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AAIC 2023 – Lilly downplays tau testing needs

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But subgroup analyses from Trailblazer-Alz 2 show that earlier is better for donanemab.

When Lilly reported topline pivotal data on donanemab in May one question was whether tau testing would be needed in clinical practice, given a better performance in patients with intermediate tau levels versus the whole trial population. Lilly today insisted that such testing was not necessary to determine who could get the therapy.

“We stratified our patients by tau, but we didn’t find a group of patients that isn’t in everyone else’s trial,” Mark Mintun, the group’s vice-president of neuroscience R&D, said during a press briefing ahead of presentation of the full phase 3 Trailblazer-Alz 2 data today at the Alzheimer's Association International Conference. Tau testing could be “useful”, he added, “but I don’t think it’s at the level of being a mandatory step”.

Still, the full data, which were simultaneously published in Jama, show just how strongly the result was driven by the intermediate tau group. In a post-hoc analysis of high tau patients alone, there was a merely a trend in favour of donanemab on the trial’s primary endpoint, the iADRS, with a 6% relative slowing versus placebo.

On the key secondary endpoint of CDR-SB a 21% relative slowing did hit significance, Lilly said – but the result was less impressive than the 36% slowing previously reported in the intermediate tau population. In its earlier data release Lilly combined the intermediate and high tau cohorts, but did not split out high tau.

Despite these results the company does not believe that high tau patients should be denied therapy with the anti-amyloid antibody. “It can’t tell you whether this person will have a good response or not,” said John Sims, senior medical director at Lilly. “It gives you a sense of probability… but you’re still going to treat the patient and give them a chance.”

Notably, the phase 3 Clarity AD of Eisai and Biogen's Leqembi did not stratify by tau status; that product has full approval in Alzheimer’s patients without a need for tau testing.

Earlier the better

Tau status is a reflection of disease progression, and Lilly today presented subgroup analyses showing improved results in patients under 75 years of age, and with mild cognitive impairment, among the intermediate tau group.

“One of most important components of this data is the earlier you get to patients in their clinical decline, it

appears the better results [are] we see with this drug," said Mintun.

Getting to patients earlier will require better diagnosis, and on this point he added: "We think it's really important to have a blood test that can help doctors diagnose Alzheimer's disease. There are some tests coming out. We believe there need to be more of them and they need to be reimbursed."

Selected subgroup analyses in intermediate tau patients in Trailblazer-Alz 2 (NCT04437511)		
Endpoint	**iADRS**	**CDR-SB**
Intermediate tau pts (n=1,182)	35%	36%
- Mild cognitive impairment pts (n=214)*	60%	46%
- Mild dementia pts (n=534)*	38%	30%
- Pts <75 (n=542)**	48%	45%
- Pts ≥75 (n=551)**	25%	29%
*Note: results at 18 months, all relative slowing vs placebo; *prespecified subgroup analysis; **post-hoc subgroup analysis. CDR-SB = Clinical Dementia Rating-Sum of Boxes; iADRS = integrated Alzheimer's Disease Rating Scale. Source: company release, AAIC & JAMA.*		

One group that did not do so well on efficacy was ApoE4 homozygotes. This group also had a 41% rate of Aria-E, higher than the 24% rate seen across the trial.

This echoes what was seen with Leqembi, where there was a 45% rate of Aria-E in ApoE4 homozygotes in Clarity AD, although a lower 13% rate of Aria-E overall.

More details were also available on three donanemab-related deaths in the trial: one patient had the bleeding disorder superficial siderosis at baseline, which Lilly flagged as another risk factor for Aria-E.

None of the patients who died were receiving anticoagulants; two were ApoE4 heterozygotes, while one was a non-carrier.

Retreatment?

One unique aspect of donanemab is that it is designed to be given until patients are clear of plaque – in Trailblazer-Alz 2, patients who had a certain level of plaque clearance were switched to placebo. Around half of patients were able to come off and the treatment effect continued to widen even after switching.

