Biotech Daily

Friday August 4, 2023

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: 814,204,825; **Share price:** 47 cents; **Market cap:** $382.7 million

Chief executive: Prof Silviu Itescu

Board: Joseph Swedish (chair), Prof Itescu, William Burns, Dr Eric Rose, Michael Spooner, Philip Facchina, Michael Spooner, Dr Philip Krause, Jane Bell

Financials (June quarter 2023): receipts $US1.83 million, cash outflows $US16.278 million, cash of $US71.32 million*, drawn debt $US90 million, undrawn debt $US40 million

Year to June 30 2023: receipts $US7.48 million, cash outflows $US63.27 million

Identifiable major shareholders: Prof Silviu Itescu 9.2%, M&G Investment Group 6.38%, G to the Fourth Investments LLC 6.62%. Thorney Holdings ceased to be a substantial holder in August 2022, having last disclosed a 5.3 percent stake in August 2021. The company cited dilution as a result of the August 2022 $US45 million capital raising.

Oh, gawd!

This week's US Food and Drug Administration (FDA) adjudication on Mesoblast's graft versus host disease (GvHD) therapy was a bombshell for both the long-suffering company and the life sciences sector as whole.

To management's chagrin, the FDA knocked back the company's marketing application to sell its lead candidate, remestemcel-L, in the US for paediatric GvHD.

Assent would have marked the first commercial product for Mesoblast in a major market and endorsed its stem-cell science for other indications including back pain and heart disease.

Strictly speaking, the FDA says it requires more supportive data and has told the company to do a phase III trial. The company will do that, albeit with highest-need adult patients.

The so-called Biologics licence application (BLA) was Mesoblast's second attempt: the FDA rejected a similar entreaty in 2020, despite an advisory committee voting nine to one in favor of approval.

"It is clear they [the FDA] would like additional data to get the comfort the product continues to demonstrate survival benefits in the hardest-to-treat, highest-risk patients," Mesoblast founder and CEO Prof Silviu Itescu said today.

He adds: "We remain steadfast in making remestemcel-L available to both children and adults suffering from this devastating disease and have received substantial clarity on how to bring this much-needed product to these patients."

Investors took a less charitable view, slicing close to half a billion dollars from the value of Mesoblast shares and sending them to a 22-year low.

The FDA refusal follows Mesoblast's setbacks with its heart, back pain and Covid-19 programs, while its Nasdaq listing failed to deliver the expected value uplift.

What just happened?!

When the FDA rejected the company's application in 2020, the agency told the company at the time to do another trial.

A baffled Prof Itescu said the company went through a prolonged "resolution process", in which the FDA asked for improved potency assays and the like - but dropped the trial requirements.

The agency found no safety issues with the 1,300 patients treated with the therapy to date. FDA inspectors also visited Mesoblast's Singapore stem cell manufacturing operations and found no outstanding issues.

"We had fully anticipated the additional clinical data including long-term survival benefits would be sufficient to allow a sequenced approach to the market," Prof Itescu says.

'Sequenced' refers to kids first, adults next. About 80 percent of GvHD sufferers are adults.

Bell Potter analyst John Hester remarked: "It seems the FDA keeps moving the goalposts here."

Usually associated with bone marrow recipients suffering blood cancers, GvHD is commonly treated with steroids but this treatment is ineffective for many patients.

From where did Mesoblast stem?

Mesoblast was founded by Prof Itescu, a recognized adult stem cell guru who worked in New York.

The company's technology was developed over 10 years by the Institute of Medical and Veterinary Sciences and the Hanson Institute in Adelaide.

Prof Itescu had founded Angioblast Systems Inc, which specialized in heart stem cell therapies.

Mesoblast listed on the ASX in December 2004, having raised $21 million at 50 cents apiece and then on the Nasdaq in late 2015. Mesoblast acquired one-third of Angioblast at the time of the initial public offer (IPO) and mopped up the remainder in 2010.

In another seminal deal, it bought the intellectual property of US pharma group Osiris Therapeutics in 2013, for around $US100 million including milestones – mostly in scrip. Crucially, this delivered the GvHD indication.

The company receives royalties or milestones on two non-US approved products: for GvHD in Japan (Temcell, marketed by JCR Pharmaceuticals) and for peri-anal fistulas in Europe (Alofisel, marketed by Tigenix). Perianal fistulas are a common complication of Crohn's disease.

How it all works

As we mentioned, the GvHD program pertains to the mesenchymal stem cell (MSC) platform, acquired from US pharma group Osiris Therapeutics in 2013.

Prof Itescu's original tech was something else called mesenchymal precursor cells, relevant for ailments including congestive heart failure, lower back pain and arthritis, and previously diabetes.

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.

GvHD treatment is hard graft

Graft-versus-host disease (GvHD) affects about half of all allogeneic (off-the-shelf) bone marrow transplant recipients, affecting the skin, liver and gastrointestinal tract.

