Neuren (NEU) – ASX Announcement **13 March 2023**

FDA approval of DAYBUE™ (trofinetide) - the first approved treatment for Rett syndrome

Highlights:

- **Acadia Pharmaceuticals announces US FDA approval of DAYBUE™ (trofinetide) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older**
- **First and only approved treatment for Rett syndrome**
- **Acadia expects DAYBUE to be available by the end of April 2023**
- **Rare Pediatric Disease Priority Review Voucher (PRV) granted in connection with approval**
- **Neuren to receive US$40 million on first commercial sale, royalties on net sales, potential sales milestone payments and one third of the market value of the PRV**

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today announced that its 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. Acadia expects DAYBUE to be available by the end of April 2023. DAYBUE is the first and only approved treatment for Rett syndrome.

The announcement by Acadia is attached, which includes details for attending a conference call and webcast by Acadia management on Monday 13 March 2023 at 8:30 am US EDT (11.30 pm AEDT). Neuren will host an investor webinar on Tuesday 14 March 2023, details to be announced separately.

Neuren CEO Jon Pilcher commented: "Many people have shown great determination over the long journey to reach this historic outcome. The greatest has been shown by the Rett syndrome community and I am delighted for them. For Neuren, this is a transforming milestone that places us in a position to make the most of the opportunities ahead of us, as we work with the communities to make a difference in four other neurodevelopmental disorders."

Neuren revenue outlook

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. The next milestone payment to Neuren is US$40 million, payable following the first commercial sale of trofinetide in the United States, which is anticipated at the end of April 2023. Neuren is eligible to receive ongoing 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

In 2018, Neuren and Acadia entered into an exclusive license agreement for Acadia to develop and commercialise trofinetide for the treatment of Rett syndrome and other indications in North America (US, Canada and Mexico). 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 intends to pursue registration and commercialisation of trofinetide through partners and is currently advancing discussions with a number of third parties. Currently Neuren does not have the necessary approvals or available drug supply to enable any compassionate use or named patient programs.

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.

On 10 March 2023, the US Food and Drug Administration (FDA) approved DAYBUE™ (trofinetide) 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.

Acadia Pharmaceuticals Announces U.S. FDA Approval of DAYBUE™ (trofinetide) for the Treatment of Rett Syndrome in Adult and Pediatric Patients Two Years of Age and Older

-- First and only approved therapy for Rett syndrome, a rare, neurodevelopmental disorder, which affects 6,000 to 9,000 patients in the U.S.[1]

-- Company expects DAYBUE to be available by the end of April, 2023

-- Rare Pediatric Disease Priority Review Voucher granted in connection with approval

-- Conference call and webcast to be held March 13, 2023 at 8:30 a.m. Eastern Time

SAN DIEGO--(BUSINESS WIRE) — March 10, 2023 – Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) today announced that the U.S. Food and Drug Administration (FDA) has approved DAYBUE™ (trofinetide) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older, including male and female patients. DAYBUE is the first and only drug approved for the treatment of Rett syndrome.

"Today marks an important milestone for the Rett community and Acadia. As the first FDA-approved drug for the treatment of Rett syndrome, DAYBUE now offers the potential to make meaningful differences in the lives of patients and their families who have lacked options to treat the diverse and debilitating array of symptoms caused by Rett syndrome," said Steve Davis, Acadia's Chief Executive Officer. "We are grateful to all of the Rett syndrome patients, caregivers, clinical investigators and our employees who have contributed to making today a reality and look forward to getting DAYBUE to patients as quickly as possible."

"Rett syndrome is a profoundly debilitating and complex, rare, neurodevelopmental disorder that presents differently across patients and can lead to an array of unpredictable symptoms throughout the course of a patient's life," said Jeffrey L. Neul, M.D., Ph.D., Annette Schaffer Eskind Chair and Director, Vanderbilt Kennedy Center, Professor of Pediatrics, Division of Neurology, Pharmacology, and Special Education, Vanderbilt University Medical Center and Phase 3 LAVENDER™ study investigator. "Now, for the first time after decades of clinical research, healthcare providers finally have a treatment option to address a range of core behavioral, communication and physical symptoms for their patients living with Rett syndrome."

