Biotech Daily

Friday August 2, 2024

Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Actinogen Medical

By TIM BOREHAM

ASX code: ACW

Share price: 7.1 cents; **Shares on issue:** 2,711,639,883; **Market cap:** $192.5 million

Chief executive officer: Dr Steven Gourlay

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

Financials (June quarter 2024): revenue $100,000, cash outflows $5.1 million, cash balance $9.5 million, quarters of funding: 1.9, but says it has resources to late 2025.

Identifiable major holders: Biotech Venture Fund 9.2%, Dr Steven Gourlay 3.6%

An imminent trial result may validate whether Actinogen's Xanamem is 'the next Ozempic'.

Originally developed for diabetes and embraced as a weight loss drug by the beautiful people, Ozempic is also showing promise in the $US4.8 billion-a-year Alzheimer's disease treatment market.

Actinogen chief Dr Steve Gourlay says type 2 diabetes is a known risk factor for Alzheimer's and GLP-1 drugs have been shown to reduce the chance of developing the disease in diabetics.

Not surprisingly, drug companies are on the GLP-1 case, with Novo Nordisk and Eli Lilly both carrying out large phase III oral formulation trials. A drug could be approved by as early as 2027.

Xanamem shares some similar traits to the mechanisms of GLP-1 drugs, in that it improves insulin sensitivity and may share some of the same metabolic benefits in the brain.

However, it has been developed by Actinogen to target the toxic effects of the “stress hormone” cortisol in the brain - something that GLP-1 drugs don’t do.

Xanamem also has a different safety profile.

“GLP-1 drugs work by in part by preventing your stomach emptying, which makes you feel full, with nausea as a main side effect,” Dr Gourlay says. “This is not a good profile for many Alzheimer’s patients who forget to eat and are already losing weight.”

A bit of history

Actinogen listed in October 2007 at 50 cents apiece, with an initial focus on soil-derived antibiotic-like compounds called actinomycetes (hence the Actinogen name).

In a radical course correction, Actinogen acquired Xanamem as UE2343 in 2014 from Edinburgh University, which had completed a phase I trial.

Australian clinical development started in 2015.

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 chair) at GBS Venture Partners.

As founding chief medical officer of the San Francisco-based Principia Biopharma, he helped to take two immunology programs to advanced trials, at which point Sanofi acquired the company for $US3.7 billion ($A5.5 billion).

About Xanamem

Xananem is a brain tissue cortisol synthesis inhibitor, potentially with applications for psychiatric and neuro-degenerative diseases beyond Alzheimer’s and depression (such as Fragile X syndrome and cognitive impairment in schizophrenia).

Other Alzheimer's drugs work by inhibiting the formation of amyloid proteins, which form as plaques and are thought to be a key contributor to the disease.

Xanamem takes a different tack by inhibiting production of cortisol, which is synthesized by an enzyme called 11 beta HSD1.

Cortisol is a naturally occurring stress hormone and essential for the body, but elevated levels over a long period are thought to contribute to both Alzheimer's and mild cognitive impairment (which can often lead to the former).

Xanamem is expected not to interact with other drugs so could be used in older patients taking medications for conditions such as cholesterol and blood pressure.

To be effective, any drug first must cross the blood-brain barrier, the organ's natural defence against foreign agents. Xanamem appears to do this.

To date, Actinogen has studied 11 beta HSD1 inhibition in more than 350 patients and volunteers.

Learning from past mistakes

Actinogen has staged a remarkable recovery from the dark days of mid-2019, when its key trial - Xanadu - failed.

The study of 185-patients with clinical mild Alzheimer's disease showed Xanamem over 12 weeks worked no better than placebo.

But the company cut the data another way - as you do - by examining the stored blood samples of 72 of the enrollees to see if they had 'confirmed' Alzheimer's. This was measured by elevated blood levels of a protein biomarker called pTau181 or phosphorylated tau.

The results showed half the patients had a low level of the biomarker and showed no progression at all - and thus possibly didn't have Alzheimer's disease in the first place.

In patients with a high level of the biomarker, indicating 'real' Alzheimer's, twice as many Xanamem-treated patients had stable or improved disease relative to placebo, with a 60 to 80 percent reduction in disease progression over 12 weeks.

On trial (1)

The company is running two phase II trials, the first of which is about to report results.

The phase IIa trial, Xanacidd, is studying the ability of Xanamem to improve cognitive dysfunction (difficulty thinking, remembering and solving problems) associated with major depression.

The trial has completed visits with 167 patients enrolled and will report top-line data on the primary endpoint of cognition, with secondary endpoints including reducing depression.

Over six weeks, the patients receive 10 milligrams of either Xanamem or a placebo daily (in some cases in addition to their existing anti-depressant drugs).

The primary endpoint is a composite of three computerized Cogstate tests for working memory and attention. A key secondary endpoint is the commonly used Montgomery-Asberg Depression Rating Scale.

