



Neuren (NEU) – ASX announcement

7 December 2021

Positive top-line results from pivotal Phase 3 trial in Rett syndrome

Highlights:

- Trofinetide met co-primary efficacy endpoints demonstrating statistically significant improvement over placebo in the Rett Syndrome Behaviour Questionnaire (RSBQ) ($p=0.0175$) and the Clinical Global Impression of Improvement (CGI-I) ($p=0.0030$)
- Trofinetide met key secondary endpoint demonstrating statistically significant improvement over placebo in CSBS-DP-IT–Social ($p=0.0064$), caregiver scale of ability to communicate
- Acadia plans Pre-New Drug Application meeting with the FDA in Q1 2022 and New Drug Application (NDA) around mid-year 2022
- Neuren web conference to be held today at 11.00 am AEDT

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today reported that its partner for trofinetide in North America, Acadia Pharmaceuticals (Nasdaq: ACAD), has 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 announcement by Acadia is attached.

Neuren CEO Jon Pilcher commented: “We are delighted with these robustly positive results and are now eager to see trofinetide progress through the regulatory approval process. We are very grateful to the Rett syndrome community – the patients, their caregivers, study site personnel, physicians and everyone who participated in the Lavender study, as well as in Neuren’s two Phase 2 studies that paved the way.”

The development and commercialisation of trofinetide in North America is fully funded by Acadia and Neuren is eligible to 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 New Drug Application for trofinetide.

Neuren would earn revenue over 2022 and 2023 for Rett syndrome in the US alone of A\$111 million plus double-digit percentage royalties on net sales if a New Drug Application is approved by the FDA and trofinetide is launched in the US. This assumes a USD/AUD exchange rate of 0.75 and that Neuren receives US\$33 million as its share of the market value of a Rare Pediatric



Disease Priority Review Voucher awarded on approval of a New Drug Application. Neuren retains all rights to trofinetide in countries outside North America and has free and full access to all data from the US development program. Neuren expects to engage commercial partners for Europe and Asia.

Neuren will host a web conference today at 11.00 am AEDT, for which the registration link is shown below.

Investor Zoom Webinar 11:00am AEDT today

You are invited to register using this link:

https://zoom.us/webinar/register/WN_DSKXGVZOSO2Bz_GIHX9JLw

Questions may be tabled as you register or during the webinar

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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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.

ASX Listing Rules information

This announcement was authorized to be given to the ASX by the CEO of Neuren Pharmaceuticals Limited, Suite 201, 697 Burke Road, Camberwell, VIC 3124

Acadia Pharmaceuticals Announces Positive Top-line Results from the Pivotal Phase 3 Lavender Trial of Trofinetide in Rett Syndrome

- Trofinetide met co-primary efficacy endpoints demonstrating statistically significant improvement over placebo in the Rett Syndrome Behaviour Questionnaire (RSBQ) ($p=0.0175$) and the Clinical Global Impression of Improvement (CGI-I) ($p=0.0030$)

- Trofinetide met key secondary endpoint demonstrating statistically significant improvement over placebo in CSBS-DP-IT–Social ($p=0.0064$), caregiver scale of ability to communicate

- Pre-New Drug Application meeting with the U.S. FDA planned for the first quarter 2022

- Conference call and webcast to be held today at 4:30 p.m. Eastern Time

SAN DIEGO--([BUSINESS WIRE](#))-- Acadia Pharmaceuticals Inc. (Nasdaq: ACAD) today 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).

“These are encouraging results for patients and families affected by Rett syndrome. Patients reported improvements in core symptoms, like being able to respond to a choice when asked by their parents, or experiencing more freedom from the repetitive hand movements that create obstacles in other areas of their lives,” 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 Lavender study investigator. “The positive Lavender study results support a potential treatment for Rett syndrome and represent an important step forward in addressing this rare and serious neurological disease.”

Study treatment discontinuation rates related to treatment emergent adverse events (TEAEs) were 17.2% in the trofinetide group as compared to 2.1% in the placebo group. The most common adverse events were diarrhea (80.6% with trofinetide vs. 19.1% with placebo), of which 97.3% in the trofinetide arm were characterized as mild-to-moderate, and vomiting (26.9% with trofinetide vs. 9.6% with placebo), of which 96% in the trofinetide arm were characterized as mild-to-moderate. Serious adverse events were observed in 3.2% of study participants in both the trofinetide and placebo groups. Patients completing the Lavender study had the opportunity to continue to receive trofinetide in the open-label Lilac and Lilac-2 extension studies. More than 95% of participants who completed the Lavender study elected to roll-over to the Lilac open-label extension study. The results from this study will be submitted for presentation at upcoming medical meetings.

