Biotech Daily

Friday August 4, 2023

Daily news on ASX-listed biotechnology companies

*** ASX UP, BIOTECH DOWN: PRESCIENT UP 7%; MESOBLAST DOWN 57%**

*** MESOBLAST FALLS 58% ON FDA 2nd REMESTEMCEL-L FOR GvHD CRL**

*** DR BOREHAM'S CRUCIBLE: MESOBLAST**

*** RESMED REVENUE UP 18% TO $6.4b; PROFIT UP 14% TO $1.9b**

*** ADALTA STARTS AD-214 EXTENSION TRIAL**

*** ADHERIUM: ALLERGY PARTNERS ADOPTS HAILIE ASTHMA MONITOR**

*** LBT $13.4m APAS NON-CASH IMPAIRMENT CHARGE**

*** RESPIRI REQUESTS 'SHORTFALL PLACEMENT' TRADING HALT**

*** AROA EGM 35% OPPOSE DIRECTOR OPTIONS**

*** SHENASABY, CALLAHANS INCREASE, DILUTED TO 5.25% IN BOTANIX**

MARKET REPORT

The Australian stock market was up 0.19 percent on Friday August 4, 2023, with the ASX200 up 13.6 points to 7,325.3 points. Thirteen of the Biotech Daily Top 40 stocks were up, 19 fell, seven traded unchanged and one was untraded. All three Big Caps fell.

Prescient was the best, up 0.5 cents or 7.1 percent to 7.5 cents, with 350,944 shares traded. Universal Biosensors climbed 6.5 percent; Impedimed improved 4.9 percent; Actinogen was up 3.45 percent; Emvision and Nanosonics rose more than two percent; Medical Developments, Opthea and Polynovo were up one percent or more; with Clinuvel, Cyclopharm, Next Science and Pro Medicus up by less than one percent.

Mesoblast led the falls, losing as much as 58.3 percent to 45.5 cents before closing down 62 cents or 56.9 percent at 47 cents, with 89.8 million shares traded. Pharmaxis and Resmed lost more than nine percent; Kazia shed 6.45 percent; Dimerix was down 5.3 percent; Alcidion and Amplia fell four percent or more; Atomo and Cynata were down more than three percent; Imugene, Neuren, Starpharma and Telix shed more than two percent; 4D Medical, Genetic Signatures, Nova Eye, Orthocell, Paradigm and Proteomics were down more than one percent; with Cochlear, CSL and Volpara down by less than one percent.

MESOBLAST

Mesoblast fell as much as 58.3 percent following the US Food and Drug Administration's second refusal of injected remestemcel-L for paediatric graft versus host disease.

Mesoblast said the FDA had provided a complete response letter (CRL) to its biologics licence application (BLA) resubmission for remestemcel-L, or Ryoncil, for paediatric steroid-refractory acute graft versus host disease (SR-aGVHD).

The company said the FDA "requires more data to support marketing approval".

In 2020, Mesoblast said the FDA required a further trial of Remestemcel-L for graft versus host disease and "recommended that [it] conduct at least one additional randomized, controlled study in adults and/or children to provide further evidence of the effectiveness of remestemcel-L for … graft versus host disease" (BD: Oct 2, 2020).

Today, a conference caller said the additional trial was not required, and the company said that "to obtain the data required … [it would] conduct a targeted, controlled study in the highest-risk adults with the greatest mortality".

Mesoblast said the adult study was "in line with our overall commercial strategy, which envisioned a sequenced progression from paediatric to adult SR-aGVHD indications".

The company said that adults comprised 80 percent of the SR-aGVHD market.

In the media release, Mesoblast chief executive Prof Silviu Itescu said: "FDA's inspection of our manufacturing process resulted in no observed concerns, the Agency raised no safety issues across more than 1,300 patients who have received remestemcel-L to date, and acknowledged improvements to our potency assay."

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

The company said it intended to enrol adult patients at the highest mortality risk with SR-aGVHD where existing therapy had not improved outcomes, and 90-day survival was as low as 20 percent to 30 percent.

Mesoblast said it generated pilot data through its emergency investigational new drug application program in adults showing a survival benefit with remestemcel-L.

The company said that "in-line with our overall commercial strategy to expand into the adult SR-aGVHD indication" it had been working to establish the adult follow-on study protocol, potentially utilizing established clinical trials networks and it would "seek alignment with FDA on the trial design … within 45 days".

The company said prior to the resubmission, the FDA guided Mesoblast to resolve outstanding chemistry, manufacturing and controls issues before any additional trial.

