



Semorinemab, an anti-tau monoclonal antibody, did not improve functional and global outcomes in patients with mild-to-moderate Alzheimer's disease (the phase II Lauriet study) | 1

Alzheimer's disease (AD) is characterized by the accumulation of extracellular amyloid- β peptide-containing plaques and intracellular neurofibrillary tangles containing the tau protein aggregates in the brain neocortex. The assessment of tau levels in cerebrospinal fluid (CSF) or plasma, and tau positron emission tomography (PET) imaging studies revealed an increase in protein tau levels with disease progression. Therefore, anti-tau immunotherapies were proposed as a possible treatment for AD. In the Lauriet multicenter, randomized, double-blind, placebo-controlled, phase II study, the effect of semorinemab, an anti-tau monoclonal antibody, was evaluated in patients with mild-to-moderate AD.

Semorinemab is a humanized IgG4 monoclonal antibody that targets the N-terminal domain of tau protein and binds to all known isoforms of full-length tau. The original hypothesis was that semorinemab could prevent cell-to-cell spread of tau. The experimental studies demonstrated that the murine version of semorinemab reduced *in vitro* tau-related toxicity in cell culture and *in vivo* tau accumulation in tau-transgenic mice.

In the phase I study, semorinemab demonstrated dose-dependent target engagement and a favorable safety profile in patients with mild-to-moderate AD. The phase II Lauriet study was therefore designed to address the primary research question of whether the treatment with semorinemab could slow cognitive and functional decline in patients with mild-to-moderate AD.





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About the study

The Lauriet study is a multicenter, randomized, double-blind, placebo-controlled, phase II study conducted at 49 locations across the United States and Europe.

The study enrolled two cohorts. Cohort 1 comprised all subjects who completed the originally planned 48 weeks of blinded treatment before the protocol amendment implementation and/or had not missed any blinded study drug doses. Cohort 2 included all subjects who had missed at least one dose of the blinded study drug because of the pandemic. The duration of treatment was extended to 60 weeks only for cohort 2.

A centralized system randomly assigned mild-to-moderate AD patients to receive either semorinemab 4500 mg or placebo intravenously. The first three drug doses were administered biweekly, followed by every four-week dosing. Participants in cohort 2 who missed two or more consecutive study drug doses during the placebo-controlled period resumed dosing with a biweekly regimen for the first three doses, with subsequent doses every four weeks.

There were three predetermined populations: a) the modified intent-to-treat population (mITT) that included all participants who received the study drug, had a baseline assessment and at least one valid post-baseline assessment), b) the restricted mITT that included all participants from the mITT population who missed no more than 1 dose of the study drug compared to the total number, and c) the safety evaluable population that included all participants who received at least one dose of the study drug.

The co-primary efficacy endpoints were the change in the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog11) and the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) scale from baseline to week 49 for both cohorts and week 61 for cohort 2. The ADAS-Cog11 is an 11-item cognitive scale used to assess cognitive domains most often affected by AD (lower scores indicate better cognitive performance). The ADCS-ADL scale quantifies the performance of activities of daily living in patients diagnosed with AD and is administered to the care partners (higher scores indicate better function). The secondary efficacy endpoints were changes in the Mini-Mental Status Examination (MMSE) and the Clinical Dementia Rating-Sum of Boxes (CDR-SB). Safety, pharmacokinetics, and pharmacodynamic effects were also evaluated.

Optional lumbar punctures were performed in a subset of participants at baseline and at week 49 (cohort 1) or week 61 (cohort 2). Semorinemab total tau, ptau181, ptau217, and N-



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terminal tau were measured in the CSF samples.

Results

267 individuals received at least 1 dose of semorinemab or placebo. The mITT population consisted of 238 participants. Approximately one-third of the mITT participants were assigned to cohort 2. According to CDR-GS, 90% of the mITT population was classified as having mild AD, and 10% as having moderate AD.

Participants treated with semorinemab 4500 mg for 48 or 60 weeks had a significantly slower cognitive decline measured by the cognitive outcome measure ADAS-Cog11 than those treated with placebo. Semorinemab significantly reduced cognitive decline at 49 weeks (cohorts 1 and 2) by 42.2% based on the ADAS-Cog11 compared to placebo. Most of the benefits seen with semorinemab on the ADAS-Cog11 appear to be in the memory domain, specifically, the word recognition items.

However, semorinemab did not affect other measures of functional (ADCS-ADL, co-primary endpoint), global (CDR-SB, secondary endpoint), or cognitive decline (MMSE, secondary endpoint). These findings were consistent at week 61 (cohort 2 only), and in the restricted mITT population at week 49 (cohorts 1 and 2).

Semorinemab was safe and well-tolerated. The most frequently reported systemic adverse events were chills, dizziness, headache, and hypertension/blood pressure increase, evaluated as grade 1 or 2 in severity.

Plasma total tau and plasma ptau217 levels increased more than 20 times in participants treated with semorinemab compared to baseline. The levels for both tau species remained elevated throughout treatment. However, total tau, ptau181, and ptau217 were significantly reduced in CSF samples of AD patients treated with semorinemab, but not with placebo. According to the authors, these data suggest that semorinemab can reach the brain and modulate tau species which are considered disease-relevant.

Conclusion

This study showed that treatment with semorinemab, a humanized IgG4 monoclonal antibody that targets the N-terminal domain of the tau protein, had a modest positive cognitive effect in patients with mild to moderate AD, but, did not result in improved functional or global outcomes. The authors suggested that the lack of functional or global



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improvement suggests that semorinemab may not meet established regulatory standards for a disease-modifying drug for AD. Nevertheless, these results may warrant further investigation of semorinemab or other anti-tau therapies in this patient population.

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