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:** MESO (American depositary receipts)

Share price: $3.37

Market cap: $1,967.9 million

Shares on issue: 583,949,612

Chief executive: Prof Silviu Itescu

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

Financials (nine months to March 2020)*: revenue $US31.5 million (up 113 percent), loss of $US45.3 million (previously a $US69.1 million deficit), cash balance $US60.1 million** (up 19%).

March quarter: revenue $US12.2 million (up 870%), loss of $US17.2 million (previously $US27.1 million loss)

* $US1.00 = 68 Australian cents; ** Before $US90 million capital raising

Identifiable major holders: Prof Itescu 11.8%, M&G Investments 10.86%, Thorney Holdings 5%.

The world's biggest listed pure-play stem cell developer has a busy slate of clinical work, notably in therapies for advanced heart failure, chronic back pain and graft-versus-host disease (GvHD).

Now these programs are approaching a thrilling denouement and, as the Demtel man enthused, there's more: Mesoblast is also undertaking an expanded coronavirus trial after a 12-patient effort showed promising results in treating acute respiratory distress syndrome (Ards), the usual cause of death with Covid-19.

The patients received infusions of Mesoblast's allogeneic (off the shelf) mesenchymal stem cell candidate, remestemcel-L, acquired from Osiris for $106 million in 2013.

Meanwhile, results from two phase III trials are expected this (September) quarter: a 566-patient effort for chronic heart failure and a 404-patient trial for chronic lower back pain caused by disc degeneration.

And in September, the US Food and Drug Administration will rule on whether or not the company can market its GvHD therapy on American shores.

Mesoblast founder and CEO Prof Silviu Itescu notes that across all its therapies the company is targeting the most severe cases where alternative therapies don't exist.

Stem cells for dummies

Mesoblast's proprietary process 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 (cells) churn our inflammatory factors that damage heart muscle and 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."

Mesoblast's patchy history

Backed by the Pratt family's listed investment vehicle Thorney Investments, Mesoblast debuted on the ASX in 2004 and reached a peak valuation of $2.5 billion in 2011 before suffering a reality check.

Culprits included a phase II heart trial that failed to meet primary endpoints, a badly executed Nasdaq listing and Israel pharma house Teva Pharmaceutical's decision to walk away from a heart program partnership in 2016.

Mesoblast dual listed on the Nasdaq in November 2015, accompanied by a $US63 million capital raising.

Mesoblast's Ards and GvHD programs are based on mesenchymal stem cell assets acquired from US pharma group Osiris Therapeutics in October 2013.

Mesoblast's own-developed cells are called mesenchymal precursor cells and they are being developed for rheumatoid arthritis and diabetic nephropathy, as well as the aforementioned heart failure and lower back pain programs.

Covid-19: an 'Ard one to crack

Acute respiratory distress syndrome (Ards) is bought on by an excessive immune response to the virus in the lungs. The immune cells produce inflammatory cytokines, which destroy lung tissue and can also damage the liver, kidney and heart.

"Remestemcell-L has the potential to tame the cytokine storm in Ards and may offer a life-saving treatment for those unfortunate individual sufferers of Covid-19 Ards," Prof Itescu says.

Mesoblast's Covid-19 proclamations have been coming so thick and fast that it's been 'Ard(s) just to keep up. But the core excitement cluster was around Mesoblast's April 23 disclosure of the results of the trial at New York's Mt Sinai Hospital, covering moderate to acute Ards cases.

Under the compassionate use protocol, the patients were treated with two infusions of remestemcel-L over the first five days.

The results? Nine of the 12 patients came off a ventilator within a median 10 days, with 83 percent survival (the Grim Reaper's spin on this is that two of them died).

In comparison, only nine percent of patients at one reference hospital (38 out of 445 patients) were able to come off the ventilator with standard-of-care treatment.

Another US hospital reported that only 38 patients of 320 – or 12 percent - survived.

But the jury's out

Of course, 12 people good and true are adequate numbers for a jury, but sub-optimal to comprise a statistically significant trial.

Thus, the company is enrolling 300 patients in a phase III, randomized, controlled trial of severe Ards patients at 30 sites.

The first patients were dosed in early May, with about 15 sites established as the company 'chases' the disease from the north-east to the southern states.

Mesoblast chief medical officer Prof Fred Grossman says the company is carefully choosing “hot spots” such as Alabama which, as of late May had the ‘no vacancy’ signs outside its intensive care wards.

“The sites are recruiting quite quickly,” he says. “There is a tremendous interest in this study.”

The trial leaders will undertake an interim analysis at 30 days, and when 30 percent of patients have reached their primary endpoint. At that point the trial can be dumped on futility grounds, or expanded to the control group because it appears to be working.

