

NNZ-2591 in Children and Adolescents With Phelan-McDermid Syndrome

Single-Group, Open-Label, Phase 2 Trial Results

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Abstract

Background and Objectives

Phelan-McDermid syndrome (PMS) is a rare genetic neurodevelopmental disorder with no currently approved treatments. NNZ-2591, a synthetic analog of the insulin-like growth factor 1 metabolite cyclic glycine-proline, was evaluated in children and adolescents with PMS in a phase 2, multisite, open-label clinical trial.

Methods

Participants aged 3–12 years at screening received twice-daily oral NNZ-2591 for 13 weeks; doses were uptitrated from 4 mg/kg to 12 mg/kg over 6 weeks (NCT05025241). Safety and pharmacokinetic profiles were primary end points; 14 efficacy assessments were secondary end points, which included global and symptom-specific PMS assessments, quality of life, communication, behavior, adaptive behavior/self-care, gastrointestinal health, and sleep assessments. Wilcoxon signed-rank tests evaluated change from or observed change relative to baseline vs the null median, with $p < 0.05$ indicating significance.

Results

Eighteen participants received NNZ-2591 (mean [SD] age 8.6 years, mean [SD] weight: 30.4 [10.8] kg). NNZ-2591 was well tolerated; most treatment-emergent adverse events were mild to moderate. Significant improvements from baseline were observed in 10 of 14 efficacy assessments at week 13, including global and symptom-specific PMS assessments, quality of life, behavior, gastrointestinal symptoms, and sleep. At week 13, the PMS-specific Clinical Global Impression (CGI) of Improvement mean (SD) score was 2.4 (0.9) and the median (range) score was 2.0 (1.0, 4.0) ($p < 0.0001$), with 16 of 18 participants showing improvement; the PMS-specific Caregiver Impression of Change mean (SD) score was 2.7 (1.0) and the median (range) score was 3.0 (1.0, 5.0) ($p = 0.0003$), with 15 of 18 participants showing improvement. PMS-specific assessment subdomains of communication, cognition/learning, and socialization showed consistent improvements. A 24-hour steady-state area under the curve ($AUC_{24,ss}$) was estimated for each participant using a one-compartment, linear, population pharmacokinetic model where clearance and volume of distribution parameters were scaled by body weight. Participants with an NNZ-2591 $AUC_{24,ss} > 300 \mu\text{g} \cdot \text{h/mL}$ experienced improvements in the PMS-specific CGI of Improvement scores.

Discussion

For children and adolescents with PMS, NNZ-2591 appeared generally safe, with clinicians and caregivers reporting meaningful improvements in important symptoms of PMS. The benefit-risk and pharmacokinetic profiles support continued evaluation of NNZ-2591 for PMS.

Trial Registration Information

ClinicalTrials.gov; NCT05025241. Submitted August 24, 2021. First participant enrolled on August 8, 2022.

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Supplementary Material

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Glossary

ABC-2 = Aberrant Behavior Checklist, version 2; **AUC_{24,ss}** = 24-hour steady-state area under the curve; **BPI-SF** = Behavior Problems Inventory–Short Form; **CGI** = Clinical Global Impression; **CGI-I** = CGI of Improvement; **CGI-S** = CGI of Severity; **CIC** = Caregiver Impression of Change; **CSHQ** = Child Sleep Habits Questionnaire; **GIHQ** = Gastrointestinal Health Questionnaire; **IGF-1** = insulin-like growth factor 1; **MB-CDI** = MacArthur-Bates Communicative Development Inventory; **ORCA** = Observer-Reported Communication Ability; **PMS** = Phelan-McDermid syndrome; **PMS-DSRS** = PMS Clinician Domain-Specific Rating Scale; **TEAE** = treatment-emergent adverse event; **QI-Disability** = Quality of Life Inventory–Disability; **VABS-3** = Vineland Adaptive Behavior Scales-3.

Introduction

Phelan-McDermid syndrome (PMS) is a rare genetic condition associated with delayed neurodevelopment, caused by chromosomal 22q13.3 deletions or pathogenic sequence variants affecting the *SHANK3* gene.^{1,2} Individuals with PMS can experience neonatal hypotonia, global developmental delay or mild-to-profound intellectual disability, absent or severely impaired speech, and behavioral differences.² PMS manifestations can be medically complex and severe, leading to reduced quality of life in people with PMS and high levels of stress in caregivers and families.^{3,4}

There are currently no therapies approved to treat PMS. Therefore, PMS treatment approaches focus on symptom management and typically align with general guidelines for treating developmental disorders.^{2,5} Caregivers have emphasized a critical need for treatments of PMS that improve quality of life, communication, cognition, motor function, self-care, behavior, sleep, seizures, gastrointestinal functions, social interactions, and sensory problems.³

Insulin-like growth factor 1 (IGF-1) plays an important role in brain development, maturation, and neuroplasticity and is a treatment target of interest for childhood neurodevelopmental disorders.⁶ In preclinical models of PMS, including a *Shank3*-deficient mouse model and neurons derived from pluripotent stem cells from patients with PMS, treatment with IGF-1 led to improvements.^{7,8} NNZ-2591 is a synthetic analog of the IGF-1 metabolite cyclic glycine-proline that is being evaluated as a treatment for PMS. Cyclic glycine-proline regulates IGF-1 bioavailability and homeostasis through an autoregulatory mechanism.⁹ NNZ-2591 is hypothesized to treat PMS by mimicking the natural actions of cyclic glycine-proline in maintaining IGF-1 homeostasis. We report outcomes from a phase 2, open-label clinical trial of NNZ-2591 in children and adolescents with PMS, including safety, pharmacokinetics, and efficacy assessments.

