Neuren (NEU) – ASX Announcement **31 January 2023**

Q4 2022 Activity Report

Highlights:

- **Prescription Drug User Fee Act (PDUFA) action date of 12 March 2023 for US Food and Drug Administration (FDA) review of Acadia's New Drug Application (NDA) for trofinetide to treat Rett syndrome**
- **Subject to approval of the NDA, Neuren expects to receive revenue in 2023 for Rett syndrome in the US alone of A$104 million plus double-digit percentage royalties on net sales**
- **Discussions with potential partners for trofinetide ex-North America are continuing**
- **First patients completed treatment in Phase 2 clinical trials of NNZ-2591 in Angelman and Phelan-McDermid syndromes, with good safety and tolerability profile**
- **Investigational New Drug (IND) application submitted to FDA for Phase 2 trial of NNZ-2591 in Prader-Willi syndrome – FDA clearance received in January 2023**
- **A$40.2 million cash at 31 December 2022**
- **Net cash inflow of A$12.9 million in Q4, including US$10 million received from Acadia following acceptance by FDA of the NDA for Rett syndrome**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today filed its quarterly activity and cash flow report for Q4 2022.

Neuren CEO Jon Pilcher commented: "Neuren ended 2022 in a very strong position with cash of $40 million and on track for the transforming catalysts anticipated in 2023, including the FDA target action date for trofinetide in Rett syndrome now less than six weeks away."

Commentary on events since 30 September and outlook

Trofinetide for Rett syndrome

In October Neuren received a milestone payment of US$10 million from its North America partner Acadia Pharmaceuticals (Nasdaq: ACAD), after the US Food and Drug Administration (FDA) accepted for review Acadia's New Drug Application (NDA) for trofinetide to treat Rett

syndrome in adults and pediatric patients two years of age and older. The FDA granted a Priority Review and assigned a Prescription Drug User Fee Act (PDUFA) action date of 12 March 2023. The FDA also informed Acadia that they were not planning to hold an Advisory Committee meeting. The trofinetide program has Orphan Drug, Fast Track and Rare Pediatric Disease designations from the FDA. If approved, trofinetide will be the first drug for the treatment of Rett syndrome.

If the NDA is approved by the FDA, Neuren expects to earn revenue in 2023 for Rett syndrome in the US alone of A$104 million plus royalties. The next potential milestone payment to Neuren would be US$40 million (A$57 million at an assumed exchange rate of 0.70), payable following the first commercial sale of trofinetide in the United States. Subsequently, Neuren is eligible to receive double-digit percentage royalties on net sales of trofinetide in North America, plus milestone payments of up to US$350 million (A$500 million) on achievement of a series of four thresholds of total annual net sales, plus one third of the market value of a Rare Pediatric Disease Priority Review Voucher if awarded by the FDA upon approval of the NDA, with the one third share estimated by Neuren as US$33 million (A$47 million). 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.

Acadia has exclusive rights to develop and commercialize trofinetide in North America, which is fully funded by Acadia. Neuren retains all rights to trofinetide for all countries outside North America and has a fully paid-up, irrevocable licence for use in those countries to all data generated by Acadia. Rett syndrome is a devastating condition with no approved therapies and there is urgent unmet need around the world for a treatment. Neuren has received strong interest for potential commercial partnerships and discussions are continuing under a process to secure the optimum outcome.

NNZ-2591 for multiple neurodevelopmental disorders

Neuren is developing NNZ-2591 for four serious neurological disorders that emerge in early childhood and have no or limited approved treatment options. Phase 2 clinical trials are currently ongoing in children with each of Angelman, Phelan-McDermid and Pitt Hopkins syndromes and in preparation for Prader-Willi syndrome. All four programs have been granted Orphan Drug designation by the FDA. 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.

During Q4 Neuren made important progress in the ongoing trials, with the first subjects completing treatment. The open label Phase 2 trials are each enrolling up to 20 children to

examine safety, tolerability, pharmacokinetics and efficacy over 13 weeks of treatment with NNZ-2591. All subjects receive NNZ-2591 as an oral liquid dose twice daily, with escalation in two stages up to the target dose during the first 6 weeks of treatment, subject to independent review of safety and tolerability data.

The trials are enrolling subjects in three age groups. Safety and tolerability data in the oldest age group must be independently reviewed before proceeding with dosing in the second age group and then safety and tolerability data in the second age group must be independently reviewed before proceeding with dosing in the youngest age group.

The study begins with 4 weeks of observation to thoroughly examine baseline characteristics prior to treatment, against which safety and efficacy are assessed for each child. This is followed by the treatment period of 13 weeks. A follow-up assessment is made 2 weeks after the end of treatment.

