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Review

Evoke (+) trials of semaglutide for early alzheimer's disease: Innovations, lessons, and implications

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A B S T R A C T

The evoke and evoke+ trials for the treatment of early Alzheimer's disease (AD) with semaglutide were founded on the observation that semaglutide reduced the incidence of dementia in patients with type 2 diabetes. Non-clinical investigations support an effect of semaglutide on AD pathology. The evoke and evoke+ trials were large, well conducted, and innovative. These trials were negative, showing no clinical benefit of treatment with 14 milligrams of semaglutide for two years. Semaglutide produced a statistically significant and robust reduction in high sensitivity C-reactive protein consistent with suppression of peripheral inflammation. There was no effect on most plasma measures collected. CSF analyses showed nominally significant effects on biomarkers of the core biology of AD; YKL-40 and glial fibrillary acidic protein in CSF were decreased indicating a reduction in astroglial activation. The magnitude of these changes was small (7%-10%) and there was no correlative effect on AD progression. The discrepancy between observations in real world data and the trial outcomes indicates that treatment of symptomatic AD confirmed with biomarkers differs from treatment of patients with diabetes who were cognitively unimpaired and at risk for all cause cognitive decline. The evoke and evoke+ trials suggest that reduction in peripheral inflammation may be insufficient to produce beneficial clinical effects in AD. The results of the evoke(+) trials do not exclude the possibility that AD populations enriched for elevated levels of markers of peripheral inflammation or use of brain penetrant GLP-1 RAs could produce therapeutic benefit.

1. Introduction

The evoke and evoke+ (hereafter referred to as evoke(+) when both trials are addressed together) trials of semaglutide for the treatment of early Alzheimer's disease (AD) are among the largest trials of symptomatic AD ever conducted and had numerous design innovations. The trials were informed by real-world observations of decreased incidence of dementia in type 2 diabetes (T2D) patients treated with semaglutide, a glucagon like peptide 1 receptor agonist (GLP-1 RA) known to decrease peripheral inflammation in patients with type 2 diabetes (T2D) and obesity. Non-clinical studies support efficacy of semaglutide and other GLP-1RAs for the treatment of AD. The evoke(+) trials tested the therapeutic hypothesis that decreasing peripheral inflammation by semaglutide would reduce brain inflammation and slow progression of AD. The evoke(+) trials were negative and showed no drug-placebo differences on primary or secondary outcomes [1]. The evoke(+) trials outcomes warrant an examination of the relationship of real-world data to clinical trial planning. The trial results have implications for therapies addressing anti-inflammatory targets, trial planning for vascular cognitive impairment (VCI), and further development of GLP-1RA drugs for treatment of AD.

We briefly review the evoke(+) trials and their outcomes. We summarize the innovations in these trials that may be of value to stakeholders involved in AD drug development. We examine the discrepancy between real-world outcomes and the findings of the evoke(+) trials and discuss the implications of these trials for AD treatment development.

2. evoke(+) trial design and outcomes

The design and baseline characteristics of the evoke(+) trials have been reported [2,3]. Briefly, evoke (NCT04777396) and evoke+ (NCT04777409) were randomized, double-blind, placebo-controlled, parallel-group trials investigating the efficacy and safety of 14 mg of oral semaglutide. The two trials had identical designs, with the exception that evoke+ allowed participation of patients with evidence of small vessel pathology at baseline. Participants had mild cognitive impairment (MCI) or mild AD dementia defined as a Clinical Dementia Rating (CDR) global score of 0.5 or 1 respectively. In addition, trial candidates were required to have Mini-Mental State Examination (MMSE) scores ≥ 22 and a Repeatable Battery for the Assessment of Neuropsychological

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Status (RBANS) delayed memory index score of ≤85. The clinical diagnosis of AD was confirmed in all participants by amyloid positron emission tomography (PET) or cerebrospinal fluid (CSF) amyloid-beta protein (Aβ) studies. The primary outcome was the drug-placebo difference on the CDR-sum of boxes (CDR-SB) at week 104 and participants continued in a double-blind extension phase to week 156. Drug-placebo difference in change from baseline on the Alzheimer's Disease Cooperative Study Activities of Daily Living MCI version (ADCS-ADL-MCI) was a confirmatory secondary analysis. Difference in progression to a CDR global score of ≥1·0 among participants with a baseline CDR global score of 0·5 using the pooled data from evoke and evoke+ was an additional secondary outcome. High sensitivity C-Reactive Protein (hsCRP) measured peripheral inflammation. AD-related plasma measures of neurofilament light chain (NfL), glial fibrillary acidic protein (GFAP), phosphorylated tau (p-tau) 181, p-tau 217, np-tau 217, and p-tau 217/np-tau 217 were measured or calculated [4]. A CSF substudy collected AD core biomarkers (Aβ, tau, p-tau) and measures of neurodegeneration, inflammation, oxidation, synaptic function, vascular factors, and blood brain barrier (BBB) integrity.

