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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Paradigm Biopharmaceuticals

By TIM BOREHAM

ASX code: PAR

Share price: 43 cents

Shares on issue: 281,756,625 (pre capital raise)

Market cap: $121.2 million

Executive chair: Paul Rennie

Board: Mr Rennie, Dr Donna Skerrett (chief medical officer), Amos Meltzer, Helen Fisher (John Gaffney resigned on October 20, 2023)

Financials (year to June 30 2023): revenue from continuing operations $46,760 (down 41%), loss of $51.9 million (previous deficit $39.2 million), cash $69.4 million (proforma, post capital raising excluding options exercise).

Identifiable major holders: Paul Rennie and related entities 7.3%.

The golden rule of biotech is never to waste a positive announcement - let alone two of them - by shunning the opportunity to fill the coffers.

On October 10, Paradigm released a clinical update that confirmed the efficacy of its repurposed wonder drug Zilosul (pentosan polysulphate sodium) for dodgy knees and joints.

A week later the company released data from magnetic resonance imaging (MRI) scans that suggests Zilosul results in ‘functional’ improvement to the joints - an outcome well beyond the previous known effects of relieving pain and improving function.

The key findings were that cartilage reduction had not just been halted but the volume of this connective tissue had increased, with bone lesion damage reducing.

OK, the study was based on a small active cohort of 15 patients, but it marks the first time that any drug has been shown to have such an effect.

Before you could say ‘trick or treat’, on October 30 the company was doing the rounds for $30 million by way of a placement and underwritten entitlement issue.

Spooky, eh?

The MRI results could pave the way for earlier provisional approval from Australia’s Therapeutic Goods Administration (TGA), bearing in mind that more than 600 patients have been treated under the agency’s special access scheme (SAS).

In 2018, the FDA knocked back the company’s approval application and demanded a phase III trial.

There are more than 530 million osteo-arthritis (OA) sufferers worldwide, including 30 million in the US.

It’s a dog’s life

PPS is an anti-inflammatory, heparin-like compound made from beechwood hemicellulose and has been used as to treat a bladder condition and deep-vein thrombosis.

The manufacturing involves not just chucking bark in a vat, but a complex process to produce the final formulation.

Currently, osteo-arthritis commonly is treated with non-steroidal anti-inflammatory drugs or opioid-based painkillers, which are either ineffectual or undesirable.

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

Paradigm has an exclusive 25-year exclusive supply deal with the only approved PPS maker, Germany’s Bene Pharmachem. Paradigm also has relevant patents (see below).

The deal pertains to human osteo-arthritis (OA) applications and not veterinary purposes. For some years PPS has been used to treat canine joint pain, including on Biotech Daily’s editor David Langsam’s faithful hound, Ripley.

Ripley is now deceased - believe it or not - but as far as we know this sad event had no causal link with the treatment.

Paradigm shifts

Paradigm was founded by Paul Rennie and Graeme Kaufman and listed on the ASX on August 18, 2015, having raised $8 million at 35 cents apiece.

Mr Rennie was Mesoblast's head of product development. Mr Kaufman was CSL's chief financial officer through the plasma behemoth's privatization and was Mesoblast's vice prez.

Mr Kaufman stepped down as a Paradigm director (and chair) in June 2020 for health reasons.

In November 2021, Mr Rennie ceded his chief executive role and continued as chair. But in November last year he returned to the CEO role while continuing as (now executive) chair.

Mr Rennie replaced US-based healthcare exec Marco Polizzi, who came on as CEO in July last year but didn't last the gestation period, having clocked off on February 20 this year.

Where's the evidence?

Paradigm's evidence so far consists of two phase II trials - Para 005 and Para OA 008 - and the 600 'real world' patients. Many of the latter are former footballers, including Paradigm's investor relations guy Simon White.

Ten former US National Football League players have also been treated under a US special access scheme.

Para 005 achieved a primary endpoint of reduction in pain and improved function among its 121 subjects.

Covering 61 patients, Para 008 kicked off in 2021 with the remit of measuring the change in the synovial fluid biomarkers associated with pain, inflammation and osteo-arthritis disease, relative to placebo.

Having tabled positive results at days 56 and 168, Paradigm last month reported "clinically meaningful outcomes" at 365 days compared to placebo.

These included significant pain reduction and functional improvements and durable improvements in stiffness, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (Womac) questionnaire.

The company also reported reduced use of pain medication, with the placebo group resorting to paracetamol (or such) five times more than the treated group.

The participants received two milligrams per kilograms of bodyweight, twice weekly for six weeks and the company now believes this regimen is ideal.

Moving to phase III

The first phase III program, Para-OA-002 is designed to maximise the potential of PPS for osteo-arthritis pain.

Granted FDA fast-track approval, the trial recruited 468 healthy volunteers for the first dosing stage, now completed, across 120 sites in seven countries.

In early 2024, the company expects to confirm the 2.0mg/kg dosing as optimal.

The trial then moves to a pivotal stage, covering 900 patients with a top-line data readout expected in mid-2025.

The program then moves to a confirmatory trial, dubbed - you guessed it - Para-OA-003 with enrolment starting by July 2024.

