

## In Phase 3, priced like Phase 2

### The Neuren/Acadia deal has been misunderstood

When Neuren Pharmaceuticals, a drug development company focused on neurology drugs, partnered its lead molecule, called Trofinetide, to Acadia Pharmaceuticals in August 2018, the result was a sudden decline in the share price, from the \$2.65 level of early August to a low of \$1.04 by 28 August. To us that doesn't make sense, given the quality of the Phase 2 data which Neuren has generated in two Orphan diseases – Rett Syndrome and Fragile X. It also doesn't make sense in the light of Acadia's agreeing to pay US\$105m in development and regulatory milestones and US\$350m in sales milestones, plus double-digit royalties on all Trofinetide sales, for North American rights only.

### Investment case: A fast path to market

Acadia expects to take Trofinetide into Phase 3 next year and file for FDA approval in Rett Syndrome potentially in 2021. We believe the market has misunderstood the massive opportunity Neuren and Acadia are working on with Trofinetide, particularly with regard to its speed to market. Since Orphan drugs often sell for very high prices, we see potential for Trofinetide to become a blockbuster.

### Neuren has a great partner in Acadia

Acadia Pharmaceuticals is a significant player on the US biotechnology scene, with a current market capitalisation of nearly US\$3bn and membership in the elite Nasdaq Biotechnology Index. The company gained FDA approval for its first drug, Nuplazid for Parkinson's disease psychosis (PDP), in 2016 and is now seeking to grow based on strong focus and expertise in the neurology space.

### Valuation range of A\$4.17 – A\$6.31 per share

We value Neuren at \$4.17 per share base case and \$6.31 per share optimistic case using a probability-weighted DCF approach. We believe the market has chosen to price Neuren like a Phase 2 company rather than the Phase 3 company which it really is. We see Neuren being re-rated towards our valuation range as the market starts to appreciate the quality of the deal with Acadia, as Neuren negotiates a deal for the ex-North America rights for Trofinetide and as Acadia prepares for the US pivotal studies.

**Share Price: A\$1.40**

**Valuation range: A\$ 4.17 – A\$ 6.31**

**ASX: NEU**

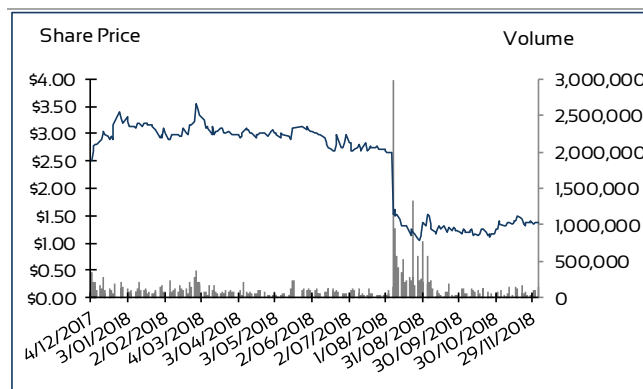
**Sector: Pharmaceuticals**

**5 December 2018**

Market Cap. (A\$ m)	137.2
# shares outstanding (m)	100.2
# share fully diluted	102.7
Market Cap Ful. Dil. (A\$ m)	140.7
Free Float	100%
12 months high/low	3.56 / 1.04
1 / 3 / 12-month performance	-50% / 22% / 10%
Website	<a href="http://neurenpharma.com">neurenpharma.com</a>

Source: Company, Pitt Street Research

### Share price (A\$) and avg. daily volume (k, r.h.s.)



Source: FactSet, Pitt Street Research

Valuation metrics	
DCF fair valuation range (A\$)	4.17 – 6.31
WACC	15%
Assumed terminal growth rate	None

Source: Pitt Street Research

**Analyst: Stuart Roberts**

**Tel: +61 (0)447 247 909**

**[Stuart.roberts@pittstreetresearch.com](mailto:Stuart.roberts@pittstreetresearch.com)**



## Table of Contents

<b>Introducing Neuren Pharmaceuticals, ASX: NEU</b>	<b>3</b>
<i>What is Trofinetide? .....</i>	<i>3</i>
<i>What is Rett Syndrome? .....</i>	<i>4</i>
<i>What is Fragile X Syndrome? .....</i>	<i>4</i>
<i>How can Neuren and Acadia make money serving such small patient populations? .....</i>	<i>4</i>
<i>What happened to Neuren's former lead programme in Traumatic Brain Injury? .....</i>	<i>4</i>
<i>If Neuren is so good, how come the share price came down markedly with the Acadia deal? .....</i>	<i>5</i>
<b>Ten reasons to look at Neuren</b>	<b>5</b>
<b>Evidence that Trofinetide can treat Rett Syndrome</b>	<b>6</b>
<i>Why Neuren decided that Trofinetide could work in Rett Syndrome. ....</i>	<i>7</i>
<i>How Neuren moved into the Rett space with Trofinetide between 2010 and 2014. ....</i>	<i>7</i>
<i>Choose your rating scale - How to study a potential drug treatment for Rett Syndrome in the clinic. ....</i>	<i>8</i>
<i>Two successful Phase 2 studies in Rett Syndrome move Trofinetide towards Phase 3 .....</i>	<i>9</i>
<b>Evidence that Trofinetide can work in Fragile X Syndrome</b>	<b>10</b>
<i>Neuren has pre-clinical evidence that NNZ-2566 works in Fragile X Syndrome. ....</i>	<i>10</i>
<i>Neuren's Phase 2 in Fragile X was a success, with further studies warranted. ....</i>	<i>10</i>
<b>A company-making licensing agreement with Acadia Pharmaceuticals</b>	<b>11</b>
<i>Without question, a great licensing deal .....</i>	<i>11</i>
<i>Acadia is a great partner for Neuren to have secured .....</i>	<i>11</i>
<i>Acadia can move quickly to complete Rett Syndrome Phase 3. ....</i>	<i>12</i>
<i>We believe that Acadia will initiate further clinical work on Fragile X from 2019. ....</i>	<i>12</i>
<i>The Priority Review Voucher upside could be significant. ....</i>	<i>13</i>
<b>Why Trofinetide could become a blockbuster</b>	<b>13</b>
<i>Trofinetide could prove cost effective over time .....</i>	<i>14</i>
<i>Orphan drugs often take a while to mature .....</i>	<i>14</i>
<b>Good things could be coming from NNZ-2591</b>	<b>14</b>
<b>Neuren's solid management team</b>	<b>15</b>
<b>Valuing Neuren</b>	<b>16</b>
<b>Re-rating Neuren</b>	<b>18</b>
<b>Appendix I – A Neuren glossary</b>	<b>19</b>
<b>Appendix II – Neuren's intellectual property</b>	<b>21</b>
<b>Appendix III – Neuren's capital structure</b>	<b>22</b>
<b>Appendix IV – Major shareholders</b>	<b>22</b>
<b>Appendix V – Papers relevant to Neuren</b>	<b>23</b>
<b>Appendix VI – Companies to watch</b>	<b>25</b>
<b>Risks related to Neuren</b>	<b>26</b>
<b>General advice warning, Disclaimer &amp; Disclosures</b>	<b>28</b>



## Introducing Neuren Pharmaceuticals, ASX: NEU

Neuren Pharmaceuticals is a Melbourne-based drug developer. This company's lead compound is Trofinetide, for the treatment of two Autism Spectrum Disorders, Rett Syndrome and Fragile X Syndrome. The company has generated favourable Phase 2 data in both these conditions and in August 2018 was able to license the North American rights to Trofinetide to Acadia Pharmaceuticals<sup>1</sup>, a US specialty pharma company based in San Diego with a market capitalisation of about US\$3 billion.

### Acadia deal worth US\$450M

Acadia paid US\$10m upfront and may pay US\$105m in development and regulatory milestones and US\$350m in sales milestones, plus double-digit royalties on all Trofinetide sales. Acadia will now proceed with and fully fund a Phase 3 study in Rett Syndrome and commence further clinical work on Fragile X Syndrome. The US company expects to be filing for FDA approval in Rett Syndrome potentially in 2021 ahead of a 2022 approval following a 6-month Priority Review. Significantly, Neuren retains the Rest-of-World rights to Trofinetide and is currently negotiating a potential deal on these rights with Acadia.

### What is Trofinetide?

Trofinetide is a synthetic tripeptide drug that has its origins in the hormone Insulin-like Growth Factor 1 (IGF-1). This hormone, which is central to the normal growth and functioning of the central nervous system, has long been known to play a role in brain development<sup>2</sup>. In the 1990s the laboratory of Sir Peter Gluckman at the University of Auckland in New Zealand did a great deal of work on the neuroprotective and neurotrophic properties of Glypromate, a tripeptide<sup>3</sup> that cleaves off the N terminus of IGF-1<sup>4</sup> and is known to upregulate in the brain after hypoxic-ischemic injury<sup>5</sup>.

Neuren Pharmaceuticals was founded in 2001 and did its IPO on the ASX in 2005 in order to develop Glypromate for the prevention of cognitive impairment following cardiac surgery, where the drug failed in Phase 3 in late 2008. Dist. Prof. Margaret Brimble and her group at the University of Auckland produced a synthetic analogue of Glypromate initially called NNZ-2566, which is more stable, able to be administered orally and more readily crosses the blood-brain barrier.

Neuren initially worked on this compound as a potential neuroprotective in Traumatic Brain Injury, before shifting the development focus to the Orphan Drug programs Rett Syndrome and Fragile X Syndrome in late 2012. NNZ-2566 was renamed 'Trofinetide' in early 2015 when the World Health Organisation accepted this name for inclusion on the list of International Nonproprietary Names<sup>6</sup>. The effects of Trofinetide can be summarised as reducing neuroinflammation, restoring the normal function of microglia (the brain's immune cells) and improving connectivity between brain cells.

*Neuren and Acadia may be filing for FDA approval of Trofinetide in 2021*

*Neuren has been working on Trofinetide in Rett Syndrome since 2012*

<sup>1</sup> San Diego, Ca., Nasdaq: ACAD, [www.acadia-pharm.com](http://www.acadia-pharm.com).

<sup>2</sup> Neuroscience. 2016 Jun 14;325:89-99. Epub 2016 Mar 31.

<sup>3</sup> Glypromate gets its name from the fact that the three peptides are GLYcine, PROline and GlutaMATE.

<sup>4</sup> That is, the start of the hormone's amino acid chain.

<sup>5</sup> Brain Res. 2001 Dec 13;922(1):42-50.

<sup>6</sup> This was confirmed in August 2015.



