Clinicians support trofinetide uptake

MST has undertaken discussions with specialist clinicians regarding the results of the Phase 3 trials in Rett (RTT) Syndrome. The clinicians' support of both the strength of Phase 3 trial results and trofinetide's potential role in patient management has given confidence to increase NEU's valuation to A$6.21ps (prev $5.05).

MST's valuation reflects a number of drivers of trofinetide's potential commercial uptake;

- if approved, it is a treatment for seriously debilitating, life-long condition
- no existing approved treatment
- very strong Phase 3 trial results showing meaningful clinical benefit
- acceptable adverse effect profile

Trofinetide potentially offers a disease modifying (DM) role to improve/slow the progressive disease. It has not been included in the current valuation and therefore offers upside risk.

CY22/23 Milestones to Trigger US Revenues

NEU's North American (NAM) partner, Acadia Pharmaceuticals (NASDAQ:ACAD) plans to submit is New Drug Application (NDA) for US FDA approval in mid CY22. The NDA filing, approval and US market entry are expected to trigger payments of ~A$111m over CY22 and CY23 to NEU, with double-digit royalties on net sales to flow from CY23. NEU is expected to confirm the licensing rights for ex-NAM RTT markets over CY22. In MST's view, the strong results will support NEU's negotiations. We have increased the forecast sign on-payment from US$20m to US$40m.

NNZ-2591 to Come

Following FDA queries, NEU has re-submitted its NNZ-2591 drug application to begin Phase 2 trial in Angelman Syndrome with Phelan- McDermid and Pitt Hopkins syndromes to follow. A Phase 2 trial in Prader-Willi syndrome is planned to commence in mid CY22. NNZ-2591 looks to offer both greater clinical potential than trofinetide and manufacturing efficiencies. MST assumes a licensing deal over CY23 with a US$20m sign-on payment. There is upside risk if the preclinical results translate well into the clinical setting.

Financials, Valuation, Risks, Sensitivities

Following discussions with RTT treating physicians we have upgraded NEU's valuation to $6.21ps on a 12-month forward risk-adjusted DCF basis (prev $5.05ps). Averaged market share across the US, EU and ROW now peaks at 21% (prev 15%). Key driver is FDA approval. Potential upside exists through the planned 2-5 year old patient RTT trial, disease modifying action and extension of US patent to 2035. Further risks/sensitivities are detailed in the report.

Neuren Pharmaceuticals is an ASX-listed biotechnology company developing drugs for debilitating neurodevelopmental disorders. Trofinetide and NNZ-2591 are targeting six disorders for which there are no approved therapies. Top-line results of the Phase 3 trial of trofinetide in Rett Syndrome showed strong clinical significance. NNZ-2591 is planned to start four Phase 2 trials in CY22.

Board and management are well credentialled with in-depth experience in drug development and commercialisation.

Company data	
Stock	ASX: NEU
Primary Exchange	ASX
Price	A$3.96
Market Cap	A$536.49m
Valuation	A$800.4m
Valuation ps	A$6.21
Net cash (30/09/21)	A$36.8m
Shares on issue	126m
Options/Rights	3m

Next steps

- Q1CY22 ACAD Pre-NDA meeting with FDA
- CY22 Commence NNZ-2591 Phase 2 trials
- mid CY22 NDA submission to FDA for approval

Share price performance (12 months)

Rosemary Cummins
rosemary.cummins@mstaccess.com.au

Further NEU research reports are available at https://www.mstaccess.com.au **Source:Factset**

Exhibit 1 – NEU Financial Summary

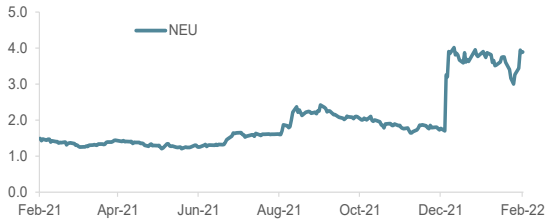
Neuren Pharmaceuticals Limited — NEU-AU

Year end 31 December

MARKET DATA

Share Price	**A$**	**3.96**
52 week high / low	A$	4.49 - 1.20
Valuation (12 month forward)	**A$**	**6.21**
Market capitalisation	**A$m**	**499**
Shares on issue	m	126
Options	m	3
Other equity	m	-
Potential shares on issue (diluted)		129

