

RESEARCH

Open Access



evoke and evoke+: design of two large-scale, double-blind, placebo-controlled, phase 3 studies evaluating efficacy, safety, and tolerability of semaglutide in early-stage symptomatic Alzheimer's disease

Jeffrey L. Cummings^{1,15*}, Alireza Atri^{2,3,4}, Howard H. Feldman⁵, Oskar Hansson^{6,7}, Mary Sano⁸, Filip K. Knop^{9,10,11,12}, Peter Johannsen¹², Teresa León¹² and Philip Scheltens^{13,14}

Abstract

Background Disease-modifying therapies targeting the diverse pathophysiology of Alzheimer's disease (AD), including neuroinflammation, represent potentially important and novel approaches. The glucagon-like peptide-1 receptor agonist semaglutide is approved for the treatment of type 2 diabetes and obesity and has an established safety profile. Semaglutide may have a disease-modifying, neuroprotective effect in AD through multimodal mechanisms including neuroinflammatory, vascular, and other AD-related processes. Large randomized controlled trials are needed to assess the efficacy and safety of semaglutide in early-stage symptomatic AD.

Methods evoke and evoke+ are randomized, double-blind, placebo-controlled phase 3 trials investigating the efficacy, safety, and tolerability of once-daily oral semaglutide versus placebo in early-stage symptomatic AD. Eligible participants were men or women aged 55–85 years with mild cognitive impairment or mild dementia due to AD with confirmed amyloid abnormalities (assessed by positron emission tomography or cerebrospinal fluid [CSF] analysis). After a maximum 12-week screening phase, an anticipated 1840 patients in each trial are randomized (1:1) to semaglutide or placebo for 156 weeks (104-week main treatment phase and 52-week extension). Randomized participants follow an 8-week dose escalation regimen (3 mg [weeks 0–4], 7 mg [weeks 4–8], and 14 mg [weeks 8–156]). The primary endpoint is the semaglutide–placebo difference on change from baseline to week 104 in the Clinical Dementia Rating – Sum of Boxes score. Analyses of plasma biomarkers, collected from all participants, and a CSF sub-study (planned $n = 210$) will explore semaglutide effects on AD biomarkers and neuroinflammation.

Results Enrollment was undertaken between May 18, 2021, and September 8, 2023. Completion of the trials' main phase is expected in September 2025, and the 52-week extension (in which participants and investigators remain blinded to treatment assignment) will continue to October 2026.

*Correspondence:
Jeffrey L. Cummings
[jcummings@cnsinnovations.com](mailto:jcumplings@cnsinnovations.com)

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

Conclusion evoke and evoke+ are the first large-scale trials to investigate the disease-modifying potential of semaglutide in participants with early-stage symptomatic AD, including exploration of effects on AD biomarkers and neuroinflammation. The trials will provide data on the potential disease-modifying effects of semaglutide and will be important in evaluating its utility in the treatment of early-stage symptomatic AD.

Trial registration Clinicaltrials.gov, NCT04777396 and NCT04777409. Date: 02/03/2021

Keywords Alzheimer's disease, Clinical trial, Design, evoke, evoke+, Neuroinflammation, Semaglutide

Background

Alzheimer's disease (AD) is characterized by the presence of amyloid β (A β) protein plaques, phosphorylated tau (p-tau)-containing neurofibrillary tangles, and neurodegeneration [1]. AD is a heterogeneous disease with a complex pathophysiology, and multiple factors are responsible for its progression. Neuroinflammation has been identified as a key contributor to the pathobiology of AD [2–4] and occurs at early disease stages [2, 5–7]. Within the neurovascular unit, blood–brain barrier (BBB) dysfunction is observed early in the disease course of AD and comprises one aspect of the pathogenesis of chronic neuroinflammation [8]. Additionally, microvascular dysfunction may contribute to disease progression [9, 10]. In recent years, there have been advances in the development of disease-modifying therapies (DMTs) for AD, with the approval by the US Food and Drug Administration (FDA) of the anti-amyloid monoclonal antibodies aducanumab, lecanemab, and donanemab [11, 12]. Anti-amyloid antibodies are intravenously administered therapies that slow cognitive decline in AD; their use is associated with side effects including amyloid-related imaging abnormalities [13]. New DMTs with different targets and complementary modes of action, enhanced efficacy, greater convenience, and improved safety are urgently required for patients with early-stage symptomatic AD (i.e. mild cognitive impairment [MCI] due to AD or mild AD dementia).

Glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) are approved for the treatment of type 2 diabetes (T2D) and obesity, and their safety and tolerability profiles are well established in these populations; the most common adverse events are gastrointestinal [GI]-related [14, 15]. GLP-1RAs activate GLP-1 receptors that are found throughout the body, including the brain [16]. They are involved in multiple biological pathways that could be beneficial in AD including improvement of BBB integrity and vascular health, promotion of homeostasis in microglia and astrocytes, positive effects on adaptive immune cells (including natural killer cells and activated regulatory T cells), improvement of synaptic viability, and neuroprotection [17–26].

Peripheral inflammation may exacerbate neuroinflammation [2]. GLP-1RAs have effects on systemic

inflammation such as reduction in high-sensitivity C-reactive protein (hs-CRP) that are not mediated by weight loss or glycemic control [15, 27, 28]. GLP-1RAs may be beneficial for preservation of brain glucose metabolism and cognitive function in AD as supported by the results of two randomized, placebo-controlled trials in patients with mild-to-moderate AD dementia treated with the GLP-1RA liraglutide for 6 months and 12 months, respectively [29–31]. In the ELAD study, patients receiving liraglutide retained more temporal lobe volume and total cortical volume than those receiving placebo and had greater preservation of cognitive function (assessed by the Alzheimer's Disease Assessment Scale Cognitive Subscale and Executive domain scores of the Neuropsychological Test Battery) after 12 months of treatment [30].

Further clinical evidence and real-world data support the potential beneficial effects of GLP-1RAs in dementia. In a post hoc analysis of three large cardiovascular outcome trials (LEADER, SUSTAIN 6, and PIONEER 6), patients with T2D treated with GLP-1RAs had a statistically significant 53% lower risk of all-cause dementia diagnosis versus patients receiving placebo [32]. An exploratory analysis of the REWIND trial demonstrated that long-term treatment with the GLP-1RA dulaglutide reduced cognitive decline in patients with T2D [33]. Real-world evidence studies from the USA and Denmark showed a significant 11–42% lower risk of all-cause dementia and up to 64% lower risk of AD after GLP-1RA exposure for the treatment of T2D [32, 34–37]. In a registry-based cohort, a reduced rate of dementia was observed with increasing exposure to GLP-1RAs versus other non-insulin diabetes treatments [32].

Semaglutide is a potent, long-acting GLP-1RA approved for the treatment of T2D (once daily [OD] oral and once weekly [OW] subcutaneous [s.c.]) and obesity (OW s.c.) [38–40]. In clinical trials, semaglutide reduced peripheral inflammation [41] and decreased the risk of major adverse cardiovascular (CV) events (MACE) compared with placebo [38–40, 42–45]. The precise mechanism of action of semaglutide in AD remains to be fully elucidated. Preclinical results in murine models treated with GLP-1RAs suggest that the potential effects of semaglutide in AD may be exerted via impact on several

AD-related pathophysiologic processes including neuroinflammatory pathways, vascular and BBB integrity, reduced synaptic loss, and neuroprotection [19, 21, 23–26, 46–48]; these effects may be mediated indirectly rather than via direct brain action, since semaglutide may have limited ability to cross the BBB [49]. However, studies in animals have shown that semaglutide interacts with the circumventricular regions and specifically accesses GLP-1R–positive brain regions following peripheral administration, including the area postrema in the hind-brain, the arcuate nucleus of the hypothalamus, and the lateral septal nucleus [50]. These observations suggest that semaglutide may have at least limited direct access to the brain as well as exerting peripheral effects.

