



Neuren (NEU) - ASX Announcement

22 March 2017

Neuren's Phase 2 trial of trofinetide demonstrates significant clinical benefit in pediatric Rett syndrome

Melbourne, Australia, 22 March 2017: Neuren Pharmaceuticals (ASX: NEU) today reported top-line results for its Phase 2 clinical trial in girls with Rett syndrome aged 5 to 15. Rett syndrome is a serious and life threatening condition caused by a gene mutation, for which there are currently no approved treatments.

Neuren's trial was a double-blind, randomized, placebo controlled study that tested three doses of trofinetide compared with placebo in 82 subjects. The highest dose of trofinetide achieved statistically significant clinical benefit compared with placebo for each of three syndrome-specific efficacy measures, the Rett Syndrome Behaviour Questionnaire ($p=0.042$), the Clinical Global Impression of Improvement ($p=0.029$) and the Rett Syndrome Domain Specific Concerns ($p=0.025$). These measures included assessments of both clinicians and caregivers. Clinical improvements of 15% to 16% from baseline were observed, which was considered by leading Rett syndrome physicians to be clinically meaningful, particularly in a short duration trial. The improvement increased through to the time that treatment ceased. This suggests that further benefit may be achieved with longer treatment duration.

These results provide strong evidence of biological activity of the high dose across multiple symptom areas, indicating the potential for disease modification rather than simply addressing isolated symptoms. In addition, trofinetide was well tolerated and had a good safety profile in these younger subjects, with no dose-limiting effects observed.

Neuren now intends to discuss with the US Food and Drug Administration (FDA) plans for a pivotal trial commencing in 2018 using the Rett Syndrome Behaviour Questionnaire (RSBQ) as a primary efficacy measure, supported by the Clinical Global Impression of Improvement (CGI-I) as a key secondary efficacy measure. In parallel, as previously reported, Neuren will now move to complete the necessary chronic toxicity studies and manufacturing scale-up.

Walter Kaufmann, MD, Ravenel Boykin Curry Chair of Genetic Therapeutics and Director of the Center for Translational Research at the Greenwood Genetic Center, was an investigator for this trial and was also the original principal investigator for the clinical trial of IGF-1 in children with Rett Syndrome at Boston Children's Hospital. Dr Kaufmann commented:

"The outcome of this trial is very encouraging. Safety, the primary goal, was achieved. As important and with broad implications, there was a clear clinical improvement covering several common symptoms in Rett syndrome, which are known to impair the quality of life of girls affected by the disorder. The variety of improved symptoms suggests that trofinetide is a drug that targets mechanisms underlying the disorder rather than a symptomatic medication. Similar to the previous adult trial, the results are particularly significant because of the relatively short duration of the trial. The impact of the study goes

beyond the suggested efficacy of trofinetide, since it shows the potential of neurobiologically-based drugs for the treatment of Rett syndrome and other neurodevelopmental disorders.”

Alan Percy, MD, Professor of Neurology and Director of Clinical Neuroscience at the Civitan International Research Center & Sparks Clinics, The University of Alabama at Birmingham, was an investigator for this trial and for Neuren’s previous trial in adults and adolescents with Rett syndrome. Dr Percy commented:

“The clear results from this trial of trofinetide in children support and strengthen the promising results that were obtained in the Neuren trial in older individuals with Rett syndrome. I now look forward to the pivotal trial.”

Steve Kaminsky, PhD, Chief Science Officer of Rettsyndrome.org commented:

“These pediatric study results are very exciting. The data suggest that trofinetide is having a positive change on a number of challenges of Rett syndrome. We at Rettsyndrome.org are very proud to have supported this game-changing study, believing that the best is yet to come.”

Background to the Phase 2 trial

The Phase 2 trial was conducted at 12 sites in the United States, led by clinicians experienced in the diagnosis and treatment of Rett syndrome and supported by Rettsyndrome.org. This trial in a younger population built on the results of Neuren’s Phase 2 trial, completed in 2014 and conducted in older subjects aged 16 to 45 with Rett syndrome, which showed consistent trends of clinical benefit. The current trial design incorporated a number of refinements and additional features:

