Safety, Efficacy, and Exposure-Response of NNZ-2591, a Synthetic Analog of Cyclic Glycine-Proline (cGP), an IGF-1 Metabolite, for the Treatment of Phelan-McDermid Syndrome in Children and Adolescents

Russell Wada, PhD[1]; Helen Kastrissios, PhD[1]; Mark A Milad, PharmD[2]; Milad Ghomlaghi, PhD[1]; Nancy E Jones, PhD[3]; Liza Squires, MD[3]; Larry Glass, BA[3]

[1]QuanTx Consulting, Mountain View, CA, USA; [2]Milad Pharmaceutical Consulting, Plymouth, MI, USA; [3]Neuren Pharmaceuticals, Camberwell, Vic, AUS

Objective

To evaluate the treatment effects and pharmacokinetics of NNZ-2591, a synthetic analog of the insulin-like growth factor 1 metabolite cyclic glycine-proline, in children and adolescents with Phelan-McDermid syndrome (PMS)

Conclusions

NNZ-2591 appeared well tolerated and demonstrated a favorable safety profile in children and adolescents with PMS

Clinicians and caregivers observed meaningful improvements in clinically important aspects of PMS with NNZ-2591 treatment, including communication, behavior, cognition/learning, and socialization

Systemic NNZ-2591 exposure was estimated using a population pharmacokinetic model; improvements in the Clinical Global Impression of Improvement overall score were generally observed in participants with a 24-hour steady-state area under the curve >300 µg·h/mL

Background

Phelan-McDermid syndrome (PMS) is a rare genetic condition associated with delayed neurodevelopment that is usually caused by genetic deletions or abnormalities affecting the *SHANK3* gene[1]

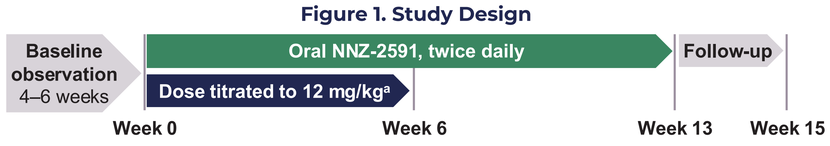
- People with PMS can experience broad and severe symptoms, including global developmental delay, intellectual disability, absent or severely delayed speech, and behavioral differences (eg, autistic behaviors)[1]
- There are no approved treatments for PMS[1]; current treatment approaches focus on symptom management
- NNZ-2591 is a synthetic analog of cyclic glycine-proline (cGP), which is a metabolite of insulin-like growth factor 1 (IGF-1) that is naturally present in the brain
- NNZ-2591 is being evaluated in children and adolescents with PMS

Methods

Study Design and Participants

- Twice-daily orally administered NNZ-2591 was evaluated in a phase 2, 13-week, multisite, open-label clinical trial (NCT05025241; Figure 1)
- Eligible participants were aged 3–12 years at screening, had a clinical PMS diagnosis, and had a disease-causing genetic abnormality of the *SHANK3* gene
- Primary endpoints were safety, tolerability, and pharmacokinetics (PK); secondary endpoints were efficacy measures

Figure 1. Study Design



[a]NNZ-2591 doses were titrated up from 4 mg/kg to 8 mg/kg to 12 mg/kg; a data safety monitoring committee reviewed data before each dose increase.

Assessments

Safety

- Treatment-emergent adverse events (TEAEs) were monitored from the first dose of study drug through the end of the follow-up period

Pharmacokinetics

- Blood samples were collected before and after dosing at weeks 2, 6, and 13
- NNZ-2591 concentrations were determined with a validated liquid chromatography-tandem mass spectrometry method

Efficacy

- Signs and symptoms relevant to PMS were evaluated with 14 assessments, including 5 PMS-specific assessments (Figure 2)

Figure 2. Assessments

PMS-Specific Assessments

Global
- Clinical Global Impression of Improvement[2]
- Caregiver Impression of Change
- Clinical Global Impression of Severity[2]

