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New drug candidate targeting synaptic resilience well tolerated in Alzheimer's patients

April 3, 2025

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A small clinical trial suggests that a new type of drug may be safe for people with Alzheimer's disease and could potentially mitigate some of the brain damage caused by the condition. Findings from the NIA-funded study, published in *Nature Medicine*, support further research to assess the drug's long-term safety and effectiveness.

The drug, known as LM11A-31, is designed to block the activity of a protein receptor called p75 neurotrophin, which can contribute to the disconnection of neurons. This receptor, found throughout the brain, can trigger chemical signals that either protect or harm neurons. By targeting this receptor, LM11A-31 aims to promote neuronal survival and strengthen brain connections. Previous studies have indicated that the p75 receptor and its chemical pathways may play a role in Alzheimer's.

This Phase 2a clinical trial primarily focused on the safety of LM11A-31 in 242 participants with



mild to moderate Alzheimer's. Participants were randomly assigned to one of three groups: a placebo group, a group receiving 200 mg of LM11A-31, or a group receiving 400 mg. Each participant took two pills daily for 26 weeks.

Experts from the study's Data Safety Monitoring Board reviewed the primary outcomes (main results) and concluded that the drug is safe and tolerable enough for larger trials. Twelve participants in the 400 mg group and three in the 200 mg group left the trial early, compared to five in the placebo group. In the 400 mg group, most participants left due to nonserious side effects, particularly diarrhea, which prompted two participants to withdraw. In the 200 mg group, none of the withdrawals were due to diarrhea, but some participants left because of other mild side effects. Serious side effects, such as higher white blood cell levels (eosinophilia), led to three participants being permanently removed from the study — two in the 400 mg group and one in the 200 mg group.

Although the study was focused on safety and tolerability, participants also completed cognitive tests to begin to explore potential effects. Results showed no significant difference between the drug and placebo groups in cognitive performance. However, further exploratory analyses revealed that participants taking LM11A-31 had lower levels of Alzheimer's-related biomarkers in cerebrospinal fluid, such as beta-amyloid, tau, synaptosomal-associated protein 25, and neurogranin, compared to those who received the placebo. Brain scans also showed smaller reductions in gray matter and glucose metabolism in key brain regions among those taking the drug.

Overall, these findings suggest that targeting the p75 neurotrophin receptor with LM11A-31 could counteract some of the brain damage caused by Alzheimer's. The results indicate that LM11A-31 is safe for use and warrants further testing in larger clinical trials to better assess the potential to slow or prevent Alzheimer's-related neurodegeneration.

This research was funded in part by NIA grants 1R01AG051596, P30AG072980, R01AG053798, and R35AG71476.

NIA leads NIH's systematic planning, development, and implementation of [research milestones](#) to achieve the goal of effectively treating and preventing Alzheimer's and related dementias. This research is related to Milestone 4.U, "Incorporate VCID mechanisms derived from basic science animal/human studies into the design of human trials targeting prevention or treatment of dementia/mild cognitive impairment."

Reference: Shanks HRC, et al. [P75 neurotrophin receptor modulation in mild to moderate Alzheimer disease: A randomized, placebo-controlled phase 2a trial](#). *Nature Medicine*. 2024;30(6):1761-1770. doi: 10.1038/s41591-024-02977-w.

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