NNZ-2591 for the Treatment of Angelman Syndrome: Results From a Phase 2 Open-Label Study

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Objective

To evaluate the safety and efficacy of treatment with oral liquid NNZ-2591, a synthetic analog of the insulin-like growth factor 1 metabolite cyclic glycine-proline, in children and adolescents with Angelman syndrome in a phase 2, 13-week, open-label clinical trial

Conclusions

NNZ-2591 was generally safe and well tolerated in children and adolescents with Angelman syndrome

Significant and meaningful improvements were seen by both clinicians and caregivers in global efficacy measures designed specifically to evaluate Angelman syndrome

Improvements occurred in important aspects of Angelman syndrome, including communication, behavior, cognition, and motor abilities

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References

1. Maranga C, et al. *FEBS J*. 2020;287:2154–75.
2. Manssen L, et al. *Neuropediatrics*. 2025;56:69–82.
3. Duis J, et al. *Mol Genet Genomic Med*. 2022;10:e1843.
4. Guan J, Gluckman PD. *Br J Pharmacol*. 2009;157:881–91.

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Background

- Angelman syndrome (AS) is a rare neurodevelopmental disorder caused by a loss of function of *UBE3A* on the maternal allele[1–3]
- AS is characterized by developmental delays, communication and motor disorders, ataxia, and seizures[1–3]
- There are no advanced therapies available to treat AS to date; the current standard-of-care treatment for AS is focused on managing symptoms[1–2]
- NNZ-2591 is a synthetic analog of cyclic glycine-proline, a metabolite of insulin-like growth factor 1 (IGF-1) that occurs naturally in the brain, and is formulated to be stable, is orally bioavailable, and can readily cross the blood-brain barrier[4]
- NNZ-2591 is an investigative drug under evaluation in children and adolescents with AS

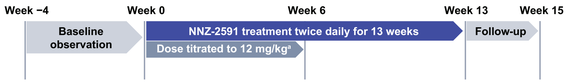
Methods

Study Design and Participants

- NNZ-2591 was evaluated for AS in a phase 2, 13-week, open-label clinical trial conducted at 3 sites in Australia (NCT05011851; Figure 1)
- Participants were aged 4–17 years with genetically confirmed AS and a Clinical Global Impression-Severity (CGI-S) score ≥ 3 at baseline
- Primary endpoints included safety and tolerability; secondary endpoints included efficacy measures

Methods (cont'd)

Figure 1. Study Design



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

Assessments and Analysis

- Safety was evaluated by summarizing the number and frequency of treatment-emergent adverse events (TEAEs)
- There are currently few clinical outcome measures specific to AS; thus, we used recently developed AS-specific efficacy measures
- Clinician- and caregiver-assessed AS-specific measures of treatment change included the Clinical Global Impression of Improvement (CGI-I) and Caregiver Impression of Change (CIC; Figure 2)
  - CGI-I and CIC scores reflect overall improvement from baseline rated on a 7-point scale
  - The clinician or caregiver gives an overall score and a score for each domain
- Other efficacy assessments included the Bayley Scales of Infant Development 4 (Bayley-4) scales (clinician assessed)
- Safety was assessed in all participants who received ≥ 1 dose of NNZ-2591, while efficacy measures were assessed among participants who completed the end-of-treatment visit
- Changes in efficacy measures were evaluated using the Wilcoxon signed-rank test
- Statistical tests were nominal and there was no type I error control

Figure 2. Clinician- and Caregiver-Assessed Outcomes for AS

Parameter	Measures of Improvement	
	CGI-I	CIC
Assessor	Clinician	Caregiver
Scale	Very much improved (1) – Much improved (2) – (Minimally) improved (3) – No change (4) – (Minimally) worse (5) – Much worse (6) – Very much worse (7)	
Domains	Behavior, communication, gross motor function, fine/oral motor function, and sleep	Behavior, communication, motor abilities, seizures, cognitive abilities/ability to learn, self-care skills, and GI symptoms

AS, Angelman syndrome; CGI-I, Clinical Global Impression of Improvement; CIC, Caregiver Impression of Change; GI, gastrointestinal.
Clinician raters completed training to calibrate scoring and anchor interpretation (at study initiation and again during the study).
Parentheses around "minimally" reflect that this term is used for the CGI-I and not used for the CIC.