Rett syndrome is a complex, rare, neurodevelopmental disorder typically caused by a genetic mutation on the MECP2 gene.[2,3] It is characterized by a period of normal development until six to 18 months of age, followed by significant developmental regression with loss of acquired communication skills and purposeful hand use.[4] Symptoms of Rett syndrome may also include development of hand stereotypies, such as hand wringing and clapping, and gait abnormalities.[5] Rett syndrome is believed to affect 6,000 to 9,000 patients in the U.S., with a diagnosed population of approximately 4,500 U.S. patients.[1,6]

The FDA approval of DAYBUE was supported by results from the pivotal Phase 3 LAVENDER study evaluating the efficacy and safety of trofinetide versus placebo in 187 female patients with Rett syndrome five to 20 years of age. In the study, treatment with DAYBUE demonstrated statistically significant improvement compared to placebo on both co-primary efficacy endpoints, as measured by the change from baseline in Rett Syndrome Behaviour Questionnaire (RSBQ) total score ($p=0.018$) and the Clinical Global Impression-Improvement (CGI-I) scale score ($p=0.003$) at week 12. The

RSBQ is a caregiver assessment that evaluates a range of symptoms of Rett syndrome including vocalizations, facial expressions, eye gaze, hand movements (or stereotypies), repetitive behaviors, breathing, night-time behaviors and mood. The CGI-I is a global physician assessment of whether a patient has improved or worsened. In the study, the most common side effects were diarrhea (82%) and vomiting (29%).

"This is a historic day for the Rett syndrome community and a meaningful moment for the patients and caregivers who have eagerly awaited the arrival of an approved treatment for this condition," said Melissa Kennedy, Chief Executive Officer of the International Rett Syndrome Foundation. "Rett syndrome is a complicated, devastating disease that affects not only the individual patient, but whole families. With today's FDA decision, those impacted by Rett have a promising new treatment option that has demonstrated benefit across a variety of Rett symptoms, including those that impact the daily lives of those living with Rett and their loved ones."

DAYBUE is expected to be available in the U.S. by the end of April, 2023.

In 2018, Acadia entered into an exclusive license agreement with Neuren Pharmaceuticals Limited (ASX: NEU) for the development and commercialization of trofinetide for the treatment of Rett syndrome and other indications in North America.

With the FDA approval of DAYBUE, Acadia has received a Rare Pediatric Disease Priority Review Voucher, which can be used to obtain priority review for a subsequent application.

Acadia Connect® Offers Dedicated Patient and Family Support and Resources

Acadia Connect® is a multi-faceted support program that will offer personal assistance, financial resources and prescription support to patients and caregivers starting and continuing appropriate DAYBUE therapy. Each dedicated support team includes a nurse care coordinator, a family access manager and 24/7 clinical pharmacist support. For more information, visit AcadiaConnect.com or call 1-844-737-2223, Monday to Friday, 8 a.m. to 8 p.m. Eastern Time.

Conference Call and Webcast Information

Acadia management will discuss the FDA approval of DAYBUE for the treatment of Rett syndrome via conference call and webcast on Monday, March 13, 2023 at 8:30 a.m. Eastern Time. The conference call may be accessed by registering for the call here. Once registered, participants will receive an email with the dial-in number and unique PIN number to use for accessing the call. The registration link will also be available on Acadia's website, www.acadia.com, under the investors section and will be archived there until April 13, 2023.

Important Safety Information for DAYBUE™ (trofinetide)

Important Safety Information

- **Warnings and Precautions**
    - **Diarrhea**: In a 12-week study and in long-term studies, 85% of patients treated with DAYBUE experienced diarrhea. In those treated with DAYBUE, 49% either had persistent diarrhea or recurrence after resolution despite dose interruptions, reductions, or

concomitant antidiarrheal therapy. Diarrhea severity was of mild or moderate severity in 96% of cases. In the 12-week study, antidiarrheal medication was used in 51% of patients treated with DAYBUE.

Patients should stop taking laxatives before starting DAYBUE. If diarrhea occurs, patients should notify their healthcare provider, consider starting antidiarrheal treatment, and monitor hydration status and increase oral fluids, if needed. Interrupt, reduce dose, or discontinue DAYBUE if severe diarrhea occurs or if dehydration is suspected.

- **Weight Loss**: In the 12-week study, 12% of patients treated with DAYBUE experienced weight loss of greater than 7% from baseline, compared to 4% of patients who received placebo. In long-term studies, 2.2% of patients discontinued treatment with DAYBUE due to weight loss. Monitor weight and interrupt, reduce dose, or discontinue DAYBUE if significant weight loss occurs.