*Neuren and Acadia may have the first ever drug treatment for Rett Syndrome*

## What is Rett Syndrome?

Rett Syndrome is a serious and debilitating neurodevelopmental condition that almost exclusively affects females. It is caused by a mutation in a gene located on the X chromosome called MeCP2. Rett Syndrome is characterised first and foremost by severe intellectual disability, but also by unsteady breathing, cardiac arrhythmia and unusual hand movements. Prevalence of the condition has been estimated at 1 in 10,000 or 1 in 15,000 females<sup>7</sup> and we estimate that there are ~10,000 females in the US currently living with the condition.

Females with Rett have been known to live into their 40s and beyond, however many die before this, and many suddenly die because of respiratory failure, apnoea or cardiac arrhythmia<sup>8</sup>. As yet, there are no approved drug treatments. Neuren and Acadia hope to change all that with Trofinetide, which has performed well in two Phase 2 studies in Rett Syndrome patients. Because Trofinetide aims to improve the underlying brain biology rather than treating one symptom, the target market is the entire Rett population.

## What is Fragile X Syndrome?

Fragile X Syndrome is, like Rett Syndrome, a monogenic disorder (i.e. caused by a single gene defect), in this case by mutations in the *fmr1* gene, also on the X chromosome. It's called 'Fragile X' because, when viewed under a microscope, the X chromosome at the point of the mutated *fmr1* is so narrow it looks as if it would break<sup>9</sup>. Fragile X Syndrome affects both sexes, but males more than females. The condition is characterised by intellectual disability, as well as by a long face and other atypical physical features<sup>10</sup>, social withdrawal, hyperactivity and seizures. We estimate there are around 40,000 Fragile X patients in the United States<sup>11</sup>. Neuren has completed a successful Phase 2 in Fragile X Syndrome.

## Orphan drugs can command extremely high prices

Since the 1980s many countries have had measures in place to encourage the development of so-called Orphan Drugs affecting small patient populations. In the US an Orphan Drug is defined as one affecting less than 200,000 people in that country annually. Since around 2008 there has been a strong push by US pharma and biotech companies to enter the Orphan Drug space because of the high prices that are often charged for such drugs, and the ease with which they can gain regulatory approval. We estimate that Trofinetide can become a blockbuster based on Orphan-style pricing in the order of US\$200,000 per patient.

## What happened to Neuren's former lead programme in Traumatic Brain Injury?

As we noted above, Neuren initially developed Trofinetide for the treatment of Traumatic Brain Injury. This programme was able to attract US Army funding in 2009, and a Phase 2 trial in TBI patients, called INTREPID-2566<sup>12</sup>, treated its first patient in 2010. This study recruited 261 patients with moderate-to-severe TBI with results reported in April 2016. It's fair to say

<sup>7</sup> Br Med J (Clin Res Ed). 1985 Aug 31;291(6495):579-82.

<sup>8</sup> Eur Child Adolesc Psychiatry. 1997;6 Suppl 1:71-4.

<sup>9</sup> Am J Hum Genet. 2012 Apr 6;90(4):579-90.

<sup>10</sup> Such as macroorchidism in the case of boys.

<sup>11</sup> Am J Med Genet A. 2014 Jul;164A(7):1648-58. Epub 2014 Apr 3.

<sup>12</sup> See NCT01366820 at clinicaltrials.gov.



*Neuren was marked down after the Acadia deal because of the low upfront. Smart investors will value the milestones*

that, like most of the TBI studies that have been conducted with other drugs, the results of this study were lacklustre, there being no noticeable difference between Trofinetide and placebo in three core efficacy measures<sup>13</sup>. That said, a fourth measure, called RBANS (Repeatable Battery for the Assessment of Neuropsychological Status<sup>14</sup>) yielded a highly significant result for Trofinetide in severe TBI ( $p=0.008$ ). On the basis of this, the US Army may consider funding a second study in severe TBI, however this programme is now non-core for Neuren.

## If Neuren is so good, how come the share price came down markedly with the Acadia deal?

After the announcement of the Acadia deal, Neuren's share price declined from the \$2.65 level of early August to a low of \$1.04 by 28 August. We believe that the market was disappointed with the Acadia partnering because the headline upfront in the deal was only US\$10m. We also believe such disappointment is unwarranted. Firstly, US\$455m in development and sales milestones plus double-digit royalties is a large deal in anyone's book when it comes to Pharma partnering, and the deal also removed a heavy development funding burden from Neuren.

Secondly, Trofinetide is moving into Phase 3, in which it has to repeat the result that was obtained in Phase 2, so the risk of clinical failure is considerably lower than was the case in Phase 2.

Thirdly, there is potential for Trofinetide to become a blockbuster once it comes on the market after 2022.

And fourthly, Neuren's partner Acadia is a well-regarded US drug developer with a track record of success as demonstrated by Nuplazid (pimavanserin), which the FDA designated a Breakthrough Therapy for Parkinson's Disease Psychosis in 2014 and which gained marketing approval in April 2016. Nuplazid enjoyed US\$125m in net sales in 2017, its first full year of commercial release. We see strong potential for Neuren to re-rate as the market starts to appreciate the quality of its August 2018 deal.

## Ten reasons to look at Neuren

1. **Neuren is a Phase 3 CNS drug developer in areas of urgent unmet need**, with Trofinetide having performed well in two Phase 2 studies in Rett Syndrome and one Phase 2 in Fragile X Syndrome. Following an end-of-Phase 2 meeting with the FDA for Rett syndrome in October 2017, Trofinetide only needs to repeat the result from the second Phase 2 trial in a single Phase 3 trial prior to Neuren's partner Acadia filing for FDA approval. Given the speed with which Neuren's previous studies have recruited, Trofinetide could potentially become an approved drug for Rett Syndrome by 2022.
2. **Neuren has a lucrative partnering deal with Acadia Pharmaceuticals**. Neuren's partnering deal with Acadia, signed in August 2018, came with total milestone payments of up to US\$465m plus double-digit royalties on net sales of Trofinetide in North America. It provides a clear path to market for Trofinetide in Rett Syndrome and Fragile X Syndrome.
3. **Trofinetide performed particularly well in the Phase 2 for pediatric Rett Syndrome**. This randomised, placebo-controlled study, which completed in 2017, generated statistically significant improvements across a range of domains and core measures and helped shape the design of the upcoming

*Trofinetide turned in some good data in pediatric Rett Syndrome*

<sup>13</sup> GOS-E, mPAI-4 and mortality.

<sup>14</sup> J Clin Exp Neuropsychol. 1998 Jun;20(3):310-9.





Phase 3. Two of the measures that showed statistically significant improvement are the primary endpoints for the Phase 3 trial.

4. **Neuren has the support of the key physicians and advocacy groups.** Neuren's studies have been conducted with strong support and collaboration from the leading Rett Syndrome physicians and the largest patient advocacy group Rettsyndrome.org, which is critical for development and commercial success.
5. **Neuren is funded for its next stage of development.** With Neuren holding A\$24m in cash as at September 2018, and Acadia funding further development of Trofinetide estimated at US\$60m for Rett Syndrome alone, we see Neuren as being free from near-term funding pressures.
6. **There is potential for Acadia to take Rest-of-World rights for Trofinetide,** with a second exclusive negotiating period having commenced in October 2018. Should these discussions proceed satisfactorily, we see potential for further cash infusions, as well as the potential for a re-rating of Neuren stock given the de-risking represented by such a transaction. If the parties don't reach agreement on a deal, Neuren will be free to negotiate with other interested parties.
7. **Neuren is an Orphan Drug developer.** Both Rett Syndrome and Fragile X are Orphan diseases with, at present, no approved drug treatments. There is potential for Neuren and Acadia to therefore enjoy high pricing for Trofinetide should the drug come to market.
8. **NNZ-2591 has potential across a wide range of conditions.** As per preclinical evidence, NNZ-2591 has demonstrated potent neuroprotective and neurotrophic properties across a range of CNS conditions. Development of NNZ-2591 offers further opportunities for Neuren to expand its drug portfolio for neurological disorders.
9. **Neuren has a strong management team.** The company's management team is led by its Executive Chairman, Dr. Richard Treagus, who has >20 years of experience in the biopharmaceutical industry on aspects such as development and commercialization of new pharmaceutical products, FDA approval for novel products, and product licensing deals. Richard is part of a well-equipped board that has extensive experience in building a successful life sciences company.
10. **Neuren is undervalued, on our numbers.** We value Neuren at \$4.17 per share base case and \$6.31 per share optimistic case using a probability-weighted DCF valuation approach. We see Neuren being re-rated towards our valuation range as the market starts to appreciate the quality of the deal with ACADIA, as Neuren negotiates a deal for the ex-North America rights for Trofinetide and as Acadia prepares for the US pivotal studies.

## Evidence that Trofinetide can treat Rett Syndrome

Neuren first started publicly talking about the potential of Trofinetide to treat Rett Syndrome in mid-2010<sup>15</sup>. The previous year, the laboratory of Mriganka Sur, who is an authority on brain development and neuroplasticity at MIT, had published an important paper related to the use of IGF-1 to treat Rett. Specifically, the Sur lab had used the Glypromate peptide fragment of IGF-1 in a mouse model of Rett – where the MeCP2 gene had been knocked out<sup>16</sup> – and found that such treatment would correct many of the obvious symptoms of Rett.

For example, the irregularity in heart rates of the mice were reduced, and their breathing patterns became more normal. Significantly the life span of

*Neuren has been  
working on Rett  
Syndrome since 2010*

<sup>15</sup> See the company's half yearly report, dated 28 August 2010.

<sup>16</sup> The so-called Jaenisch model - see at Genet. 2001 Mar;27(3):327-31.



*Neuren's drug works by improving synaptic connectivity*

*Neuren has Fast Track designation from the FDA for Trofinetide in Rett Syndrome*

the mice increased<sup>17</sup>. This paper was sufficiently interesting to the Rett Syndrome Research Trust that it commenced a collaboration with Neuren on the potential use of Trofinetide to treat Rett Syndrome.

## Neuren decided that Trofinetide could work in Rett Syndrome.

Once Neuren and its scientific collaborators had absorbed the implications of the Sur paper – that they had inadvertently developed a drug with potential to treat the most serious of the Autism Spectrum Disorders (ASDs) – they got to work on trying to understand mechanisms. They knew from the company's work in Traumatic Brain Injury that Trofinetide could act on microglia<sup>18</sup>, and began to hypothesise that this mechanism was one of the reasons why the Sur lab enjoyed their success with Glypromate in the MeCP2-deficient mice.

