NNZ-2591, A Novel IGF-1–Related Treatment for Neurodevelopmental Disorders, Demonstrates Efficacy for Children and Adolescents With Phelan-McDermid Syndrome

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Objective

To evaluate the effects of treatment with 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) in a phase 2 open-label clinical trial

Conclusions

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

Clinicians and caregivers reported significant and meaningful improvements with NNZ-2591 across 10 of 14 efficacy assessments, including those evaluating PMS-specific symptoms, quality of life, behavior, gastrointestinal symptoms, and sleep

Improvements were observed by clinicians and caregivers across important aspects of PMS, including cognition and learning, behavior, socialization, and communication

Introduction

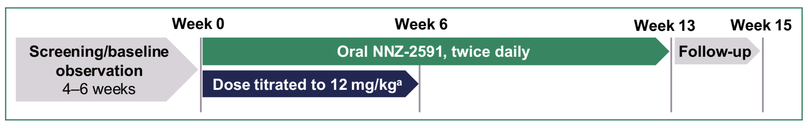
- Phelan-McDermid syndrome (PMS) is a rare neurodevelopmental condition commonly caused by genetic deletions or abnormalities affecting the *SHANK3* gene[1]
- PMS manifestations can be severe and medically complex; symptoms may include neonatal hypotonia, global developmental delay, intellectual disability, maladaptive behaviors, speech delay or absence, gastrointestinal reflux disease, and seizures[1]
- Current approaches to treat PMS focus on managing symptoms, as there are no approved therapies for PMS[1,2]
- NNZ-2591 is a synthetic analog of cyclic glycine-proline, which is a metabolite of insulin-like growth factor 1 (IGF-1) that is naturally present in the brain
- NNZ-2591 is under evaluation in children and adolescents with PMS

Methods

Study Design and Participants

- In a 13-week, multisite, open-label, phase 2 clinical trial, twice-daily oral administration of NNZ-2591 was evaluated (NCT05025241; **Figure 1**)
- Eligible participants had a clinical PMS diagnosis with a disease-causing genetic abnormality of the *SHANK3* gene, were aged 3–12 years at screening, and weighed ≥ 12 kg
- The primary endpoints included safety and tolerability; the secondary endpoints were efficacy assessments

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 recorded from the time of the first study drug dose to the end of the study follow-up period

Efficacy

- A total of 14 efficacy assessments were evaluated, including 5 PMS-specific assessments (**Figure 2**)
- PMS-specific efficacy assessments included:
  - Global assessments
    - Clinical Global Impression (CGI) of Improvement (CGI-I) and CGI of Severity (CGI-S) based on core PMS symptom domains common to all individuals with PMS[3]
    - Caregiver Impression of Change (CIC), with domains based on clinically important symptoms of PMS
  - Symptom-specific assessments
    - Caregiver Top 3 Concerns Likert scale, measuring 3 signs or symptoms of PMS that each caregiver identified as a priority sign/symptom for treatment at baseline
    - PMS Clinician Domain-Specific Rating Scale, with domains evaluating PMS symptoms that are highly impactful but that may not be relevant for all individuals with PMS

Figure 2. Efficacy Assessments

PMS-Specific Assessments

Global
- Clinical Global Impression of Improvement
- Caregiver Impression of Change
- Clinical Global Impression of Severity

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

- Safety was summarized as the number and frequency of TEAEs
- A Wilcoxon signed-rank test was used to evaluate improvements from baseline to week 13 in efficacy outcomes

Results

Participants

- Of the 18 participants enrolled in the study, 15 completed the study
- Two-thirds of study participants were male and most were White (**Table 1**)
- The average PMS severity at screening and baseline visits reflected moderate to marked impairment (mean [SD] CGI-S score, 4.5 [1.0])

Safety

- NNZ-2591 was well tolerated and demonstrated a favorable safety profile (**Table 2**)
- Most TEAEs were mild or moderate in severity; 1 serious TEAE of gastroenteritis occurred during the posttreatment safety follow-up period and was considered unrelated to study drug
- Of the 3 participants who discontinued the study due to TEAEs, none of the TEAEs were considered related to study drug (COVID-19, 2; seizure, 1)
- The most frequently reported TEAE was psychomotor hyperactivity (reported for 4 participants); COVID-19, decreased appetite, pyrexia, and somnolence were each reported for 3 patients
- No clinically significant changes in laboratory values, vital signs, ophthalmic evaluations, electrocardiograms, or other safety parameters were reported

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)

Demographic information is reported at baseline.

Table 2. Safety Overview

Event, n (%)	NNZ-2591 N = 18
Any TEAE	17 (94.4)
Serious TEAE	1 (5.6)
Severe TEAE	1 (5.6)
TEAE leading to study discontinuation	3 (16.7)
Death due to TEAE	0
TEAEs occurring in ≥2 participants	
Psychomotor hyperactivity	4 (22.2)
COVID-19	3 (16.7)
Decreased appetite	3 (16.7)
Pyrexia (fever)	3 (16.7)
Somnolence	3 (16.7)
Aggression	2 (11.1)
Constipation	2 (11.1)
Diarrhea	2 (11.1)
Fatigue	2 (11.1)
Insomnia	2 (11.1)
Nasopharyngitis	2 (11.1)
Nausea	2 (11.1)
Otitis media	2 (11.1)
Rhinorrhea	2 (11.1)
Vomiting	2 (11.1)

TEAE, treatment-emergent adverse event.

