Neuren (NEU) – ASX announcement **18 December 2023**

Phase 2 trial shows significant improvements in Phelan-McDermid syndrome

Highlights:

- **Significant improvement was assessed by both clinicians and caregivers across multiple efficacy measures**
- **Improvements were consistently seen across clinically important aspects of Phelan-McDermid syndrome, including communication, behaviour, cognition/learning and socialisation**
- **Clinician and caregiver global efficacy measures showed a level of improvement typically considered clinically meaningful:**
    - **Clinical Global Impression of Improvement (CGI-I) - mean score of 2.4, with 16 out of 18 children showing improvement assessed by clinicians**
    - **Caregiver Overall Impression of Change (CIC) – mean score of 2.7, with 15 out of 18 children showing improvement assessed by caregivers**
- **For 10 out of 14 efficacy endpoints, improvement from baseline on overall/total scores was statistically significant (Wilcoxon signed rank test $p<0.05$)**
- **NNZ-2591 was safe and well tolerated, with no clinically significant changes in laboratory values or other safety parameters during treatment**

Investor Webinar 10:30am AEDT Monday 18 December

You are invited to register using this link:
https://us06web.zoom.us/webinar/register/WN_5VJTnzQMQNumrAkUAf1uFw#/registration

Participants may submit questions at registration or during the session

Melbourne, Australia: Neuren Pharmaceuticals (ASX: NEU) today announced top-line results from its Phase 2 clinical trial of NNZ-2591 in children with Phelan-McDermid syndrome (PMS). Significant improvement was observed by both clinicians and caregivers from treatment, across multiple efficacy measures. Improvements were consistently seen across many of the core PMS characteristics. PMS has severe quality of life impacts for those living with the syndrome, as well as parents and siblings. There are no approved treatments for PMS despite its severely debilitating impact.

Neuren CEO Jon Pilcher commented "The strength and consistency of these results has exceeded our expectations and gives us high confidence as we strive to accelerate the development of a potential first therapy to address the overwhelming unmet medical need of PMS. We are very grateful to all the people at the trial sites in the United States and in the PMS community who enabled this groundbreaking trial to be completed successfully."

Elizabeth Berry-Kravis, MD, PhD, Professor Department of Pediatrics at Rush University Medical Center in Chicago and an Investigator in the study, commented: “Although the Phase 2 trial was an open label study, I am very encouraged that both clinicians and caregivers observed pervasive improvements across multiple, clinically important features of PMS including communication, cognition, learning, socialisation and behaviour. Improvements typically considered clinically meaningful were achieved in the clinician rated CGI-I as well as the caregiver rated CIC. I look forward to seeing this program advance to the next stage of development for the PMS community”.

Study design

The open label Phase 2 trial in up to 20 children aged 3 to 12 years at four hospitals in the United States examined safety, tolerability, pharmacokinetics and efficacy over 13 weeks of treatment with NNZ-2591. NNZ-2591 was administered to all subjects as an oral liquid dose twice daily, with escalation in two stages up to the target dose of 12 mg/kg during the first 6 weeks of treatment, subject to independent review of safety and tolerability data. The study commenced with at least 4 weeks of screening and observation to thoroughly examine baseline characteristics prior to treatment, followed by the treatment period of 13 weeks. A follow-up assessment was made 2 weeks after the end of treatment. 23 children were screened, 5 failed screening and 18 entered the study. The mean age was 8.6 years.

The primary endpoints of this first trial in children were safety, tolerability and pharmacokinetics. Secondary endpoints included 14 efficacy measures assessed by clinicians and by caregivers. Efficacy measures included global measures assessing overall change, measures assessing specific symptom areas and measures assessing quality of life.

