Neuren Pharmaceuticals Limited

Milestones from CY21/22 to Crystallise Value

Progress Report

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CY21/CY22 to Crystallise Value

We expect key milestones for Neuren Pharmaceuticals' (NEU) two drug candidates, trofinetide and NNZ-2591, to trigger licensing revenues and add significant value over CY21/22.

CY21/22: Trofinetide Approval to Trigger Revenue

Acadia Pharmaceuticals (NASDAQ: ACAD), NEU's North American (NAM) partner for trofinetide, has announced that the impact of COVID-19 on trial recruitment is not expected to change the release of the results in CY21. Positive results in the Phase III trial in Rett Syndrome with subsequent application to the FDA for approval will trigger milestone payments of estimated ~US$55m over CY21/22. Sales royalties estimated at 10% of net sales will also commence on market entry.

CY21/22: Revenues from Ex-NAM Market Agreement

Following positive trial results, NEU will seek a licensing partner for the ex-NAM markets. Generally, agreements post pivotal trials when risk has been substantially mitigated attract higher upfront payments.

CY22: NEU to Seek Licensing Agreement on Positive Phase II Trial Results for NNZ-2591

A Phase II trial for NNZ-2591 is planned for CY21. Positive trial results would bring the first signs of efficacy in humans, a key step in drug development. NEU plans to license NNZ-2591 for its Phase III trial and commercialisation. An agreement usually includes an upfront payment, with NNZ-2591 potentially delivering the first revenue streams in CY22.

Valuation: A$3.88 on DCF suggests a Re-Rating

Our risk-adjusted discounted cash flow (DCF) valuation of A$398m implies a share price of A$3.88. NEU is trading at a significant discount to its pre-COVID value and its peers, ASX-listed biotechs, Opthea (OPT) (~A$800m) and Paradigm (PAR) (~A$600m), both about to commence Phase III trials.

We believe that positive trial outcomes over CY21/CY22 would trigger a re-rating of the stock. Trofinetide is in the final stage of clinical trial. Positive results would add 60% to its current risk adjusted valuation. Similarly, on positive Phase II results in CY22, NNZ-2591's transition to Phase III would result in a probability of approval of 50%-60%, against 19% currently.

Risks: Approval, Timelines, Licensing

The commercial performance underlying the DCF is based on a number of assumptions, including the drugs' approvals and licensing terms of trofinetide in ex-NAM markets and the global rights for NNZ-2591.

Neuren Pharmaceuticals is an ASX-listed biotechnology company developing two drugs, trofinetide and NNZ-2591.

Trofinetide and NNZ-2591 are targeting five disorders. Their mechanism of action offers the potential to address a much wider range of neural diseases and trauma related injury.

Acadia Pharmaceuticals has licensed the North American (NAM) rights to trofinetide.

Trofinetide's Phase III trial results in Rett Syndrome are expected over CY21. NNZ-2591 is in Phase I clinical trial.

Board and management are well credentialled with expertise in drug development and commercialisation.

Stock	ASX: NEU
Price	A$1.72
Market cap	A$177.5m

Company data	
Net cash (Mar CY20)	A$13.4m
Shares on issue	102.7m
Code ASX	NEU
Primary exchange	ASX

Next key steps

Phase III results for trofinetide in Rett Syndrome in CY21
Phase I results for NNZ-2591 in CY20
Phase II results for NNZ-2591 in CY22

2020 share price performance

Investment Case: CY21/22 Re- rating on Success of Trials' Milestones

Neuren Pharmaceuticals (NEU) has two drug candidates: trofinetide and NNZ-2591. The drug candidates are optimised versions of two neural acting peptides, which play a key role in the body's nervous system. They are targeting five neurodevelopmental disorders, none of which has an approved treatment.

Trofinetide is in Phase III clinical trial for Rett Syndrome and has completed a Phase II trial for Fragile X. The NAM rights are licensed to US biopharmaceutical company Acadia Pharmaceuticals (NASDAQ: ACAD). NEU retains the rights for ex-NAM markets.

NNZ-2591, targeting Phelan McDermid (PMS), Angelman (AS) and Pitt Hopkins (PH) syndromes, has commenced a Phase I clinical trial.

Our initiation of coverage report, dated 14 November 2019, details the five syndromes targeted by these drugs and provides a detailed discussion of the clinical trial programs.

Significant Potential Catalysts to Drive Value Over the Next Two Years

Table 1 outlines some key milestones that we expect will crystallise and drive the share price towards our valuation.