12 month performance



INVESTMENT FUNDAMENTALS		FY20	FY21	FY22E	FY23E	FY24E
EPS Reported (undiluted)	¢	(8.6)	(15.7)	54.6	6.7	40.7
EPS Underlying (undiluted)	**¢**	**(8.6)**	**(15.7)**	**54.6**	**6.7**	**40.7**
Underlying EPS growth	%	n/m	n/m	n/m	n/m	n/m
P/E Reported (undiluted)	**x**	**n/m**	**n/m**	**n/m**	**n/m**	**n/m**
P/E at Valuation	x	n/m	n/m	n/m	n/m	n/m
Dividend	**¢**	**-**	**-**	**-**	**-**	**-**
Payout ratio	%	0%	0%	0%	0%	0%
Yield	**%**	**-**	**-**	**-**	**-**	**-**

KEY RATIOS (A$)		FY20	FY21	FY22E	FY23E	FY24E
Forecast year end shares	m	118	126	126	126	126
Market cap (Y/E / Spot)	**$m**	**465.7**	**498.8**	**498.8**	**498.8**	**498.8**
Net debt /(cash)	$m	(24.2)	(36.8)	(105.6)	(114.0)	(165.3)
Enterprise value	**$m**	**441.5**	**462.0**	**393.3**	**384.8**	**333.5**
EV/Sales	x	540.4	146.1	2.4	7.8	2.9
EV/EBITDA	**x**	**(47.3)**	**(21.8)**	**3.8**	**32.4**	**4.4**
EV/EBIT	x	(47.3)	(21.7)	4.0	38.8	4.7
Net debt / Enterprise Value	x	(0.1)	(0.1)	(0.3)	(0.3)	(0.5)
Gearing (net debt / EBITDA)	**x**	**2.6**	**1.7**	**(1.0)**	**(9.6)**	**(2.2)**
Operating cash flow per share	$	(0.1)	(0.1)	0.6	0.1	0.4
Price to operating cash flow	**x**	**(57.7)**	**(50.0)**	**6.6**	**47.9**	**8.9**
Free cash flow	**$m**	**(8.1)**	**(10.0)**	**68.8**	**8.4**	**51.3**
Free cash flow per share	$	(0.07)	(0.08)	0.55	0.07	0.41
Price to free cash flow	**x**	**(57.6)**	**(50.0)**	**7.3**	**59.1**	**9.7**
Free cash flow yield	**%**	**-1.7%**	**-2.0%**	**13.8%**	**1.7%**	**10.3%**
Book value / share	$	0.21	0.28	0.84	0.91	1.31
Price to book (NAV)	**x**	**19.2**	**14.2**	**4.7**	**4.4**	**3.0**
NTA / share	$	0.21	0.28	0.84	0.91	1.31
Price to NTA	**x**	**19.2**	**14.2**	**4.7**	**4.4**	**3.0**
EBITDA margin	%	n/m	n/m	64%	24%	65%
ROE (Average Equity)	%	n/m	n/m	n/m	n/m	n/m
ROA (EBIT)	%	n/m	n/m	n/m	n/m	n/m
Interest cover (EBIT / net interest)	x	n/m	n/m	90.1	4.6	27.9

PROFIT AND LOSS (A$)		FY20	FY21	FY22E	FY23E	FY24E
Total Revenue & Other Income	$m	0.8	3.2	162.6	49.2	115.1
COGS	$m	-	-	(33.3)	(10.1)	(26.2)
Gross margin	**$m**	**0.8**	**3.2**	**129.2**	**39.0**	**88.9**
Corporate costs	$m	(10.2)	(24.3)	(25.5)	(27.2)	(13.5)
EBITDA	**$m**	**(9.3)**	**(21.2)**	**103.7**	**11.9**	**75.4**
Depreciation & amortisation	$m	-	(0.1)	(6.5)	(2.0)	(4.6)
EBIT	$m	(9.3)	(21.3)	97.2	9.9	70.8
Net interest	$m	0.1	0.2	1.1	2.2	2.5
Pretax Profit	$m	(9.2)	(21.1)	98.3	12.1	73.3
Tax expense	$m	-	-	(29.5)	(3.6)	(22.0)
Minorities	$m	-	-	-	-	-
Underlying NPAT	**$m**	**(9.2)**	**(21.1)**	**68.8**	**8.4**	**51.3**