Dr Gourlay says anti-depressants might improve mood, but they do little for the cognitive impairment or foggy thinking of patients with depression. “Demonstrating improved cognition in patients with depression could pave the way for Xanamem to be used in other psychiatric conditions such as schizophrenia, where cognitive impairment is profound.”

On trial (2)

A second phase IIb trial, Xanamia, is recruiting patients with biomarker-positive mild to moderate Alzheimer’s disease.

The 220 patients are dosed over 36 weeks - also with 10mg - and are included if they have elevated p-Tau blood levels.

The patients are assessed on both cognition and Alzheimer’s progression.

“We believe we have already validated the target by showing improved cognition in healthy older volunteers and a potentially a big clinical benefit in biomarker-positive patients with Alzheimer’s,” Dr Gourlay says.

Interim results - covering the first 100 patients at the 24-week mark - are expected in mid-2025. Final results are expected in mid-2026.

What next?

Dr Gourlay says getting a depression drug to market would require at least two more pivotal trials, about twice the size of the current trial.

He expects the depression drug to be progressed with a partner, while the company would like to expand the current Alzheimer’s study to more sites, off its own bat.

“This potentially could form one of the pivotal studies,” he says. “We would start the second phase III pivotal study as soon as we could and hopefully that would bring forward approval by a year or so.”

The company expects FDA breakthrough designation for Alzheimer’s and potentially for cognitive impairment in depression.

Eyeing the competitive landscape

Plenty of Alzheimer's drug development is taking place but so far there is no magic bullet.

In July, the FDA approved Eli Lilly's Kisunla (donanemab), a monoclonal antibody infusion for mild cognitive impairment or early Alzheimer's that targets the amyloid protein.

In February, sales of Biogen's first amyloid antibody, Aduhelm (aducanumab), were discontinued, reportedly because of poor sales and/or side effects.

Biotech scholars will recall that the FDA in 2021 approved Aduhelm on the basis of only one positive phase III trial, snubbing the advice of its own 10-member expert committee. (Three of them quit, with one describing the decision as the worst drug approval in history).

Dr Gourlay says such drugs have set a low bar for approval because of their modest benefits and need for intensive safety monitoring and side effects.

"The amyloid drugs have probably shown the best data they can, so we are unlikely to see a better story emerge with amyloid as the target."

Finances and performance

Actinogen has completed a placement and rights offer that raised $8.9 million, at 2.5 cents apiece. Holders received one share for every 15 held, plus one option for every two shares subscribed for.

The options are exercisable at five cents within three years. The company also has unlisted options exercisable at 3.75 cents, expiring in 2026 and if fully exercised all of these options would raise up to $16 million.

Actinogen's new CFO Will Souter says that with around $9.5 million in the bank and an expected $8 million Federal Research and Development Tax Incentive, the company is funded to late 2025.

Current cash burn is "elevated" but is expected to subside in the December quarter with the completion of the cognition/ depression trial.

Unlike many other drug developers, Actinogen carries out most of the clinical work in house, rather than cede it to a contract research organization (CRO).

"It is significantly cheaper than using a CRO and trial staff at sites love the direct relationship," Dr Gourlay says.

Over the last year Actinogen shares have traded between two cents (in a prolonged period between August 2023 and January 2024) and the current zenith. Historically the shares peaked shortly after listing in October 2007, at 55 cents and hit a nadir of one cent in September 2019.

Dr Boreham's diagnosis:

Globally, 55 million people have Alzheimer's disease - 500,000 in Australia - and the World Health Organisation rates the disease as the seventh-biggest cause of death (as of 2020).

The global Alzheimer's therapeutics market size is estimated to grow from $US4.82 billion in 2023 to around US$8.18 billion by 2032.

If Xanamem succeeds, Edison Research estimates peak sales of $US5 billion in the early 2030s, while depression is a $US2 billion market.

Naturally, Actinogen has a long way to go, but Dr Gourlay is heartened by some big-ticket transactions in the neurology sector at pre-approval or even early stage.

Last December, Bristol Myers Squibb acquired the Nasdaq-listed Karuna Therapeutics for $US14 billion. Karuna is developing its Karxt agent for schizophrenia and Alzheimer's, having lodged an FDA submission for the former.

Karxt works by reducing dopamine levels in the brain, so we there's more than one way to skin this rabbit.

As for the Ozempic-style drugs, do they pose a competitive threat to Actinogen in the same manner as Resmed (sleep apnoea) and CSL's Vifor arm (kidney dialysis)?

Dr Gourlay's premise is there will be a place for the 'Ozempics' in the Alzheimer's space: "they probably will be better than the anti-amyloids but they won't be the safe and effective oral treatment, such as the one we are developing".

So, the short answer is "no".

Ozempics or not, the Alzheimer's treatment Olympics is still an open race to the winner's podium.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort – or a gold medal.