To further assess the potential therapeutic utility of GLP-1RAs in early-stage symptomatic AD, large randomized controlled trials are needed. Here, we describe the design of the phase 3 evoke and evoke+ trials, the first trials to investigate the efficacy, safety, tolerability, and potential disease-modifying effect of oral semaglutide up to 14 mg versus placebo in participants with early-stage symptomatic AD (MCI or mild dementia).

Methods

Trial design

evoke (NCT04777396) and evoke+ (NCT04777409) are randomized (1:1), double-blind, placebo-controlled, parallel-group trials investigating the efficacy and safety of oral semaglutide versus placebo in participants with early-stage symptomatic AD (Fig. 1). The description in this paper is based on the protocol version 10. The two trials have identical designs, with differences in inclusion criteria; evoke+ allows participation of patients with evidence of small vessel pathology on baseline imaging (described below). Participants can receive standard of care therapies (defined as treatment with an approved AD medication, including an acetylcholinesterase inhibitor, memantine, or an anti-amyloid monoclonal antibody, or combinations of these agents) during the trial.

Continuation of approved AD treatments requires a stable dose for ≥ 3 months before screening and the dose should not be changed unless medically necessary. Initiation of approved AD treatments is permitted during the trial if deemed medically necessary by investigators. Participants from 40 countries (in Asia, Europe, Latin America, North America, and rest of the world [which includes Australia, Israel, Russia, and South Africa]) comprise the planned enrollment, with an expected 80% presenting with MCI (defined as Clinical Dementia Rating [CDR] global score of 0.5) and 20% with mild AD dementia (defined as CDR global score of 1.0). Participants with T2D could be enrolled and constitute up to a planned maximum of 30% of the overall trial population, but no stratification by T2D status was conducted at randomization. Following an up to 12-week screening phase, a planned 1840 participants in each trial were to be randomized (1:1) to the semaglutide treatment or placebo arms. The treatment period is 156 weeks, including a 104-week main treatment phase and 52-week double-blinded extension phase. Following the 52-week extension phase, a follow-up period of 5 weeks is planned to allow complete wash-out of semaglutide before the final trial visit at week 161. Participants and investigators will remain blinded to treatment assignment throughout the trial period (main and extension phases).

Randomized participants initiate treatment with 3 mg OD oral semaglutide or placebo from weeks 0–4 and follow a 4-week dose-escalation regimen to 7 mg during weeks 4–8, after which a treatment dose of 14 mg is reached. This 8-week dose-escalation period is based on previous clinical trial evidence supporting a low starting dose and gradual titration of semaglutide [38, 51]. Dosing is flexible, allowing for extension of dose-escalation intervals, dose reduction, and treatment pauses. An interactive web response system is used for blind-breaking if needed to ensure patient safety. Treatment compliance was assessed and reinforced through drug accountability information (counting returned tablets) and through

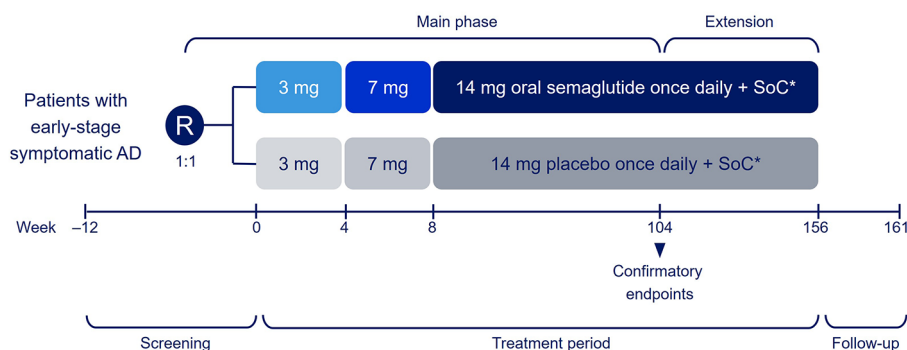


Fig. 1 Trial design of evoke/evoke+. *Participants can receive existing or add-on SoC (defined as treatment with an approved AD medication, including acetylcholinesterase inhibitor, memantine, or anti-amyloid monoclonal antibody) throughout the trial. AD, Alzheimer's disease; R, randomization; SoC, standard of care

documented discussions with participants and study partners. Physical examinations (including neurological assessments) are conducted at screening, and weeks 52, 104, and 156. ECG assessments are performed at randomization, and weeks 52, 104, and 156. Biochemistry and hematology tests are conducted at screening, and at weeks 13, 26, 52, 78, 104, and 156. Blood samples for biomarker studies are collected from all participants at baseline and 52, 104, and 156 weeks. Planned analyses of blood-based biomarkers include neurofilament light chain (NfL), plasma p-tau at threonine 181 (p-tau181), glial fibrillary acidic protein (GFAP), and hs-CRP.

Adjustments to the protocol

The sponsor engaged an independent nonprofit organization to organize and conduct virtual interviews with participants with early-stage symptomatic AD and care partners to gain their preferences about study conduct that could be reflected in the protocol. Collecting 'voice of the patient' information comprises a key aspect of patient-centered drug development. Based on the feedback received from the interviews, the following adjustments were implemented during protocol development: the frequency of site visits was reduced to mitigate the barrier associated with traveling to the sites; inclusion criteria requiring patients to have a competent study partner willing to attend clinic visits allow inclusion of participants who do not have live-in partners (minimum contact of four visits/10 hours per week); and reminders are provided to participants to ensure compliance with the trial dosing regimen.

In addition, the evoke+ protocol was amended to remove the requirement for inclusion of a specified proportion of patients with significant small vessel pathology.

Participants

In both trials, participants are male or female aged 55–85 years old (both inclusive) with MCI or mild dementia according to the National Institute on Aging and Alzheimer's Association 2018 criteria [52] with amyloid positive biomarkers on positron emission tomography (PET) or abnormal cerebrospinal fluid (CSF). Participants with MCI required a CDR global score of 0.5 along with a CDR domain score of ≥ 0.5 in at least one of the three activities of daily living categories (personal care, home and hobbies, community affairs) to promote the enrollment of participants with late MCI due to AD who may be more likely to progress to dementia during the trial (compared with people with CDR global score of 0.5 without impairment in activities of daily living categories) [53]; those with mild AD dementia were required to have a CDR global score of 1.0. In addition, participants required a Repeatable Battery for the Assessment

of Neuropsychological Status (RBANS) delayed memory index score of ≤ 85 ; and a Mini-Mental State Examination (MMSE) score of ≥ 22 . Data from historic PET scans or A β assays up to 2 years old were permitted to qualify for trial eligibility. All PET scans, including historical images, were assessed centrally in accordance with FDA guidelines for the Imaging Endpoint Process Standards [54]. CSF samples could be assessed by central or local laboratory, provided the local laboratory was part of the Alzheimer's Association quality control program at the time of analysis. evoke+ allows the inclusion of participants with significant small vessel pathology (defined as more than one lacunar infarct and/or age-related white matter changes > 2 [white matter > 20 mm] [55]) to ensure evaluation of participants with concurrent significant small vessel pathology, who are often excluded in AD trials. The key inclusion and exclusion criteria, including the list of prohibited medications, are presented in Table 1. Of note, in the evoke/evoke+ trials, computerized tomography (CT) scan could be performed if magnetic resonance imaging (MRI) was contraindicated or not available, allowing for wider patient involvement.

