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New data and developments set to shift dynamics in the anti-Aβ MAb space

Market Trend Summary

Nakka Meher Baba Kumar | November 2024

Modified titration puts Kisunla's ARIA risk on par with Leqembi's

Eli Lilly recently presented data from the **TRAILBLAZER-ALZ 6** trial demonstrating that a **modified titration** regimen for Kisunla (donanemab)—shifting one vial of the drug from the first dose to the third dose—resulted in **lower ARIA rates** compared with the drug's approved titration regimen:

- **ARIA-E rates from TRAILBLAZER-ALZ6 are comparable to those from the CLARITY-AD trial of Leqembi (14% vs. 12%, respectively):** Total ARIA (21% vs. 24%), concurrent ARIA-E and -H (10% vs. 8%) and superficial siderosis (7% vs. 6%) were also comparable. One patient in the modified titration arm who developed ARIA-E died after receiving tissue-type plasminogen activator treatment for stroke-like symptoms.
- **Biomarker efficacy was comparable to the standard dosing regimen; cognitive / functional data are not yet available:** Reduction of amyloid plaques and P-tau217 was similar in both regimens. An evaluation of the impact of the new titration regimen on cognitive decline is ongoing.

Clarivate's takeaways

Once reflected in Kisunla's label, the new titration regimen will **reduce a competitive disadvantage for Kisunla compared with intravenous Leqembi**. Leqembi's better ARIA profile was a positive differentiator for the risk-averse Alzheimer's disease (AD) prescriber base, which had the potential to offset Kisunla's dosing advantages (i.e., Q4W administration, possibility for finite dosing) and, in the eyes of some key opinion leaders, its modestly superior efficacy data.

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The road ahead for Kisunla and Leqembi

- **Regulatory submission:** Eli Lilly expects to submit data supporting the modified titration regimen to global regulators for a potential label update for Kisunla.
- **Overcoming regulatory headwinds in Europe:** Doubts raised by an initial rejection of Leqembi by the EMA's CHMP based on its risk benefit balance extended to Kisunla, especially given the latter's higher cross-trial rates of ARIA. However, in a rare move, the CHMP reversed course and approved Leqembi for early AD patients who have one or no copies of the APOE4 gene variant. Given the similar ARIA profile of Kisunla's new titration regimen to that of Leqembi's, we expect that Kisunla will also be approved by the CHMP.
- **European reimbursement hurdles:** Following approvals by the MHRA, the U.K.'s NICE initially decided against reimbursing Leqembi and Kisunla, pending additional evidence of clinical and cost-effectiveness. Although we expect similar reimbursement challenges in other European markets, we expect acceptable pricing terms will ultimately be established across the region.
- **Subcutaneous (SC) formulations:** Both Eli Lilly and Eisai /Biogen likely view subcutaneous dosing as a lever to expand the market for anti-Aβ MAbs. We expect SC Leqembi and Lilly's SC remternetug to eventually overtake their first-to-market IV formulations.

Roche's trontinemab has best-in-class potential; AbbVie acquires a similar asset

Roche's trontinemab pairs the anti-Aβ MAb gantenerumab with the company's Brainshuttle technology, which leverages transferrin receptor-mediated transport across the blood-brain barrier (BBB), to improve brain penetration and target engagement. A recent interim readout of the ongoing **BRAINSHUTTLE AD** study of trontinemab in early AD patients showed:

- **Rapid clearance of amyloid plaques:** At the highest tested doses, 67-75% of patients achieved amyloid plaque negativity at week 28. Across trials, only ~35% of patients with treated with Kisunla achieved amyloid negativity at a similar time point in its pivotal study.
- **ARIA rates appear low:** Although only interim data are available from the Phase 1/2 trial, ARIA rates in BRAINSHUTTLE AD have been low, with only 3 cases of ARIA-E in 155 patients evaluated. However, one patient in the study with baseline superficial siderosis died due to cerebral macrohemorrhage, leading to a protocol amendment excluding patients with superficial siderosis at baseline from entering the study.

Clarivate's takeaways

Based on the available data, trontinemab appears to offer **more rapid amyloid plaque clearance and the potential for a superior ARIA risk** profile compared with marketed agents in its class. However, it remains **uncertain whether more rapid clearance of plaques will translate to larger clinical effect sizes** over an 18-month trial—which would be the surest lever to drive preferential uptake of trontinemab over competitors.

The road ahead for trontinemab

- **Phase 3 trial to begin in H2 2025**: A readout is expected in 2028.
- **Accelerated approval is possible:** Roche may consider an accelerated approval pathway, as the FDA is willing to accept amyloid reduction as a surrogate for clinical outcomes.
- **A subcutaneous version is likely:** The company expects to investigate a subcutaneous formulation of the drug in the future.

AbbVie to acquire Aliada Therapeutics for ALIA-1758

- **Transferrin receptor-mediated BBB transport:** ALIA-1758 uses a similar strategy to trontinemab to enhance brain penetration.
- **Target is similar to Lilly's Kisunla:** ALIA-1758 targets N3pG Aβ, a pyroglutamate form of Aβ aggregated in amyloid plaques. A Phase 1 clinical trial ongoing.

Eli Lilly and Eisai collaborating on BBB transport technologies

- Eli Lilly has partnered with Qinotto for its BBB platform.
- Eisai partnered with BioArctic on new drug candidate utilizing latter's BrainTransporter technology.

About the authors

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Clarivate coverage of Alzheimer's disease

- Disease Landscape & Forecast: Alzheimer's disease (G7), providing comprehensive market intelligence insights
- Epidemiology: For various population segments of Alzheimer's disease across the G7 and emerging markets
- Current Treatment: Physician Insights (US), exploring prescribing trends among U.S. neurologists and PCP’s
- Current Treatment: Treatment Algorithms | Alzheimer's disease; Neuropsychiatric therapies in Alzheimer’s disease (US), exploring prescribing trends via claims data analysis
- Unmet Need: Early Alzheimer's disease; Agitation in Alzheimer's disease (US / EU), including an Excel-based target product profile simulator
- Access & Reimbursement: Alzheimer's disease (US), providing insights on the impact of payer policy on prescribing behavior in Alzheimer's disease

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