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Therapy focus – Private companies in the Alzheimer's spotlight

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Last week's decision by AstraZeneca and Lilly to advance their BACE inhibitor into phase III studies gives the stock market a new late-stage, potentially disease-modifying Alzheimer's programme on which to fixate alongside Lilly's solanezumab and Biogen's aducanumab.

But equity analysts are almost certainly overlooking a number of phase III studies run by lower-profile private companies that read out before the much-hyped outcome of Lilly's Expedition 3 trial of solanezumab, which is expected in December (see table below).

The little known Anglo-Singaporean biotech TauRx, for example, has run two large phase III studies of its Tau aggregation inhibitor TRx0237/LMTX, which will provide sufficient data to seek approval if both are positive. It has already completed the larger of these, in mild-to-moderate patients, and is in the final follow-up of the other, which enrolled mild patients and used a lower daily dose.

Disclosure

As a private entity TauRx has the luxury of deciding how and when to announce the results. It will certainly wait for the outcome of its second study before making any disclosure – so as not to risk confounding the data – but if both studies are positive it might for maximum effect reveal them at the Alzheimer's Association International Conference in July.

Although many stock watchers might be unaware of TauRx it is likely to be more closely followed by the industry, not least because it has what could be the most advanced licensing opportunity in this therapy area.

Other private companies have also managed to afford phase III studies. Archer Pharmaceuticals, a US biotech, has funded an investigator-sponsored phase III trial with the calcium-antagonist nilvadipine, which is due to render results in September. And a third private company, Accera, is running a phase III trial of AC-1204 that could report results late this year; AC-1204 addresses the metabolic defects seen in this disease.

All three compounds therefore have different and potentially complementary mechanisms. TauRx's has been perhaps the most visible, as it has spearheaded a lonely path testing the tau hypothesis, while the industry heavyweights have tended to focus on the more popular beta-amyloid theory.

The latter will be tested again with the outcome of Lilly's Expedition 3 study. There is huge interest in this, despite a low investor expectation of success – probably 20-30%. The study enrolled only mild Alzheimer's patients, after two prior phase III trials, Expedition 1 and 2, failed in mild-to-moderate disease but showed some evidence of benefit in the milder population.

Lilly recently changed the statistical analysis plan for this study to focus on a single primary endpoint of cognition, measured using the ADAS-cog scale (*More sola uncertainty sends Lilly down, March 14, 2016*).

This makes Expedition 3 similar to Biogen's two identical phase III trials with aducanumab, called Engage and Emerge, which also look at changes in cognition but use the CDR-SB score. These will not render results until early 2020 at the earliest, highlighting one of the biggest problems of developing disease-modifying drugs for Alzheimer's, which is the need to run long studies – typically lasting two years – in order to see a separation over control.

Meanwhile, after completing a safety review of the phase II portion of the Amaranth study of the BACE inhibitor AZD3293/LY3314814, Lilly and Astra have just given the formal go-ahead to the large phase III portion, also in mild patients, which could yield data in the latter part of 2019.

A general trend is to try to study all disease-modifying agents in earlier-stage patients, including those with so called prodromal Alzheimer's – which is almost without symptoms – and even in patients simply at elevated risk of developing the condition.

Phase III trials in Alzheimer's diease

Project	Company	N	Design	Type/entry criteria	Tx period	NCT ID	Data
TRx0237	TauRx	700	vs placebo	mild (MMSE 20-26)	78 wks	NCT01689233	Apr-16
TRx0237	TauRx	833	vs placebo	mild to mod (MMSE 14-26)	65 wks	NCT01689246	Apr-16
Nilvadipine/ ARC029	Archer	500	vs placebo	mild to mod (MMSE >12), stable (>3 mos) on ACHEi or memantine	78 wks	NCT02017340	Sep-16
AC-1204	Accera	418	vs placebo	mild to mod	26 wk	NCT01741194	Oct-16
Solanezumab	Lilly	2,100	vs placebo	mild (MMSE 20-26)	104 wks	NCT01900665	Dec-16
Flebogamma	Grifols	350	PEx with albumin +/ IVIG vs sham control	mild to mod	60 wks	NCT01561053	Dec-16
Verubecestat	Merck & Co	1,960	vs placebo	mild to mod, stable (>3 mths) of AChEi or memantine if taken	78 wks	NCT01739348	Jul-17
ALZT-OP1 (cromolyn + ibuprofen)	AZ Therapies	600	vs placebo	early, stable (>12 wks) on AChEi or memantine	72 wks	NCT02547818	Mar-18
Gantenerumab	Roche/ Morphosys	389	vs placebo	mild	104 wks	NCT02051608	Jul-18
Azeliragon	vTv Therapeutics	800	vs placebo	mild (MMSE 21-26), stable (>3 mos) on AChEi or mematine	78 wks	NCT02080364	Mar-18
Verubecestat	Merck & Co	1,500	vs placebo	prodromal, stable (>3mos) on AChEi or mematine if taken	104wks (part I), + up to 260 wks (part II)	NCT01953601	Jul-19
AZD3293/LY3314814	AstraZeneca/ Lilly	2,202	vs placebo	Early (MMSE 20-30)	104 wks	NCT02245737	Aug-19
Aducanumab*	Biogen	1,350	vs placebo	mild (MMSE 24-30), stable (>8 wks) on AChEi or mematine	78 wks	NCT02477800/ NCT02484547	Feb-20
Crenezumab	Roche	750	vs placebo	prodromal to mild (MMSE >22)	100 wks	NCT02670083	Aug-20
CNP520 or CAD106**	Amgen/ Novartis	1,340	CNP520 or CAD106 vs placebo	Risk for the onset of AD	up to 234 wks	NCT02565511	Aug-23

JNJ-54861911	J&J	1,650	vs placebo	asymptomatic, at risk of AD	234 wks	NCT02569398	Apr-23

*Notes: Excludes programmes for non-cognitive aspects of condition, such as agitation; *two identical studies; **two agents tested separately in one study.*

Symptomatic therapies

While the industry's focus has for some time been on the holy grail of a disease-modifying drug, there is some work still on drugs that can achieve symptomatic improvement. These have the advantage of shorter studies, typically 24 weeks in duration.

This year should see the outcome of the first of three phase III studies with Lundbeck's idalopirdine, a 5-HT6 antagonist that falls firmly into this category. It also has an important read-across for what was one of 2015's more controversial IPOs, Axovant, which has a project with the same mechanism, also in phase III.

Alzheimer's remains the industry's most difficult indication, and at the same time one that offers potentially the greatest financial rewards. With some 25 phase III or II/III studies now under way the industry pipeline is probably richer than ever. It would be pleasing if some of this investment translated into therapeutic progress in the field this year.

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