Endpoints and assessments

The primary endpoint is change in the CDR – Sum of Boxes (CDR-SB) score from baseline to week 104 in the treatment group compared with the placebo group. The CDR-SB score is derived by adding the individual box scores of the six domains of the CDR (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) and ranges from 0 to 18, with higher scores representing greater impairment [56]. Confirmatory secondary endpoints are change from baseline in AD Cooperative Study Activities of Daily Living – MCI (ADCS-ADL-MCI) score and time to progression to a CDR global score of ≥ 1.0 among participants with a CDR global score of 0.5 at baseline, both assessed at week 104 (see discussion and Table 2). Supportive secondary endpoints are shown in Table 2; exploratory endpoints are shown in Table 3.

The primary outcome analysis will involve the data collected up to and including week 104. Participants will continue the trial for an additional 52 weeks without unblinding. No futility or interim analyses are planned.

CSF sub-study

A CSF sub-study is being conducted in 15 countries as part of evoke and evoke+ to explore the effect of semaglutide on CSF biomarkers, including markers of AD, neuroinflammation, neurodegeneration, BBB integrity, oxidative stress, synaptic integrity, and vascular integrity (Table 3). In each trial, participants are stratified by CSF sub-study participation (yes/no) to ensure 1:1 randomization in the sub-study population (Fig. 2). The optional

Table 1 evoke/evoke+: key eligibility criteria

Inclusion	Exclusion
Male or female aged 55–85 years (both inclusive).	Evidence of neurologic disorders other than AD (e.g. Parkinson's disease, Lewy body disease, frontotemporal dementia of any type, Huntington's disease).
Amyloid abnormalities (confirmed by amyloid PET scans [visual read] or CSF A β 1–42 or CSF A β 1–42/A β 1–40; historical data up to 2 years on amyloid abnormalities can be used).	Evidence of a clinically relevant or unstable psychiatric disorder based on Diagnostic and Statistical Manual of Mental Disorders criteria.
MCI or mild dementia of the Alzheimer's type defined as: CDR global score of 0.5 with a CDR domain score of ≥ 0.5 in at least one of the three instrumental activities of daily living categories, or CDR global score of 1.0, respectively.	MRI or CT scan suggestive of clinically significant structural CNS disease other than the changes allowed for evoke+ (e.g. cerebral large-vessel disease [large vessel (cortical) infarcts > 10 mm in diameter], prior macro-hemorrhage [> 1 cm ³], cerebral vascular malformations, cortical hemosiderosis, intracranial aneurism(s), intracranial tumors, changes suggestive of normal pressure hydrocephalus).
RBANS delayed memory index score ≤ 85 .	For the evoke trial, ARWMC = 3 was also an exclusion criterion.
MMSE score of ≥ 22 .	Current or previous GLP-1RA treatment in the 90 days prior to screening; regular use (> 2 doses weekly) of anticholinergic medications of moderate or greater potency within 4 weeks of screening; anti-parkinsonian medications within 3 months of screening; anticonvulsants within 3 months of screening; neuroleptics within 3 months of screening; antidepressants without anticholinergic properties of moderate potency or greater where the dose has not been stable for 4 weeks prior to screening (antidepressants are allowed provided stable dose for 4 weeks prior to screening; regular use (> 2 doses weekly) of benzodiazepines and sedatives within 4 weeks of screening; morphine and narcotic analgesics within 3 months of screening. A short use (< 5 days) in relation to surgery or acute injury > 4 weeks before screening is not exclusionary; stimulant medications (e.g. amphetamine, methylphenidate, atomoxetine, modafinil) within 4 weeks of screening; medical marijuana, cannabis and cannabidiol (CBD); any approved or non-approved investigational medicinal product within 90 days before screening or 5 half-lives, whichever is longer.
Continuation of approved AD treatments is allowed (must be a stable dose for ≥ 3 months before screening).	Diagnosis of type 1 diabetes mellitus; personal or first-degree relative(s) history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma; uncontrolled and potentially unstable diabetic retinopathy or maculopathy in patients with T2D; presence or history of malignant neoplasms (other than basal or squamous cell skin cancer, in situ carcinomas of the cervix, or in situ prostate cancer) within 5 years prior to the day of screening; end stage renal disease or chronic or intermittent hemodialysis or peritoneal dialysis; myocardial infarction, stroke, hospitalization for unstable angina pectoris, or transient ischemic attack within 90 days prior to the day of screening; chronic heart failure classified as being in New York Heart Association (NYHA) Class IV at screening; known or suspected hypersensitivity to trial product or related products; female who is pregnant, breast-feeding or intends to become pregnant or is of child-bearing potential and not using a highly effective contraceptive method; history of major surgical procedures involving the stomach or small intestine potentially affecting absorption of drugs and/or nutrients, as judged by the investigator; clinically significant abnormalities in thyroid function, or clinically significant vitamin B12 or folate deficiency at screening as determined by the investigator (patients with adequately treated thyroid disease [excluding medullary thyroid carcinoma] are eligible); any disorder which in the investigator's opinion might jeopardize the subject's safety or compliance with the protocol.
In evoke+, participants with significant small vessel disease (defined as ARWMC > 2 and/or > 1 lacunar infarct) are eligible to enroll.	

A β , amyloid beta; AD, Alzheimer's disease; ARWMC, age-related white matter changes; CDR, Clinical Dementia Rating; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computerized tomography; GLP-1RA, glucagon-like peptide-1 receptor agonist; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MRI, magnetic resonance imaging; PET, positron emission tomography; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; T2D, type 2 diabetes

Table 2 Primary and secondary endpoints in the evoke and evoke+ trials

Endpoint		Domain	Time frame
Primary	Change in CDR-SB score	Cognitive, functioning	Baseline to week 104
Confirmatory secondary	Change in ADCS-ADL-MCI score	Functioning	Baseline to week 104
	Time to progression to dementia (CDR global score ≥ 1.0) among participants with MCI (CDR global score = 0.5) at baseline ^a	Cognitive, functioning	
Supportive secondary	Change in MMSE score	Cognitive	Baseline to week 104
	Change in MoCA score	Cognitive	
	Change in ADAS-Cog-13 score	Cognitive	
	Change in ADCOMS score	Cognitive (composite)	
	Change in NPI score	Behavioral, functioning	
	Time to progression in disease stage based on global CDR score	Cognitive, functioning	
	Number of TEAEs	Clinical	
	Change in high-sensitivity CRP level	Clinical	
	Time to first occurrence of stroke	Clinical	
	Time to first occurrence of MACE comprising nonfatal myocardial infarction, nonfatal stroke, and all-cause death	Clinical	
	Change in EQ-5D-5L proxy score	Health-related quality of life	
	Change in CDR-SB score	Cognitive, functioning	Baseline to week 156
	Change in ADCS-ADL-MCI score	Functioning	
	Time to progression to dementia (CDR global score ≥ 1.0) among participants with MCI (CDR global score = 0.5) at baseline ^a	Cognitive, functioning	

^a Analysis is planned based on pooled data for the subgroup of participants with MCI (CDR global score = 0.5) at baseline in the combined evoke/evoke+ populations
ADAS-Cog-13, 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 – Mild Cognitive Impairment; CDR-SB, Clinical Dementia Rating – Sum of Boxes; CRP, C-reactive protein; EQ-5D-5L, EuroQol-5 Dimension 5 Level; MACE, major adverse cardiovascular event; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NPI, Neuropsychiatric Inventory; TEAE, treatment-emergent adverse event

sub-study is being conducted at sites with CSF sampling experience and willingness to participate. The sub-study is planned for 210 participants from the two trials to be included. CSF sampling, including biobank sampling, is performed pre-randomization and at week 78. Biosamples will be stored in a biobank for future analyses.

