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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: 96.5 cents

Shares on issue: 232,680,798 (5,085,003 in ASX escrow)

Market cap: $224.5 million

Chief executive officer: Marco Polizzi

Board: Paul Rennie (chair), Dr Donna Skerrett, John Gaffney, Amos Meltzer, Helen Fisher

Financials (March quarter 2022): receipts $14,000, cash outflows $15.2 million, cash balance $39.8 million, quarters of available funding 2.63 **(**The company received an $8.2 million Federal Research and Development Tax Incentive in early June)

Identifiable major holders: Paul Rennie (Kzee Pty Ltd) 8.7%, Nancy Edith Wilson-Ghosh 1.68%

Paradigm Biopharmaceuticals' investment relations guy Simon White is a bit different to your average biotech corporate gun for hire, given he's actually tried the remedy he is promoting.

A footballer with the AFL's Carlton Football Club, Mr White had no fewer than eight knee surgeries over his eight-year, 87-game playing career, including multiple reconstructions.

When the defender retired in 2017, his joints were not in a good way.

“I was having really bad night ache. I would go for a run and I would be awake for five or six hours because I couldn’t get comfortable.”

After trying everything from stem cells to liposuction, he went to Carlton club doctor Philip Bloom and joined the 400 or so sportspeople the medico had treated with the reinvented old drug pentosan polysulfate sodium (PPS).

PPS is not approved, but is used under the Therapeutic Goods Administration’s special access scheme.

Three years on, Mr White is sleeping much more soundly and still pulling on the boots for amateur team East Doncaster (Eastern Football League). Mr White’s Carlton team mate, the high-flying Andrew Walker has also benefited from PPS, his aerial gymnastics having extracted a heavy toll on his knees.

“I played him in a pre-season scratch match last year and he is still moving as well as he ever has,” Mr White says.

Paradigm’s long list of athlete patients - including Carlton legend Mark ‘Diesel’ Williams - exemplifies the persuasive power of real world evidence (RWE).

But while the US Food and Drug Administration is more receptive to RWE, anecdotes don’t quite have the gravitas of a large scale, properly-constructed, clinical trial. On that note, the agency finally has allowed Paradigm to forge ahead with two phase III trials that will prove (or otherwise) that its repurposed drug is the bee’s knees.

Zilosul by the doseful

Okay - let’s take a step back.

Renamed Zilosul by Paradigm, PPS is an anti-inflammatory compound made from beech-wood hemicellulose (don’t laugh: aspirin used to be made from willow bark). Over time, PPS has been used to treat a bladder condition and deep vein thrombosis.

As far as osteoarthritis goes, there are commonly prescribed non-steroidal anti-inflammatory drugs, which the company claims are often ineffectual at the dealing with the root cause, or opioid-based painkillers.

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

As well as AFL kickers of the Sherrin football, 10 American (National Football League) footballers have been treated for their creaking joints, under a US special access program.

A phase II trial has also been carried out (see below).

As well as dodgy knees, Paradigm is eyeing other conditions including viral osteoarthritis (Ross River fever) and the rare disease muco-poly-saccharidosis (MPS). Given the inflammation angle, Covid-19 is also in the mix.

But what is PPS's origin?

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 supply deal with the only approved PPS maker, Germany's Bene Chempharma.

Otherwise, Paradigm has patents on the relevant indications in injected oral or topical form. The patents run until 2035 or 2040.

The company describes the supply deal with Bene Chempharma - under which Bene receives a two percent royalty - as being as good as patent protection.

Paradigm management 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, was a Mesoblast executive vice president and Bionomics chair.

Mr Kaufman stepped down as a Paradigm director (and chair) in June 2020 for health reasons. In November last year, Mr Rennie ceded his chief executive role and now fills the chair's seat.

Director and chief medical officer Dr Donna Skerrett stepped up as acting head banana, but she can now return to chief medical officer duties after the appointment of US healthcare executive Marco Polizzi.

Clocking on from July 1, Mr Polizzi has 30 years' pharma industry experience in varied commercial roles. At Sandoz, he created a hospital and speciality markets unit and he also established new divisions at Mallinckrodt Pharmaceuticals and JHP Pharma.

Mr Polizzi will remain US based, which is okay in our books given that's where the pivotal trial is taking place.

Clinical update (and recap)

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.

Interestingly, at the time broker Morgans broke from the cheer squad and dubbed the phase IIb (and follow up) osteoarthritis results as "unconvincing and lacking substantive clinical evidence". Party poopers!

The FDA concurred and in April 2020 the FDA knocked back Paradigm's request for approval, which was predicated on one planned phase III trial and "published literature" (no, not Emily Bronte).

