CLOSER LOOK

MEMORANDUM

Novo Nordisk's semaglutide did not confer statistically significant reduction in Alzheimer's disease progression in phase 3 evoke trials – November 24, 2025

Topline results to be released next week; one-year extension period for evoke and evoke+ trials will be discontinued based on preliminary results

Novo Nordisk announced today that oral semaglutide did not confer a statistically significant reduction in Alzheimer's disease progression compared to placebo, according to its two-year primary analysis of the phase 3 evoke and evoke+ trials (n=3,808). Both trials showed improvements in certain undisclosed Alzheimer's-related biomarkers, but did not translate to a delay in disease progression, as measured by change in Clinical Dementia Rating-Sum of Boxes (CDR-SB) score compared to baseline. Neither evoke nor evoke+ met its primary endpoint, with both failing to demonstrate superiority of semaglutide versus placebo in slowing the progression of Alzheimer's disease. Semaglutide appeared to have a safe and well-tolerated profile consistent with previous trials. This is quite disappointing given several epidemiological and observational studies (see below) showing that people with diabetes on GLP-1s have significantly lower risk of dementia compared to people with diabetes on other drugs.

The one-year extension period for the evoke and evoke+ trials will be discontinued based on the overall study population's efficacy results. Novo Nordisk will share topline results both studies at the Clinical Trials in Alzheimer's Disease Conference on December 3, 2025, and full results at the 2026 Alzheimer's and Parkinson's Disease Conference in March 2026.

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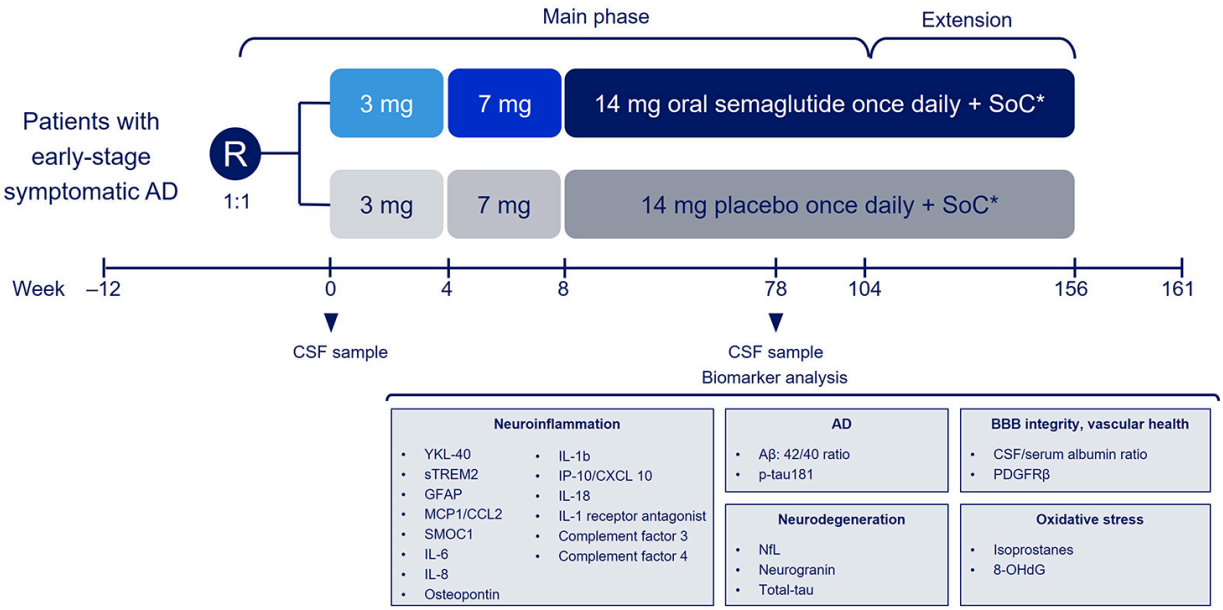
Study design: evoke and evoke+ trials included participants with early-stage symptomatic Alzheimer's disease

Phase 3 evoke (n=1,855) and evoke+ trials (n=1,835) enrolled participants aged 55-85 years with mild cognitive impairment (MCI) due to Alzheimer's disease and confirmed amyloid positivity across 350 and 398 global sites, respectively. Specifically, evoke+ also included participants with evidence of small vessel pathology (i.e., multiple lacunar infarcts or age-related white matter changes >20 mm). Therefore, evoke+ is deemed as a broader trial intended to expand generalizability of the program's findings to real-world populations that often have both Alzheimer's and vascular brain injury. According to the trial design, people with T2D were allowed to enroll and made up around 30% of the entire study population.

