Evaluate Vantage

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Cortexyme and Lilly remind investors that Alzheimer's failures happen

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While Lilly has thrown in the tau towel with zagotenemab, Cortexyme still sees reasons to press on with atuzaginstat.

Cortexyme's theory that hitting the cause of gum disease could treat Alzheimer's had always looked like a long shot. So perhaps the most surprising thing about the failure of the phase 2/3 Gain study of atuzaginstat, announced after-hours yesterday, was that it surprised investors.

The company's stock opened down 68% this morning on the news, but the group is not done with atuzaginstat yet, having found a subgroup to pursue. However, signs of liver toxicity could scupper the project even if lack of efficacy does not.

Meanwhile, the tau hypothesis took another blow yesterday with the mid-stage failure of Lilly's anti-tau antibody zagotenemab, slipped out during third-quarter results. With several other flops in the tau space this year it will be a nervous time for the host of other groups betting on this mechanism.

Gingipain pain

Cortexyme's atuzaginstat, or COR388, is an oral inhibitor of gingipains, enzymes produced by and needed for survival of *Porphyromonas gingivalis*, the bacterium involved in gum disease. The company reckons that *P gingivalis* infection causes Alzheimer's, by triggering the release of amyloid and promoting inflammation.

This theory now looks in doubt after the 643-patient Gain study failed to show a difference between atuzaginstat and placebo on its co-primary endpoints, Adas-Cog11 and ADCS-ADL.

Cortexyme is clinging to results in a prespecified subgroup of 242 patients with detectable levels of *P gingivalis* in their saliva. Here the higher dose of atuzaginstat, 80mg twice daily, led to a 57% slowing of cognitive decline, as measured by Adas-Cog11. Cortexyme cited a nominal p value of 0.02, but this finding can only be considered exploratory.

No benefit was seen in this subgroup on the ADCS-ADL co-primary.

During a bizarrely upbeat conference call yesterday, Cortexyme's chief executive officer, Casey Lynch, said the company was "poised to execute very quickly" on a confirmatory study in patients with *P gingivalis*.

Still, execs did not rule out filing for early approval based on the Gain data. Cortexyme is already in the process

of scheduling a meeting with the FDA.

The regulator might have something to say about atuzaginstat's safety profile, though. The open-label portion of Gain has been on clinical hold since February because of adverse liver events, and yesterday's data were hardly reassuring on this point.

Gain found liver enzyme elevations above three times the upper limit of normal in 7% and 15% of patients receiving atuzaginstat 40mg and 80mg twice daily, respectively. Two patients in the 80mg arm also had concomitant bilirubin elevations without an alternative explanation.

This could put atuzaginstat at risk of meeting Hy's law, suggesting risk of fatal drug-induced liver injury, according to the FDA's definition. In its defence, Cortexyme said the liver enzyme increases were not clinically significant, and that both patients with bilirubin increases recovered fully with no long-term effects.

The group reckons it can combat these issues with dose titration, but the path forward for atuzaginstat looks questionable.

Tau takedown

Elsewhere, Lilly has called it quits on anti-tau antibodies after zagotenemab fell short in its phase 2 study.

The group now reckons this is the wrong approach, given that the relevant tau is mostly inside cells, where antibodies cannot reach. If true this would be bad news for the various groups developing anti-tau antibodies, listed in the table below.

But this is only the latest setback in this space, with the likes of Biogen's gosuranemab and Abbvie's ABBV-8E12 also failing this year. And a recent success with AC Immune and Roche's semorinemab was far from emphatic.

Still, Lilly is not out of tau completely, and yesterday highlighted an oral O-GlcNAcase inhibitor, LY3372689, which recently went into phase 2.

Selected tau-targeting projects in clinical development			
Project	**Company**	**Description**	**Note**
Phase 3			
LMTM/ TRx0237	Taurx Pharmaceuticals	Tau aggregation inhibitor	Lucidity completes Mar 2022
Phase 2			
Semorinemab/ RG6100	Roche/AC Immune	Anti-tau MAb (targets N-terminus)	Sep 2020 failed Tauriel in prodromal/mild Alz Sep 2020; Aug 2021 met one co-primary in Lauriet in mild/moderate Alz
Zagotenemab/ LY3303560	Lilly	Anti-tau MAb (targets N-terminus)	Oct 2021 failed early Alz study
LY3372689	Lilly	O-GlcNAcase inhibitor	Early Alz study completes May 2024
Bepranemab/ UCB0107	UCB/Roche	Anti-tau MAb (targets central region)	MCI/mild Alz study, first data due H1 2025
AADvac1	Axon Neuroscience	Anti-tau vaccine	Further development planned despite failure of ph2 Adamant trial
Phase 1/2			
BIIB080/ IONIS-MAPTRx	Biogen/Ionis	Tau antisense oligonucleotide RNAi therapeutic	Mild Alz study; part 1 showed safety/tolerability & tau lowering, part 2 ongoing
ACI-35.030	AC Immune/J&J	Anti-tau vaccine	Interim data from early Alz study reported Feb 2021; high-dose data due Q4 2021
JACI-35.054	AC Immune/J&J	Anti-tau vaccine	Early Alz study; higher dose initiated
Phase 1			
PNT001	Pinteon Therapeutics	Anti-tau MAb (targets cis-pT231 tau)	Healthy volunteer study reported Feb 2021; acute brain injury study completes Jan 2023
BIIB076	Biogen/Eisai	Anti-tau MAb (targets central region)	Volunteer/Alz study completed Mar 2020; still in Biogen's pipeline
E2814	Eisai	Anti-tau MAb (targets microtubule binding region)	Volunteer study completed Sep 2021; inherited Alz study completes Apr 2024; selected for Dian-Tu tau study Mar 2021
BEY2153	Beyondbio	Beta-amyloid & tau aggregation inhibitor	Volunteer study completes Oct 2021
ASN51	Asceneuron	O-GlcNAcase inhibitor	Volunteer/Alz study completes Jan 2022
Lu AF87908	Lundbeck	Anti-tau MAb (targets C-terminus)	Volunteer/Alz study completes Jul 2022
PRX005	Prothena/Bristol Myers Squibb	Anti-tau MAb (targets microtubule binding region)	Ph1 began & Bristol opt-in June 2021
Source: Evaulate Pharma & clinicaltrials.gov.			

The table in this story has been updated to include Asceneuron's ASN51.