In total, 3808 participants were randomized (1855 to evoke and 1953 to evoke+). The trials were negative, demonstrating no drug-placebo difference on the primary or secondary outcomes at week 104 [1]. Examination of the key subgoups (sex, age, presence or absence of diabetes) revealed none that were apparently responsive. hsCRP levels decreased significantly with semaglutide treatment in both trials (placebo remained relatively unchanged). Plasma studies in the evoke participants revealed significant elevations of GFAP with treatment; evoke (+) participants had significantly elevated GFAP and NfL with treatment. In the CSF sub-study, there were nominally significant reductions with semaglutide treatment versus placebo in biomarkers of AD pathology (p-tau181, p-tau217, np-tau181 and np-tau 205) and biomarkers of neuroinflammation (YKL-40), neurodegeneration (total tau) and synaptic function (neurogranin). The magnitudes of the drug-placebo differences were 10% or less, did not remain significant after adjustment for multiple comparisons, were not accompanied by similar changes in plasma measures of core pathology or inflammation, and did not translate into measurable slowing of disease progression. Biomarkers of inflammation, synaptic function, oxidation, vascular factors, and BBB integrity showed no drug-placebo differences. Safety and tolerability data revealed the weight loss expected with an agent approved for treatment of obesity/overweight; no unanticipated adverse event patterns were observed. Weight loss following bariatric surgery has been associated with increased plasma levels of NfL and GFAP, and weight changes may have contributed to the elevations of plasma GFAP and NfL observed with semaglutide treatment [5]. Weight loss has been reported to increase CSF p-tau and tau levels and is not likely to explain the reductions of levels of these core AD biomarkers observed with semaglutide exposure [6].

3. evoke(+) innovations

The evoke(+) program had multiple novel aspects. The evoke(+) trials are among the largest trials performed for individuals with symptomatic biomarker-confirmed early AD. The trials were well conducted with good participant retention, complete data collection, and small standard deviations on scores of endpoint measures. Participants were enrolled from 566 sites located in 40 countries from 8 global regions. The trials demonstrated the feasibility of conducting rigorous clinical trials on a global scale. The global distribution of sites allowed participation of individuals from diverse cultural, ethnic, and racial backgrounds. Anti-amyloid monoclonal antibodies (MABs) were approved for use in the US and some other countries close to the time of initiation of the evoke(+) trials. Whether to allow patients on these treatments into trials is a current key trial planning decision. The evoke (+) trials permitted patients to be on anti-amyloid MABS to enter the trials (1 participant) and allowed participants to remain in the trials if they initiated therapy with a MAB (78 participants). This approach makes the outcomes of trials more applicable to clinical circumstances where add-on combinations are common. As a non-amyloid and non-monoclonal antibody approach to AD therapy, there was limited concern about producing amyloid-related imaging abnormalities (ARIA) and the requirement for a baseline scan was satisfied by either magnetic resonance imaging (MRI) or x-ray computed tomography, anticipating variably resourced clinical care circumstances. Input from potential patients and their care partners was sought for the evoke(+) trial design. Based on interviews, the trials were adjusted in terms of frequency of required visits, definition of an allowable care partner, and provision of reminders for compliance with the dosing regimen. These changes may have improved trial recruitment, satisfaction, and completion rates.

Several outcome innovations were integrated into the evoke(+) trials. The primary readout was week 104 and participants remained on their assigned treatment for an additional 52-week double blind extension to allow more data to be collected. Participants and sites remained blinded to treatment assignment for the entire 156 weeks of treatment. A supportive secondary outcome was the time to progression from CDR 0.5 to CDR ≥1 in the participants with CDR 0.5 at baseline. This stage transition measure of time before dementia diagnosis is a key outcome for patients, care partners, and clinicians. Time-to-event analyses have less power than continuous measures and the evoke(+) stage transition analysis prespecified a pooled analysis of the evoke and evoke+ data to ensure an adequate sample size for the analysis [7]. Estimands are relatively new to AD drug development and are required by the US Food and Drug Administration (FDA) and the European Medicine Agency (EMA) [8]. The use of two estimand analyses — hypothetical, treatment, and composite strategy (Hybrid-HTC) estimand and treatment policy estimand — allowed examination of the effect of intercurrent events (e.g., initiating treatment with an anti-amyloid MAB) occurring during the evoke(+) trials and met evolving regulatory requirements for use of estimands [9].