In both trials, the primary endpoint was the change from baseline to Week 104 in CDR-SB score. A subgroup of participants (n=210) also underwent biomarker analyses using cerebrospinal fluid samples to assess neuroinflammation, neurodegeneration, blood brain barrier integrity, synaptic integrity, vascular health, and oxidative stress. Both the evoke and evoke+ trials were originally planned to last three years, with a two-year main phase and a one-year blinded

extension phase.

Figure 1. Trial design of evoke and evoke+



Source: Cummings et al., *Alzheimer's Research and Therapy* 2025

Baseline characteristics: 11%-21% of study participants had T2D

According to baseline characteristics presented in 2024, evoke and evoke+ participants were on average 72-73 years old, respectively, with 52%-53% being female and 77% white. Geographically, most participants were from Europe (n=1,986), followed by North America (n=707), Asia (n=602), Latin America (n=303), and Rest of World (n=208).

Clinically, 60% and 55% of evoke and evoke+ trial participants, respectively, were on at least one medication for Alzheimer's disease. Mean CDR-SB score was 3.7 for both studies, which indicate questionable cognitive impairment and very mild dementia. Notably, 11%-21% of study participants had T2D across different regions.

Post-hoc and real-world analyses showed potential protective effects of GLP-1 RAs on dementia

In a post-hoc analysis (n=15,820) of the LEADER, SUSTAIN 6, and PIONEER 6 cardiovascular outcomes trials of liraglutide, injectable semaglutide, and oral semaglutide, respectively, GLP-1 RAs were associated with 53% reduced risk of all-cause dementia diagnosis in people with T2D compared to placebo. Similarly, an exploratory analysis (n=9,901) of the REWIND trial found that at five years, dulaglutide was associated with 14% reduced risk of cognitive impairment in people with T2D when adjusted for individual baseline scores.

In observational studies, a real-world analysis (n=33,858) published in *JAMA Neurology* found that GLP-1 RA use was associated with a 33% lower risk of Alzheimer's disease and related dementias (ADRD), when compared to other second-line glucose-lowering drugs. This association corresponded to roughly two to three fewer cases per 1,000 person-years. Likewise, in a trial emulation (n=1,094,761), semaglutide was linked with 67% reduced risk of first-time diagnosis of Alzheimer's disease compared to insulin therapy and 41% reduced risk compared to other GLP-1 RAs.

These findings suggest neuroprotective effects of GLP-1 RAs in individuals with T2D and cardiometabolic diseases, who are at a heightened risk for accelerated cognitive decline and dementia. However, it is important to note that the patient population of these exploratory studies significantly differs from those of the evoke and evoke+ trials. These studies include people with T2D but without prior history of dementia and with T2D, while the evoke and evoke+ trials recruited those with symptomatic dementia regardless of baseline T2D. We are curious if semaglutide demonstrated benefits in specific subgroups, such as those with earlier stages of dementia or baseline metabolic diseases.

While Novo Nordisk "always" believed programs had "low likelihood of success," exciting research ahead may yet yield progress

CEO Mr. Mike Doustdar and CSO Dr. Martin Holst Lange shared similar responses to today's news. On LinkedIn, Mr. Doustdar posted a short video, noting such results were "not the outcome we would have hoped for" and that the company "always knew there would be a low likelihood of success". While this is true, of course, hope springs eternal.

As we understand it, the Alzheimer's field is still very much in a learning stage for how trials should be designed, which endpoints to use, etc. Dementia events and dementia severity scores are quite "difficult" outcomes that create a very high bar for drugs. We have been advised to keep in mind from those in the know that Alzheimer's disease/dementia is a disease that develops over the course of decades; people in this trial who were at the beginning stages of showing cognitive decline probably have had Alzheimer's brain pathology building up in their brains for 20 years before any cognitive symptoms became visible. We imagine most Alzheimer's researchers would agree that for a drug to have a chance at significantly preventing/delaying Alzheimer's disease, it would need to be given much earlier in the course of the disease. Of course, this requires early detection, and this is something that the field don't have the technology for *yet*. Currently, detecting brain pathology requires expensive brain imaging or very invasive collection of cerebrospinal fluid from a spinal tap; this only rarely occurs unless someone is already at an advanced stage of disease and reporting cognitive symptoms.