- Two new measures were included as core efficacy measures – the RSBQ and the Rett Syndrome Domain Specific Concerns Visual Analog Scale (RTT-DSC). The RSBQ has previously been used as a key efficacy measure in two clinical trials in younger girls with Rett syndrome, which were conducted at the Boston Children’s Hospital, with data on the first trial published in 2014.
- The excellent safety and tolerability profile enabled the highest dose group to be increased from 70mg/kg BID to 200mg/kg BID.
- The duration of treatment was increased from 4 weeks to 6 weeks. Notwithstanding the increase, this remained a trial of short duration for a disease-modifying agent in a syndrome with severe and complex features.
- All subjects completed a single blind period of 14 days on placebo prior to commencement of randomized treatment. Efficacy measurements were taken on day 14, during randomized treatment on days 28, 42 and 54 as well as post-cessation of treatment on day 66. Changes in efficacy measurements were calculated compared with the measurements taken on day 14, at the end of the placebo run-in.

Key outcomes from the trial

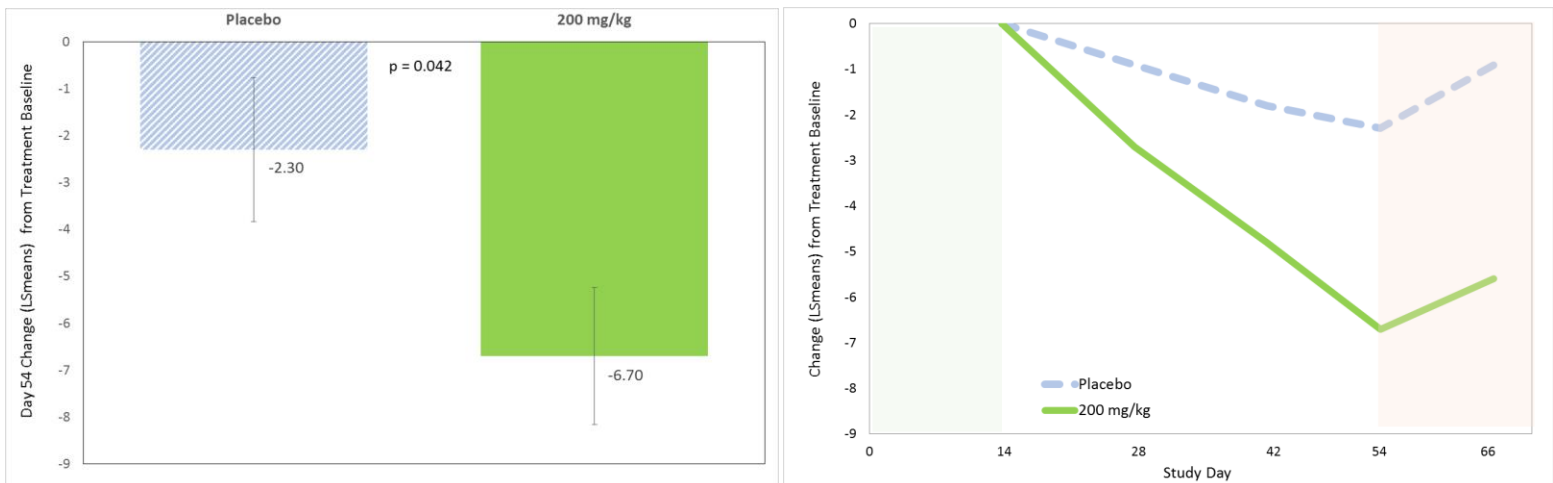
82 subjects were randomized into the following groups: 24 to placebo BID, 27 to 200mg/kg BID, 16 to 100mg/kg BID and 15 to 50mg/kg BID. The mean and median age, weight and BMI did not differ significantly between the four groups.

The prespecified efficacy analyses prioritized 5 core syndrome-specific measures:

- The *RSBQ*, a rating scale in which the subject's caregiver rates the frequency of symptoms.
- The *CGI-I*, in which the clinician rates how much the subject's overall illness has improved or worsened, relative to baseline.
- The *RTT-DSC*, in which the clinician assesses on a visual analog scale the severity of concerns identified for each subject on an individual basis.
- The *Motor Behavior Assessment (MBA)*, a rating scale in which the clinician rates the subject's current level of function.
- The *Caregiver Top 3 Concerns (Top 3)*, in which the subject's caregiver assesses on a visual analog scale the severity of concerns identified for each subject on an individual basis.

