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## FROM THE ALZHEIMER'S ASSOCIATION INTERNATIONAL CONFERENCE 2024 GLP-1 DRUG LIRAGLUTIDE MAY PROTECT AGAINST DEMENTIA

### Key Takeaways

- **A GLP-1 agonist — the class of drugs shown to help with diabetes and weight loss and reduce the risk of heart disease — also may protect the brain.**
- **In a Phase 2b trial, liraglutide appears to reduce shrinking in the parts of the brain that control memory, learning, language and decision-making by nearly 50% compared to placebo.**

**PHILADELPHIA, July 30, 2024** — A glucagon-like peptide-1 (GLP-1) drug appears to slow cognitive decline by protecting the brain, according to Phase 2b clinical trial data reported today at the [Alzheimer's Association International Conference](#)® (AAIC®) 2024, in Philadelphia and online.

GLP-1 receptor agonists, which mimic the natural hormone glucagon-like peptide released by the stomach after eating, can help people manage diabetes, lose weight and lower their risk of heart disease, stroke and kidney disease. Research in animal models of Alzheimer's disease suggests these drugs may have neuroprotective effects, reduce early forms of amyloid, normalize the brain's processing of glucose, and improve memory and learning. Liraglutide (Novo Nordisk) likely works by multiple mechanisms in the brain.

This new research reported at AAIC 2024 suggests liraglutide may protect the brains of people with mild Alzheimer's disease and reduce cognitive decline by as much as 18% after one year of treatment compared to placebo by slowing the shrinking of the parts of the brain that are vital for memory, learning, language and decision-making.

“We are in an era of unprecedented promise, with new treatments in various stages of development that slow or may possibly prevent cognitive decline due to Alzheimer's disease,” said Maria C. Carrillo, Ph.D., Alzheimer's Association chief science officer and medical affairs lead. “This research provides hope that more options for changing the course of the disease are on the horizon.

“Repurposing drugs already approved for other conditions has the advantage of providing data and experience from previous research and practical use — so we already know a lot about real-world effectiveness in other diseases and side effects,” Carrillo added.

The Alzheimer's Association [Part the Cloud](#) research grants program has invested more than \$82 million to advance 68 clinical trials targeting a variety of compounds, including repurposed drugs, addressing known and potential new aspects of the disease.

The randomized, double-blind, placebo-controlled Evaluating the Effects of the Novel GLP-1 Analogue Liraglutide in Alzheimer's Disease (ELAD) trial led by Prof. Paul Edison, M.D., Ph.D., professor of science from Imperial College London, included 204 patients with mild Alzheimer's disease seen at 24 clinics throughout the United Kingdom. Each received a daily subcutaneous injection for one year: half (102) received up to 1.8 mg of liraglutide and half (102) received a placebo. Before the study began, all patients had magnetic resonance imaging (MRI) to evaluate brain structure and volumes, glucose metabolism PET scans and detailed memory testing. These were repeated at the end of the study with regular safety visits.

The study's primary endpoint was change in the cerebral glucose metabolic rate in the cortical regions of the brain (hippocampus, medial temporal lobe and posterior cingulate), which was not met. However, the secondary endpoint of change in scores for clinical and cognitive measures and the exploratory endpoint of brain volume showed statistically significant benefit.

“The slower loss of brain volume suggests liraglutide protects the brain, much like statins protect the heart,” said Dr. Edison. “While further research is needed, liraglutide may work through various mechanisms, such as reducing inflammation in the brain, lowering insulin resistance and the toxic effects of Alzheimer’s biomarkers amyloid-beta and tau, and improving how the brain’s nerve cells communicate.”

Edison added that those in the study who received liraglutide had nearly 50% less volume loss in several areas of the brain, including frontal, temporal, parietal and total gray matter, as measured by MRI. These areas are responsible for a variety of critical functions that often are affected by Alzheimer’s disease, including memory, language and decision-making.

Researchers also conducted cognitive testing in the patients — before treatment and at 24 and 52 weeks. Although the study was not powered to assess cognitive changes, researchers found that patients who received liraglutide had an 18% slower decline in cognitive function in a year compared to those who got the placebo.

