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Daily news on ASX-listed biotechnology companies

Dr Boreham's Crucible: Neuren Pharmaceuticals

By TIM BOREHAM

ASX Code: NEU

Share price: $13.23; **Shares on issue:** 126,265,676; **Market cap:** $1.67 billion

Chief executive officer: Jon Pilcher

Board: Patrick Davies (chair), Mr Pilcher, Dr Trevor Scott, Dianne Angus, Dr Jenny Harry, Joe Basile

Financials (year to December 31, 2022): revenue $14.55 million***** (previously nil), net profit $184,000 ($7.8 million loss previously), cash balance $40.1 million up 9%

***** Acadia licencing payment

Major shareholders: Milford Asset Management 5.08%, Cameron Richard Pty Ltd 3.4%, Stuart Andrew Pty Ltd 1.95%, Linwierik Super 1.5%, Essex Castle 1.88%, Smithley Super Pty Ltd 1.6%.

Last Saturday, was a typical balmy autumnal afternoon in Melbourne, but Neuren chief Jon Pilcher was despondent as he awaited news from the company's US partner Acadia on whether the US Food and Drug Administration (FDA) had approved Neuren's neurological drug trofinetide.

As 5.30 pm Friday ticked by in the US, he assumed the FDA's bureaucrats had stowed their HB pencils for the weekend.

He sought solace by repairing to one of his favorite beaches, the wild and woolly surfie hangout of Cape Paterson.

“I went to the ocean to clear my head by diving into the waves, then got out and saw the email,” he says. “I didn’t plan to be on the beach but it was a nice place to find out.”

The email from Acadia confirmed that the FDA had approved trofinetide for the treatment of the rare disorder Rett syndrome in adults and children aged two or more.

Now dubbed Daybue - and thanks for that one, Acadia - trofinetide is one of only a handful of drugs developed from scratch in Australia (with help from the Kiwis) in this case) and approved by the FDA.

It’s the first since the agency green-lighted Telix Pharmaceuticals’ Illucix prostate cancer diagnostic in December 2021.

Earlier ones were Pharmaxis’s Bronchitol for cystic fibrosis in 2020 and Clinuvel’s Scenesse to treat the rare skin diseases erythropoietic protoporphyria (in 2019).

And let’s not forget Hatchtech, which won FDA approval for its head lice treatment Xeglyze in 2020 or Medicines Development for Global Health’s moxidectin for river blindness in 2018.

The FDA approval is great news for sufferers of the hitherto untreatable genetic disorder Rett syndrome, which affects only girls.

The news also vindicates the faith of investors who have piled into the stock over the last 12 months, in anticipation of approval. Neuren is now poised to receive hundreds of millions of dollars of sales milestones and royalties (see below).

And there’s more: the approval crystallizes receipt of a Rare Paediatric Disease Priority Review Voucher (PRV), a Willy Wonka-style ticket that enables fast-track FDA approval of a second drug. Neuren receives one-third of the value of these fungible devices, estimated at $US33 million.

Neuren’s long journey

The FDA approval is the culmination of an estimated $US250 million expended by Neuren and Acadia on developing the drug.

Strictly speaking, Acadia won the approval, but this is no time for splitting hairs. A neurology specialist, Acadia is listed on the Nasdaq and has an $US8 billion market cap.

The approval was not exactly unexpected, given Daybue (trophinetide) had orphan and rare paediatric diseases status.

Neuren started working on the drug almost a decade ago, when it started its first Rett syndrome trial. Trofinetide was invented 20 years ago at Auckland University, in a program spearheaded by eminent chemist Prof Margaret Brimble.

Neuren's therapies are based on naturally-occurring molecules in the brain, targeting the underlying problem of deficient signaling between brain cells caused by genetic mutations. Symptoms include behavioral and cognitive problems, deficient motor skills and breathing and cardiovascular issues.

Both Daybue and Neuren's second drug candidate NNZ-2591 seek to reduce inflammation associated with excessive inflammatory cytokines and normalize abnormally low levels of the insulin growth factor hormone 1, IGF-1.

Mr Pilcher describes Daybue as a copy of the molecules already in the IGF-1 pathway, but makes more of it available in the brain.

"It's not a symptomatic treatment, it's trying to improve the architecture of the brain but it doesn't fix the underlying mutation," he says. "So, if you stop taking it, we think the brain will destroy itself again."

Neuren's chief financial officer since 2003, Mr Pilcher succeeded Dr Richard Treagus who stepped down in 2020 after seven years in the top job.

About Rett syndrome

Rett syndrome is marked by problems including difficulties in talking, breathing, eating and sleeping. Often the girls appear to be normal until about 18 months, but then they stop meeting developmental milestones. While there's a higher mortality rate, most will become adults.

The disease is similar to autism, but quite different in some respects.

"They don't suffer to the same extent, it is very variable," Mr Pilcher says, adding that the disease is no more prevalent in one geography over another. Environmental factors also appear not to be relevant.

There are about 10,000 sufferers in the US, 15,000 in Europe (including Eastern Europe) and 28,000 in China.

Lavender trial smells like roses

In 2021, Acadia released the results of a phase III trial, which led to the filing of the FDA new drug application in July 2022.

Enrolling 187 females between five and 20 years, the double-blinded trial was carried out over 12 weeks. An open-label phase involving 154 of these patients continues for 52 weeks, with the 40-week results so far read out.