Evoke(+) employed biomarker innovations to provide biological information complementary to clinical measures. All participants had diagnostic confirmation of AD diagnosis with amyloid biomarkers. hsCRP is a serum marker of peripheral inflammation and served as a mechanistic/ proof of principle biomarker for the peripheral anti-inflammatory effects of semaglutide. This biomarker is elevated in T2D and is reduced with treatment in trials of semaglutide in diabetic patients [10,11]. In evoke(+) trials, serum hsCRP was significantly decreased by treatment, confirming the proposed anti-inflammatory effect. The large repertoire of blood and CSF biomarkers included in evoke(+) trials provide insight into the effects and lack of effects observed in these studies. Novel biomarkers such as plasma Microtubule-Binding Domain Region (MTBR)-tau243, that correlates with tau PET, were collected longitudinally [12].

4. Discrepancy between evoke(+) outcomes and real-world observations

Several streams of evidence informed the conceptual framework of the evoke(+) trials. A study of the Danish National Diabetes Registry demonstrated a decreased incidence of dementia among patients with T2D treated with GLP-1 RAs [13]. Analyses of data from semaglutide trials of T2D documented reduction of dementia in those receiving GLP-1RAs compared to those receiving other type of diabetes treatments [14]. Short term human studies suggested a stabilization of metabolic function in patients with AD treated with GLP-1 RAs compared to placebo [15]. Data collected after initiation of evoke(+) have continued to support a decreased incidence of dementia among diabetics treated with GLP-1 RAs including target trial emulation studies [16]. Non-clinical studies documented a decrease in tau phosphorylation in mouse models of tauopathy, increased hippocampal neuronal numbers and improved memory in the senescence accelerated model of AD, and decreased neuroinflammation and neurodegeneration in other models

assessing AD-relevant effects of semaglutide [17–19]. These epidemiologic and non-clinical studies did not accurately predict the posited benefit of treatment with semaglutide in early AD.

There are many differences between the design of the evoke(+) studies and the registry and T2D trial observations (Table 1). The main observation in the real-world population was decreased incidence of dementia among diabetics, a population at high risk for AD and VCI [20]. The evoke(+) studies involved participants with established cognitive changes (not incident cases); most evoke(+) patients (86%) did not have T2D; baseline hsCRP levels were normal in the evoke(+) participants, not elevated as they are in T2D; the evoke patients had AD confirmed by biomarkers, not all cause dementia as observed in registries and trials of patients with diabetes; the prevalence of white matter abnormalities and evidence of cerebrovascular disease was very low in evoke(+) (1.4% when both trials are combined) and is present in many patients with T2D; exposure periods for GLP-RAs in registries is often longer than the evoke(+) trials; and participants in studies of T2D are younger than those in evoke(+).

The decreased incidence of dementia in the real-world settings was not investigated with biomarkers and the proportion attributable to AD is unknown. Autopsy studies have found no increase in AD pathology among individuals diagnosed with diabetes in life [21,22]. T2D is associated with cerebrovascular disease and GLP-1 RAs improve cerebrovascular outcomes in T2D patients [23,24]. Beneficial cerebrovascular effects of semaglutide could reduce VCI or mixed AD/VCI syndromes but there were few patients with cerebrovascular disease in the evoke(+) trials. Biomarkers suggest that the BBB is compromised in T2D and markers of BBB integrity are normal in evoke(+)(e.g., platelet-derived growth factor receptor β (PDGFRβ) [24,25].

Differences in exposure levels of semaglutide due to the dosing and titration regimen do not explain the real-world/evoke(+) discrepancy. Population pharmacokinetic studies show the blood levels of semaglutide in evoke(+) trial participants to be comparable to the levels observed in the trials of semaglutide in T2D trials associated with a decreased incidence of dementia.

Together, the contrasting circumstances of the populations in which the reduced incidence of dementia was observed and the evoke(+) studies may explain the epidemiologic/trial discrepancy and the negative outcomes. Unexplained is the cause of the dementia emerging among patients with T2D and the mechanism of its reduction by semaglutide.