Sample size calculation

The sample size calculation was based on the assumptions of a mean difference in the primary endpoint CDR-SB score of −0.44 points (relating to a 20% difference between semaglutide and placebo when assuming a mean increase in the placebo arm of 2.2 points), standard deviation of 2.6 points, and one-sided significance level of 0.025. With these assumptions, 1840 participants randomly assigned to semaglutide or placebo will provide 95% power to confirm superiority of semaglutide for the primary endpoint (change from baseline to week 104 in CDR-SB score).

Discussion

evoke and evoke+ are the first trials designed to evaluate the clinical efficacy and disease-modifying effects of the GLP-1RA semaglutide administered orally (14 mg OD) versus placebo in participants with biomarker-confirmed early-stage symptomatic AD. The safety and tolerability

of semaglutide in this population will be elucidated in these trials.

The safety profile of semaglutide has been extensively studied outside of AD and is well characterized in T2D and obesity [15, 57–59]. In evoke and evoke+, the safety and tolerability of semaglutide will be assessed in a population of individuals with AD aged 55–85 years old. Consistent with other GLP-1RAs, the most frequently expected adverse events in individuals receiving semaglutide are GI-related events, such as nausea, vomiting, and diarrhea [38, 60]. To minimize the risk of GI-related events and increase tolerability in the evoke and evoke+ trials, several strategies are being implemented. First, an 8-week dose-escalation period is implemented. Second, the trials allow for flexible dose adjustment, including dose reductions and extension of dose-escalation intervals. Finally, treatment pauses of no fixed length are allowed to improve tolerability in the event of persistent GI-related adverse events.

The rationale for studying semaglutide in the phase 3 evoke/evoke+ program without prior phase 1/2 trials of semaglutide in early AD was based on several factors. Clinical and real-world evidence have demonstrated the potential of GLP-1RAs to reduce the risk of all-cause dementia and dementia due to AD in people with T2D [32, 34–36], and liraglutide has been shown to reduce neurodegeneration and the speed of decline in cognitive

Table 3 Exploratory biomarker endpoints in the evoke and evoke+ trials

Study	Sample type	Exploratory endpoints	Biomarker information	Time frame
Main study	Blood	Change in NfL level	Neuroaxonal damage	Baseline to week 104
		Change in GFAP level	Astrogliosis	
		Change in p-tau181 level	Amyloid burden	
CSF sub-study	CSF	Change in sTREM2 level	Neuroinflammation	Baseline to week 78
		Change in MCP1/CCL2 level ^a		
		Change in YKL-40 level		
		Change in GFAP level		
		Change in IL-8 level ^a		
		Change in IL-6 level ^a		
		Change in SMOC1 level ^a		
		Change in osteopontin level ^a		
		Change in IL-1 β level ^a		
		Change in IP-10/CXCL10 level		
		Change in IL-1 receptor antagonist level ^a		
		Change in IL-18 level ^a		
		Change in NfL level	Neurodegeneration	
		Change in neurogranin level		
		Change in total tau level		
		Change in amyloid β 42/40 level	Alzheimer's disease	
		Change in p-tau181 level		
		Change in sPDGFR β level ^a	Vascular health/blood–brain barrier integrity	
		Change in CSF/serum albumin ratio ^b		
		Change in isoprostanes level ^a	Oxidative stress	
		Change in 8-OHdG level ^a		
		Change in complement factor 3 level ^a	Complement system	
		Change in complement factor 4 level ^a		
		Semaglutide concentration in CSF ^a	Other	Week 78

^a Analysis will be performed only if a validated reliable assay is available at the end of study

^b Albumin will be analyzed from biochemistry samples collected for the trial

8-OHdG, 8-hydroxy-2'-deoxyguanosine; CCL2, chemokine (C-C motif) ligand 2; CSF, cerebrospinal fluid; CXCL10, C-X-C motif chemokine ligand 10; GFAP, glial fibrillary acidic protein; IL, interleukin; IP-10, interferon gamma-inducible protein-10; MCP1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; p-tau181, phosphorylated tau at threonine 181; SMOC1, secreted modular calcium-binding protein 1; sPDGFR β , soluble platelet-derived growth factor receptor beta; sTREM2, soluble triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1

function in people with AD [29, 30]. Semaglutide and liraglutide are structurally similar molecules with high selectivity for the GLP-1 receptor, though there are some pharmacologic differences between the two – notably, liraglutide has a higher steady state concentration and greater receptor binding affinity than semaglutide, while semaglutide has an increased affinity for serum albumin (thereby improving resistance to degradation) and a longer half-life than liraglutide [38, 61, 62]. Clinical data using semaglutide and liraglutide at equivalent exposure levels show beneficial effects on neuroinflammation, dementia risk, and cognitive decline [29, 30, 32]. Semaglutide has demonstrated beneficial cardiovascular and anti-inflammatory effects and has been shown to have effects relevant to AD in non-clinical models. Semaglutide has a well-established safety profile in people with T2D and obesity, including in people aged 65 years and older, suggesting that it will be well tolerated in the evoke/evoke+ populations with early AD [15, 27, 41–44, 57, 58, 63]. The 14 mg oral semaglutide dose selection was based

on its well-established safety profile and approval for the treatment of T2D [38], with exposure levels overlapping with those for the 1.0 mg s.c. formulation [64].

Weight loss could be an unintended consequence of participation in the evoke/evoke+ trials. Semaglutide is approved for the treatment of obesity in a subcutaneous formulation at a dose of 2.4 mg OW. However, the exposure levels of this parenteral formulation are higher than those used in the evoke/evoke+ trials, and weight loss is more common in patients with severe dementia than in those included in evoke/evoke+ [65]. To mitigate potentially detrimental weight loss in the evoke/evoke+ population, the weight of participants is being monitored throughout the trials, and a flexible-dosing approach is being implemented. Weight loss could be beneficial to some participants with overweight or obesity, who comprise 34.7% and 15.5%, respectively, of the evoke/evoke+ population [66].

One of the main challenges of clinical trials in AD, particularly in the US, is the recruitment of a representative

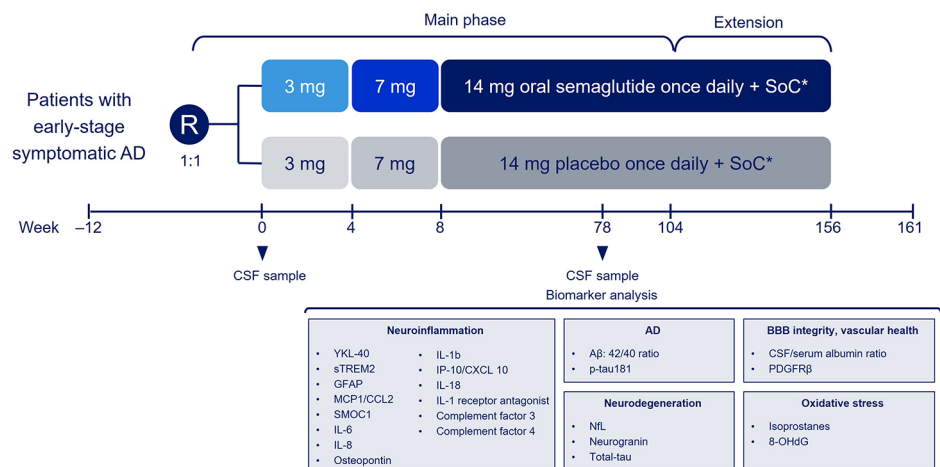


Fig. 2 Trial design of the CSF sub-study. *Participants can receive existing or add-on SoC (defined as treatment with an approved AD medication, including acetylcholinesterase inhibitor, memantine, or anti-amyloid monoclonal antibody) throughout the trial. 8-OHdG, 8-hydroxy-2'-deoxyguanosine; Aβ, amyloid beta; AD, Alzheimer's disease; BBB, blood–brain barrier; CCL2, chemokine (C-C motif) ligand 2; CSF, cerebrospinal fluid; CXCL10, chemokine ligand 10; GFAP, glial fibrillary acidic protein; IL, interleukin; IP-10, interferon gamma-inducible protein 10; MCP1, monocyte chemoattractant protein 1; NfL, neurofilament light chain; PDGFRβ, platelet-derived growth factor receptor beta; p-tau181, phosphorylated tau at threonine 181; R, randomization; SMOC1, secreted modular calcium-binding protein 1; SoC, standard of care; sTREM2, soluble triggering receptor expressed on myeloid cells 2; YKL-40, chitinase-3-like protein 1