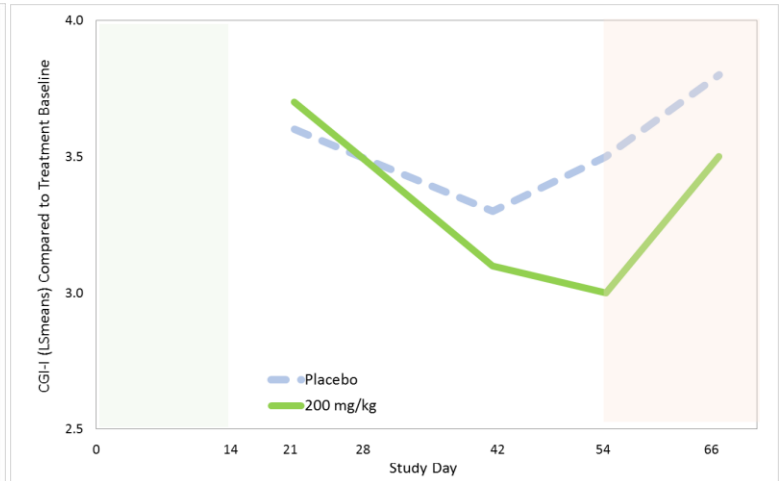
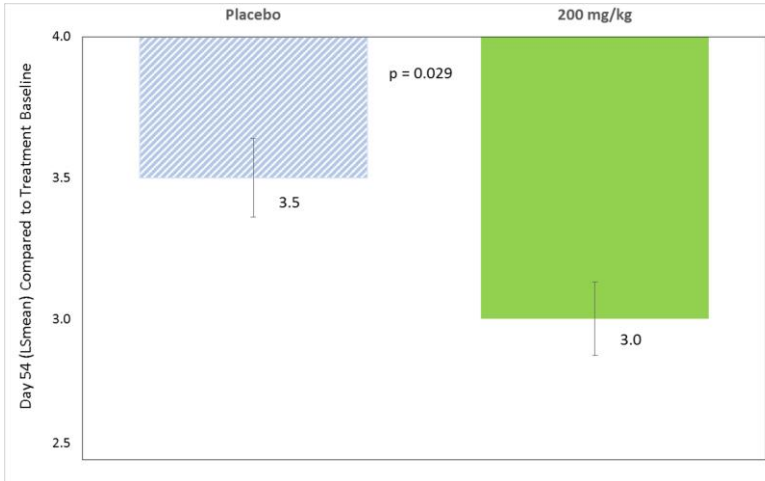
The first three of these measures each demonstrated improvement for the highest dose, compared with placebo, which was both statistically significant and clinically meaningful. The improvement increased throughout the course of treatment right through to the time that treatment ceased. This suggests that further benefit may be achieved with even longer treatment duration. Some regression of benefit was observed after treatment ceased. These results are illustrated in the following charts, in which a downward movement represents an improvement from day 14 baseline:

RSBQ



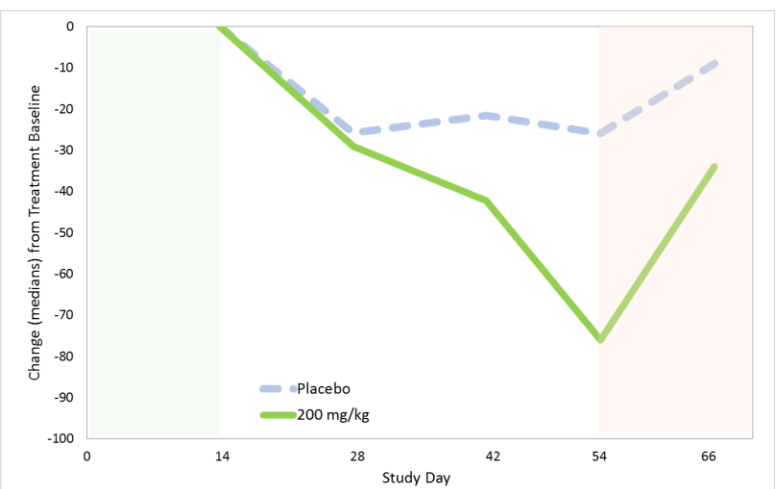
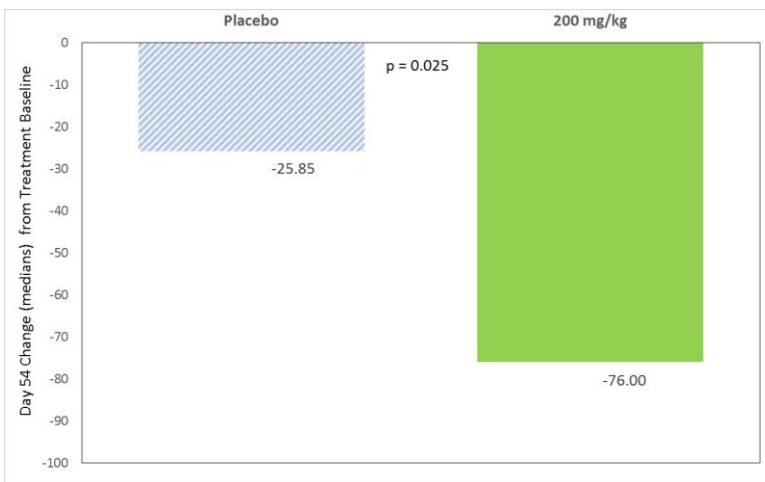
The mean (LSmeans) improvements at day 54 for the 200mg/kg and placebo groups were, respectively, 16% and 6% of the day 14 baseline.

