Neuren (NEU) – Q1 Activity Report **29 April 2022**

Neuren remains on track for three major catalysts

Highlights:

- **Neuren remains on track for major catalysts across three large value drivers:**
  - **Acadia plans to submit Rett syndrome NDA to the FDA mid-year 2022, with potential for approval in Q1 2023 - Neuren expects to receive revenue over 2022 and 2023 for Rett syndrome in the US alone of A$115 million plus double-digit percentage royalties on net sales**
  - **Discussions with potential partners for trofinetide ex-North America are progressing, with strong interest received**
  - **NNZ-2591 for multiple neurodevelopmental disorders with global rights retained provides large potential upside – Phase 2 trials in four disorders are commencing in 2022, with results expected in 2023**
- **Key events since 31 December 2021:**
  - **Acadia conducted pre-NDA meetings with FDA in preparation for the pending trofinetide Rett syndrome application**
  - **Neuren received FDA approvals for NNZ-2591 IND applications and Phase 2 trials in each of Angelman, Phelan-McDermid and Pitt Hopkins syndromes**
  - **Trofinetide Phase 3 data was presented at the American Academy of Neurology 2022 Annual Meeting and the ASCEND 2022 Rett Syndrome National Summit**
- **$34.1 million cash at 31 March 2022 – well funded to execute NNZ-2591 Phase 2 trials and foundational work for Phase 3 across all indications, notwithstanding the anticipated material cash flows from trofinetide**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today filed its quarterly activity and cash flow report for Q1 2022.

Neuren CEO Jon Pilcher commented: “Across all three areas of our business, Neuren has remained on track for the catalysts that could lead to a large step-up in value. The New Drug Application to the FDA for Rett syndrome is approaching, discussions are progressing with

potential partners for trofinetide ex-North America and we received FDA approval for our ground-breaking clinical trials in Angelman, Phelan-McDermid and Pitt Hopkins syndromes."

Commentary on Q1 events and outlook

Trofinetide for Rett syndrome in North America

Data from the positive Lavender™ Phase 3 trial was presented by Jeff Neul, MD, at the American Academy of Neurology 2022 Annual Meeting and at the 2022 IRSF Rett Syndrome Scientific Meeting, which was part of the ASCEND 2022 Rett Syndrome National Summit in Nashville.

The trofinetide program has Orphan Drug, Fast Track and Rare Pediatric Disease designations from the US Food and Drug Administration (FDA). Neuren's partner for North America, Acadia Pharmaceuticals, plans to submit a New Drug Application (NDA) to the FDA around mid-year 2022. A NDA with Orphan Drug Designation is eligible for Priority Review in 6 months, compared with the standard review period of 10 months, which means potential for marketing approval in Q1 2023. The NDA will be based on pivotal efficacy from the positive Lavender™ Phase 3 trial, supportive efficacy from Neuren's positive Phase 2 trial and safety data from completed and ongoing studies, which include the Lilac™ open label extension trial and the Daffodil™ trial evaluating safety and pharmacokinetics in children aged 2 to 5 years. During Q1, Acadia conducted pre-NDA meetings with the FDA to discuss the clinical data package and the chemistry, manufacturing and controls package that will be included in the NDA.

Under the terms of the licence agreement with Acadia, the development and commercialisation of trofinetide in North America is fully funded by Acadia and Neuren may receive potential milestone payments of up to US$455 million, plus double-digit percentage royalties on net sales of trofinetide in North America, plus one third of the market value of a Rare Pediatric Disease Priority Review Voucher if awarded by the FDA upon approval of a NDA for trofinetide. These vouchers are tradeable and published sales since 2019 have fetched between US$95 million and US$110 million.

Neuren expects to receive revenue over 2022 and 2023 for Rett syndrome in the US alone of A$115 million plus double-digit percentage royalties on net sales. The expected revenue in addition to the royalties comprises:

- A milestone payment in 2022 of US$10 million (A$14 million at assumed exchange rate of 0.72) following acceptance of the NDA for review by the FDA

- A milestone payment in 2023 of US$40 million (A$55 million), following the first commercial sale of trofinetide in the United States
- US$33 million (A$46 million) in 2023 as Neuren's one third share of the market value of a Priority Review Voucher, estimated as US$100 million.