The ASDs are best described, at a biochemical level, as disorders of either excessive or reduced synaptic connectivity in affected brain regions<sup>19</sup>. Basically, the brains of people on the Spectrum just aren't wired up properly. Rett Syndrome, probably the most severe of the ASDs, features too few synaptic connections<sup>20</sup>, while Fragile X features too many<sup>21</sup>.

By 2011 a body of work had started to emerge showing the importance of microglia in the pathology of the ASDs, where the active surveillance of the microglia in the various microenvironments in the brain was interfering with synaptic connectivity and the maturation of brain circuitry<sup>22</sup>. Glypromate and therefore Trofinetide, by modulating microglia, would help restore the proper level of connectivity. Interestingly, Rett patients treated with whole IGF-1<sup>23</sup> – which as the Ipsen<sup>24</sup> drug Increlex<sup>25</sup> is approved for the treatment of severe primary IGF-1 deficiency – have been known to have improvements in their cognitive, social, and autonomic abilities<sup>26</sup>.

## Neuren moved into the Rett space with Trofinetide between 2010 and 2014.

In 2010 Neuren was primarily focused on developing Trofinetide for Traumatic Brain Injury, with significant funding coming from the US government for what became the INTREPID-2566 Phase 2 study. However, when the Sur lab generated the *in vivo* data on the use of Glypromate in Rett, it quickly became apparent that this could become an obvious new programme for Trofinetide.

For one thing, Neuren had been working on an oral formulation of Trofinetide for mild Traumatic Brain Injury and, potentially, for stroke recovery, and the same formulation would be suitable for Rett.

For another, a Rett programme could reasonably garner strong support from a tight-knit patient advocacy community. The International Rett Syndrome Foundation (IRSF)<sup>27</sup> could help co-ordinate the efforts of parents and caregivers, as well as key opinion leaders, making recruitment into a Phase 2 study relatively straightforward, and the IRSF Foundation could also be a source of grant funding. Significantly, when Neuren held a pre-IND meeting

<sup>17</sup> Proc Natl Acad Sci U S A. 2009 Feb 10;106(6):2029-34.

<sup>18</sup> J Neurotrauma. 2009 Jan;26(1):141-54.

<sup>19</sup> Front Neurosci. 2015 Sep 24;9:313.

<sup>20</sup> J Neurosci. 2009 Sep 9;29(36):11263-70.

<sup>21</sup> Cereb Cortex. 2012 Jun;22(6):1333-42. Epub 2011 Aug 19.

<sup>22</sup> Neuron Glia Biol. 2011 Feb;7(1):85-97. Epub 2012 Apr 30.

<sup>23</sup> The entire protein is 70 amino acids in length.

<sup>24</sup> Ipsen (Paris, France, Euronext Paris: IPA, [www.ipсен.com](http://www.ipсен.com)) is a French specialty pharma company with a rare disease franchise.

<sup>25</sup> [www.increlex.com](http://www.increlex.com).

<sup>26</sup> Proc Natl Acad Sci U S A. 2014 Mar 25;111(12):4596-601. Epub 2014 Mar 12.

<sup>27</sup> [Rettsyndrome.org](http://Rettsyndrome.org).

*Rett Syndrome patient outcomes can be measured, allowing drug efficacy to be clinically evaluated*

at the FDA in May 2012 to discuss the path forward for Trofinetide in Rett, the meeting was attended by, among others, Dr Steven Kaminsky, Chief Science Officer of the ISRF, as well as Drs Daniel Glaze and Jeffrey Neul of the Blue Bird Circle Rett Center in Houston, the world's leading Rett treatment facility. The initial Phase 2 study in adolescent and adult Rett patients which emerged from this pre-IND meeting initiated in early 2013.

Six months later Neuren's Rett programme received a Fast Track designation from the FDA and the Phase 2 read out favourable topline data in November 2014. The drug was granted Orphan Drug status for Rett Syndrome by the FDA in February 2015 and by the EMA for Europe in August 2015.

## Choose your rating scale - How to study a potential drug treatment for Rett Syndrome in the clinic

The challenge of proving that a drug could work in Rett Syndrome was to choose the appropriate rating scale with which to evaluate if the patients were doing better or worse. Thankfully for Neuren and its collaborators, as they moved towards designing their first Phase 2, a number of such scales existed, while others could be developed and then used once regulators were comfortable with them. Neuren evaluated Trofinetide using four 'efficacy domains', namely a) specific measures by physicians; b) 'global' measures by physicians' c) measures by caregivers, and d) physiological measures. Within these domains were a number of core outcome measures, such as:

- **Caregiver Top 3 Concerns.** This rating scale asks the patient's caregiver – who obviously will know the patient best – to rate using a Visual Analogue Scale the changes in their three priority concerns from baseline.
- **Clinical Global Impression of Improvement (CGI-I).** This rating scale is an 'overall' assessment tool where doctors rate whether they think their patients are better or worse. It is commonly used in studies of neurology drugs.
- **Motor-Behaviour Assessment Change Index.** A Motor-Behaviour Assessment allows the severity of core symptoms such as motor, behaviour, and respiratory dysfunction to be assessed.
- **Rett Syndrome Behavioural Questionnaire (RSBQ).** This Questionnaire, developed in the early 2000s<sup>28</sup>, allows behaviours such as breath holding or screaming to be tracked.
- **Rett Syndrome Domain-Specific Concerns.** This scale is similar to the Caregiver Top 3 Concerns although this time it reflects the greatest concerns of the physicians.

As we shall see, the use of multiple ratings scales, particularly those involving caregivers (who until recently, it is fair to say, had little input into clinical trial measurement<sup>29</sup>), enhanced the chances of detecting that Trofinetide provided some measurable benefit to Rett patients.

<sup>28</sup> J Child Psychol Psychiatry. 2002 Nov;43(8):1099-110.

<sup>29</sup> But have been influential in helping to gain FDA approval for Sarepta's Duchenne Muscular Dystrophy drug.





## Two successful Phase 2 studies in Rett Syndrome move Trofinetide towards Phase 3

**A successful maiden study of Trofinetide in adolescent and adult Rett patients – 2012-2014.** The IND for Trofinetide in Rett was cleared by the FDA in late 2012. Neuren's initial Phase 2 for Trofinetide<sup>30</sup>, which was supported by the IRSF, took only 18 months to recruit 53 female Rett patients over the age of 16. Patients received the drug orally at two dose levels over 28 days at either 35 mg/kg of body weight twice daily, or 70 mg/kg twice daily, and were followed out to day 40. They were tracked across six 'core measures' from four 'efficacy domains' in an analysis plan that was pre-specified and submitted to the FDA before the data was unblinded.

Neuren's drug was safe and well tolerated and the study generated favourable topline efficacy data which was released in November 2014. In the prespecified analysis the agency and investigators were looking for improvement in two core measures from two efficacy domains, and no clinically significant worsening in the other core measures. At the 70 mg/kg dose, Trofinetide delivered the goods, registering improvements in three core measures from three efficacy domains, and no worsening in the other core measures, by day 26. The three core measures in which Trofinetide was successful were the Motor-Behaviour Assessment Change Index, the CGI-I and the Caregiver Top 3 Concerns.

This study had obvious limitations – a relatively short duration and a small number of subjects with advanced disease, however the efficacy trends at the higher doses were obvious. The results were published in the journal *Pediatric Neurology* in July 2017<sup>31</sup>.

**A second Phase 2 study in pediatric Rett patients – 2016-2017.** Neuren and its collaborators took what they had learned from the adolescent and adult Phase 2 in Rett and crafted a second study in pediatric patients which initiated in April 2016<sup>32</sup>. This randomised, placebo-controlled study had initially intended to recruit 64 patients, randomising 1:1 between drug and placebo. This study had three dose levels - 50 mg/kg, 100 mg/kg, and 200 mg/kg twice daily - on the reasonable assumption that the top dose had yet to be reached in Rett. Also, the patients were treated for a longer period – 6 weeks – with the main efficacy measures including the CGI-I which had been encouraging in the previous Phase 2 study.

In August 2016 Neuren announced that more patients would be recruited in the 200 mg/kg versus placebo cohort due to fast enrolment, good subject availability and excellent tolerability. Recruitment had been completed in January 2017, another indication of the speed with which studies in Rett could be organised. Topline results became available in March 2017 and showed, at the top dose of 200 mg/kg, Trofinetide significantly outperforming placebo on the RSBQ (p=0.042), the CGI-I (p=0.029) and the Rett Syndrome Domain-Specific Concerns (p=0.025). Trofinetide also had a good safety profile.

**The End-of-Phase 2 meeting confirms a single Phase 3, late 2017.** Neuren had its End-of-Phase 2 meeting with the FDA for Trofinetide in Rett Syndrome in October 2017. At that meeting the Agency agreed with Neuren's plan for a single Phase 3 study where the patients would randomise 1:1 to a single dose group or placebo, the treatment duration would be six months, and the co-primary endpoints would be improvement in the RSBQ and the CGI-I where the Phase 2 data was compelling.

*Neuren's initial Phase 2 in Rett delivered improvements across multiple core measures*

*Trofinetide can gain FDA approval after a single Phase 3*

<sup>30</sup> See NCT01703533 at [clinicaltrials.gov](http://clinicaltrials.gov).

<sup>31</sup> *Pediatr Neurol.* 2017 Nov;76:37-46. Epub 2017 Jul 8.

<sup>32</sup> See NCT02715115 at [clinicaltrials.gov](http://clinicaltrials.gov).



Neuren currently envisages this Phase 3 will recruit ~180 patients. Essentially, the Phase 3 trial will need to repeat the Phase 2 result with a longer treatment period and 3 times the sample size. We believe it was that Phase 2 data and the clear line of sight through to a potential New Drug Application that attracted Acadia Pharmaceuticals with its August 2018 partnering.

**Trofinetide is not officially a Breakthrough Therapy...yet.** The month after the initial Phase 2 data was reported, Neuren applied to the FDA for Breakthrough Therapy Designation. Since 2012<sup>33</sup> the Administration has been able to grant this designation to new drugs that treat serious or life-threatening disease conditions, where the preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies and where there are clinically significant endpoints that can be used to justify an early approval for the drug (ie, often after Phase 2).