Table 3. Efficacy Outcomes

Assessment, Overall or Total Score, Mean (SD)	NNZ-2591 N = 18 Baseline[a]	Week 13	Change From Baseline	*P* value
PMS-Specific Assessments				
CGI-I[b]	—	2.4 (0.9)	—	<.0001***,[c]
CIC[b]	—	2.7 (1.0)	—	.0003***,[c]
CGI-S[d]	4.5 (1.0)	4.1 (1.0)	−0.4 (0.5)	.0156*
Caregiver Top 3 Concerns[e]	25.9 (3.4)[f]	20.1 (7.1)[f]	−5.9 (5.9)	.0005***
PMS-DSRS[g]	5.7 (2.1)	4.7 (2.2)	−0.9 (1.7)	.0156*
Other Assessments				
QI-Disability[h]	64.7 (8.1)	70.9 (11.7)	6.1 (8.9)	.0066**
ICND[i]	3.3 (0.9)	3.7 (1.1)	0.3 (0.7)	.1094
MB-CDI Vocabulary[j]	266.0 (242.1)	278.3 (248.9)	12.3 (35.2)	.0647
ORCA[k]	50.0 (13.4)	52.9 (14.8)	2.8 (5.7)	.0714
ABC-2[l]	70.4 (20.8)	53.2 (21.6)	−17.2 (19.7)	.0013**
BPI-SF[m]	28.2 (15.6)[f]	22.7 (11.1)	−5.1 (9.4)	.0326*
VABS-3 ABC [n]	39.4 (13.1)	42.2 (14.7)	2.8 (7.8)	.1710
GIHQ Frequency[o]	41.6 (29.6)	32.1 (25.6)	−9.6 (10.8)	.0013**
CSHQ[p]	46.1 (8.0)	42.5 (5.0)	−3.6 (5.7)	.0191*

ABC-2, Aberrant Behavior Checklist-2; BPI-SF, Behavior Problems Inventory – Short Form; 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 ABC, Vineland Adaptive Behavior Scales-3 Adaptive Behavior Composite.

*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.

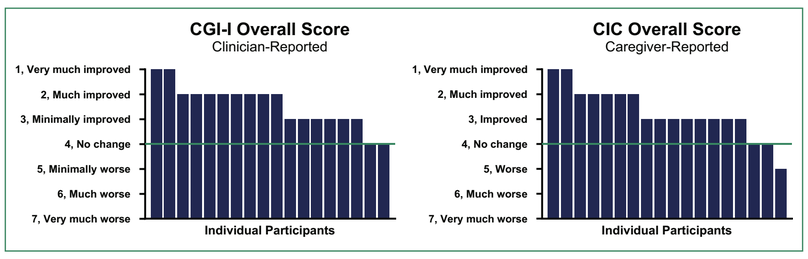
[a]Baseline scores were determined as the average scores from visits during the baseline/screening period for assessments collected at more than 1 visit during the baseline/screening period. [b]CGI-I and CIC overall scores range from 1–7; lower scores indicate improvement (below 4), a score of 4 indicates no change, and higher scores (above 4) indicate worsening. [c]Null median of 4 (no change). [d]CGI-S overall scores range from 1–7; higher scores indicate greater impairment. [e]Caregiver Top 3 Concerns total severity scores range from 0–30; higher scores indicate more severe symptoms. [f]n = 17. [g]PMS-DSRS total severity scores range from 0–20; higher scores indicate more severe symptoms. [h]QI-Disability overall scores range from 0–100; higher scores indicate a better quality of life. [i]ICND Overall QoL scores range from 1–6; higher scores indicate a better quality of life. [j]MB-CDI total vocabulary scores range from 0–680; higher scores indicate greater language development. [k]ORCA total scores range from 26.82–83.24; higher scores indicate greater communication ability. [l]ABC-2 total scores range from 0–174; higher scores indicate more behavior issues. [m]BPI-SF total frequency scores range from 0–120; higher scores indicate greater frequency of behavior problems. [n]VABS-3 adaptive behavior composite scores range from 20–140; higher scores reflect better adaptive behavior/self-care skills. [o]GIHQ total frequency scores range from 0–197; higher scores indicate greater gastrointestinal problems. [p]CSHQ total scores range from 33–99; higher scores reflect more disturbed sleep behavior.