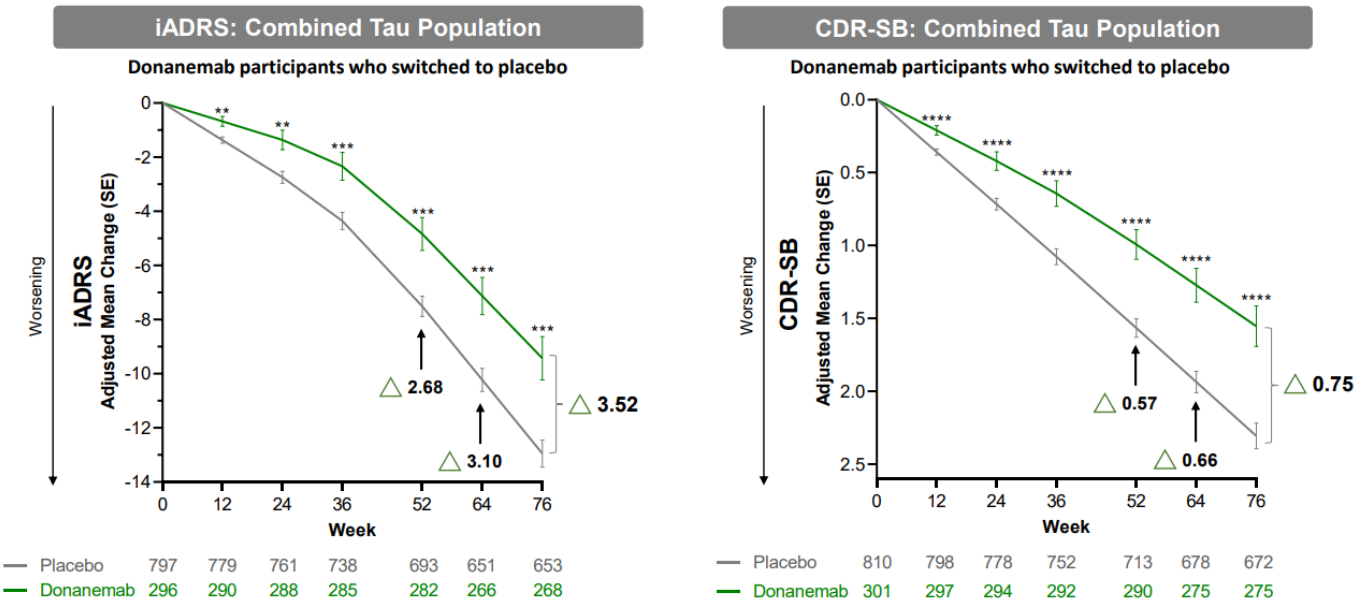
On the question of whether patients might eventually need retreatment, Mintun said: "We're clearing out amyloid plaque that's accumulated over 20 years. It doesn't come back with any sort of vengeance. It will take years before it builds back up to some sort of level that starts accelerating disease."

That will be a consideration for the future. For now, questions around which patients will be most suitable for therapy remain more pressing. Lilly has now filed donanemab and expects an FDA decision on approval by the year-end.

This story has been updated following a Lilly investor call.

Treatment Effect Continues to Widen Even After Participants are Switched to Placebo Based on 6 or 12 Month PET Scan

Mean time in trial prior to switch to placebo for these participants: 47 weeks



iADRS and CDR-SB used the NCS model with 2 degrees of freedom adjusted for basis expansion terms (two terms), basis expansion term-by-treatment interaction, and covariates for age at baseline, pooled investigator, baseline tau level, and baseline acetylcholinesterase inhibitor/memantine use. Participants that did not stop treatment were also included in the model but are not plotted here. Nominal P-values: ** P<0.01, *** P<0.001, **** P<0.0001. Abbreviations: CDR-SB = Clinical Dementia Rating – Sum of Boxes; iADRS = Integrated Alzheimer's Disease Rating Scale; n = number of participants; SE = Standard Error; SD = standard deviation; w = weeks

Source: AAIC & company presentation.