Table 1 – Potential Milestones for Trofinetide and NNZ-2591 to Drive Value

Timeframe	Drug candidate	Catalyst
CY20	NNZ-2591	Results Phase I clinical trials in healthy adult volunteers
CY21	NNZ-2591	Start Phase II trials in the three syndromes
CY22	NNZ-2591	Results Phase II clinical trials
CY21	Trofinetide	Results of Phase III clinical trial in Rett Syndrome
CY21/22	Trofinetide	FDA New Drug Application (NDA) approval in Rett Syndrome
CY21/22	Trofinetide	Milestone payments from NEU's NAM partner, Acadia Pharmaceuticals
CY22	Trofinetide	Licensing agreements for ex NAM rights
CY22	NNZ-2591	NNZ-2591 Global Licensing Agreement

Source: NEU, MST Estimates

Unlocking Value for Trofinetide

Positive trial and approval to trigger Acadia agreement revenues in NAM

NEU has licensed the NAM rights of trofinetide to Acadia Pharmaceuticals. The agreement covers the clinical development and the sales/marketing rights for Rett and Fragile X syndromes

Rett Syndrome is the more advanced program with results of its Phase III trial expected in CY21. Positive results of the trial would see the filing of a New Drug Application (NDA) with the FDA; if approved, market entry would follow in CY21/22. The Acadia agreement entails US$105m in milestone payments for both indications. We estimate that ~50% of the milestone payments relate to Rett Syndrome. We expect FDA approval of trofinetide and market entry to trigger ~US$55m of payments over CY21/22.

Sales royalties are expected to flow from market launch. The agreement allows for double-digit percentage royalties on net sales. Our forecast assumes royalty payments of 10% on market entry, increasing in-line with sales as per the licensing agreement. A further US$350m of performance payments are contingent on the achievement of thresholds of annual total net sales of trofinetide in North America.

In addition, the FDA has confirmed that trofinetide in Rett Syndrome qualifies for a Rare Paediatric Disease Priority Review Voucher. The program allows for the FDA to designate a drug as a 'rare paediatric disease' indication, based on the merits of the drug. The sponsor may use the voucher to receive a priority review of a subsequent marketing application or sell the voucher. Under the Acadia agreement, NEU is to receive one third of the voucher's market value. Recent voucher sales have averaged around US$100m.

The Acadia agreement also covers the use of trofinetide in Fragile X Syndrome. NEU's pilot Phase II clinical trial in Fragile X Syndrome patients showed clinical improvement in many of the symptoms. Acadia has yet to announce its development plan for Fragile X. Our valuation model assumes another Phase II trial and market entry in CY25.

Ex-NAM market revenues: NEU to seek potential partners, market entry in CY23

NEU has the rights to use the technical, clinical and regulatory data developed by Acadia to seek approval and commercialise trofinetide in countries outside NAM for both Rett Syndrome and Fragile X. In March 2020, after considering potential partnering options, NEU decided to retain the rights and crystallise potential higher value post–Phase III results.

Positive trial results are likely to stimulate interest from potential partners. Our valuation forecast balances the lower values of the EU and Japan markets against expected higher upfront payments to reflect the lower risk from the positive trial result.

Our model assumes market entry in CY23. However, this will depend on the timing of the ex-NAM licensing agreement and the approval processes of regulatory bodies in the EU and Japan. Acadia Phase III trials have been conducted in the US. EU regulatory approval may be contingent on the inclusion of some European-based data. Thus, there may be a requirement to conduct additional trials, delaying the forecast market entry.

In terms of licensing opportunity, trofinetide offers a number of advantages:

- With positive Phase III results, trofinetide would be a 'de-risked' asset from a development perspective, effectively adding 60% to our current risk-adjusted valuation.
- The European Medicines Agency (EMA) has awarded trofinetide orphan drug status. This confers market protection from generic drugs in the EU for 10 years. There is a paediatric extension of 2 years of further protection.
- In terms of licensing partners, rare disease drugs have become 'attractive' with both specialty and large pharma companies acquiring them to optimise product portfolios. To compensate for the high costs of drug development for a smaller patient population, higher prices for orphan drugs are generally accepted by payers. Industry data reports that orphan drugs on average are 25 times more expensive than non-orphan equivalent drugs. The average annual orphan drug cost rose from US$7,136 in 1997 to US$186,758 in 2017, according to American Health Insurance Plans 2019).

- The high cost and effectively life-long care of Rett patients and in other neurodevelopmental conditions, may result in compelling arguments for reimbursement from healthcare payers.

- Trofinetide's mechanism of action (MOA) targets Insulin Growth Factor 1 (IGF-1). Its critical role in the nervous system offers the potential to treat a number of neurodevelopmental disorders. It creates the possible use of trofinetide in off-label use where patients have no effective therapies.

Outlook for trofinetide: strong proof to date; no approved competing treatments

From a scientific perspective, trofinetide is well credentialled. Trofinetide and NNZ-2591 are synthetic versions of the two neuropeptides that regulate the body's IGF-1. IGF-1 has been shown to have a critical role in childhood growth, brain development and other body functions. It is a well-validated treatment target in Rett Syndrome and a number of other neurodevelopmental disorders (see Appendix 1 for supporting preclinical data).

Two Phase II trials provide further support. A statistically significant and clinically meaningful improvement was reported in trofinetide's Phase II trial in the high-dose cohort of girls with Rett Syndrome (aged between 5 and 15 years). Trofinetide was well tolerated and no safety concerns were identified. This trial followed positive trends observed in an earlier Phase II trial in adolescents and adults aged 16 to 45 years.

The Phase II trial data has informed the protocols for the Phase III trial, thereby increasing its chance of success.

