

## Neuren's trofinetide successful in proof of concept Phase 2 clinical trial in Fragile X syndrome

### Highlights:

- **Positive top-line results provide a strong rationale to move forward with development of trofinetide for Fragile X syndrome**
- **Primary endpoint achieved - both dose levels were well tolerated and no safety concerns were identified**
- **Higher dose (70 mg/kg twice daily) demonstrated a consistent pattern of clinical improvement, observed in both clinician and caregiver assessments**
- **Improvements across a range of core symptoms of Fragile X syndrome were captured by Fragile X-specific measures as well as by the Aberrant Behavior Checklist (ABC)**
- **Results provide a clear basis to explore a longer duration of treatment, higher doses and potential benefits in younger subjects**
- **Trial results and drug development plan to be discussed with the FDA in early 2016**
- **Beneficial effects of trofinetide have now been observed in two different neurodevelopmental disorders, Fragile X syndrome and Rett syndrome, which is consistent with the known biological actions of trofinetide on brain function**

**Melbourne, Australia, 7 December 2015:** Neuren Pharmaceuticals (ASX: NEU) today announced top-line results from its Phase 2 clinical trial in Fragile X syndrome. The trial has successfully established proof of concept and provides a strong rationale for Neuren to move forward with developing trofinetide for Fragile X syndrome. In this initial small trial with a relatively short treatment period, trofinetide was very well tolerated, with the high dose (70 mg/kg twice daily) demonstrating a consistent pattern of clinical improvement, observed in both clinician and caregiver assessments.

After only 28 days of treatment, improvements were seen across core symptoms of Fragile X syndrome, including higher sensory tolerance, reduced anxiety, better self-regulation and more social engagement. Beneficial effects of trofinetide have now been observed in two different neurodevelopmental disorders, Fragile X syndrome and Rett syndrome. This is consistent with known actions of trofinetide, expected to normalize a number of biological processes in the brain that are impacted by each syndrome.

The effects observed following treatment with the low dose of trofinetide (35 mg/kg twice daily) were less consistent and the magnitude of improvement did not meet pre-specified targets, but there was evidence of a dose response. Given the excellent tolerability profile of trofinetide and the observed dose response profile, there is a clear rationale to study higher doses.

Based on these results and feedback from clinical experts in Fragile X syndrome, Neuren is strongly encouraged to advance to the next step in clinical development. This will likely involve a study in

younger children with Fragile X syndrome and may examine a longer treatment duration with higher doses. This next study will also refine the outcome measures that may be used in a Phase 3 study. Neuren intends to discuss the trial results and drug development plan with the US Food and Drug Administration (FDA) in early 2016.

Randi Hagerman MD, Medical Director of the University of California Davis MIND Institute and Director of the Fragile X Research and Treatment Center, commented: “Trofinetide has a unique mechanism of action very different from any other molecule that has been tested before in Fragile X syndrome. Its derivation from a naturally occurring neurotrophic factor makes it a promising candidate to treat a wide range of the core symptoms of Fragile X syndrome and potentially other neurological disorders. The results of this trial and the clinical improvements that investigators observed are an exciting first step”.

Elizabeth Berry-Kravis MD, PhD, Professor of Pediatrics, Neurology and Biochemistry at Rush University Medical Center, has directed the Fragile X Clinic and Research Program at Rush since 1992. She commented: “This was the first industry-sponsored study to look at a full range of meaningful symptoms using a number of Fragile X-specific outcome measures. The results are very encouraging and fully support moving to the next step in development. The design and analyses were both innovative and appropriate for this proof of concept trial.”

Neuren Executive Chairman, Richard Treagus commented: “We are extremely grateful to the patients and families affected by Fragile X syndrome, as well as the clinical investigators and staff at the trial sites, who have made this very important study possible. These results further underscore the value of trofinetide as a potential treatment for complex neurodevelopmental disorders. We have taken a great deal of encouragement from these results and the expert opinion of our clinical advisers, and I can confirm that Neuren remains fully committed to furthering the development of trofinetide for both Rett syndrome and Fragile X syndrome.”

### **Summary of top-line results**

Neuren’s randomized, double-blind, placebo-controlled, parallel group, fixed dose trial enrolled males aged 12 to 45 years with confirmed Fragile X syndrome at 16 sites in the United States. The trial was overseen by leading clinical experts in Fragile X syndrome. 70 subjects received double-blind randomized treatment in three groups; placebo (25 subjects), 35 mg/kg twice per day (24 subjects) and 70 mg/kg twice per day (21 subjects). The dosage form was a strawberry-flavored liquid that was taken orally.

