neuren pharmaceuticals

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Neuren (NEU) – ASX announcement **9 August 2024**

Phase 2 trial shows significant improvements in Angelman syndrome

Highlights:

- **Clinician and caregiver global efficacy measures specifically designed for Angelman syndrome showed a level of improvement from baseline after 13 weeks that was statistically significant (Wilcoxon signed rank test p<0.05) and considered clinically meaningful:**
  - **Clinical Global Impression of Improvement (CGI-I) - mean score of 3.0, with 11 out of 13 children showing improvement assessed by clinicians (p=0.0010)**
  - **Caregiver Overall Impression of Change (CIC) – mean score of 3.2, with 8 out of 12 children showing improvement assessed by caregivers (p=0.0273)**
- **Every child in the younger age segment of 3-12 years showed improvement measured by both the CGI-I (mean score 2.8 p=0.0078) and the CIC (mean score 2.6 p=0.0078)**
- **Improvements were seen in clinically important aspects of Angelman syndrome, including communication, behavior, cognition and motor abilities**
- **NNZ-2591 was safe and well tolerated as an oral liquid dose, with no serious adverse events and no meaningful trends in laboratory values or other safety parameters during treatment**
- **Results further strengthen confidence in potential of NNZ-2591 for multiple neurodevelopmental disorders**

Investor Webinar 11:00am AEST Friday 9 August 2024

You are invited to register using this link:

https://us06web.zoom.us/webinar/register/WN_J1seq1baSeO1HCRtAHtWiA#/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 Angelman syndrome (AS). NNZ-2591 was safe and well tolerated as an oral liquid dose and improvements were seen in clinically important aspects of AS. Clinician and caregiver global efficacy measures specifically designed for Angelman syndrome showed a level of improvement from baseline that was statistically significant and considered clinically meaningful. There are no approved treatments for AS despite its severely debilitating impact on the lives of patients, as well as their parents and siblings.

Neuren CEO Jon Pilcher commented "These results provide additional confirmation that NNZ-2591 as an oral liquid dose may address the core symptoms of diverse neurodevelopmental disorders, independent of the origin of the underlying genetics. We are very grateful to the people in the Angelman syndrome community and at the trial sites in Australia who enabled the successful completion of the trial."

Study design

The open label Phase 2 trial in children aged 3 to 17 years (mean age 10 years) at three hospitals in Australia examined safety, tolerability, pharmacokinetics and efficacy over 13 weeks of treatment with NNZ-2591. Children with all AS genotypes apart from mosaicism were eligible to enroll in the trial. NNZ-2591 was administered to all participants 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. A follow-up assessment was made 2 weeks after the end of treatment.

The primary endpoints of this first trial in children with AS were safety, tolerability and pharmacokinetics. Secondary endpoints included efficacy measures specifically designed for AS assessed by clinicians and by caregivers, as well as efficacy measures that were not designed for use in AS but have been used in other neurodevelopmental conditions. 16 participants were dosed in the trial. Two participants were required to discontinue due to testing positive for COVID-19 and one participant discontinued because they were unable to complete the safety monitoring procedures required by the study protocol. Safety and tolerability data is presented for all 16 participants (Intention-to-Treat or ITT population) and efficacy data is presented for the 13 participants who completed dosing (modified Intention-to-Treat or mITT population). There was no meaningful difference in the demographics of the ITT and MITT populations.

Safety and tolerability

NNZ-2591 was well tolerated and demonstrated a good safety profile. Most Treatment Emergent Adverse Events (TEAEs) were mild or 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 participants are listed in the table below.

Event	N=16 n (%)	Event	N=16 n (%)
Viral Infection	5 (31)	Drooling	2 (13)
Nasopharyngitis	4 (25)	Epistaxis	2 (13)
Seizure	4 (25)	Insomnia	2 (13)
Upper Respiratory Tract Infection	3 (19)	Pyrexia	2 (13)
Somnolence	3 (19)	Skin Abrasion	2 (13)
Constipation	3 (19)	Urinary Tract Infection	2 (13)
Diarrhea	2 (13)	Vomiting	2 (13)

