

## Neuren's NNZ-2566 successful in demonstrating clinical benefit in Rett syndrome Phase 2 trial

### Highlights:

- Achieved primary endpoint - both dose levels of NNZ-2566 were well tolerated after 28 days of treatment and no safety concerns were identified
- Higher dose (70mg/kg twice daily) exceeded the pre-specified criteria for improvement in core efficacy measures compared with placebo
- The clinical benefit in the trial encompassed core symptoms of Rett syndrome and was observed in both clinician and caregiver assessments
- Meeting with FDA expected in Q1 2015 to discuss further development in Rett syndrome
- Results will enable applications for both Orphan Drug and Breakthrough Therapy designation

**Melbourne, Australia, 12 November 2014:** Neuren Pharmaceuticals (ASX: NEU) today announced top-line results from its Phase 2 clinical trial in Rett syndrome, which successfully demonstrated clinical benefit from treatment with NNZ-2566. Neuren intends to submit applications to the US Food and Drug Administration (FDA) for both Orphan Drug and Breakthrough Therapy designation. Neuren expects to meet with the FDA in the first quarter of 2015 to discuss the trial results and the requirements for the further development of NNZ-2566 in Rett syndrome.

There are currently no approved medicines for the treatment of Rett syndrome, which is a severe neurological disorder caused by mutations of the *MECP2* gene on the X chromosome. The disorder has an onset in early childhood and is often progressive into adolescence and adulthood. Neuren's trial was conducted at Baylor College of Medicine (Daniel Glaze MD and Jeffrey Neul MD), University of Alabama at Birmingham (Alan Percy MD) and Gillette Children's Specialty Healthcare (Tim Feyma MD and Art Beisang MD). This was the first multi-site, sponsor-led clinical trial in Rett syndrome and was the first trial in an adolescent and adult population.

Walter Kaufmann MD, Professor of Neurology at Harvard Medical School and Director of the Rett Syndrome Program at the Boston Children's Hospital, who was not involved in the trial, commented: "The outcome of this trial is very promising in terms of both safety and clinical improvement. It was a challenging study since the older age of the cohort and the short duration of the trial made it less likely to show a positive effect. It opens not only the possibility of successful treatment of adults with Rett syndrome, but also of early interventions modifying the course of the disease."

Alan Percy MD, Professor of Pediatric Neurology at the University of Alabama was one of the trial investigators. He commented: "The results of this trial suggest a very promising proof of concept as we continue on the pathway to develop a disease-altering treatment for girls and women with Rett syndrome. Not only was this short-term trial managed successfully, but also the data analyses were conducted in a very robust fashion."

The trial was supported by the International Rett Syndrome Foundation (IRSF). Steven Kaminsky PhD, IRSF Chief Science Officer, commented: “These are exciting times for Rett syndrome and this trial firmly sets our rudder in the water for the near future. The results will enable engagement with the FDA on the further development of NNZ-2566. This is what we, as the Rett community, have been hoping for.”

53 subjects aged 16 to 45 years completed the double-blind placebo-controlled trial. Two different dose levels of NNZ-2566 were tested: 35mg /kg twice per day and 70mg/kg twice per day. The dosage form was a strawberry flavoured liquid that could be taken orally.

The primary endpoint for the trial was to evaluate the safety and tolerability of each of the two dose levels of NNZ-2566 as compared to placebo. The trial was also enriched with a number of outcome measures that provided insight into efficacy. These included 6 core measures in 4 efficacy domains. The analysis plan was pre-specified and submitted to the FDA before the data was unblinded. The analysis compared clinical responses in the core measures for each subject individually, as well as the mean clinical responses for each treatment group.

Evidence of clinical benefit in the group-level analysis required improvement in at least 2 core outcome measures from 2 different efficacy domains, with no clinically significant worsening in all other core endpoints. This requirement was exceeded at day 26 in the higher dose (70mg/kg) group, with 3 measures from 3 different efficacy domains achieving the target: the Motor-Behavior Assessment Change Index, the Clinical Global Impression of Improvement and the Caregiver Top 3 Concerns. The pre-specified criterion of no clinically significant worsening in the remaining 3 core endpoints was also met.

Additionally, for the 70mg/kg dose group the pre-specified criterion of benefit was achieved in the subject-level efficacy analysis, in which the changes in 6 core outcome measures for each subject were combined in a subject-specific efficacy score and the mean efficacy scores were then compared for NNZ-2566 and placebo.