Neuren's application was declined in March 2015 on the grounds that there wasn't enough statistical proof from the initial Phase 2 demonstrating that Trofinetide offered 'substantial improvement over existing therapies' in Rett. We believe that data from the subsequent pediatric study, as well as the upcoming Phase 3, could allow Neuren and Acadia to go back to the FDA and ask again for the Breakthrough Designation, which, if nothing else, would draw attention to the groundbreaking nature of Neuren's lead candidate.

## Trofinetide can work in Fragile X Syndrome

### Neuren has pre-clinical evidence that NNZ-2566 works in Fragile X Syndrome.

The *in vivo* data on the success of Glypromate in mouse models of Rett also alerted Neuren to the potential for Trofinetide to work in Fragile X Syndrome, since, as we have seen above, Fragile X is also understood to be a disorder of synaptic connectivity. In November 2012 Neuren reported pre-clinical evidence that Trofinetide could reduce the symptoms and biological abnormalities of Fragile X in *fmr1* knockout mice.

Trofinetide was able to reduce the hyperactivity of the mice as well as their deficits in learning and social behaviour. Following receipt of these results Neuren proceeded to organise a Phase 2 study. The Fragile X programme received Fast Track and Orphan Drug status for NNZ-2566 from the FDA in Fragile X in October 2013. It was granted Orphan Drug status in Europe for Fragile X in August 2015.

### Phase 2 in Fragile X was a success, with further studies warranted.

The Phase 2 study of Trofinetide in Fragile X initiated in September 2013<sup>34</sup>. This study, which was double-blind and placebo-controlled, recruited 70 male patients and, as with the initial Rett study, tested 35 mg/kg of body weight twice daily and 70 mg/kg twice daily against placebo over 28 days. This study, which once again found Trofinetide to be safe and well tolerated, read out topline results in December 2015. While it wasn't powered for statistical significance, the investigators found that the 70 mg/kg dose could bring about noticeable clinical improvement as observed by both physicians and caregivers in ratings scales such as the CGI-I for Fragile X and the Caregiver Top 3 Concerns. We believe that this Fragile X data, while early, provided

***Trofinetide has Orphan  
Drug status for Fragile X  
Syndrome***

<sup>33</sup> After the passage of the Food and Drug Administration Safety and Innovation Act.

<sup>34</sup> See NCT01894958 at [clinicaltrials.gov](http://clinicaltrials.gov).



further comfort to the Acadia Pharmaceuticals team as they were doing their due diligence during 2018 on Trofinetide.

## A company-making licensing agreement with Acadia Pharmaceuticals

### Without question, a great licensing deal

The Phase 2 data in Rett was sufficiently attractive for Neuren to attract a licensing partner for Phase 3 in the form of Acadia Pharmaceuticals. This San Diego-based specialty pharma company paid US\$10m upfront and agreed to pay US\$105m in development and regulatory milestones and US\$350m in sales milestones for North American rights only, albeit to both Rett and Fragile X, plus double-digit percentage royalties on all sales.

Neuren will also receive one-third of the proceeds from selling any Priority Review Voucher the FDA may issue to Acadia, which, as we will see below, could be very lucrative. The US company will now proceed to fund and run the Phase 3 study in Rett Syndrome and commence further work on the development plan for Fragile X Syndrome. The market reacted negatively to this deal because of the apparently low US\$10m upfront as well as some uncertainty surrounding Acadia as the partner. We argue, contrary to the market, that this is an outstanding licensing deal for Neuren considering the following:

- 1) Acadia had, in May 2018, taken a US\$4m equity investment in Neuren when it requested and was subsequently granted an exclusive three-month negotiating period for Trofinetide. Acadia's entry price was A\$4.00 per share.
- 2) Acadia will fund Trofinetide's Phase 3 program, which at US\$60m for Rett Syndrome alone would have been a too heavy an investment for Neuren.
- 3) Since Neuren's drug is moving into Phase 3, the company's chances of obtaining the developmental milestones are fairly high.
- 4) Acadia is an experienced and successful developer of CNS drugs, having brought to market the ground-breaking Nuplazid drug for the treatment of Parkinson's Disease Psychosis in 2016.
- 5) As we shall see below, Trofinetide could become a blockbuster, allowing the hefty sales milestones to be collected as well.
- 6) Priority Review Vouchers have tended to sell for very high prices in recent years, often greater than US\$100m.

### Acadia is a great partner for Neuren

Acadia Pharmaceuticals is a significant player on the US biotechnology scene, with a current market capitalisation of nearly US\$3bn<sup>35</sup> and membership in the elite Nasdaq Biotechnology Index. We argue that the secret to its success as a small company was to stick with neurology at a time when everyone seemed to have decided that the whole field was a 'drug developers' graveyard' and were getting out.

- **Acadia has already brought to market its first potential blockbuster.** Acadia's 'company-making' drug was pimavanserin for Parkinson's disease psychosis (PDP), which it took into Phase 3 in 2010, a time when CNS drug candidates were not popular. PDP is potentially a large market opportunity since Parkinson's Disease affects 1-2 per 1000 of the population at any time<sup>36</sup> and

*The milestones in the Acadia deal are high*

*Acadia's specialty is neurology drugs*

<sup>35</sup> ~US\$2.86bn as at 4 December 2018 close on Nasdaq.

<sup>36</sup> J Neural Transm (Vienna). 2017 Aug;124(8):901-905. Epub 2017 Feb 1.



PDP, where the patient experiences hallucinations and delusions, may develop in up to 60% of Parkinson's patients<sup>37</sup>. Pimavanserin, a selective serotonin 5-HT<sub>2A</sub> inverse agonist, turned in outstanding Phase 3 data in 2012, showing a statistically significant reduction in psychosis in just under 200 patients<sup>38</sup>. The FDA designated a Breakthrough Therapy for PDP in 2014 and granted marketing approval as Nuplazid<sup>39</sup> in April 2016. In October 2017 the FDA granted a second Breakthrough Therapy Designation to pimavanserin, this time for dementia-related psychosis, an even bigger market opportunity. Other indications in schizophrenia and Major Depressive Disorder are being worked on.

**Acadia has the  
resources to take  
Trofinetide forward**

- Acadia has specialist expertise in neurology gained from the ground up. Pimavanserin is a drug that is 'home grown', having originated from a late 1990s chemical genomics effort by Acadia scientists aimed at improving the understanding of the targets for drugs acting on the CNS<sup>40</sup>. The kind of specialist understanding that allowed the clinical development of pimavanserin will likely prove valuable in bringing Trofinetide to market. Acadia has also recently further strengthened its development team, bringing impressive experience from other companies in successfully developing and commercialising neurology and Orphan products.
- Acadia has the resources to take Trofinetide forward. As at September 2018 Acadia held US\$214m in cash and investments on its balance sheet and it has just completed a further large equity raise of approximately US\$300m. It will only take US\$60m of that to run the Rett Syndrome Phase 3, and Acadia is now rapidly growing revenue from Nuplazid. Net sales in calendar 2017, its first full year of commercial release, were US\$125m and current sales are approximately US\$55m per quarter.
- Around the time of Neuren's deal with Acadia, concerns emerged in the mainstream media over the safety of Nuplazid<sup>41</sup>, with many patients prescribed the drug since its 2017 launch having known to have died. These concerns led the FDA to do an analysis of the available data. That review, completed in September 2018, confirmed the positive benefit-risk profile for patients with PDP.

### **Acadia can move quickly to complete Rett Syndrome Phase 3**

The US company, which has already organised a very successful Phase 3 for pimavanserin, expects to initiate its Rett Phase 3 in the second half of calendar 2019 and complete this study within two years, putting Acadia on track to gain FDA approval in Rett Syndrome by 2022. While the speed of such a Phase 3 may seem surprising, the reader is reminded of the speed with which Neuren could run the second Phase 2 study in Rett – since there are at present no drug treatments for Rett, Neuren has gained the support of all key opinion leaders and clinical specialists in the field, easing the access to an eager caregiver community and, through them, to the patients themselves.

### **We believe that Acadia will initiate further clinical work on Fragile X from 2019.**

Obviously, it is still early days for Trofinetide clinical story in Fragile X, with only a single exploratory Phase 2 having been performed. We expect that

<sup>37</sup> Expert Rev Clin Pharmacol. 2017 Nov;10(11):1161-1168. Epub 2017 Oct 17.

<sup>38</sup> Lancet. 2014 Feb 8;383(9916):533-40. Epub 2013 Nov 1.

<sup>39</sup> See [www.nuplazid.com](http://www.nuplazid.com).

<sup>40</sup> Neurochem Res. 2014; 39(10): 2008–2017.

<sup>41</sup> The original story was *FDA worried drug was risky; now reports of deaths spark concern* by Blake Ellis and Melanie Hicken, CNN Investigates, 9 April 2018.



**Priority Review  
Vouchers often sell for  
very high prices**

after a review of the available data Acadia will initiate another Phase 2, this one with a longer dosing window and higher dose ranges.

## The Priority Review Voucher upside could be significant.

In 2007 the US Congress created a 'Priority Review Voucher' program to encourage development of drugs for neglected or rare pediatric diseases. Under the program, the developer of such a drug, when that drug gains FDA approval, receives a bonus Priority Review Voucher (PRV) for another drug which it can then sell to other drug developers who wish to access the benefits of Priority Review for their drug. Neuren and Acadia are expecting that Trofinetide for Rett Syndrome will qualify and Neuren receives one third of any sales proceeds. In which case, there is considerable upside coming Neuren's way, as the price of recent PRV sales has suggested:

**Table 1: Recent Priority Review Voucher transactions**

Vendor	Acquirer	Price (USDm)	Date
BioMarin	Sanofi and Regeneron	68	Jul-14
Knight	Gilead Sciences	125	Nov-14
Retrophin	Sanofi	80	May-15
United Therapeutics	AbbVie	350	Aug-15
Sarepta Therapeutics	Gilead Sciences	125	Feb-17
BioMarin	Unnamed	125	Nov-17
UltraGenyx	Novartis	130	Dec-17
Spark Therapeutics	Jazz Pharmaceuticals	110	Apr-18
UltraGenyx and Kyowa	Unnamed	81	Jul-18
Siga Technologies	Eli Lilly	80	Nov-18
Average		127	

Source: Pitt Street Research

## Why Trofinetide could become a blockbuster

**Orphan Drugs are, financially speaking, no longer orphaned.** One of the paradoxes of the modern biotech and pharmaceutical industry is the high prices that can prevail for drugs that serve small patient populations. In one sense this is nothing new – healthcare systems in advanced industrial countries have been paying up for Orphan Drugs ever since Genzyme brought Ceredase to market for the treatment of Gaucher's Disease in 1991<sup>42</sup>. Genzyme was able to charge >US\$150,000 per patient, but in effect maintained that pricing even after it replaced Ceredase with Cerezyme, a recombinant version of the same therapeutic protein with markedly lower production costs<sup>43</sup>. However, the years since around 2007 have seen an explosion of Orphan Drug development with high price tags a notable part of the endgame. Witness just three examples:

US\$300,000 p.a. for Sarepta's<sup>44</sup> Exondys 51 for Duchenne Muscular Dystrophy<sup>45</sup>.

