



# Biotech Daily

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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:** \$1.37

**Shares on issue:** 114,608,108

**Market cap:** \$157.0 million

**Chief executive officer:** Jon Pilcher

**Board:** Patrick Davies (chairman), Dr Trevor Scott, Dianne Angus, Dr Jenny Harry

**Financials (December half 2020):** revenue \$164,000 (interest), net loss \$9.2 million (previously \$10.8 million deficit), cash of \$24.1 million, quarters of available funding: 14.9

**Major shareholders:** Karst Peak Capital 12.5%, Cameron Richard Pty Ltd 5.2%, Stuart Andrew Pty Ltd 2.5%, Linwierik Super 2.3%, Essex Castle 2.1%, Smithley Super Pty Ltd 1.9%.

What sounds more appealing for investors: a billion-dollar blockbuster drug with mass market appeal, or an 'orphan' drug targeting a market of perhaps several thousand patients?

Yes - it's a trick question.

According to Neuren chief executive Jon Pilcher, drug makers have a better commercial chance with an orphan candidate and not just because of the expedited pathway offered by regulators.

“People get seduced by the notion of a product taking 10 percent of a \$10 billion market, but it’s not that simple,” he says.

“Unless you have a product much better than the others, trying to out-market entrenched big companies is not easy. With orphan drugs you are targeting a leadership position with little or no competition at a higher price.”

With this philosophy in mind, the rare neurological disorders house is sweating on the results of a phase III trial of its lead drug, trofinetide, to treat the neuro-developmental conditions Rett syndrome and Fragile X syndrome.

The company is also targeting four other related disorders with a second compound, NNZ-2591.

Mr Pilcher should know about the market opportunities, given his experience with both orphan and mainstream drugs.

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

(Dr Treagus was actually executive chair, with Patrick Davies now assuming the non-executive chair part of the role).

### **Rett: frankly, we do give a damn**

Neuren’s therapies are based on naturally-occurring molecules in the brain, targeting the underlying problem of deficient signalling between brain cells caused by genetic mutations.

Symptoms include behavioral and cognitive problems, deficient motor skills and breathing and cardiovascular issues.

For those partial to a bit of biotech dirty talk: both drug candidates seek to reduce inflammation associated with excessive inflammatory cytokines and normalize abnormally low levels of the insulin growth factor hormone, IGF-1.

They also “normalize the phenotype of microglia for effective synaptic pruning and maintenance”.

Mr Pilcher says the company is seeking to treat the “whole syndrome, not just the symptoms”.

Strictly speaking, Rett is rare but not ultra-rare, affecting about 10,000 women in the US and 16,000 in Europe and Japan (Neuren’s key target markets).

The patient numbers for Fragile X are slightly higher: 30,000 in the US and 48,000 in Europe and Japan.

The separate compound NNZ-2591 brings three other ailments on to the slate, with a fourth one just announced (see below). The existing ones are Phelan-McDermid, Angelman and Pitt Hopkins syndromes, the common thread being they all affect children.

The company has 'orphan indication' status for all five illnesses in the US and EU, after the US Food & Drug Administration granted 'orphan indication' to Phelan-McDermid, Angelman and Pitt Hopkins, followed recently by the European Medicines Agency.

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

### **Howdy, partner**

With trofinetide, Neuren is partnered with the \$US8 billion (\$AUD10.3 billion) market cap, Nasdaq-listed neurology specialist Acadia Pharmaceuticals.

Acadia has the North American rights to trofinetide and, crucially, is funding the Rett and Fragile X trials (the latter program is in a state of quiescence after phase II trials were completed).

The Acadia deal involves up to \$US455 million (\$A590 million) of potential milestones for Neuren, consisting of \$US105 million in development and regulatory milestones and \$US350 million of sales-based targets. Neuren is also eligible for double-digit percentage royalties on all sales.

Neuren also shares one-third of the value of any paediatric review voucher granted by the US Food and Drug Administration. As biotech old timers would know, these rights are tradeable and last year changed hands for an average \$US100 million.

"Very importantly we have free and full access to all the [clinical] data for use outside of the US," Mr Pilcher says.

Outside North America, Neuren's distribution options include the 1960s swingers' party approach (multiple partners) or the Bunnings approach (DIY). Acadia may or may not be interested in these broader rights.

### **Lavender trial smells good**

Neuren expects Acadia to reveal the Rett syndrome phase III trial results in the second half of 2021.