BALANCE SHEET (A$)		FY20	FY21	FY22E	FY23E	FY24E
Cash	$m	24.2	36.8	105.6	114.0	165.3
Receivables	$m	0.8	0.8	6.7	2.0	4.7
Inventory	$m	-	-	-	-	-
PPE	$m	0.0	0.0	0.0	0.0	0.0
Intangibles	$m	-	-	-	-	-
Other	$m	-	-	-	-	-
Total Assets	**$m**	**25.0**	**37.6**	**112.3**	**116.1**	**170.1**
Payables	$m	0.8	2.4	6.7	2.0	4.7
Borrowings	$m	-	-	-	-	-
Leases	$m	-	-	-	-	-
Provisions	$m	-	-	-	-	-
Other	$m	-	-	-	-	-
Total Liabilities	**$m**	**0.8**	**2.4**	**6.7**	**2.0**	**4.7**
Shareholder's Equity	**$m**	**24.2**	**35.2**	**105.6**	**114.0**	**165.3**

CASH FLOW (A$)		FY20	FY21	FY22E	FY23E	FY24E
Receipts from customers	$m	-	-	133.3	40.5	104.9
Payments to suppliers and employees	$m	(1.4)	(2.7)	(39.0)	(13.9)	(31.3)
R&D	$m	(7.8)	(9.8)	(19.9)	(23.4)	(8.4)
Govt Grants, Rebates & Milestones	$m	0.9	2.5	29.2	8.6	10.2
Interest	$m	0.2	0.1	1.1	2.2	2.5
Tax	$m	-	-	(29.5)	(3.6)	(22.0)
Operating cash flow	**$m**	**(8.1)**	**(10.0)**	**75.3**	**10.4**	**55.9**
Capex	$m	(0.0)	(0.0)	(6.5)	(2.0)	(4.6)
Acquisitions	$m	-	-	-	-	-
Other	$m	-	-	-	-	-
Investing cash flow	**$m**	**(0.0)**	**(0.0)**	**(6.5)**	**(2.0)**	**(4.6)**
Borrowings (Net)	$m	-	-	-	-	-
Equity	$m	19.1	22.2	-	-	-
Dividend	$m	-	-	-	-	-
Financing cash flow	**$m**	**19.1**	**22.2**	**-**	**-**	**-**
Change in Cash / FX	$m	11.1	12.2	68.8	8.4	51.3
Year end cash	**$m**	**24.2**	**36.8**	**105.6**	**114.0**	**165.3**

Source: NEU Reports, MST Estimates

Transformative Phase 3 results

In December 2021, MST upgraded its valuation of NEU from $3.58ps to $5.05ps on the announcement by NEU's North American partner, Acadia Pharmaceuticals (NASDAQ:ACAD) of strong RTT clinical trial results. The Lavender trial comprised a 12-week randomised, double-blinded, placebo- controlled Phase 3 trial of 187 girls and women with RTT aged between 5-20 years old. The data were very supportive from both regulatory and commercial perspectives.

Trial Key Take-aways

ENDPOINT		TYPE	ASSESSMENT	p VALUE	EFFECT SIZE
Rett Syndrome Behaviour Questionnaire	RSBQ	Primary	Caregiver	**0.0175**	0.37
Clinical Global Impression – Improvement	CGI-I	Primary	Physician	**0.003**	0.47
CSBS-DP-IT Social Composition Score	CSBS-DP-IT	Secondary	Caregiver	**0.0064**	0.43

- Clinical trial p values of ≤0.5 are regarded as 'significant' or positive. The strength of the Lavender data with clear clinical significance across the three key trial endpoints leaves little room for debate around trofinetide's efficacy.
- Consistency of data was also a key feature and is important to regulators. The Phase 3 results trended along those reported in the Phase 2 trial and are in keeping with data emerging from ACAD's Lilac extension trial. There was also a consistency of the results across the different age groups, severity of disease and subscores of the Rett Syndrome Behavioural Questionnaire (RSSBQ). All will be important to the regulators and supportive of potential broader label indications to expand the eligible treatment population.
- >95% of the participants continued to the Lilac extension trial which strongly signals patient/carer support.
- Adverse effects were generally not significant. Diarrhea was the main cause of patients who withdrew from the trial. The diarrhea was attributed to an interaction of trofinetide with laxative medications. ACAD has designed a protocol to manage these patients to minimize the effect.