The probability of observing this combined degree of clinical benefit both in the group-level and subject-level analyses and no clinically significant worsening in any endpoint purely by chance (the “false-positive” rate) was determined as 2.3% ( $p=0.023$ ) by permutation testing. In the permutation testing, randomly simulated allocations of patients to NNZ-2566 and placebo were repeated 1000 times and positive outcomes in the data were counted. The statistical approach used in the analysis of the trial results, including permutation testing, has been published in a peer-reviewed journal and used in previous trials in other therapeutic areas, including for the development of a product recently granted Breakthrough Therapy designation by the FDA.

The lower dose level (35mg/kg twice daily) exhibited improvement in a number of core outcome measures, however the magnitude of improvement did not meet the targets pre-specified in the analysis plan. Both dose levels showed trends of increasing effect with the duration of treatment.

Neuren intends to publish and present full analyses of results from the trial in the first half of 2015.

Neuren Executive Chairman, Richard Treagus commented: “We are very grateful to the patients and families affected by Rett syndrome, as well as the support provided by IRSF, that have made this groundbreaking clinical trial possible. The trial results have exceeded our expectations and we look forward to discussing with the FDA the remaining requirements to develop NNZ-2566 for the treatment of Rett syndrome.”

### **About Rett syndrome**

Rett syndrome is a post-natal neurological disorder that occurs almost exclusively in females following apparently normal development for the first six months of life. Typically, between 6 to 18 months of age, patients experience a period of rapid clinical decline that stabilizes later in life. 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. Rett syndrome strikes all racial and ethnic groups and occurs worldwide in approximately 1 in every 10,000 live female births. There are approximately 20,000 females with Rett syndrome in the United States and more than 50,000 worldwide.

The young women enrolled in Neuren’s trial were in the late stage of the disease which is typically characterized by an inability to speak, walk and use one’s hands. Additional signs and symptoms in young women with Rett syndrome include autonomic dysfunction (which can affect the rate and rhythm of the heart), breathing abnormalities, seizures, abnormal curvature of the spine, irritability, unusual behaviors such as prolonged bouts of crying and screaming, and muscle rigidity or spasticity. On the whole, older individuals with Rett syndrome tend to have more severe symptoms and a greater degree of overall debilitation relative to children with this disorder.

### **About NNZ-2566**

NNZ-2566 is a synthetic analogue of a naturally occurring neurotrophic peptide derived from IGF-1, a growth factor produced by brain cells. In animal models, NNZ-2566 exhibits a wide range of important effects including inhibiting neuroinflammation, normalizing the role of microglia and correcting deficits in synaptic function. NNZ-2566 is being developed both in intravenous and oral formulations for a range of acute and chronic conditions. The intravenous form of NNZ-2566 is presently in a Phase 2 clinical trial in patients with moderate to severe traumatic brain injury. The oral form of NNZ-2566 is in Phase 2 development in Rett syndrome, Fragile X syndrome and mild traumatic brain injury (concussion). Three programs have received Fast Track designation from the US FDA and the Fragile X syndrome program has also received Orphan Drug designation.

### **About Neuren**

Neuren Pharmaceuticals Limited (Neuren) is a biopharmaceutical company developing new therapies for brain injury, neurodevelopmental and neurodegenerative disorders. The novel drugs target chronic conditions as well as acute neurological injuries. Neuren presently has a clinical stage molecule, NNZ-2566 in Phase 2 clinical trials as well as NNZ-2591 in pre-clinical development.

*Forward-looking Statements*

*This ASX-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.*

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**Investor conference call, Wednesday 12 November 2014 at noon (AEDT)**

Neuren will host a conference call to discuss this announcement, which can be accessed using the dial-in details below and conference identification number 558514:

Australia 1800 558 698 (or +61 2 9007 3187)

New Zealand 0800 453 055

United States 1855 8811 339

Canada 1855 8811 339

Hong Kong 800 966 806

United Kingdom 0800 051 8245

Singapore 800 101 2785

China 4001 200 659

India 0008 0010 08443

Japan 0053 116 1281

Other countries +61 2 9007 3187

## APPENDIX

### Summary of trial

Trial type	Double-blind, placebo-controlled dose escalation Phase 2 trial of two dose levels of NNZ-2566: 35 mg per kg of body weight twice daily and 70 mg per kg of body weight twice daily
Trial sites	Three hospitals in the United States: Baylor College of Medicine, University of Alabama at Birmingham and Gillette Children's Specialty Healthcare
Trial subjects	56 female subjects aged 16 to 45 years were randomized to trial medication, with 53 subjects completing the trial
Treatment groups	Cohort 0 (9 patients): 35 mg/kg bid vs. placebo, 14 days of treatment, post-treatment follow-up at Day 28
	Cohort 1 (18 subjects): 35 mg/kg bid vs. placebo, 28 days of treatment, post-treatment follow up at Day 40
	Cohort 2 (29 patients): 70 mg/kg bid vs. placebo, 28 days of treatment, post-treatment follow up at Day 40
Primary endpoint	Evaluation of safety and tolerability of NNZ-2566 compared with placebo

