Biotech Daily

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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Actinogen Medical

By TIM BOREHAM

ASX code: ACW

Market cap: $215.7 million

Share price: 12 cents

Shares on issue: 1,797,393,817

Chief executive officer: Dr Steven Gourlay

Board: Dr Geoff Brooke (chair), Dr Gourlay, Dr George Morstyn, Malcolm McComas

Financials (September quarter 2022): revenue nil, cash outflows $3.38 million, cash balance $17.2 million, quarters of available funding: five

Identifiable major holders: Biotech Venture Fund 13.77%, Dr Steve Gourlay 3.7%, Edinburgh University Technology Fund 2.68%, Tisia Nominees (Henderson family) 1.86%, JSC Wealth Management 2.49%.

Actinogen chief Dr Steve Gourlay does not demur on his assessment of the company's lead drug Xanamem, to treat the notoriously difficult Alzheimer's disease.

"This is probably going to be the most successful drug in the world's history because nothing else really works in Alzheimer's and this appears to do the trick," he says.

Dr Gourlay's confidence stems from the drug's success to date in improving the cognition of patients with Alzheimer's disease, which is forecast to be the world's number two killer behind heart disease.

The company is about to launch its biggest clinical effort to date: a phase IIb study enrolling 330 patients with mild to moderate cognitive impairment.

Dr Gourlay rates the trial as having a 70 to 80 percent chance of success, because it uses the same patients and endpoints as a recently-completed smaller study. But just to hedge its bets, the company is launching a smaller trial to treat cognitive impairment in major depression sufferers.

From actinomycetes to Alzheimer's

Actinogen listed in October 2007 at 50 cents apiece and initially was focused on soil-derived antibiotic-like compounds called actinomycetes (hence the Actinogen name).

Xanamem hails from Edinburgh University, which completed an early-stage trial of a predecessor drug with the $25 million backing of the Wellcome Trust charity.

Clinical development of Xanamem started in 2013.

Actinogen acquired Xanamem by purchasing Corticrine Limited, an arm of Edinburgh University, in August 2014.

Dr Bill Ketelbey joined the company as CEO in December 2014. Dr Ketelbey was involved in developing Aricept, which remains the leading Alzheimer's treatment despite being developed almost 30 years ago. Dr Gourlay succeeded Dr Ketelbey in early 2021.

Dr Gourlay previously worked in senior roles at Genentech and then with Dr Geoff Brooke (now Actinogen chairman) at GBS Venture Partners.

Dr Gourlay returned to the US and with some "Genentech mates" and took on novel small molecule development at Principia Biopharma in San Francisco. They progressed two small molecules from pre-clinical to phase III and floated the company on the Nasdaq in 2018, before selling out to Sanofi for $US3.7 billion ($A5.5 million) in 2020.

All about Xanamem

Xanamem inhibits production of cortisol, a naturally occurring stress hormone. Elevated cortisol levels are thought to be a cause of both Alzheimer's and mild cognitive impairment (which can often lead to the former).

The drug acts by inhibiting an enzyme called the 11 beta HSD1. To achieve this, any drug first must negotiate the blood-brain barrier, the organ's natural defence against foreign agents.

Dr Gourlay stresses the drug is not based on amyloid mechanisms, on which most of the other Alzheimer's drug developers have focused.

"The drug has the potential to be rapidly cognitive enhancing, improving memory in a few weeks," Dr Gourlay says.

"It is potentially disease modifying and may well be an anti-depressant as well."

So far more than 300 volunteers and patients have been treated without any safety concerns, for up to 12 weeks.

"We have seen a positive effect on attention and working memory and cognition in two independent, placebo-controlled trials in healthy, older volunteers," he says.

Actinogen also has a quiescent secondary program underway to treat Fragile X syndrome, a genetic condition resulting from the mutation of the X chromosome in new-borns.

Out of the poo after Xanadu

Actinogen's prospects looked far from upbeat in May 2019, when the results of its then key trial, Xanadu, proved a 'box office' flop in the same way as the 1980 musical of the same name (and vale Olivia Newton-John).

The company's shares lost four-fifths of their value after the results showed Xanamem worked no better than placebo, on a 185-patient sample of mild Alzheimer's sufferers.

The data from Xanadu was re-examined using a modern blood test to choose the patients with amyloid-based, 'real' Alzheimer's disease.

Strong signals of protection against cognitive decline were evidenced in these 34 patients, who had elevated levels of the biomarker phosphorylated tau, or p-Tau. P-Tau is not an Asian religion, but a protein blood biomarker indicative of Alzheimer's.

The prophylactic effect was measured by a US Food and Drug Administration-approved endpoint called the Clinical Dementia Rating Scale-Sum of Boxes (CDR-SB).

A so-called functional endpoint, CDR-SB assesses patients on six criteria and rates them on a scale of 0.5 to 3.0 ranging from questionable impairment to severe dementia.

Twice as many Xanamem-treated patients had stable or improved disease relative to placebo, meaning there was a 60 to 80 percent reduction in disease progression over 12 weeks.