**Orphan Drugs often sell  
for high prices**

<sup>42</sup> J Intraven Nurs. 1996 Mar-Apr;19(2):83-8.

<sup>43</sup> See The World's Most Expensive Drugs by Matthew Herper, Forbes, 22 February 2010.

<sup>44</sup> Cambridge, Ma., Nasdaq: SRPT, www.sarepta.com.

<sup>45</sup> See How the FDA Approved a \$300,000-a-Year Drug Its Own Experts Didn't Believe Worked by Susan Pulliam and Brody Mullins, the Wall Street Journal, 18 May 2017.





US\$500,000 p.a. for Alexion Pharmaceuticals<sup>46</sup> Soliris, monoclonal antibody for the treatment of paroxysmal nocturnal haemoglobinuria<sup>47</sup>.

US\$550,000 p.a. for Ravicti, a drug from Horizon Pharma<sup>48</sup> that treats urea cycle disorders<sup>49</sup>.

**Why Orphan Drugs like Neuren's and Acadia's will continue to enjoy favourable pricing.** The reason for this high pricing is, we think, threefold.

The small patient populations generally had no drug treatments before the new drug came along.

Often the high prices make sense when considered from a healthcare economics perspective.

Policymakers tends to only focus on the cost of drugs when the drugs are mass market<sup>50</sup> or where a previously low-priced (and, for some, essential) drug suddenly becomes a high-priced drug<sup>51</sup>.

Consequently, we think there is reasonable potential for Acadia to sell Trofinetide for a price approximating US\$200,000 p.a. This would make it a blockbuster just in Rett Syndrome in the US, where treating even half of a 10,000-patient population would make it a US\$1bn seller.

## Trofinetide could prove cost effective over time

Cost effectiveness in healthcare is generally measured in terms of cost per Quality-Adjusted Life Year (QALY). If a drug comes in at under US\$100,000 per QALY it is considered cost-effective. If one argues that Rett patients currently have a low quality of life and could live longer with Trofinetide with much better quality, the lifetime costs of the drug may be close to cost effective on this measure. Future healthcare economic analysis will likely be required on this issue for jurisdictions such as the UK where drug pricing is not as free as it is in the US.

## Orphan drugs often take a while to mature

Theoretically a new drug for an Orphan disease condition that hitherto had few drug treatment options should enjoy 100% uptake by the relevant patient population in year 1. In reality, it takes many years for this to happen, due to lack of insurance or patient and physician awareness. Take the above-mentioned Soliris as a good example, where the US market is estimated at 4,000-6,000 patients. It gained FDA approval in 2007, but despite the high pricing didn't become a blockbuster until 2012. Sales in 2017 of US\$3.1bn may indicate that finally, a decade after launch, the drug is reaching most of the patient populations where it is approved. We believe Trofinetide's path to blockbuster status may be similar.

## Good things could be coming from NNZ-2591

Neuren's second drug, a cyclic dipeptide with 100% oral bioavailability, is, like Trofinetide, related to IGF-1. It was originally developed as a backup candidate

*NNZ-2591 has shown intriguing in vivo efficacy in a wide range of CNS disorders*

<sup>46</sup> New Haven, Ct, Nasdaq: ALXN, [www.alexion.com](http://www.alexion.com).

<sup>47</sup> *Why Is Soliris The Most Expensive Drug In The US?* by Chuck Dinerstein, American Council on Science and Health, 27 May 2017.

<sup>48</sup> Dublin, Ireland, Nasdaq: HZNP, [www.horizonpharma.com](http://www.horizonpharma.com)

<sup>49</sup> See *FDA Approves Age-Range Expansion on One of World's Most Expensive Drugs* by Thomas Castles, MD Magazine, 30 April 2017

<sup>50</sup> Witness US President Trump's consistent rhetoric against drug pricing – see *What Big Pharma Fears Most: A Trump Alliance With Democrats to Cut Drug Prices* by Robert Pear, the New York Times, 20 October 2018.

<sup>51</sup> Witness the outrage over Mylan's price increases related to the EpiPen – see *Another look at the surge in EpiPen costs* by Lisa Rapaport, Reuters, 28 March 2007.

to Trofinetide but showed, *in vivo*, intriguing efficacy in a wide range of CNS disorders including Parkinson's Disease, peripheral neuropathy and mild cognitive impairment. In July 2013 Neuren was able to show, in a Fragile X animal model, that NNZ-2591 would treat Fragile X at around one third the dose required of NNZ-2566. Neuren has indicated that it will now advance development of NNZ-2591 during 2019.

## Neuren's solid management team

Neuren's current top management team has extensive sector experience and the ability to take the company forward in terms of creating shareholder value.

Executive Chairman, **Dr. Richard Treagus**, is a physician and has >20 years of experience in the biopharmaceutical industry. He has closely worked with major pharmaceutical companies in Australia and South Africa, and has collaborated with various pharmaceutical companies in the US, Europe, and Asia. Prior to joining Neuren in January 2013, Richard worked as a Chief Executive with Acrux Limited, an Australia-based specialty and generic topical pharmaceuticals manufacturer, for about 7 years. He played a vital role in obtaining FDA approval for Acrux's 3 novel pharmaceutical products and closing a product licensing deal with Eli Lilly.

Executive Director and Chief Science Officer (CSO), **Larry Glass**, has >30 years of experience in the life sciences industry, including basic and applied research, clinical trials, diagnostics, epidemiologic studies, and pharmaceutical product development. Prior to joining Neuren in 2004, Larry worked as a consultant to provide strategic, management, and business development services to various biotech companies. He has also worked as CEO of a contract research organization (CRO) to provide preclinical research and clinical trials support for major pharmaceutical companies and the US government.

Chief Financial Officer (CFO), **Jon Pilcher**, joined Neuren in August 2013. Previously, he served Acrux as CFO and Company Secretary for ~11 years. Jon was a significant contributor during the development and FDA approval of Acrux's three drug products, Acrux's initial public offering (IPO) and listing on the ASX, and the company's product licensing transaction with Eli Lilly.

Vice President of Neuren's Clinical Operations, **James Shaw**, has ~20 years of experience in drug development and commercialization for large pharma companies and CROs. Before joining Neuren in August 2013, James worked with Quintiles in Sydney and Singapore, and AstraZeneca in the UK to provide business development, drug development, clinical trial, and commercialization support.

Vice President of Neuren's Clinical Development, **Dr. Nancy Jones**, joined Neuren in January 2013. Previously, she worked at a senior position with Autism Speaks, a US-based autism advocacy organization dedicated to research and treatment of autism-related disorders. She also worked as a Director of Autism Treatment Network and Clinical Projects – a network of hospitals, physicians, researchers, and other medical centers – for six years.

Vice President of Neuren's Product Development and Technical Affairs, **Clive Blower**, has >20 years of experience in drug development and commercialization. He has played essential roles in the development and launch of >25 pharmaceutical products. Prior to joining Neuren in August 2014, Clive served Acrux for seven years (as the Director of Product Development and Technical Affairs department, and Chief Operating Officer). He played an important role in providing chemistry, manufacturing, and

*Neuren's current top management team has extensive sector experience*

controls (CMC) services for the development of Acrux's lead product through Phase III clinical trials, its FDA approval, and launch.

**Neuren's current board**, which includes Dr. Treagus, is experienced and has various skills required for building a successful life sciences company.

- Dr. Trevor Scott, currently a Non-executive Director, has been a member of Neuren's Audit Committee and Remuneration Committee since 2002. Trevor founded T.D. Scott and Co., an accountancy and consulting company, in 1988. He is a member of various advisory boards across different industries.
- Dianne Angus, the Non-executive Director of Neuren since July 2018, has >25 years of experience in various industries such as biotechnology, biopharmaceutical, and agricultural technology. She is also involved in various partnerships such as Prana Biotechnology, Gerolymatos International, Florigene, Suntory, and Monsanto – which focus on the production of novel medical, pharmaceutical, and agricultural products.
- Patrick Davies has been Non-executive Director at Neuren since July 2018 and holds >20 years' experience in various sectors such as pharmacy, primary care, pharmaceutical, and consumer products in Australia and New Zealand. He previously worked as Chief Executive Officer (CEO) of EBOS Group Limited, an Australia-based wholesaler and distributor of pharmaceutical and medical products.
- Dr Jenny Harry, the Non-executive Director of Neuren since July 2018, has 20 years of experience of executive management in the biotechnology and biopharmaceutical sectors. Jenny is also the Managing Director (MD) of Ondek, an Australia-based biopharmaceutical company dedicated to novel therapies for pediatric allergy. Previously, she has worked as the CEO and MD of Tyrian Diagnostics, an Australia-based diagnostic products manufacturer.

## Valuing Neuren

*We value Neuren at over \$4.00 per share base case*

We value Neuren at \$4.17 per share base case and \$6.31 per share optimistic case using a probability-weighted DCF valuation approach.

- Our WACC was 15.3% (Speculative)<sup>52</sup>;
- We modelled payoffs for Trofinetide in both North America and globally;
- We model commercial exclusivity for each product until 2032, which is when the method patents for both Rett and Fragile X expire<sup>53</sup>;
- Our probability weighting for Trofinetide reaching the market for Rett syndrome and Fragile X syndrome was respectively 71% and 38%, reflecting the historical probability for large molecules in Phase 3 and Phase 2<sup>54</sup>;
- We modelled a corporate overhead of A\$0.6m per month.

