Evaluate Vantage

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Alzheimer’s catalysts round off a year dominated by Biogen

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Clinical data near for Alzheimer’s antibodies from Roche and Lilly, while Cortexyme and Biohaven test small molecules.

The path to tackling Alzheimer's disease is littered with failures, but when a company generates even early hints of promise the rewards are high. Take tiny Inmune Bio, whose shares rocketed 78% this week on phase Ib data with XPro1595, a TNF inhibitor said to decrease neuroinflammation.

A number of other developers are lining up Alzheimer’s readouts this year, with numerous clinical catalysts on the horizon. This includes data from big players like Roche and Lilly, as well as smaller groups like Biohaven and Cortexyme, which could also experience big swings in share prices on their results.

News from AC Immune this week is a case in point: an announcement that the group was starting to test a high dose of its anti-tau vaccine ACI-35.030 pushed its stock 19% higher. The history of development in this space suggests that little can be read into such a move, however, and investors would be wise to wait for data before assuming progress.

Targeting tau is one of the dominant mechanisms found in the Alzheimer's pipeline, alongside beta-amyloid approaches, although doubts remain about the utility of both techniques. Tau is a protein that largely accumulates inside neurons, and how to best to clear it from the brain remains an open question.

A major test of the tau approach is near, however: **Roche** and **AC Immune's semorinemab** could yield data in the coming months. The primary completion date of the phase II Tauriel study was in June. The study, in 460 prodromal to mild subjects, tests three active doses versus placebo for 16 months; the primary endpoint is efficacy at 18 months.

Wolfe Research suggests that the trial is large and long enough to potentially generate a signal of efficacy, though it might not be sufficiently powered to hit significance. At a minimum, the study will need to show a reduction of tau burden in the brain.

Abbvie and Biogen have shown how tricky targeting tau can be: development of their own anti-tau MAbs, ABBV-8E12 and gosuranemab respectively, was scrapped in a different tauopathy, progressive supranuclear palsy, owing to a lack of efficacy. Development of these projects in Alzheimer’s continues, highlighting the sizeable risks and rewards.

Beta amyloid

Roche also has skin in the beta-amyloid game, and early data from a next-generation beta-amyloid MAb are expected before the end of the year. **RG6102** is a version of gantenerumab formulated in “brain shuttle” technology, which is said to increase antibody concentrations in the brain.

The trial, in 34 healthy men, is primarily evaluating safety. Secondary measures include CSF antibody concentrations three or five days after dosing, and anti-RG6102 antibodies up to two months after.

Data are also due from the open-label portion of the Scarlet Road trial testing **gantenerumab** in its original form. The study has had a chequered past and in 2014 it was was terminated early owing to lack of interim efficacy. Prodromal patients had initially been given 105mg or 225mg once a month.

A post-hoc analysis suggested that there had been a trend towards a benefit in fast progressors, and the study was converted to an open-label extension with patients titrated up to 1,200mg.

Roche will most hope that, if it can dose high enough and for long enough, an efficacy signal might be teased out, as was seen with aducanumab (*Biogen stacks the deck but the path forward is no clearer in Alzheimer’s, December 6, 2019*). The Swiss group is effectively testing this theory in the pivotal Graduate 1 and 2 trials, with patients titrated up to 1,020mg, but data from these studies are not expected until 2022 at the earliest.

Elsewhere on the beta-amyloid front, **Lilly’s donanemab** targets a form of the protein that is aggregated in amyloid plaques. The Trailblazer-Alz study, in 266 patients with early disease, should report early next year.

MAbs aside

An interim analysis of **Cortexyme's** Gain trial is due in the fourth quarter, and this futility test could determine the future of the group’s **atuzaginstat,** which is taking a completely different approach to cracking the Alzheimer’s puzzle.

The company has hypothesised that *Porphyromonas gingivalisin*, the bacterium responsible for gingivitis − gum disease − can infect the brain and cause Alzheimer’s. It hopes that atuzaginstat, a first-in-class gingipain inhibitor, will neutralise gingipains in the brain, protect neurons and reduce inflammation, preventing further cognitive decline.

The 570-patient phase II/III Gain trial, in mild to moderate Alzheimer’s, will compare two doses of atuzaginstat against placebo, with the interim analysis conducted after approximately 100 patients in each of the three study arms have completed six months of treatment.

If Cortexyme passes this vital test topline results are expected in the fourth quarter of 2021. The company's weighty $1.3bn market cap rests entirely on the fate of the project.

Results are expected in the first quarter of 2021 for **Biohaven’s troriluzole,** another move away from the amyloid hypothesis. Troriluzole, which is thought to work by reducing levels of glutamate in synapses, is being studied in the T2 Protect AD trial.

There is some evidence for the role of glutamate in Alzheimer's: Lundbeck's Namenda, which is approved for Alzheimer's, targets the NMDA glutamate receptor. And troriluzole has passed the first hurdle, an interim futility and safety analysis after 100 patients had completed 26 weeks' treatment. The project had to demonstrate numerically greater benefit over placebo on at least one of two prespecified criteria: cognitive function as measured by Adas-Cog, or MRI-assessed hippocampal volume.

The project's turbulent development history does not raise hopes, however. In February it flunked a pivotal study in general anxiety disorder, failing to beat placebo, a feat it repeated in June in a phase II/III trial for obsessive compulsive disorder. There was also an earlier failure in spinocerebellar ataxia.

By far the biggest event on the horizon for this field, however, is the US review of Biogen’s aducanumab; confirmation that the FDA has accepted the filing for consideration is keenly awaited. Considering the project's questionable efficacy profile, reassurance that regulators are willing to look leniently on Alzheimer's treatments could give the field as much of a boost as breakthrough data.

Selected upcoming Alzheimer's disease readouts in 2020 and early 2021						
Company	**Project**	**Mechanism**	**Trial (AD setting)**	**AD Setting**	**Estimated timing**	**Primary endpoint(s) vs baseline**
Roche/AC Immune	Semorinemab (RG6100)	Anti-Tau MAb	Tauriel	Prodromal/mild (ph2)	Primary completion was Jun	CDR-SB: 73 wk
Roche	Gantenerumab (brain shuttle) / RG6102	Anti-Aβ MAb	NCT04023994	Volunteers (ph1)	Primary completion Aug	Adverse events
Roche	Gantenerumab	Anti-Aβ MAb	Scarlet Road	Prodromal (ph3)	Primary completion Aug	CDR-SB: 104 wk
Cortexyme	Atuzaginstat (COR388)	Gingipain inhibitor	Gain	Mild to moderate (ph2/3)	Interim analysis due Q4; completion late 2021	Adas-Cog 11: 48 wk CDR-SB: 48 wk
Lilly	Donanemab (LY3002813)	N3pG-Aβ MAb	Trailblazer-Alz	Early symptomatic (ph2)	Data Jan 2021	iADRS: 18 mth
Biohaven	Troriluzole	Glutamate modulator	T2 Protect AD	Mild to moderate (ph2/3)	Data due Q1 2021	ADAS-Cog 11: 48 wk CDR-SB: 48 wk

CDR-SB; Clinical Dementia Rating Scale Sum of Boxes, Adas-Cog 11; Assessment Scale-Cognitive Subscale 11, iADRS; Integrated Alzheimer's Disease Rating Scale. Sources: EvaluatePharma, company statements & clinicaltrials.gov.

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