There are more than 30,000 bone marrow transplants annually, of which about 6,000 are children (1,500 of them in the US)

In the case of patients resistant to the standard-of-care of steroids, mortality rates are as high as 90 percent.

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

The data from 51 patients showed a 51 percent survival rate at year two, compared with 35 percent for the standard of care.

More trials and tribulations

Mesoblast plans a so-called type A meeting with the FDA within the next 45 days to nut out the size and scope of the adult trial.

Prof Itescu can’t provide too much detail until then, but says the trial will cover as many as 40 US sites. Given the participants will not have responded to treatment and are very ill, there will not be a placebo arm.

As for the cost, the company is working with academic parties in the bone marrow space to share the funding burden and access available inventory (bone marrow samples).

“We expect this to be funded as a bone marrow study,” he says.

Prof Itescu notes the intended patients have a 90-day survival rate as low as 20-30 percent, whereas adult emergency use of the stem-cell therapy showed much better outcomes.

Overcoming heartburn

Mesoblast’s heart program has been plagued by setbacks, but it is still beating.
In 2016, partner Teva walked away from a deal by which it would have funded the heart program (sending Mesoblast shares down 42 percent in a day).

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 (LVADs).

In 2020, a 537-patient heart trial, Dream-HF also failed to reach its primary endpoint of reducing heart failure events in chronic heart failure patients. But that’s not the end of the story (see below).

Dubbed Dream-HF, the randomized, double blinded, placebo-controlled effort showed that MSCs strengthened heart function at 12 months.

This was measured by left ventricle ejection fraction - how much blood the heart spurts - and decreased deaths from myocardial infarction and stroke over a 30 month follow up.

This was in relation to New York Heart Association (NYHA) class II and class III patients - the third worst category of four. Of the 301 patients with high inflammation, the efficacy increased to 45 percent.

Having been granted FDA assent to do so, Mesoblast now plans to launch two follow-up phase III trials for class II-III and late-stage patients on death's door.

A pain in the back

Mesoblast also has permission for a second pivotal phase III trial for chronic lower back pain, which affects about 30 million Americans and 40 million Europeans and really is ... a pain.

In February 2021, a 404-patient 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 key motivator is that a whopping 50 percent of US opioid prescriptions are for chronic back pain, Of the 168 patients prescribed opioids, there was a 40 percent reduction in opioid use over this period.

The new phase III trial will be testing rexlemestrocel-L alongside the standard of care of hyaluronic acid. The company hopes to start enrolling across US and European sites in the current quarter.

Finances and performance

Mesoblast has a knack of raising money when it needs it and sure enough in April 2023 it rustled up $US40 million via a placement.

The book was filled by mainly existing local and offshore investors.

In August last year, the company raised $US45 million, also in a placement, backed by British fund manager M&G Investments which became a substantial holder.

The company reported receipts of $US1.8 million in the June 2023 quarter, derived mainly from Japan from Temcell royalties. Total receipts for the year were $US7.48 million.

Cash burn for the quarter was $US16.28 million and $US63.27 million for the year.

The company has drawn debt of $US90 million and undrawn debt of $US40 million, mainly from facilities with Novaquest and Oaktree Capital Management.

Believe us - these arrangements are a tad more complicated than 'we lend, you pay us back': the Oaktree facility involves the issue of warrants, while the Novaquest tranche is only paid back after the GvHD drug is on the market.

Replenished by the April raising, Mesoblast had end-of-quarter cash of $US71.3 million. Dr Itescu now suggests that in order to preserve funds, the new GvHD trial will be prioritized over the back and heart programs

Mesoblast shares peaked at $9.30 in October 2011, briefly rendering Mesoblast the most valuable ASX biotech with a $2.7 billion market capitalization.

The stock today traded as low as 45.5 cents, just off the May 2005 record low of 39 cents.

Dr Boreham's diagnosis:

In Mesoblast's 2004 IPO prospectus the board noticed - presciently - that the $21 million raised "clearly ... would not be sufficient to deliver regulatory approval to sell the products".

As of June 2022, the AFR claimed the company had raised a staggering $US717 million ($A1,090 million).

The prospectus also envisaged a drug application being lodged within two to three years, which means the company remains about two decades behind schedule.

We guess that will make victory all the sweeter when a Mesoblast therapy is approved, but investors rightly question whether this majestic day will arrive for the accident-prone company.

Prof Itescu argues the company was always going to do an adult trial at around this time, but obviously wanted the paediatric product launched first.

In a revenue sense, GvHD approval for kids alone would not have been exactly company-making, with broker Bell Potter estimating peak sales of $US137 million.

But in terms of validating the company's science and product pipeline, an FDA tick of approval would have been priceless.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. His Go Fund Me efforts to date have failed to raise anywhere near $US717 million.