We believe there is a lot of exciting research on non-invasive blood-based biomarkers for Alzheimer's brain pathology - this is a very hot topic in the field at present. If these could one day be implemented in clinical practice, it would go a long way to identify Alzheimer's disease much earlier, and this could support earlier intervention. Biomarkers that hold great interest are pTau-217, as well as AB42/40, NfL, and GFAP, among others.

When the full evoke results are presented in March, our main curiosity is whether semaglutide was related to improvements in any of these biomarkers (which were tested as secondary outcomes) or other "earlier" measures like cognitive test scores, brain imaging markers, and CSF biomarkers. If this is the case it could raise the possibility that GLP-1 receptor agonists could be effective if given far earlier in the course of the disease. Now, of course, this may well require lots of further trials ahead, and longer trials, but yet and still, where there is a will, there may well be some ways.

While the one-year extension period for the evoke and evoke+ trials will be discontinued based on the overall study population's efficacy results, we look forward to post-hoc analyses to shed more light on potential effects of semaglutide on neuroinflammation and neurodegeneration.

Evoke results: Not all failed trials are necessarily "failures"

While the trials did not meet their primary endpoints, they are far from "failures." We believe that the evoke program can elucidate better understanding of semaglutide's effects on neurodegenerative diseases with the rigor of randomized controlled trials. We are especially curious which patient subgroups responded best with semaglutide, and which biomarkers improved the most – these findings can help identify patients who may benefit most from semaglutide.

Moreover, observation studies and post-hoc analyses showed semaglutide's benefits on Alzheimer's disease prevention. While not tested in the evoke program, we are hopeful that semaglutide confers protective effects in those at risk of Alzheimer's disease, such as those with T2D, but without prior diagnosis.

- When considering this, we consider some of the early trials with intermittently scanned CGM in the basal-bolus T2D population. Abbott's REPLACE trial, for example, missed its primary endpoint but offered an important look at the technology's benefits beyond A1c. The trial's profound reductions in hypoglycemia, including a ~75% drop in time spent <45 mg/dl, demonstrate clinical value that is not captured by A1c alone. These results foreshadow what we now see in real-world CGM adoption: payers expanding coverage based on safety, reduced acute events, and strong patient demand, even though this early RCT showed mixed glycemic outcomes. REPLACE also highlighted how trial design choices can impact outcomes, such as the lack of treat-to-target insulin adjustment, which could have diminished effects on A1c effects without reducing its long-term potential. As CGM reimbursement for T2D continues to grow, the field increasingly recognizes that these meaningful improvements to hypoglycemia and quality of life *can* drive uptake and payer support, even if an early trial doesn't deliver a "win" in the way that the field is used to perceiving wins.

KOL Commentary

On today's announcement, Dr. Alice Cheng shared, "although these preliminary results from evoke and evoke+ is not what was hoped for, it provides critical scientific information that will help to guide future research in Alzheimer's disease. This is an important reminder that prospective clinical trials are needed to better understand the potential role of any therapy and that reliance on observational data alone can be flawed. In addition, all results from well conducted clinical trials are useful - positive, neutral or negative. Having said all of that, the detailed publication will be interesting to see if the diabetes subgroup (albeit small) had any signal of a differential effect as the suggestive observational data were predominantly demonstrated in those with diabetes. One can always continue to hope!"

Close Concerns' Questions

1. Why did Novo Nordisk choose to use oral semaglutide, rather than its injectable form, in the phase 3 evoke program? Does the company expect similar results with injectable semaglutide given the potential differences in bioavailability and brain access? Is there confidence that the therapy was taken as it should be (nothing eaten for 30 minutes after each dose)?
2. Given that Alzheimer's disease begins significantly before symptoms arise, does Novo Nordisk believe enrolling patients with symptomatic Alzheimer's may have been too late to impact disease progression?
3. Might Novo Nordisk consider investigating a prevention-based approach for semaglutide in Alzheimer's disease for at-risk individuals?
4. How did the effects of semaglutide differ across people with and without T2D at baseline?
5. Were there any learnings on those with pre-T2D and any impact on this condition, even if this was not the primary outcome being analyzed?
6. What might the one-year extension phase have demonstrated in terms of clinical impact on disease progression?
7. What parts, if any, of the trial design might future researchers alter that they believe could have impacted the outcomes?

--by Elizabeth Rose, Kat Moon, Monica Oxenreiter, and Kelly Close