The real-world/evoke(+) discrepancy suggests that when extrapolating real-world data to clinical trial design, fidelity to the precise characteristics of the real-world observations may enhance the probability of success of the trial.

5. Implications of evoke(+) for alzheimer's drug development

The evoke(+) trials were well conducted, appropriately powered, and definitively negative. Further studies of semaglutide in early AD are unwarranted unless hypothesis-generating subgroup observations emerge. Semaglutide has minimal BBB penetration and central effects hypothesized to be based on mitigation of peripheral inflammation were very modest and without clinical relevance. Semaglutide's lack of central activity suggests that it is unlikely to create a meaningful additive or synergistic effect in AD when combined with another agent or other interventions. GLP-1 receptors are widely distributed in the brain particularly in the circumventricular organs [26], and it is possible that brain penetrant GLP-1 RAs or use of BBB transporter mechanisms in conjunction with GLP-1s could impact the pathophysiology of AD [27].

Drug development programs are more likely to succeed if they have a mechanistic target-engagement biomarker related to the proposed indication [28]. Target engagement by a GLP-1RA involves some measure of the effect of the agent on the GLP-1 receptor such as suppression of post-prandial glucagon secretion [29]. No target engagement biomarker was included in the evoke(+) trials. hsCRP functioned as a proof-of-principal biomarker for the anti-inflammatory effect of semglutide that was expected and confirmed. The mechanistic relationship between GLP-1 RA activity and decreased inflammation is attributed to the modulating effects of GLP-1 RAs on CRP and indirect effects on nuclear factor-kappa B (NF-κB)-related inflammatory pathways [30,31].

Non-clinical and real-world observations — like those informing the evoke(+) trials— are typically followed by phase 1 studies (which were less relevant for semaglutide, a repositioned agent with phase 1 studies in T2D) and phase 2 studies in which safety, target engagement, and dose (ideally with dose-dependent effects) are explored. Phase 2 trials were not integrated into the semaglutide development program. A phase 2 trial with biomarker outcomes – CSF core AD biomarkers and measures of inflammation – might have predicted the negative outcome of evoke(+). Pharmacodynamic biomarker changes may be observed with shorter treatment exposures and smaller sample sizes than those required to demonstrate changes in clinical outcomes supporting the use of biomarkers as primary outcomes in phase 2 trials [32]. Appropriate powering of such a phase 2 study would have been complex. True positive findings could have informed sample size calculations, dose, and endpoint selection for phase 3. A true negative phase 2 outcome might have led to discontinuation of the program, avoiding the cost and efforts of phase 3 evoke(+) trials. A false negative outcome (type 2 error) based on not showing an effect in an underpowered study might have risked discontinuing the development program of a possibly efficacious agent.

Epidemiologic observations showing that semaglutide reduces the incidence of dementia in diabetes suggest that a trial of semaglutide in a cognitively normal T2D population might show protective effects in this high-risk population. Blood based biomarkers of AD (e.g., p-tau 217, GFAP) could determine if the emergent dementia is due to AD and if biomarker changes are deferred.

AD prevention studies with semaglutide or other GLP-1 RAs might be considered. Primary prevention studies could use emergence of abnormal plasma p-tau 217 in participants with normal levels at baseline as a biomarker outcome (lack of a drug-placebo difference at interval measures could function as an indicator of futility), and secondary prevention trials could assess the emergence of cognitive impairment in participants with positive p-tau 217 at baseline. Most individuals with preclinical AD do not have T2D, and the study would be less aligned with the real-world data. Identifying candidate participants with elevated plasma levels of biomarkers of inflammation might enrich the population for a treatment response. Lack of significant BBB penetration by semaglutide and absence of elevations of peripheral measures of inflammation in early AD represent important challenges to planning such trials. Addressing these issues in phase 2 trials would be useful to inform later stage trials in preclinical populations. At the time of inception of the evoke(+) studies, plasma biomarkers had not been developed to the current level of availability and accuracy.

The evoke(+) studies have implications for the development of drugs targeting inflammation in AD. Semaglutide reduced hsCRP in evoke(+) indicating an effect on peripheral inflammatory mechanisms. In T2D the elevations in hsCRP are accompanied by increased tumor necrosis fac-

Table 1
Differences between real-world data and evoke(+) trials.