Fragrantly dubbed 'Lavender', the trial is a 12-week study enrolling 180 girls (half treated and half control).

Lavender began recruiting in November 2019, but Covid-19 then paused enrolments between March and June.

The trial compares the results against baseline, subject to caregiver and physician co-primary endpoints.

“We always thought that if you treated them for longer, we would get a better result and in this trial we are treating them twice as long,” Mr Pilcher says. “We also have three times the sample size, which gives the trial greater statistical significance.”

Aged between five and 20 years, the participants can continue the treatment for another nine months under an open label extension trial, known as ‘Lilac’.

Mr Pilcher says Lavender needs only to replicate the results of Neuren’s phase II trial, which scored well on the caregiver and physician measures.

The earlier trial also ran for only six weeks, with improving efficacy in the final stages which suggests the 12-week trial should produce superior results. Still, nothing’s a given in drug development, is it?

### **Secondary program, but not second rate**

Flush with the cash and following “stellar” animal trials, Neuren started a phase I trial of NNZ-2591 in May last year.

The results are now in: the twice-daily dosage was safe and well-tolerated among healthy volunteers.

The company is now prepping for phase II trials for Phelan-McDermid, Angelman and Pitt Hopkins syndromes.

“When we get to phase II, this year, we will have done it in little more than two years, which is extremely fast,” Mr Pilcher says.

Previous mouse models of the three syndromes showed the diseases stemmed from mutations or deletions in different genes.

“However, they share an underlying impairment in the connections and signalling between brain cells,” Mr Pilcher says.

This month the company added another target indication for NNZ-2591: Prader-Willi syndrome. This condition affects one child in every 10,000 to 30,000 - males and females equally - and is characterized by insatiable hunger, diabetes, intellectual disabilities and behavioral problems.

The company is encouraged by the results of a mouse study, showing “compelling effects” on rodents modeled with the disease.

“The foundational work for NNZ-2591 completed over the last two years should mean Neuren can go straight to a phase II trial for Prader-Willi and any other new indications,” Mr Pilcher says.

## **Finances and performance**

Neuren in July last year raised a meaty \$20.2 million to pursue its NNZ-2591 programs, bearing in mind the trofinetide studies are fully funded by Acadia.

As of the end of December, Neuren held cash of \$24.1million - enough to cover the phase II trials with change left over.

Acadia expected Rett to be a \$US500 million a year market in the US - and Europe and Asian numbers may be just as high. Based on Acadia's quarterly filings, Mr Pilcher estimates Acadia will have spent more than \$US100 million on developing trofinetide for Rett syndrome.

In the last 12 months Neuren shares have traded between \$2.74 (February 21, 2020) and 97 cents (March 21, 2020).

## **Rivals 'crash and burn'**

Neuren shares appear to have been affected by some 'whoopsies' elsewhere in Rett syndrome drug development. But Mr Pilcher argues the failed results elsewhere have helped Neuren by removing potential competitors.

In November last year, GW Pharmaceuticals terminated a phase III trial of its oral cannabis drug Epidiolex, which is approved for seizures.

GW cited the "significant challenges" of continuing the trial, made worse by the pandemic. The blinded results to date were not known and thus not part of the decision.

In May, Italian minnow Newron Pharmaceuticals halted its phase II/III trial of sarizotan, aimed at treating breathing difficulties. The results were no better than placebo.

In December, Ovid Therapeutics ditched a trial for an Angelman drug, also after poor results.

"I'm not concerned that these events imply any issue for us," Mr Pilcher says. "They had a very different mechanism of action and different development paths. The setbacks mean we are at the forefront of all these disorders which is a good place to be."

## **Dr Boreham's diagnosis**

Neuren exemplifies what we've seen across the ASX-listed biotech !!!space !!!in the pandemic: not despair but cashed-up companies with late-stage trials and a renewed sense of purpose.

Mr Pilcher says a key factor driving Neuren will be crystallizing the company's share of value from Acadia's trofinetide program post the (presumably positive) data this year.

US regulatory approval could come as early as 2022.

Then there's the imperative to extract as much value as possible from trofinetide outside of North America.

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.

With the Rett results pending and the phase II trials for NNZ-2591 likely to spark up this year, there will be plenty to amuse Neuren investors this year.

"2021 has got off to a flying start and is going to be a massive year for us," Mr Pilcher says.

***Disclosure: Dr Boreham is not a qualified medical practitioner and does not possess a doctorate of any sort. He is a firm believer in regular synaptic pruning and maintenance.***