<sup>52</sup> For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.6%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

<sup>53</sup> See Treatment of Autism Spectrum Disorders using glycyl-L-2-methylprolyl-L-glutamic acid, WO/2012/102832, priority date January 27, 2011

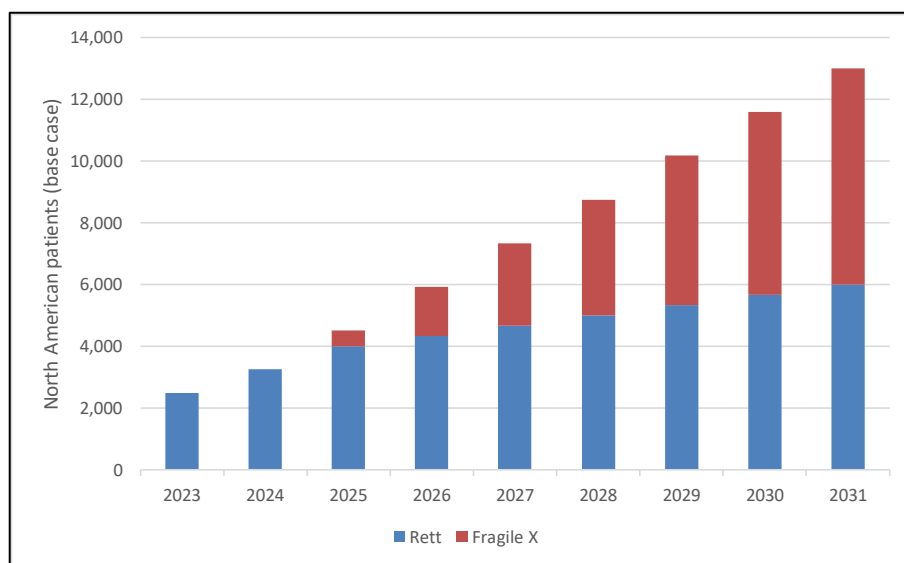
<sup>54</sup> Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.



**Trofinetide North American rights.** We assumed that the Rett product launches in 2022 (both base and optimistic cases) and all sales milestones are collected by Neuren.

- We assume a royalty from Acadia that over time escalates from 10% to 12% (base case) and 14% (optimistic case), reflecting that annual sales are recorded in tiers, with an escalating double-digit percentage royalty rate applied to the sales in each tier. This means that the average royalty rate will increase over time as the annual sales increase.
- We assume that a Fragile X indication is added to the initial Rett indication after three years (optimistic case) or four years (base case).
- For Rett, we understand that approximately half of the 10,000 Rett women and girls in the US are on a register with rettsyndrome.org and therefore are likely to access Trofinetide as soon as possible after launch. We forecast 4,000 (base case) to 6,000 (optimistic case) patients by 2026, reaching to 6,000 patients (base case) to 8,000 patients (optimistic case) by 2032.
- For Fragile X, our assumptions have been more modest in terms of market penetration. We assume 7,000 (base case) to 10,000 (optimistic case) by 2032.

**Figure 1: Our base case assumptions on North American patient numbers for Trofinetide**



Source: Pitt Street Research

*We believe Trofinetide has potential to become a blockbuster*

- We modeled peak North American sales of US\$2.6bn (base case) and \$3.6bn (optimistic case), comprising US\$1.2bn to US\$1.6bn for Rett and US\$1.4bn to US\$2bn for Fragile X, an assumption which may prove conservative if Trofinetide yields strong data in Fragile X.

**Trofinetide PRV one third share.** We modeled the gross value of the Trofinetide PRV sale at US\$80m (base case) and US\$120m (optimistic case).

**Trofinetide Rest of World rights.** For conservatism's sake we have modeled no licensing fees here but assumed an extension of the North American royalty rates to the Rest of the World and a one year lag on approvals, but ten years exclusivity post-approval, reflecting the 10 years exclusivity granted for all



Orphan Drugs in the EU (pediatric Orphan drugs get 12<sup>55</sup>) and pediatric Orphan Drugs in Japan<sup>56</sup>. For the RoW we modeled peak sales of \$0.8bn (base case) to \$1.6bn (optimistic case), which assumes lower penetration of a more fragmented market and lower pricing compared with the US.

**NNZ-2591.** We have not included any value for this product at this stage, which remains as upside.

**Capital.** We assume that Neuren's current cash is enough to fund the company going forward without more having to be raised.

**Table 2: Our valuation of Neuren**

	Base	Optim.
Trofinetide (N. America) (A\$m)	351.2	495.3
Trofinetide (RoW) (A\$m)	53.3	118.9
Sale of PRV (A\$m)	18.8	28.1
Total programme value	423.3	642.4
Value of tax losses	10.0	10.0
Corporate overhead	-33.1	-33.1
Cash now (A\$m)	23.9	23.9
Cash to be raised (A\$m)	0.0	0.0
Option exercises (A\$m)	4.4	4.4
Total value (A\$m)	428.4	647.6
Total diluted shares (million)	102.7	102.7
Per share valuation range	\$4.17	\$6.31
Valuation midpoint	\$5.24	
Share price now (A\$ per share)	\$1.370	
Upside to midpoint	282.5%	

Source: Pitt Street Research

## Re-rating Neuren

Neuren compares favourably to a range of comparables in terms of current market capitalisation (see Appendix VI). We see the following main factors helping to re-rate Neuren towards our valuation range:

- The market starting to appreciate the quality of the deal with Acadia
- The move into Phase 3 of Trofinetide for Rett Syndrome.
- The move into the next Phase 2 trial of Trofinetide for Fragile X Syndrome.
- Discussions with regulators outside the US regarding the preferred development pathway for Trofinetide.
- Potential partnerships regarding Rest-of-World rights for Trofinetide.
- NNZ-2591 advancing in preclinical development and Neuren confirming which neurological conditions will be targeted.

<sup>55</sup> See Regulation (EC) No 1901/2006.

<sup>56</sup> Intractable Rare Dis Res. 2012 May; 1(2): 95–97.





## Appendix I – A Neuren glossary

**Amino acid** – The building blocks of peptides and proteins. There are around 20 naturally-occurring amino acids.

**Autism Spectrum Disorder (ASD)** – A developmental disability with similar symptoms to autism. Rett’s Syndrome is considered an Autism Spectrum Disorder.

**Autonomic** – Relating to the autonomic nervous system, which controls bodily functions not consciously directed, such as breathing.

**Bioavailability** – The extent and rate at which a drug/metabolite enters systemic circulation, and thus accesses the site of action.

**Blockbuster** – A pharmaceutical drug with more than US\$1bn in annual sales.

**Blood–brain barrier** – A semipermeable membrane separating the blood from the cerebrospinal fluid, and constituting a barrier to the passage of cells, particles, and large molecules.

**Breakthrough therapy** – An expedited program intended to streamline the drug development and regulatory review processes for medicines catering to unmet needs for serious diseases. Such a designation comes with benefits ranging from Fast Track program features to a commitment that the FDA will work closely with the sponsor on an efficient drug development program.

**Central Nervous System (CNS)** – The brain and the spinal column, which is mostly made up of nerve cells.

**Chromosome** – A thread-like structure of nucleic acids and protein found in the nuclei of most living cells, which carries genetic information in the form of genes.

**Clinical Global Impression of Improvement (CGI-I)** – A seven-point scale that requires a clinician to assess how much a patient has improved or regressed, compared with the baseline state at the beginning of the treatment.

**Clinical trial** – A type of research study that tests how well a new medical approach is working in humans.

**CNS** – See Central Nervous System.

**Endpoint** – The outcome or outcomes that a clinical trial is designed to evaluate, such as disease progression or death. Generally clinical trials have primary and secondary endpoints.

**Fast Track** – An FDA designation that accelerates the approval of Investigational New Drugs. Companies with drugs on the Fast Track receive more frequent meetings and written correspondence with the FDA.

**FDA** – The Food and Drug Administration, a US-based drug regulatory body.

**Fragile X** – An Autism Spectrum Disorder.

**Glypromate** – Neuren’s name for IGF-1(1-3). The name comes from GLYcine-PROline-GlutaMATE, the three amino acids from which it is constructed.

**Growth hormone** – A peptide hormone that stimulates growth, cell reproduction, and cell regeneration in humans and other animals.

**Hypoxic-ischemic injury** – Brain damage caused by reduced blood flow to the brain (ischemia) as well as reduced brain oxygen (hypoxia).



**IGF-1** – Insulin-like Growth Factor I is a protein similar to insulin that plays a role in growth and metabolism. Glypromate, or IGF-1(1-3), is the first three amino acids of 1GF-1.

**IND** – Short for Investigational New Drug application. It is a request filed with the FDA for authorization to conduct human trials of a new drug or biological product in the United States.

**International Nonproprietary Name (INN)** – The official generic and non-proprietary name given to a pharmaceutical drug or an active ingredient. For example, the monoclonal antibody drug Herceptin has an INN of trastuzumab. INNs are granted by the World Health Organisation.

**Macroorchidism** – Abnormally large testes.

**Microglia** – Specialised cells which provide the brain with its own immune system by attacking and engulfing foreign bodies.

**Motor behaviour** – Behaviour related to movement, particularly abnormal movement.

**Neurons** – A specialized nerve cell that transmits nerve impulses.

**NNZ-2566** – See Trofinetide.

**N terminus** – The start of a string of amino acids.

**Orphan Drug** – A drug that benefits less than 200,000 potential patients in the US. Orphan drug designation provides tax benefits as well as market exclusivity in both Europe and the US.

**Peptide** – A short chain of amino acids linked by peptide bond.

**Pharmacokinetics** – The branch of pharmacology concerned with the movement of drugs within the body.

**Phase** – A stage of the clinical trialling process for a drug candidate. Phase I tests for safety. Phase II tests for efficacy in a small sample.

**Priority Review** – A commitment by the FDA to decide whether or not to approve a drug within six months of the application's submission, rather than the usual 10 months or so<sup>57</sup>.

**p-value** – A measure of statistical significance. Generally a p-value below 0.05 is considered 'statistically significant'.

**Rett Syndrome Behaviour Questionnaire (RSBQ)** – A checklist of characteristic Rett syndrome behavioural and emotional features, to test the type and specificity of behavioral features of RS against those found in girls with severe–profound mental retardation.

**Seizures** – A sudden attack of illness, especially a stroke or an epileptic fit.

**Small molecules** – Drugs that have a low molecular weight (<500 daltons), making them easier to penetrate cell membranes and the blood-brain barrier.

**Statistical significance** – The probability, measured by the 'p-value', that an observed outcome of an experiment or trial is due to chance alone. Generally p-values below 0.05 are taken as markers of statistical significance.

---

<sup>57</sup> A 2010 report from Tufts found that Orphan products receiving Priority Review status rose from 35% of all orphan NMEs in 2000-02 to 50% in 2006-08. Source: Tufts Center for the Study of Drug Development Impact Report, Volume 12, Number 1, January/February 2010.