Remestemcell-L has investigational new drug (IND) status with the US Food and Drug Administration, meaning the company swiftly can initiate trials on patients with “very dismal” prospects.

Have a heart

Long-suffering Mesoblast investors will recall that the company’s shares tumbled 28 percent in November 2018 after a 159-patient trial of Rexlemestrocel-L (Revascor) for end-stage heart failure did not meet its primary endpoint of weaning patients from left ventricle assist devices (LVADs or heart pumps).

The company claimed the endpoint was set by the independent !!! investigators and was of little real clinical interest. What really mattered was that the trial showed reduced gastrointestinal bleeding by 76 percent and hospitalizations by 65 percent.

Investors are now nervously awaiting the first readout of the broader 566-patient chronic heart failure trial across 59 US sites.

Mesoblast targeted patients with class three or four disease, the sickest 15 to 20 percent of patients who have failed standard-of-care drugs.

Class three patients have a 20 percent chance of dying within two years while with class four it’s a case of flip a coin that you will be around in 12 months.

At this stage, Mesoblast retains its heart treatment rights except in China, where it is partnered with Tasly Pharmaceutical.

A pain in the … back

Mesoblast’s phase III back pain trial aimed to enroll 404 patients with lower back pain caused by degenerative disc disease. The endpoint of the trial, dubbed MPC-06-ID, is an “improvement in pain and function” over 24 months.

As with the heart trial, results are imminent and it’s a toss-up as to what release will hit the ASX announcements feed first.

The company is liaising with its global back pain partner Grunenthal GmbH about the clinical protocol for a European phase III confirmatory trial.

Graft-versus-host disease

In Japan, Mesoblast is partnered with JCR Pharmaceutical for its approved GvHD treatment called Temcell - and it's off and racing in that smallish but enthusiastic market.

Meanwhile, the company is angling to enter the US market for a similar GvHD treatment, branded Ryoncil.

GvHD afflicts about half of the 30,000 patients annually undergoing allogeneic bone marrow transplant, typically for blood cancers, with their bodies rejecting the 'alien' transplant.

In March, the FDA granted priority review with a September 30 'action date', but we might have a good idea of the outcome in August.

Why? Because that's when the FDA's relevant advisory committee meets to vote on the matter - and the (virtual) gathering is open to the public.

A date is yet to be set. While advisory committee views are not binding on the FDA, they usually presage the final decision.

If approved, Mesoblast could be selling Ryoncil in the US by the time we're carving the Christmas turkey (badly, in the case of your columnist).

Finances and performance

Buoyed by the Covid-19 results, Mesoblast in May wasted no time tapping institutional investors for an idle $US90 million in a placement.

Mesoblast already had a healthy cash balance of $US60 million. The raising was struck at $3.20 a share, a modest seven percent discount to the prevailing price.

The funds, in the main, will be used to scale-up manufacturing of remestemcell-L and to support the phase III trial, as well as for "working capital and general corporate purposes".

The company also has $US67 million available through existing financing facilities and partnerships.

Mesoblast reported revenue of $US31.45 million for the nine months to March 2020, up 113 percent. The reported loss narrowed 34 percent to $US45.3 million, reflecting curtailed research and development spend by $US7.5 million, or 15 percent.

The revenue included $US5.9 million of JCR royalties from Temcell sales in Japan and milestone revenue of $US25 million.

The company stands to pocket up to $US150 million of royalties and milestones from Grunenthal prior to any European launch of Revascor. Successful sales could result in up to $US1 billion in milestone payments.

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). Mesoblast was elevated to the ASX200 index on June 12.

Dr Boreham's diagnosis:

To the Meso-sceptics the company has promised far too much with limited commercial success, while raising $1 billion since listing 16 years ago.

Dare we say that Mesoblast now looks more focused and to be getting somewhere?

When we last covered Mesoblast in March 2019, Prof Itescu said he was "95 percent" certain the company would do what no other Aussie biotech in phase III had done: win FDA drug approval.

Well, Clinuvel has stolen that "Aussie first" honor, but Mesoblast is well placed to get over the line with a GvHD treatment in the US, which presents a market eight times the size of Japan's.

It's certainly rare for a biotech to expect results for three major trails and a key regulatory decision in the space of months.

If the heart and back pain results are definitively positive and the FDA green lights GvHD, the company hits the jackpot. If two or more of them bomb … let's not go there.

Your ultra conservative columnist regards the Covid-19 stuff as the icing on the cake with an outside chance of success, especially given the hundreds of other programs in the coronavirus-busting sector.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. But he hopes to become proficient in turkey carving by December 25.