Neuren (NEU) – ASX announcement **27 May 2024**

Phase 2 trial shows significant improvements in Pitt Hopkins syndrome

Highlights:

- **Statistically significant improvement from baseline assessed by both clinicians and caregivers in all four efficacy measures specifically designed for Pitt Hopkins syndrome (Wilcoxon signed rank test $p<0.05$)**
- **Clinician and caregiver global efficacy measures showed a level of improvement considered clinically meaningful:**
  - **Clinical Global Impression of Improvement (CGI-I) - mean score of 2.6, with 9 out of 11 children showing improvement assessed by clinicians**
  - **Caregiver Overall Impression of Change (CIC) – mean score of 3.0, with 8 out of 11 children showing improvement assessed by caregivers**
- **Improvements were seen in clinically important aspects of Pitt Hopkins syndrome, including communication, social interaction, cognition and motor abilities**
- **NNZ-2591 was safe and well tolerated, with no serious or severe adverse events and no meaningful trends in laboratory values or other safety parameters during treatment**
- **Second positive Phase 2 trial result further strengthens confidence in NNZ-2591's potential relevance for multiple neurodevelopmental disorders**

Investor Webinar 11:00am AEST Monday 27 May 2024

You are invited to register using this link:
https://us06web.zoom.us/webinar/register/WN_yAci99rgQdikV3m8LV6BzQ

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 Pitt Hopkins syndrome (PTHS). Statistically significant improvement from baseline was observed by both clinicians and caregivers from treatment, across all 4 efficacy measures that were specifically designed to assess the core characteristics of PTHS. There are no approved treatments for PTHS despite its severely debilitating impact on the lives of patients, as well as their parents and siblings.

Neuren CEO Jon Pilcher commented "We are very excited about the results of this first clinical trial in Pitt Hopkins patients. This underserved community has such urgent unmet need and we can now continue towards our goal of developing a first approved treatment. We are very grateful to the people in the Pitt Hopkins community and at the trial sites in the United States who enabled the successful completion of this extremely challenging, but groundbreaking trial."

Elliott Sherr, M.D., Ph.D., Professor of Neurology and Pediatrics at the University of California San Francisco, and Director, Brain Development Research Program was an investigator in the trial. Dr Sherr commented: "I am optimistic about the results in the PTHS specific measures. The mechanism of action of NNZ-2591 supports this response seen in PTHS and its potential in other highly impactful neurodevelopmental disorders."

Dr. Nancy Jones, Neuren Vice President of Clinical Development commented: "The consistent results on the PTHS specific assessments affirm the need for syndrome specific measurements in severe neurodevelopmental disorders where measures that were developed for broader populations may not be as appropriate. Neuren appreciates the collaboration of Dr. Cassandra Newsom, Associate Professor at the University of Alabama, Birmingham (an investigator in the trial), the Pitt-Hopkins Research Foundation, and others who contributed to the development of these important measures."

Study design

The open label Phase 2 trial in 16 children aged 3 to 17 years (mean age 9 years) at five 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 define 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.

The primary endpoints of this first trial in children with PTHS were safety, tolerability and pharmacokinetics. Secondary endpoints included four efficacy measures specifically designed for PTHS assessed by clinicians and by caregivers, as well as ten efficacy measures that were not designed for use in PTHS but have been used in other neurodevelopmental conditions.

Safety and tolerability

NNZ-2591 was well tolerated and demonstrated a good safety profile. All Treatment Emergent Adverse Events (TEAEs) were mild to moderate and most were considered not related to study drug. There were no Serious TEAEs and no meaningful trends in laboratory values, electrocardiogram (ECG) or other safety parameters were observed during treatment. TEAEs occurring in two or more subjects are listed in the table below.

Event	NNZ-2591 (N=16) n (%)		Event	NNZ-2591 (N=16) n (%)	
Constipation	3 (19)	2 mild, 1 mod	Contusion	2 (13)	all mild
Diarrhea	4 (25)	all mild	Gastroenteritis-viral	2 (13)	1 mild, 1 mod
Vomiting	2 (13)	all mild	Nasopharyngitis	3 (19)	all mild
Fatigue	4 (25)	3 mild, 1 mod	Cough	2 (13)	all mild
Somnolence	2 (13)	all mild	Rhinorrhea	2 (13)	all mild
Irritability	2 (13)	all mild	Decreased appetite	2 (13)	all mild

11 subjects completed the trial. One subject discontinued because they were unable to complete the safety monitoring procedures required by the study protocol. Four subjects discontinued due to TEAEs, all of which resolved. For two of those subjects the TEAEs (COVID-19 and mild vomiting/diarrhea/lethargy) were considered not related to study drug and for two subjects the TEAEs (moderate constipation/self-injury/abdominal distention/fatigue and mild sleep disorder/constipation) were considered related to study drug.