**Synapses** – A junction between two nerve cells, consisting of a minute gap across which impulses pass by diffusion of a neurotransmitter.

**Traumatic Brain Injury** – The loss of cognitive function that results from a blow to the head. Traumatic brain injury is classified as mild, moderate, or severe.

**Trofinetide** – Neuren’s lead candidate, a synthetic analogue of Glypromate that Neuren called NNZ-2566 until 2015. Trofinetide is G-2Methyl PE. The drug is currently being developed for the treatment of Rett Syndrome and Fragile X Syndrome.

## Appendix II – Neuren’s intellectual property

Neuren’s intellectual property pertaining to Trofinetide and NNZ-2591 derives from the following applications:

**GPE analogs and peptidomimetics**, WO/2002/094856, priority date May 24, 2001, invented by Norman Abood and Margaret Brimble<sup>58</sup>.

- This patent application pertains to the composition and use of G-2MePE peptidomimetic (Gly-2-methyl Pro-Glu) to enhance cognitive function and treat memory loss. The peptidomimetic is capable of reversing both disease- and age-associated memory losses.

**Analogues of glycyl-prolyl-glutamate**, WO/2006/127702, priority date 23 May 2005, invented by Margaret Brimble, Paul Harris and Frank Sieg<sup>59</sup>.

- This patent application covers analogues of Glypromate other than Trofinetide.

**Oral formulations of glycyl-2-methylprolyl-glutamate**, WO/2007/106555, priority date March 14, 2006, invented by Jingyuan Wen, Gregory Brian Thomas, and Mike John Bickerdike<sup>60</sup>.

- This patent application pertains to orally administrable forms of G-2MePE peptidomimetic (Gly-2-methyl Pro-Glu.) The therapeutic composition – available in the form of microparticles, nanoparticles, and microemulsions – has improved bioavailability and is convenient to use.

**Treatment of Autism Spectrum Disorders using glycyl-L-2-methylprolyl-L-glutamic acid**, WO/2012/102832, priority date January 27, 2011, invented by Larry Glass, Mike Bickerdike, and Michael Snape<sup>61</sup>.

- This patent application covers the use of a G-2MePE peptidomimetic (Gly-2-methyl Pro-Glu) to treat autism spectrum disorders – which include autism, pervasive development disorder, Fragile X syndrome, and Rett syndrome. The therapeutic composition can be administered orally as well as intravenously.

**Treatment of Autism Spectrum Disorders using glycyl-L-2-methylprolyl-L-glutamic acid**, WO/2014/085480, priority date November 28, 2012, Invented by Larry Glass, Mike Bickerdike, Michael Snape, and Patricia Pérez-Cogram.

- This patent application covers new molecular forms of a G-2MePE peptidomimetic (Gly-2-methyl Pro-Glu) to cure autism spectrum disorders.

<sup>58</sup> This patent application has been granted in the US as Patent No. 7,041,314 in May 2006; as Patent No. 7,605,177 in October 2009; as Patent No. 7,714,020 in May 2010; and as Patent No. 8,637,567 in January 2014.

<sup>59</sup> This patent application was granted in the US as Patent No. 7,863,304 in January 2011.

<sup>60</sup> This patent application was granted in the US as Patent No. 7,887,839 in February 2011.

<sup>61</sup> This patent application was granted in the US as Patent No. 9,212,204 in December 2015 and as Patent No. 9,708,366 in July 2017.



**Neuroprotective bicyclic compounds and methods for their use in treating autism spectrum disorders and neurodevelopmental disorders**, WO/2015/013397, priority date July 25, 2013, invented by Larry Glass, Mike Bickerdike, Michael Snape, and Patricia Pérez-Cogram<sup>62</sup>.

- This patent application covers the use of cyclic glycyl proline derivatives, such as cyclic glycyl-2-allyl proline and cyclic cyclohexyl-glycyl-2-methyl proline, for treatment of autism spectrum disorders – which include autism, pervasive development disorder, Fragile X syndrome, and Rett syndrome. The therapeutic composition can be administered orally as well as intravenously.

**Neuroprotective bicyclic compounds and methods for their use**, WO/2005/023815, priority date September 3, 2003, invented by Margaret Brimble, Jian Guan, and Frank Sieg<sup>63</sup>.

- This patent application covers the composition and therapeutic use of cyclic G-2-allyl proline to treat memory loss – which includes spatial memory loss, long-term memory loss, and loss of novelty recognition. These can be used to treat symptoms of memory loss in Alzheimer's disease.

## Appendix III – Neuren's capital structure

		% of fully diluted
Ordinary shares, ASX Code NEU (million)	100.2	97.6%
Unlisted options (million)	0.0	0.0%
Performance rights (million)	2.5	2.4%
Fully diluted shares	102.7	

Current market cap:	A\$137.2 million (US\$101.3 million)
Current share price	\$1.370
Twelve month range	\$1.04 - \$3.56
Average turnover per day (last three months)	0.09 million

## Appendix IV – Major shareholders

- Lang Walker, a Sydney-based businessman whose fortune has largely been built on property development<sup>64</sup>, holds 18%.
- Neuren's Board and management hold approximately 10%.

<sup>62</sup> This patent application has been granted in the US as Patent No. 9,867,823 in January 2018.

<sup>63</sup> This patent application has been granted in the US as Patent No. 7,776,876 in August 2010; as Patent No. 8,067,425 in November 2011; as Patent No. 8,791,117 in July 2014; and as Patent No. 9,119,851 in September 2015.

<sup>64</sup> Walker currently ranks 1,103 on the Forbes billionaires list.



## Appendix V – Papers relevant to Neuren

**Anagnostou et. al. (2015)**, *Measuring social communication behaviors as a treatment endpoint in individuals with autism spectrum disorder*. Autism. 2015 Jul;19(5):622-36. Epub 2014 Aug 5.

- This report discusses the relative strengths and weaknesses of existing social communication measures for use in clinical trials and identifies specific areas in need of further development. Additionally, it considers 6 measures which are appropriate for evaluation of social communication out of a total of 38 measures which were considered.

**Bickerdike et. al. (2009)**, *NNZ-2566: a Gly-Pro-Glu analogue with neuroprotective efficacy in a rat model of acute focal stroke*. J Neurol Sci. 2009 Mar 15;278(1-2):85-90. Epub 2009 Jan 20.

- This research paper discusses NNZ-2566, a structural analogue of Glypromate, which is a tripeptide molecule that demonstrates neuroprotective effects in numerous *in vitro* and *in vivo* models of brain injury. In an *in vivo* rat model, NNZ-2566 showed reduction in injury size in rat subjects.

**Brimble et. al. (2005)**, *Synthesis and pharmacological evaluation of side chain modified glutamic acid analogues of the neuroprotective agent glycyl-L-prolyl-L-glutamic acid (GPE)*. Bioorg Med Chem. 2005 Jan 17;13(2):519-32.

- In this paper, pharmacological evaluation of the novel compounds was undertaken to further understand the role of the glutamate residue on the observed neuroprotective properties of the endogenous tripeptide GPE.

**Cartagena et. al. (2013)**, *Mechanism of action for NNZ-2566 anti-inflammatory effects following PBBI involves upregulation of immunomodulator ATF3*. Neuromolecular Med. 2013 Sep;15(3):504-14. Epub 2013 Jun 14.

- This paper discusses the mechanism of action of NNZ-2566, which demonstrates neuroprotective efficacy in TBI models. In PBBI (penetrating ballistic-like brain injury), NNZ-2566 decreased injury-induced upregulation of inflammatory cytokines, including TNF- $\alpha$ , IFN- $\gamma$ , and IL-6. However, the mechanism by which NNZ-2566 acts has yet to be determined.

**Glaze et. al. (2017)**, *A double-blind, randomized, placebo-controlled clinical study of trofinetide in the treatment of Rett Syndrome*. Pediatr Neurol. 2017 Nov;76:37-46. Epub 2017 Jul 8.

- This study aimed to determine the safety and tolerability of trofinetide, and to evaluate efficacy measures in adolescent and adult females with Rett syndrome.

**Lai et. al. (2005)**, *Synthesis and pharmacological evaluation of glycine-modified analogues of the neuroprotective agent glycyl-L-prolyl-L-glutamic acid (GPE)*. Bioorg Med Chem. 2005 Jan 17;13(2):533-48.

- This paper outlines the pharmacological evaluation of the novel compounds was undertaken to further understand the role of the glycine residue on the observed neuroprotective properties of the endogenous tripeptide GPE.

**Lane et. al. (2017)**, *Assessment of Caregiver Inventory for Rett Syndrome*. J Autism Dev Disord. 2017 Apr;47(4):1102-1112.





- The paper discusses the caregiver inventory assessment for caregivers of individuals with Rett syndrome. The assessment is designed based on the Alzheimer's Disease's Caregiver Burden Inventory.  
**Neul et. al. (2015)**, *Improving treatment trial outcomes for Rett Syndrome: The development of Rett-specific anchors for the Clinical Global Impression Scale*. J Child Neurol. 2015 Nov;30(13):1743-8. Epub 2015 Apr 20.
- This paper discusses the methods used to develop specific anchors for the CGI scale for Rett syndrome.  
**Oosterholt et. al. (2017)**, *Population pharmacokinetics of NNZ-2566 in healthy subjects*. Eur J Pharm Sci. 2017 Nov 15;109S:S98-S107. Epub 2017 May 15.
- The paper demonstrates the pharmacokinetics of NNZ-2566 after administration of single and repeated ascending doses in healthy subjects.  
**Scahill et. al. (2015)**, *Measuring repetitive behaviors as a treatment endpoint in youth with autism spectrum disorder*. Autism. 2015 Jan;19(1):38-52. Epub 2013 Nov 20.
- This paper evaluates the readiness of available measures for use as outcome measures in clinical trials, with respect to restricted interests and repetitive behaviors among children and adolescents with autism spectrum disorder.  
**Trotter et. al. (2005)**, *Synthesis and neuroprotective activity of analogues of glycyl-L-prolyl-L-glutamic acid (GPE) modified at the alpha-carboxylic acid*. Bioorg Med Chem. 2005 Jan 17;13(2):501-17.
- In this paper, pharmacological evaluation of the novel compounds was undertaken to further understand the role of the glutamate residue on the observed neuroprotective properties of the endogenous tripeptide GPE.  
**Vo LC et. al. (2016)**, *No Apparent Cardiac Conduction Effects of Acute Treatment with Risperidone in Children with Autism Spectrum Disorder*. J Child Adolesc Psychopharmacol. 2016 Dec;26(10):900-908. Epub 2016 Oct 11.
- This study evaluates the effects of risperidone on cardiac conduction in children with Autism Spectrum Disorder.  
**Bellesheim KR et. al. (2018)**. *Family-Driven Goals to Improve Care for Children With Autism Spectrum Disorder*. Pediatrics. 2018 Sep; Epub 2018 Aug 14.
- The study was aimed at implementing and refining practice pathways associated with constipation and insomnia in clinical settings for children with Autism Spectrum Disorder.  
**O'Leary HM et. al. (2018)**. *Placebo-controlled crossover assessment of mecasermin for the treatment of Rett syndrome*. Ann Clin Transl Neurol. 2018 Jan 31;5(3):323-332. eCollection 2018 Mar.
- The aim of the study was to measure the efficacy of mecasermin (recombinant human insulin-like growth factor 1, rhIGF-1), for treating symptoms of Rett syndrome (RTT) in a pediatric population using a double-blind crossover study design.  
**Deacon RM et. al. (2015)**. *NNZ-2566, a novel analog of (1-3) IGF-1, as a potential therapeutic agent for Fragile X syndrome*. Neuromolecular Med. 2015 Mar; Epub 2015 Jan 23.
- The paper investigates NNZ-2566 as an innovative treatment for symptoms associated with Fragile X syndrome.



