Evaluate Vantage

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Alzheimer's just BACE instinct for Astra and Lilly

Jonathan Gardner

For all the failure dealt to Alzheimer's disease candidates, the draw of a population forecast to number more than 100 million worldwide by mid-century remains too strong for big pharma to resist. AstraZeneca and Eli Lilly became the latest to advance a risky new project as they announced a massive phase III trial for the beta secretase-targeting agent AZD3293.

The Amaranth trial will enroll 1,500 patients and will not return results until late this decade, which will leave Lilly uniquely exposed to failure risk as its study of solanezumab is also well underway. The fate of Merck & Co's competing beta secretase project MK-8931 will be closely watched by these two partners, as '8931's progress in phase III will be a sign of whether '3293 will be any more successful than shelved projects like Lilly's own LY2811376.

If there are to be any new disease-modifying drugs in Alzheimer's disease in the next decade, the sector needs to hope that applying the prevalent approach of targeting beta amyloid to prevent or slow neuron-damaging amyloid lesions pays off. The main approaches are neutralising beta amyloid directly through antibodies or vaccines, or by inhibiting beta secretase (BACE), an enzyme that cleaves amyloid precursor protein and creates beta amyloid.

The beta amyloid hypothesis has experienced late-stage setbacks in the failure of such agents as Elan's bapineuzumab and Lilly's solanezumab to delay disease progression in many patients – in the latter case, patients with mild disease have seen some benefit, which has prompted Lilly to forge ahead with a new trial.

Roche's crenezumab looks destined for the same scrapheap after phase II readout, although the Swiss group remains very much alive with an 1,800 patient phase III programme for gantenerumab (*Crenezumab fails to live up to its limited billing, July 17, 2014*).

Right drug, right patient

The data from these trials of amyloid beta inhibiting antibodies suggest that selecting the right patient group may be just as important as selecting the right agent in achieving clinical success.

Solanezumab, perhaps the most closely watched project in the Alzheimer's space, will be tested on patients with scores of 20 to 26 on the mini mental state examination (MMSE) in Expedition 3, in the mild range of disease progression. Gantenerumab is in two separate trials, one in mild patients and one in prodromal disease, an even earlier stage of the condition in which activities of daily living are not impaired.

Likewise, AZD3293's patients will need to have an MMSE score of 21-28 before they will be enrolled, and Amaranth and Expedition 3 will have similar-looking populations.

Astra and Lilly trail Merck by two years in getting a beta secretase inhibiting project into phase III, but '3293 should not be underestimated (see table).

Beta secretase agents listed in clinical development			
MK-8931	Merck & Co	Phase III	NCT01953601 NCT01739348
AZD3293	AstraZeneca/Eli Lilly	Phase III	NCT02245737
VTP-37948	Boehringer Ingelheim	Phase I	
E2609	Eisai/Biogen Idec	Phase I	NCT02207790 NCT02222324
TAK-070	Takeda	Phase I	
JNJ-54861911	Johnson & Johnson	Phase I	NCT01978548

Astra itself gave a rosy, non-risk-adjusted peak sales forecast of $5bn – an estimate that came as it was

fending off a hostile takeover bid from Pfizer (*Don’t blame Soriot, he’s just doing his job, May 7, 2014*). Although that was a self-serving manoeuvre, combined with the Pfizer bid it made analysts paid it attention in their forecasts. Analysts from Bank of America-Merrill Lynch now foresee $300m in sales in 2023.

Eli Lilly’s interest in the project is perhaps a more encouraging sign. The Indiana-based group signed a co-development and marketing deal that could be worth up to $500m in milestones to Astra – Lilly is expected to pay the first $50m fee in early 2015. More significantly, Lilly will lead clinical development, which could help the ‘3293 team avoid repeating any mistakes from the solanezumab trials.

That sharing of risk and reward is looking increasingly common for Lilly when it comes to its more expensive late stage ventures, as with its work in diabetes. Given the huge trials and the long lead time necessary to prove an Alzheimer’s agent works, it would not be surprising to see more companies follow Lilly's lead – the history of disappointment may necessitate it.

To contact the writer of this story email Jonathan Gardner in London at jonathang@epvantage.com or follow @JonEPVantage on Twitter