Efficacy

The mean improvement from baseline was statistically significant (Wilcoxon signed rank test $p<0.05$) for each of the four efficacy measures that were specifically designed for Pitt Hopkins syndrome, whether calculated for the subjects that completed the study (n=11), or including discontinued subjects (n=15):

Efficacy measure	P value N=11	P value N=15
PTHS CGI-I	**0.0039**	**0.0205**
PTHS CIC	**0.0234**	**0.0137**
PTHS CGI-S	**0.0313**	**0.0078**
Caregiver Top 3 Concerns	**0.0077**	**0.0024**

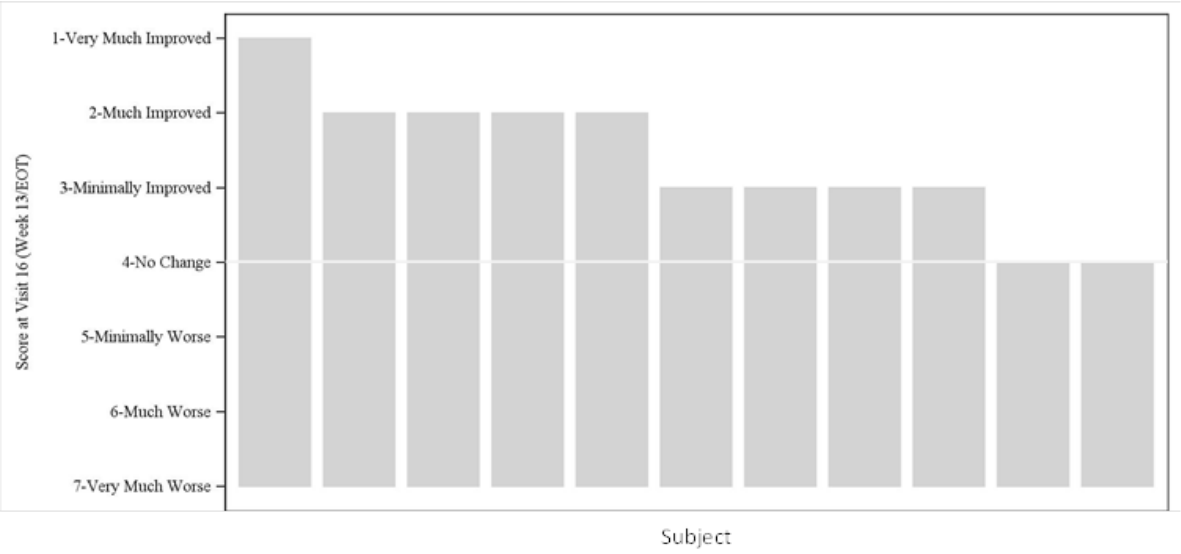
Changes from baseline were not statistically significant for the efficacy measures that were not designed for use in PTHS but have been used in other neurodevelopmental conditions.

Results for efficacy measures specifically designed for Pitt Hopkins syndrome

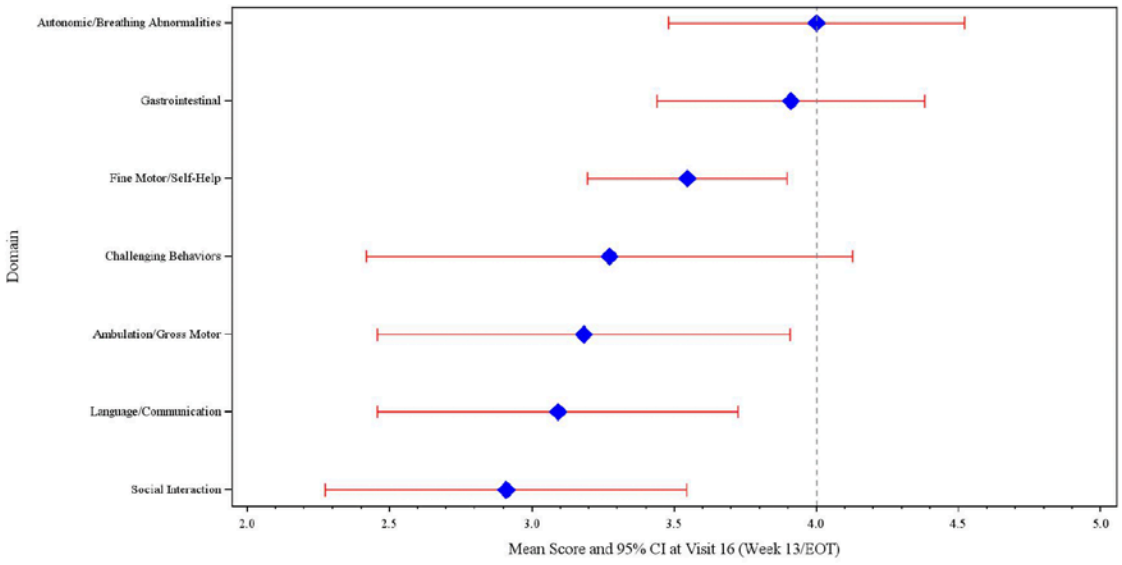
The results for the global measures rated by both clinicians and caregivers showed a level of improvement considered clinically meaningful. 9 out of 11 children that completed the trial showed improvement measured by the PTHS Clinical Global Impression of Improvement (CGI-I), an assessment by the clinician of the child's overall status compared with baseline. The mean CGI-I score was 2.6. Five