**Wei HH et. al. (2009).** *NNZ-2566 treatment inhibits neuroinflammation and pro-inflammatory cytokine expression induced by experimental penetrating ballistic-like brain injury in rats.* J Neuroinflammation. 2009 Aug 5;6:19. doi: 10.1186/1742-2094-6-19.

- The aim of this research study is to assess the effects of NNZ-2566 on inflammatory cytokine expression and neuroinflammation induced by penetrating ballistic-like brain injury (PBBi) in rats.

**Lu XC et. al. (2009).** *NNZ-2566, a glypromate analog, attenuates brain ischemia-induced non-convulsive seizures in rats.* J Cereb Blood Flow Metab. 2009 Dec;29(12): Epub 2009 Jul 29.

- The paper evaluated the effect of NNZ-2566 to reduce the severity of non-convulsive seizures caused by permanent middle cerebral artery occlusion (pMCAo) in rats.

**Lu XC et. al. (2009).** *NNZ-2566, a glypromate analog, improves functional recovery and attenuates apoptosis and inflammation in a rat model of penetrating ballistic-type brain injury.* J Neurotrauma. 2009 Jan;26(1)

- This study evaluated NNZ-2566 in a rat model of penetrating ballistic-type brain injury (PBBi) and determined its effects on injury-induced histopathology, behavioral deficits, and molecular and cellular events associated with inflammation, as well as apoptosis.

## Appendix VI – Companies to watch

**Anavex Life Sciences.** This company, which develops drugs targeting a class of CNS receptor called ‘sigma receptors’<sup>65</sup>, has completed Phase 2 with Anavex 2-73 in Alzheimer’s disease, with favourable two-year data<sup>66</sup>. After favourable animal data the IND for a Phase 2 study in Rett was cleared in October 2018.

**Cerecor.** This CNS drug developer has been to Phase 2 with CERC-301, an NMDA antagonist that missed its primary endpoint in Major Depressive Disorder in late 2016. This drug is now being explored for various Orphan indications such as Neurogenic Orthostatic Hypotension.

**MediciNova.** This company’s lead molecule, in the mid-stage of clinical development is ibudilast, a drug that acts on neuroinflammatory factors including activated glia cells. The company is working on ibudilast in neurodegenerative diseases such as MS and ALS and in addition as well as neuropathic pain. A Phase 3 for ALS is being prepared. The FDA granted ibudilast Orphan Drug Designation in ALS in 2016.

**Newron Pharmaceuticals.** This company developed Xadago, a new Parkinson’s Disease drug that gained European approval in 2015 and FDA approval in 2017. The company is in a Phase 3 study in respiratory symptoms of Rett syndrome with Sarizotan, a serotonin 5-HT1A receptor agonist.

**Omeros.** This company was originally built around a platform called PharmacoSurgery designed to identify combinations of already approved drugs where the combination, used peri-operatively, can pre-empt potential complications of surgery. The first product from this platform, called Omidria, gained FDA approval in mid-2014 for use in eye surgery. Beyond PharmacoSurgery, Omeros has a number of drugs in the pipeline led by

<sup>65</sup> A common protein target of drugs of abuse and addiction – see Expert Rev Clin Pharmacol. 2009 Jul; 2(4): 351–358.

<sup>66</sup> See the Anavex press release dated 4 November 2017 and headlined ‘Anavex Life Sciences - new clinical data on Alzheimer’s disease’.



OMS721, an anti-inflammatory drug being developed for various Orphan indications including IgA nephropathy, where the drug has Breakthrough Therapy Designation. A number of CNS drugs are in Phase 2.

**Regenxbio.** This gene therapy technology company is in Phase 1/2 in various retinal, metabolic and neurodegenerative conditions. RGX-111 has Orphan Drug status for a rare recessive genetic disease called Mucopolysaccharidosis type I, while. RGX-121 also has Orphan Drug status, this time for Mucopolysaccharidosis Type II.

**Ultragenyx.** This company markets Cryssvita for X-linked hypophosphatemia (XLH) and Mepsevii for Mucopolysaccharidosis Type VII. UX007 for Long-Chain Fatty Acid Oxidation Disorders is in Phase 2.

**Zogenix.** This company has successfully completed Phase 3 with Fintepla (ZX008), a derivative of the amphetamine-like drug fenfluramine that was in development for Dravet syndrome, a rare pediatric epilepsy. A rolling NDA submission to the FDA for the drug is underway.

**Table 3: Comparable companies<sup>67</sup>**

Company	Location	Code	Market cap (USDm)	Web
Ultragenyx Pharmaceutical	Novato, Ca.	Nasdaq: RARE	2,750	<a href="http://www.ultragenyx.com">www.ultragenyx.com</a>
REGENXBIO	Rockville, Md	Nasdaq: RGNX	2,160	<a href="http://www.regenxbio.com">www.regenxbio.com</a>
Zogenix	San Diego, Ca.	Nasdaq: ZGNX	1,820	<a href="http://www.zogenix.com">www.zogenix.com</a>
Omeros	Seattle, Wa.	Nasdaq: OMER	688	<a href="http://www.omeros.com">www.omeros.com</a>
MediciNova	La Jolla, Ca.	Nasdaq: MNOV	406	<a href="http://www.medicinova.com">www.medicinova.com</a>
Cerecor	Baltimore, Md	Nasdaq: CERC	141	<a href="http://www.cerecor.com">www.cerecor.com</a>
Newron Pharmaceuticals	Milan, Italy	SIX: NWRN	138	<a href="http://www.newron.com">www.newron.com</a>
Anavex Life Sciences	New York, NY	Nasdaq: AVXL	104	<a href="http://www.anavex.com">www.anavex.com</a>
Neuren			101	

Source: Pitt Street Research

## Risks related to Neuren

**Risks specific to Neuren.** We see four major risks for Neuren as a company and as a listed stock:

- Clinical risk. There is the risk that Trofinetide may fail to meet the primary or secondary endpoints in the upcoming Phase 3
- Partnering risk. There is the risk that Neuren may not succeed in partnering Rest-of-World rights for Trofinetide.
- Timing risk. There is the risk that the Trofinetide Phase 3 study in Rett Syndrome may take longer than we expect to complete.
- Regulatory risk. There is the risk that regulatory decisions may slow or stop the progress of Trofinetide in to the marketplace.

**Risks related to pre-revenue Life Science companies in general.** The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology and medical device

<sup>67</sup> 3 December 2018 close on Nasdaq and elsewhere.



## Neuren Pharmaceuticals

companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector. The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.

***Caveat emptor.*** Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Neuren.

# General advice warning, Disclaimer & Disclosures

## Terms & Conditions

The information contained herein ("Content") has been prepared and issued by Pitt Street Research Pty Ltd ACN 626365615 ("Pitt Street Research"), an Authorised Representative (no: 1265112) of BR Securities Australia Pty Ltd. ABN 92 168 734 530, AFSL 456663. All intellectual property relating to the Content vests with Pitt Street Research unless otherwise noted.

## Disclaimer

The Content is provided on an as is basis, without warranty (express or implied). Whilst the Content has been prepared with all reasonable care from sources we believe to be reliable, no responsibility or liability shall be accepted by Pitt Street Research for any errors or omissions or misstatements howsoever caused. Any opinions, forecasts or recommendations reflect our judgement and assumptions at the date of publication and may change without notice. Pitt Street Research will not accept any responsibility for updating any advice, views, opinions or recommendations contained in this document.

No guarantees or warranties regarding accuracy, completeness or fitness for purpose are provided by Pitt Street Research, and under no circumstances will any of Pitt Street Research officers, representatives, associates or agents be liable for any loss or damage, whether direct, incidental or consequential, caused by reliance on or use of the Content.

## General Advice Warning

The Content has been prepared for general information purposes only and is not (and cannot be construed or relied upon as) personal advice nor as an offer to buy/sell/subscribe to any of the financial products mentioned herein. No investment objectives, financial circumstances or needs of any individual have been taken into consideration in the preparation of the Content.

Financial products are complex, entail risk of loss, may rise and fall, and are impacted by a range of market and economic factors, and you should always obtain professional advice to ensure trading or investing in such products is suitable for your circumstances, and ensure you obtain, read and understand any applicable offer document.

## Disclosures

Pitt Street Research has been commissioned to prepare the Content. From time to time, Pitt Street Research representatives or associates may hold interests, transact or hold directorships in, or perform paid services for, companies mentioned herein. Pitt Street Research and its associates, officers, directors and employees, may, from time to time hold securities in the companies referred to herein and may trade in those securities as principal, and in a manner which may be contrary to recommendations mentioned in this document.

Pitt Street Research receives fees from the company referred to in this document, for research services and other financial services or advice we may provide to that company. The analyst has received assistance from the company in preparing this document. The company has provided the analyst with communication with senior management and information on the company and industry. As part of due diligence, the analyst has independently and critically reviewed the assistance and information provided by the company to form the opinions expressed in the report. Diligent care has been taken by the analyst to maintain an honest and fair objectivity in writing this report and making the recommendation. Where Pitt Street Research has been commissioned to prepare Content and receives fees for its preparation, please note that NO part of the fee, compensation or employee remuneration paid will either directly or indirectly impact the Content provided.