Methods

Study Design and Treatment

NNZ-2591 was evaluated in children and adolescents with PMS in a phase 2, open-label clinical trial (NCT05025241). Primary end points were safety, tolerability, and pharmacokinetics;

secondary end points were efficacy assessments. This study was conducted at 4 clinical sites in the United States and consisted of a 4–6-week screening and baseline observation period, a 13-week treatment period, and a 2-week follow-up period (eFigure 1).

Participants received orally administered open-label NNZ-2591 twice daily for 13 weeks. NNZ-2591 was administered at 4 mg/kg for approximately 3 weeks, 8 mg/kg for approximately 3 weeks, and 12 mg/kg for the remainder of the 13 weeks. The data safety monitoring committee reviewed data from each participant after 2 weeks of administration of each NNZ-2591 dose level and approved dose escalation before the next higher dose was administered. The first dose of NNZ-2591 was administered in the clinic; subsequent doses were administered at home by caregivers. Doses could be taken over a 10-minute period, with at least 8 hours between doses.

Participants

Children and adolescents aged 3–12 years at screening who weighed ≥ 12 kg and had a clinical PMS diagnosis and a disease-causing (i.e., pathogenic) genetic abnormality of the *SHANK3* gene were eligible for study participation. Eligible participants may have overall PMS severity ranging from “mildly impaired” to “the most severely impaired,” as assessed by the investigator using the Clinical Global Impression (CGI) of Severity (CGI-S) rating scale with an overall score ≥ 3 . Participants could not be actively experiencing regression or loss of skills. Participants were recruited by physician or caregiver referral. Participants’ PMS genotypes were classified as terminal deletions class I (which includes deletion of only *SHANK3*, or deletion of *SHANK3* with *ARSA* and/or *ACR* and *RABL2B*), terminal deletions class II (all other terminal deletions), ring 22, unbalanced translocation, interstitial deletion, *SHANK3* pathogenic variant, and other.

Standard Protocol Approvals, Registrations, and Participant Consents

The institutional review boards at each study site reviewed and approved the study protocol, amendments, and informed consent forms before the study was initiated (Rush Institutional Review Board [IRB00001362]; Baylor Institutional Review Board [IRB00002777]; Boston Children’s Institutional Review Board [IRB00000352, IRB00010042]; and Mass General Brigham Institutional Review Board [IRB00012706, IRB00012707]). The study was conducted in accordance with the ethical principles of the Declaration of

Helsinki, the International Conference for Harmonization guidelines, and local requirements. Participants' legally authorized representatives provided written informed consent before initiating study-related activities; participants who were capable were given the opportunity to assent to participation. This study was registered on ClinicalTrials.gov, NCT05025241; the first participant was enrolled on August 8, 2022.

Assessments

Safety

Treatment-emergent adverse events (TEAEs) were recorded from the first dose of study drug through the end of the follow-up period and were summarized using the Medical Dictionary of Regulatory Activities (version 25.1). TEAEs were identified and reported by clinicians, based on clinical history and conversations with caregivers. Vital sign measurements, laboratory measures, physical examination results (neurologic, ophthalmologic, and general), and findings on electrocardiograms were evaluated throughout the study.

Pharmacokinetics

Blood samples for pharmacokinetic assessments were collected before and after dosing at weeks 2, 6, and 13. Plasma concentrations of NNZ-2591 were determined using a validated liquid chromatography with tandem mass spectrometry method, with a lower limit of quantitation of 200 ng/mL.

Efficacy

A total of 14 efficacy assessments evaluated signs and symptoms relevant to individuals with PMS. The core PMS phenotype was evaluated by clinicians and caregivers using PMS-specific global assessments (CGI of Improvement [CGI-I], Caregiver Impression of Change [CIC], and CGI-S). The PMS-specific CGI-I and CGI-S assessments were used by clinicians to measure improvement from baseline and severity of the disorder, respectively. Both CGI assessments include domains that reflect core PMS symptoms: expressive communication, receptive communication, gross motor function, fine motor function, social interaction, cognition and learning, and self-care. CGI assessment domains were developed iteratively based on data from the PMS natural history study (NCT02461420), guidance from clinicians with expertise in PMS, and feedback from PMS advocacy organizations. The CGI-I and CGI-S overall and domain scores were reported on a 7-point Likert scale; for CGI-I, lower scores reflect greater improvement; for CGI-S, lower scores reflect less severity. Clinicians scored each CGI assessment domain and then provided an overall global score considering the total clinical experience. The PMS-specific CIC is an assessment completed by caregivers that measures changes in PMS symptoms compared with baseline. Caregivers scored participants' overall function and well-being, as well as the specific symptom domains of communication, social interaction, motor abilities, seizures, cognitive and learning abilities, self-care, gastrointestinal symptoms, sensory problems, and behavior. Specific behaviors considered included hyperactivity,

aggressive behavior, tantrums, impulsivity, self-injury, and repetitive behaviors. The CIC overall score and domain scores were reported on a 7-point Likert scale, with lower scores reflecting more improvement.