Put in context, the injectable drug called Lecanemab had a 27 percent reduction in disease over 18 months. Pundits expect the FDA to approve the drug.

Alzheimer's v dementia

"There are 500,000 people in Australia with dementia," Dr Gourlay says. "Two thirds of people with dementia have Alzheimer's, which means they have amyloid in the brain.

"But others might have Lewy body dementia, strokes, fronto-temporal dementia or strokes."

Given that, the original Xanadu trial certainly had at least one-third of patients with non-Alzheimer's dementia - and maybe even more. Those patients typically do not progress over a short period such as 12 weeks, whereas Alzheimer's sufferers do.

Dr Gourlay says the company's approach is "not data dredging, but the real deal" using a rigorous new protocol.

"One of the reasons I took the job is that I looked at the clinical results from that study in detail," he says. "I knew the 10-milligram dose had been proved to be active and there were some sub-groups where patients really benefited. We have now proved that very clearly".

More trials, more validation

In April this year, the company reported the top-line results from a phase Ib dose ranging component of a study, called Xanamia.

There's a lot of science-y stuff in the presentation, but the digestible bottom line is that Xanamem was safe and effective for dosages at or below 10 milligrams.

The results confirmed the findings of an earlier, smaller trial called Xanahes.

Mamma mia! It's Xanamia

The next whopper stage is the Xanamia phase IIb trial to study improvements in cognitive ability for patients with biomarker-confirmed early Alzheimer's.

The placebo-controlled study aims to sign up 330 patients over multiple countries, including Australia, with enrolment starting in early 2023.

"We are quite optimistic about enrolment because it is a simple oral drug taken once a day, not a complicated antibody infusion," Dr Gourlay says.

Describing Xanamia as a quasi-phase III trial, Dr Gourlay hopes the US Food and Drug Administration (FDA) will view it as a pivotal trial for registration purposes, although a second phase III effort would be required.

Results are expected towards the end of 2024.

Tackling the black dog

The company expects to start enrolling a 160-patient proof-of-concept depression trial within the next month or so, with results in late 2023 or early 2024.

“We didn’t want to put all the eggs in one basket and having a second indication makes the story just that much bigger,” Dr Gourlay says.

He says that while anti-depressants might improve mood, they do nothing for the “foggy thinking” of Alzheimer’s patients.

“The hope is that Xanamem might have a dual action in improving depression and cognitive impairment,” he says.

Proving efficacy with depression could pave the way for Xanamem to be used in other psychiatric conditions, such as schizophrenia.

Aduhelm underwhelms

Controversially, the FDA approved Biogen’s Alzheimer’s drug Aduhelm (aducanumab), which targets amyloid plaque in the brain and had just entered phase I trials. In doing so, the agency snubbed the view of its own 10-member expert committee, with three quitting and one dubbing the decision “the worst drug approval in recent history”.

Dr Gourlay opines that Biogen was overly ambitious charging $US56,000 for a drug with accelerated - rather than full - FDA approval.

Biogen is trying again with the aforementioned Lecanemab, which has been subject to an 1,800-patient study. The FDA is expected to approve the fortnightly antibody infusion.

Finances and performance

Actinogen had $13 million of cash at the end of September quarter, with research and development tax incentive received in October taking the tally to around $17 million.

Cash burn will step up as the trials progress (September quarter outflows were $3.38 million). Not surprisingly, partnerships are a source of non-dilutive funding, as are grants.

US research house Edison estimates Actinogen will burn $39 million in 2023-’24 and will need $390 million to fund both clinical programs to global marketing approvals. The company last raised equity ($12.4 million) in December last year.

Over the last year Actinogen shares have traded between four cents (mid-June this year) and 19 cents (early November last year). Historically the shares peaked shortly after listing in October 2007, at 55 cents and fell to a nadir of one cent in September 2019.

Dr Boreham's diagnosis:

Despite drug companies throwing not just the kitchen sink but the bath as well at the problem, Alzheimer's is as intractable problem as ever.

What drugs are approved for Alzheimer's disease?

Aducanumab (as it's generically known) is the only disease-modifying medication currently approved to treat Alzheimer's.

"Whichever way you look at it, it is a gazillion dollar opportunity," Dr Gourlay says.

He notes that three independent trials have shown that Xanamem works. If the FDA agrees and eventually approves the drug, Actinogen will be worth many billions of dollars - even "gazillions" - rather than the current $220 million.

While Dr Gourlay rates Xanamia as a 70 to 80 percent chance of success, he's a realist who believes there's a 50 percent chance of the drug actually getting to market.

"Some US [Alzheimer's drug developers] are worth $US2.5 billion and they don't have anywhere near the amount of data that we have," Dr Gourlay says.

Meanwhile, Edison ascribes only a 10 percent chance of marketing success, while Bell Potter concurs that it's more a 50-50 bet. Nonetheless, Edison values Actinogen shares at 36 cents - thrice the level they're at now - while Bells plumps for a more conservative 15 cent valuation.

So, take your pick.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort – as far as he can remember.