Mesoblast said the FDA completed the pre-licence inspection of the manufacturing facility, did not issue any Form 483, and found no objectionable conditions, and acknowledged in the resubmission review that changes implemented appeared to improve assay performance relative to the original assay version used in the paediatric phase III trial.

Mesoblast said it met the pre-specified primary endpoint, prospectively agreed with the FDA, of a single-arm phase 3 trial in 54 children with SR-aGvHD.

The company said the resubmission included long-term follow-up data from the phase III trial by the Center for International Blood and Marrow Transplant Research showing 50 percent survival through more than four years of follow-up for remestemcel-L treated patients for whom less than 20 percent survival at two years was expected based on disease severity.

Mesoblast said the resubmission included a post-hoc, propensity-matched study showing six-month survival was 67 percent with remestemcel-L compared to 10 percent with other unapproved therapies in highest-risk patients.

Mesoblast was down 62 cents or 56.9 percent at 47 cents with 89.8 million shares traded.

DR BOREHAM'S CRUCIBLE: MESOBLAST

By TIM BOREHAM

ASX code: MSB

Nasdaq code (American depository shares): MESO

ASX shares on issue: 814,204,825

Nasdaq ADSs: 162.84 million

ASX 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, quarters of available funding: 6.8

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%

***** Long term holder Thorney Holdings ceased to be a substantial shareholder in August 2022, having last disclosed a 5.3 percent stake in August 2021. The company cited dilution as a result of the $US45 million capital raising in August 2022.

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 has resolved to 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 also 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.

RESMED INC

Resmed says revenue for the year to June 30, 2022 was up 18.0 percent to $US4,222,993,000 ($A6,428,929,000) with net profit up 14.1 percent to $US1,224,400,000 ($A1,863,981,000).

Resmed said the increase in revenue was driven by higher demand for its sleep and respiratory care devices as well as reduced competitive supply, and increased sales of its software-as-a-service portfolio.

The company said it provided both US generally accepted accounting principles (GAAP) and non-GAAP data.

Resmed said it "uses non-GAAP information internally in planning, forecasting, and evaluating the results of operations in the current period and in comparing it to past periods ... [and] believes this information provides investors better insights".

This report quotes the non-GAAP data.

Resmed said it would pay a dividend up 9.1 percent to 48 US cents per US share for the three months to June 30, for the record date of August 17 and to be paid on September 21, 2023.

The company said its non-GAAP diluted earnings per share was up 11.2 percent to $US6.44.

Resmed said it had cash and cash equivalents of $227,891,000 at June 30, 2023, compared to $273,710,000 in the previous corresponding period.

Resmed chief executive officer Mick Farrell said the company continued "to produce and deliver cloud-connected flow generator device volume to meet the ongoing strong global demand from patients, accompanied by high growth of our market-leading patient interface and software solutions".

Mr Farrell said the company's supply of its cloud-connected platforms Airsense 10 and Airsense 11 enabled it to support customer demand for [continuous positive airway pressure] and [auto-adjusting positive airway pressure] devices.

"The strong growth of our mask and patient interfaces business was supported by new patient setups as well as ongoing resupply activity as we focus on increasing therapy adherence to improve patient outcomes and quality-of-life," Mr Farrell said.

"We continue to significantly grow our impact each quarter, improving over 160 million lives in the last 12 months, well on our way to helping 250 million lives in 2025," he said.

Resmed fell $3.15 or 9.3 percent to $30.70 with 8.8 million shares traded.

ADALTA

Adalta says it has dosed the first of up-to eight-patients in its phase I extension study of AD-214 for idiopathic pulmonary fibrosis and other human fibrotic diseases.

In May, Adalta said it had raised $3.15 million through a rights offer to fund a phase I extension study and in June said it had ethics approval for an up-to 16-patient, phase I, trial of AD-214 for lung and kidney disease (BD: May 25, Jun 29, 2023).

Today, the company said the study returned AD-214 to clinical trials "more than a year earlier than forecast in 2022" with data to be used to inform the safety profile and target dosing schedule for future phase II studies of the drug.

Adalta said the trial would dose six participants with AD-214 and two with placebo, with the first group of two patients having received the first of four 10mg/kg doses of the drug or placebo with no issues reported.

Adalta said it expected interim results by the end of 2023, with final assessment visits to be completed and full results expected to be available by April 2024.

Adalta was up 0.1 cents or 4.35 percent to 2.4 cents.

ADHERIUM

Adherium says the Asheville North Caroline-based Allergy Partners will adopt its Hailie asthma sensor technology, user application and clinician portal platform.