Other important symptoms frequently occurring in individuals with PMS were evaluated through PMS symptom-specific assessments (PMS Clinician Domain-Specific Rating Scale [PMS-DSRS] and Caregiver Top 3 Concerns). The PMS-DSRS assessment is a clinician-completed assessment that evaluates highly impactful symptoms often comorbid with PMS, which may not be experienced by all individuals with PMS, thus capturing PMS-associated symptoms that are not included in the CGI assessments. PMS-DSRS symptom domains include gastrointestinal symptoms, seizures, sleep, sensory sensitivity, and behavior. When evaluating behavior, clinicians considered hyperactivity, aggressive behaviors, biting, hair pulling, tantrums, impulsivity, self-injury, and repetitive behaviors. The severity of each domain was rated on a 5-point Likert scale, with lower scores representing less severity; the PMS-DSRS total severity score reflects the sum of the domain scores. The PMS-specific Caregiver Top 3 Concerns assessment evaluates 3 signs or symptoms of PMS that caregivers identified at baseline to be a priority sign or symptom influencing their child's daily functioning and well-being. Caregivers identified 3 concerns from 10 clinically important symptom domains, with each concern drawn from a different symptom domain; domains included communication, social interaction, gross motor skills, fine motor skills, behavior, gastrointestinal problems, seizures, sleep, sensory sensitivity, and self-care skills. The severity of each concern was reported on a 10-point Likert scale, with lower scores reflecting less severity; the Caregiver Top 3 Concerns total severity score reflected the sum of the scores for the 3 individual concerns.

Additional assessments included measures of quality of life (Quality of Life Inventory–Disability [QI-Disability] overall score,¹⁰ Impact of Childhood Neurologic Disability Scale overall quality-of-life score¹¹), communication (MacArthur-Bates Communicative Development Inventory [MB-CDI] total vocabulary score,¹² Observer-Reported Communication Ability [ORCA] total score¹³⁻¹⁵), behavior (Aberrant Behavior Checklist, version 2 [ABC-2] total score [ABC-2 is generally reported as individual subscales],¹⁶ Behavior Problems Inventory–Short Form [BPI-SF] total frequency score¹⁷), adaptive behavior/self-care (Vineland Adaptive Behavior Scales-3 [VABS-3] adaptive behavior composite score¹⁸), gastrointestinal health (Gastrointestinal Health Questionnaire [GIHQ] total frequency score¹⁹), and sleep (Child Sleep Habits Questionnaire [CSHQ] total score²⁰).

Statistical Analysis

Sample Size

The planned sample size for this study was 20 participants. The sample size was calculated to provide a power of 0.90 to

detect a treatment difference of 0.55 units on the CGI-I using a 2-sided significance level of 0.05 based on the Wilcoxon signed-rank test.

Safety

Safety was summarized for all participants in the intent-to-treat population, consisting of all participants enrolled in the study. Safety was reported as the number and frequency of TEAEs.

Efficacy

Efficacy outcomes were evaluated in the intent-to-treat population. Within-participant changes in efficacy assessments from baseline to week 13 were evaluated. Baseline scores were based on the average scores from visits during the screening/baseline period for assessments collected at more than 1 visit during the screening/baseline period. Wilcoxon signed-rank tests evaluated the significance of the change from baseline (or observed change relative to baseline for CGI-I and CIC) vs null median. In addition, efficacy outcomes for individual participants were summarized descriptively. There was no imputation of data for completely missing assessments; if 3 or fewer items were missing from a single assessment, the last observation for that item was carried forward. Statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC).

Pharmacokinetics

A population pharmacokinetic model for NNZ-2591 was developed based on sparse pharmacokinetic sampling data from the phase 2 study of NNZ-2591 in children and adolescents with PMS reported herein, and serial pharmacokinetic sampling data from a phase 1 study of NNZ-2591 in healthy adults (NCT04379869). A base pharmacokinetic model was chosen after assessments of the compartmental structure and scaling based on allometric principles. The covariate model was developed based on assessments of covariates of interest (e.g., demographics, disease status, baseline renal and hepatic function, and genotype [deletion vs nondeletion]), with significant covariates identified in a stepwise forward-addition ($p < 0.05$) and backward-elimination ($p < 0.01$) process using the likelihood ratio test. Final model selection was based on standard residual-based diagnostics, with qualification using a prediction-corrected visual predictive check method. Individual NNZ-2591 exposures were estimated using participant-specific pharmacokinetic parameters calculated from the population pharmacokinetic model. Using an exploratory approach, 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 overall CGI-I score for each participant. CGI-I scores were plotted as rated by the investigator; scores of 1, 2, or 3 indicate improvement from baseline.

Data Availability

The data reported are part of an ongoing sponsor-led clinical development program. Given the small number of study

participants, complete data sets will not be made available within this report to protect participant privacy. The study protocol and statistical analysis plan are available in the supplementary material (eSAP).

Results

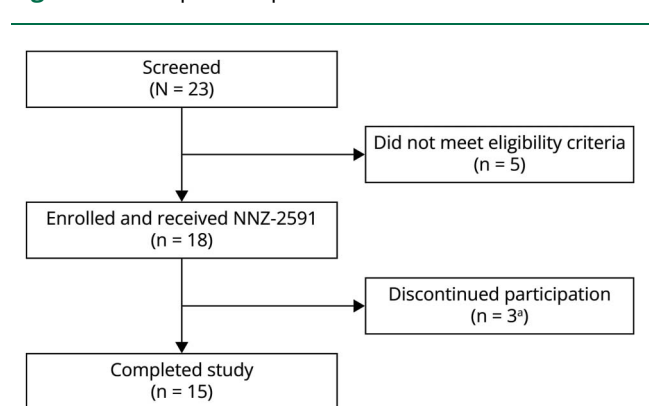
Participants

This phase 2 study was conducted between August 3, 2022, and November 1, 2023. Eighteen participants with PMS enrolled and received NNZ-2591; 15 participants completed the study (Figure 1). At baseline, participant age ranged from 4.4 to 13.0 years (Table 1); 1 participant who was 12 years old at the time of screening turned 13 years old by the baseline time point. Participants' body weights ranged from 16.8 to 51.0 kg. Most of the participants were male and White. All participants had a disease-causing (i.e., pathogenic) genetic abnormality of *SHANK3*. The most common PMS genotypes were class I terminal deletions (which include the deletion of only *SHANK3*, or deletion of *SHANK3* with *ARSA* and/or *ACR* and *RABL2B*) and *SHANK3* pathogenic variants. The average PMS severity at baseline reflected moderate-to-marked impairment (mean [SD] baseline CGI-S score of 4.5 [1.0]).