Symptom-Specific
- Caregiver Top 3 Concerns
- PMS Clinician Domain-Specific Rating Scale

Other Assessments

Quality of Life
- Quality of Life Inventory – Disability
- Impact of Childhood Neurological Disability

Adaptive Behavior/Self-Care
- Vineland Adaptive Behavior Scales-3

Communication
- MacArthur-Bates Communicative Development Inventory
- Observer-Reported Communication Ability

Gastrointestinal Health
- Gastrointestinal Health Questionnaire

Behavior
- Aberrant Behavior Checklist-2
- Behavior Problems Inventory – Short Form

Sleep
- Child Sleep Habits Questionnaire

PMS, Phelan-McDermid syndrome.

Analyses

- A Wilcoxon signed-rank test was used to evaluate improvements from baseline in efficacy outcomes
- A population PK model was developed using sparse PK sampling data from the phase 2 trial of NNZ-2591 in children and adolescents with PMS and serial PK sampling from a phase 1 study of NNZ-2591 in healthy adults (NCT04379869)
- Each participant's NNZ-2591 exposure was calculated using participant-specific PK parameters estimated from the population PK model
- The minimum effective NNZ-2591 exposure was visually determined from an exposure-response plot of the relationship between 24-hour steady-state area under the curve ($AUC_{24,ss}$) and Clinical Global Impression of Improvement (CGI-I) scores

Methods (cont'd)

- Simulations of NNZ-2591 exposures for a virtual pediatric population were performed
  - A virtual pediatric population was created by sampling the body weight distribution by age for children aged 3–12 years, reported by the Centers for Disease Control and Prevention
  - PK parameters were generated by sampling interparticipant variability from the population PK model
  - Steady-state NNZ-2591 exposures following 12 mg/kg and 13 mg/kg dosing regimens were simulated for the virtual pediatric population; exposure projections were summarized by weight bands (>20 kg or ≤20 kg)

Results

Participants

- Of the 18 participants enrolled in the phase 2 study, two-thirds were male, and most were White (Table 1)

Table 1. Demographics

Characteristic	NNZ-2591 N = 18
Sex, n (%)	
Male	12 (66.7)
Female	6 (33.3)
Age, years	
Mean (SD)	8.6 (2.7)
Median (range)	8.3 (4.4, 13.0)
Race, n (%)	
White	16 (88.9)
Black	1 (5.6)
Multiple	1 (5.6)
Weight, kg	
Mean (SD)	30.4 (10.8)
Median (range)	28.7 (16.8, 51.0)

Safety

- NNZ-2591 was well tolerated and demonstrated a favorable safety profile (Table 2)
  - Most TEAEs were mild or moderate in severity and not related to study drug
  - 3 participants discontinued the study due to TEAEs, none of which were related to study drug

Table 2. Safety Overview

Event, n (%)	NNZ-2591 N = 18
Any TEAE	17 (94.4)
Serious TEAE	1 (5.6)[a]
Severe TEAE	1 (5.6)
TEAE leading to study discontinuation	3 (16.7)[b]
Death due to TEAE	0

TEAE, treatment-emergent adverse event.
[a]1 serious adverse event of gastroenteritis occurred during the posttreatment safety follow-up period; the event was considered not related to study drug.
[b]3 participants discontinued due to adverse events (COVID-19, 2; seizure, 1); all were considered not related to study drug.

Pharmacokinetics

- An allometrically scaled 1-compartment population PK model with first-order absorption and linear clearance was developed to describe the PK of NNZ-2591 in children and adolescents with PMS
  - The exponents used to scale the apparent clearance (CL/F) and the apparent volume of distribution (V/F) by body weight were 0.75 and 1, respectively
  - PK was dose proportional over the dose range of 3 to 12 mg/kg
- The NNZ-2591 PK parameters for a child with PMS weighing 30 kg were estimated based on the population PK model (Table 3)

Table 3. Pharmacokinetic Parameters of NNZ-2591 Estimated for Children With PMS

Parameter	NNZ-2591 12 mg/kg, twice daily
Apparent clearance (CL/F), L/h	1.89
Apparent volume of distribution (V/F), L	20.2
Half-life, h	7.4
$AUC_{24,ss}$[a], µg•h/mL	381

$AUC_{24,ss}$, 24-hour steady-state area under the curve; h, hour; PMS, Phelan-McDermid syndrome.
[a]$AUC_{24,ss}$ was calculated as the daily dose divided by apparent clearance.