CGI-I



22% of subjects in the 200mg/kg dose group received a CGI-I score of 2 (“much improved”) compared with 4% of subjects in the placebo group.

RTT-DSC



The group analysis of RTT-DSC was carried out using the Exact Median Test rather than the Least-squares Means that were calculated for the other four core endpoints. This was because the Statistical Analysis Plan prespecified that if the data for a measure did not meet statistical assumptions of a general linear model, then a non-parametric analysis method would be used. Standard error limits are not applicable in the Exact Median Test and consequently are not presented on the bar chart.

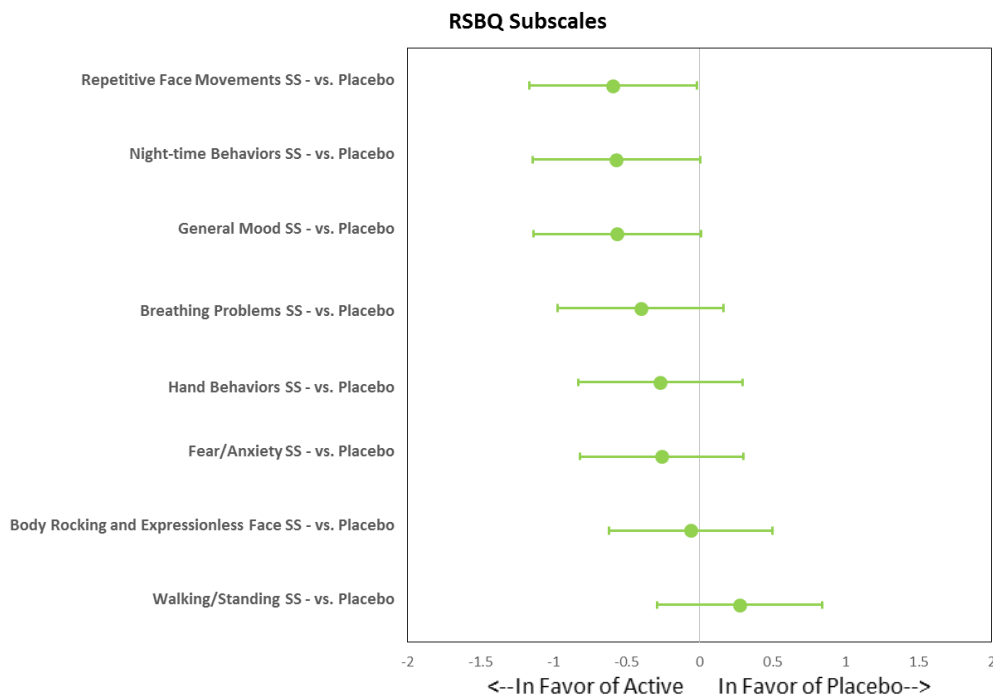
The median improvements at day 54 for the 200mg/kg and placebo groups were, respectively, 15% and 5% of the day 14 baseline.

