



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: \$56.0 million

Share price: 5.0 cents

Shares on issue: 1,119,231,320

Chief executive officer: Dr Bill Ketelbey

Board*: Dr Geoff Brooke (chairman), Dr Ketelbey, Dr George Morstyn, Malcolm McComas

* Dr Jason Loveridge resigned in November last year

Financials (year to June 30, 2019): revenue \$204,536 (bank interest, investments; up 123%), loss of \$9.9 million (previously \$6.3 million deficit), cash \$7.6m (down 22%)

Identifiable major holders: Biotech Venture Fund 19.9%, Edinburgh Technology Fund 4.3%, Platinum Asset Management (sub 5%), Tisia Nominees (Henderson family) 2.67%, Sarah Cameron 2.25%, Jinark family 1.82%, Bannaby Investments 1.62%.

It may not have been quite a case of Lazarus with a triple bypass, but a recovery of miraculous proportions happened in the biotech sector this week as Actinogen jagged some remarkable efficacy results from what otherwise was a bog-standard safety trial.

But don't take our word; take the gospel of investors. Post Tuesday's clinical results revelation, Actinogen shares shot up from the 0.7 cents a share death zone to close at 5.1 cents - a 467 percent gain for anyone prescient enough to invest at those levels.

The phase I results showed that Actinogen's Alzheimer's disease candidate Xanamem improved the cognition of a cohort of 30 healthy elderly patients, compared to the 12 who received a placebo.

This improvement - measured by the industry standard Cogstate Cognitive Test Battery - came after 12 weeks of dosing at 20 milligrams.

The study was called Xanahes, as in 'Xanamem in Healthy Elderly Subjects'. The "breakthrough results" reinforce the company's key hypothesis that lowering persistently-raised cortisol levels in the brain can enhance cognition.

Actinogen shares tanked in May after the company reported that its phase II Alzheimer's trial of 186 patients missed both primary and secondary endpoints, having failed to show any significant difference between Xanamem (delivered at 10mg daily over 12 weeks) and a placebo.

"We are back on track but on a different track," says Actinogen chief Dr Bill Ketelbey. "But that's the reality of biotech research."

He says Actinogen pretty much tacked on the efficacy endpoint as an afterthought. The company was inspired by a 2014 Edinburgh University study that also identified "cognitive signals" in a group of 24 elderly patients.

"We added the cognitive model to see if we could replicate it," Dr Ketelbey says.

With a decent cash kitty, Actinogen is now mulling its next move in tackling Alzheimer's and/or the cognitive effects of schizophrenia and bipolar disorder.

The company is most interested in mild Alzheimer's, which presents a \$US7.5 billion (\$11 billion) global market.

A brief history of Actinogen

Actinogen carries on the fine work of Edinburgh University, which completed a phase I study of what now is known as Xanamem or UE2343 (originally developed for type 2 diabetes) with the backing of the Wellcome Trust charity.

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

The scrip deal introduced the learning institution as a major Actinogen holder.

Actinogen itself listed way back in October 2007 at 50 cents apiece, but at the time it was focused on soil-derived antibiotic-like compounds called actinomycetes (hence the Actinogen name).

Dr Ketelbey joined the company in December 2014. Dr Ketelbey was involved in developing Aricept at Pfizer, which remains the leading Alzheimer's treatment despite being developed 25 years ago.

Chairman Dr Geoff Brooke is well known as founder of venture capital firms Medvest Inc and GBS Venture Partners.

Questions, questions

Xanamem seeks to inhibit production of the naturally occurring stress hormone cortisol in the brain, with research linking excessive cortisol with the development and progression of Alzheimer's.

Xanamem aims to negotiate the blood-brain barrier and thus deliver the active ingredient more effectively.

But Dr Ketelbey says the results raise "intriguing questions" about the role of elevated cortisol levels - the condition Xanamem seeks to modulate - and cognitive decline in both Alzheimer's patients and healthy patients with normal age-related cognitive diminution.

The patients in the second trial were aged between 50 and 75 years, with a mean age of about 65 years.

The obvious question is why the Xanahes trial succeeded while Xanadu crashed (technically, the trial showed cortical reduction, but not the cognitive improvement).