Results (cont'd)

Efficacy

- Participants who received NNZ-2591 experienced statistically significant improvements from baseline for 10 out of 14 efficacy outcomes assessing clinically important symptoms of PMS, including both clinician- and caregiver-assessed outcomes (Table 4)

Table 4. Efficacy Outcomes With NNZ-2591

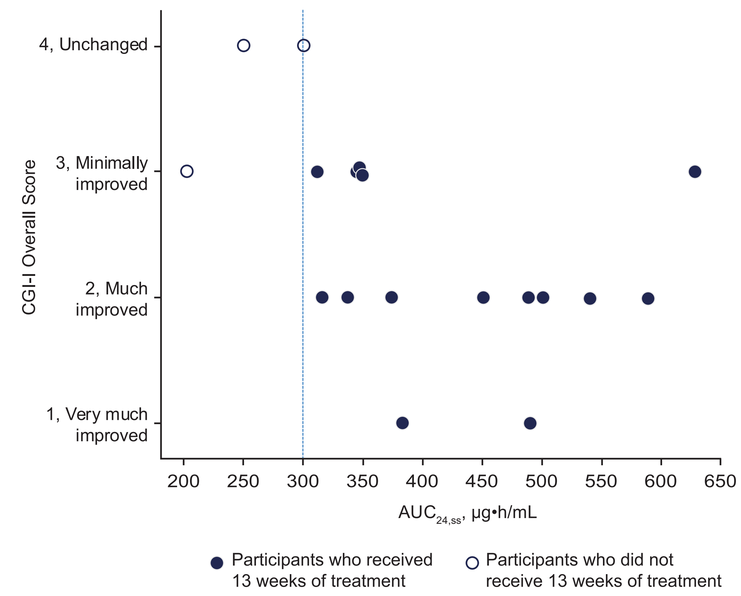
Assessment, Overall or Total Score, mean (SD)	NNZ-2591 N = 18		
	Baseline	Week 13	*P* value
CGI-I	—	2.4 (0.9)	<.0001***[,a]
CIC	—	2.7 (1.0)	.0003***[,a]
CGI-S	4.5 (1.0)	4.1 (1.0)	.0156*
PMS-DSRS	5.7 (2.1)	4.7 (2.2)	.0156*
Caregiver top 3 concerns	25.9 (3.4)[b]	20.1 (7.1)[b]	.0005***
GIHQ frequency	41.6 (29.6)	32.1 (25.6)	.0013**
QI-Disability	64.7 (8.1)	70.9 (11.7)	.0066**
ICND	3.3 (0.9)	3.7 (1.1)	.1094
MB-CDI vocabulary	266.0 (242.1)	278.3 (248.9)	.0647
ORCA	50.0 (13.4)	52.9 (14.8)	.0714
CSHQ	46.1 (8.0)	42.5 (5.0)	.0191*
ABC-2	70.4 (20.8)	53.2 (21.6)	.0013**
BPI frequency	28.2 (15.6)[b]	22.7 (11.1)	.0326*
VABS-3	39.4 (13.1)	42.2 (14.7)	.1710