- The key measures or end points of the Phase III trial include the same primary endpoints that were statistically significant in the Phase II trial.
- The 6-week Phase II trial reported that the clinical improvement continued to increase through to the end of treatment. The Phase III trial of 12 weeks' treatment is likely to capture the trend of an ongoing increase in improvement.
- Similarly, the results help determine the number of subjects required in the Phase III trial to elicit a statistically significant result.
- The pharmacokinetic analyses of the Phase II subjects have helped to optimise the Phase III dosing regimen.

In terms of competitor therapies, there are currently no approved treatments for any of the neurodevelopmental conditions that NEU is targeting. Patient care is generally based on ad hoc treatment of the presenting symptoms, such as anticonvulsants for seizures, physiotherapy for movement impairment and speech therapy for language delay.

Newron Pharmaceuticals SpA's (SWX: NWRN) drug Sarizotan, a repurposed Parkinson's Disease drug candidate, recently failed its Phase II/III trial. Sarizotan has a different mechanism of action and focused on sleep apnea associated with breathing problems. Little can be drawn in relation to trofinetide. Trofinetide targets more broadly by aiming to normalise the connections and signals between the nerve cells. Newron seemingly proceeded directly from preclinical data to a pivotal Phase II/III trial. Conversely, NEU has strong Phase II trial results to both support and inform the current Phase III trial.

Unlocking Value for NNZ-2591

Clinical trials commenced, with results of Phase II expected CY22

NNZ-2591 is targeting three neurodevelopmental disorders: Phelan McDermid Syndrome, Angelman Syndrome and Pitt Hopkins Syndrome. The development program benefits from NEU management's experience in developing trofinetide, with both drug candidates and targeted indications sharing a number of characteristics.

Preclinical data provides strong support in all three indications. Appendix 1 presents the results of a dose-ranging study in PMS. It provides clear evidence of therapeutic effect and optimal dosing levels.

- **Phase I trial:** NNZ-2591 has commenced a Phase I trial to confirm safety and pharmacokinetic profile in healthy adult volunteers.

- **Phase II trial:** In CY21, NEU plans to submit an Investigational New Drug (IND) application to the FDA for approval to conduct a Phase II trial in patients from the three targeted disorders. It is planned to be a 12-week treatment duration with the purpose of establishing the size of the clinical response and confirming the optimal dose and safety. The results are expected to follow in CY22.

Positive results to facilitate potential licensing agreement in CY22

NEU plans to license NNZ-2591 for its Phase III trial and commercialisation. Positive Phase II trial results would represent the first signs of efficacy in humans, a key step in drug development. Positive trial results would support a potential licensing agreement, which we would expect to include an upfront payment (as is usual in such agreements).

As a percentage of the deal value, the amount of the upfront payment depends on how the risk is shared. The agreements can be 'backloaded' (with the majority of the value in the royalty streams and approval terms, as per the Acadia agreement) or 'front loaded' (with higher upfront payments). Our model assumes payment in line with the more 'backloaded' Acadia agreement. However, given the related mechanism of action (MOA) of trofinetide and NNZ-2591, positive Phase III of trofinetide results may influence the negotiations.

Longer-Term Product Protection for Trofinetide and NNZ-2591: Patents, Fast Tracking, and Orphan Drug Status

The patents relating to composition of matter expire in 2022 for trofinetide and in 2024 for NNZ-2591. Method of treatment patents and applications for trofinetide's use in treating autism spectrum disorders, issued in the US, Europe, Japan, Israel and Australia, extend to 2032. Patents for method of treatment are pending in Canada and Brazil. NNZ-2591 has been granted patents for treatment of neurodevelopmental disorders in the US, Japan and in Europe; these expire in 2034. Under legislation in the US, EU and Japan, New Chemical Entities (NCEs) attract additional coverage. In relation to an NCE, a patent once nominated may receive a 5-year extension of protection. The selection of the patent will be determined on approval.

FDA fast-track designation has been approved for trofinetide for Rett and Fragile X.

The FDA and European Medicines Agency have granted orphan drug status to trofinetide in the treatment of Rett and Fragile X syndromes. The FDA has also granted orphan drug status to NNZ-2591 in the treatment of Phelan McDermid Syndrome, Angelman Syndrome and Pitt Hopkins Syndrome. Orphan drug status confers several advantages, including protection from generic drug competition. The length of the protection varies across the key markets. The protection lasts for 7 years in the US, 10 years in the EU, and 10 years in Japan. For drugs that treat pediatric disorders, the US grants a 6-month extension, while the EU offers a 2-year extension.

Board and Management

NEU's Board and senior management offer significant experience in both the development and commercialization of pharmaceutical products. Patrick Davies was appointed as Chairman on 27 May 2020. Patrick joined the board as a non-executive director in July 2018 as part of changes to augment the skills and experience of the board for the next stage of development. His experience includes 10 years as CEO of EBOS Group (formerly Symbion) during which the enterprise value grew from $450 million to more than $3.1 billion. He provides strategic advice to a range of healthcare businesses and investors.

Jon Pilcher was appointed as CEO of Neuron on 27 May 2020. He joined Neuren in 2014 after 11 years at ASX-listed company, Acrux Limited. His experience spans Acrux's IPO with the ASX, development of three FDA approved novel pharmaceutical products and negotiation of licensing agreements. He is a Chartered Accountant and has degree in biotechnology.