sample of participants that includes minority groups, allowing the generalizability of the trial results to the wider population [67]. The inclusion of participants from 40 countries and 566 centers should facilitate the enrollment of an ethnically diverse population, improving the representativeness of the trial population. In the USA, dedicated resources, including strategies focused on diverse recruitment and retention and outreach efforts, are being implemented to include participants from ethnic and racial minorities, as well as those from different socioeconomic backgrounds, who are usually underrepresented in AD clinical trials [67]. The study design was adapted following consultation with participants and care partners, to facilitate trial participation and improve participants' experience during the trial.

Small vessel pathology is a common comorbidity in patients with AD and has been implicated in the pathogenesis of AD [68]. Therefore, the inclusion of participants with small vessel pathology in evoke+ (defined as more than one lacunar infarct and/or age-related white matter changes > 2 [white matter > 20 mm] [55]) may improve the representativeness and generalizability of the study results to real-world AD populations. In previous clinical trials, semaglutide has demonstrated significant reductions in MACE, including CV-related death, non-fatal myocardial infarction, and non-fatal stroke [38–40, 42–45]. Given that semaglutide may protect vascular structure and improve endothelial permeability, treatment may provide additional benefits to this subpopulation of participants in evoke+. Additionally, structural brain imaging for screening can be done either via MRI or CT scan. The latter allows for patients for whom MRI

is contraindicated (e.g. many participants with pacemakers) to be included in the trials, which may further contribute to the representativeness of the trial populations.

The option to continue or initiate treatment with approved AD medications during the trial, including cholinesterase inhibitors and recently approved anti-amyloid monoclonal antibody treatments that may be available during trial execution, will allow for important information to be gathered on the safety of concurrent use of these medications with different mechanisms of action and provides flexibility in an evolving therapeutic landscape. This strategy is potentially important in the retention of participants who initiate other treatments during the long evoke/evoke+ trials and likely reflects how semaglutide would be used in real-world therapeutic regimens.

The evoke/evoke+ design includes an analysis of time to dementia progression (from MCI to mild dementia) among those with MCI at baseline. To fully assess the effects of semaglutide in slowing disease progression, the evoke/evoke+ trials enrolled participants with late-stage MCI (defined as a CDR global score of 0.5 along with a CDR domain score of ≥ 0.5 in at least one of the three activities of daily living categories), who may be more likely to progress to mild AD dementia during the trial. However, as the number of participants who show evidence of progression to dementia during the trials may be limited, pooled data from evoke and evoke+ will be used for this analysis. The time-to-dementia progression analysis and a “time saved” analysis on the primary endpoint will provide important measures of the clinical meaningfulness of changes observed with semaglutide treatment

[69–71]. The incorporation of a 104-week treatment period and 52-week extension, resulting in a total treatment period of 156 weeks in evoke/evoke+, allows for a comprehensive evaluation of the time to dementia progression in participants with baseline MCI, as well as long-term efficacy.

Biomarkers play an increasingly important role in AD drug development and clinical trials [72, 73]. In the evoke and evoke+ trials, participants are required to have positive amyloid PET or amyloid CSF markers to confirm the presence of A β plaques, a fundamental feature of AD pathophysiology. Moreover, a variety of plasma and CSF biomarkers are employed as pharmacodynamic biomarkers to determine the effects of semaglutide on peripheral inflammation, core biomarkers of AD, oxidative stress, vascular integrity, synaptic function, and BBB integrity. These biomarker analyses will provide valuable insights into the mechanism of action of semaglutide on neuroinflammation and neurodegeneration in participants with early-stage symptomatic AD.

Although there are no standard criteria for the clinical and biomarker evidence required to support disease modification, clinical measures such as a change in trajectory of decline, an increasing drug versus placebo difference over time, an increased time to event, and an enduring change after discontinuation support this terminology. Likewise, biomarker results supportive of disease modification include effects on key pathophysiologic features of AD, including an impact on tau biology and neurodegenerative processes [73]. In evoke/evoke+, not all biomarkers are expected to show robust changes in response to treatment, and alterations in A β are not expected since semaglutide is not an A β -directed agent; nevertheless, biomarker changes consistent with the hypothesized effect of semaglutide on neuroinflammation and related processes are anticipated.

Limitations

The evoke/evoke+ trial design has limitations. First, implementing the protocol in 40 countries and 50 languages has logistical challenges and assumes that the outcome measure variability and effect sizes are similar enough to stay within the assumptions of the sample size modeling. Additionally, the trial design may lead to higher screening failure rates in non-White populations and thus trial populations may not be representative. Furthermore, the option to continue or initiate new AD medication during the trial, including the amyloid lowering monoclonal antibodies, was not a randomization stratification factor and may therefore act as a confounding factor if their use across treatment arms is unequal. A sensitivity analysis may be required to address this potential effect.

Conclusions

Treatment with GLP-1RAs significantly decreases risk of dementia, and in preclinical studies, the GLP-1RA semaglutide has shown positive effects on neuroinflammatory, vascular, and other processes hypothesized to be involved in AD pathophysiology. evoke and evoke+ are the first large-scale, global trials to investigate the disease-modifying potential of semaglutide on slowing of disease progression in participants with early-stage biomarker-confirmed AD, including exploration of the effect of semaglutide on plasma and CSF biomarkers of multiple pathophysiologic processes including neuroinflammation. Enrollment was completed on September 8, 2023, and the baseline characteristics of the participants will be described in a separate publication. Completion of the main phase of the trials is expected in 2025, and the 52-week extension will continue to October 2026.

Abbreviations

A β	Amyloid β
AD	Alzheimer's disease
BBB	Blood–brain barrier
CSF	Cerebrospinal fluid
CV	Cardiovascular
FDA	US Food and Drug Administration
GLP-1	Glucagon-like peptide-1
GLP-1RA	Glucagon-like peptide-1 receptor agonist
hs-CRP	High-sensitivity C-reactive protein
MACE	Major adverse cardiovascular event
MCI	Mild cognitive impairment
OD	Once daily
OW	Once weekly
p-tau	Phosphorylated tau
s.c.	subcutaneous
T2D	Type 2 diabetes

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13195-024-01666-7>.

Supplementary Material 1

Acknowledgements

The authors acknowledge the contributions of Wiesje van der Flier, a member of the evoke/evoke+ Steering Committee, in the preparation of the current manuscript. Medical writing support was provided by Diana Marouco, PhD, and Liam Gillies, PhD, of Apollo, OPEN Health Communications, and funded by Novo Nordisk A/S, in accordance with Good Publication Practice 3 (GPP3) guidelines (www.ismpp.org/gpp3).

Author contributions

Jeffrey L. Cummings, Alireza Atri, Howard H. Feldman, Oskar Hansson, Mary Sano, Filip K. Knop, Peter Johannsen, Teresa León and Philip Scheltens contributed to the study concept and design; drafting of the manuscript; and critical revision of the manuscript for important intellectual content. Jeffrey L. Cummings, Filip K. Knop, Peter Johannsen, and Teresa León agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the manuscript are appropriately investigated and resolved. Jeffrey L. Cummings, Alireza Atri, Howard H. Feldman, Oskar Hansson, Mary Sano, Filip K. Knop, Peter Johannsen, Teresa León, and Philip Scheltens were involved in the decision to submit the manuscript and have contributed to the drafting and revisions of the manuscript as well as approving the final submitted version.