Safety

TEAEs were reported for 17 of 18 participants (Table 2). Most TEAEs were mild to moderate in severity. One severe TEAE of hyperactivity was considered possibly related to the study drug; the hyperactivity resolved the following day without modification of the NNZ-2591 dose. One serious TEAE of mild gastroenteritis, considered not related to study drug, was reported during the study follow-up period. Three participants discontinued participation because of TEAEs considered unrelated to the study drug (2 due to COVID-19 and 1 due to seizures). The most common TEAE was psychomotor hyperactivity ($n = 4$); COVID-19, decreased appetite, pyrexia, and somnolence were each reported for 3

Figure 1 Participant Disposition



*Three participants discontinued participation because of TEAEs (COVID-19, 2; seizure, 1), none of which were considered related to the study drug. TEAE = treatment-emergent adverse event.

Table 1 Baseline Demographics and Characteristics

Characteristics	NNZ-2591 N = 18
Sex, n (%)	
Male	12 (66.7)
Female	6 (33.3)
Age, y	
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)
Ethnicity, n (%)	
Hispanic or Latino	3 (16.7)
Not Hispanic or Latino	15 (83.3)
Weight, kg	
Mean (SD)	30.4 (10.8)
Median (range)	28.7 (16.8–51.0)
Height, cm, mean (SD)	130.6 (15.2)
Current seizures, n (%)	2 (11.1)
PMS genotype, n (%)	
Terminal deletions class I ^a	7 (38.9)
Terminal deletions class II ^b	3 (16.7)
Interstitial deletion	1 (5.6)
SHANK3 pathogenic variant	6 (33.3)
Comorbid psychiatric disorders, n (%)	
Autism spectrum disorder	14 (77.8)
Attention deficit disorder	5 (27.8)
Other	1 (5.6)
Stanford-Binet Intelligence Scale Nonverbal IQ standard score, mean (SD)	47.7 (5.4) ^c
Mullen Scales of Early Learning Nonverbal Developmental Quotient score, mean (SD)	15.7 (7.3) ^d

Abbreviation: PMS = Phelan-McDermid syndrome. Data are based on the intent-to-treat population.

^a Terminal deletions class I were defined as deletion of only *SHANK3*, or deletion of *SHANK3* with *ARSA* and/or *ACR* and *RABL2B*.

^b Terminal deletions class II were defined as all other terminal deletions that are not a class I deletion.

^c n = 9.

^d n = 8.

participants. No clinically significant changes were observed in laboratory values, electrocardiograms, or other safety parameters. No deaths were reported.

Population Pharmacokinetic Model

The pharmacokinetics of NNZ-2591 in children and adolescents with PMS was best described using a 1-compartment model with first-order absorption and linear clearance and volume of distribution. The exponents used to allometrically scale apparent clearance and volume of distribution by body weight were fixed at 0.75 and 1, respectively. The pharmacokinetic parameters were linear over the entire dose range. For a typical child with PMS weighing 30 kg, the values for apparent clearance, volume of distribution, and half-life were 1.89 L/hour, 20.2 L, and 7.4 hours, respectively. The estimated AUC_{24,ss} was 381 µg · h/mL after administering a twice-daily NNZ-2591 dose of 12 mg/kg for a typical child with PMS weighing 30 kg.

Assessments of Efficacy

At the end of the treatment period, participants receiving NNZ-2591 experienced statistically significant improvements from baseline in the total or overall scores of 10 of the 14 efficacy assessments evaluating clinically important aspects of PMS (Tables 3 and 4; Figure 2). Statistically significant improvements with NNZ-2591 were reported for all PMS-specific assessments, as well as quality of life, behavior, gastrointestinal symptoms, and sleep. When considering the specific symptoms comprising the PMS-specific efficacy assessments, improvements were consistently seen in communication, cognition/learning, and social interaction (Figure 2; eFigures 2 and 3).

At the end of the treatment, clinicians reported global improvements in PMS symptoms compared with baseline for 16 of 18 participants on the CGI-I overall score (Figure 2A). Caregivers reported improvements for 15 of 18 participants on the CIC overall score (Figure 2B). In total, 13 of 18 participants improved on both the clinician-reported CGI-I overall score and caregiver-reported CIC overall score from baseline to the end of treatment. Of the 5 participants who did not improve on both the CGI-I and CIC overall scores, 2 improved on the CIC with no change on the CGI-I, 2 improved on the CGI-I with no change on the CIC, and 1 improved on the CGI-I and worsened on the CIC. At the end of treatment, 16 of 18 participants had CGI-I and CIC overall scores within 1 point of each other, which is generally considered reliable for inter-rater scores of global improvement assessments. The Pearson correlation coefficient between the CGI-I and the CIC overall scores at the end of treatment was 0.29. From baseline to the end of treatment, 7 of 18 participants experienced a 1-point reduction in clinician-reported global symptom severity as measured by the CGI-S overall score.