The company is eyeing a new drug application to the FDA by the end of 2025.

MRI data really resonates

With 15 active patients and 22 on placebo, the magnetic resonance imaging (MRI) sample was small, but it still showed a significant difference between these arms.

The analysis saw an increase in cartilage volume and thickness from baseline, by an average 0.06 millimetres. Among the placebo group, the cartilage loss averaged 0.04 millimetres.

The improvement was most notable in the medial compartment, where most knee osteo-arthritis occurs.

There was also a 17 percent reduction in bone marrow lesion volumes - compared with a two percent increase for the placebo cohort - and a reduction in synovitis inflammation.

Under normal conditions, cartilage reduces by four percent a year and the standard- of-care treatments such as corticosteroids are known to accelerate cartilage loss.

“Nothing else has shown the ability to halt disease progress, let alone regenerate cartilage,” broker Bell Potter chimes.

What’s next?

TGA provisional approval is extended to drug candidates with decent phase II data, for cases of high unmet needs for significant diseases.

“The TGA was impressed with the phase II data out to day-86 and wants to know the duration effect,” Mr Rennie says.

Naturally, the company would be obliged to continue a phase III trial and seek full approval down the track.

Australia has around three million osteo-arthritis sufferers - and the company reckons about 80 percent are unhappy with their current medication.

That implies an addressable market of hundreds and millions of dollars.

The company is confident of approval in early 2025.

Meanwhile, FDA approval remains Paradigm's key priority, with the MRI data potentially supporting a disease-modifying indication.

"Pain and function is a huge market but if we can increase the label to 'disease modifying' it not only increases the price, but potentially how early it is bought forward by prescribing doctors in disease progressions," Mr Rennie says.

Finances and performance

Three weeks ago, Mr Rennie asserted a capital raising at the prevailing subdued share price would be "too dilutive and devalue the asset".

But the share valuation partially reflected the market's expectation of a raising, so it gets a bit chicken-and-eggy.

Paradigm announced an $18 million institutional placement, followed by the $12 million non-renounceable rights offer of one share for every 10 shares held, with both struck at 43 cents a share, a hefty 30 percent discount to the prevailing price.

The rights leg also included a sweeter of three options for every four shares subscribed, exercisable at 65 cents by November 30, 2024.

Underwritten by lead manager Bell Potter, the raising takes the company's pro forma cash position to $69 million, with the exercise of the options potentially adding $33.8 million.

Assuming the options are exercised, the proforma $103 million of cash is enough to fund the company to mid-2025 (and the phase III read-out).

The company also expects to pocket a $7.3 million Federal Research and Development Tax Incentive in the current quarter.

In August last year, Paradigm raised $66 million in a placement and rights issue, at $1.30 apiece.

Paradigm shares are trading at close to their five-year low point, well adrift of the peak of $4.17 in January 2020.

How watertight are the patents?

While Paradigm has made great strides in proving that Zilosul might be a wonder drug for osteo-arthritis patients, there's always the question of the strength of the company's patent position.

The exclusive supply deal with Bene Pharmachem aside, Paradigm has patents on the relevant indications in injected oral or topical form, expiring in 2035 and 2040.

Nonetheless, Bell Potter opines that the validity of these patents is "highly likely" to be challenged, especially if the drug succeeds commercially.

The firm adds the supply contract is a "crucial piece of the company's value as it effectively prevents, or delays, the creation of generics".

Mr Rennie notes that Elmiron has been off-patent for years and has never had generic competition.

Paradigm highlights collaborative research that shows Zilosul differs to other available PPS drug substances "both with respect to their respective structure and biological characteristics".

This means a generic PPS manufacturer would need to perform their own clinical efficacy and safety studies to gain marketing approval.

That takes care of third parties, but could Bene Pharmachem be so cheeky as to put out their own osteo-arthritis drug?

"They can't and they wouldn't," Mr White says.

"Their skills set lies in manufacturing and their sole focus it to produce as much PPS as they can. As part of the exclusivity deal, we do the clinical trials and they refer to us as their clinical arm."

Dr Boreham's diagnosis:

A former footballer for the AFL club Carlton, Mr White endured no fewer than eight knee surgeries - and multiple reconstructions - over his eight-year, 87-game playing career.

When Mr White retired in 2017 his knees were shot, but now he can "still kick a footy and run around on hard surfaces".

"If you have had it [PPS], you are certainly a believer," he says. "Patients don't want to go back to where they were."

Another true believer is principal investigator (and Carlton Football Club chief medical officer) Dr Philip Bloom, who has prescribed PPS to more than 300 patients under the special access scheme.

“I have seen myriad people seeing positive changes to their lifestyles and getting back to things they previously may have been unable to do due to the pain and dysfunction caused by their disease,” he trills.

Paradigm certainly is at an interesting juncture, with the potential TGA provisional approval promising some early revenues.

But the limp share valuation shows that many investors think the Paradigm story is too good to be true.

Within the next two years we should know whether the sceptics or the true believers are right.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He was once offered a shot of Zilosul but happily he has no kneed – yet.