MST's forecasts are based on:

- RTT is a progressive, severely debilitating disease, affecting all aspects of life. It significantly impacts the patient and family with a high demand on health services. The patients commonly display normal development for the first 6–18 months of life, followed by a loss of acquired motor and language skills. Seizures, autistic behaviours and growth retardation usually follow. Breathing irregularity, gait abnormalities and hand wringing are also commonly found.

- As discussed, the Phase 3 trial data demonstrated clear efficacy in the trial's key three endpoints. The high enrolment of >95 % in the follow on Lilac trial is also very supportive. Adverse effects were not regarded significant with protocols developed to manage the key issue, associated diarrhea.

- The opportunity to have discussions with health professionals involved in the care of RTT patients has seen an upward revision of MST forecasts. The discussions highlighted the significant awareness of the trial, the strength of the trial results and the pressing need for a treatment option.

Potential Disease Modifying Role

Rett Syndrome arises from a mutation of MeCP2 gene. It plays an important role in regulating the function of the synapses which are the transmission areas of signals between the neurons (nerve cells). Studies have identified that RTT leads to insufficient synapses that display 'stunted' development as the children grow. There is excessive revision or 'pruning' of the neurons' dendrites that connect neuron to neuron. The ability of the nerve signals to be passed along the neural network is hindered. The nervous system underlies all body systems and function seeing profound impact.

Trofinetide is a novel synthetic analog or replica of a key neural peptide, glycine-proline-glutamate (GPE), a growth factor for the brain. GPE is believed to play an important role in nerve transmission and the development and maintenance of the synapses. Research studies in tissues from individuals with Rett syndrome as well as in animal models of Rett syndrome have demonstrated that GPE helps normalize neurons and supporting glial cell abnormalities.

Trofinetide as a GPE 'surrogate' is believed to improve the synaptic structure and neural transmission of the signals along the nerves. In MST's view, patients/families, clinicians and healthcare payers would support early intervention to halt/slow the debilitating progression of RTT. Confirmation of a DM is expected to drive significant uptake. MST forecasts do not include the potential upside.

Potential Milestones

Q1 CY22 Pre-NDA submission meeting with FDA by ACAD
mid CY22 NDA submission for approval of trofinetide in RTT
CY22 Commencement of Phase 2 trials of NNZ-2591 in four conditions
CY22 Licensing agreements/upfront payments for trofinetide in ex-NAM markets
CY22/23 NDA submission, FDA approval, market entry of trofinetide to trigger A$111m milestone payments
CY22/23 ACAD to announce plans for the development of trofinetide in Fragile X Syndrome
CY23 Licensing agreement for NNZ-2591 post positive Phase 2 trials

Valuation, Key Risks and Sensitivities

We value NEU at $6.21 per share on a 12-month forward risk-adjusted DCF basis (previously $5.05ps). Following discussions with clinicians, we have increased market share across the different markets. Averaged market share across the US, EU and ROW now peaks at 21% (prev15%). The probability of approval of 25% for NNZ-2591 and other valuation assumptions are unchanged.

Our valuation is subject to the usual upside/downside risks and sensitivities regarding efficacy, safety, clinical trial timing, market approval and entry, pricing, market penetration and sales royalties/licensing payments. Approval by the FDA in Rett Syndrome is a key milestone. Requirements of the EU regulator are yet to be established. The ACAD agreement includes the rights for use of trofinetide in Fragile X. ACAD is yet to confirm further development plans for the additional indication. NEU is yet to confirm licensing agreements for ex NAM markets. All bring upside /downside risk to MST forecasts.

CY22/23 are also expected to be watershed years for NEU's second drug, NNZ-2591. NEU plans to commence Phase 2 trials of NZ-2591 in four neurodevelopmental conditions in CY22, with first clinical results expected in CY23. If positive, licensing agreements are expected to follow. NEU faces the usual risks of drug development including safety, efficacy, delay, trial abandonment, commercial terms if approved. COVID pandemic may affect the timing and patient recruitment.

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