Clinicians reported statistically significant improvements from baseline for the symptom domains of expressive and receptive communication, cognition and learning, social interaction, fine and gross motor functions, and self-care skills, based on CGI-I scores at week 13 (Figure 2C). Caregivers reported statistically significant improvements from baseline

Table 2 Safety Overview

Event, n (%)	NNZ-2591 N = 18
Any TEAE	17 (94.4)
Serious TEAEs	1 (5.6) ^a
TEAEs leading to study discontinuation	3 (16.7) ^b
Severe TEAEs	1 (5.6)
Death due to TEAEs	0
TEAEs occurring in ≥3 participants	
Psychomotor hyperactivity	4 (22.2)
COVID-19	3 (16.7)
Decreased appetite	3 (16.7)
Pyrexia	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)

Abbreviation: TEAEs = treatment-emergent adverse events.

^a One serious adverse event of gastroenteritis occurred during the post-treatment safety follow-up period; the event was considered not related to the study drug.

^b Three participants discontinued participation because of adverse events (2, COVID-19; 1, seizures); all were considered not related to the study drug.

in communication, cognition and learning, social interaction, behavior, self-care skills, motor abilities, and sensory sensitivities, based on CIC scores (Figure 2D). Communication, cognition and learning, and social interaction consistently had the greatest improvements from baseline to week 13, based on the CGI-I and CIC scores. Clinicians reported statistically significant reductions in symptom severity related to cognition and learning, social interaction, and fine motor function based on CGI-S scores (eFigure 2).

Statistically significant improvements were reported for PMS symptom-specific assessments at the end of the treatment period compared with baseline (Caregiver Top 3 Concerns, PMS-DSRS) (Table 3). Decreased severity in the top 3 concerns identified by caregivers was reported for 14 of 17 participants (Caregiver Top 3 Concerns total severity score); caregivers reported statistically significant reductions in

symptom severity related to social interaction, behavior, and communication (eFigure 3). At the end of the treatment, 7 of 18 participants experienced reductions in the clinician-reported PMS-DSRS total symptom severity score, with the greatest improvements reported in sleep and behavior.

At week 13 of NNZ-2591 treatment, statistically significant improvements were reported for assessments evaluating quality of life (QI-Disability overall score), behavior (ABC-2 total score, BPI total frequency score), gastrointestinal symptoms (GIHQ total frequency score), and sleep (CSHQ total score) (Table 4). Assessments evaluating communication outcomes showed statistically significant improvements at the end of treatment for the VABS-3 receptive communication subdomain (raw score change from baseline: mean [SD], 7.5 [7.8]; median [range], 6.0 [-3.0, 29.0]; $p = 0.0001$; growth scale value change from baseline: mean [SD], 12.1 [13.7]; median [range], 8.0 [-3.0, 51.0]; $p = 0.0002$) and expressive communication subdomain (raw score change from baseline: mean [SD], 3.3 [5.7]; median [range], 3.5 [-9.0, 14.0]; $p = 0.0298$; growth scale value change from baseline: mean [SD], 6.8 [9.6]; median [range], 7.0 [-10.0, 25.0]; $p = 0.0130$). Numerical improvements at week 13 of treatment were reported for other measures of communication (ORCA total score, MB-CDI total vocabulary score).

Exposure-Response Relationship

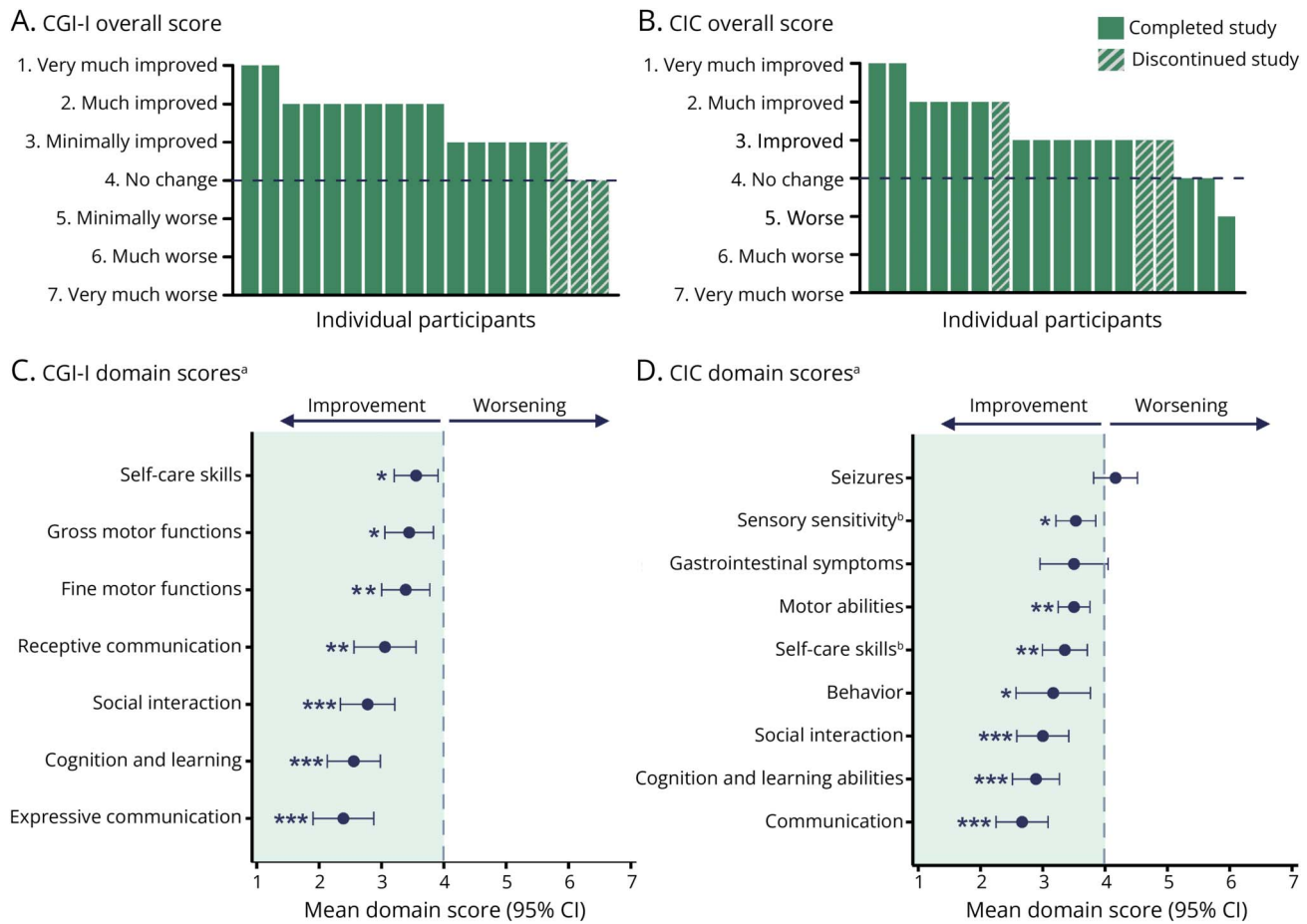
All 15 participants who received 13 weeks of treatment with NNZ-2591 had an $AUC_{24,ss} > 300 \mu\text{g} \cdot \text{h/mL}$ and showed improvement on the PMS-specific CGI-I (Figure 3). Thus, $300 \mu\text{g} \cdot \text{h/mL}$ was established as the target minimum NNZ-2591 exposure.

