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Spotlight on Axovant after Lundbeck’s Alzheimer’s failure

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The phase III failure of Lundbeck’s idalopirdine is yet another example of just how difficult Alzheimer’s drug development is, and another nail in the coffin for the 5-HT6 antagonist class.

It is therefore likely to be bad news for Lundbeck's rival Axovant, which uses the same approach with its own phase III project intepirdine. While some analysts were adamant that idalopirdine’s stumble was not a bad omen, it is hard to remain optimistic after the second late-stage collapse of a 5-HT6 antagonist this year – the other involved Pfizer’s PF-05212377, which was discontinued in February for lack of efficacy in a phase II trial.

Axovant investors seemed inclined to agree: the company’s stock fell 12% yesterday. Meanwhile, Lundbeck was down as much as 15% today after yesterday's post-market release of data, and its partner Otsuka declined 3%.

The analysts were in accord on one thing: this is likely the end of the road for idalopirdine, which will nevertheless limp on in two more phase III trials. These studies seem unlikely to return positive results after the Starshine trial failed to show a benefit on the primary endpoint, the ADAS-cog score, at either dose of idalopirdine – 30mg or 60mg on top of 10mg of Aricept against Aricept plus placebo.

The project also failed to demonstrate an improvement on secondary endpoints. ABG Sundal Collier analysts were particularly scathing, writing: “We find nothing [in] the announcement to support any sort of optimism around idalopirdine being a potentially approvable drug.”

The ongoing Starbeam study is testing idalopirdine at 10mg or 30mg on top of 10mg of Aricept, while Starbright evaluates 30mg or 60mg in combination with an unnamed acetylcholinesterase inhibitor – the same drug class as Aricept.

Lower dose

Some believe that this relatively low dose could be the reason for idalopirdine’s downfall – necessary because the higher dose used in phase II was linked with liver toxicity.

“We believe that Lundbeck may have simply not been able to dose idalopirdine high enough in the phase III program, which minimizes read-through from today’s failure to Axovant’s Mindset phase III study,” wrote HC Wainwright & Co analysts.

Others were less bullish about intepirdine’s prospects. And the signs pointing to a simpler explanation, that 5-HT6 antagonists just do not work, are mounting up. Even if Axovant succeeds, its drug would only be used to treat the symptoms of Alzheimer’s, in contrast to other projects in development that aim to halt disease progression.

Project	Company	Pharmacology class	2022e sales ($m)
Verubecestat	Merck & Co	Bace 1 inhibitor	1,804
Solanezumab	Eli Lilly	Amyloid beta MAb	1,632
Intepirdine	Axovant Sciences	5-HT6 antagonist	1,224
Aducanumab	Biogen	Amyloid beta MAb	907
Idalopirdine	Lundbeck/OtsukaHoldings	5-HT6 antagonist	756
Crenezumab	Roche	Amyloid beta MAb	524
Lanabecestat	AstraZeneca	Bace 1 inhibitor	43
CAD106	Novartis	Amyloid beta vaccine	29
Gantenerumab	Roche	Amyloid beta MAb	18
AMG 520	Amgen/Novartis	Bace 1 inhibitor	13

One of these potential disease-modifying drugs, Lilly's amyloid beta MAb solanezumab, is set for a phase III readout by the end of the year, which seems to have fuelled a mini-Alzheimer's bubble (*All the elements of an Alzheimer's bubble – but look out for December, September 2, 2016*).

The enthusiasm for new Alzheimer's candidates helped Axovant float for a staggering $315m, and others are still going public, including the Swiss company AC Immune, which began trading today after a $66m IPO.

But the statistics are stark: 123 Alzheimer's assets failed between 1998 and 2014, according to the industry body PhRMA. Any hope that idalopirdine could reverse that trend now looks unfounded, and the chances are that intepirdine will follow in its wake.

Project	Study	Trial ID	Primary completion
Idalopirdine	Starshine	NCT01955161	Reported
Idalopirdine	Starbeam	NCT02006641	Mar 2017
Idalopirdine	Starbright	NCT02006654	Mar 2017
Intepirdine/RVT-101	Mindset	NCT02585934	Oct 2017
Solanezumab	Expedition-3	NCT01900665	Oct 2016

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