Efficacy

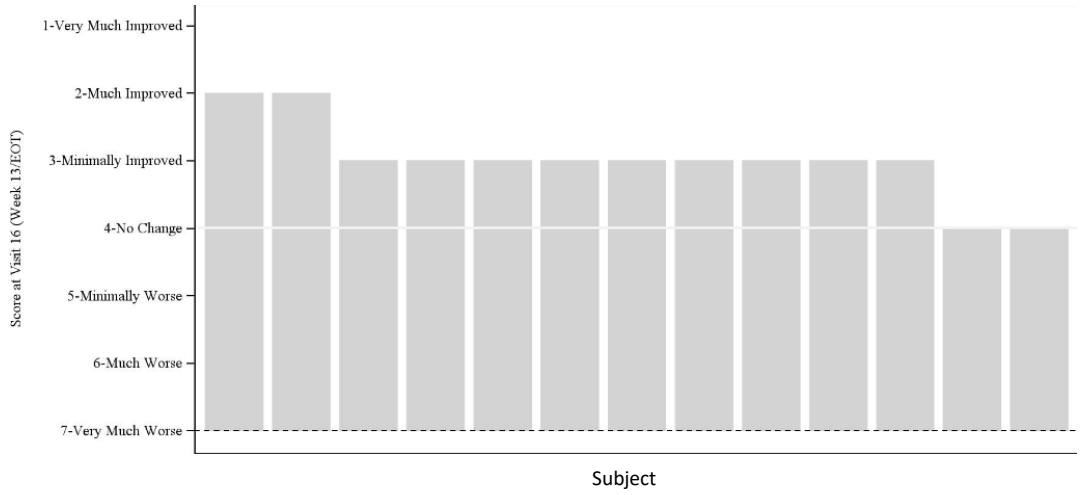
Clinician and caregiver global efficacy measures specifically designed for Angelman syndrome showed a level of improvement from baseline that was statistically significant (Wilcoxon signed rank test $p<0.05$) and considered clinically meaningful. The mean improvement from baseline was statistically significant, whether calculated for the subjects that completed dosing (mITT population), or including discontinued subjects (ITT population). Improvements were seen in clinically important aspects of Angelman syndrome, including communication, behavior, cognition and motor abilities.

AS Clinical Global Impression of Improvement (CGI-I)

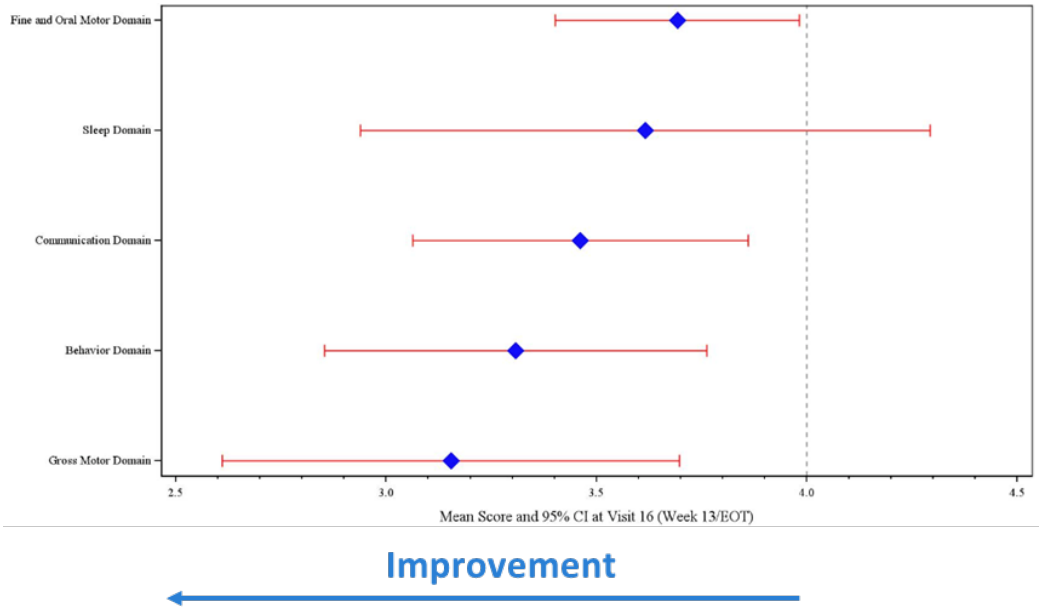
11 out of 13 children showed improvement measured by the AS Clinical Global Impression of Improvement (CGI-I), an assessment by the clinician of the child's overall status compared with baseline. The mean CGI-I score was 3.0 ($p=0.0010$). Two children received a score of 2 ("much improved"). In the 3-12 years age group all 8 children showed improvement, with a mean score of 2.8 ($p=0.0078$).

Scores by subject and by domain are shown in the following figures:

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



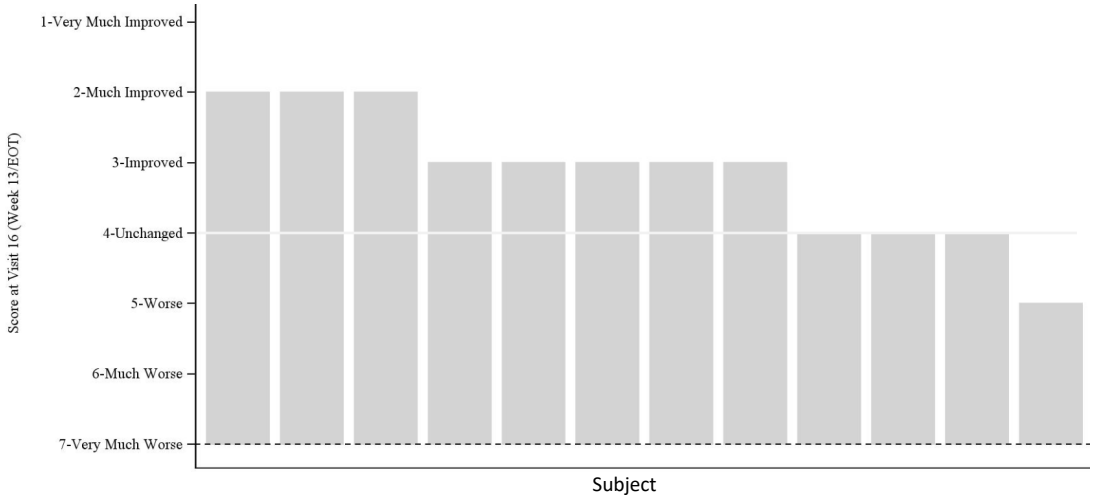
AS Clinical Global Impression of Improvement (CGI-I) mean score at end of treatment by domain