Safety and tolerability

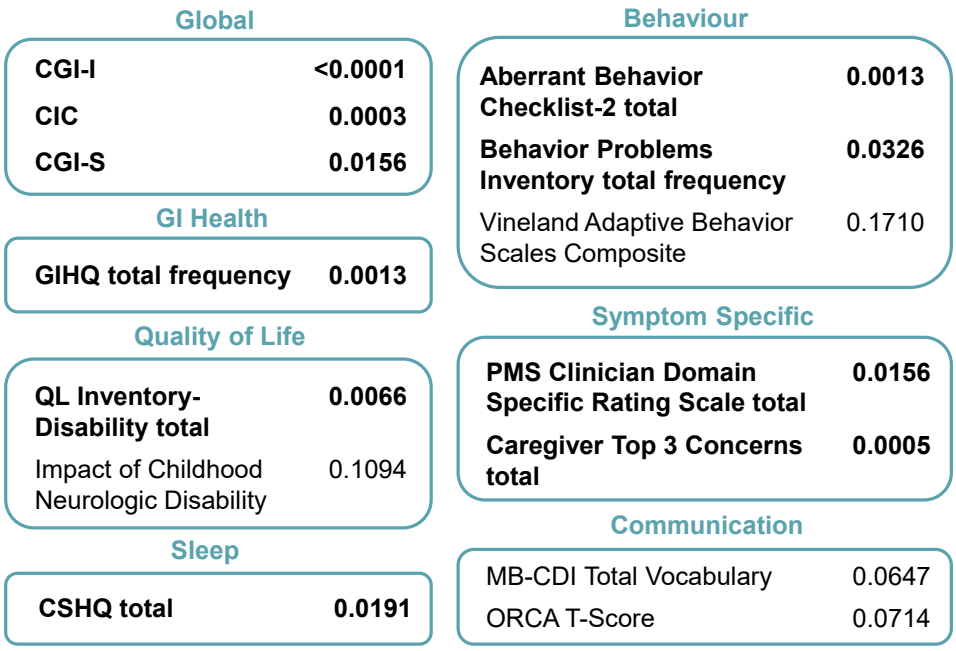
NNZ-2591 was well tolerated and demonstrated a good safety profile. Most Treatment Emergent Adverse Events (TEAEs) were mild to moderate. There was only one Serious TEAE (gastroenteritis), which was not related to study drug and occurred during the safety follow-up period after end of treatment. Three subjects discontinued due to TEAEs, two testing positive for COVID-19 and one due to seizures that were not related to study drug. No clinically significant changes in laboratory values, electrocardiogram (ECG) or other safety parameters were observed during treatment.

TEAEs occurring in two or more subjects are listed in the following table:

Event	NNZ-2591 (N=18) n (%)	Event	NNZ-2591 (N=18) n (%)
Constipation	2 (11.1)	Somnolence	3 (16.7)
Diarrhea	2 (11.1)	Pyrexia	3 (16.7)
Nausea	2 (11.1)	Fatigue	2 (11.1)
Vomiting	2 (11.1)	Aggression	2 (11.1)
COVID-19	3 (16.7)	Insomnia	2 (11.1)
Nasopharyngitis	2 (11.1)	Decreased Appetite	3 (16.7)
Otitis Media	2 (11.1)	Rhinorrhea	2 (11.1)
Psychomotor Hyperactivity	4 (22.2)		

