Neuren (NEU) – ASX Announcement **24 February 2023**

Neuren reports 2022 full-year results

Highlights:

Trofinetide

- **New Drug Application (NDA) to treat Rett syndrome submitted by Acadia to US Food and Drug Administration (FDA) and granted Priority Review**
- **US$10 million received from Acadia on FDA acceptance of the NDA for review**
- **Prescription Drug User Fee Act (PDUFA) action date of 12 March 2023**
- **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 ex-North America are advancing**

NNZ-2591

- **Four Investigational New Drug (IND) applications approved by FDA for NNZ-2591 in Phelan-McDermid, Angelman, Pitt Hopkins and Prader-Willi syndromes**
- **Phase 2 clinical trials commenced for Phelan-McDermid, Angelman and Pitt Hopkins syndromes**
- **First patients completed treatment in Angelman and Phelan-McDermid syndrome trials, with good safety and tolerability profile**
- **Start-up activities ongoing for Phase 2 clinical trial in Prader-Willi syndrome**
- **CMC and non-clinical studies progressing as planned in preparation for Phase 3 across multiple indications**

Financials

- **NEU promoted into the S&P/ASX 300 index**
- **A$40.2 million cash at 31 December 2022**
- **A$0.2 million profit after tax, compared with a loss of A$7.8 million in 2021**
- **A$3.6 million net cash received from operating activities, compared with net cash used in operating activities of A$10.0 million in 2021**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today filed its full-year financial results for 2022.

Neuren CEO Jon Pilcher commented: "The substantial progress that was made in 2022 across the whole business leaves Neuren very well placed for the transforming catalysts that have been anticipated to crystallise in 2023. We are now approximately two weeks away from the first of those – the FDA PDUFA action date for trofinetide in Rett syndrome. The Neuren team is excited about the year ahead and the prospects for both trofinetide and NNZ-2591."

Commentary on events and outlook

Trofinetide for Rett syndrome

In December 2021 Neuren's partner for trofinetide in North America, Acadia Pharmaceuticals (Nasdaq: ACAD), announced positive top-line results from the pivotal, Phase 3 Lavender™ study evaluating the efficacy and safety of trofinetide in 187 girls and young women aged 5-20 years with Rett syndrome. The 12-week placebo-controlled study demonstrated a statistically significant improvement over placebo for both co-primary endpoints. In September 2022 the US Food and Drug Administration (FDA) accepted for review the New Drug Application (NDA) for trofinetide to treat Rett syndrome in adults and pediatric patients two years of age or older, that was submitted in July by Acadia. 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. If approved, trofinetide will be the first drug for the treatment of Rett syndrome. The trofinetide program has Orphan Drug, Fast Track and Rare Pediatric Disease designations from the FDA.

In October 2022, Neuren received from Acadia a milestone payment of US$10 million following the acceptance of the NDA for review by the FDA. 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 ongoing 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. Neuren has received strong interest for potential commercial partnerships and discussions are advancing 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.

In July and August 2022, Neuren announced the commencement of Phase 2 clinical trials of NNZ-2591 for Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome, after receiving in March 2022 approval from the FDA for Investigational New Drug (IND) applications to conduct the trials. In December 2022, Neuren submitted an IND application to the FDA for approval to proceed with a Phase 2 trial in Prader-Willi syndrome and received approval from the FDA in January 2023.

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 current 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 December 2022, Neuren announced that in the Phelan-McDermid syndrome trial and in the Angelman syndrome trial, the first subject in the oldest age group had completed the treatment period of 13 weeks, 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.

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, commencing with Phelan-McDermid syndrome in H2 2023.

In order to accelerate the overall development plan, in parallel with conducting the Phase 2 trials Neuren is executing additional development work required 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

Profit after tax for the year ended 31 December 2022 was A$0.2 million compared with a loss of A$7.8 million in 2021. Revenue of A$14.6 million was received under the licence agreement with Acadia (2021: nil) and foreign exchange gains were A$1.2 million (2021: A$0.4 million). These were offset by an increase of A$3.2 million in research and development costs, due to higher expenditures in 2022 for the NNZ-2591 Phase 2 clinical trials and the foundational work to prepare for Phase 3 development of NNZ-2591 across multiple indications. There was also an increase in corporate and administrative costs of A$1.5 million, mainly due to share-based payments and higher employee benefits expense, reflecting some expansion for the NNZ-2591 program. In addition, a loss of A$0.7 million on the fair value of outstanding forward contracts to sell Australian dollars and buy US dollars was recognised at 31 December 2022. Prudent control of expenditure continues to be an important principle in the Group's operations and financing.

Cash reserves at 31 December 2022 were $40.2 million (2021: $36.8 million). Net cash received from operating activities was $3.6 million, compared with net cash used in operating activities of $10.0 million in 2021. The increase of $13.6 million was due to the receipt of the first milestone payment from Acadia of $15.9 million (2021: nil), offset by higher payments for employees and directors of $2.8 million (2021: $1.8 million) and a lower receipt under the R&D Tax Incentive program of $1.4 million (2021: $2.5 million). Net cash from financing activities for 31 December 2022 was nil, compared with $22.2 million in 2021 from the issue of new ordinary shares in a share placement and share purchase plan.

The large increase in market capitalization during the year resulted in Neuren being promoted in September into the S&P/ASX 300 index.

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 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.