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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Mesoblast

By TIM BOREHAM

ASX code: MSB

Nasdaq code (American depository receipts): MESO

ASX Share price: $1.27

ASX shares on issue: 498,626,208

Market cap: $633.3 million

Nasdaq ADRs on issue: 99.8m.

Chief executive officer: Prof Silviu Itescu

Board: Brian Jamieson (chairman)*****, Prof Itescu, William Burns, Donal O'Dwyer, Dr Eric Rose, Michael Spooner, Joseph Swedish, Shawn Tomasello

***** Mr Jamieson retires at the end of March. His successor as chairman is yet to be announced.

Financials (December half): revenue of $US13.5 million ($A18.8 million), loss of $US44.1 million ($A61.5 million), cash balance $US77 million ($A108 million)

Identifiable major shareholders: M&G Investment Group 13.7%, Prof Silviu Itescu 14.4%, Capital Group 7.95%, Thorney Holdings 5.1%.

Mesoblast founder and CEO Prof Silviu Itescu says he's "95 percent" certain the stem cell drug developer is on the cusp of doing what no other Aussie biotech in phase III trial stage has done in its own right: winning US Food and Drug Administration approval for a new therapy.

In which case it's 95 percent certain that Mesoblast should be worth a lot more than its current depressed valuation - perhaps many times more.

The drug in question is Remestemcel-L, a treatment for graft versus host disease (GvHD) that afflicts half of all allogeneic bone marrow transplant recipients.

Via its Japanese partner JCR Pharma, Mesoblast won Japanese approval and Temcell is generating royalties for Mesoblast.

Mesoblast is currently investing in a US sales force to sell the GvHD drug. Because half of bone marrow procedures in the US are carried out by 15 centres, it doesn't involve too many feet on the ground.

Prof Itescu says US approval would open up more than a market for which there is no other treatment.

"GvHD for us will be a bellwether for the whole platform," he says. "It will send a signal that US regulators are comfortable with mesenchymal stem cells, our manufacturing capability and safety."

The program is based on mesenchymal stem cell assets acquired from US pharma group Osiris Therapeutics in October 2013, for which Mesoblast paid $US50 million in cash and scrip plus $US50 million in milestones.

Prof Itescu's own developed cells are called mesenchymal precursor cells and they are in development for everything from congestive heart failure, lower back pain, arthritis and (previously) diabetes.

A tortured path

The world biggest listed player in mesenchymal stem cells and so-called precursor cells, since listing in 2004, Mesoblast has had more false starts than the Sydney to Melbourne fast rail.

From a peak valuation of $2.5 billion, Mesoblast's market cap has withered to around $600 million.

Culprits include a heart trial that failed to meet primary endpoints, a badly executed Nasdaq listing and Teva's decision to walk away from the heart program.

Or maybe the whole darn thing is just taking too long.

Still, Mesoblast is in the unprecedented position of having two approved therapies on market, while it's also in the throes of two phase III trials.

The company has also scheduled a pow-wow with the FDA to discuss potential fast track approval for its heart drug Revascor, as a preventative for gastrointestinal bleeding in artificial heart patients.

Mechanism of action

Using a proprietary process, Mesoblast selects precursor and stem cells from the bone marrow of healthy adults, creating a master cell bank. This cell kitty is then expanded into thousands of doses for off-the-shelf use, without the need for tissue matching.

Mesoblast is targeting a common market across all its disease indications: inflammation.

In the case of heart disease, tissue macrophages churn our inflammatory factors that damage heart muscle, cause fibrosis and vascular dysfunction.

The stem cells respond to severe inflammation by switching the culprit macrophages 'off' and converting them to nice cells that actually protect the heart muscle.

"This is the central mechanism in each of our disease states: heart failure, back pain, GvHD and rheumatoid arthritis," Prof Itescu says. "We have the potential to make a big difference in some very big disease states where inflammation is central."

What's what at Mesoblast

Mesoblast's approved therapies are for the aforementioned Temcell in Japan, as well as for perianal fistulas in Europe (renamed Alofisel for that market).

The fistulas are the number one surgical complication for Crohn's disease sufferers, occurring in about one in every 10 patients.

Ahead of a commercial launch in Europe, Mesoblast's global partner Takeda is negotiating pricing and reimbursement and also undergoing phase III fistula trials in the US.

"It's not one of our core products but it demonstrates that our intellectual property [IP] is the dominant IP in the mesenchymal stem cell space," Dr Itescu says.

Mesoblast is funding two phase III trials off its own bat in view of FDA filings: a whopper 566-patient one for chronic heart failure and a 404-patient effort for chronic lower back pain caused by disc degeneration.

Via its Chinese partner Tasly, Mesoblast is seeking Chinese approval for a phase III chronic heart failure trial.

Have a heart

The key motivation for the heart trial is that current medications such as beta blockers and statins have been around for 20 years or more. Meanwhile, heart disease is growing at a faster rate than ever with eight million new patients expected by 2030 in the US alone.