One possible reason is a complex disease like Alzheimer's adds all sorts of variables, which may have contributed to the dud phase II result. Or the patient sample was too heterogeneous, or too early or too advanced in their disease.

"Alzheimer's disease is confounded by heterogeneity, meaning that all patients are different and there's a broad array of presentation of symptoms and response to therapy," Dr Ketelbey says. "Because there's not one distinct biomarker or target for treating the disease, it's a difficult disease to research and to treat."

The other possible explanation is that the Xanadu dosage was at half the level as the Xanahes dosage, so may have been insufficient. Or else the patients needed to be treated for longer than the three months.

Another possibility is that by the time a patient has been diagnosed with Alzheimer's disease it may be far too late – by 20 years - to intervene, whereas the healthy elderly patients had a positive response.

What's next?

“Clearly we are not trying to develop a drug for age-related cognitive impairment,” Dr Ketelbey says. “We will go for pathologies where there are chronically raised cortisol levels.”

The conditions include Alzheimer's, schizophrenia, bipolar disease, diabetes, Parkinson's disease and epilepsy (as we said, the company will focus on the former three).

“We are at the point of shaping-out the next full set of studies,” Dr Ketelbey says. “We are urgently working on [the next step] as we have such compelling cognitive data.”

Actinogen has also launched a phase I ‘occupancy study’, which tests the absorption of Xanamem into the brain, as measured by its occupancy of the target enzyme that promotes cortical production.

Finances and performance

Actinogen had \$7.63 million in the bank as at the end of June, with \$4.5 million of research and development rebates expected to flow in over the next month.

Dr Ketelbey says the funds are more than enough to fund Actinogen's current research, but monetary requirements thereafter depend on what clinical path the company decides to take.

The company last raised \$5.28 million in an oversubscribed placement at 4 cents a share in December 2018, thus fully funding the Xanadu trial.

Despite its setback, Actinogen is heavily backed by the Biotech Venture Fund (BVF), which has the maximum allowable 19.9 percent stake.

Platinum owns a decent wad of scrip, while Australian Ethical sold out immediately after the May setback, taking an unconfirmed loss of about \$1.6 million.

“Since the share price collapse in May the shareholdings have been pretty stable, whether retail or institutional,” Dr Ketelbey says.

Actinogen shares peaked at 15 cents in April 2015 and troughed at 0.7 cents in September this year.

At its share price nadir, the company was valued at around \$8 million - in effect less than cash backing - and now it's worth \$56 million.

The company also has \$39 million in accumulated losses, so can ward off the taxman pretty much forever.

Dr Boreham's diagnosis:

There's no shortage of research dollars being spent on Alzheimer's disease, which is expected to become the world's biggest killer as the population ages. The www.clinicaltrials.gov site lists 536 active and recruiting Alzheimer's trials, including 27 in Australia.

But while there are drugs to treat the symptoms, there is no effective treatment of the cause, with at least a dozen proposed drugs biting the dust.

Dr Ketelbey says: "They have mainly targeted beta amyloids [abnormal protein produced by the bone marrow] but the general view is that while amyloids are important the traditional approach to treating Alzheimer's to prevent amyloids forming with is not the way forward.

"Now people are looking at novel approaches and that's where we begin to stand out."

Helpfully, Edinburgh University is interested in funding future diabetes and cognitive impairment trials - so no quips please about Scots having short arms and deep sporrans.

While Actinogen's programs remain at an early stage, the company is a potential takeover target. Last year, Abbvie, Takeda and Eli Lilly all executed pre-clinical Alzheimer's deals.

"Big pharma in the past has said 'we like what you do, but bring us a signal that your hypothesis has some clinical substance'," Dr Ketelbey says.

Xanahas trial lead investigator Prof Michael Woodward from Melbourne's Austin Health says that given the many past failures in the development of Alzheimer's drugs, the Xanahas results "renewed hope for a treatment breakthrough for this devastating disease".

Let's hope so.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. Being on the wrong side of 50 he is eligible to participate in Actinogen's trials, but probably would forget to turn up.