Valuation of A$3.88 Per Share Implies Significant Upside

We derive our valuation of NEU stock from a risk-adjusted discounted cash flow (DCF). Our investment case is based on the use of trofinetide and NNZ-2591 in the nominated indications. We have not ascribed any value to other potential clinical indications. As drugs in development, assumptions have been made regarding the probability and timing of regulatory approval to enter the markets and likely commercial performance. Our assumptions carry both upside and downside risk.

Valuation Methodology: Risk-Adjusted DCF; Recognising Drug Milestones

Our risk-adjusted DCF valuation of NEU at A$398m implies a share price of A$3.88. This compares to A$436m in the initiation report, which assumed earlier revenues from an EXNAM licensing agreement. Our valuation recognises the upcoming milestones for both drugs. Trofinetide is in the final stage of clinical trial, carrying a higher probability of approval at 60%. Positive trial results would see a 60% increase in our current valuation of trofinetide revenues. Similarly, on positive Phase II results in CY22, NNZ-2591's transition to Phase III would result in a probability of 50-60%, against 19% in its current risk adjusted valuation.

Valuation Compared With Peers Suggests Upside Risk

NEU's current valuation can be compared with ASX-listed biotechs, Opthea (OPT; market capitalisation around A$800m) and Paradigm (PAR; market capitalisation around A$600m). Both companies are about to commence Phase III trials. In our view, NEU presents significant upside risk, with positive trial outcomes over CY21/CY22 likely to trigger re-rating of the stock.

Table 2 - Key Valuation Assumptions

Key Valuation Assumptions		
Probability of Approval		
Trofinetide	Rett	60%
	Fragile X	25%
	Phelan Mc Dermid	19%
	Angelman	19%
	Pitt Hopkins	19%
Milestone Payments		
	Trofinetide	US$775m
	NNZ-2591	US$370m
Market Entry		
	Rett	CY22
	Fragile X	CY24/25
	Phelan Mc Dermid	CY25
	Angelman	CY25
	Pitt Hopkins	CY25
Pricing		
	US	US$160K
	EU	US$100K
	ROW	US$110K

Table 3 Financial Summary

NEUREN PHARMACEUTICALS							
Year ending 31 December 2019	A$000						
STATEMENT OF COMPREHENSIVE INCOME	**2018A**	**2019A**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Revenue							
Revenue from License	13,544			36,250	79,750	72,500	27,530
Australian R&D tax incentive	446	495	500	1,000	500	500	500
Gross Profit	13,098	300	500	37,250	80,250	73,000	28,030
Expenses							
R&D	-6,101	-9,858	-5,000	-15,000	-1,500	-1,500	-1,500
Administration	-2,074	-1,713	-2,000	-2,000	-2,000	-2,000	-2,000
Other	-3,921	-261					
Amortisation of intangibles	-72	-72	-72	-72	-72	-72	-72
Depreciation	-6	-6	-6	-6	-6	-6	-6
Operating profit (loss)	1,002	-12,686	-6,578	20,172	76,672	69,422	24,452
Interest received	218	389	192		558	1,805	2,642
Interest Paid							
Net Interest Received	218	389	192		558	1,805	2,642
Profit (loss) before income tax	3,073	-10,816	-6,386	20,172	77,230	71,227	27,094
Income tax expense							
Total comprehensive profit (loss) attributable	3,073	-10,816	-6,386	20,172	77,230	71,227	27,094
Marginal tax rate							
Profit after tax	3,073	-10,816	-6,386	20,172	77,230	71,227	27,094

STATEMENT OF FINANCIAL POSITION	**2018A**	**2019A**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
Current Assets							
Trade and other receivables	942	522	522	522	522	522	522
Cash and cash equivalents	23,576	13,844	27,488	47,660	124,890	196,117	223,211
Other	2,121						
Total current assets	26,639	14,396	28,010	48,182	125,412	196,639	223,733
Non-Current Assets							
Property, plant and equipment	2	10	10	10	10	10	10
Intangible Assets	1						
Total non-current assets	3	10	10	10	10	10	10
Total Assets	26,639	14,406	28,020	48,192	125,422	196,649	223,743
Current Liabilities							
Trade and other payables	1,973	559	559	559	559	559	559
Total current liabilities	1,973	559	559	559	559	559	559
Non-Current Liabilities							
Total Liabilities	1,973	559	559	559	559	559	559
Net Assets	24,669	12,519	27,461	47,633	124,863	196,090	223,184
Minority Interst							
Net assets attributable	24,669	13,847	27,461	47,633	124,863	196,090	223,184
Equity	126,426	126,426	146,426	146,426	146,426	146,426	146,426
Other Reserves	-8,497	-8,503	-8,503	-8,503	-8,503	-8,503	-8,503
Accumulated Deficit	-93,260	-104,076	-110,462	-90,290	-13,060	58,167	85,261
Total Equity	24,669	13,847	27,461	47,633	124,863	196,090	223,184

