Neuren (NEU) – ASX Announcement **28 April 2023**

Q1 2023 Activity Report

Highlights:

- **DAYBUE™ (trofinetide) approved on 10 March by US Food and Drug Administration (FDA) as the first treatment ever approved for Rett syndrome:**
  - **Launched in the US by Acadia on 17 April**
  - **US$40 million milestone payment earned by Neuren on first commercial sale**
- **Neuren to receive quarterly royalties on net sales, plus milestone payments of up to US$350 million subject to achievement of annual net sales thresholds, plus one third of the market value of Rare Pediatric Disease Priority Review Voucher awarded to Acadia**
- **Partnering process for trofinetide ex-North America is advancing**
- **Enrolment and treatment continuing in Phase 2 clinical trials of NNZ-2591 in Phelan-McDermid, Pitt Hopkins and Angelman syndromes:**
  - **First top-line result anticipated in Q4 2023 for Phelan-McDermid syndrome**
  - **Treatment to date continuing to show good safety and tolerability profile**
- **Investigational New Drug (IND) application cleared by FDA for Phase 2 trial of NNZ-2591 in Prader-Willi syndrome – final trial preparations in progress**
- **A$37.3 million cash at 31 March 2023**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today filed its quarterly activity and cash flow report for Q1 2023.

Neuren CEO Jon Pilcher commented: "The FDA approval and launch of DAYBUE™ has transformed Neuren's financial outlook, placing us in a very strong position to make the most of the opportunities ahead as we strive to make a difference to patients and families impacted by neurodevelopmental disabilities."

Commentary on events since 1 January and outlook

Trofinetide for Rett syndrome

On 10 March, Neuren's North America partner Acadia Pharmaceuticals (NASDAQ: ACAD) received US Food and Drug Administration (FDA) approval of DAYBUE™ (trofinetide) for the

treatment of Rett syndrome in adult and pediatric patients two years of age and older. DAYBUE is the first and only approved treatment for Rett syndrome. On 17 April, Acadia announced the commercial launch of DAYBUE in the United States.

The first commercial sale earned Neuren a milestone payment of US$40 million. Neuren is eligible to receive ongoing quarterly royalties on net sales of trofinetide in North America, plus milestone payments of up to US$350 million on achievement of a series of four thresholds of total annual net sales, plus one third of the market value of the Rare Pediatric Disease Priority Review Voucher that was awarded to Acadia by the FDA upon approval of the NDA, with the one third share estimated by Neuren as US$33 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. The royalty rates and sales milestone payments are related to the total amount of annual net sales of trofinetide in all indications, as set out in the following tables:

Tiered royalty rates (% of net sales)[1]		Sales Milestone payments	
Annual Net Sales	**Rates**	**Net Sales in one calendar year**	**US$m**
≤US$250m	10%	≥US$250m	50
>US$250m, ≤US$500m	12%	≥US$500m	50
>US$500m, ≤US$750m	14%	≥US$750m	100
>US$750m	15%	≥US$1bn	150

[1] Royalty rates payable on the portion of annual net sales that fall within the applicable range. Each sales milestone payment is payable once only.

Acadia has exclusive rights to develop and commercialize trofinetide in the United States, Canada and Mexico, which is fully funded by Acadia. Neuren retains all rights to trofinetide for all other countries 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 and there is urgent unmet need around the world for a treatment. Neuren intends to pursue registration and commercialization of trofinetide through partnerships and discussions are well advanced with a number of third parties.

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 Phelan-McDermid, Pitt Hopkins and Angelman syndromes and a Phase 2 trial is 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 Q1 enrolment and treatment continued in the three ongoing trials. 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 at least 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

To date, treatment across all three trials has continued to demonstrate a good safety and tolerability profile. The Phelan-McDermid syndrome trial is currently enrolling in all three age groups and top-line results are anticipated in Q4 2023, with results from the other trials to follow.

In January, the FDA gave approval for Neuren to proceed with a Phase 2 clinical trial in children with Prader-Willi syndrome after reviewing Neuren's Investigational New Drug (IND) application. The final preparations for the trial are currently in progress, informed by the experience of the other trials. 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. 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.

Financials

Cash reserves at 31 March 2023 were A$37.3 million, compared with A$40.2 million at 31 December 2022. In Q1 net cash of A$3.2 million was used in operating activities, with R&D payments of A$2.1 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. Administration and corporate payments were increased due to the timing of annual insurance premiums. The effect of movement in exchange rates on cash held was a decrease of A$0.8m, mostly the realisation of the loss on settled forward contracts, due to the strengthening of the AUD against the USD since entering into the forward contracts. An unrealised loss of $0.7 million in the fair value of the contracts at 31 December was accrued in

the 2022 financial statements. 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 new drug therapies to treat multiple serious neurological disorders that emerge in early childhood and have no or limited approved treatment options.

DAYBUE™ (trofinetide) is approved by the US Food and Drug Administration (FDA) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older. 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 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 2023

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	(2,094)	(2,094)
	(b) product manufacturing and operating costs	-	-
	(c) advertising and marketing	-	-
	(d) leased assets	-	-
	(e) staff costs	(729)	(729)
	(f) administration and corporate costs	(686)	(686)
1.3	Dividends received (see note 3)	-	-
1.4	Interest received	296	296
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**	**(3,213)**	**(3,213)**

2.	**Cash flows from investing activities**		
2.1	Payments to acquire or for:		
	(a) entities	-	-
	(b) businesses	-	-
	(c) property, plant and equipment	-	-
	(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**	**-**	**-**

3.	**Cash flows from financing activities**		
3.1	Proceeds from issues of equity securities (excluding convertible debt securities)	1,104	1,104
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	(7)	(7)
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**	**1,097**	**1,097**

4.	**Net increase / (decrease) in cash and cash equivalents for the period**		
4.1	Cash and cash equivalents at beginning of period	40,180	40,180
4.2	Net cash from / (used in) operating activities (item 1.9 above)	(3,213)	(3,213)
4.3	Net cash from / (used in) investing activities (item 2.6 above)	-	-

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)	1,097	1,097
4.5	Effect of movement in exchange rates on cash held	(801)	(801)
4.6	**Cash and cash equivalents at end of period**	**37,263**	**37,263**

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	1,683	2,304
5.2	Call deposits	35,580	37,876
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)**	**37,263**	**40,180**

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)	(3,213)
8.2	Cash and cash equivalents at quarter end (item 4.6)	37,263
8.3	Unused finance facilities available at quarter end (item 7.5)	-
8.4	Total available funding (item 8.2 + item 8.3)	37,263
8.5	**Estimated quarters of funding available (item 8.4 divided by item 8.1)**	11.6

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: 28 April 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.