Other core efficacy measures

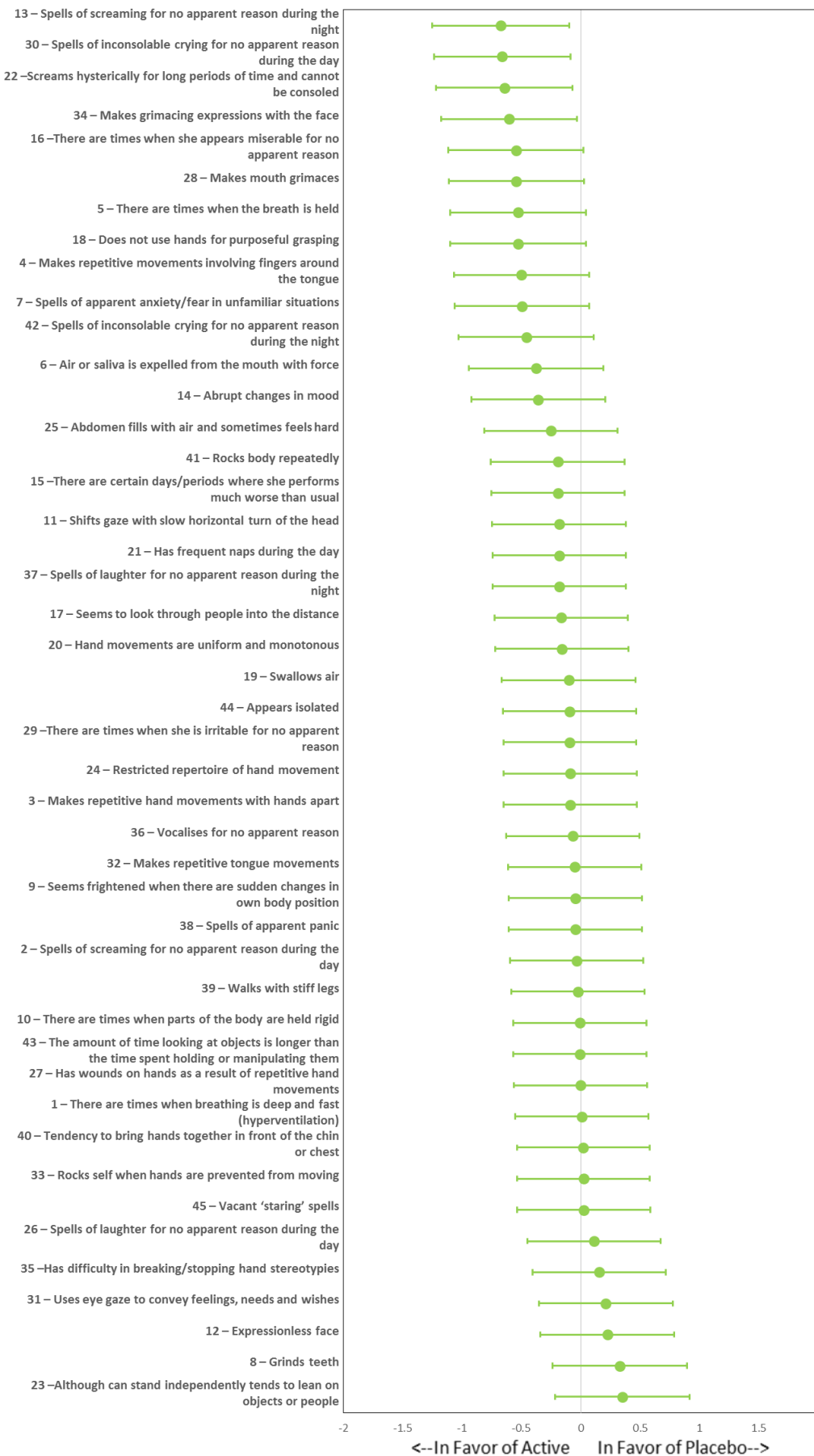
The other two core efficacy measures, MBA and Top 3, both showed improvement from baseline in the 200mg/kg group that was larger than placebo (MBA: -2.9 versus -2.6 and Top 3: -18.54 versus -12.52), but the differences were not statistically significant or clinically meaningful. As an efficacy measure the MBA did not appear to be sensitive to change in this younger population and therefore Neuren intends to use the RSBQ as the primary efficacy measure in a future pivotal trial. There is evidence that the MBA may be more appropriate as a measure for older age groups. The MBA instrument was designed and has mainly been used as a measure for long-term observational studies rather than to measure change in short-term clinical trials.