Discussion

In this phase 2, open-label, clinical trial, NNZ-2591 was well tolerated with a favorable safety profile in children and adolescents with PMS. Most TEAEs were mild to moderate in severity, and no deaths were reported. No clinically significant changes in laboratory values, electrocardiograms, or other safety parameters were reported. Among participants who discontinued the study because of TEAEs, none of the TEAEs were considered related to the study drug.

Participants with PMS who received NNZ-2591 experienced significant improvements from baseline in 10 of 14 efficacy assessments evaluating signs and symptoms of PMS, with concordance between clinician-reported and caregiver-reported assessments. There is currently no widely accepted gold-standard PMS outcome assessment or syndrome-specific rating scale for PMS that is appropriate for use in clinical trials evaluating PMS treatment.³ Five PMS-specific efficacy measures were developed and used in the phase 2 trial of NNZ-2591 for PMS (PMS-specific CGI-I/CGI-S, CIC, Caregiver Top 3 Concerns, and PMS-DSRS); PMS-specific efficacy measures were designed to capture both global and

Figure 2 Impressions of Overall PMS Symptom Improvement at Week 13 by Clinicians (A) and Caregivers (B), and Impressions of Individual Symptom Domain Improvements by Clinicians (C) and Caregivers (D) on the PMS-Specific CGI-I and CIC



* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ for observed change relative to baseline vs null median of 4 (no change) based on the Wilcoxon signed-rank test. ^a $n = 18$ (unless otherwise noted). ^b $n = 17$. CGI-I and CIC overall scores and domain scores range from 1 to 7; lower scores indicate improvement (below 4), a score of 4 indicates no change, and higher scores (above 4) indicate worsening. CIC = Caregiver Impression of Change; CGI-I = Clinical Global Impression of Improvement; PMS = Phelan-McDermid syndrome.

symptom-specific improvements after NNZ-2591 treatment. Together, these measures evaluated domains reflecting the core PMS phenotype (expressive communication, receptive communication, gross motor function, fine motor function, social interaction, cognition and learning, and self-care), and other highly impactful comorbid symptoms often seen in individuals with PMS (gastrointestinal symptoms, seizures, sleep, sensory sensitivity, and behavior). Significant improvements with NNZ-2591 were reported for all PMS-specific assessments. Both clinicians and caregivers reported improvements in communication, cognition and learning, and social interaction across PMS-specific assessment subdomains. Notably, communication and cognitive function were identified as the primary symptoms caregivers wished to improve for individuals with PMS during a patient-focused listening session.³ Complementary improvements were observed in non-PMS-specific assessments, including those evaluating quality of life, behavior, gastrointestinal symptoms,

and sleep; it is important to note that these symptom areas were identified as areas of concern for people with PMS, based on caregiver observation.³ Using PMS-specific assessments that are capable of capturing change in important aspects of PMS, such as those used in this study, may help guide treatment decisions and support additional clinical trials for individuals with PMS.³

Visual assessment of the pharmacokinetic exposure-response relationship showed that the target minimum $AUC_{24,ss}$ exposure of NNZ-2591 associated with clinical improvements in children with PMS is $300 \mu\text{g} \cdot \text{h}/\text{mL}$. Exposure projections support using similar dose levels of NNZ-2591 as were evaluated in the phase 2 clinical trial to achieve the target minimum NNZ-2591 exposure in future studies of children with PMS. Based on the mechanism of action of NNZ-2591, extended or ongoing treatment in future studies is expected to yield sustained or improved results by mimicking the natural actions of cyclic glycine-proline through restoring depressed