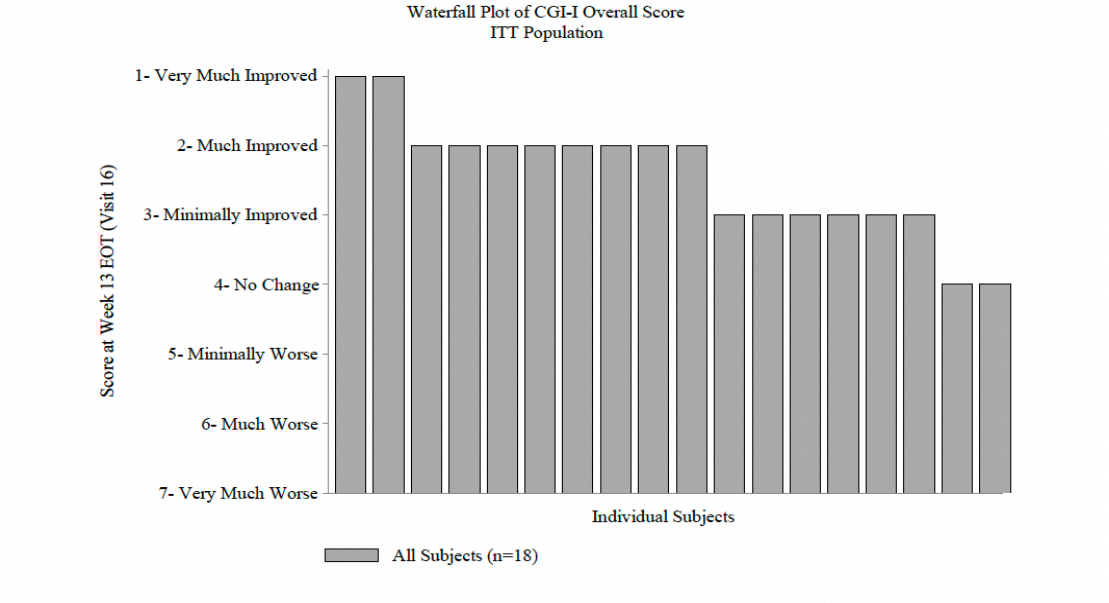
Efficacy

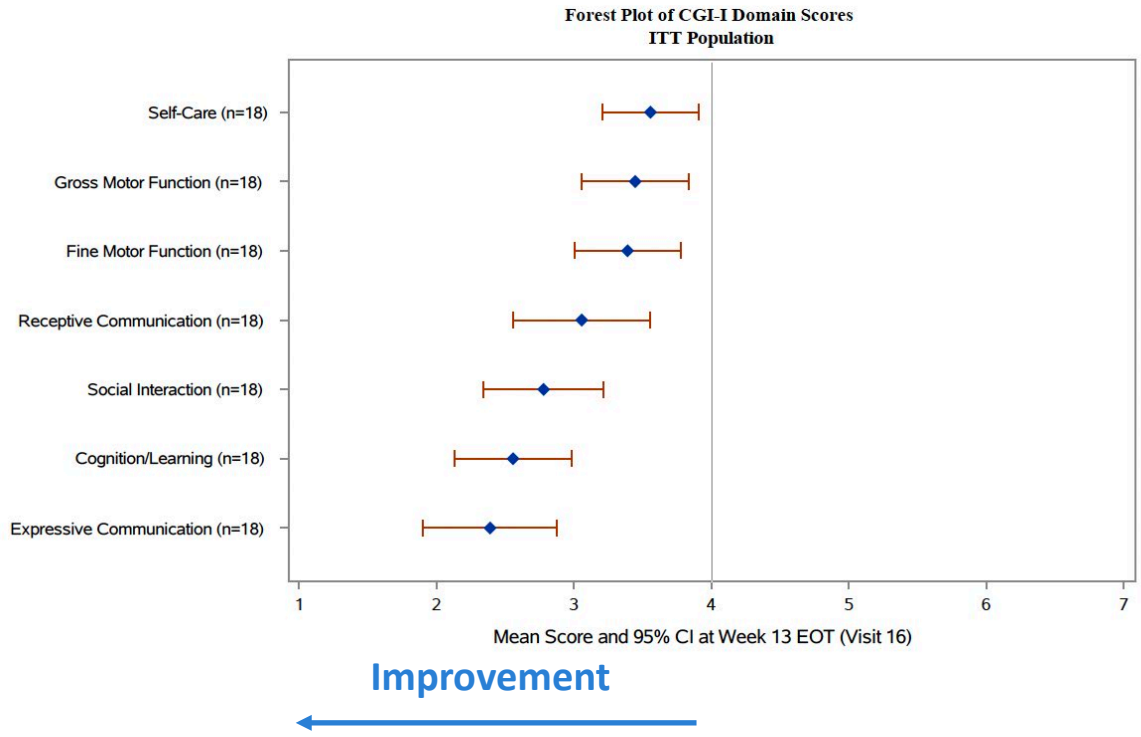
Improvement from baseline on overall/total scores was statistically significant (Wilcoxon signed rank test $p<0.05$) for 10 out of 14 efficacy endpoints, as shown in the following figure:



The results for the global measures rated by both clinicians and caregivers showed a level of improvement typically considered clinically meaningful. 16 out of 18 children showed improvement measured by the Clinical Global Impression of Improvement (CGI-I), an assessment by the clinician of the child's overall status compared with baseline. The mean CGI-I score was 2.4. 10 children received a

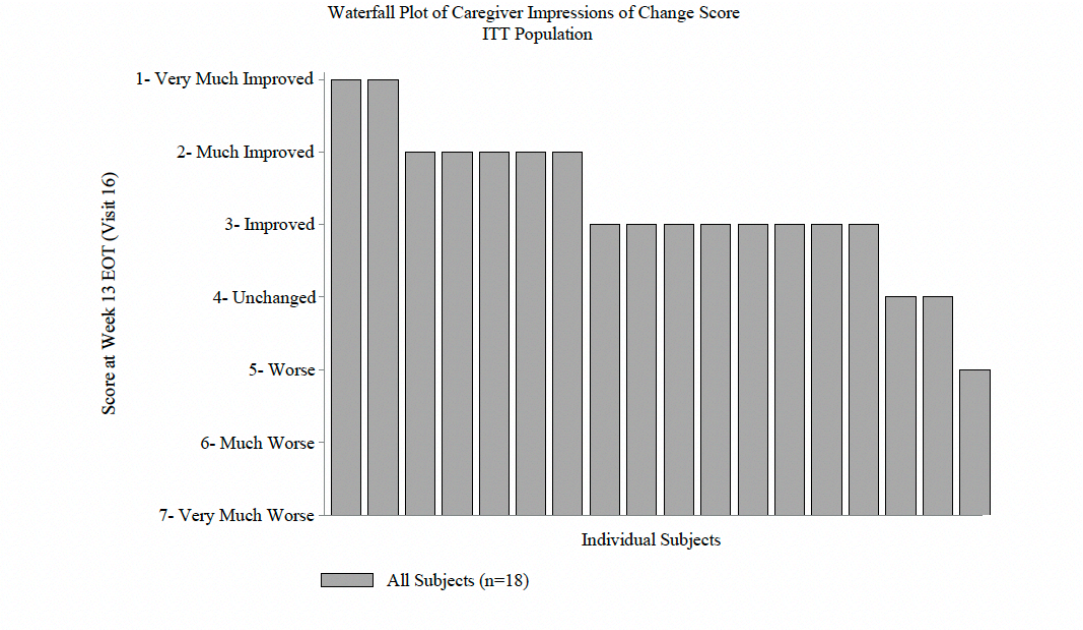
score of either 1 ("very much improved") or 2 ("much improved"). Results by subject and by domain are shown in the following figures:

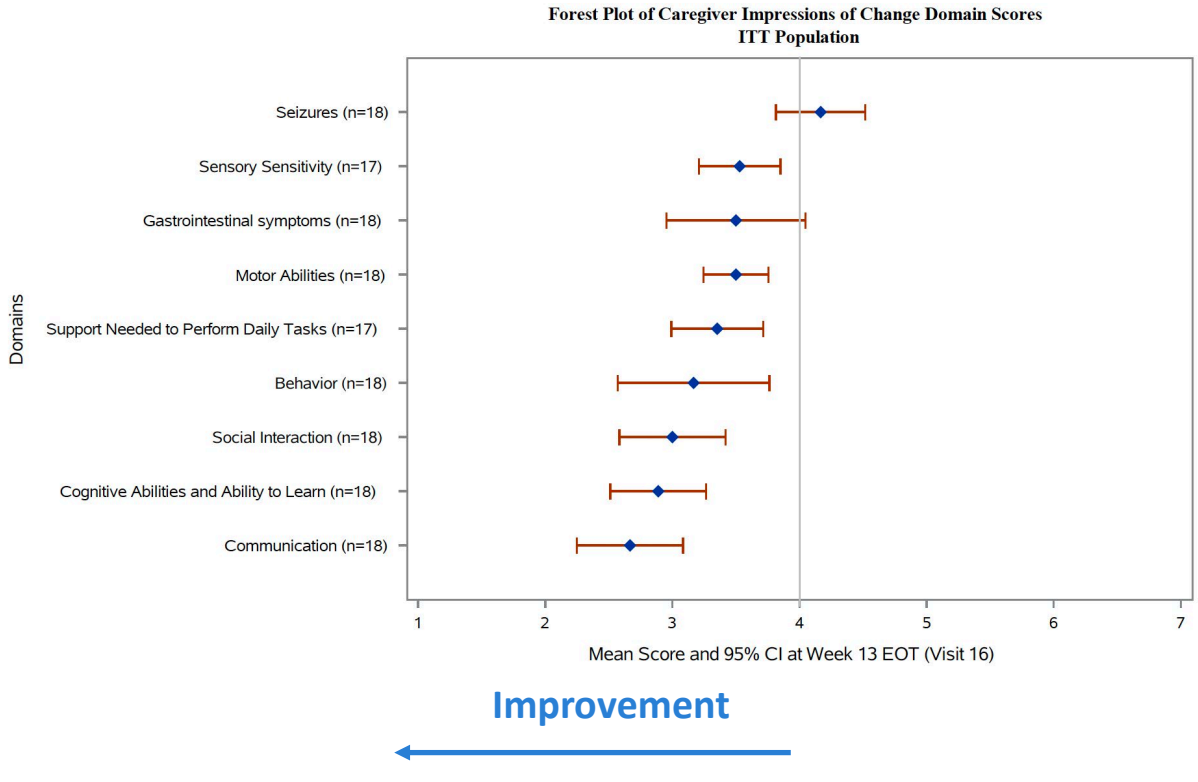




15 out of 18 children showed improvement measured by the Caregiver Overall Impression of Change (CIC), an assessment by the caregiver of the child's overall status compared with baseline. The mean CIC

score was 2.7. Seven children received a score of either 1 ("very much improved") or 2 ("much improved"). Results by subject and by domain are shown in the following figures:





Other ongoing Phase 2 trials of NNZ-2591

Neuren is also conducting Phase 2 clinical trials of NNZ-2591 in children with three other neurodevelopmental disorders – Pitt Hopkins syndrome, Angelman syndrome and Prader-Willi syndrome. Top-line results from the Pitt Hopkins syndrome trial are expected in Q2 2024. All four programs have been granted Orphan Drug designation by the US Food and Drug Administration (FDA) and are being developed under Investigational New Drug (IND) applications. Each syndrome is a seriously debilitating neurological disorder that emerges in early childhood and has no or limited approved treatment options.

About Phelan-McDermid syndrome

Phelan-McDermid syndrome is caused by a deletion or other change in the 22q13 region of chromosome 22, which includes the *SHANK3* gene, or a mutation of the gene. PMS is also known as 22q13 deletion syndrome. The *SHANK3* gene codes for the shank3 protein, which supports the structure of synapses between nerve cells in the brain. It is estimated that between 1 in 8,000 and 1 in 15,000 people have PMS. There are no medications, drugs, or therapies specifically for PMS, which has an overwhelming unmet medical need.

PMS has severe quality of life impacts on those living with it, as well as on parents and siblings. The most common characteristics are moderate to severe developmental and intellectual impairment and developmental delay, delayed or absent speech, symptoms of autism, low muscle tone, motor delays, mild to severe epilepsy, difficulties with toilet training and problems with eating.

Further information about PMS is available at: www.pmsf.org

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. 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.

DAYBUE™ (trofinetide) is approved by the US Food and Drug Administration (FDA) for the treatment of Rett syndrome in adult and pediatric patients two years of age and older. Neuren has granted an exclusive worldwide licence to Acadia Pharmaceuticals Inc. for the development and commercialisation of trofinetide.

Neuren’s second drug candidate, NNZ-2591 is in Phase 2 development for each of Phelan-McDermid syndrome, Angelman syndrome, Pitt Hopkins syndrome and Prader-Willi syndrome.

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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.