Funding

This study was funded by Novo Nordisk A/S.

Data availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The evoke and evoke+ trials are being conducted in accordance with the consensus ethical principles derived from international guidelines including the Declaration of Helsinki and applicable ICH Good Clinical Practice (GCP) Guideline, as well as local laws and regulations. The trials were approved by local ethics committees and institutional review boards (listed in Additional file 1 in Supplementary Information). All participants and study partners provided written informed consent to participate in the trials.

Consent for publication

Not applicable.

Competing interests

JC: provided consultation to Acadia, Actinogen, Acumen, Alpha Cognition, Aprinolia, AriBio, Artery, Biogen, BioVie, Cassava, Cerecin, Diadem, EIP Pharma, Eisai, GenVax, Genentech, GAP Innovations, Janssen, Jocasta, Karuna, Lilly, Lundbeck, LSP, Merck, NervGen, Novo Nordisk, Oligomerix, Optoceutics, Ono, Otsuka, PRODEO, Prothena, reMYND, Roche, Sage Therapeutics, Signant Health, Simcere, Suven, SynapseBio, TrueBinding, Vaxxinity, and Wren Therapeutics. AA: has received honoraria or support for consulting; participating in independent data safety monitoring boards; providing educational lectures, programs, and materials; or serving on advisory boards for AbbVie, Acadia, Allergan, the Alzheimer's Association, Axovant, AZTherapies, Biogen, Eisai, Grifols, Harvard Medical School Graduate Continuing Education, JOMDD, Lundbeck, Merck, Novo Nordisk, ONO, Prothena, Qynapse, Roche/Genentech, Sunovion, Suven, and Synexus. AA receives book royalties from Oxford University Press for a medical book on dementia. AA receives institutional research grant/contract funding from National Institute on Aging/National Institutes of Health (1P30AG072980), NIA/NIH U24AG057437, AZ DHS (CTR040636), Foundation for NIH (FNIH), Washington University in St. Louis, and Gates Ventures. AA's institution receives/received funding for clinical trial grants, contracts, and projects from government, consortia, foundations, and companies, for which he serves/served as contracted site principal investigator. AA has received/receives honoraria from Novo Nordisk for consulting activities including for service on the evoke/evoke+ program Steering Committee. HHF: reports grants to the University of California San Diego (UCSD) from LuMind Foundation, Annovis (QR Pharma), AC Immune, Biohaven Pharmaceuticals, and Vivoryon (Probiobrug). He also reports service agreements through UCSD for consulting with Arrowhead Pharmaceuticals, Axon Neuroscience, LuMind Foundation, and Novo Nordisk. He reports serving on a data monitoring committee and data and safety monitoring board for Janssen Research & Development LLC and Roche/Genentech Pharmaceuticals with service agreements through UCSD, as well as serving on the Scientific Advisory Board for the Tau Consortium. He reports travel expenses through UCSD from Novo Nordisk and Royal Society of Canada. He receives personal funds for Detecting and Treating Dementia Serial Number 12/3- 2691 U.S. Patent No. PCT/US2007/07008, Washington DC, U.S. Patent and Trademark Office. He also received philanthropic support for Alzheimer's therapeutic research through the Epstein Family Alzheimer's Research Collaboration. OH: acquired research support (for the institution) from ADx, AVID Radiopharmaceuticals, Biogen, Eisai, Eli Lilly, Fujirebio, GE Healthcare, Pfizer, and Roche; and received consultancy/speaker fees from AC Immune, ALZpath, Amylyx, BioArctic, Biogen, Cerveau, Eisai, Eli Lilly, Fujirebio, Genentech, Novartis, Novo Nordisk, Roche, and Siemens. FKK: has served on scientific advisory panels and/or been part of speaker's bureaus for, served as a consultant to, and/or received research support from 89bio, Amgen, AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, MedImmune, MSD/Merck, Mundipharma, Norgine, Novo Nordisk, Sanofi, Structure Therapeutics, Zealand Pharma, and Zucara; is a co-founder of and minority shareholder in Antag Therapeutics, and owns shares in Eli Lilly, Novo Nordisk, and Zealand Pharma; is an employee of Novo Nordisk A/S. MS: has served as a scientific advisory board member

for Medivation and as a consultant for Bayer Schering Pharma, Bristol Myers Squibb, Elan, Genentech, Janssen, Medivation, Medpace, Otsuka, Pfizer, Takeda, and United BioSource. PJ: is an employee of Novo Nordisk A/S. TL: is an employee of Novo Nordisk A/S. PS: is a full-time employee of EQT Life Sciences (formerly LSP). He reports having received consultancy fees (paid to Vrije Universiteit Amsterdam) from AC Immune, Alzheon, BrainStorm Cell, FUJIFILM/Toyama, Green Valley, and Novo Nordisk. No remuneration was received by any author for the development of this manuscript.

Author details

¹Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, Kirk Kerkorian School of Medicine, University of Nevada, Las Vegas, NV, USA

²Banner Sun Health Research Institute, Sun City, AZ, USA

³Banner Alzheimer's Institute, Phoenix, AZ, USA

⁴Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA

⁵Department of Neurosciences, University of California San Diego, La Jolla, San Diego, CA, USA

⁶Clinical Memory Research Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden

⁷Memory Clinic, Skåne University Hospital, Malmö, Sweden

⁸Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY, USA

⁹Center for Clinical Metabolic Research, Gentofte Hospital, University of Copenhagen, Hellerup, Denmark

¹⁰Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

¹¹Steno Diabetes Center Copenhagen, Herlev, Denmark

¹²Novo Nordisk A/S, Søborg, Denmark

¹³Alzheimer Center Amsterdam, Department of Neurology, Vrije Universiteit Amsterdam, Amsterdam UMC, Amsterdam, The Netherlands

¹⁴EQT Life Sciences, Amsterdam, The Netherlands

¹⁵Chambers-Grundy Center for Transformative Neuroscience, Department of Brain Health, School of Integrated Health Sciences, University of Nevada, Las Vegas, NV, USA

Received: 6 September 2024 / Accepted: 23 December 2024

Published online: 08 January 2025

References

- Scheltens P, De Strooper B, Kivipelto M, Holstege H, Chélatel G, Teunissen CE, et al. Alzheimer's disease. *Lancet*. 2021;397(10284):1577–90.
- Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurol*. 2015;14(4):388–405.
- Cummings JL, Tong G, Ballard C. Treatment combinations for Alzheimer's disease: current and future pharmacotherapy options. *J Alzheimers Dis*. 2019;67(3):779–94.
- Dhapola R, Hota SS, Sarma P, Bhattacharyya A, Medhi B, Reddy DH. Recent advances in molecular pathways and therapeutic implications targeting neuroinflammation for Alzheimer's disease. *Inflammopharmacology*. 2021;29(6):1669–81.
- Bellaver B, Povala G, Ferreira PCL, Ferrari-Souza JP, Leffa DT, Lussier FZ, et al. Astrocyte reactivity influences amyloid- β effects on tau pathology in preclinical Alzheimer's disease. *Nat Med*. 2023;29(7):1775–81.
- Bellenguez C, Küçükali F, Jansen IE, Kleindam L, Moreno-Grau S, Amin N, et al. New insights into the genetic etiology of Alzheimer's disease and related dementias. *Nat Genet*. 2022;54(4):412–36.
- Bieger A, Rocha A, Bellaver B, Machado L, Da Ros L, Borelli WV, et al. Neuroinflammation biomarkers in the AT(N) framework across the Alzheimer's disease continuum. *J Prev Alzheimers Dis*. 2023;10(3):401–17.
- Zenaro E, Piacentino G, Constantin G. The blood-brain barrier in Alzheimer's disease. *Neurobiol Dis*. 2017;107:41–56.
- Govindpani K, McNamara LG, Smith NR, Vinnakota C, Waldvogel HJ, Faull RL, et al. Vascular dysfunction in Alzheimer's disease: a prelude to the pathological process or a consequence of it? *J Clin Med*. 2019;8(5):651.
- Steinman J, Sun HS, Feng ZP. Microvascular alterations in Alzheimer's disease. *Front Cell Neurosci*. 2020;14:618986.