Table 3 PMS-Specific Efficacy Assessments With NNZ-2591

Assessment	NNZ-2591 N = 18			p Value
	Baseline ^a	Week 13	Change from baseline	
CGI-I overall score^b				
Mean (SD)	—	2.4 (0.9)	—	
Median (range)	—	2.0 (1.0–4.0)	—	<0.0001*** ^c
CIC overall score^b				
Mean (SD)	—	2.7 (1.0)	—	
Median (range)	—	3.0 (1.0–5.0)	—	0.0003*** ^c
CGI-S overall score^d				
Mean (SD)	4.5 (1.0)	4.1 (1.0)	–0.4 (0.5)	
Median (range)	4.5 (3.0–6.0)	4.0 (2.0–6.0)	0.0 (–1.0 to 0.0)	0.0156*
Caregiver Top 3 Concerns, total severity score^e				
Mean (SD)	25.9 (3.4) ^f	20.1 (7.1) ^f	–5.9 (5.9) ^f	
Median (range)	26.7 (18.3–30.0) ^f	20.0 (9.0–30.0) ^f	–6.7 (–21.0 to 3.0) ^f	0.0005***
PMS-DSRS total severity score^g				
Mean (SD)	5.7 (2.1)	4.7 (2.2)	–0.9 (1.7)	
Median (range)	5.5 (2.0–10.0)	4.0 (2.0–10.0)	0.0 (–6.0 to 0.5)	0.0156*

Abbreviations: CGI-I = Clinical Global Impression of Improvement; CGI-S = Clinical Global Impression of Severity; CIC = Caregiver Impression of Change; PMS = Phelan-McDermid syndrome; PMS-DSRS = PMS Clinician Domain-Specific Rating Scale.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ for change from baseline (or observed change relative to baseline for CGI-I and CIC) vs null median based on the Wilcoxon signed-rank test.

^a Baseline scores were determined as the average scores from visits during the screening/baseline period for assessments collected at more than 1 visit during the screening/baseline period.

^b CGI-I and CIC overall scores range from 1 to 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 to 7; higher scores indicate greater impairment.

^e Caregiver Top 3 Concerns total severity scores range from 0 to 30; higher scores indicate more severe symptoms.

^f $n = 17$.

^g PMS-DSRS total severity scores range from 0 to 20; higher scores indicate more severe symptoms.

bioavailability of IGF-1, reducing overactivity of the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) signaling pathway (which is crucial for synaptic plasticity), and decreasing expression of inflammatory signaling molecules.

Limitations of this study include the short duration of 13 weeks and the follow-up period of 2 weeks, which may have limited the ability to observe changes in symptoms that are more variable or slower to change. By design, this study was open label and did not include a placebo comparator; future blinded studies with a placebo control group will enhance understanding of the safety and efficacy of NNZ-2591. Furthermore, clinician-rated and caregiver-rated measures, particularly global impression instruments, may be subject to expectancy bias, which could have influenced study outcomes. This study included a relatively small number of participants who received NNZ-2591. Owing to the small sample size, multiplicity adjustments were not conducted for statistical evaluation of end points, which increased the risk of type I

error. When prioritizing key end points in future placebo-controlled studies, syndrome-specific global impression measures such as the CGI-I and CIC are important because they can capture the broad and heterogeneous symptoms of PMS; in addition, given the importance of improved communication for caregivers³ and the observed improvements in communication with NNZ-2591, the VABS-3 receptive communication subdomain should also be considered for prioritization. The visual approach used to estimate the target minimum $AUC_{24,ss}$ associated with clinical improvements based on the CGI-I was exploratory and may have been subject to interpretation bias. In addition, study participants had a range of different PMS genotypes (terminal deletions, interstitial deletions, and *SHANK3* pathogenic variants), which may have contributed to variation in PMS presentation among participants at baseline because the PMS genotype can affect the PMS phenotype.²¹

In this phase 2, open-label clinical trial, NNZ-2591 was safe and well tolerated at doses up to 12 mg/kg over 13 weeks.

Table 4 Other Efficacy Assessments With NNZ-2591

Assessment	NNZ-2591 N = 18			p Value
	Baseline ^a	Week 13	Change from baseline	
QI-Disability overall score^b				
Mean (SD)	64.7 (8.1)	70.9 (11.7)	6.1 (8.9)	
Median (range)	64.4 (44.6–81.3)	68.9 (47.4–90.1)	4.7 (–9.3 to 23.3)	0.0066**
ICND overall QoL score^c				
Mean (SD)	3.3 (0.9)	3.7 (1.1)	0.3 (0.7)	
Median (range)	3.5 (2.0–5.0)	4.0 (1.0–5.0)	0.0 (–1.0 to 0.0)	0.1094
MB-CDI total vocabulary score^d				
Mean (SD)	266.0 (242.1)	278.3 (248.9)	12.3 (35.2)	
Median (range)	206.5 (0.0–680.0)	250.0 (9.0–679.0)	10.5 (–63.0 to 114.0)	0.0647
ORCA total score^e				
Mean (SD)	50.0 (13.4)	52.9 (14.8)	2.8 (5.7)	
Median (range)	48.9 (25.8–72.3)	54.2 (25.8–79.2)	0.9 (–4.0 to 17.0)	0.0714
ABC-2 total score^f				
Mean (SD)	70.4 (20.8)	53.2 (21.6)	–17.2 (19.7)	
Median (range)	74.3 (37.0–112.7)	48.0 (9.0–97.0)	–15.2 (–71.7 to 9.7)	0.0013**
BPI-SF total frequency score^g				
Mean (SD)	28.2 (15.6) ^h	22.7 (11.1)	–5.1 (9.4)	
Median (range)	27.0 (1.0–71.0)	23.5 (0.0–40.0)	–2.0 (–32.0 to 5.0)	0.0326*
VABS-3 ABC standard scoreⁱ				
Mean (SD)	39.4 (13.1)	42.2 (14.7)	2.8 (7.8)	
Median (range)	38.5 (24.0–69.0)	41.5 (24.0–72.0)	0.5 (–5.0 to 31.0)	0.1710
GIHQ total frequency score^j				
Mean (SD)	41.6 (29.6)	32.1 (25.6)	–9.6 (10.8)	
Median (range)	32.7 (6.7–116.0)	29.0 (1.0–86.0)	–8.5 (–33.0 to 7.3)	0.0013**
CSHQ total score^k				
Mean (SD)	46.1 (8.0)	42.5 (5.0)	–3.6 (5.7)	
Median (range)	46.5 (34.5–61.0)	42.0 (34.0–52.0)	–2.7 (–14.0 to 8.5)	0.0191*