RSBQ - further information and detailed results

The RSBQ is a well-validated instrument that has been used in other Rett syndrome clinical trials. It has been correlated with quality of life outcomes and has been characterized and validated in peer-reviewed publications. The RSBQ is designed to measure the frequency of 45 neurobehavioral items, reflecting the severity of the syndrome. The items are rated from 0 to 2, with a score of zero indicating the item is not true for an individual; 1 meaning the item is somewhat or sometimes true in the individual; and 2 meaning that the item is often or very true in the individual. The items are organized into eight subscales: General Mood, Breathing Problems, Hand Behaviors, Repetitive Face Movements, Body Rocking and Expressionless Face, Night-time Behaviors, Fear/Anxiety, and Walking/Standing. In this trial the high dose of trofinetide showed a positive effect on many of the items and across these subscales, as illustrated in the following charts of the Cohen's D effect size for each subscale and each item:



RSBQ Individual Items Ranked 1 - 45



Dr Kaufmann commented on the RSBQ: *“The recent improvements in the care of individuals with Rett syndrome has made evident that affected girls and women display a variety of neurobehavioral problems, and that these symptoms affect their quality of life. At present, the Rett Syndrome Behaviour Questionnaire (RSBQ), is the only available instrument for evaluating the wide range of abnormal behaviors in Rett syndrome. An open label trial of IGF-1 demonstrated mild improvements in anxiety and mood, as measured by the RSBQ and another behavior rating scale, supporting use of the RSBQ for detecting improvements in clinical trials.”*

Lower dose groups and pharmacokinetics

The two lower dose groups of 50mg/kg BID and 100mg/kg BID did not demonstrate evidence of efficacy. However, two important observations were confirmed by pharmacokinetic analyses:

- The level of efficacy measured by each of the RSBQ, CGI-I and RTT-DSC correlated with exposure to drug (which varies within dose groups).
- Lighter subjects experienced lower levels of drug in their blood compared with heavier subjects receiving the same dose. This was also observed in Neuren’s previous trial in older subjects as well as in the completed Phase 2 trial in Fragile X syndrome. In this younger population, the effect was that the nearly threefold increase in the highest dose compared with the previous trial resulted in significantly lower actual exposure to drug than expected. In a pivotal trial, Neuren intends to use dosing that will aim to achieve similar exposure in subjects regardless of their weight.

Safety

The primary endpoint of the trial was safety in this younger population. The safety profile appears benign, with the following key observations:

- There were no time-dependent patterns of adverse events (AEs) and no pattern of AEs evident with initiation or cessation of treatment.
- The majority of AEs during double-blind treatment period were either mild or moderate in intensity. The most commonly reported AE across trofinetide treatment groups was diarrhea, which was not dose-limiting.
- Four serious adverse events unrelated to treatment were reported in 3 subjects.
- There was one discontinuation – the caregiver withdrew the subject from the study due to AEs of vomiting and diarrhea.
- There was no systematic pattern of objective laboratory, vital sign, funduscopy/tongue or ECG abnormalities.

In conclusion, Neuren’s Executive Chairman Dr Richard Treagus commented: *“This was a profoundly important study for all Rett families, neuroscience research and for Neuren. These are deeply encouraging results that build on the clinical data generated from our first Rett syndrome study. Taken together, this data provides a strong basis to move forward with the remaining steps in trofinetide's development. We will discuss the results of this trial and our future plans with the FDA Division of Neurology as soon as possible and also provide the safety data to the Division of Psychiatry for consideration in our Fragile X syndrome development program. Neuren is grateful to the girls, families, clinical experts and the Rettsyndrome.org team, all of whom made a very significant contribution towards the completion of this clinical trial.”*

For more information, please contact:

Dr Richard Treagus, Executive Chairman: rtreagus@neurenpharma.com ; +61 417 520 509

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, correcting deficits in synaptic function and regulating oxidative stress response. Trofinetide is being developed both in intravenous and oral formulations for a range of acute and chronic conditions. The most advanced program is for Rett syndrome, supported by Rettsyndrome.org. Both the Rett syndrome and Fragile X syndrome programs have been granted Fast Track designation by the US Food and Drug Administration (FDA) and have orphan drug designation in both the United States and the European Union. Following marketing authorization, orphan drug designation provides a market exclusivity period of 7 years in the United States and 10 years in the European Union.

About Neuren

Neuren Pharmaceuticals Limited (Neuren) is a biopharmaceutical company developing new therapies for neurodevelopmental disorders, neurodegenerative diseases and acute brain injury. 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.