Neuren (NEU) – ASX Announcement **24 February 2022**

2021 results - a transformational year for Neuren

Highlights:

- **Robustly positive results in the Lavender™ Phase 3 trial of Trofinetide in Rett syndrome:**
  - **Both co-primary efficacy endpoints and key secondary endpoint demonstrated statistically significant improvement over placebo**
  - **Acadia plans to submit New Drug Application (NDA) to the US Food and Drug Administration (FDA) mid-year 2022**
  - **NDA with Orphan Drug designation is eligible for Priority Review in 6 months, which means 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:**
  - **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**
  - **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 estimated one third share of the market value of a Priority Review Voucher**
- **Discussions with potential partners for trofinetide ex-North America progressing, with strong interest from multiple parties**
- **NNZ-2591 for multiple neurodevelopmental disorders with global rights retained provides large potential upside:**
  - **Phase 1 trial completed successfully**
  - **Prader-Willi syndrome added to pipeline following positive results in pre-clinical model and grant of Orphan Drug designation by FDA**
  - **Commencement of Phase 2 trials in Phelan-McDermid, Angelman and Pitt Hopkins syndromes pending FDA approval of updated protocols and IND applications, which have been submitted for all three indications**
- **$36.8 million cash at 31 December 2021 – well funded to execute NNZ-2591 Phase 2 trials and foundational work for Phase 3 across all indications**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today filed its full-year financial report for 2021.

Neuren CEO Jon Pilcher commented: "2021 was a transformational year for Neuren, with the robustly positive Phase 3 results for Rett syndrome positioning the business for a much larger step-change in 2022. We expect material cash flows to commence from trofinetide in the US as the NDA process unfolds. In the meantime, we are advancing discussions with potential partners for trofinetide outside North America and preparing for the NNZ-2591 Phase 2 trials."

Commentary on 2021 progress and outlook

Trofinetide for Rett syndrome in North America

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. On the Rett Syndrome Behaviour Questionnaire (RSBQ), change from baseline to week 12 was -5.1 vs. -1.7 (p=0.0175; effect size=0.37). The Clinical Global Impression–Improvement (CGI-I) score at week 12 was 3.5 vs. 3.8 (p=0.0030; effect size=0.47). The RSBQ is a caregiver assessment of the core symptoms of Rett syndrome and the CGI-I is a global physician assessment of worsening or improving of Rett syndrome. Additionally, trofinetide demonstrated a statistically significant separation over placebo on the key secondary endpoint, the Communication and Symbolic Behavior Scales Developmental Profile™ Infant-Toddler Checklist–Social composite score (CSBS-DP-IT–Social) change from baseline to week 12 was -0.1 vs. -1.1 (p=0.0064; effect size=0.43).

The trofinetide program has Orphan Drug, Fast Track and Rare Pediatric Disease designations from the US Food and Drug Administration (FDA). Acadia plans to submit a New Drug Application (NDA) to the US Food and Drug Administration (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 approval in the first quarter of 2023.

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 tiered escalating 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.

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 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; and
- US$33 million (A$46 million) in 2023 as Neuren's estimated one third share of the market value of a Priority Review Voucher.

Trofinetide for Rett syndrome ex-North America

Under the licence agreement with Acadia, Neuren retained all rights to trofinetide outside North America and has a fully paid-up, irrevocable licence to all data for use in those countries. There is urgent unmet need for a treatment for Rett syndrome around the world. Neuren has received strong interest for potential commercial partnerships and the number of interested parties has increased significantly since the Phase 3 results were announced. Discussions are now in progress under a process to secure the best outcome for shareholders and for patients.

NNZ-2591 for multiple neurodevelopmental disorders

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

In February 2021, Neuren announced completion of a Phase 1 clinical trial in Australia, in which twice daily oral dosing of NNZ-2591 for seven days was safe and well tolerated in healthy volunteers at doses expected to be within the effective therapeutic range. An extensive range of non-clinical toxicology and manufacturing studies were also completed. In September 2021, Neuren submitted to the FDA three Investigational New Drug (IND) applications for review and clearance to start Phase 2 trials in each of Phelan-McDermid syndrome, Angelman syndrome and Pitt Hopkins syndrome. Following feedback from the FDA, Neuren was required to add

additional clinical assessments to each trial protocol to enhance safety monitoring during these first trials in pediatric patients. Neuren worked with expert clinical advisors to address all the detailed feedback that was received from the FDA and has recently submitted the updated protocols and IND applications for all three indications. The programs are supervised by the FDA Office of Neuroscience, with Phelan-McDermid and Pitt Hopkins reviewed by the Division of Neurology 1 and Angelman reviewed by the Division of Psychiatry.

A fourth disorder, Prader-Willi syndrome was added to the NNZ-2591 development pipeline in February 2021, when Neuren announced 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 defects. The FDA granted Orphan Drug designation to NNZ-2591 for the treatment of Prader-Willi syndrome in September 2021. Neuren is planning to commence a Phase 2 clinical trial in Prader-Willi syndrome in mid-2022. Neuren is also executing the foundational work to prepare for Phase 3 development of NNZ-2591 across all four syndromes. Neuren is well funded from current cash reserves to execute the NNZ-2591 Phase 2 trials and Phase 3 preparation.

Financials

The loss after tax in 2021 was $7.8 million compared with $9.2 million in 2020. This was mainly due to the R&D Tax incentive income of $3.2 million (2020: $0.7 million) following AusIndustry's approval of an Advance and Overseas finding for the development of NNZ-2591 as a novel therapy for neurodevelopmental disorders. Research and development costs were $1.7 million higher, due to an increase in expenditures in 2021 for the NNZ-2591 non-clinical studies, Phase 1 trial, Phase 2 trials and manufacture of the required drug for the Phase 2 trials. In addition, foreign exchange gains were $0.4 million compared with foreign exchange losses of $0.6 million in 2020. This is due to an increase in the carrying value in AUD of USD cash held to eliminate exchange risk for USD expenditure, as a result of the strengthening of the USD against the AUD. Prudent control of expenditure continues to be an important principle in operations and financing.

Cash reserves at 31 December 2021 were $36.8 million (2020: $24.2 million). Financing provided cash of $22.2 million, received for the issue of new ordinary shares in the capital raise and share purchase plan, compared with $19.1 million in 2020.

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.