadia, Actinogen, Acumen, AlphaCognition, ALZpath, Aprinoia, AriBio, Artery, Biogen, Biohaven, BioVie, Bio X Cel, 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. He is supported by National Institute of General Medical Sciences grant P20GM109025, National Institute on Aging (NIA) grant R35AG71476, NIA grant R25 AG083721-01, Alzheimer's Disease Drug Discovery Foundation, Ted and Maria Quirk Endowment, and Joy Chambers-Grundy Endowment. AA has, in the last 10 years, served as a consultant or received honoraria or support for consulting; participating in independent data safety monitoring boards; providing educational lectures, programmes, and materials; and serving on advisory boards for AbbVie, Acadia, Allergan, Alzheimer's Disease International, the Alzheimer's Association, AriBio, Axovant, Axsome, AZTherapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Johnson & Johnson, Life Molecular Imaging/Lantheus, Lundbeck, Merck, Michael J Fox Foundation, Novo Nordisk, ONO, Otsuka, Prothena, Qynapse, Roche/Genentech, Sunovion, Suven, Synexus, and Vaxxinity. He receives book royalties from Oxford University Press for a medical book on dementia. He receives institutional research grant or contract funding from the NIA/National Institutes of Health (NIH; 1P30AG072980, U24AG057437, 1P30AG072980, R01AG070883, R01AG086363, U01AG082350, U24AG057437), Arizona Department of Health Services (CTR040636), Foundation for the NIH, Washington University in St. Louis, Michael J. Fox Foundation, and Gates Ventures. His institution receives or has received funding for clinical trial grants, contracts, and projects from government, consortia, foundations, and companies, for which he serves or has served as a contracted site principal investigator. He has received or receives honoraria from Novo Nordisk for consulting activities, including for service on the evoke(+) program Steering Committee. MS has served on the Scientific Advisory Board for Medication and as a consultant for Eisai, Avenir, vTv, Biogen, Bio X Cel, F. Hoffman LaRoche, Merck, Novo Nordisk, Novartis, Otsuka, Genentech, and BioVie. She is a member of the Alzheimer Association Medical and Scientific Advisory Group and Chair of the data safety monitoring board for the Phase II Trial to Evaluate Safety and Efficacy of GM-CSF/Sargramostim in Alzheimer's Disease (SESAD; sponsor: University of Colorado). HZ reports a relationship with AbbVie, Acumen, Alector, Alzinova, ALZpath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Enigma, LabCorp, Merck Sharp & Dohme, Merry Life, NervGen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Quanterix, Red Abbey Labs, ReMYND, Roche, Samumed, ScandiBio Therapeutics AB, Siemens Healthineers, Triplet Therapeutics, and Wave that includes consulting or advisory services. He reports a relationship with AlzeCure, BioArctic, Biogen, Cellectricon, Fujirebio, LabCorp, Lilly, Novo Nordisk, Oy Medix Biochemica AB, Roche, and WebMD that includes speaking and lecture fees. He reports a relationship with Brain Biomarker Solutions in Gothenburg AB that includes equity or stocks. FKK, PJ, RMA, and CAW are employees and minor shareholders of Novo Nordisk. TL was an employee and minor shareholder of Novo Nordisk at the time of the analysis. PS is a full-time employee of EQT Life Sciences (formerly LSP) and Professor Emeritus at Amsterdam UMC. He is co-Chair of the Steering Committee for the phase 3 trials evoke and evoke+ with Novo Nordisk. HHF reports a consulting service agreement with Novo Nordisk for serving on the evoke + Steering Committee with funds including travel support for its meetings paid to UC San Diego. He receives no financial support for the present manuscript. Other disclosures include his receiving grants for UC San Diego from Allyx Therapeutics and Vivoryon Therapeutics (Probiodrug). He holds service agreements through UC San Diego for consulting with Biosplice Therapeutics, Arrowhead Pharmaceuticals, Axon Neuroscience, and LuMind Foundation. He provides service as a member of data and safety monitoring boards for Janssen Research & Development and Roche/Genentech and is a Scientific Advisory Board Chair for the Tau Consortium Rainwater Charitable Foundation through a UC San Diego service agreement. He has received travel support from Royal Society of Canada, Translating Research for Elder Care (TREC), Association for Frontotemporal Dementia (AFTD), Rainwater Charitable Foundation, Banner Health, Invictus, Summeet, and Novo Nordisk. He receives philanthropic support for Alzheimer's disease therapeutic research through the Epstein Family Alzheimer's Research Collaboration as well as personal funds for Detecting and Treating Dementia (Serial Number 12/3- 2691 US Patent Number PCT/US2007/07008, Washington DC, US Patent and Trademark Office).

Data sharing

An authorised researcher can request access to clinical study data by submitting a research proposal for review and approval by Novo Nordisk and an internal independent review panel. Requests are usually considered after the research is finished and the main results have been published. If the research supports a regulatory application, requests will be considered after the product and its intended use are approved in both the EU and the USA. Participants' clinical data will be anonymised, following an approved internal process, before data are shared to external third parties. For details on how to request access to clinical data, visit novonordisk-trials.com.

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