“The consistent efficacy across primary and key secondary endpoints in the Lavender study demonstrates the potential of trofinetide to treat Rett syndrome,” said Kathie Bishop, Ph.D., Acadia’s Senior Vice President, Chief Scientific Officer and Head of Rare Disease. “We want to thank the patients, their caregivers, study site personnel, physicians and everyone who participated in the Lavender study for their contribution to making this milestone a reality. We look forward to continuing this important work and potentially delivering an FDA-approved treatment for this rare and devastating disease.”

Acadia is preparing for a pre-NDA meeting with the U.S. Food and Drug Administration (FDA) in the first quarter of 2022 and plans to submit a New Drug Application (NDA) around mid-year 2022. Trofinetide has been granted Fast Track Status and Orphan Drug Designation for Rett syndrome. Trofinetide has also been granted Rare Pediatric Disease (RPD) designation by the FDA. An NDA with Orphan Drug Designation is eligible for priority review. With an

RPD NDA we would expect to be awarded a Priority Review Voucher if approved, subject to final determination by the FDA.

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

Conference Call and Webcast Information

Acadia will discuss top-line results from its Lavender study of trofinetide for the treatment of Rett syndrome via conference call and webcast today at 4:30 p.m. Eastern Time. The conference call can be accessed by dialing 855-638-4820 for participants in the U.S. or Canada and 443-877-4067 for international callers (reference passcode 7989366). A telephone replay of the conference call may be accessed through December 20, 2021 by dialing 855-859-2056 for callers in the U.S. or Canada and 404-537-3406 for international callers (reference passcode 7989366). The conference call will also be webcast live on Acadia's website, www.acadia-pharm.com, in the investors section and archived until January 3, 2022.

About Lavender™

The Lavender study was a Phase 3, 12-week, double-blind, randomized, placebo-controlled study of trofinetide in 187 girls and young women aged 5-20 years with Rett syndrome, designed to evaluate its efficacy and safety. The co-primary endpoints of Lavender included both a caregiver (Rett Syndrome Behaviour Questionnaire [RSBQ]) and physician (Clinical Global Impression–Improvement [CGI-I]) assessment. The key secondary endpoint was also a caregiver assessment designed to evaluate communication skills, the Communication and Symbolic Behavior Scales Developmental Profile™ InfantToddler Checklist – Social Composite Score (CSBS-DP- IT–Social).

About Rett Syndrome

Rett syndrome is a rare, debilitating neurological disorder that occurs primarily in females following apparently normal development for the first six months of life. Rett syndrome is often misdiagnosed as autism, cerebral palsy, or non-specific developmental delay. Rett syndrome is caused by mutations on the X chromosome on a gene called *MECP2*. There are more than 200 different mutations found on the *MECP2* gene that interfere with its ability to generate a normal gene product.

Rett syndrome occurs worldwide in approximately one of every 10,000 to 15,000 female births and in the United States impacts 6,000 to 9,000 patients. Rett syndrome causes problems in brain function that are responsible for cognitive, sensory, emotional, motor and autonomic function. Typically, with symptoms presenting between six to 18 months of age, patients experience a period of rapid decline with loss of purposeful hand use (fine motor skills), development of hand stereotypies, absent or impaired mobility (gross motor skills), loss of communication skills (including eye contact) and inability to independently conduct activities of daily living. Symptoms also include seizures, disorganized breathing patterns, an abnormal side-to-side curvature of the spine (scoliosis), and sleep disturbances. Currently, there are no FDA-approved medicines for the treatment of Rett syndrome.

About Trofinetide

Trofinetide is an investigational drug. It is a novel synthetic analog of the aminoterminal tripeptide of IGF-1 designed to treat the core symptoms of Rett syndrome by potentially reducing neuroinflammation and supporting synaptic function. Trofinetide is thought to stimulate synaptic maturation and overcome the synaptic and neuronal immaturities that are characteristic of Rett syndrome pathophysiology. In the central nervous system, IGF-1 is produced by both of the major types of brain cells – neurons and glia. IGF-1 in the brain is critical for both normal development and for response to injury and disease. Trofinetide has been shown to inhibit the production of inflammatory cytokines, inhibit the overactivation of microglia and astrocytes, and increase the amount of available IGF-1 that can bind to IGF-1 receptors.

Trofinetide has been granted Fast Track Status and Orphan Drug Designation for Rett syndrome. Trofinetide has also been granted Rare Pediatric Disease (RPD) designation by the FDA. Upon FDA approval of a product with RPD designation, the sponsor can receive a Priority Review Voucher, which can be used to obtain FDA review of a New Drug Application for another product in an expedited period of six months.

About Acadia Pharmaceuticals

Acadia is trailblazing 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 therapy for hallucinations and delusions associated with Parkinson's disease psychosis. Our late-stage development efforts are focused on dementia-related psychosis, negative symptoms of schizophrenia and Rett syndrome, and in early-stage clinical research we are exploring novel approaches to pain management, and cognition and neuropsychiatric symptoms in central nervous system disorders. For more information, visit us at www.acadia-pharm.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, 2020 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.

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