AS Caregiver Overall Impression of Change (CIC)

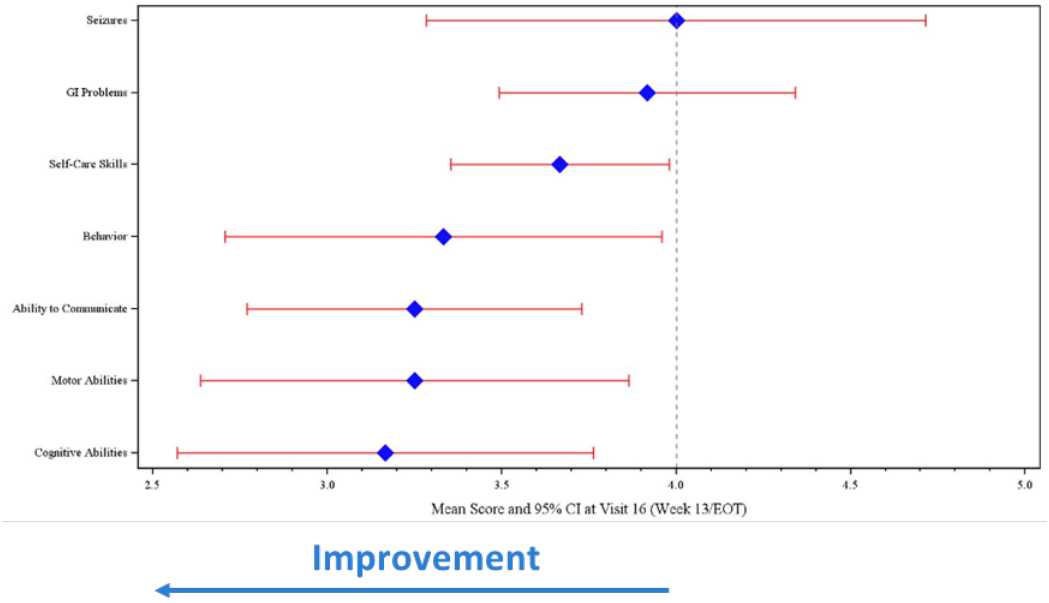
8 out of 12[1] children showed improvement measured by the AS Caregiver Overall Impression of Change (CIC), an assessment by the caregiver of the child's overall status compared with baseline. The mean CIC score was 3.2 (p=0.0273). Three children received a score of 2 ("much improved"). In the 3-12 years age group all 8 children showed improvement, with a mean score of 2.8 (p=0.0078). Scores by subject and by domain are shown in the following figures:

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



[1] CIC score for one subject inadvertently not completed by caregiver at site visit

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



Other measures

Four children showed improvement measured by the AS 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 Bayley Scales of Infant and Toddler Development (Bayley-4) were included in the trial as exploratory efficacy measures, although they are designed to measure outcomes over a longer time period than the duration of this clinical trial. Notwithstanding the limited treatment duration of 13 weeks, for each of the 6 Bayley subscales more than 50% of the children showed improvement in raw scores.

Development of NNZ-2591 in multiple neurodevelopmental indications

Neuren is developing NNZ-2591 for multiple seriously debilitating neurological disorders with different genetic origins that emerge in early childhood and have no or limited approved treatment options. In December 2023 and May 2024, positive results were announced from Phase 2 trials on NNZ-2591 in Phelan-McDermid syndrome and Pitt Hopkins syndrome respectively. An End of Phase 2 Meeting with the US Food and Drug Administration (FDA) for NNZ-2591 in Phelan-McDermid syndrome is scheduled for September 2024, at which Neuren will seek guidance on the remaining development program. In parallel, manufacture of supplies for Phase 3 clinical trials is in progress. Neuren has an open IND with the FDA for NNZ-2591 in Prader-Willi syndrome and is also conducting pre-clinical studies for NNZ-2591 in other undisclosed indications.

About Angelman syndrome

Angelman syndrome (AS) is a rare neurodevelopmental disorder that is estimated to occur in between one in 10,000 and 20,000 live births. It is caused by a loss of function of the *UBE3A* gene in chromosome 15 derived from the mother. Angelman syndrome shares symptoms and characteristics with other disorders, which means that misdiagnosis occurs often. Children and adults with AS typically have balance issues, motor impairments and can have debilitating seizures. Disruptive sleep is often a serious challenge. Some never walk and most do not speak. Individuals with AS have a normal life expectancy but require continuous care and are unable to live independently. Further information is available at: www.cureangelman.org and www:angelman.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, Pitt Hopkins syndrome and Angelman 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.