Neuren's additional ongoing revenue from sales has two components:

- Double digit percentage royalties on sales of trofinetide in all indications. The annual sales are recorded in tiers and an escalating percentage is applied to each successive tier. The potential peak annual net sales for trofinetide in Rett syndrome has been estimated by Acadia as at least US$500 million.
- Payments of up to US$350 million (approximately A$486 million) on achievement of a series of 4 thresholds of total annual sales for all indications.

No royalties or similar costs are payable by Neuren to third parties, which means that Neuren's revenue from Acadia will flow through to pre-tax profit.

Trofinetide for Rett syndrome ex-North America

Acadia has exclusive rights to trofinetide in all indications for the United States, Canada and Mexico. Neuren retained all rights to trofinetide for countries outside North America and has a fully paid-up, irrevocable licence for use in those countries to all data generated by Acadia.

There is urgent unmet need for a treatment for Rett syndrome around the world. Neuren has received strong interest for potential commercial partnerships and discussions are in progress under a process to secure the optimum outcome for shareholders and for patients.

NNZ-2591 for multiple neurodevelopmental disorders

In March Neuren received approval from the FDA for Investigational New Drug (IND) applications to commence Phase 2 clinical trials of NNZ-2591 for each of Phelan-McDermid syndrome (PMS), Angelman syndrome (AS) and Pitt Hopkins syndrome (PTHS). The trials are scheduled to commence in Q2 2022, with results anticipated in H1 2023. Neuren is also planning a Phase 2 trial in a fourth disorder, Prader-Willi syndrome, to commence in H2 2022 with results in H2 2023.

Neuren has Orphan Drug designation from the FDA for NNZ-2591 in all four syndromes, which are serious neurodevelopmental disorders with no approved medicines. The estimated number of potential patients being targeted across these four disorders is more than five times larger than Rett syndrome. Neuren retains all global rights to NNZ-2591.

The overall aim of these first trials in patients is to expedite the generation of data that will enable the subsequent trials to be designed as registration trials. Prioritising fast enrolment of subjects, the AS trial is being conducted in Australia, whilst the PMS and PTHS trials are being conducted in the US.

The primary aim is to confirm the safety and pharmacokinetics of NNZ-2591 in pediatric patients. However, each trial will also assess the treatment impact across multiple efficacy measures to generate data to select the best primary efficacy endpoint or endpoints for the registration trials. The trials maximise the opportunity to demonstrate effects by focusing on pediatric patients and treating them for 13 weeks.

In order to expedite the overall development plan, in parallel with conducting the Phase 2 trials Neuren is executing the additional development work required to be ready for Phase 3 development. This includes non-clinical toxicity studies to support longer clinical trials and commercial use of the product, as well as optimisation of the drug product and drug substance manufacturing arrangements.

Neuren is well funded from current cash reserves to execute the Phase 2 trials and Phase 3 preparation, notwithstanding the anticipated material cash flows from trofinetide.

Investor relations

Neuren's business and prospects were featured in the Australian Financial Review on 4 April. Neuren has presented or is scheduled to present at the healthcare conferences of Jefferies, Goldman Sachs, Wilsons and PAC Partners. During Q1 Milford Asset Management increased its substantial shareholding and Neuren was added to the ASX All Ordinaries Index.

Financials

Cash reserves at 31 March 2022 were $34.1 million, compared with $36.8 million at 31 December 2021. In Q1 net cash of $2.5 million was used in operating activities, with R&D payments of $1.2 million mainly relating to the NNZ-2591 Phase 2 clinical trials. Payments to related parties of approximately $182,000 comprised the Managing Director's executive remuneration and non-executive directors' fees.

About Neuren

Neuren is developing two new drug therapies to treat multiple serious neurological disorders that emerge in early childhood, none of which have any approved medicines.