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:

PTHS Clinical Global Impression of Improvement (CGI-I) score by subject at end of treatment

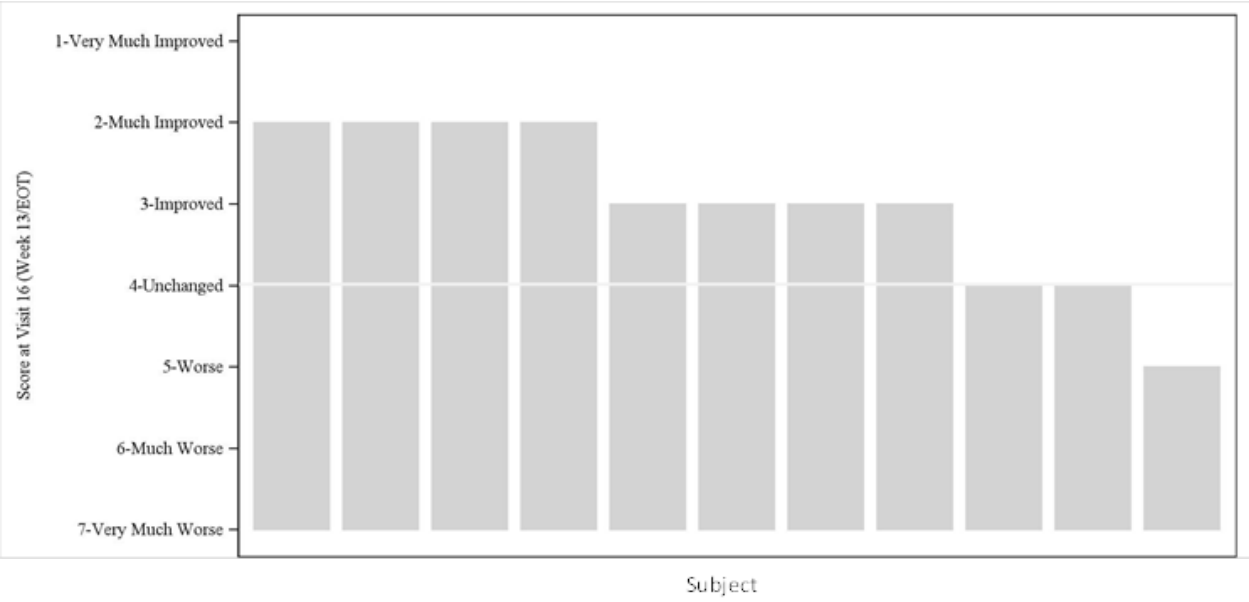


PTHS Clinical Global Impression of Improvement (CGI-I) mean score at end of treatment by domain