	Phelan-McDermid	**Pitt Hopkins**	**Angelman**
Subjects	Up to 20, aged 3 to 12	Up to 20, aged 3 to 17	Up to 20, aged 3 to 17
Number of sites	4 (US)	5 (US)	3 (Australia)
www.clinicaltrials.gov	NCT05025241	NCT05025332	NCT05011851

In the Phelan-McDermid syndrome trial and in the Angelman syndrome trial, the first subject in the oldest age group completed the treatment period of 13 weeks in Q4, with a good safety and tolerability profile. Each subject was successfully escalated up to the target dose following safety and tolerability reviews by an independent data and safety monitoring committee (DSMC). No serious adverse events were reported and no dose modifications were required. Most of the adverse events reported were mild and not considered to be related to study drug. There were no clinically relevant observations in safety laboratory measurements or cardiac tests.

In the Phelan-McDermid trial, enrolment in the second age group was approved following review by the DSMC of safety and tolerability data for subjects in the oldest age group.

In January 2023 the FDA gave approval for Neuren to proceed with a Phase 2 clinical trial in children with Prader-Willi syndrome (PWS) after reviewing Neuren's Investigational New Drug (IND) application, which was submitted in December. Neuren previously reported positive results in the *Magel2*-null mouse model of Prader-Willi syndrome, in which treatment with NNZ-2591 for 6 weeks normalized fat mass, insulin levels, IGF-1 levels and all behavioural deficits.

The overall aim of these first clinical trials in patients is to expedite the generation of data that will enable the subsequent trials to be designed as registration trials. The four trials will likely complete at different times, with a series of top-line results announcements anticipated from H2 2023, commencing with Phelan-McDermid syndrome.

In order to accelerate 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 conferences

During the quarter, Neuren presented at the Australian healthcare conferences of Evans & Partners, Bell Potter, Wilsons, MST and Goldman Sachs, as well as at the ASX Small and Mid-Cap conference. Neuren also attended and presented at the Jefferies London Healthcare Conference.

Financials

Cash reserves at 31 December 2022 were A$40.2 million, compared with A$27.3 million at 30 September 2022. In Q4 net cash of A$13.4 million was generated from operating activities. A$15.9 million was received under the licence agreement with Acadia for trofinetide in North America and A$1.4 million was received under the Australian R&D Tax Incentive. R&D payments of A$3.1 million mainly related to the NNZ-2591 Phase 2 clinical trials and the foundational work to prepare for Phase 3 development of NNZ-2591 across multiple indications. The carrying value in AUD of USD cash held to mitigate exchange rate risk for USD expenditure decreased by A$0.5m for the quarter, due to the strengthening of the AUD against

the USD. Payments to related parties of approximately A$194,000 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 and have no or limited approved treatment options.

A New Drug Application for the lead compound, trofinetide, to treat Rett syndrome is under Priority Review by the US Food and Drug Administration (FDA), with a PDUFA action date of 12 March 2023. 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 conducting 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 December 2022

Consolidated statement of cash flows		**Current quarter $A'000**	**Year to date (12 months) $A'000**
1.	**Cash flows from operating activities**		
1.1	Receipts from customers	15,921	15,921
1.2	Payments for		
	(a) research and development	(3,098)	(9,772)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	-	-
	(d) leased assets	-	-
	(e) staff costs	(745)	(2,814)
	(f) administration and corporate costs	(152)	(1,317)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	114	188
1.5	Interest and other costs of finance paid	-	-
1.6	Income taxes paid	-	-
1.7	Government grants and tax incentives	1,393	1,393
1.8	Other (provide details if material)	-	-
1.9	**Net cash from / (used in) operating activities**	**13,433**	**3,599**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire or for:		
	(a) entities	-	-
	(b) businesses	-	-
	(c) property, plant and equipment	-	(19)
	(d) investments	-	-
	(e) intellectual property	-	-
	(f) other non-current assets	-	-

Consolidated statement of cash flows		Current quarter $A'000	Year to date (12 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**	**-**	**(19)**

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)
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)**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	27,292	36,783
4.2	Net cash from / (used in) operating activities (item 1.9 above)	13,433	3,599
4.3	Net cash from / (used in) investing activities (item 2.6 above)	-	(19)

Consolidated statement of cash flows		Current quarter $A'000	Year to date (12 months) $A'000
4.4	Net cash from / (used in) financing activities (item 3.10 above)	-	(2)
4.5	Effect of movement in exchange rates on cash held	(545)	(181)
4.6	**Cash and cash equivalents at end of period**	**40,180**	**40,180**

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	2,304	1,912
5.2	Call deposits	37,876	25,380
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)**	**40,180**	**27,292**

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	194
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)	13,433
8.2	Cash and cash equivalents at quarter end (item 4.6)	40,180
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	40,180
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	N/A

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: 31 January 2023

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.