The lead compound, trofinetide, achieved positive results in a Phase 3 clinical trial for Rett syndrome and has also completed a Phase 2 clinical trial in Fragile X syndrome. Both programs have Fast Track designation from the US Food and Drug Administration (FDA). Neuren has granted an exclusive licence to Acadia Pharmaceuticals Inc. for the development and commercialisation of trofinetide in North America, while retaining all rights outside North America.

Neuren is preparing to initiate Phase 2 trials of its second drug candidate, NNZ-2591, for each of Phelan-McDermid syndrome, Angelman syndrome, Pitt Hopkins syndrome and Prader-Willi syndrome.

Recognising the urgent unmet need, all six programs have been granted "orphan drug" designation in the United States. Orphan drug designation provides incentives to encourage development of therapies for rare and serious diseases.

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ASX Listing Rules information
This announcement was authorized to be given to the ASX by the board of directors of Neuren Pharmaceuticals Limited, Suite 201, 697 Burke Road, Camberwell, VIC 3124

Forward-looking Statements

This announcement contains forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks and important factors that may cause the actual results, performance or achievements of Neuren to be materially different from the statements in this announcement.

Appendix 4C

Quarterly cash flow report for entities subject to Listing Rule 4.7B

Name of entity	
Neuren Pharmaceuticals Limited	
ABN	**Quarter ended ("current quarter")**
72 111 496 130	31 March 2022

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (3 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers	-	-
1.2	Payments for		
	(a) research and development	(1,270)	(1,270)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	-	-
	(d) leased assets	-	-
	(e) staff costs	(590)	(590)
	(f) administration and corporate costs	(607)	(607)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	13	13
1.5	Interest and other costs of finance paid	-	-
1.6	Income taxes paid	-	-
1.7	Government grants and tax incentives	-	-
1.8	Other (provide details if material)	-	-
1.9	**Net cash from / (used in) operating activities**	**(2,454)**	**(2,454)**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire or for:		
	(a) entities	-	-
	(b) businesses	-	-
	(c) property, plant and equipment	(5)	(5)
	(d) investments	-	-
	(e) intellectual property	-	-
	(f) other non-current assets	-	-

Consolidated statement of cash flows		Current quarter $A'000	Year to date (3 months) $A'000
2.2	Proceeds from disposal of:		
	(a) entities	-	-
	(b) businesses	-	-
	(c) property, plant and equipment	-	-
	(d) investments	-	-
	(e) intellectual property	-	-
	(f) other non-current assets	-	-
2.3	Cash flows from loans to other entities	-	-
2.4	Dividends received (see note 3)	-	-
2.5	Other (provide details if material)	-	-
2.6	**Net cash from / (used in) investing activities**	**(5)**	**(5)**

3.	**Cash flows from financing activities**		
3.1	Proceeds from issues of equity securities (excluding convertible debt securities)	-	-
3.2	Proceeds from issue of convertible debt securities	-	-
3.3	Proceeds from exercise of options	-	-
3.4	Transaction costs related to issues of equity securities or convertible debt securities	(2)	(2)
3.5	Proceeds from borrowings	-	-
3.6	Repayment of borrowings	-	-
3.7	Transaction costs related to loans and borrowings	-	-
3.8	Dividends paid	-	-
3.9	Other (provide details if material)	-	-
3.10	**Net cash from / (used in) financing activities**	**(2)**	**(2)**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	36,783	36,783
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(2,454)	(2,454)
4.3	Net cash from / (used in) investing activities (item 2.6 above)	(5)	(5)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (3 months) $A'000
4.4	Net cash from / (used in) financing activities (item 3.10 above)	(2)	(2)
4.5	Effect of movement in exchange rates on cash held	(196)	(196)
4.6	**Cash and cash equivalents at end of period**	**34,126**	**34,126**

5.	Reconciliation of cash and cash equivalents at the end of the quarter (as shown in the consolidated statement of cash flows) to the related items in the accounts	Current quarter $A'000	Previous quarter $A'000
5.1	Bank balances	5,731	6,912
5.2	Call deposits	28,395	29,873
5.3	Bank overdrafts	-	-
5.4	Other (provide details)	-	-
5.5	**Cash and cash equivalents at end of quarter (should equal item 4.6 above)**	**34,126**	**36,785**

6.	Payments to related parties of the entity and their associates	Current quarter $A'000
6.1	Aggregate amount of payments to related parties and their associates included in item 1	182
6.2	Aggregate amount of payments to related parties and their associates included in item 2	-

Note: if any amounts are shown in items 6.1 or 6.2, your quarterly activity report must include a description of, and an explanation for, such payments.