### Safety and tolerability results

Safety data measurements included:

- Physical Examination
- Adverse events
- Discontinuations of treatment due to adverse events
- Complete blood count, serum chemistries, urinalysis
- Fundoscopy, tonsil size, vital signs
- ECG

Dose-dependent and time-dependent patterns were not observed in the adverse events reported during the trial.

No consistent dose-dependent trends in observations or laboratory measurements were detected.

Four serious adverse events were reported, all of which were deemed unrelated to treatment and two of which occurred after the treatment period had completed. One subject discontinued treatment following two serious adverse events, although the events were deemed unrelated to treatment.

### Core efficacy outcome measure results

The six core efficacy outcome measures were classified into four efficacy domains:

1) Rating scales specific to Rett syndrome signs and symptoms, completed by the clinician - Motor Behavior Assessment Change Index and Clinical Severity Scale Change Index;

2) Global assessments keyed to the specific signs and symptoms of Rett syndrome, completed by the clinician - Clinical Global Impression of Improvement;

3) Rating scales keyed to specific Rett syndrome signs and symptoms - Top 3 Concerns - and general rating scales - Aberrant Behavior Checklist total score - completed by caregivers;

4) Physiological measures – Modified Apnea Index.

**Summary of core efficacy outcome measures results for 70mg/kg dose in Modified Intent to Treat Population**

	<b>Results against pre-specified improvement criteria compared with placebo and against no worsening criteria</b>
<b>Group-level analysis (comparison of mean changes):</b>	
Motor-Behavior Assessment Change Index	Met improvement criteria
Clinical Severity Scale Change Index	Met no worsening criteria
Clinical Global Impression of Improvement	Met improvement criteria
Caregiver Top 3 Concerns	Met improvement criteria
Aberrant Behavior Checklist total score	Met no worsening criteria
Modified Apnea Index	Met no worsening criteria
<b>Subject-level analysis</b>	Met improvement criteria

**Further information on the outcome measures that exceeded target**

The **Rett syndrome Motor-Behavior Assessment Scale (MBA)** is a clinician completed scale evaluating the severity of core Rett symptoms. The MBA consists of 37 items grouped in three subscales: Behavior/Social, Orofacial/Respiratory, and Motor/Physical. Severity of symptoms is rated on a Likert scale of 0-4 based on current functioning. A total score is also calculated with a maximum score of 148. Higher scores are associated with greater severity.

The MBA Change Index is a scoring rubric that focuses on the subset of Rett syndrome phenotypic items that hold the prospect of manifesting change during relatively short courses of treatment (e.g., one month) as identified by experts in the clinical management of Rett syndrome. The MBA has undergone a preliminary assessment of validity for use as an instrument for baseline assessment and for the assessment of change during treatment studies. The MBA Change Index is comprised of a subset of 17 items including regression of communication skills, poor eye/social contact, irritability/crying/tantrums, does not respond to spoken words, aggressive behavior, seizures, speech disturbance, bruxism/grinding teeth, breath holding, hyperventilation, air-saliva expulsion/drooling, hand clumsiness, stereotypic hand

washing, clapping, stroking, kneading-when unrestrained, truncal rocking/shifting weight-voluntary, dystonia, dyskinesias-Chorea/athetosis or oromotor, and vasomotor disturbance.

The MBA Change Index is a sum of these 17 items, each ranging from 0-4, therefore the sum may range from 0 to 68. The direction of benefit is that a lower score is better.

**The Clinical Global Impression of Improvement scale (CGI-I)** is a 7-point scale that requires the clinician to rate how much the patient's illness has improved or worsened relative to a baseline state. A seven point scale is used from 1 = very much improved, 2 = much improved, 3 = minimally improved, 4 = no change, 5 = minimally worse, 6 = much worse, 7 = very much worse.

