Safety, Efficacy, Pharmacokinetics, and Pharmacodynamics of NNZ-2591 in Children and Adolescents With Pitt Hopkins Syndrome

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Objective

To evaluate the treatment effects, pharmacokinetics, and pharmacodynamics of NNZ-2591 for children and adolescents with Pitt Hopkins syndrome (PTHS)

Conclusions

NNZ-2591 was safe and well tolerated in children and adolescents with PTHS

Significant improvements were observed in all clinician- and caregiver-reported PTHS-specific efficacy measures

The pharmacokinetic model and exposure-response findings support the dose selection and continued evaluation of NNZ-2591 for PTHS

Background

- Pitt Hopkins syndrome (PTHS), a rare genetic neurodevelopmental disorder caused by mutations affecting the *TCF4* gene, is associated with developmental delay[1]
- PTHS symptoms are broad and severe, commonly including intellectual impairment, language deficits, respiratory abnormalities, sleep challenges, gastrointestinal dysfunction, motor impairment, sensory processing differences, repetitive behaviors, and self-injury[1]
- While medications can help manage PTHS symptoms, there are no available therapies that treat the underlying syndrome[1]
- NNZ-2591, an investigative drug that is a synthetic analog of the insulin-like growth factor 1 (IGF-1) metabolite cyclic glycine-proline, is being evaluated to treat PTHS in children and adolescents

Methods

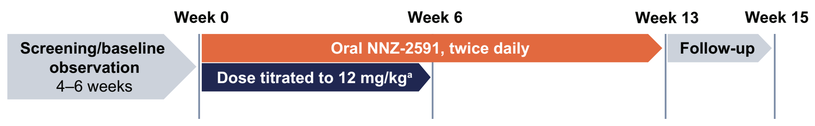
Study Design and Participants

- NNZ-2591 was evaluated to treat PTHS in a multi-site, 13-week, open-label, phase 2 clinical trial (NCT05025332; **Figure 1**)
- Eligibility criteria included a clinical PTHS diagnosis with a documented disease-causing genetic etiology, age of 3–17 years, and weight ≥ 12 kg at screening

Methods (cont'd)

- Primary endpoints included safety, tolerability, and pharmacokinetics (PK); secondary endpoints included efficacy measures

Figure 1. Study Design



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

Assessments and Analysis

Safety

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

Efficacy

- Efficacy assessments evaluated clinically important symptoms of PTHS and included 4 measures developed to specifically evaluate PTHS:
  - Clinical Global Impression of Improvement (CGI-I)
  - Clinical Global Impression of Severity (CGI-S)
  - Caregiver Impression of Change (CIC)
  - Caregiver Top 3 Concerns Severity
- Other efficacy assessments measured gastrointestinal health, quality of life, sleep, communication, behavior, adaptive behavior/self-care, and motor function
- Improvements in efficacy measures vs baseline were evaluated using the Wilcoxon signed-rank test; statistical tests were nominal and there was no type I error control

Pharmacokinetics

- Sparse 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
- A population PK model was developed by updating a previous model of NNZ-2591 PK (developed from studies in healthy adults [NCT04379869] and individuals with Phelan-McDermid syndrome [PMS; NCT05025241])[2] with the addition of PK sampling data from the phase 2 trial of NNZ-2591 in children and adolescents with PTHS
- Each participant's estimated NNZ-2591 exposure was calculated by sparse non-compartmental analysis
- An exposure-response plot illustrated the relationship between participants' 24-hour steady-state area under the curve ($AUC_{24,ss}$) of NNZ-2591 and CGI-I scores

Results

Participants

- Of the 16 participants enrolled, 11 completed the study
- Among participants enrolled in the study, half were female, the mean age was 9.1 years, and most were White (**Table 1**)

Table 1. Demographics

Characteristic	NNZ-2591 N = 16
Sex, n (%)	
Female	8 (50)
Male	8 (50)
Age, years	
Mean (SD)	9.1 (4.6)
Median (range)	9.5 (3, 16)
Race, n (%)	
White	11 (69)
Asian	3 (19)
Black	1 (6)
Other	1 (6)
Weight, kg	
Mean (SD)	28.6 (12.3)
Median (range)	26.2 (12.3, 50.0)