Based on the primary endpoints around caregiver and physician assessment, the drug showed "sustained and continual improvement", relative to a baseline measure. In short, Lavender needed only to replicate the results of an earlier phase II trial and it came up smelling of roses.

Only the beginning?

What happens after Daybue's US debut?

While winning approval in the world's most important medical market is a momentous occasion, greater joy could be in store elsewhere.

That's because Neuren retains the rights to trofinetide outside of North America (defined, by the way, as the US, Canada and Mexico).

Elsewhere, the company is "advancing discussions with a number of third parties".

Earlier, Mr Pilcher said some parties were interested in a holus-bolus 'rest of world' deal, while others were interested in Europe and Japan.

Australia has hundreds of Rett sufferers, but a well-established Rett Association.

"I want to make sure it gets to Australia but we need to go through the TGA [Therapeutic Goods Administration] process, which is not a slam dunk," Mr Pilcher says.

Acadia also has purview over a separate program for Fragile X syndrome, another neurological disorder potentially treatable with Daybue.

There are more Fragile X patients than Rett patients, but their conditions are more variable and they exhibit more difficult behavior. The program is shelved, but never say never.

Neuren's second drug front

The company is also targeting four other related disorders with a second compound, NNZ-2591. "All are genetic conditions from the start of life, with a broad range of problems," Mr Pilcher says.

Affecting both males and females, these conditions are the Phelan-McDermid, Angelman, Pitt Hopkins and Prader-Willi syndromes. The company has orphan indication for all of these diseases.

Perks of orphan status include seven and a half years of market exclusivity in the US and 12 years in the European Union.

Following successful phase I trials that established safety and tolerance, the company has started phase II trials of up to 60 patients here and in the US, across the former three indications. After gaining FDA trial approval last January, a Prader-Willi trial is also in the offing.

The results will be released sequentially starting with Phelan-McDermid by July 2023.

Mr Pilcher says that as well as mitigating the risk of pursuing a single drug, the NNZ-2591 program eventually could be more valuable than trofinetide.

Patient wise, the market is five times bigger. Neuren estimates 56,000 sufferers across all four diseases in the US, 71,000 in Europe and 205,000 in Asia.

“There’s a massive unmet need with all of them,” Mr Pilcher says. “If we can be successful in all of them, it completely dwarfs Daybue from an economic point of view.”

Finances and performance

Like Mr Pilcher, Neuren will be swimming … but in cash.

Neuren’s December 31, 2022 cash balance was $40 million, partly courtesy of a $US10 million milestone from Acadia.

Under the terms of the Acadia tie-up, Neuren gets $US40 million on first commercial US sales - expected as early as next month - with royalties on net sales and potential sales milestone payments.

The milestones are valued up to $US350 million, if four tiered sales thresholds are met. Sales need to be $US250 million or more for the first $US50 million to be realized, while the benefit caps out at $US1 billion of sales.

Under the uncapped tiered royalty arrangements, the company receives 10 percent on sales under $US250 million, rising to 15 percent on any sale over $US750 million.

On Monday, Mr Pilcher cited a typical orphan drug pricing in the US of $US186,758 a year - to be exact - and bear in mind patients probably will have to take the drug for the rest of their lives.

A few hours later, Acadia revealed its pricing at a staggering $US375,000 a year. According to broker Wilsons, between 60 percent and 67 percent of the addressable patients are covered by the US Medicaid program and a further 30 percent by private insurance.

Let’s hope the parents of the remaining three percent have deep pockets or a kindly maiden aunt.

Mr Pilcher notes that about half of the 10,000 US Rett suffers have been diagnosed and are thus identifiable. Covering half of this cohort - a conservative assumption - equates to almost a $US1 billion-a-year market.

If Acadia furthers a second indication or even more, the sales count towards the milestone payments, thus making Neuren’s targets all the more achievable.

As for the Willy Wonka vouchers, Mr Pilcher says the last six or so have changed hands for between $US90 million and $US110 million: “The market for them has been very stable.”

Investors reacted to Monday's initial news by sending the shares up $1.67, or 22 percent to $9.35. After Acadia's pricing news they piled on another 10 percent on Tuesday and were at it again on Wednesday, taking the cumulative gain to $4.22, or 55 percent.

Over the last 12 months Neuren shares have traded between $3.45 (May 2022) and Wednesday's zenith of $11.90. Two years ago, the shares were worth less than $1. This followed a 20-to-one consolidation in 2017 when shares were around 16 cents.

Dr Boreham's diagnosis:

The surf-loving Mr Pilcher dubs the FDA approval as an "historic occasion" - but is it merely a beach head for the company?

"For Neuren, this is a transforming milestone that places us in a position to make the most of opportunities ahead of us as we work … to make a difference in [the] four other neuro-development disorders," he says.

Meanwhile, Mr Pilcher says the beauty of Rett syndrome is that it's rare - but not ultra rare - which puts Neuren and Acadia in a Goldilocks position in the US.

The US reimbursement position is supported by the argument the drug will avoid multiple, expensive hospitalizations over a patient's lifetime.

"But because volumes are relatively small it is not costly in comparison to, say, a diabetes drug," Mr Pilcher says.

The market being the market, investors are already looking at what happens beyond Acadia initiating its first commercial US sales of Daybue.

European approval would almost certainly create waves, but the NNZ-2591 could cause spur a longer-term earnings tsunami.

Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He often feels he is swimming in it, but not in cash or pristine surf.