The primary objective of the trial was to evaluate the safety and tolerability of each of the two dose levels of trofinetide as compared to placebo.

The trial also incorporated a number of secondary and exploratory outcome measures that provided insight into efficacy, including two rating scales developed in consultation with Fragile X syndrome clinical experts. The plan for analyses of the efficacy measures was pre-specified and submitted to the FDA before the data was unblinded.

## Safety and tolerability

Safety data measurements included:

- Adverse events
- Discontinuations of treatment due to adverse events
- Hematology, serum chemistries, urinalysis
- Vital signs
- Fundoscopy, tonsil size
- ECG

No serious adverse events were reported and no subject discontinued due to adverse events during the double-blind treatment period.

Dose-dependent and time-dependent patterns were not observed in the adverse events reported during the trial. In addition, there was no pattern of adverse events evident with initiation or cessation of treatment.

No consistent dose-dependent trends in objective safety assessments or laboratory measurements were detected.

## Core efficacy measures

The following five measures were pre-specified in the statistical analysis plan as core measures for the efficacy analyses:

Core measure	Type of measure
Fragile X Syndrome Rating Scale	Clinician-completed syndrome-specific
Fragile X Domain Specific Concerns	Clinician-completed syndrome-specific
Clinical Global Impression - Improvement Scale (CGI-I)	Clinician-completed syndrome-specific global
Caregiver Top 3 Concerns	Caregiver-completed syndrome-specific
Aberrant Behavior Checklist (ABC) Total Score	Caregiver-completed non-syndrome specific

The Fragile X Syndrome Rating Scale is a rating scale based on studies that have evaluated the natural history of Fragile X syndrome and involved input from clinical experts in Fragile X (Snape et al. 2014). The development of novel Fragile X-specific assessments was a key recommendation from the National Institutes of Health (NIH) Outcomes Initiative (Berry-Kravis et al. 2013).

The Fragile X Domain-Specific Concerns Visual Analog Scale is a clinician-completed scale that uses Visual Analogue Scales to assess domain-specific individualized symptoms that are identified by the clinician as key areas of impairment. Concerns are identified on an individual, per-subject basis in one of six domains related to the subject's Fragile X syndrome: Repetitive Behaviors, Speech and Language, Anxiety, Phobias and Social Withdrawal, Motor Performance, Sensory Over-sensitivity, and Cognition.

The Clinical Global Impression of Improvement scale (CGI-I) is a global clinical assessment that requires the clinician to rate how much the patient’s illness has improved or worsened relative to a baseline state. Scoring on the CGI-I was done using a standardized scoring rubric that was specific to the clinical features of Fragile X syndrome.

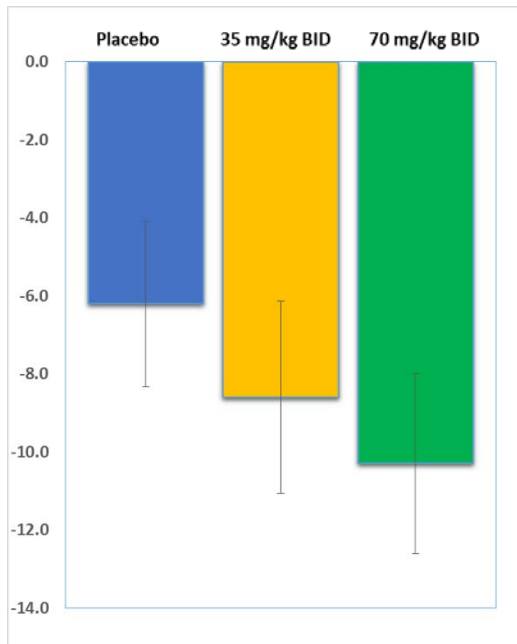
The Caregiver Top Three Concerns is a caregiver-completed Visual Analog Scale that is intended to be syndrome-specific. Caregivers identify three priority concerns related to the subject’s Fragile X syndrome which they would like to see change as a result of treatment.