STATEMENT OF CASH FLOWS	**2018A**	**2019A**	**2020E**	**2021E**	**2022E**	**2023E**	**2024E**
License Agreement Receipts	13,544			36,250	79,750	72,500	27,530
Tax paid							
Australian R&D Tax Incentive Receipts	446	450	500	1,000	500	500	500
Interest Received	165	413	192		558	1,805	2,642
GST Refunded	95	102					
Payments for Employees and Directors	-1,909	-1,742	-2,000	-2,000	-2,000	-2,000	-2,000
R&D and Other Payments	-6,118	-10,942	-5,048	-15,078	-1,578	-1,578	-1,578
Net Cash Flow from Operating Activities	6408	-11719	-6,356	20,172	77,230	71,227	27,094
Net Cash Flow from Investing Activities		-12					
Cash Flows from Financing Activities							
Proceeds from Issue of Shares	11,730	1,860	20,000				
Payments of Shares Issue Expenses	-16						
Net Cash Provided from Financing Acitivites	11,714	1,860	20,000				
Net Increase/Decrease in cash	18,122	-9,871	13,644	20,172	77,230	71,227	27,094
Cash equivalents at beginning of year	4,706	23,576	13,844	27,488	47,660	124,890	196,117
Cash & equivalents at end of year	23,576	13,844	27,488	47,660	124,890	196,117	223,211

Source: NEU, MST estimates.

Risks and Sensitivities

The valuation is based on a number of assumptions using market data. They hold upside and downside risk.

Drug Development Program Vulnerable to Delays

Forecasted timelines may be adversely impacted by a number of factors. Delays in clinical trials from slow patient recruitment or other factors may impact timing and therefore financial forecasts. For trofinetide, the Phase III trial for Rett Syndrome (being conducted by Acadia in the US) has been paused due to the impact of the COVID-19 pandemic. However, in a recent update, Acadia announced that it expects the trial to recommence in Q2CY20 with the results still planned to be announced in CY21. Other clinical trials NEU has planned may also be affected.

Given that Acadia's Phase III trials are being conducted in the US, we note that the EU regulatory authorities may require European data. This could therefore delay expected approval and market entry timelines.

Probability of Approval:

Trofinetide for Rett Syndrome is in a Phase III trial, the last stage before submitting for approval. Industry data shows a probability of around 58% of success. Our valuation assumes a probability of 60%. This is a blended figure, recognising that the Phase II trial demonstrated a statistically significant improvement in a number of key endpoints. Trofinetide for Fragile X, having completed a pilot Phase II trial, and NNZ-2591 in a Phase I trial carry lower probabilities of 25% and 19% respectively. The Fragile X study showed a trend to positive results. The 25% probability reflects some early proof of efficacy combined with the possibility of a formal Phase II trial to be undertaken.

Trials Continuing to Assess Safety of Both Drugs

In the trials to date, trofinetide has been well tolerated with no safety concerns. NNZ-2591 is in Phase I trial in healthy adults. It is the first in-human trial with the purpose of assessing its safety profile. Both drugs are synthetic versions of naturally occurring molecules and expected to carry lower risk in terms of their ability to cross the blood-brain barrier—a key hurdle for central neurological treatments. Pharmacokinetic data show high availability of the drugs. However, safety will continue to be assessed through the trial program as adverse effects may only emerge as more patients are exposed to the drug.

Costs and Funding: Partners, Additional Funding Needed

In terms of development costs, trofinetide is licensed to Acadia for its clinical development and commercialisation for the treatment of Rett and Fragile X syndromes in NAM markets. Our model assumes that, in ex-NAM markets, NEU will negotiate a licensing deal with all related costs such as registration and marketing passed on to the partner.

Similarly, we assume NNZ-2591 will be licensed for all markets after the Phase II trial with further development and commercial costs passing to the acquiror. Delays in securing a partner may affect the timing of our financial forecasts. NEU may assume the regulatory filings and marketing/distribution role, which would also impact our forecasts.

Cash reserves at 31 March 2020 were A$13.4m. Our financial model assumes that additional funding will be required to undertake the Phase II trial for NNZ-2591; we assume a capital raising of ~A$20m.

Licensing Revenues: Timing and Amount of Milestone Payments and Royalties

The model assumes NAM Rett Syndrome revenues from CY22/23. The development milestone schedule under the Acadia agreement amounts to a total of US$105m in revenues for both Rett and Fragile X syndromes. We estimate that ~50% relate to Rett Syndrome and therefore FDA approval and market entry over CY22/23 would trigger payments of ~US$50m.

Additional milestone payments are likely to form part of licensing agreements for ex-NAM rights for trofinetide in Rett Syndrome, Fragile X and NNZ-2591.The model assumes EU market entry for trofinetide in Rett Syndrome over

CY23/24. There is risk of delay as the licensing arrangements are yet to be finalised. In addition, there is risk that the European Medicines Agency (EMA) and other regulatory bodies may require European/local clinical data. The Phase III trials have only been conducted in the US. The model assumes payments reflective of the lower value of the EU and Japanese markets.

On positive results from its Phase II trial in CY22, NEU plans to licence NNZ-2591. Upfront and milestone payments and sales royalties usually form part of the agreement and therefore included in the valuation.

We have modelled commercial performance on market data. We have estimated market size based on disease prevalence, assuming that patients will require ongoing treatment. (These drugs do not address the underlying gene mutation but rather act as a 'supplement' and therefore would be needed on an ongoing basis.)

