Biotech Daily

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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Antisense Therapeutics

By TIM BOREHAM

ASX code: ANP

Share price: 22.5 cents; **Shares on issue*:** 574,476,343; **Market cap*:** $129.3 million

***** Ahead of this week's $20 million share placement and $16.8 million one-for-9.4 rights offer, at 24 cents a share to raise $16.8 million. Combined, the raisings will increase shares on issue by approximately 153.3 million or 22%

Managing-director: Mark Diamond

Board:** Dr Charmaine Gittleson (chairman), Mr Diamond, Robert Moses, Prof Graham Mitchell, Dr Gary Pace, Dr Gil Price, William Goolsbee
****** Prof Mitchell, Mr Goolsbee and Mr Moses retire at this year's AGM

Financials (year to June 30, 2021): revenue nil, loss of $8.06 million (previously $5.9 million deficit), cash of $6.02 million******* (up 48%).

Identifiable major holders*:** Platinum Asset Management (sub 5%), Citicastle Pty Ltd (Leon Serry) 2.5%, Altor Capital 2.20%, Esarad Holdings 1.84%, Dale Anthony Reed 1.79%
******* Ahead of the $36.8 million capital raising.

Even under the best circumstances when things flow smoothly, drug development entails mind-numbing leg-work before the elation of selling the therapy for the benefit of sick people and for the enrichment of investors.

Antisense certainly knows about the drudgery as it seeks US and European regulatory approval to progress human trials for its ATL1102 treatment for the rare genetic disorder Duchenne muscular dystrophy (DMD).

Things were progressing at a glacial pace, but this week the company announced the equivalent of the melting ice caps - debated (and we use the term loosely) at this week's Glasgow talkfest.

In news we would file under 'boring but important', the European Medicines Agency in effect approved the company's Paediatric Investigation Plan, a blueprint for how the company would develop its Duchenne muscular dystrophy drug on the Continent.

The approval - or final positive opinion, strictly speaking - opens the way for Antisense to carry out a phase IIb/III trial across 30 European sites in nine countries.

"This study could turn out to be a pivotal trial," says Antisense chief executive Mark Diamond.

"In other words, if we get the requisite data showing significant clinical improvement in upper limb function, we could submit for European approval."

Not wanting to waste the moment, Antisense also rounded up $20 million in an institutional placement, with a follow-on rights issue slated to raise a further $16.8 million.

A chunky $36.8 million? There's nothing boring or unimportant about that.

Biotech goes upmarket

But let's step back a bit. The only biotech based in the ritzy Melbourne suburb of Toorak, Antisense sprung from Circadian Technologies (reputed to be the first ASX-listed biotech).

Mr Diamond has the status of the longest-serving CEO of any Australian biotech, having joined Antisense just after the Twin Towers toppled in 2001.

Antisense's key asset is ATL1102, licenced from the Nasdaq-listed Ionis Pharmaceuticals (formerly ISIS, but Middle East events encouraged a name change).

Initially, Antisense focused on a treatment for multiple sclerosis (MS), based on its RNA-targeted therapeutics. RNA refers to ribonucleic acid, which is present in all cells and carries 'instructions' from DNA to control the expression of proteins.

In 2010, big pharma Teva pulled out from an exclusive global deal with Antisense to develop ATL1102 for multiple sclerosis.

A phase IIa trial showed that ATL1102 was good for cleaning up brain lesions, but the dosage was very high (400 milligrams compared to 25 milligrams for the DMD trials).

Antisense's second compound, ATL1103, targeted acromegaly. But in August 2019 an early access program was shelved after the company learned more clinical work would be needed to access the European market.

Acromegaly is an enlargement of hands, face and feet usually caused by a non-cancerous tumor.

DMD in the spotlight

Now, Antisense's sights are firmly on ATL1102 as a treatment for Duchenne muscular dystrophy, a rare genetic degenerative muscular condition that affects only boys and is regressive, fatal and poorly treated.

DMD is caused by a mutation in the muscle dystrophy gene, leading to severe progressive muscle loss and premature death. The current standard of care, corticosteroids, have limited efficacy and significant side effects when used continuously, as required.

The disorder affects about one in 3,500 males from birth to 18 years, or about 48,000 boys in the US and Europe. It's the biggest fatal genetic disorder.

In-licenced from Ionis, ATL1102 is an antisense inhibitor of the VLA-4 protein, also known as CD49d, a target for the treatment of multiple sclerosis. ATL1102 inhibits the inflammation caused by the lack of the protein dystrophin, which erodes muscle function.

Antisense's key evidence to date is the outcome of a phase II study, carried out at the Melbourne's Royal Children's Hospital's neuromuscular centre.

The trial enrolled nine non ambulant (wheelchair bound) patients, who were treated with ATL1102 over six months (with all but one remaining on the standard-of-care, cortico-steroids).

The boys' muscle function was then compared with the recorded results from 20 boys treated with corticosteroids only. This data was held by leading DMD expert Prof Eugenio Mercuri, of Rome's Catholic University.

Measuring up

In results dubbed as statistically significant, the ATL1102-treated boys performed better on the muscle function assessment score after 24 weeks.