The Aberrant Behavior Checklist (ABC) (Aman et al., 1985) is a symptom checklist for assessing problem behaviors of children and adults with intellectual disabilities within multiple settings. Its use has been validated in a variety of clinical populations, including in autism spectrum disorder and Fragile X syndrome, and it has been used as a primary and secondary outcome measure in previous multi-site clinical trials in Fragile X syndrome. The scores were analyzed using the Fragile-X specific scoring approach reported in Sansone et al. 2012. Using this scoring rubric, the ABC renders a total score as well as scores on 6 subscales: Irritability, Socially Unresponsive/Lethargic, Stereotypy, Hyperactivity, Inappropriate Speech and Social Avoidance.

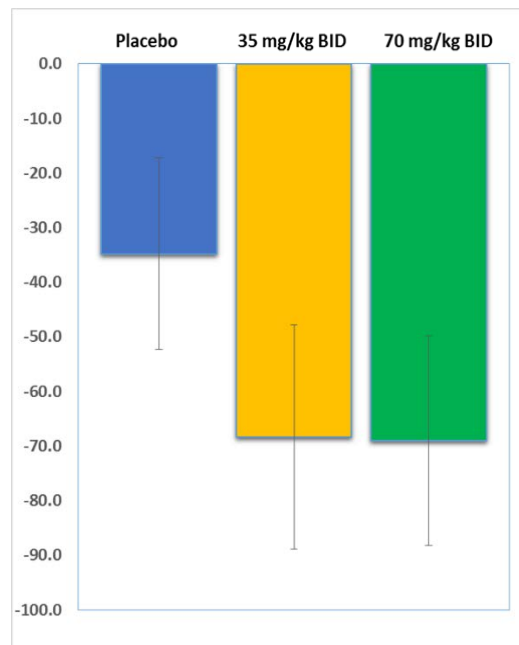
The analyses compared the mean clinical responses in the three treatment groups for each core measure, as well as comparing the collective clinical responses in all the core measures for each subject individually. The individual analysis was designed to confirm that the treatment benefit shown by the group mean responses was broadly evident and not simply due to a few large outlier responses.

The following charts illustrate the clinical responses measured at the end of treatment. The direction of benefit is *downwards* for the five core measures and *upwards* for the individual subject analysis.