The strength of the trial data will also impact market usage. Clear demonstrated benefit is likely to drive uptake. Pricing and reimbursement are based on market averages. Pricing dynamics vary significantly across the different markets. The US commands a significant premium to the EU and Rest of World (ROW). Our valuation model takes the pricing differences into account. New competitor drugs which have higher efficacy or other attributes that attract market share would represent a risk to our usage forecasts.

The MOA of both trofinetide and NNZ-2591 act to 'normalise' the underlying pathological features of the diseases, and therefore both drugs are likely to be applicable to additional neurodevelopmental conditions. Formal approval may be undertaken and/or the drugs may be used 'off label' as clinicians try to relieve shared symptoms with other neurological conditions. We have not assigned any value to these potential additional applications.

Appendices

Appendix 1: Understanding Trofinetide and NNZ-2591

This section provides information on the scientific rationale and preclinical supporting data for the use of trofinetide and NNZ-2591 in neurodevelopmental disorders.

Trofinetide and NNZ-2591: analogues critical to IGF-1 function

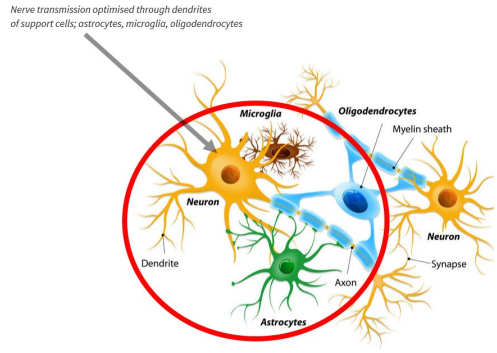
Trofinetide and NNZ-2591 are synthetic versions of two neuropeptides: glycine-proline glutamate or glypromate (GPE) and cyclic-glycine-proline (cGP), respectively. These neuropeptides play important functions in the regulation of the IGF-1 growth factor, which has a critical role in:

- childhood growth
- brain development
- bodily functions, including coordination of movement, cognition, control of the autonomic nervous system and transmission of signals along the neural pathways to the muscles, blood vessels, gastrointestinal tract and other organs.

Treating neurodevelopmental disorders by regulating IGF-1: new approaches

Research studies provide strong validation of IGF-1 as a treatment target in a number of neurodevelopmental disorders, including Rett Syndrome. The different syndromes are characterised by reduced IGF-1 levels and deficits in synaptic maturation and dendrites, leading to poor signalling between the nerve cells. IGF-1's validation is further supported by the use of recombinant IGF-1 as a treatment. IGF-1 improves the associated behaviours and, at the nerve level, excitatory transmission and synapse density in brain's cortical neurons.

Figure 1 – Effect of Trofinetide (NNZ-2566) on increasing IGF-1 Levels in Fragile X Mice Models



Dendrites of the Microglia and Astrocytes optimise nerve signal transmission

Tropea[1] showed that the use of GPE in a Rett Syndrome mouse model extended life span, improved movement, reduced heart and respiratory symptoms and increased synapse transmission and maturation with more dendritic

1 *Tropea D1, Giacometti E, Wilson NR, Beard C, McCurry , Fu DD, Flannery R, Jaenisch R, Sur M et al roc Natl Acad Sci U S A. 2009 Feb 10;106(6):2029-34. i: 10.1073/pnas.0812394106.Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice).*

spines. However, as a potential therapy, IGF-1 has not been successful. Its ability to cross the blood-brain barrier (BBB) is debated. High doses are required to deliver therapeutic levels in the brain, bringing side effects to organs in other areas of the body. The use of GPE or cGP provides another mechanism to regulate IGF-1.

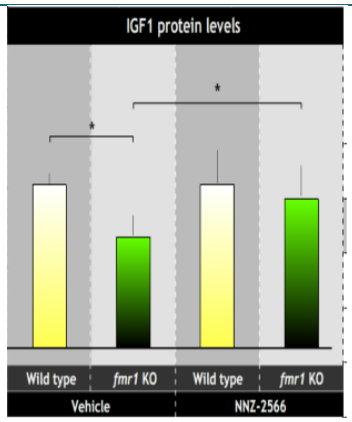
As potential treatments, trofinetide and NNZ-2591 are well suited. They are small molecule drugs that can cross the BBB and present the convenience of an oral formulation.

Results of Tronfinetide and NNZ-2591 in preclinical studies

Preclinical studies in mice models of neurodevelopmental disorders have demonstrated reduced IGF-1 levels. Both drugs stimulate or upregulate IGF-1 production and have been shown to be effective in correcting three key characteristics of neurodevelopmental disorders:

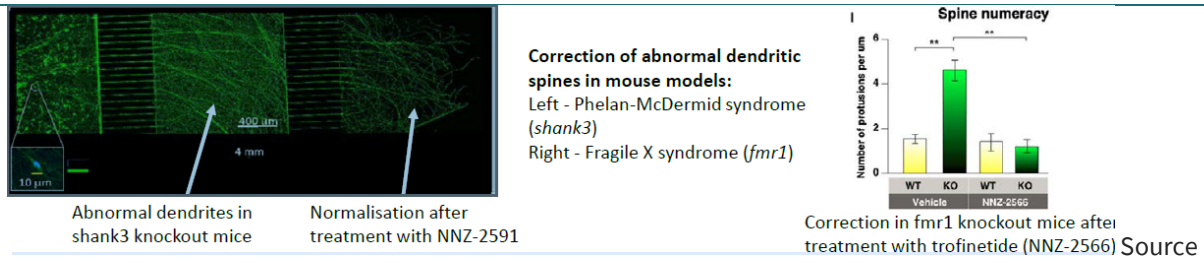
- normalise the abnormally low levels of IGF-1
- help restore the nerve signalling by correcting the abnormal dendritic spines of connecting neurons
- reduce inflammation to normalise the function of microglia and astrocytes, nerve support cells.