ABC-2, Aberrant Behavior Checklist-2; BPI, Behavior Problems Inventory; CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; CSHQ, Child Sleep Habits Questionnaire; GIHQ, Gastrointestinal Health Questionnaire; ICND, Impact of Childhood Neurological Disability scale; MB-CDI, MacArthur-Bates Communicative Development Inventory; ORCA, Observer-Reported Communication Ability; PMS, Phelan-McDermid syndrome; PMS-DSRS, PMS Clinician Domain-Specific Rating Scale; QI-Disability, Quality of Life Inventory – Disability; VABS-3, Vineland Adaptive Behavior Scales-3.
*P <.05; **P <.01; ***P <.001 for change from baseline (or observed change relative to baseline for CGI-I and CIC) vs null median based on Wilcoxon signed-rank test.
[a]Null median of 4 (no change).
[b]n = 17.
Baseline scores were determined as the average scores from visits during the baseline/screening period for assessments collected at more than 1 visit during the baseline/screening period.
CGI-I overall scores and CIC total scores range from 1–7; lower scores indicate improvement (below 4), a score of 4 indicates no change, and higher scores (above 4) indicate worsening.
CGI-S overall scores range from 1–7; higher scores indicate greater impairment.
PMS-DSRS overall scores range from 0–20; higher scores indicate more severe symptoms.
Caregiver top 3 concerns overall severity scores range from 0–30; higher scores indicate more severe symptoms.
GIHQ total frequency scores range from 0–197; higher scores indicate greater gastrointestinal problems.
QI-Disability overall scores range from 0–100; higher scores indicate a better quality of life.
ICND overall scores range from 1–6; higher scores indicate better quality of life.
MB-CDI total vocabulary scores range from 0–680; higher scores indicate greater language development.
ORCA total scores range from 26.82–83.24; higher scores indicate greater communication ability.
CSHQ total scores range from 33–99; higher scores reflect more disturbed sleep behavior.
ABC-2 total scores range from 0–174; higher scores indicate more behavior issues.
BPI total frequency scores range from 0–120; higher scores indicate greater frequency of behavior problems.
VABS-3 adaptive behavior composite scores range from 20–140; higher scores reflect better adaptability.

Exposure-Response Relationship

- All 15 participants who received 13 weeks of treatment with NNZ-2591 had an $AUC_{24,ss}$ >300 µg•h/mL and showed symptomatic improvement on the PMS-anchored CGI-I scale, establishing the target minimum exposure (Figure 3)
- Exposure projections estimate over 80% of children will achieve the target minimum exposure of 300 µg•h/mL with an NNZ-2591 dose of 12 mg/kg or 13 mg/kg twice daily for children weighing >20 kg or ≤20 kg, respectively

Figure 3. CGI-I Scores by NNZ-2591 Exposure at Week 13 in Children With PMS



$AUC_{24,ss}$, 24-hour steady-state area under the curve; CGI-I, Clinical Global Impression – Improvement; PMS, Phelan-McDermid syndrome.
Dashed line represents target minimum exposure, which was determined based on visual assessment.

Disclosures and Acknowledgments

Disclosures: Russell Wada, Helen Kastrissios, and Milad Ghomlaghi are employees of QuanTx Consulting and serve as paid consultants to Neuren Pharmaceuticals in connection with this work. Mark A Milad is an employee of Milad Pharmaceutical Consulting, LLC, and serves as a paid consultant to Neuren Pharmaceuticals in connection with this work. Nancy E Jones, Liza Squires, and Larry Glass are executives at Neuren Pharmaceuticals and may hold Neuren stock or stock options.

Neuren participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this poster for submission. All authors had access to the data and participated in the development, review, and approval of the poster. Neuren funded the research for this study. Medical writing assistance, funded by Neuren, was provided by Morgan A Gingerich, PhD, and Lisa M Pitchford, PhD, ISMPP CMPP, of JB Ashtin.

Presented at the 2025 American College of Medical Genetics and Genomics Clinical Genetics Meeting, Los Angeles, California, March 19–21, 2025
Data first presented at the American Academy of Child and Adolescent Psychiatry 2024 Annual Meeting, Seattle, Washington, October 14–19, 2024

References

1. Phelan K, et al. GeneReviews®. May 2005 [Updated Jun 6, 2024]. Accessed Aug 23, 2024. https://www.ncbi.nlm.nih.gov/books/NBK1198/
2. Berry-Kravis, et al. *Neurology*. 2022;98(Supp 18):P17–6.001.

neuren pharmaceuticals