Biotech Daily

Friday June 18, 2021

Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Actinogen Medical

By TIM BOREHAM

ASX code: ACW

Market cap: $215.9 million

Share price: 13 cents

Shares on issue: 1,660,558,547

Chief executive officer: Dr Steven Gourlay

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

Financials (March quarter 2021): revenue nil, cash outflows $1.04 million, end of quarter cash balance $15.2 million, quarters of available funding 14.6

Identifiable major holders: Biotech Venture Fund 14.5%, Dr Steve Gourlay 3.9% Edinburgh University Technology Fund 2.9%, Tisia Nominees (Henderson family) 2.8%, JSC Wealth Management 2.7%.

Whether it's ultimately justified or not, the US Food and Drug Administration's approval of an apparently less-than-effective drug for Alzheimer's disease has created a ripple of excitement around the sector.

This is evidenced by a mob called Acumen Pharmaceuticals filing for a $US100 million ($A130 million) public offering on the Nasdaq exchange, a mere two days after the FDA last week green-lighted Biogen's Alzheimer's drug Aduhelm (aducanumab).

NOTE: Dr Steven Gourlay was the founding CMO but not one of the original founders of Principia.

While the Virginia-based Biogen had slaved away on its drug candidate since 1996, Acumen only entered phase I studies this year for its monoclonal antibody.

The Biogen approval and the big-ticket Acumen raising are music to the ears of Actinogen, which in early June said a much-anticipated trial of its lead candidate Xanamem would progress after receiving ethics approval.

“This molecule is looking pretty good to me. We look forward to progressing it to approval as fast we can,” says CEO Dr Steven Gourlay, who recently replaced Dr Bill Ketelbey.

The ‘dirt’ on Actinogen

Actinogen listed in October 2007 at 50 cents apiece, just before the onset of the global financial crisis.

At the time the company 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 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 Caledonian learning institution as a major Actinogen holder.

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 25 years ago.

On February 8, Dr Ketelbey stepped down, effective immediately.

Dr Gourlay previously worked in senior roles at Genentech and then with Dr Geoff Brooke (now Actinogen chairman) at GBS Venture Partners. There, they designed clinical trials for portfolio companies.

Dr Gourlay returned to the US and with some “Genentech mates” started Principia Biopharma.

They took two small molecules from pre-clinical to phase III stage, before selling out to Sanofi for $US3.7 billion.

While skeptical of Principia, at first, Dr Gourlay was “blown away by the quality of the science and the opportunity” his colleagues demonstrated.

“Actinogen is a similar story. It has really interesting clinical data, including cognition in humans and a good safety profile.”

What Xanamem does

Xanamem inhibits production of cortisol, a naturally occurring stress hormone. Elevated cortical 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 (for 1980s nostalgia freaks, not a Peter Brock Holden Special Vehicle).

To achieve this, any drug first has to negotiate the blood-brain barrier, the organ's natural defence against foreign agents.

The unsuccessful trial was called Xanadu, which was not a reference to the eponymous 1980s film flop, but could have been.

The follow up study was called Xanahes, as in 'Xanamem in Healthy Elderly Subjects'.

Enrolling 30 elderly but hearty patients and primarily a safety study, the trial 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.

Dr Gourlay believes the failed study was well-designed, but the 12-week outcome was too soon to demonstrate the chosen endpoints that typically required six months.

While the 20mg dose showed "excellent clinical efficacy", initially it was thought the 10mg dose was too low.

"We now have direct evidence that 10mg fully suppresses the enzyme function in the brain itself," Dr Gourlay says.

Another possible reason for the Xanadu floperoo was that the cohort was "heterogeneous". For example, it could have included patients who had had strokes.

Xanamia: here we go again

Called Xanamia, the latest Xanamem trial is designed to study improvements in cognitive ability in older volunteers, as well as patients with mild cognitive impairment in the first clinical stage of Alzheimer's disease.

The study will be conducted at four clinics in Australia, and enrol about 100 healthy volunteers aged 50 years and over.

Xanamia has also been re-tweaked to a dose-ranging effort, Part A, testing 5mg and 10mg administrations against placebo.

Part B will measure the presence or otherwise of blood bio-markers for beta amyloids, an abnormal protein.

“These biomarkers could not have been measured before,” Dr Gourlay says. “We now have better endpoints and understand the stages of the disease and can measure things in blood.”

Participants are assessed by the computerized Cogstate cognitive function tests (as used to gauge concussion in groggy footballers).

Results from Part A are expected in the first half of 2022, with the Part B (biomarker) read-out expected in 2023.