"We'll have two adequate and well-controlled phase III trials, thanks," the regulator told the company.

Having been on FDA 'clinical hold' for the best part of nine months, the requested two phase III confirmatory and pivotal trials are now underway.

Enrolling about 900 and 735 knee osteoarthritis patients respectively, the pivotal and confirmatory trials will be carried out across 56 sites, about half of them in the US. The remainder are in Europe, Britain and Australia.

The treatment involves weekly self-administered injections over six weeks.

In the US the key endpoint is pain, using the 24-question Western Ontario and McMaster Universities (Womac) pain scale. Knee function is a secondary endpoint.

In Europe pain and function (versus placebo) are the secondary endpoints.

Later this year, the company hopes to release interim data from a phase II exploratory study of the disease modifying potential on knee osteoarthritis patients, looking at disease progression biomarkers and radiographic imaging of any bone marrow lesions.

Paradigm is also carrying out two smaller phase II studies for muco-poly-saccharidosis, in view of a co-development deal to progress it beyond that.

Finances and performance

While Paradigm had just under $40 million in the bank as of the end of March - and in June cashed a $8.9 million Federal Research and Development Tax Incentive - the harsh reality is that it will need more lucre to complete the trials.

Bell Potter assumes a circa $70 million raising in 2023.

Paradigm has not disclosed the cost of the trials, although the $80 million has been bandied around. Or at least we've bandied that number around …

In the happier days of yore, Paradigm raised $35 million in 2020 and a monstrous $78 million (via a placement and rights offer) in 2019.

Over the last 12 months, Paradigm shares have lurched between $2.53 (early November 2021) and 90 cents currently. They peaked at $4.20 in late January 2020.

The shares have lost 53 percent of their value over the last 12 months and were kicked out of the ASX300 in March. But don't take it personally: that fate befell a number of other biotechs.

Compelling economics …

Based on the work of a global market research company using de-identified patient data from payers (insurers) and doctors, Paradigm is confident that it can charge $US2,500 per course of treatment.

Management hopes that by the time a new drug application is filed in 2025, re-treatment data will be available. The significance of this is that the drug would be able to treat osteoarthritis as an ongoing chronic condition and this would be on the label.

“We are looking at a second line therapy for pain and function at the moment,” Mr White says. “This doesn’t bring in the fact that we will investigate disease modifying properties that would have taken the price through the roof.”

US and European regulatory feedback also suggests the company could do a smaller trial for hip osteoarthritis and also win a label for that.

Hips and knees account for 70 percent of the total addressable market for osteoarthritis.

…. but the natives are restless

Presumably reflecting investor frustration at the long development path, shareholders voted a remuneration report second strike at the January 25 annual general meeting, as well as a proposal to grant incentive shares to Mr Rennie.

In fact, a whopping 68 per cent of voting holders opposed the latter. The remuneration proposal didn’t meet the 75 percent approval threshold, with 38 percent of shareholders voting against.

Given the same thing happened last year, the ‘no’ vote was deemed a second strike, which triggered a motion to spill the board. But as is the case with the vast majority of second strikes, investors weren’t quite so bolshie and soundly rejected the spill vote.

The AGM, by the way, was delayed to enable an in-person meeting, as allowed under covid rules. As it happened, the jamboree was held virtually, anyway.

Dr Boreham’s diagnosis:

The Paradigm story caused quite a tizz among the company’s retail-heavy register - at least before it dawned on investors that the FDA wouldn’t be convinced by sportsmen’s yarns about a miraculous cure alone.

The global biotech sector’s dramatic retreat - a function of general risk aversion and the end of the era of cheap money - doesn’t help.

Of course, the problem goes beyond athletes: there are more than 30 million osteoarthritis sufferers in the US and about three million here.

To a degree, the phase III trial results are binary, in that the endpoints will or won't be met. "The reality is that if your lead program fails, you are on Struggle Street," Mr Rennie told your columnist in April 2020.

But in this age of data mining patient subsets, something is likely to be salvageable from a poor result. And pain - though very real - is a subjective measure.

Given America's entrenched opioid problem, the FDA could well give the benefit of the doubt if the trial results are half decent.

In Bell Potter's words: "Zilosul has the potential to become one of the largest selling drugs of all time if the claims of disease modification and pain reduction are met."

Mr White notes that with trial sites in multiple geographies, the trial could open up approval in Europe and Australia and possibly Canada: "the market might have missed that a bit."

With multiple approvals, Paradigm would truly be kicking goals. But for the time being it's a quarter-by-quarter proposition - against a stiff breeze - as the crucial trials unfold.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. But he does have a decent set of patellofemorals and tibiofemorals and that's all he kneeds.