- **Adverse Reactions:** The common adverse reactions (≥5% for DAYBUE-treated patients and at least 2% greater than in placebo) reported in the 12-week study were diarrhea (82% vs 20%), vomiting (29% vs 12%), fever (9% vs 4%), seizure (9% vs 6%), anxiety (8% vs 1%), decreased appetite (8% vs 2%), fatigue (8% vs 2%), and nasopharyngitis (5% vs 1%).

- **Drug Interactions: Effect of DAYBUE on other Drugs**
  - DAYBUE is a weak CYP3A4 inhibitor; therefore, plasma concentrations of CYP3A4 substrates may be increased if given concomitantly with DAYBUE. Closely monitor when DAYBUE is used in combination with orally administered CYP3A4 sensitive substrates for which a small change in substrate plasma concentration may lead to serious toxicities.
  - Plasma concentrations of OATP1B1 and OATP1B3 substrates may be increased if given concomitantly with DAYBUE. Avoid the concomitant use of DAYBUE with OATP1B1 and OATP1B3 substrates for which a small change in substrate plasma concentration may lead to serious toxicities.

- **Use in Specific Population: Renal Impairment**
  - DAYBUE is not recommended for patients with moderate or severe renal impairment.

DAYBUE is available as an oral solution (200mg/mL).

Please read the accompanying full Prescribing Information, also available at DAYBUE.com

About Rett Syndrome
Rett syndrome is a rare, complex, neurodevelopmental disorder that may occur over four stages and affects approximately 6,000 to 9,000 patients in the U.S., with approximately 4,500 patients currently diagnosed according to an analysis of healthcare claims data.[1,2,4,6] A child with Rett syndrome exhibits an early period of apparently normal development until six to 18 months, when their skills seem to slow down or stagnate. This is typically followed by a duration of regression when the child loses acquired communication skills and purposeful hand use. The child may then experience a plateau period in which they show mild recovery in cognitive interests, but body movements remain severely diminished. As they age, those living with Rett may continue to experience a stage of motor deterioration which can last the rest of the patient's life.[4] Rett syndrome is typically caused by a

genetic mutation on the MECP2 gene.[3] In preclinical studies, deficiency in MeCP2 function has been shown to lead to impairment in synaptic communication, and the deficits in synaptic function may be associated with Rett manifestations.[3,7,8]

Symptoms of Rett syndrome may also include development of hand stereotypies, such as hand wringing and clapping, and gait abnormalities.[5] Most Rett patients typically live into adulthood and require round-the-clock care.[2,9]

About DAYBUE ™ (trofinetide)
Trofinetide is a synthetic version of a naturally occurring molecule known as the tripeptide glycine-proline-glutamate (GPE). The mechanism by which trofinetide exerts therapeutic effects in patients with Rett syndrome is unknown. In animal studies, trofinetide has been shown to increase branching of dendrites and synaptic plasticity signals.[10,11]

About Acadia Pharmaceuticals
Acadia is advancing breakthroughs in neuroscience to elevate life. For more than 25 years we have been working at the forefront of healthcare to bring vital solutions to people who need them most. We developed and commercialized the first and only approved therapies for hallucinations and delusions associated with Parkinson's disease psychosis and for the treatment of Rett syndrome. Our clinical-stage development efforts are focused on treating the negative symptoms of schizophrenia, Alzheimer's disease psychosis and neuropsychiatric symptoms in central nervous system disorders. For more information, visit us at www.acadia.com and follow us on LinkedIn and Twitter.

Forward-Looking Statements
Statements in this press release that are not strictly historical in nature are forward-looking statements. These statements include but are not limited to statements regarding the timing of future events. These statements are only predictions based on current information and expectations and involve a number of risks and uncertainties. Actual events or results may differ materially from those projected in any of such statements due to various factors, including the risks and uncertainties inherent in drug development, approval and commercialization. For a discussion of these and other factors, please refer to Acadia's annual report on Form 10-K for the year ended December 31, 2022, as well as Acadia's subsequent filings with the Securities and Exchange Commission. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. This caution is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. All forward-looking statements are qualified in their entirety by this cautionary statement and Acadia undertakes no obligation to revise or update this press release to reflect events or circumstances after the date hereof, except as required by law.

References
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