What the Biogen approval means

Biogen’s Adulhelm has a different mechanism of action to Xanamem, targeting the build-up of amyloid plaque in the brain that’s a suspected - and disputed - cause of Alzheimer’s disease.

There have been screeds of scholarly material on what the Aduhelm means in terms of the FDA’s stance on other drug approval applications where the evidence is also underwhelming.

In potted terms, two earlier trials of Aduhelm were discontinued on ‘futility’ grounds, but on further parsing of the data, the drug was deemed beneficial to a highly-dosed cohort.

More precisely, they slowed the progression of the amyloid plaques by 22 percent. The FDA itself admitted the evidence was imperfect, but with no other effective treatment available it snubbed its own expert committee and approved the $US56,000 ($A72,000) a year drug.

Three of the 10 members of the committee that recommended rejecting Aduhelm have quit in disgust, with one dubbing the agency’s subsequent approval decision as “probably the worst drug approval decision in recent history”.

We’re not sure about that: wasn’t there Thalidomide?

Dr Gourlay believes the approval ‘bar’ has been enshrined rather than lowered - as it was quite low in the first place.

“I have studied the FDA information carefully and believe they made a reasonable, balanced decision to approve the drug conditionally in this difficult disease,” he says.

The “accelerated approval” means marketing approval depends on the results of at least one new, major trial confirming efficacy and safety.

He notes the agency’s observation that the negative trial might have been influenced by a small number of “rapid progressors”.

“All of that said, the efficacy levels in the approval are relatively modest and there are some safety issues associated with the drug.”

Whatever the merits of Aduhelm or otherwise, the FDA approval sends a message that it is amenable to approving novel therapies for difficult to treat indications such as Alzheimer’s.

Tackling Fragile X

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

Also pertaining to elevated cortisol levels, Fragile X affects about one in 2,400 to 4,000 males and one in 7,000 to 8,000 females. This discrepancy results from females having two X chromosomes, while males have the X-Y combo which increases the risk.

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

In early February, Actinogen won rare paediatric disease designation (RPDD) status from the US Food and Drug Administration.

Benefits include lower approval hurdles, tax credits and – potentially - a valuable paediatric review voucher (PVR).

Called Xanafx, the study aims to recruit up to 40 adolescents and will be run under the auspices of Melbourne’s Murdoch Children’s Research Institute, a world leader in Fragile X research.

The company expects to start enrolling patients shortly with the first data read-out expected in 12 months, from what in essence is a proof-of-concept study.

Finances and performance

In October last year Actinogen launched a $10.9 million capital raising, by way of a $5 million placement and $4.9 million one-for-five rights issue. Both were struck at 2.2 cents apiece.

The rights issue fell short but was eventually filled by investors including Dr Gourlay, who chipped in $300,000 of his own dosh.

Dr Gourlay says the company is funded for both trials and possibly a third one pertaining to a mystery indication that he can’t talk about.

Battered Actinogen shares spent much of 2019 trading at one cent and lingered at two cents for much of 2020, before taking off in mid-March this year to hit their current ten year high of 18 cents on June 1.

The shares peaked at 55 cents shortly after the October 2007 listing.

Dr Boreham's diagnosis:

Dr Brooke notes that Actinogen's current $260 million-ish market valuation compares with recent Alzheimer's related corporate transactions valued at $160 million to $2.4 billion.

"If we were on the Nasdaq with this story our market cap would be three to five times higher at least," Dr Brooke says.

Lest we forget, Alzheimer's disease is becoming a leading cause of death, especially in women.

Dr Gourlay cites estimates of $US13.7 billion in peak sales by 2036, but that's likely to be an underestimate if drugs with different mechanisms of action are available.

"No one has the magic bullet," he cautions. "We hope the biology of our molecule might contribute to delay or prevent disease progression but we have to wait to do longer trials."

While Actinogen's path to a receptive FDA remains littered with hazards, let's not forget that 1980 flop Xanadu - dubbed "stupendously bad" by one critic - cost $US23 million to make and reaped only $US20 million at the box office.

The more recent film version of Cats - which won a rare 'no star' raspberry from some critics - cost $US95 million and clawed back only $US30 million.

Our point? Drug development might not always hit the right note, but at least it's still a less risky proposition than investing in musicals.

Disclosure: Dr Boreham is not a qualified medical practitioner. He does not possess a doctorate of any sort, forged or otherwise. He wishes to stress that Xanadu flopped despite - not because of - 'our' Olivia Newton-John's sparkling leading role.