Evaluate Vantage

September 26, 2017

Axovant scraps Alzheimer’s bid – now back to the amyloid hypothesis

Jacob Plieth

Alzheimer’s disease takes another scalp. Intepirdine has failed to show any benefit in mild to moderate patients in combination with Aricept, prompting Axovant to cancel all efforts in Alzheimer’s.

The failure prompted investors to throw Axovant out of the billionaire’s club, with its shares tumbling 74% in early trading today. Alzheimer’s looks like a quiet field for some time to come – the next major readouts will be for agents following the divisive amyloid hypothesis, which has had more than its share of setbacks (see table below).

Done with Alzheimer's

Intepirdine’s Mindset study missed the co-primary endpoints of improvement over baseline in ADAS-Cog and ADCS-ADL endpoints. Intepirdine was combined with Aricept and compared against Aricept alone in this trial in mild and moderate disease.

A secondary endpoint, clinician interview-based impression of change plus caregiver interview, showed an improvement of 0.12 points and a nominal p value of 0.02, but this sole glimmer of hope was not enough to convince Axovant to press on. “We do not plan to further develop intepirdine for Alzheimer’s disease,” Axovant's chief executive, David Hung, said unequivocally.

More equivocal was the reluctance to terminate all work on the asset, which the group is testing in Lewy body dementia in the phase IIb Headway trial due to read out by the end of 2017.

Investors obviously see less promise in that venture, wiping away $1.9bn in market valuation. By comparison Lilly lost more than $8bn in valuation when it finally pulled the plug on its amyloid-beta antibody solanezumab last year. Axovant shares are now less than half the price at which they were in 2015 when the group was spun out of Roivant in an initial public offering.

The writing was probably on the wall for intepirdine when Lundbeck’s similarly acting idalopirdine bombed in phase III earlier this year (*Snippet roundup: Pressure is on for Axovant and Glaxo, February 10, 2017*).

Next up

The twin failures of intepirdine and idalopirdine suggests that blocking the 5-HT6 receptor to stimulate production of the neurotransmitter acetylcholine is not a promising pathway in Alzheimer’s. The main approach has for years been seeking to limit the damage of beta amyloid lesions in the brain, one of the markers of this degenerative disease – yet repeated failure has not dissuaded pharma from persisting here.

The next big readout in Alzheimer’s is likely to be a phase II trial of Biogen and Eisai’s BAN2401, which binds to beta amyloid profibrils. Phase II often leads to success in Alzheimer’s, and Biogen will take a Bayesian approach to statistical analysis of the data, something that could favour responders to increase the odds of success.

12-month data are due for BAN2401 by the year’s end. 2019 looks like a bigger period for Alzheimer’s, when no fewer than three phase III trials of beta amyloid agents estimated to report data, comprising two Bace inhibitors and one beta amyloid antibody in the form of Biogen and Eisai's lead agent aducanumab.

Identifying likely responders and improving the potency of these agents represent the primary progress in Alzheimer's research, and given the unmet need even a small edge could be rewarded with approval and substantial sales. It is disappointing that there do not seem to be signs of companies testing innovative pathways; perhaps this will only come if amyloid beta is declared an irredeemable failure.

Late-stage trials in Alzheimer's					
Project	**Company**	**Status**	**Mechanism**	**Trial ID**	**Data?**

BAN2401	Biogen/Eisai	Phase II	Anti-beta-amyloid protofibril MAb	Early AD; NCT01767311	12mth readout YE17, 18mth data Jul 2018
Azeliragon*	vTv Therapeutics	Phase III	Receptor for advanced glycation endproducts (RAGE) antagonist	Steadfast; mild AD; part A; NCT02080364	Early 2018
Elenbecestat (E2609)	Eisai/Biogen	Phase II	Bace inhibitor	Mild to moderate AD; NCT02322021	Mar 2018
Azeliragon	vTv Therapeutics	Phase III	Receptor for advanced glycation endproducts (RAGE) antagonist	Steadfast; mild AD; part B; NCT02080364	Late 2018
Verubecestat (MK-8931)	Merck & Co	Phase III	Bace inhibitor	Apecs; prodromal AD; NCT01953601	Feb 2019
LY3202626	Lilly	Phase II	Bace inhibitor	Navigate-AD; mild AD; NCT02791191	May 2019
AADvac1	Axon Neuroscience	Phase II	Tau vaccine	Adamant; NCT02579252	Jun 2019
Lanabecestat	Astrazeneca/Lilly	Phase III	Bace inhibitor	Daybreak-Alz; mild AD; NCT02783573	Aug 2019
Lanabecestat	Astrazeneca/Lilly	Phase II/III	Bace inhibitor	Amaranth; early AD; NCT02245737	Sep 2019
Aducanumab	Biogen/Eisai	Phase III	Beta-amyloid MAb	Engage; early AD; NCT02477800	Nov 2019
Aducanumab	Biogen/Eisai	Phase III	Beta-amyloid MAb	Emerge; early AD; NCT02484547	Feb 2020
Elenbecestat (E2609)	Eisai/Biogen	Phase III	Bace inhibitor	MissionAD1; early AD; NCT02956486	Jun 2020
Elenbecestat (E2609)	Eisai/Biogen	Phase III	Bace inhibitor	MissionAD2; early AD; NCT03036280	Aug 2020
Crenezumab	Roche	Phase III	Beta-amyloid MAb	Cread; prodromal to mild AD; NCT02670083	Aug 2020
Crenezumab	Roche	Phase II	Beta-amyloid MAb	Preclinical PSEN1 E280A mutation carriers; NCT01998841	Sep 2020
ABBV-8E12	Abbvie/C2N Diagnostics	Phase II	Anti-tau MAb	Early AD;NCT02880956	Dec 2020
Crenezumab	Roche	Phase III	Beta-amyloid MAb	Cread 2; prodromal to mild AD; NCT03114657	Oct 2021
		Phase		A4; preclinical	

Solanezumab	Lilly	Phase III	Beta-amyloid MAb	AD; NCT02008357	Jul 2022
JNJ-54861911	Johnson & Johnson/Shionogi	Phase II/III	Bace inhibitor	Early; at-risk population; NCT02569398	Apr 2023
Gantenerumab or solanezumab or JNJ-54861911	Washington Uni Med School with collaborators incl. Lilly and Roche	Phase II/III	Beta-amyloid MAbs	DIAN-TU; early-onset AD; NCT01760005	Sep 2023
CAD106 + CNP520	Novartis	Phase II/III	Beta-amyloid vaccine	Generation S1; at-risk population; NCT02565511	May 2024
CNP520	Novartis/Amgen	Phase II/III	Bace inhibitor	Generation S2; at-risk population; NCT03131453	Jul 2024
*Source: Evaluate Pharma, company reports. *This table has been updated to include Azeliragon.*					

To contact the writer of this story email Jonathan Gardner in Virginia at jonathang-us@epvantage.com or follow @ByJonGardner on Twitter