7.	**Financing facilities** *Note: the term "facility' includes all forms of financing arrangements available to the entity.* *Add notes as necessary for an understanding of the sources of finance available to the entity.*	**Total facility amount at quarter end $A'000**	**Amount drawn at quarter end $A'000**
7.1	Loan facilities	-	-
7.2	Credit standby arrangements	-	-
7.3	Other (please specify)	-	-
7.4	**Total financing facilities**	-	-

7.5	**Unused financing facilities available at quarter end**	-

7.6 Include in the box below a description of each facility above, including the lender, interest rate, maturity date and whether it is secured or unsecured. If any additional financing facilities have been entered into or are proposed to be entered into after quarter end, include a note providing details of those facilities as well.

8.	**Estimated cash available for future operating activities**	**$A'000**
8.1	Net cash from / (used in) operating activities (item 1.9)	(2,454)
8.2	Cash and cash equivalents at quarter end (item 4.6)	34,126
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	34,126
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	13.9

Note: if the entity has reported positive net operating cash flows in item 1.9, answer item 8.5 as "N/A". Otherwise, a figure for the estimated quarters of funding available must be included in item 8.5.

8.6 If item 8.5 is less than 2 quarters, please provide answers to the following questions:

8.6.1 Does the entity expect that it will continue to have the current level of net operating cash flows for the time being and, if not, why not?

Answer: N/A

8.6.2 Has the entity taken any steps, or does it propose to take any steps, to raise further cash to fund its operations and, if so, what are those steps and how likely does it believe that they will be successful?

Answer: N/A

8.6.3 Does the entity expect to be able to continue its operations and to meet its business objectives and, if so, on what basis?

Answer: N/A

Note: where item 8.5 is less than 2 quarters, all of questions 8.6.1, 8.6.2 and 8.6.3 above must be answered.

Compliance statement

1 This statement has been prepared in accordance with accounting standards and policies which comply with Listing Rule 19.11A.

2 This statement gives a true and fair view of the matters disclosed.

Date: 29 April 2022

Authorised by: The Board
(Name of body or officer authorising release – see note 4)

Notes

1. This quarterly cash flow report and the accompanying activity report provide a basis for informing the market about the entity's activities for the past quarter, how they have been financed and the effect this has had on its cash position. An entity that wishes to disclose additional information over and above the minimum required under the Listing Rules is encouraged to do so.

2. If this quarterly cash flow report has been prepared in accordance with Australian Accounting Standards, the definitions in, and provisions of, *AASB 107: Statement of Cash Flows* apply to this report. If this quarterly cash flow report has been prepared in accordance with other accounting standards agreed by ASX pursuant to Listing Rule 19.11A, the corresponding equivalent standard applies to this report.

3. Dividends received may be classified either as cash flows from operating activities or cash flows from investing activities, depending on the accounting policy of the entity.

4. If this report has been authorised for release to the market by your board of directors, you can insert here: "By the board". If it has been authorised for release to the market by a committee of your board of directors, you can insert here: "By the [*name of board committee – eg Audit and Risk Committee*]". If it has been authorised for release to the market by a disclosure committee, you can insert here: "By the Disclosure Committee".

5. If this report has been authorised for release to the market by your board of directors and you wish to hold yourself out as complying with recommendation 4.2 of the ASX Corporate Governance Council's *Corporate Governance Principles and Recommendations*, the board should have received a declaration from its CEO and CFO that, in their opinion, the financial records of the entity have been properly maintained, that this report complies with the appropriate accounting standards and gives a true and fair view of the cash flows of the entity, and that their opinion has been formed on the basis of a sound system of risk management and internal control which is operating effectively.