Biotech Daily

Friday April 24, 2020

Daily news on ASX-listed biotechnology companies

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MARKET REPORT

The Australian stock market was up 0.49 percent on Friday April 24, with the ASX200 up 25.5 points to 5,242.6 points. Twenty-two of the Biotech Daily Top 40 stocks were up, 13 fell, four traded unchanged and one was untraded.

Mesoblast was the best, up 76.5 cents or 39.9 percent to $2.73 with 37.7 million shares traded. Immutep climbed 16.7 percent; Osprey was up 10 percent; Proteomics rose 8.8 percent Patrys was up 7.1 percent; Actinogen and Next Science were up five percent or more; Imugene, LBT, Nanosonics and Prescient improved more than four percent; Ellex was up 3.6 percent; Amplia, Antisense, CSL, Optiscan and Starpharma rose more than two percent; Clinuvel, Medical Developments and Polynovo were up more than one percent; with Genetic Signatures, Opthea and Pro Medicus up by less than one percent.

Cynata led the falls, down four cents or 5.7 percent to 66 cents, with 143,729 shares traded. Both Impedimed and Universal Biosensors lost five percent; Avita and Resonance fell more than four percent; Cyclopharm and Paradigm shed more than two percent; Compumedics, Kazia, Neuren, Pharmaust, Resmed and Volpara were down more than one percent; with Cochlear and Telix down by less than one percent.

DR BOREHAM'S CRUCIBLE: PARADIGM BIOPHARMACEUTICALS

By TIM BOREHAM

ASX code: PAR

Share price: $1.495 **Shares on issue:** 224,737,176; **Market cap:** $336.0 million

Chief executive officer: Paul Rennie

Board: Graeme Kaufman (chairman), Paul Rennie, John Gaffney, Christopher Fullerton

Financials (half year to December 2019): income (bank interest) $694,904 (previously $11,125), loss of $5.1 million (previously $4.4 million deficit), cash of $108 million (post this month's $35 million capital raising)

Identifiable major holders (post capital raising): Paul Rennie 11.95%, Nancy Edith Wilson-Ghosh 1.74%, MJGD (technology vendor) 1.23%.

We know that gambling dens aren't open in these days of social distancing, but metaphorically speaking Paradigm is plonking it all on the black in terms of its "ballsy" pursuit of US approval for its drug for osteoarthritis pain.

On April 6, the company revealed the US Food and Drug Administration had knocked back its request for approval based on one phase III trial and "published literature" !!!!! to confirm efficacy.

Instead, the regulator demanded two "adequate and well controlled" trials, costing $80 million in all.

A setback indeed, albeit spun by the company as good news about gaining regulatory clarity. But even amid the Covid-19 market turmoil, two days later Paradigm had raised $35 million in a heavily oversubscribed capital raising to fully fund both trials.

CEO Paul Rennie says that one US fund manager dubbed the raising as "ballsy but brilliant".

"It was ballsy in that if we didn't raise the money the market would have wondered what had happened," he said.

"From management's point of view, it's a simple and straightforward program. We don't have to worry about the next raise, which is done and dusted."

All Paradigm has to do now is to convince the regulator that its repurposed drug is better than the opioid based alternative, which we guess makes the investment in the trials a considered investment rather than a rash bet.

Subverting the pain paradigm

The drug in question is the anti-inflammatory pentosan polysulfate sodium (PPS), a semi-synthetic drug made from beech-wood hemicellulose.

Renamed as the snappier Zilosul by Paradigm, PPS has been used to treat a bladder condition and deep vein thrombosis.

As well as dodgy knees, Paradigm is eyeing other conditions including viral osteoarthritis (Ross River fever) and the rare disease muco-poly-saccharidosis (MPS).

Paradigm listed on August 18, 2015, having raised $8 million at 35 cents apiece.

Paradigm's driving forces are Mr Rennie and chairman Graeme Kaufman.