"We are targeting patients with class three or four disease, the sickest 15 to 20 percent of patients who have failed standard-of-care drugs," Prof Itescu says.

“Once you are in class three heart failure the likelihood of death over the next two years is as high as 20 percent. Once you are class four or end-stage heart failure, your chance of mortality in 12 months is 50 percent.”

He says any Tasly heart trial should generate data to support an FDA filing, or the US data could be used to support a Chinese application. “The closer they are in terms of patient population and endpoints the easier it is to use both filings,” Dr Itescu says.

The point about endpoints

“Primary endpoint” is a sensitive term at Mesoblast’s Collins Street HQ after a 159-patient trial of Revascor for end-stage patients using left ventricle assist devices (LVADs or heart pumps) came a cropper last year.

Well, in the eyes of the market it did, because the shares tumbled 28 percent.

In short, the trial - carried out by independent investigators at New York’s Mt Sinai School of Medicine and funded by the US Government National Institutes of Health - did not meet its primary endpoint of temporarily weaning patients from the LVADs.

But Prof Itescu stresses the “academic” endpoint was set by the investigators - not Mesoblast - and was never viewed by the FDA as clinically relevant.

“That [weaning] was not something of any interest to us,” he says. “What we were interested in, based on FDA guidance in writing, was reducing the major clinically meaningful problem of recurrent hospitalizations from major gastrointestinal bleeding.”

“And we did. We reduced bleeding rates by 76 percent and hospitalization by 65 percent and these numbers were identical to an earlier pilot trial.”

Mesoblast is now using an “innovative” endpoint that measures hospitalizations - a measure not targeted in early stage heart patient trials because thousands of patients are required to show a statistically valid result.

Under what’s known as ‘joint frailty’ model commonly used in cancer patients, the total burden of the disease is taken into account.

The secondary endpoint - the time to and incidence of mortalities - is simple enough. The ideal data package will result in reduced deaths and hospitalizations, but not reduced hospitalizations because more of the patients are dying.

Finances and performance

Mesoblast lost a cool $US44.1 million during the half, on revenue of $US13.5 million (including $US11 million of milestone payments from Tasly).

But with a cash balance of $US92 million, Mesoblast is well placed to absorb inevitable further losses as the phase III trials advance. The December end balance of $US77

million was bolstered by a payment of $US15 million in January from Hercules Capital, triggered after the company met its bleeding and hospitalization secondary heart endpoints.

Given Mesoblast's sickly share price, management has steered clear of equity funding in favor of innovative non-dilutive debt funding.

One is a facility with Novaquest, by which the capital is not paid until the company reaps revenue from Remestemcel in the US.

"This sort of financing does not exist in Australia but is commonplace in the US," Prof Itescu says. "When we have a strong share price we would probably do equity. The good news is that in the US structured financing is very attractive."

Over the last decade Mesoblast's ASX shares have traded as high as $9 (October 2011) and as low as $1.03 (December last year).

Around eight percent of Mesoblast stock is 'shorted' which means it's in the hands of arbitrageurs who have sold the stock in the hope of buying it at a lower price.

NASDAQ 'victory'

When Mesoblast dual-listed on the Nasdaq in November 2015 - accompanied by a $US63m capital raising - it was assumed the American depositary receipts would benefit from those sophisticated Yankee investors re-rating the stock.

It didn't pan out that way - the shares dropped by one-third - but the company claims victory anyway.

Why? The primary aim of the exercise was to enhance liquidity and this is what occurred. The twist is that the boosted volumes have related to the ASX 'home' stock, not the Nasdaq ADRs. But the Nasdaq listing has removed the impediment of most US funds being confined to stocks subject to US governance.

Dr Boreham's diagnosis:

Mesoblast has its fans and detractors - possibly not much in between - and finally the company is at a juncture where one camp will be proved right and the other wrong.

The US institutions covering the stock are firmly in the bullish camp: Cantor Fitzgerald ascribes a 'price target' for the ADRs, currently trading at $US4.39 a share, of $US23. Maxim Group and Oppenheimer guesstimate they're worth $US16 and $US14, respectively.

Despite its zeal, Cantor Fitzgerald cites the heart failure program as the biggest market opportunity, but ascribes only a 40 percent chance of success. It also notes that Mesoblast's core patents expire in 2029.

The short-term proof lies in whether the FDA does indeed approve Remestemcel-L for GvHD and then whether it bestows fast-track status on the gastrointestinal bleeding program.

Meanwhile, the back-pain program offers a potential solution to the US scourge of opioid abuse.

Prof Itescu says the brutal truth is that 50 percent of drugs will fail after phase III stage. Even so, Mesoblast is confident of joining the pantheon of 'Aussie global biotech champions' alongside the likes of CSL and Cochlear.

"Australian investors need to understand [that drug development] is not for the faint-hearted," he says. "It's expensive, but this is how you build an industry. You can't skimp on it and it's not for short term returns."

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He's 95 percent sure he doesn't really understand the science of stem cells but neither does the market.