Figure 2 – Effect of Trofinetide (NNZ-2566) on increasing IGF-1 Levels in Fragile X Mice Models



Source: NEU Data

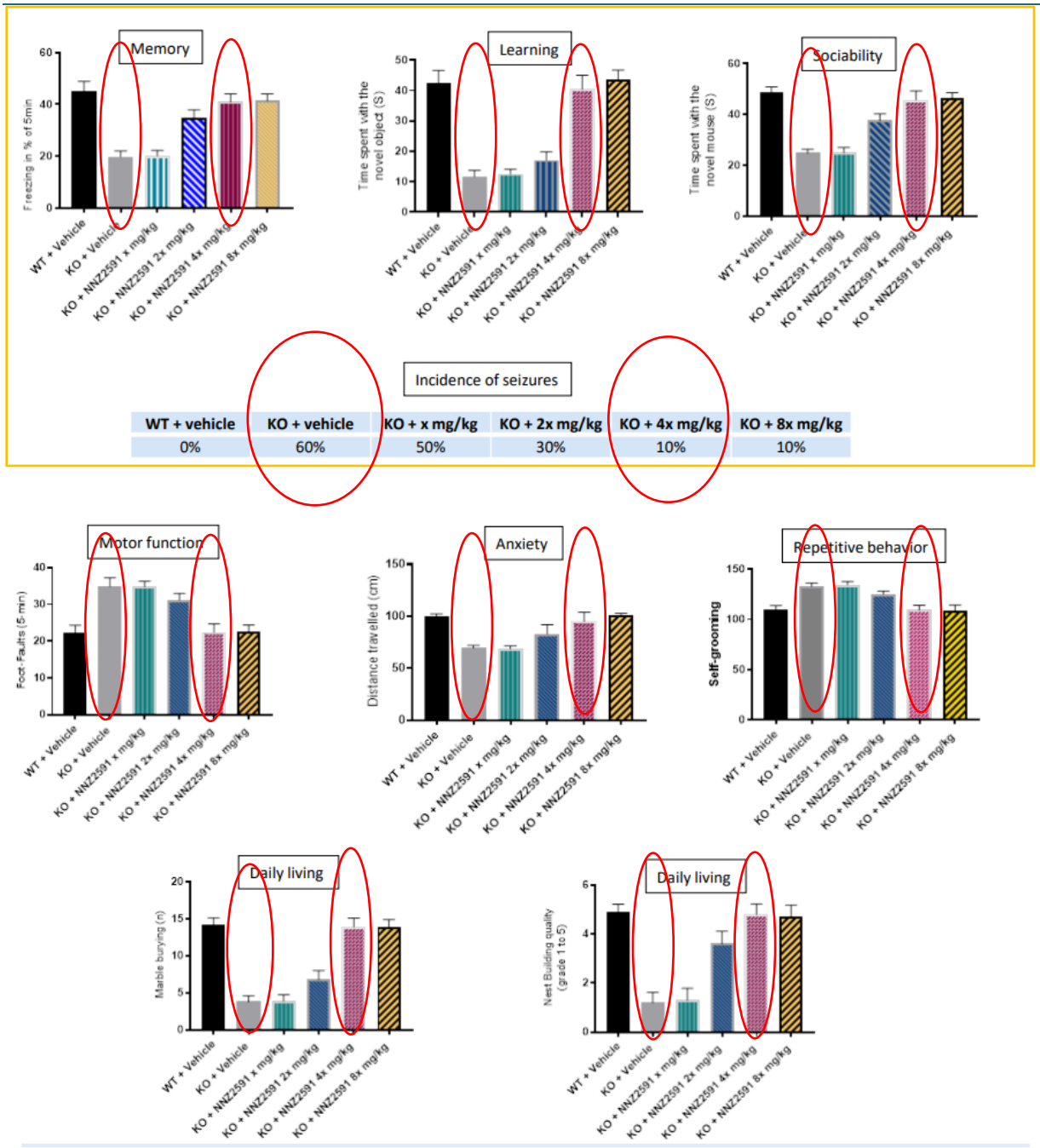
Figure 3 – Preclinical Studies in mice models showing the therapeutic effect of NNZ-2591 in PMS and trofinetide in Fragile X on the dendrites and spines (small extensions from the dendrites) which are immature, too long and too numerous.



Source

Source: Neuren Data

Figure 4– PMS Mice Models Show Optimum Dose



Source: Neuren Data

NNZ-2591 has been tested in a number of preclinical studies with respect to its three targeted neurodevelopmental disorders: Phelan McDermid (PMS), Angelman (AS) and Pitt Hopkins (PHS) syndromes.

