Biotech Daily

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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 shares): MESO

ASX shares on issue: 648,696,070
Nasdaq ADSs: 129,739,214

ASX share price: $1.555; **Market cap:** $1.01 billion

Chief executive officer: Prof Silviu Itescu

Board: Joseph Swedish (chair), Prof Itescu, William Burns, Donal O'Dwyer, Dr Eric Rose, Michael Spooner, Philip Facchina, Shawn Cline Tomasello

Financials (September quarter 2021): revenue $US3.59 million (up 175%), loss of $US22.7 million (previously a $US25.3 million deficit), cash balance $US116.0 million (down 15%), borrowings $US96.4 million (up 2.2%)

Year to June 30, 2021: revenue of $US7.46 million (down 77%), loss of $US98.8 million (previously $US77.2 million deficit), cash balance $US136.9 million (up 5.8%), debt $US94.24 million (up 5%) - $US1.00 = $A1.41

Identifiable major shareholders: Prof Silviu Itescu 10.8%, M&G Investment Group 8.2%, Thorney Holdings 5.3%.

When we last covered the stem cell developer in March 2019, the world was a different place in which medical knowledge pertaining to viruses and vaccines was the preserve of virologists and epidemiologists (which, by the way, no one could spell).

But as our former French friends say: *plus ça change, plus c'est la même chose*.

At the time, Mesoblast founder and CEO Prof Silviu Itescu was “95 percent” certain the company would do what no other Aussie biotech in phase III trial stage had achieved. And that was winning US Food and Drug Administration (FDA) approval for a new therapy.

As it happened, that accolade went to the public, not-for-profit Medicines Development for Global Health and Mesoblast is still awaiting its maiden FDA approval, for its proposed treatment for children’s graft-versus-host disease (GvHD) called remestemcel-L.

The company got awfully close, with an FDA oncological expert committee overwhelmingly recommending approval, but the FDA itself would not budge and demanded at least one additional trial.

Then Covid hit and Mesoblast entered the race to develop an effective treatment for the respiratory effects of Covid-19 and is pursuing late-stage treatments for chronic heart failure and chronic lower back pain.

The company is extremely keen on GvHD approval because it will show the FDA is comfortable with its mesenchymal stem cell platform, acquired from US pharma group Osiris Therapeutics in 2013.

In turn, this will help its Covid-19 program.

The story to date

For close to two decades Mesoblast has taken investors on a whipsaw up-and-down journey that makes New Jersey’s Kinga Ka - dubbed the world’s scariest roller coaster - look like a merry-go-round ride.

The world’s biggest listed player in mesenchymal stem cells and so-called precursor cells, the Melbourne-based Mesoblast was founded by Prof Itescu.

The company listed on the ASX in 2004 and then on the Nasdaq in late 2015.

The Osiris assets were acquired in 2013.

Mesoblast’s setbacks include the heart trial failing to meet primary endpoints, a botched Nasdaq listing and a decision by Teva to walk away from the heart program tie-up.

Where it all stems from

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, and arthritis to (previously) diabetes.

The company receives royalties or milestones on two non-US approved products: for GvHD in Japan (Temcell, marketed by JCR Pharmaceuticals) and for perianal fistulas in Europe (Alofisel, marketed by Tigenix).

Perianal fistulas are a common complication of Crohn's disease.

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 out 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.

The inflammation mechanism-of-action means the platform is relevant for conditions including heart failure, back pain, GvHD and rheumatoid arthritis.

The heart of the matter

In 2018, a phase III, 159-patient investigator-led trial of Revascor (rexlemestrocel-L) for chronic heart failure failed to reach its primary endpoint of temporarily weaning patients from left-ventricle assist devices.

The targeted patients had class III or IV heart disease (as categorized by the New York Heart Association, or NYHA) and had failed standard of care drugs.

Mesoblast shares tumbled 28 percent on the news, but the narrative quickly moved on from what Prof Itescu dubbed "academic" endpoints set by the regulators.

The company turned to data showing that Revascor reduced gastro-intestinal bleeding by 76 percent and hospitalization by 65 percent. In June 2019, the company won FDA orphan drug status for the gastro-intestinal bit, but not much seems to have happened since.

In 2020, Mesoblast's own 537-patient, phase III, cardiac trial also missed its primary endpoints, but the company said it reduced cardiac events.

In a 'late breaking' presentation to the American Heart Association's pow-wow in November 2021, the company's co-principal investigator Dr Emerson Perin outlined a "significant relationship" between the presence of systemic inflammation (as quantified by a protein biomarker) and rexlemestrocel-L treatment.

Dr Perin is managing director of the Texas Heart Institute.

'Late breaking' is not about a Jimmy Olsen scoop for the Daily Planet, but is original work completed after submission deadline. The contents must be deemed to be of urgent and significant scientific important.

The gist of the findings is that when combined with standard-of-care treatment, rexlemestrocel-L reduced the incidence of cardiovascular death, heart attacks and strokes by 33 percent. This was in relation to NYHA class II and class III patients.
Of the 301 patients with high inflammation, the efficacy increased to 45 percent.