Mr Rennie was Mesoblast's head of product development. Mr Kaufman chaired Bionomics and was executive vice president at Mesoblast.

Oh, and he was also CSL's chief financial officer through the behemoth's privatisation.

So far Zilosul has been used on about 600 patients, mainly through special access schemes but also in a 112-patient phase IIb trial.

The drug is widely used by 40 to 50 past and present AFL footballers to clear up knee and joint complaints and osteitis pubis. American (National Football League) footballers have also been treated for their creaking joints.

Shortly, the company expects to announce the results of the first 35 patients treated with the product intended to be used in the phase III trials.

Mr Rennie said the clinical outcomes were being measured in the same way as the proposed methods for the phase III trials.

"While it's not a trial, this data will give insight in terms of how the product is performing ... in patients with osteoarthritis ahead the trial."

By the September quarter the company hopes to have 100 to 200 results on hand.

Trial and error

Paradigm had hoped the FDA would accept the real-world evidence of the drug's safety and efficacy, but the regulator wanted to see more patients subject to controlled trails.

"We were a little bit surprised but it was not completely out of the realms of possibility," Mr Rennie says.

"This is Paradigm's first time in front of the Agency. We put up a good case but it's not unusual for the agency to fall back to a conservative position."

He maintains the regulator didn't have a problem with the data as such.

Paradigm is now preparing to lodge an investigational new drug application (IND), which will pave the way for the US trials.

"We think we have a very clear roadmap not only to IND but also to [a new drug application]," Mr Rennie says.

The first trial will enrol 750 patients and appraise the results after 22 months. The second (confirmatory) trial will enrol 400 patients over 12 months.

The trials will run concurrently, with a 12-month readout of all the patients expected by October 2022.

The endpoint is the same as the phase IIb effort: a reduction in pain from baseline at day-53, as assessed by the 24-question Western Ontario and McMaster Universities (WOMAC) pain scale.

As reported in December 2018, the local phase IIb trial showed that 46 percent of patients had a 50 percent or more reduction in pain after 53 days, compared with 22.5 percent for the placebo group.

The trial injected PPS into the knee and compared it to injected saline. Some have questioned how injected PPS compares to oral – and commonly prescribed – non-steroidal anti-inflammatory drugs (NSAIDS).

The phase III trials will be designed to support a European approval application.

Locally, the company met with the Therapeutic Goods Administration on November 11 last year, in view of obtaining provisional compassionate use approval.

For Mr Rennie, the Remembrance Day pow-wow was unforgettable.

"That was a knockout meeting," he says. "The TGA agreed there was an unmet medical need for treatment of chronic pain, especially in chronic osteoarthritis."

The company hopes for TGA approval this year.

Meanwhile, Paradigm plans to lodge a joint scientific advice submission to the FDA and European Medicines Agency, in view of a common protocol for a simultaneous muco-poly-saccharidosis trial.

A phase IIa trial for viral osteoarthritis, or Ross River fever, produced "very impressive results, not only clinical and patient-assessed pain outcomes but good objective data with hand grip strength and other [measurements]".

Paradigm also has patents for post-operative pain and is working on a respiratory indication, which sounds intriguing in this Covid-19 world.

Exclusive supply

Paradigm has an exclusive supply deal with the only approved pentosan polysulfate sodium maker, Germany's Bene Chempharma.

Crucially, Mr Rennie says, the FDA confirmed the company's view that no-one else would be able to produce an acceptable PPS product.

He says the FDA is "well and truly familiar" with the Bene product, especially its "molecule within molecules" structure that can lead to safety issues.

Janssen Pharmaceuticals (Johnson & Johnson) sells an oral formulation of PPS under the name Elmiron, to treat a painful bladder disease called interstitial cystitis.

Otherwise Paradigm has PPS all tied up like pussy's bow, with patents on the relevant indications in injected oral or topical form.

The patents run until 2035 or 2040.

Mr Rennie says the exclusive supply deal with Bene Chempharma - under which Bene receives a 2.0 percent royalty - is as good as patent protection.