Abbreviations: ABC-2 = Aberrant Behavior Checklist, version 2; BPI-SF = Behavior Problems Inventory–Short Form; CSHQ = Child Sleep Habits Questionnaire; GIHQ = Gastrointestinal Health Questionnaire; ICND = Impact of Childhood Neurologic Disability Scale; MB-CDI = MacArthur-Bates Communicative Development Inventory; ORCA = Observer-Reported Communication Ability; PMS = Phelan-McDermid syndrome; QI-Disability = Quality of Life Inventory–Disability; VABS-3 ABC = Vineland Adaptive Behavior Scales-3 adaptive behavior composite.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ for change from baseline vs null median based on the Wilcoxon signed-rank test.

^a Baseline scores were determined as the average scores from visits during the screening/baseline period for assessments collected at more than 1 visit during the screening/baseline period.

^b QI-Disability overall scores range from 0 to 100; higher scores indicate a better quality of life.

^c ICND overall QoL scores range from 1 to 6; higher scores indicate better quality of life.

^d MB-CDI total vocabulary scores range from 0 to 680; higher scores indicate greater language development.

^e ORCA total scores range from 26.82 to 83.24; higher scores indicate greater communication ability.

^f ABC-2 total scores range from 0 to 174; higher scores indicate more behavior issues.

^g BPI total frequency scores range from 0 to 120; higher scores indicate greater frequency of behavior problems.

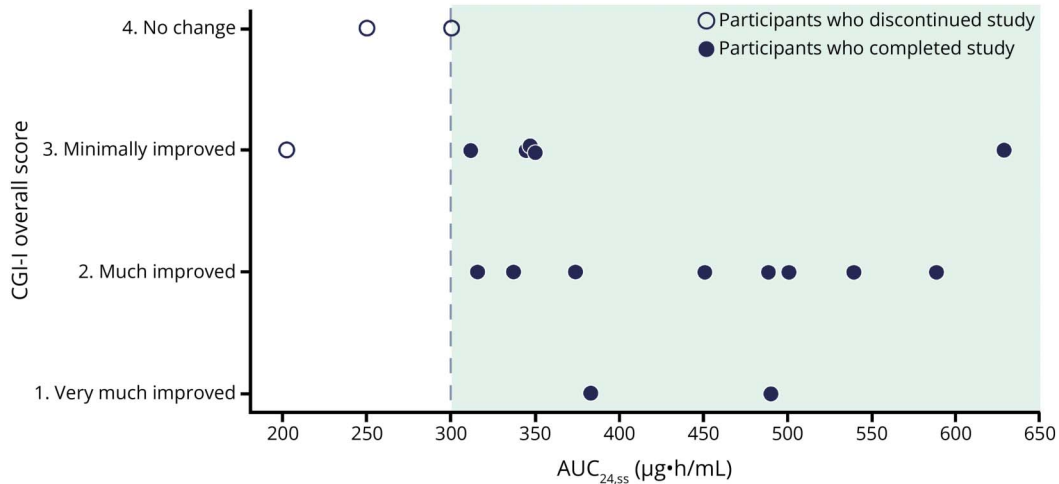
^h $n = 17$.

ⁱ VABS-3 composite scores range from 20 to 140; higher scores reflect better adaptive behavior/self-care skills.

^j GIHQ total frequency scores range from 0 to 197; higher scores indicate greater gastrointestinal problems.

^k CSHQ total scores range from 33 to 99; higher scores reflect more disturbed sleep behavior.

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



AUC_{24,ss} was calculated as the daily dose divided by apparent clearance. Dashed line represents target minimum exposure, which was determined based on visual assessment. AUC_{24,ss} = 24-hour steady-state area under the curve; CGI-I = Clinical Global Impression of Improvement; PMS = Phelan-McDermid syndrome.

Improvements were reported across important aspects of PMS, including global clinician-reported and caregiver-reported assessments of PMS, quality of life, behavior, gastrointestinal symptoms, and sleep, providing preliminary evidence of efficacy. Improvements were noted for PMS symptoms that caregivers consider important, including communication and cognitive function.³ Given the lack of treatment options for PMS, these findings are encouraging. The favorable benefit-risk assessment of NNZ-2591 described herein supports its continued evaluation for the treatment of PMS.

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Author Contributions

A.M. Neumeyer: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. S. Srivastava: drafting/revision of the manuscript for content, including medical writing for content;

major role in the acquisition of data. J.L. Holder Jr.: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. M.A. Milad: analysis or interpretation of data. L. Squires: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. N.E. Jones: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. L. Glass: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. E. Berry-Kravis: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data.

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