Scoring on the CGI-I was accomplished using a standardized scoring rubric that was specific to the clinical features of Rett syndrome, as identified by the Rett Syndrome Natural History Study. Clinicians administering the CGI participated in regularly scheduled scoring calibration sessions to ensure interpretation of the scoring rubric was normalized amongst the raters.

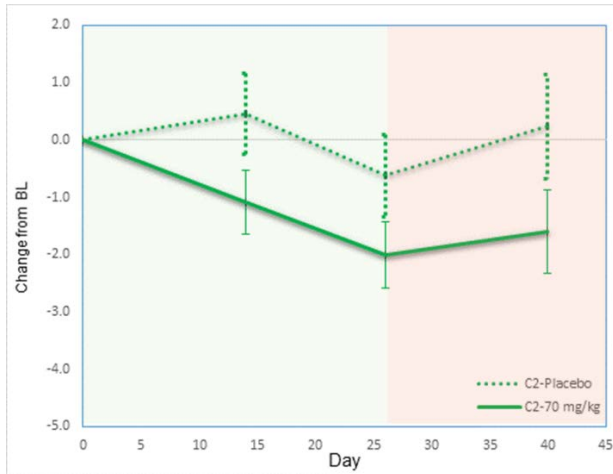
The **Caregiver Top Three Concerns** is a caregiver-completed Visual Analog Scale. This type of outcome measure has been validated in clinical trials involving individuals with neurodevelopmental disorders. In the present study, caregivers identify three priority concerns related to the subject's Rett syndrome which they would like to see change as a result of treatment. The measure is directed towards signs and symptoms in an individualized per-patient fashion. The severity of these concerns is rated by the caregiver at baseline and is evaluated again at subsequent follow-up visits. The current level of severity of each concern is rated along the Visual Analogue Scale. The anchors range from a concern that is "completely absent", and thus not severe, to "very severe", which includes concerns at the highest range of severity.

**Charts of change from baseline for 70mg/kg dose (solid line) versus placebo (dotted line)**

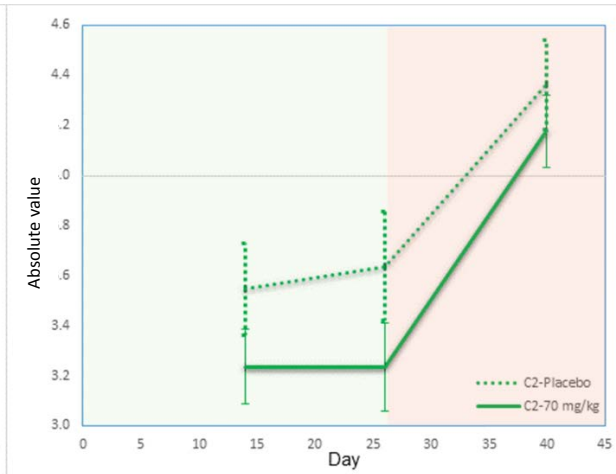
In the charts below, the two different shaded areas indicate the treatment period and the period post-treatment. In all charts except for the Individual Subject-Level Efficacy Score, a decrease indicates increasing benefit.

**Measures that met improvement criteria compared with placebo:**

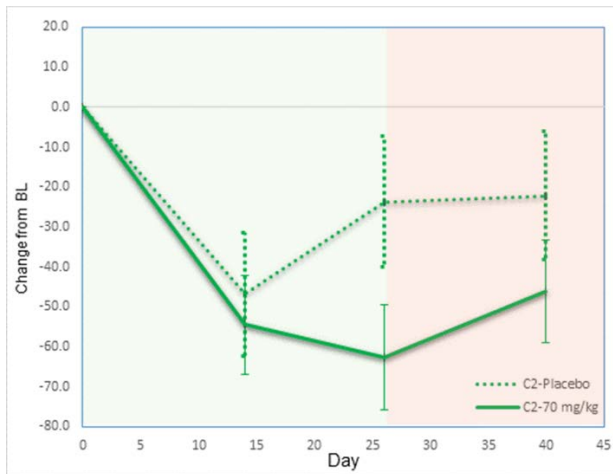
**Motor Behavior Assessment Change Index**