While Johnson & Johnson's patent expired in 2010, no generic alternative has been approved in the US.

"It's now clear why that's the case," Mr Rennie says. "It's almost impossible for another company to produce the identical product to Bene."

Finances and performance

Paradigm now has $108 million in the bank, having raised $78 million in a placement and rights offer last year,

Mr Rennie says the company has always worked in "cash preservation mode" - which suits the current zeitgeist to a tee. "We have always tried to have a very low burn rate and continue to do that without massive cost cutting," he says.

To date, Paradigm has drawn modest revenue from the special access programs here, or the expanded access programs in the US.

"We will continue to preserve cash until we get into the middle of our [phase III] trials, when our expenditure will increase," Mr Rennie says.

The latest raising was done at $1.30 apiece, a 23 percent discount to the prevailing price of $1.69.

While the stock has held up well post-raising, it's well off the peak valuation of $4.35 just before the February market meltdown. Over time they have traded as low as 26 cents.

Party pooper

Paradigm has a legion of supportive retail holders, with the latest raising bolstering the institutional component on the register. But it's not all backslapping at 10 paces, with broker Morgans dubbing the phase IIb (and follow up) osteoarthritis results as "unconvincing and lack[ing] substantive clinical evidence".

"We view the osteoarthritis data as an interesting trend," the firm says in a research note. "But it will likely require a more stringent trial design and analysis to flush out critical design parameters for a phase III trial and draw out a realistic commercial opportunity."

Morgans had the stock as a "reduce" - a polite way of saying sell - on February 17, when the stock traded at $4.17. It has since upgraded to a "hold", but remains wary that the US trials will be costlier and longer than originally expected.

Mr Rennie protests that regulatory submissions are "time consuming and exacting" and he's well aware of the number of drug developers stymied by sloppy paperwork. "It's better to answer the regulator's questions fully; otherwise we will get knocked out," he says.

Dr Boreham's diagnosis

In the US there are 31 million osteoarthritis sufferers (and three million here), so the condition is hardly confined to battle-weary professional athletes.

"Managing chronic pain is a major unmet medical need, especially in relation to opioid overuse and as we get older," Mr Rennie says.

Depending on the drug's pricing, achieving a 10 percent US market share would generate annual revenue of $US6.2 billion to $9.3 billion.

He notes that drugs that meet an unmet clinical need are generally recession proof. And as mentioned, Paradigm faces little or no competitive threat.

The benefit of repurposing a drug is that developments costs are much lower: $US30 million to $50 million compared with an average $US1.3 billion for a drug from scratch.

The chances of commercial success are also boosted, while the timeline to market is shortened from 15 years or more to perhaps fewer than five years.

Mr Rennie acknowledges that while Paradigm has the non-osteoarthritis rare diseases programs, the osteoarthritis efforts will make or break the company.

"The reality is that if your lead program fails, you are on Struggle Street," he says.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. Hopefully he is ballsy and brilliant enough to stay off Struggle Street.

MESOBLAST

Mesoblast says that 10 of 12 ventilator-dependent Covid-19 patients treated with its stem cells in New York have survived with nine no longer requiring ventilator support.

Mesoblast said that despite the small numbers, the results “contrast with only nine percent of ventilator-dependent Covid-19 patients being able to come off ventilators with standard-of-care treatment and only 12 percent survival in ventilator-dependent Covid-19 patients”.

The company said that the 10 surviving patients had moderate or severe acute respiratory distress syndrome (Ards) and were treated with two infusions of its remestemcel-L allogeneic mesenchymal stem cell therapy within the first five days under emergency compassionate use at New York City’s Mt Sinai Hospital.

Mesoblast said that nine of the 12 (75%) had ventilator support removed in a median of 10 days and seven of the 12 had been discharged from hospital.

The company said that the mesenchymal stem cell results contrasted with “only nine percent of ventilator-dependent Covid-19 patients being able to come off ventilators with standard of care treatment and only 12 percent survival in ventilator-dependent Covid-19 patients at two major referral hospital networks in New York during the same time period”.