Safety

- NNZ-2591 was well tolerated and demonstrated a favorable safety profile over 13 weeks (**Table 2**)
  - All TEAEs were mild to moderate in intensity; none were serious
  - Most TEAEs were not related to the study drug
- Among the 4 participants who discontinued the study drug due to TEAEs, all TEAEs were mild or moderate in intensity and resolved
- No meaningful trends in laboratory values, electrocardiogram findings, or other safety parameters were observed

Table 2. Safety Overview

Parameter, n (%)	NNZ-2591 N = 16
Any TEAE	15 (94)
Any serious TEAE	0
TEAE by intensity	
Mild	12 (75)
Moderate	3 (19)
Severe	0
TEAE leading to study drug discontinuation[a]	4 (25)
Death due to TEAE	0

TEAE, treatment-emergent adverse event.
[a]Included 2 due to TEAEs unrelated to study drug (COVID-19; mild vomiting, diarrhea, and lethargy); 1 due to moderate constipation, self-injury, abdominal distention, and fatigue (all related to study drug); and 1 due to mild sleep disorder and constipation (both related to study drug).

Pharmacokinetics

- An allometrically scaled 1-compartment PK model with first-order absorption and linear clearance was developed to describe the PK of NNZ-2591 in children and adolescents with PTHS
  - 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
  - The PK of NNZ-2591 was dose proportional over the evaluated range
  - A prediction-corrected visual predictive check showed that the PK model adequately captured the central tendency and range of the data in healthy participants, in children with PTHS, in children with PMS, and overall
- The PK parameters of NNZ-2591 for a typical male child with PTHS weighing 30 kg were estimated from the population PK model (**Table 3**)

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

Parameter	NNZ-2591 12 mg/kg, twice daily
Apparent clearance (CL/F), L/h	1.9
Apparent volume of distribution (V/F), L	21.3
Half-life, h	7.8
$AUC_{24,ss}$[a], µg•h/mL	379

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

Efficacy

- Clinicians and caregivers observed significant improvements in all PTHS-specific efficacy measures at the end of treatment vs baseline ($P < .05$), among all participants and those who completed the study (**Table 4**)
- Changes from baseline to the end of treatment for non–PTHS-specific measures total or overall scores did not reach significance