Real-World Observations	Evoke(+)
Incidence	Progression
All cause dementia	Alzheimer's disease (biomarker confirmed)
Diabetes	Few diabetics
Increased peripheral hsCRP	Normal hsCRP
White matter hyperintensities common	White matter hyperintensities in 1.4% of participants
Long exposure periods	2-year exposure period
Younger (55-65 in most studies)	Older (65-75)
Impaired blood brain barrier	No biomarker evidence of impaired blood brain barrier

hsCRP – high sensitivity C-reactive protein

tor- alpha (TNF-alpha). interleukin 6 (IL 6), and monocyte chemoattractant protein 1 (MCP-1), and these levels are reduced by semaglutide. Effect of semaglutide on these associated inflammatory markers in evoke(+) have not been reported. Significant changes were observed in the evoke(+) trials on CSF YKL-40, a measure of astrocytic activation in the inflammatory response cascade, but no changes were observed for other markers of central inflammation collected in the trials including soluble triggering receptor expressed on myeloid cells 2 (sTREM2), GFAP, IL6, IL8, IL-18, IL1RA, secreted modular calcium binding protein 1 (SMOC 1), osteopontin, IP10/CXCL10, or MCP-1/CCL2.. These markers are increased in CSF of AD where they correlate with tau and neurodegeneration [33]. The evoke(+) trials show that hsCRP is, on average, not increased in AD (although the range of hsCRP levels at baseline was large), and robust reduction of hsCRP is not associated with compelling changes in CSF markers of brain inflammation or clinical benefit. The evoke(+) trial outcomes suggest caution in targeting peripheral inflammation to slow the clinical decline of AD. The results also indicate the suppression of peripheral inflammation may not be associated with alterations in inflammatory biomarkers in the CNS and that use of measures of peripheral inflammation may provide limited insight into CNS anti-inflammatory drug effects. Selection of an AD population with biomarker evidence of increased peripheral inflammation for treatment with semaglutide could be considered for a next step trial. Such a trial might determine if elevated biomarkers are suppressed in AD and, if so, are the reductions associated with evidence of clinical benefit.

The evoke(+) studies have lessons for programs that address VCI or mixed VCI/AD. The evoke+ trial allowed participation of patients with a high burden of white matter hyperintensities usually excluded from AD trials. White matter abnormalities are common in T2D and the mechanism of action of semaglutide is of interest in these patients as vascular effects could contribute to the reduced incident dementia observed in trials involving T2D participants [34]. Surprisingly, evoke+ enrolled only 54 participants meeting criteria for elevated vascular pathology despite the liberalized eligibility criteria. In retrospect, protocol design features may account for this circumstance. The inclusion criteria were comprised of the AD biomarker profile and a required deficit on the memory aspect of the RBANS [35]. This led to the exclusion of trial candidates not exhibiting the amnestic pattern of memory loss characteristic of AD including those with VCI. The potential efficacy of semaglutide in patients with VCI or mixed AD/VCI syndromes was not adequately explored in the evoke(+) trials.

6. Conclusion

The evoke(+) trials were rigorously conducted and provide important scientific insights. They created a large database of clinical and biomarker measures that will facilitate future clinical trials. The evoke (+) trials establish the absence of clinical benefit of 14 mg semaglutide in early AD treated for 2 years. They do not exclude the possible benefit of semaglutide applied to other populations. They do not exclude the possibility of benefit from other GLP-1 RAs, particularly those that are brain penetrant. The number of participants with VCI included in the evoke(+) trials was too small to examine the potential benefit of semaglutide treatment of those with cerebrovascular disease. The evoke(+) trials show that, in a population not selected for elevated peripheral inflammation, treatment with semaglutide produces no slowing of clinical decline. A treatment benefit in patients with elevated plasma inflammatory biomarkers is not excluded by the trials. The negative outcomes of the evoke(+) trials suggest that the limited brain penetration of semaglutide may be a key factor in the absence of therapeutic benefit.

Disclosures

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No use of AI was made in conceptualizing or drafting the manuscript.

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CRediT authorship contribution statement

Jeffrey L. Cummings: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Philip Scheltens:** Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Jeffrey Cummings reports a relationship with AbbVie Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Acadia Pharmaceuticals Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Alkermes Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with ALZpath Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Annovis Bio Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Artery Therapeutics Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Axsome Therapeutics Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Biogen that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Bristol-Myers Squibb Company that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Eisai Inc that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Shanghai Fosun Pharmaceutical Group Co Ltd that includes: consulting or advisory. Jeffrey Cummings reports a relationship with GAP Foundation that includes: consulting or advisory. Jeffrey Cummings reports a relationship with IGC that includes: consulting or advisory. Jeffrey Cummings reports a relationship with Janssen Pharmaceuticals Inc that includes: consulting or advisory.

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