The company and the FDA are discussing the way forward, with the agency likely to require a confirmatory study for the highly inflamed cohort.

Graft-versus-host disease

Graft-versus-host disease (GvHD) affects about half of all allogeneic (off-the-shelf) bone marrow transplant recipients.

The company carried out three paediatric trials which in effect showed remestemcel-L improved the “dismal survival” of kids with chronic forms of the disorder.

“This is surely one of the cruelest diseases, striking - and often taking innocent, young children who have already undergone the ordeal of a bone marrow transplant,” chair Joseph Swedish told the company’s AGM this week.

Mesoblast thought FDA approval was a dead cert after an FDA advisory committee voted overwhelmingly in favor of the data, but then the agency itself requested that Mesoblast do more work.

It was thought the agency would demand an additional adult trial, but the talks now centre around quality control aspects such as potency assays to ensure consistent batches.

“We do not believe we will have to do any further clinical study for remestemcel-L and GvHD,” Prof Itescu says.

Acute respiratory distress syndrome (ARDS)

In December last year, the US data safety monitoring board (DSMB) advised Mesoblast to call it a day with the 223 patients it had already recruited for its Covid trial, rather than the targeted 300.

The trial pertained to ventilator-dependent patients with moderate to severe acute respiratory distress syndrome or ARDS - the cause of most Covid fatalities.

The DSMB opined the trial was unlikely to achieve the stated primary endpoint of a 43 percent reduction in ventilated patients at 30 days.

Mesoblast argued that better patient management meant that fatalities had declined overall and the issue was all about trial design.

Not one for turning, Mesoblast has ploughed on with analyzing the patient data. In July, the company said remestemcel-L reduced mortality through 60 to 90 days in the pre-specified population under 65 years old, by 48 percent.

The company plans to move forward with an additional phase III trial in Covid-19 ARDS and is discussing trial protocols with the FDA.

In November 2020, Mesoblast and Novartis entered a deal to commercialize a Covid treatment.

The compact, which is yet to be finalized, involves a potential $US50 million cash injection, $US25 million in equity and up to $US1.25 billion in additional milestones.

Chronic lower back pain

With 50 percent of US opioid prescriptions pertinent to chronic lower back pain, Mesoblast is targeting reduced use of these addictive substances.

In February this year, a phase III trial of rexlemestrocel-L for chronic lower back pain caused by disc degeneration also failed to meet its primary endpoints but showed the therapy provided a “safe, durable and effective” alternative, with best results when dispensed early in treatment.

A trial of 404 patients showed at least two years of pain reduction, relative to a saline placebo. Of the 168 patients prescribed opioids, there was a 40 percent reduction in opioid use over this period.

German pharma house Grunenthal has the European and Latin American rights to the back pain indication.

Mesoblast is entitled to $US112.5 million ahead of a European launch, of which $US17 million has already been received. Cumulative milestone payments could reach $US1 billion.

Chronic back pain affects about 30 million Americans and 40 million Europeans.

Finances and performance

Mesoblast has a history of steep losses, but it also has been adept at raising big licks of capital when needed.

The company reported a $US100 million pre-tax loss in the year to June 2021, taking losses over the last five years to $US442 million.

The company derived modest revenue from Temcell: $US7.2 million in the 2021-’21 year (up 10 percent) and $US2.4 million in the September quarter (up 90 percent year-on-year).

Following a $US110 million private placement, Mesoblast has a cash balance of $US136.9 million as of June 30 2021.

Then there’s the debt.

In 2018, Mesoblast entered a $US75 million facility with Hercules Capital Inc, $US50 million of which had been drawn.

In late November 2021 the company repaid the facility after negotiating a $US90 million arrangement with Oaktree Capital Management (with $US60 million drawn down). The first three years of the five-year loan are interest free.

Mesoblast also has a $US40 million eight-year facility with Novaquest, which has been $US30 million drawn at a 15 percent interest rate.

The aforementioned Novartis deal, if executed, is another source of funding.

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.

Dr Boreham's diagnosis:

It's been another frustrating 12 months for Mesoblast.

As chair Swedish told this week's pow-wow: "2021 has been a rollercoaster year for the world and a challenging year of both meaningful progress as well as some setbacks for Mesoblast."

He adds that the company's core therapies have "continued to deliver results that demonstrate their lifesaving potential in addressing four complex medical disorders".

One way of looking at Mesoblast is it's in an exciting position with three phase III trials. If the FDA approves just one of them, more meaningful revenues will flow. Broker Bell Potter estimates peak sales of $US137 million a year for the GvHD therapy.

As exemplified by investors taking a short position in the stock, the alternative view is that Mesoblast is a serial disappointer that's running out of excuses.

What's certain is that investors need to keep a tight grip on the guard rail as the roller coaster ride continues.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He has submitted many articles after deadline but is yet to cry: "hold the front page!"