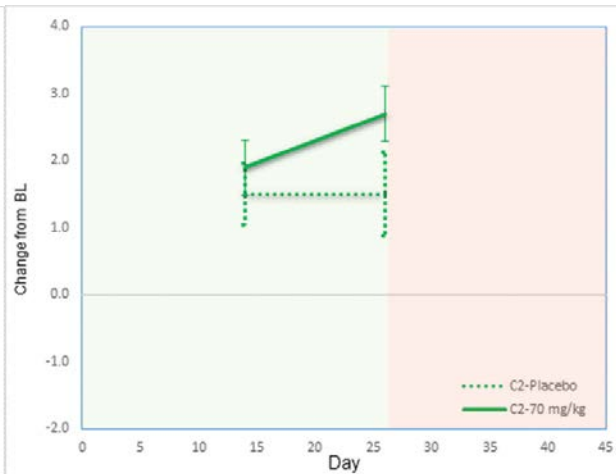
**Clinical Global Impression of Improvement**



**Caregiver Top 3 Concerns**



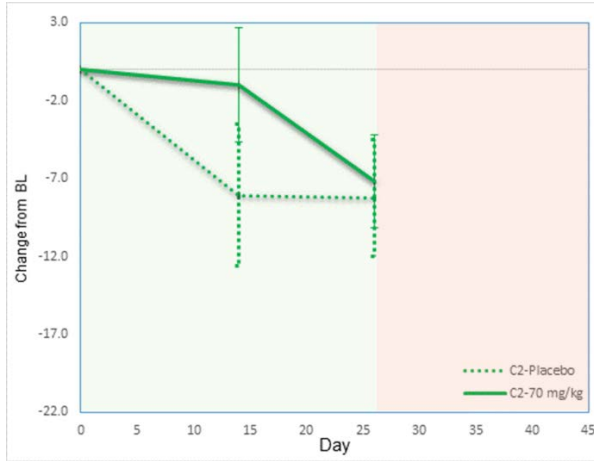
**Mean Subject-Level Efficacy Score**



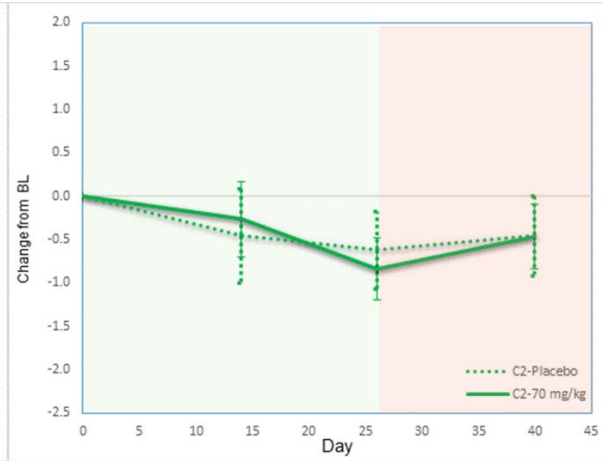


Measures that did not meet improvement criteria compared with placebo, but met pre-specified criteria for no clinically significant worsening:

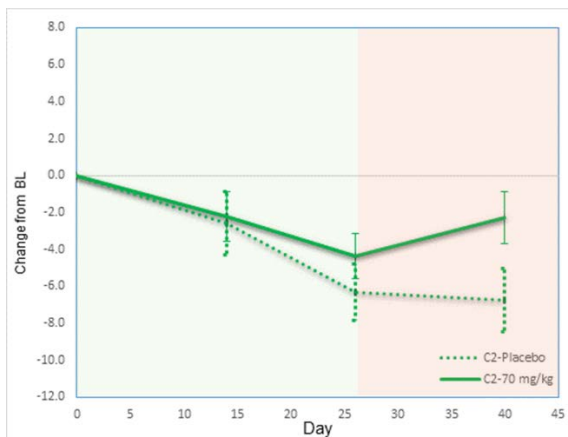
### Aberrant Behavior Checklist



### Clinical Severity Scale Change Index



### Modified Apnea Index



### About Orphan Drug and Breakthrough Therapy

Orphan drug designation is a special status that the FDA may grant to a drug to treat a rare disease or condition. Orphan drug designation qualifies the sponsor of the drug for seven years of marketing exclusivity following approval as well as various development incentives including waiver of the prescription drug user fee for a marketing application.

Breakthrough therapy designation is intended to streamline drug development and review of innovative new medicines that address unmet medical needs for serious diseases or conditions. The criteria for breakthrough therapy require preliminary clinical evidence indicating that the drug may demonstrate a substantial improvement over existing therapies on at least one clinically significant endpoint.

Breakthrough therapy designation conveys all of the fast track program features, as well as a commitment that FDA will work closely with the sponsor on an efficient drug development program.