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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: $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.