Recently announced results in PMS mice models presented efficacy of NNZ-2591 as a treatment. The mice models were assessed across a wide range of parameters. The studies compared 4 escalating dose levels of NNZ-2591 for 6 weeks in mice. The wild type (WT) represents the normal healthy mouse which served as a control. Comparison between the PMS mice treated with NNZ-2591 (NNZ-2591 4X dose) and PMS mice with placebo (KO + Vehicle clearly indicates a therapeutic effect with the second-highest dose (4X mg/kg) as the optimum dose.

Appendix 2: Board and Key Management

Table 3: Board and Senior Management

BOARD AND MANAGEMENT

John Pilcher (CEO)

Jon was appointed as CEO of Neuron on May 27 2020. He joined Neuren in 2014 after 11 years at ASX-listed company, Acrux Limited. During this time, Acrux underwent an IPO with the ASX, developed three FDA approved novel pharmaceutical products and negotiated a licensing deal with Eli Lily. Jon is a Chartered Accountant and holds a degree in Biotechnology. He is a non executive director of BTC Health Limited.

Patrick Davies (Non-executive Chairman)

Patrick was appointed as Chairman on May 27 2020. Patrick joined the Neuren board as a non-executive director in July 2018 as part of changes to augment the skills and experience of the board for the next stage of development. His experience includes 10 years as CEO of EBOS Group (formerly Symbion) during which the enterprise value grew from $450 million to more than $3.1 billion. He provides strategic advice to a range of healthcare businesses and investors.

Dr Trevor Scott (Non-executive Director)

Trevor joined the Neuren board in March 2002. He is the founder of T.D Scott and Co., an accountancy and consilting firm, which he formed in 1988. He is an experienced advisor to companies across a variety of industries. Trenvor serves on numerous corporate boards and is chairman of several other companies

Dianne Angus (Non-executive Director)

With over 25 years experience in senior executive and non-executive director roles in biotechnology, biopharmaceutical and agri-tech industries. Dianne has expertise in business development, capital raising, investor relations, regulatory affairs and intellectual property. She has created numerous global partnerships with companies including Prana Biotechnology, Florigene, Suntory Monsanto. Dianne holds a Masters degree in biotechnology and is a registered patent attorney.

Dr Jenny Harry (Non-executive Director)

Jenny has 20 years experience in executive management roles in the Australian roles in the Australian and New Zealand healthcare industry for over 25 years having performed successfully in senior roles across many industry sectors including pharmacy, primary care, pharmaceutical anc consumer products. During his 10 year period as CEO of EBOS Group Limited (and previously Symbion), the enterprise value of the group achieved compound annual growth in enterprise value of +20% (from circa $450m to in excess of $3.1B)

Senior Management

Larry Glass (Chief Science Officer CSO)

Larry joined Neuren in 2004 and was an executive director from May 2012. He has more than 30 years experience in the life sciences industry, including clinical trials, basic and applied research, epidemiologic studies, diagnostics and pharmaceutical product development

Source: Neuren Annual Report & ASX announcement 27.05.2020.

Appendix 3: Key Shareholders

Table 4: 20 Largest Shareholders of Ordinary Shares

20 Largest Shareholders of Ordinary Shares	Number of Ordinary Shares	% of Issued Share Capital
HSBC CUSTODY NOMINEES (AUSTRALIA) LIMITED-GSCO ECA	14,276,172	14.25
CAMERON RICHARD PTY LTD	5,815,830	5.81
CITICORP NOMINEES PTY LIMITED	5,091,305	5.08
ESSEX CASTLE LIMITED	2,769,251	2.76
STUART ANDREW PTY LTD	2,633,586	2.63
LINWIERIK SUPER PTY LTD	2,535,000	2.53
SMITHLEY SUPER PTY LTD	2,121,000	2.12
HSBC CUSTODY NOMINEES (AUSTRALIA)	2,108,470	2.10
DR RICHARD SPENCER TREAGUS	1,979,163	1.98
INVESTMENT CUSTODIAL SERVICES LIMITED	1,480,587	1.48
MXB INVESTMENTS LLC	1,330,000	1.33
BRISPOT NOMINEES PTY LTD	1,163,357	1.16
DR TREVOR SCOTT	1,000,000	1.00
DR ROBIN LANCE CONGREVE	991,637	0.99
UBS NOMINEES PTY LTD	839,021	0.84
CS FOURTH NOMINEES PTY LIMITED	755,507	0.75
J P MORGAN NOMINEES AUSTRALIA PTY LIMITED	732,175	0.73
FIRST COLBYCO PTY LTD	624,649	0.62
NAMARONG INVESTMENTS PTY LTD	555,556	0.55
ROXTRUS PTY LIMITED	545,000	0.54
Total	**49,347,266**	**49.26**
Balance of share register	50,821,147	50.74
Total ordinary shares of quoted on ASX	**100,168,413**	**100.00**
Unquoted loan funded shares held by Neuren Trustee Limited	2,500,000	
Total issued ordinary shares	**102,668,413**	

Source: NEU Annual Report

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