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: $31.9 million

Share price: 2.2 cents

Shares on issue: 1,450,787,169

Chief executive officer: Dr Bill Ketelbey

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

Financials (September quarter 2020): revenue nil, cash outflows $728,000, end of quarter cash balance $4.3 million (ahead of $6 million placement and $1.36 million rights offer)

Identifiable major holders: Biotech Venture Fund 17.31%, Edinburgh Technology Fund 3.32%, Surfit Capital 2.07%, Tisia Nominees (Henderson family) 2.3%, Sarah Cameron 2.76%, Brazil Farming 1.03%.

Eighteen months ago, Actinogen looked a spent force after its phase II Alzheimer's disease trial Xanadu flopped faster than its 1980 namesake musical romance that inspired the Global Raspberry awards.

Then something remarkable happened: a follow-up trial, pitched mainly at safety endpoints, ascertained that Actinogen's targeted mechanisms of action with its lead candidate Xanamem did, like, work.

The study was called Xanahes, as in ‘Xanamem in Healthy Elderly Subjects’. Enrolling 30 elderly but hearty patients, the study showed a “robust and statistically significant” improvement in cognition.

A key difference was that Xanadu involved a 10mg daily dose while Xanahes amped it up to 20mg. The Xanadu sample also might have been too heterogeneous (diverse).

As with most great medical breakthroughs, the upbeat results came almost by accident, as the efficacy endpoints were tacked on as an afterthought. Mild Alzheimer’s presents a $US7.5 billion ($A11 billion) global market.

This month, Actinogen completed a $7.36 million capital raising to support the company through a follow-up Alzheimer’s trial, as well as a separate one for the new indication of Fragile X syndrome.

Alzheimer’s is fast becoming the biggest killer as populations age. Fragile X, on the other hand is rare - or sort of. Both are difficult to treat and pertain to excessive cortical levels in the brain, which is the key target of Actinogen’s drug program.

“We are well on track to initiate both of these studies in the first half of next year,” Dr Ketelbey says.

A brief history of Actinogen

Xanamem hails from Edinburgh University, which completed an early stage trial of a predecessor drug, UE2343 for type 2 diabetes, with the backing of the Wellcome Trust charity.

Actinogen acquired Xanamem by purchasing Corticrine Limited, an Edinburgh University spin-out, in August 2014. The scrip deal introduced the Caledonian 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).

The company has since left that one to the worms.

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

Chair Dr Geoff Brooke is well known as founder of venture capital firms Medvest Inc and GBS Venture Partners. He is also a current director of the ASX-listed Acrux and Cynata Therapeutics, as well as the private Prevatex Pty Ltd.

About Xanamem

Xanamem's mechanism of action involves inhibiting 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 inhibitor (not to be confused with a Peter Brock era Holden Special Vehicle).

To achieve this, any drug first has to negotiate the blood brain barrier, the organ's natural defence against foreign agents (and more effective than the never-built Great Wall of Donald).

Dr Ketelbey says: "We can now say … we have clear evidence the drug gets in to the brain and effectively binds to or inhibits the activity of the enzyme and suppresses cortical production."

Or in layman's terms - and thanks to tireless Colgate oral health campaigner Mrs Marsh - "it does get in".

Meanwhile, Actinogen has carried out early stage studies for cognitive impairment in schizophrenia and diabetes. The company is eyeing non-dilutive grant funding to further the work.

The company's drug platform is also relevant for treating Parkinson's disease, Cushing's disease and depression.

Xanamia! Here we go again …

Called Xanamia, the all new and improved phase II Alzheimer's trial will recruit 72 patients with mild cognitive impairment related to Alzheimer's disease.

The patients will be administered a higher dose than the Xanadu trial - 10mg twice daily - and assessed over 24 weeks. This will allow more time for the drug to work and for the placebo arm to deteriorate.

Carried out at yet-to-be-determined Australian sites, the trial is expected to start early next year, with an initial data read-out within 24 months.

Dr Ketelbey notes that eight percent of 65-year olds have mild cognitive impairment and half of them have raised cortisol levels - so there's a significant risk of them developing Alzheimer's. About 10-15 percent of sufferers transition to mild Alzheimer's every year.

Dr Ketelbey says there are plenty of Australian sites for the trial, but some hospitals have complained of trial fatigue.

Why? Because of Australia's relatively Covid 19-free status, "the whole world is coming here to do trials".

Biomarker my word

Crucially, this time around, the Alzheimer's trial will not just measure cognitive function, but the presence or otherwise of biomarkers such as beta amyloids, an abnormal protein produced in the brain and originally thought to be a cause of Alzheimer's disease, now believed to be a sign of the disease.