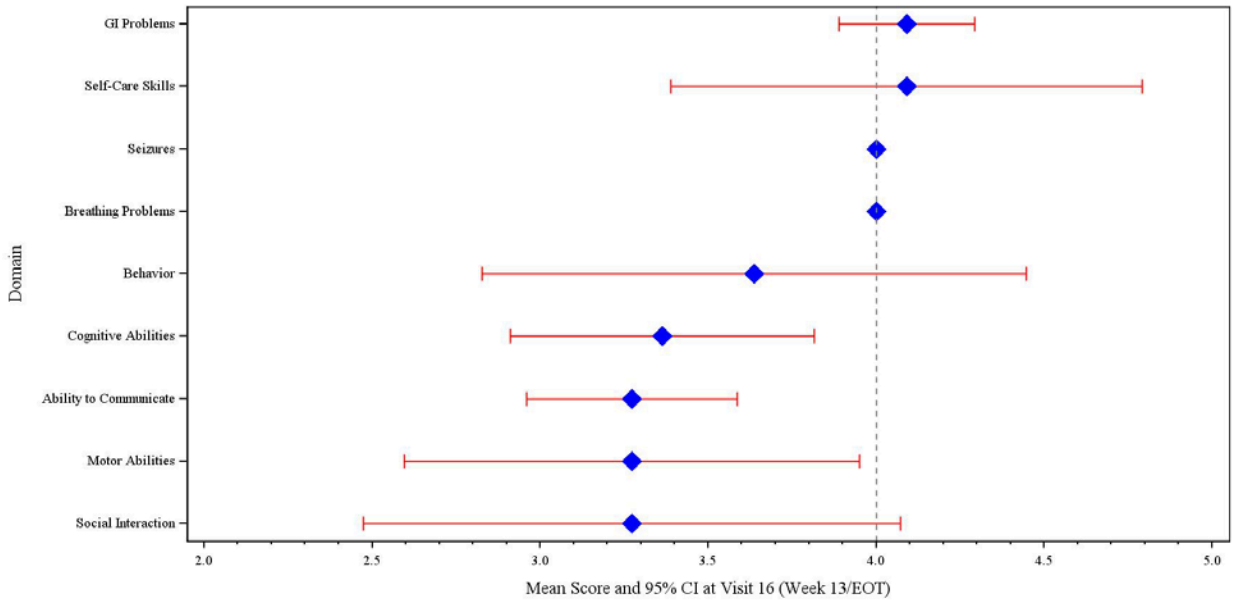


8 out of 11 children that completed the trial showed improvement measured by the PTHS Caregiver Overall Impression of Change (CIC), an assessment by the caregiver of the child's overall status compared with baseline. The mean CIC score was 3.0. Four children received a score of 2 ("much improved"). Results by subject and by domain are shown in the following figures:

PTHS Caregiver Impression of Change (CIC) score by subject at end of treatment



PTHS Caregiver Impression of Change (CIC) man score at end of treatment by domain



6 out of 11 children that completed the trial showed improvement measured by the PTHS Clinical Global Impression of Severity (CGI-S), an assessment by the clinician of the child's overall severity of illness, compared with the assessment at baseline. The CGI-S score improved from 6 to 5 for 3 children and from 5 to 4 for 3 children.

8 out of 11 children that completed the trial showed improvement measured by the Caregiver Top 3 Concerns overall score, an individualised assessment by the caregiver of their child's most concerning symptoms. Language/Communication was the most commonly chosen concern.

Development of NNZ-2591 in multiple neurodevelopmental indications

Neuren is developing NNZ-2591 for multiple seriously debilitating neurological disorders that emerge in early childhood and have no or limited approved treatment options. In December 2023, positive results were announced from a Phase 2 trial in Phelan-McDermid syndrome. Top-line results are expected in Q3 2024 from a Phase 2 trial in Angelman syndrome.

Following the positive results in Pitt Hopkins syndrome announced today, Neuren believes that the good safety and tolerability profile of NNZ-2591 in the Phelan-McDermid and Pitt Hopkins syndrome trials indicate that the trial protocol for Prader-Willi syndrome as well as future indications can and should be simplified, which would need to be agreed with the US Food and Drug Administration (FDA). The requirements of the current trial protocol are burdensome for patients and their families due to the intense schedule of safety monitoring, including frequent and challenging medical procedures. Currently, other clinical trials are available to Prader-Willi syndrome families in the United States that are less burdensome and enable patients to continue on drug therapy beyond 13 weeks. Therefore, Neuren has now paused the ongoing Phase 2 trial of NNZ-2591 in Prader-Willi syndrome. After the planned End of Phase 2 Meeting with the FDA in Q3 2024 for NNZ-2591 in Phelan-McDermid syndrome, Neuren will consider whether to proceed with an optimised protocol and design for the Prader-Willi syndrome trial. In the meantime, Neuren is also conducting pre-clinical studies for NNZ-2591 in other indications and will assess the best candidate(s) to move into Phase 2 development with an optimised protocol.

About Pitt Hopkins syndrome

Pitt Hopkins syndrome (PTHS) is a neurodevelopmental condition caused by the loss of one copy or a mutation of the TCF4 gene on chromosome 18. The incidence of PTHS has been estimated at between 1 in 34,000 and 1 in 41,000 people. Characteristics of PTHS are a range of developmental delay with moderate-to-severe intellectual disability and behavioral differences, hyperventilation and/or breath-holding while awake, seizures, gastrointestinal issues, lack of speech, sleep disturbance, stereotypic hand movements and distinctive facial features. Some individuals with PTHS are diagnosed with autism. Further information about PTHS is available at: www.pitthopkins.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 multiple neurodevelopmental disorders, with positive results achieved in Phase 2 clinical trials in Phelan-McDermid syndrome and Pitt Hopkins 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.