Efficacy

- Participants who received NNZ-2591 experienced statistically significant improvements from baseline in 10 of 14 efficacy outcomes evaluating features of PMS, including clinician- and caregiver-reported assessments (**Table 3**)
- At the end of treatment, global improvements in PMS symptoms were reported for 16 of 18 participants by clinicians and for 15 of 18 participants by caregivers (**Figure 3**)
- 13 participants improved on both the clinician-reported CGI-I and caregiver-reported CIC; 16 participants had CGI-I and CIC scores within 1 point of each other
- From baseline to the end of treatment, 7 of 18 participants had a decrease in clinician-reported global PMS symptom severity (CGI-S overall score)
- A decrease in the Caregiver Top 3 Concerns total severity score from baseline to the end of treatment was reported for 14 of 17 participants

Results (cont'd)

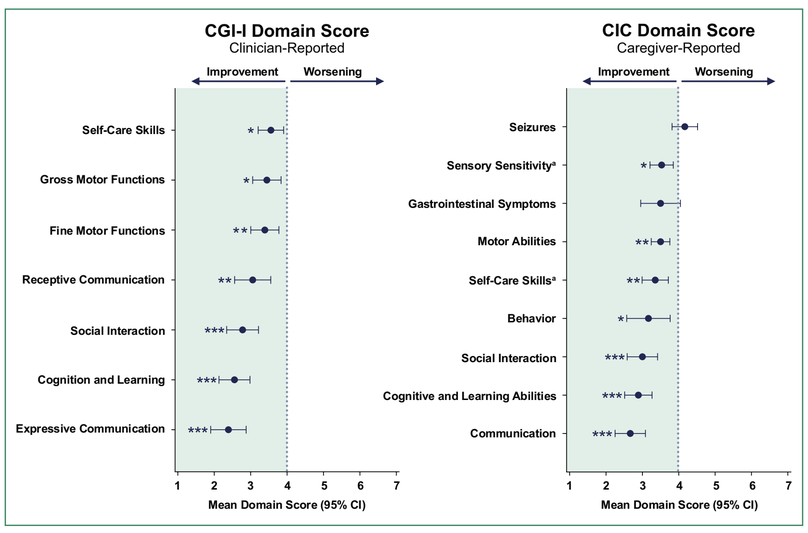
Figure 3. Global Improvements in PMS Symptoms at Week 13 Reported by Clinicians and Caregivers



CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression of Improvement; PMS, Phelan-McDermid syndrome.
CGI-I and CIC overall 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.

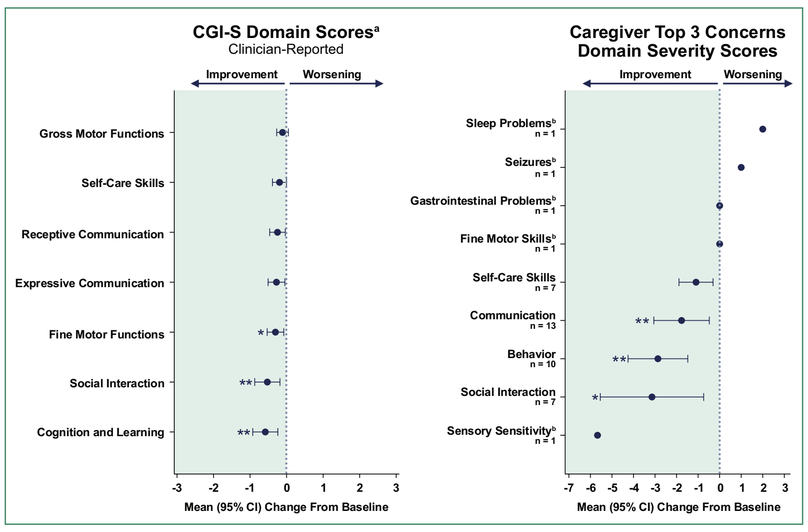
- When evaluating PMS-specific symptom domains, communication, cognition and learning, and social interaction consistently demonstrated the greatest improvements from baseline, when reported by both clinicians and caregivers (**Figure 4**)
- Clinicians reported significantly reduced symptom severity related to cognition and learning, social interaction, and fine motor function; caregivers reported significantly reduced symptom severity related to social interaction, behavior, and communication (**Figure 5**)

Figure 4. Consistent Improvements in PMS-Specific Symptoms at Week 13 Reported by Clinicians and Caregivers



CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression of Improvement; PMS, Phelan-McDermid syndrome.
*P <.05; **P <.01; ***P <.001; vs baseline based on Wilcoxon signed-rank test.
[a]n = 17.
n = 18 unless otherwise noted.
CGI-I and CIC domain 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.

Figure 5. Reduced Severity of PMS-Specific Symptoms at Week 13 Reported by Clinicians and Caregivers



CGI-S, Clinical Global Impression of Severity; PMS, Phelan-McDermid syndrome.
*P <.05; **P <.01; vs baseline based on Wilcoxon signed-rank test.
[a]n = 18. [b]For concerns that were selected by only 1 caregiver, statistical testing was not performed and error bars were not calculated.
CGI-S scores range from 1–7, with lower scores indicating less severity.
Caregiver Top 3 Concerns domain severity scores range from 0–10, with lower scores indicating less severity.

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