"Since the [Xanadu] trial, the science of Alzheimer's disease has moved on substantially and now we can pick up not just subjective cognitive measures, but the objective biomarker endpoints," Dr Ketelbey says.

Including the biomarkers as an endpoint is no afterthought: regulators such as the US Food and Drug Administration prefer to see biomarker data, along with traditional cognitive measurements which can be somewhat (or totally) subjective.

Let's face it: how many of us have thought that Uncle Arthur is 'losing it' but can't quite pin down why?

"This is not a registration trial but it will produce the data we take to the FDA to help us define and develop a pivotal registry trial," Dr Ketelbey says.

What else is happening?

Alzheimer's disease is of intense interest to the drug companies and there's a lot of clinical activity taking place. Big pharma companies including Abbvie, Takeda and Eli Lilly have all executed preclinical Alzheimer's deals in recent years. But that isn't translating into a pipeline of drugs.

The most promising developing is Biogen's aducanumab, which is awaiting FDA approval under an expedited timeline. This drug candidate targets beta amyloids, but the jury is out on whether this is the right approach.

Still, if approved, the drug would be the first new Alzheimer's treatment in almost two decades. A herbal therapy has also been approved by Chinese regulators and the less said about that one the better.

"Beyond that, we might be the next one in line," Dr Ketelbey says.

Fragile X marks the spot

Fragile X is a genetic condition resulting from the mutation of the X-chromosome in newborns.

Call it reverse discrimination, but the condition affects about one in 2,400 to 4,000 males and one in 7,000 to 8,000 females. This discrepancy results from women having two X chromosomes, while men have the X-Y combo which increases the risk.

Fragile X normally is identified between the ages of three to five years, when development problems (such as lack of language skills) become apparent.

As with Alzheimer's, it's associated with raised cortical levels.

A trial called Xanafx is enrolling up to 40 adolescents and will take place under the auspices of Melbourne's Murdoch Children's Research Institute, at the Royal Children's Hospital, a world leader in Fragile X research.

Not surprisingly, Actinogen is eyeing rare paediatric disease designation (RPDD) and/or orphan disease status from the US Food and Drug Administration.

Orphan and RPDD offer 'perks' such as lower approval hurdles, tax credits and - if you're really lucky – RPDD can lead to a valuable and fungible paediatric priority review voucher.

The Fragile X trial is expected to start in the first half of 2021, with a first data readout in 12 months.

Finances and performance

Actinogen's just-completed capital raising was by way of a $6 million institutional placement, followed up with a $4.9 million, one-for-five rights issue. Both were struck at 2.2 cents per share.

The insto component was oversubscribed, but the rights leg raised only $1.36 million. While retail holders traditionally don't flock to rights issues, it didn't help that the share registry initially provided the wrong BPay code in the acceptance form.

Still, the company appears to have more than enough of the folding stuff to support both studies. That said, the Murdoch Institute is stumping up for most of the Fragile X trial costs.

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

Dr Ketelbey says the latest raising has brought a handful of new institutional investors on board. Cornerstone shareholder Biotech Venture Fund participated in the offer and maintains a circa 17 percent stake.

"Generally, the top 20 shareholders have been solid sticky money, they remain good supporters," Dr Ketelbey says.

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

Did anyone ring the bell at those dismal levels? No, siree.

Dr Boreham's diagnosis:

Put simply - or over simply - all Actinogen needs to do is to replicate the Xanahes results in either the ongoing Alzheimer's or Fragile X trials.

"It will light the world up," Dr Ketelbey says of such an outcome. "It will be proof of concept of this idea of inhibiting cortisol production in the brain.

"What's been shown over the years is that getting any therapeutic effect out of a drug in moderate to severe Alzheimer's disease is just about impossible. You are talking about a scarred, compromised brain that is unresponsive to just about any therapy, which is why we are targeting mild cognitive impairment to start treatment early, hopefully for the best results."

Given the short nature of the trials, investors won't have to wait too long for answers.

With a circa $30 million market capitalization Actinogen is priced by ASX punters for failure. Put in context, that's only a tad more than the $23 million budget for Xanadu which flopped at the box office despite - or because of - the efforts of Olivia Newton John, Gene Kelly, Cliff Richard and the Electric Light Orchestra.

But what's clear is that Actinogen investors won't be bereft of short-term news flow.

"From a cash perspective we are in great shape," Dr Ketelbey says. "The trials are ready so everything is going to be good to go."

Disclosure: Dr Boreham is not a qualified medical practitioner, does not possess a doctorate of any sort but may suffer a fading memory. Dr Boreham is not a qualified medical practitioner, does not possess a doctorate but may suffer a fading memory.