11. Cummings J, Zhou Y, Lee G, Zhong K, Fonseca J, Cheng F. Alzheimer's disease drug development pipeline: 2023. *Alzheimers Dement* (N Y). 2023;9(2):e12385.
12. Sims JR, Zimmer JA, Evans CD, Lu M, Ardayfio P, Sparks J, et al. Donanemab in early symptomatic Alzheimer disease: the TRAILBLAZER-ALZ 2 randomized clinical trial. *JAMA*. 2023;330(6):512–27.
13. Yadollahikhales G, Rojas JC. Anti-amyloid immunotherapies for Alzheimer's disease: a 2023 clinical update. *Neurotherapeutics*. 2023;20(4):914–31.
14. Htike ZZ, Zaccardi F, Papamargaritis D, Webb DR, Khunti K, Davies MJ. Efficacy and safety of glucagon-like peptide-1 receptor agonists in type 2 diabetes: a systematic review and mixed-treatment comparison analysis. *Diabetes Obes Metab*. 2017;19(4):524–36.
15. Gao X, Hua X, Wang X, Xu W, Zhang Y, Shi C, et al. Efficacy and safety of semaglutide on weight loss in obese or overweight patients without diabetes: a systematic review and meta-analysis of randomized controlled trials. *Front Pharmacol*. 2022;13:935823.
16. Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, et al. GLP-1 receptor agonists: beyond their pancreatic effects. *Front Endocrinol (Lausanne)*. 2021;12:721135.
17. Brundin L, Bergkvist L, Brundin P. Fire prevention in the Parkinson's disease brain. *Nat Med*. 2018;24(7):900–2.
18. De Barra C, Khalil M, Mat A, O'Donnell C, Shaamile F, Brennan K, et al. Glucagon-like peptide-1 therapy in people with obesity restores natural killer cell metabolism and effector function. *Obesity (Silver Spring)*. 2023;31(7):1787–97.
19. During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. *Nat Med*. 2003;9(9):1173–9.
20. Li Z, Chen X, Vong JSL, Zhao L, Huang J, Yan LYC, et al. Systemic GLP-1R agonist treatment reverses mouse glial and neurovascular cell transcriptomic aging signatures in a genome-wide manner. *Commun Biol*. 2021;4(1):656.
21. Park JS, Kam TI, Lee S, Park H, Oh Y, Kwon SH, et al. Blocking microglial activation of reactive astrocytes is neuroprotective in models of Alzheimer's disease. *Acta Neuropathol Commun*. 2021;9(1):78.
22. Rode AKO, Buus TB, Mraz V, Al-Jaberi FAH, Lopez DV, Ford SL, et al. Induced human regulatory T cells express the glucagon-like peptide-1 receptor. *Cells*. 2022;11(16):2587.
23. Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. *Nat Med*. 2018;24(7):931–8.
24. Zhang Q, Liu C, Shi R, Zhou S, Shan H, Deng L, et al. Blocking C3d⁺/GFAP⁺ A1 astrocyte conversion with semaglutide attenuates blood-brain barrier disruption in mice after ischemic stroke. *Aging Dis*. 2022;13(3):943–59.
25. Zhao L, Li Z, Vong JSL, Chen X, Lai HM, Yan LYC, et al. Pharmacologically reversible zonation-dependent endothelial cell transcriptomic changes with neurodegenerative disease associations in the aged brain. *Nat Commun*. 2020;11(1):4413.
26. Ludwig MQ, Belmont-Rausch DM, Bentsen MA, Secher A, Hansen SAN, Egerod KL, et al. A lipopolysaccharide mouse model mirrors neuroinflammatory transcriptional signatures of human Alzheimer's disease, and the glucagon-like peptide-1 receptor agonist semaglutide attenuates neuroinflammation in this model. *Alzheimers Dement*. 2022;18(S10):e063862.
27. Lee YS, Jun HS. Anti-inflammatory effects of GLP-1-based therapies beyond glucose control. *Mediators Inflamm*. 2016;2016:3094642.
28. Mosenson O, Capehorn MS, De Remigis A, Rasmussen S, Weimers P, Rosenstock J. Impact of semaglutide on high-sensitivity C-reactive protein: exploratory patient-level analyses of SUSTAIN and PIONEER randomized clinical trials. *Cardiovasc Diabetol*. 2022;21(1):172.
29. Gejl M, Gjedde A, Egeffjord L, Møller A, Hansen SB, Vang K, et al. In Alzheimer's disease, 6-month treatment with GLP-1 analog prevents decline of brain glucose metabolism: randomized, placebo-controlled, double-blind clinical trial. *Front Aging Neurosci*. 2016;8:108.
30. Edison P, Femminella GD, Ritchie CW, Holmes C, Walker Z, Ridha BH, et al. Evaluation of liraglutide in the treatment of Alzheimer's disease. *Alzheimers Dement*. 2021;17(S9):e057848.
31. Edison P, Femminella GD, Ritchie C, Nowell J, Holmes C, Walker Z, et al. MRI changes following treatment of GLP-1 analogue, liraglutide in Alzheimer's disease. *Alzheimers Dement*. 2023;19(S21):e080538.
32. Nørgaard CH, Friedrich S, Hansen CT, Gerds T, Ballard C, Møller DV, et al. Treatment with glucagon-like peptide-1 receptor agonists and incidence of dementia: data from pooled double-blind randomized controlled trials and nationwide disease and prescription registers. *Alzheimers Dement* (N Y). 2022;8(1):e12268.
33. Cukierman-Yaffe T, Gerstein HC, Colhoun HM, Diaz R, García-Pérez LE, Lakshmanan M, et al. Effect of dulaglutide on cognitive impairment in type 2 diabetes: an exploratory analysis of the REWIND trial. *Lancet Neurol*. 2020;19(7):582–90.
34. Akimoto H, Negishi A, Oshima S, Wakiyama H, Okita M, Horii N, et al. Antidiabetic drugs for the risk of Alzheimer disease in patients with type 2 DM using FAERS. *Am J Alzheimers Dis Other Dement*. 2020;35:1533317519899546.
35. Wium-Andersen IK, Osler M, Jørgensen MB, Rungby J, Wium-Andersen MK. Antidiabetic medication and risk of dementia in patients with type 2 diabetes: a nested case-control study. *Eur J Endocrinol*. 2019;181(5):499–507.
36. Wang T, Buse JB, Pate V, Stürmer T. 1802-PUB: Liraglutide as a potential drug repurposing candidate for Alzheimer's disease and related dementia—real-world evidence. *Diabetes*. 2023;72(Suppl 1):1802–PUB.
37. Wang W, Wang Q, Qi X, Gurney M, Perry G, Volkow ND, et al. Associations of semaglutide with first-time diagnosis of Alzheimer's disease in patients with type 2 diabetes: target trial emulation using nationwide real-world data in the US. *Alzheimer's & Dementia*. 2024;20(12):8661–72.
38. FDA. RYBELSUS prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/213051s000lbl.pdf. Accessed 3 January 2025.
39. FDA. OZEMPIC prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf. Accessed 3 January 2025.
40. FDA. WEGOVY prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/215256s000lbl.pdf. Accessed 3 January 2025.
41. Verma S, Bhatta M, Davies M, Deanfield JE, Garvey WT, Jensen C, et al. Effects of once-weekly semaglutide 2.4 mg on C-reactive protein in adults with overweight or obesity (STEP 1, 2, and 3): exploratory analyses of three randomised, double-blind, placebo-controlled, phase 3 trials. *EClinicalMedicine*. 2023;55:101737.
42. Husain M, Bain SC, Jeppesen OK, Lingvay I, Sorrig R, Treppendahl MB, et al. Semaglutide (SUSTAIN and PIONEER) reduces cardiovascular events in type 2 diabetes across varying cardiovascular risk. *Diabetes Obes Metab*. 2020;22(3):442–51.
43. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2016;375(19):1834–44.
44. Husain M, Birkenfeld AL, Donsmark M, Dungan K, Eliaschewitz FG, Franco DR, et al. Oral semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2019;381(9):841–51.
45. Strain WD, Frenkel O, James MA, Leiter LA, Rasmussen S, Rothwell PM, et al. Effects of semaglutide on stroke subtypes in type 2 diabetes: post hoc analysis of the randomized SUSTAIN 6 and PIONEER 6. *Stroke*. 2022;53(9):2749–57.
46. Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM, et al. Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (Aβeta) levels and protects hippocampal neurons from death induced by Aβeta and iron. *J Neurosci Res*. 2003;72(5):603–12.
47. Grieco M, Giorgi A, Gentile MC, d'Erme M, Morano S, Maras B, et al. Glucagon-like peptide-1: a focus on neurodegenerative diseases. *Front Neurosci*. 2019;13:1112.
48. Hansen HH, Fabricius K, Barkholt P, Niehoff ML, Morley JE, Jelsing J, et al. The GLP-1 receptor agonist liraglutide improves memory function and increases hippocampal CA1 neuronal numbers in a senescence-accelerated mouse model of Alzheimer's disease. *J Alzheimers Dis*. 2015;46(4):877–88.
49. Salameh TS, Rhea EM, Talbot K, Banks WA. Brain uptake pharmacokinetics of incretin receptor agonists showing promise as Alzheimer's and Parkinson's disease therapeutics. *Biochem Pharmacol*. 2020;180:114187.
50. Gabery S, Salinas CG, Paulsen SJ, Ahnfeldt-Rønne J, Alenentalo T, Baquero AF, et al. Semaglutide lowers body weight in rodents via distributed neural pathways. *JCI Insight*. 2020;5(6):e133429.
51. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab*. 2021;46:101102.
52. Jack CR Jr, Bennett DA, Blennow K, Carrillo MC, Dunn B, Haeblerlein SB, et al. NIA-AA Research Framework: toward a biological definition of Alzheimer's disease. *Alzheimers Dement*. 2018;14(4):535–62.
53. Chang YL, Bondi MW, McEvoy LK, Fennema-Notestine C, Salmon DP, Galasko D, et al. Global clinical dementia rating of 0.5 in MCI masks variability related to level of function. *Neurology*. 2011;76(7):652–9.
54. FDA. Guidance for Industry: Clinical Trial Imaging Endpoint Process Standards. 2018.
55. Wahlund LO, Barkhof F, Fazekas F, Bronge L, Augustin M, Sjögren M, et al. A new rating scale for age-related white matter changes applicable to MRI and CT. *Stroke*. 2001;32(6):1318–22.

56. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 1993;43(11):2412–4.
57. Thethi TK, Pratley R, Meier JJ. Efficacy, safety and cardiovascular outcomes of once-daily oral semaglutide in patients with type 2 diabetes: the PIONEER programme. *Diabetes Obes Metab*. 2020;22(8):1263–77.
58. Lincoff AM, Brown-Frandsen K, Colhoun HM, Deanfield J, Emerson SS, Esbjerg S, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med*. 2023;389(24):2221–32.
59. Kosiborod MN, Abildstrøm SZ, Borlaug BA, Butler J, Rasmussen S, Davies M, et al. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. *N Engl J Med*. 2023;389(12):1069–84.
60. Shu Y, He X, Wu P, Liu Y, Ding Y, Zhang Q. Gastrointestinal adverse events associated with semaglutide: a pharmacovigilance study based on FDA adverse event reporting system. *Front Public Health*. 2022;10:996179.
61. Aroda VR, Blonde L, Pratley RE. A new era for oral peptides: SNAC and the development of oral semaglutide for the treatment of type 2 diabetes. *Rev Endocr Metab Disord*. 2022;23(5):979–94.
62. Lau J, Bloch P, Schäffer L, Pettersson I, Spetzler J, Kofoed J, et al. Discovery of the once-weekly glucagon-like peptide-1 (GLP-1) analogue semaglutide. *J Med Chem*. 2015;58(18):7370–80.
63. Sabbagh M, Boschini C, Cohen S, Fugger M, Jessen F, Martino GG, et al. Safety profile of semaglutide in people aged 55 years and over: pooled data from the PIONEER, SUSTAIN and STEP phase 3 clinical programmes. *Alzheimers Dement*. 2023;19(S21):e076540.
64. Meier JJ. Efficacy of semaglutide in a subcutaneous and an oral formulation. *Front Endocrinol (Lausanne)*. 2021;12:645617.
65. Franx BAA, Arnoldussen IAC, Kiliaan AJ, Gustafson DR. Weight loss in patients with dementia: considering the potential impact of pharmacotherapy. *Drugs Aging*. 2017;34(6):425–36.
66. Scheltens P, Atri A, Feldman H, Hansson O, Knop F, Sano M, et al. Baseline characteristics from evoke and evoke+: two phase 3 randomized placebo-controlled trials of oral semaglutide in patients with early Alzheimer's disease. *J Prev Alzheimers Dis*. 2023;10(Suppl 1):S92–3. Poster LP018; Presented at CTAD 2023.
67. Raman R, Aisen PS, Carillo MC, Detke M, Grill JD, Okonkwo OC, et al. Tackling a major deficiency of diversity in Alzheimer's disease therapeutic trials: an CTAD Task Force report. *J Prev Alzheimers Dis*. 2022;9(3):388–92.
68. Kim HW, Hong J, Jeon JC. Cerebral small vessel disease and Alzheimer's disease: a review. *Front Neurol*. 2020;11:927.
69. Assunção SS, Sperling RA, Ritchie C, Kerwin DR, Aisen PS, Lansdall C, et al. Meaningful benefits: a framework to assess disease-modifying therapies in preclinical and early Alzheimer's disease. *Alzheimers Res Ther*. 2022;14(1):54.
70. Cohen S, Cummings J, Knox S, Potashman M, Harrison J. Clinical trial endpoints and their clinical meaningfulness in early stages of Alzheimer's disease. *J Prev Alzheimers Dis*. 2022;9(3):507–22.
71. Dickson SP, Wessels AM, Dowsett SA, Mallinckrodt C, Sparks JD, Chatterjee S, et al. 'Time saved' as a demonstration of clinical meaningfulness and illustrated using the donanemab TRAILBLAZER-ALZ study findings. *J Prev Alzheimers Dis*. 2023;10(3):595–9.
72. Boxer AL, Sperling R. Accelerating Alzheimer's therapeutic development: the past and future of clinical trials. *Cell*. 2023;186(22):4757–72.
73. Cummings J. The role of biomarkers in Alzheimer's disease drug development. *Adv Exp Med Biol*. 2019;1118:29–61.

Publisher's note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.