How is the improvement measured? Good question.

The relevant gauge is the Performance of Upper Limb Function (PUL2) test. The RCH patients scored a mean improvement of 0.89 when dosed with ATL1102, which doesn't sound like much until compared with the Rome boys, who saw an average decline of 2.0.

Also, 78 percent showed no change or an improvement, compared with 33 percent for the control group.

The Continental way

Initially, management targeted the US Food and Drug Administration to win the requisite trial approvals, but then re-focused on the European Medicines Agency.

The company has finalized the design of its proposed European study, and is likely to enrol 114 patients across two dose arms of different strengths, as well as a placebo arm.

All boys will continue to be treated with corticosteroids. Under the open-label design, the boys will continue to use ATL1102 after the 12-month trial period.

In Europe there are about 20,000 boys with DMD, about half which are non-ambulant and thus eligible for the trial.

Mired down in monkey business

Meanwhile, the FDA process has been bogged down by the agency's insistence on a longer toxicology study than the six-month monkey-based trial proposed by the company in a "cogent and well supported" entreaty (Mr Diamond's words).

The FDA wanted 12 months but in a classic compromise it agreed to nine months, to be submitted before the trial reaches six-month dosing of children.

The toxicology study has been delayed because of a shortage of specially-bred monkeys, many of which are obtained from China.

The FDA is yet to approve the study, which of course would need to be carried out on US soil. Having said that, it's possible that data from the European trial could be taken into account.

The good news is that the agency is happy with the Royal Children's Hospital trial outcomes as the basis for a larger US study.

About a year ago, the FDA awarded Antisense 'rare paediatric disease designation' (RPDD) for ATL1102. RPDD designation includes a rare paediatric disease review voucher, which is an express-lane ticket for FDA approval. These bits of paper can be on-sold for many millions of bucks - and usually are.

Antisense also has 'orphan drug' designation from the FDA and the EMA.

"Orphan drug status brings additional benefits, like 10 and seven years of market exclusivity in Europe and the US respectively and waiving of certain registration fees which can be quite substantial," Mr Diamond says.

The Sarepta experience

Antisense is buoyed by the experience of the Nasdaq-listed Sarepta Therapeutics, which has won approval for not one, but three, DMD drugs.

So doesn't Sarepta thus have the market covered already?

Not so, says Mr Diamond.

The three drugs each pertain to a form of genetic mutation and, collectively, cover only 25 percent of DMD patients. They also have a different mechanism of action.

Mr Diamond says ATL1102 potentially could be used in conjunction with Sarepta's therapies, to treat both ambulant and non-ambulant boys.

He adds that Sarepta won FDA approval without showing improvement in disease progression in controlled, randomized studies.

Instead, the FDA was convinced by an improvement in dystrophin levels in the boys' muscles. Sarepta was knocked back by the European regulator, which won't accept such surrogate endpoints.

In any event, Antisense will keep an eye on the competition with former Sarepta directors William Goolsbee and Dr Gil Price on the Antisense board.

Mr Diamond notes that Sarepta was smaller than Antisense before its first drug was approved. Now the company commands a $US7.6 billion market capitalization and chalked up September quarter sales of $US167 million.

Finances and performance

As of June 30, 2021 Antisense had $6 million of cash in the bank, having expended $2.28 million in the June quarter and $6.6 million in the 2020-'21 year.

Mr Diamond was clear that the company would need more cash for a European trial and hence this week's raising, struck at 24 cents a share (an 18.6 percent discount to the last closing price of 29.5 cents on October 27.

While the shares are currently trading below the rights offer price, shareholders are induced to take them up with one option for every two shares, exercisable at 48 cents each.

Broking analysts covering the stock estimate a European trial to cost about $35 million and Mr Diamond isn't exactly arguing with that.

A US trial could cost a similar amount, although some savings may be possible if offshore data is allowed. While an equity raising seems the most likely route, a partnering arrangement is possible.

Late last year, Antisense raised $8.5 million in an oversubscribed placement and share purchase plan, which followed a $1.6 million in a placement in March 2019 and a $5 million placement in 2019.

Antisense shares over the last 12 months have wandered between nine cents (mid December 2020) and 25 cents (January and April this year).

When we last looked at Antisense in September 2019 the stock traded at 5.3 cents for a market cap of $22 million, so investors have been rewarded for their patience.

Dr Boreham's diagnosis:

Antisense has some other tricks up its sleeve to reduce fibrosis in other human diseases, including a recently-inked collaboration with the Murdoch Children's Research Institute (at the RCH) on other rare inflammatory disorders.

Commercially speaking, why focus on rare disorders?

Mr Diamond says while multiple sclerosis is a much bigger market, it's also a crowded one. So, if a rare disease isn't too rare, it can be more lucrative with lower development costs.

As we said at the outset, regulatory argy-bargy is not exactly fascinating for investors, but behind the scenes there's real progress at Antisense

What's clear is that after two decades in the chair, Mr Diamond isn't about to throw in the towel.

And if the European trial founders, it won't be for lack of cash.

Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He tried to enter Toorak once, but was turned back by blue rinse border control.