Cognitive function was calculated as a composite score of 18 different tests of memory, comprehension, language and spatial orientation (ADAS EXEC z score). For those in the study who completed 52 weeks of treatment (treatment n=79, placebo n=87), those taking the drug saw a statistically significant slowing of cognitive decline ( $p<0.01$ ).

Gastrointestinal problems such as nausea were the most common side effects, which totaled 25.5% of all adverse events in the liraglutide group. Twenty-five serious side effects occurred in 18 participants (17.6%) in the placebo arm and seven participants (6.9%) in the treatment arm. Most serious side effects were considered unlikely to be related to the study treatment, Dr. Edison said.

Well-positioned to test this further are current late-stage clinical trials of GLP-1 analogues, several of which are ongoing. For example, EVOKE Plus is a 3-year clinical trial of semaglutide in more than 1,800 people with early Alzheimer’s disease. Note: Two brands of liraglutide have been approved by the U.S. Food and Drug Administration, one for weight loss (Saxenda) and the other for diabetes (Victoza).

### **About the Alzheimer’s Association International Conference® (AAIC®)**

The Alzheimer’s Association International Conference (AAIC) is the world’s largest gathering of researchers from around the world focused on Alzheimer’s and other dementias. As a part of the Alzheimer’s Association’s research program, AAIC serves as a catalyst for generating new knowledge about dementia and fostering a vital, collegial research community.

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### **About the Alzheimer’s Association®**

The Alzheimer’s Association is a worldwide voluntary health organization dedicated to Alzheimer’s care, support and research. Our mission is to lead the way to end Alzheimer’s and all other dementia — by accelerating global research, driving risk reduction and early detection, and maximizing quality care and support. Our vision is a world without Alzheimer’s and all other dementia®. Visit [alz.org](http://alz.org) or call 800.272.3900.

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- Paul Edison, M.D., Ph.D., et al. Evaluation of Novel GLP-1 analogue in the treatment of Alzheimer’s disease. (Funding: Alzheimer’s Society, UK; Alzheimer’s Drug Discovery Foundation, Novo Nordisk AS, John and Lucille Van Geest Foundation, National Institute for Health and Care Research (NIHR) Biomedical Research Centre).

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## Proposal ID: 89799

### Evaluation of Novel GLP-1 analogue in the treatment of Alzheimer's disease.

**Background:** Liraglutide is a glucagon-like peptide-1 (GLP-1) analogue licensed for the treatment of type 2 diabetes mellitus (T2DM). Preclinical evidence in transgenic models of Alzheimer's disease suggests that liraglutide exerts neuroprotective effects by reducing amyloid oligomers, normalising synaptic plasticity and cerebral glucose uptake, and increasing the proliferation of neuronal progenitor cells.

**Method:** This is a multi-centre, randomised, double-blind, placebo-controlled, phase IIb trial of liraglutide in participants with mild to moderate Alzheimer's dementia, conducted at several centres in the UK. As a part of this study, MRI brain scans of all patients were performed at baseline and after 12 months treatment with liraglutide or matching placebo along with neuropsychometric evaluation and [18F]FDG PET. A total of 204 Alzheimer's participants were randomised to receive either liraglutide or placebo as a daily subcutaneous injection for 12 months. All subjects had regular clinical visits and neuropsychometric evaluation at regular intervals. Repeat scans were performed in all subjects who completed 52 weeks of treatment. Volumetric changes from baseline to follow-up in MRI scans were evaluated using both regional volume analysis and voxel-based morphometric analysis.

**Result:** MRI analysis demonstrated a slower decline of temporal lobe volume and total grey matter volume in liraglutide-treated patients compared to the placebo group. Voxel-based morphometry (VBM) analysis demonstrated that liraglutide-treated participants showed a slower reduction in whole cortical grey matter, frontal, temporal and parietal lobe volume in participants treated with liraglutide compared to placebo. This was associated with slower decline in cognitive function.

**Conclusion:** These findings highlight the potential of GLP-1 analogues in the treatment of Alzheimer's disease.

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