Adherium said Allergy Partners had more than 300,000 patients across 130 sites in 20 states, and the agreement included an initial roll-out of the Hailie asthma monitor platform to Allergy Partners clinics in three US states by October.

The company did not state the commercial terms of the agreement.

Adherium chief executive officer Rick Legleiter said the company welcomed “this ground-breaking partnership with Allergy Partners - part of our push to accelerate commercialization in the US through strategic, large-scale partnerships across health care systems”.

“Adherium and Allergy Partners are combining their expertise to make a powerful impact to improve patient lives with benefits for all stakeholders,” Mr Legleiter said.

Adherium was up 0.1 cents or 25 percent to 0.5 cents with 2.1 million shares traded.

LBT INNOVATIONS

LBT says it recognizes a “non-cash impairment charge of $13.4 million” relating to the carrying value of its automated plate assessment system (APAS) platform.

LBT said it also expected a non-cash write off of about $5.5 million in deferred tax assets and for both of these non-cash adjustments to be reflected in its financial results for the year to June 30, 2023.

The company said the impairment charge was based on lower-than-expected sales of its APAS culture plate imaging platform for the year to June 30, 2023, which increased the uncertainty of forecasting the expected timing of near-term and future sales.

LBT said because of this uncertainty, as well as its reduced share price and market capitalization at June 30, it believed its APAS technology had an indicative valuation that was materially below its $13.4 million carrying value.

The company said that it expected its APAS Pharma QC to be “a strong contributor to growth in future years” with Astrazeneca providing more than $1.1 million to fund its development, in anticipation of buying a number of instruments.

LBT chief executive officer Brent Barnes said the company was “confident of the opportunity for our APAS technology, but given current market valuations we believe taking a conservative position is an appropriate course of action”.

“Importantly this is an accounting focused, non-cash transaction which cleans up our balance sheet,” Mr Barnes said.

Mr Barnes said LBT continued to work with Thermo Fisher on sales and “we continue to be buoyed by positive feedback from potential customers who are pro-actively looking for solutions such as our APAS Independence and the progress being made with Astrazeneca”.

LBT was unchanged at 2.2 cents.

RESPIRI

Respiri says it has requested a trading halt regarding the placement of the shortfall in its share purchase plan announced on June 29, 2023.

In May, Respiri said it hoped to raise $2 million in a share purchase plan at 3.4 cents a share (BD: May 24, 2023).

Trading will resume August 8, 2023, or on an earlier announcement.

Respiri last traded at four cents.

AROA BIOSURGERY

Aroa says all five resolutions at its annual general meeting passed, but with up to 35.21 percent opposition to the issue of 211,000 options to director Dr Catherin Mohr.
Aroa said 92,804,908 votes (64.79%) supported Dr Mohr's options, exercisable at 87 cents by November 13, 2027, with 50,435,123 votes (35.21%) against.
The company said the 15.4 percent increase of the directors' fee pool to $NZ750,000 faced 18.77 percent opposition, John Diddams was re-elected with 93.33 percent of the vote, and the re-election of Dr Mohr and the auditors' remuneration passed overwhelmingly.
According to its most recent filing, Aroa had 343,109,468 shares on offer, meaning that the votes against Dr Mohr's options amounted to 14.7 percent of the company, sufficient to requisition extraordinary general meetings.
Aroa fell half a cent or 0.55 percent to 90.5 cents.

BOTANIX PHARMACEUTICALS

Perth's Shenasaby Investments Pty Ltd says it has increased its holding in Botanix and been diluted from 70,738,187 shares (6.52%) to 74,586,791 shares (5.25%).
Last week, Botanix said its placement raised $12.5 million, with proceeds expected to be used to extinguish future milestone and royalty payments to Fresh Track Therapeutics (BD: Jul 27, 2023) (AVW: Jul 28, 2023).
The substantial shareholder notice said that the holders were Catherine Callahan, Elise Horgan and Shenasaby Investments Pty Ltd.
Last year, Botanix executive director Matthew Callahan told Biotech Daily that Ms Callaghan was his spouse and Ms Horgan was the director of his investment company, Shenasaby, that held Botanix shares (BD: Sep 13, 2022).
Today, Shenasaby said on December 12, 2022 it bought 1,515,151 shares in a placement at 6.6 cents a share, on March 20 and May 18, 2023 it exercised a total of 2,333,333 performance rights and on July 27, 2023 it was diluted by the placement.
Botanix was up one cent or 7.1 percent to 15 cents with 6.1 million shares traded.