Table 4. PTHS-Specific Efficacy Measures

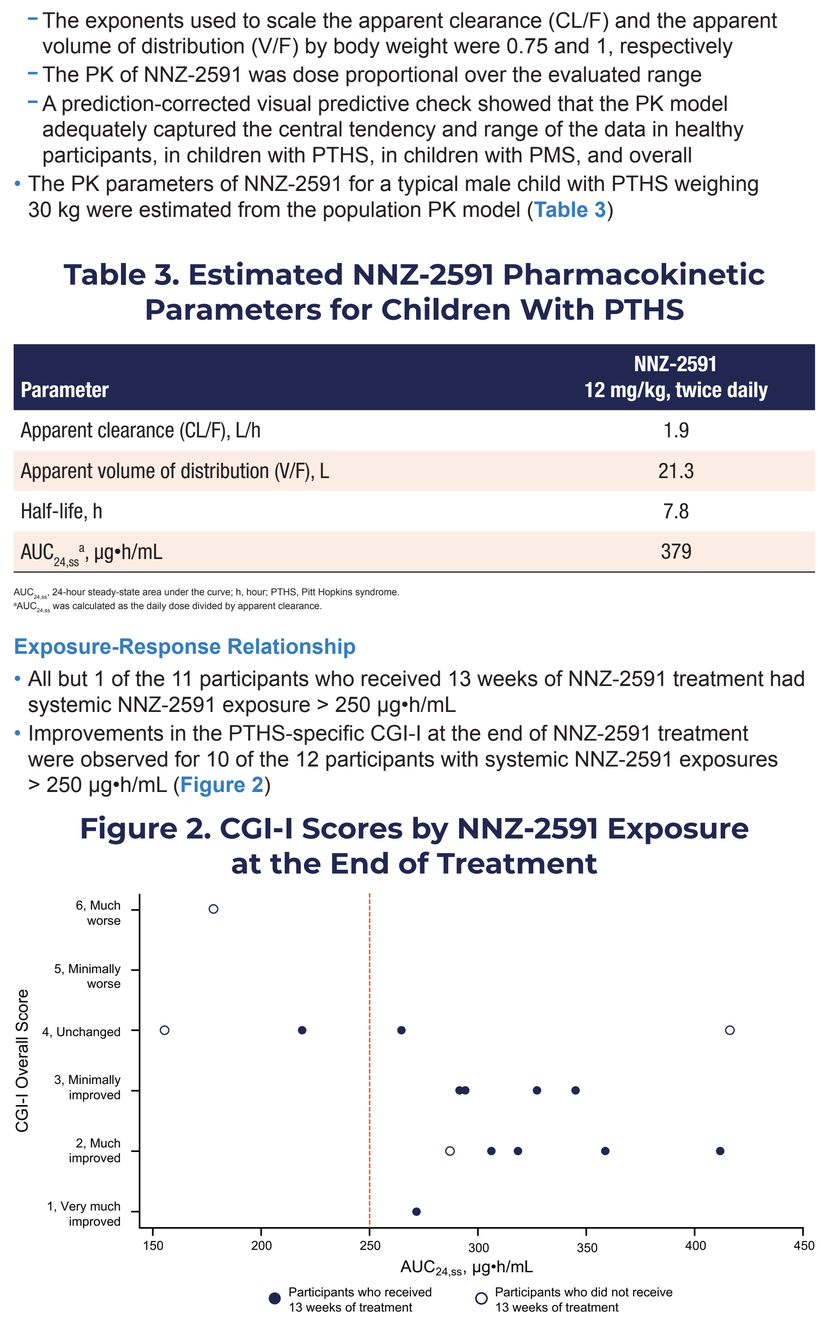
Measure, overall or total score	NNZ-2591 Participants who completed the study n = 11 Baseline	Week 13	Change from Baseline	*P* value	All participants n = 16[a] Baseline	End of Treatment	Change from Baseline	*P* value
CGI-I								
Mean (SD)	—	2.6 (0.9)	—	—	—	3.0 (1.3)	—	—
Median (range)	—	3.0 (1, 4)	—	.0039	—	3.0 (1, 6)	—	.0205
CIC								
Mean (SD)	—	3.0 (1.0)	—	—	—	3.2 (0.9)	—	—
Median (range)	—	3.0 (2, 5)	—	.0234	—	3.0 (2, 5)	—	.0137
CGI-S								
Mean (SD)	5.1 (0.7)	4.5 (0.5)	−0.5 (0.5)	—	5.0 (0.7)	4.5 (0.6)	−0.5 (0.5)	
Median (range)	5.0 (4, 6)	5.0 (4, 5)	−1.0 (−1, 0)	.0313	5.0 (4, 6)	5.0 (3, 5)	−0.5 (−1, 0)	.0078
Caregiver Top 3 Concerns								
Mean (SD)	9.4 (0.7)	7.8 (2.0)	−1.6 (1.5)	—	9.2 (0.7)	7.6 (2.0)	−1.6 (1.5)	—
Median (range)	9.8 (8.1, 10.0)	8.7 (4.0, 10.0)	−1.3 (−4.1, 0)	.0039	9.0 (8.0, 10.0)	7.8 (4.0, 10.0)	−1.5 (−4.1, 0.4)	.0015

CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; PTHS, Pitt Hopkins syndrome.
[a]Not all participants completed the study; data are reported at the end of treatment visit.

Exposure-Response Relationship

- All but 1 of the 11 participants who received 13 weeks of NNZ-2591 treatment had systemic NNZ-2591 exposure > 250 µg•h/mL
- Improvements in the PTHS-specific CGI-I at the end of NNZ-2591 treatment were observed for 10 of the 12 participants with systemic NNZ-2591 exposures > 250 µg•h/mL (**Figure 2**)

Figure 2. CGI-I Scores by NNZ-2591 Exposure at the End of Treatment



$AUC_{24,ss}$, 24-hour steady-state area under the curve; CGI-I, Clinical Global Impression of Improvement.
Dashed line represents an NNZ-2591 exposure of 250 µg•h/mL.

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