Mesoblast said that the compassionate use treatment experience had “informed the design of the clinical protocol for the randomized, placebo-controlled phase II/III trial of remestemcel-L in ventilator-dependent Covid-19 moderate [and] severe Ards patients across North America.

The company said that patients received a variety of experimental agents prior to remestemcel-L.

Mesoblast cited a current study, titled ‘Factors associated with hospitalization and critical illness among 4,103 patients with Covid-19 disease in New York City’ which documented that 38 of 445 (8.5%) of ventilator-dependent Covid-19 patients at a major referral hospital network in New York City were able to come off ventilator support when treated with standard of care during March and April 2020.

The study is at https://www.medrxiv.org/content/10.1101/2020.04.08.20057794v1.full.pdf

The company cited a second study showing that 38 of 320 (11.875%) ventilator-dependent Covid-19 patients survived at a second major referral hospital network in New York City during the same period.

Mesoblast said the poor outcomes were consistent with earlier published data from China where mortality rates of more than 80 percent were reported in patients with Covid-19 and moderate or severe Ards.

Mesoblast chief executive Prof Silviu Itescu said that “the remarkable clinical outcomes in these critically ill patients continue to underscore the potential benefits of remestemcel-L as an anti-inflammatory agent in cytokine release syndromes associated with high mortality, including acute graft versus host disease and Covid-19 Ards”.

“We intend to rapidly complete the randomized, placebo-controlled phase II/III trial in Covid-19 Ards patients to rigorously confirm that remestemcel-L improves survival in these critically ill patients,” Prof Itescu said.

Mesoblast chief medical officer Dr Fred Grossman said there was “a significant need to improve the dismal survival outcomes in Covid-19 patients who progress to Ards and require ventilators”.

“We have implemented robust statistical analyses in our phase II/III trial as recommended by the US Food and Drug Administration in order to maximize our ability to evaluate whether remestemcel-L provides a survival benefit in moderate/severe Covid-19 Ards,” Dr Grossman said.

Mesoblast climbed 76.5 cents or 39.9 percent to $2.73 with 37.7 million shares traded.

CORRECTION: ONKO-INNATE PTY LTD

Last night's edition described Onko-Innate's Dr Christine De Nardo as the managing-director. Dr De Nardo is in fact the company's general-manager.
The article also said the company was working with Gilead's Kite Pharma on chimeric antigen receptor (CAR) T-cell therapy, whereas the collaboration is for chimeric antigen receptor NK-cell (CAR-NK) therapies.
The mistake was made by the Covid-19 sub-editor who was clearly out of his depth on cancer immunotherapies and has been reassigned to curing Sars-Cov-2 with marijuana.
We apologise unreservedly for the errors.

CARDIEX

Cardiex says deriving four heart and arterial health waveforms to measure clinically relevant vital signs is a "major milestone"
Cardiex said that it used a photoplethysmogram (PPG) to detect blood volume changes in the microvascular bed of tissue and the PPG sensor was an optical sensor array used on wearable devices consisting of light emitting diodes (LEDs) and photodetectors to measure heart rate and other general fitness features.
The company said it believed the waveforms extracted from the PPG sensor would be equivalent to its Sphygmocor technology for aortic arterial pressure measurement and it would aim to assist in remote diagnosis and monitoring of hypertension and cardiovascular disease.
Cardiex said that a study of 13 human subjects by subsidiary Atcor Medical and Macquarie University provided four "unique and proprietary heart and arterial health features that we believe have never before been extracted from a PPG sensor".
Cardiex said details would be presented to Atcor's wearables partner and Mobvoi over the next few weeks and would then be presented to major consumer and wearable device companies that had requested demonstrations.
Cardiex was up 0.3 cents or 16.7 percent to 2.1 cents with 7.2 million shares traded.