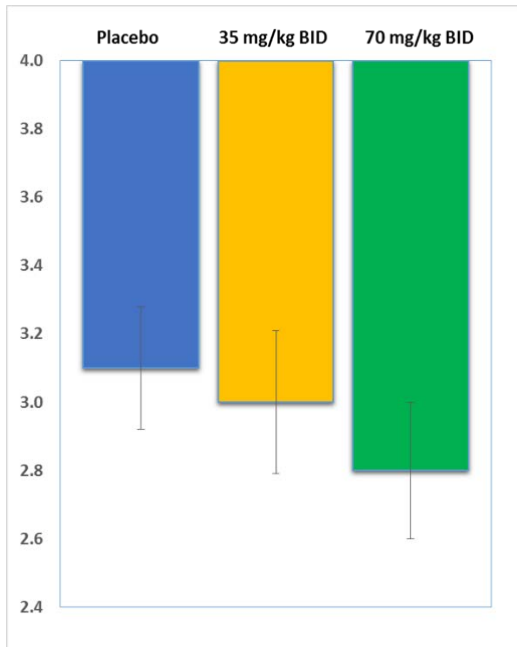
**Fragile X Syndrome Rating Scale**



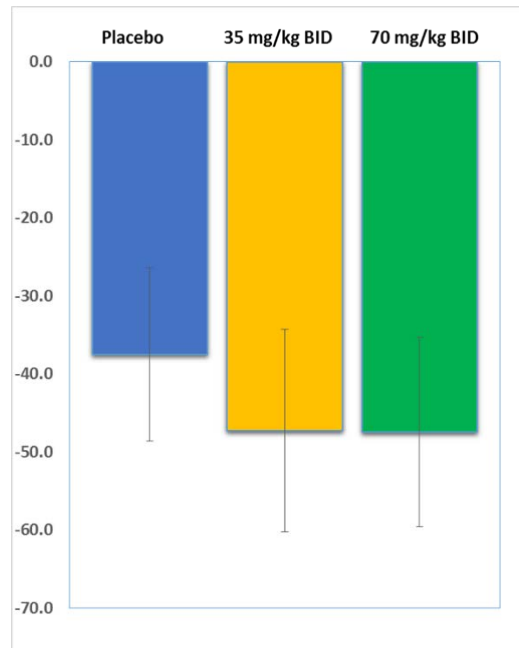
**Fragile X Domain Specific Concerns**



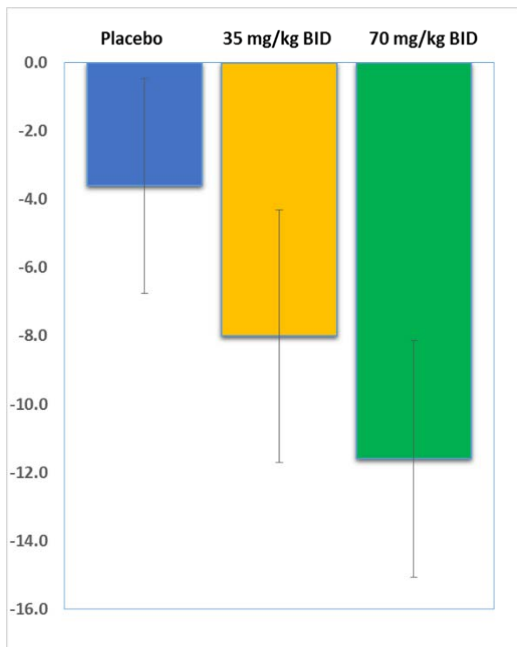
### Clinical Global Impression – Improvement Scale



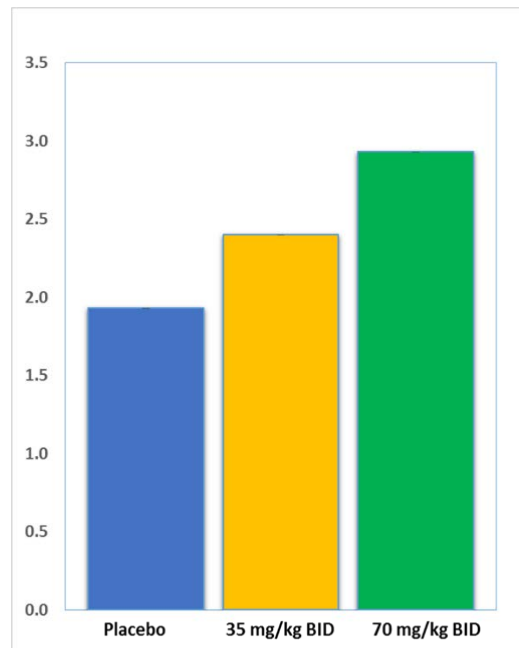
### Caregiver Top 3 Concerns



### Aberrant Behavior Checklist (ABC) Total Score



### Individual Subject Scorecard



The trial design anticipated the potential for placebo response and this was taken into account in the analyses. Following the methodology defined in the pre-specified analyses, the data was subjected to permutation testing in order to estimate the probability that the observed clinical improvement in both the group-level and subject-level analyses was observed purely by chance (the “false-positive” rate). This probability was estimated as 4.5% ( $p=0.045$ ).

## **About Fragile X syndrome**

Fragile X syndrome is the most common inherited cause of intellectual disability and the most common known cause of autism. Fragile X syndrome is due to a single gene defect on the X chromosome that impacts the FMRP protein, which is responsible for regulating the synapses of nerve cells.

Approximately one in 4,000 males and one in 6,000 females are estimated to have the full gene mutation. Generally, males are more severely affected than females, with approximately 50% of the females having features of Fragile X syndrome. Clinically, Fragile X syndrome is characterized by intellectual disability, hyperactivity and attentional problems, autistic symptoms, anxiety, emotional lability and epilepsy. The epilepsy seen in Fragile X syndrome is most commonly present in childhood, but then gradually improves towards adulthood. Physical features such as prominent ears and jaw, and hyper-extensibility of joints are frequently present but are not diagnostic. Currently, there are no medicines approved for the treatment of Fragile X syndrome.

## **About trofinetide**

Trofinetide is a synthetic analogue of a naturally occurring neurotrophic peptide derived from IGF-1, a growth factor produced by brain cells. In animal models, trofinetide exhibits a wide range of important effects including inhibiting neuroinflammation, normalizing the role of microglia and correcting deficits in synaptic function. Trofinetide is being developed both in intravenous and oral formulations for a range of acute and chronic conditions. The intravenous form of trofinetide is presently in a Phase 2 clinical trial in patients with moderate to severe traumatic brain injury. The oral form of trofinetide 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 Rett syndrome and Fragile X syndrome programs have also received Orphan Drug designation in the United States and the European Union.

## **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, trofinetide 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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