BOTANIX PHARMACEUTICALS

Botanix says the US Food and Drug Administration has granted qualified infectious disease product status for cannabinoid BTX1801 for post-surgical infections.
Botanix said it would receive an additional five years of regulatory exclusivity, which increased the commercial value of a product, and would be eligible for priority FDA review and fast-track status.
The company said priority review would expedite the review period to six months rather than the standard 12 months and fast-track status would allow it to have more frequent communication with the FDA during drug development and review to enable valuable guidance in the development program.
Botanix said that last month, it received ethics approval for a 60-patient, double-blind, vehicle-controlled, phase IIa study to evaluate safety, tolerability and efficacy of two formulations of BTX1801 to decolonize Staphylococcus aureus from the nose of healthy adults (BD: Mar 13, 2020).
The company said that as soon as travel requirements within Western Australia were eased, recruitment would resume, allowing the study to be completed by October 2020.
Botanix was up 2.1 cents or 61.8 percent to 5.5 cents with 129.3 million shares traded.

ELLEX MEDICAL LASERS

Ellex says all three resolutions at its extraordinary general meeting have passed overwhelmingly, it will divest its laser and ultrasound business and change its name.
Last month, Ellex said shareholders would vote on the proposed $100 million sale of its laser and ultrasound business to Lumibird and to change its name to Nova Eye Medical under the ticket code EYE (BD: Mar 24, 2020).
Ellex was up two cents or 3.6 percent to 57.5 cents.

IMAGION BIOSYSTEMS

Imagion has requested a trading halt pending "an announcement in relation to a corrective statement to the follow-on placement … and the issue of a supplementary prospectus".
Yesterday, Imagion said it had raised $2.05 million through an oversubscribed, two-for-five rights issue at 1.0 cent a share and raised a further $960,000 through a follow-on placement (BD: Apr 23, 2020).
Trading will resume on April 28, 2020 or on an earlier announcement.
Imagion last traded at 1.3 cents.

MGC PHARMACEUTICALS

MGC has requested a trading halt pending "the release of an announcement by the company in relation to a capital raising".
Trading will resume April 28, 2020 or on an earlier announcement.
MGC last traded at 2.9 cents.

ADHERIUM

Adherium says chief operating officer Mike Motion has been appointed as chief executive officer and a director and Anne Bell has been appointed chief financial officer.
Adherium said Mr Motion would replace Jeremy Curnock Cook, who held the role on an interim basis and continues as a non-executive director.
The company said Mr Motion had more than 35 years' corporate experience in medical devices and pharmaceuticals and previously worked for Baxter Healthcare and Biocompatibles, which later became BTG, and as head of Varithena.
Adherium said Mr Motion held a Bachelor of Science.
The company said Ms Bell was a chartered accountant and previously was an executive at Astrazeneca and Menarini Group, previously Invida.
Adherium said Ms Bell was previously an accountant at Arthur Young and Arthur Andersen, was head of strategy delivery at Colonial.
Adherium was up 0.1 cents or 3.3 percent to 3.1 cents.

ATOMO DIAGNOSTICS

The Delaware-based Global Health Investment Fund says it has become a substantial shareholder in Atomo with 63,851,280 shares or 11.38 percent of the company.
Atomo fell 1.5 cents or 3.6 percent to 40 cents with 11.5 million shares traded.

GENETIC TECHNOLOGIES

Genetic Technologies director Peter Irwin Rubinstein, Irwin Biotech Nominees and RIP Opportunities say they have ceased to be substantial shareholders in the company.
Last October, the Melbourne-based Mr Rubinstein, Irwin Biotech and RIP said that they became substantial with 248,132,009 shares or 6.11 percent (BD: Oct 31, 2019).
Today, Mr Rubinstein, Irwin Biotech and RIP said that they were diluted on April 22, 2020 following the issue of shares in two placements (BD: Apr 21, 2020).
Genetic Technologies fell 0.1 cents or 16.7 percent to 0.5 cents with 5.3 million shares traded.