Results

Participants

- A total of 16 participants were enrolled and 13 completed the study; 3 patients discontinued due to inability to complete safety measures (n = 1), protocol deviation (COVID-19 at screening, n = 1), or adverse event (COVID-19, not related to study drug, n = 1)
- Among enrolled participants, 9 (56%) were female and the mean age was 10.1 years; AS severity at baseline reflected moderate/marked impairments (Table 1)

Table 1. Baseline Demographics

Characteristic	NNZ-2591 N = 16
Sex, n (%)	
Female	9 (56)
Male	7 (44)
Age, years	
Mean (SD)	10.1 (4.5)
Median (range)	9.5 (4, 17)
Race, n (%)	
White	9 (56)
Asian	0
Black	0
Other	2 (13)
Multiple	1 (6)
Not reported	4 (25)
Weight, kg	
Mean (SD)	40.5 (18.5)
Median (range)	41.8 (17.5, 76.9)
Genotype, n (%)	
Deletion	9 (56)
Nondeletion	7 (44)
Nonverbal DQ, n (%)	
≥ 20	4 (25)
< 20	12 (75)
Baseline CGI-S, mean (SD)	4.8 (0.75)

CGI-S, Clinical Global Impression of Severity; DQ, Developmental Quotient.

Safety

- NNZ-2591 was well-tolerated over 13 weeks of treatment (Table 2)
- TEAEs were experienced by 14 of 16 participants (88%) during the study; most were mild to moderate, and not related to study drug
- There were 0 serious TEAEs, and 1 participant discontinued due to a TEAE of COVID-19 (not related to study drug)
- No meaningful changes in laboratory values, findings on electrocardiogram, or other safety parameters were observed during treatment

Table 2. Adverse Events Occurring in ≥ 2 Participants

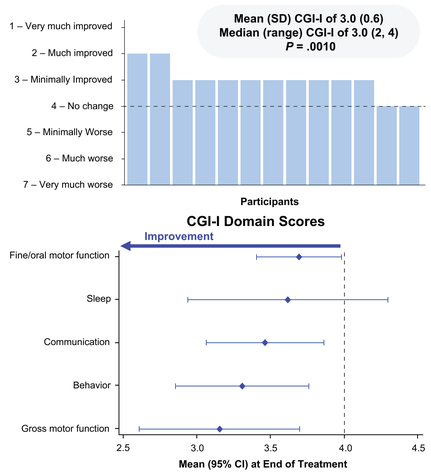
TEAE, n (%)	NNZ-2591 N = 16
Viral infection	5 (31)
Nasopharyngitis	4 (25)
Seizure	4 (25)
Upper respiratory tract infection	3 (19)
Somnolence	3 (19)
Constipation	3 (19)
Diarrhea	2 (13)
Epistaxis	2 (13)
Insomnia	2 (13)
Pyrexia	2 (13)
Skin abrasion	2 (13)
Urinary tract infection	2 (13)
Vomiting	2 (13)

TEAE, treatment-emergent adverse event.

Efficacy

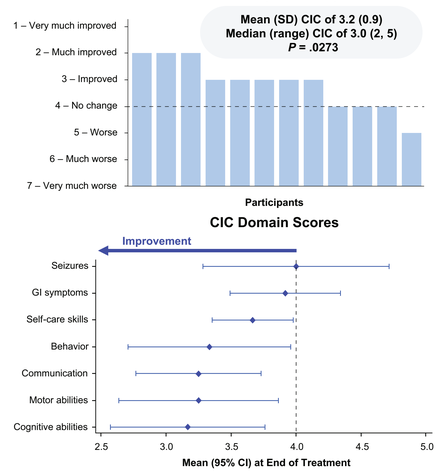
- At the end of treatment (week 13), 11 of 13 participants showed improvement on the CGI-I (Figure 3) and 8 of 12 participants showed improvement on CIC assessments (Figure 4)
  - Improvements in multiple domains including motor function, behavior, sleep, and communication were observed
- Among children (subgroup aged 4–12 years), 8 of 8 (100%) showed improvement on both the CGI-I and CIC assessments at the end of treatment (Figure 5)

Figure 3. AS-Specific CGI-I (Clinician Assessed) at Week 13



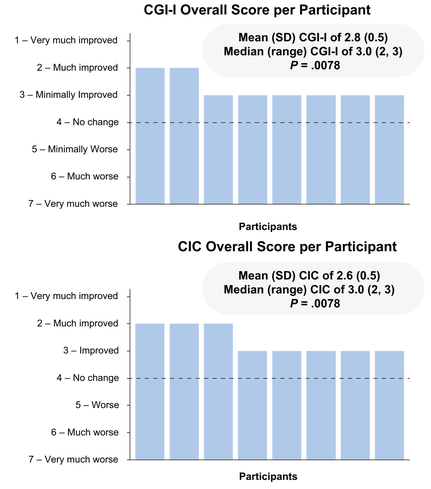
AS, Angelman syndrome; CGI-I, Clinical Global Impression of Improvement.
Modified intent-to-treat population.
P value was determined using the Wilcoxon signed-rank test.

Figure 4. AS-Specific CIC (Caregiver Assessed) at Week 13[a]



AS, Angelman syndrome; CIC, Caregiver Impression of Change; GI, gastrointestinal.
Modified intent-to-treat population.
P value was determined using the Wilcoxon signed-rank test.
[a]The CIC score for 1 participant was inadvertently not completed by the caregiver at week 13.

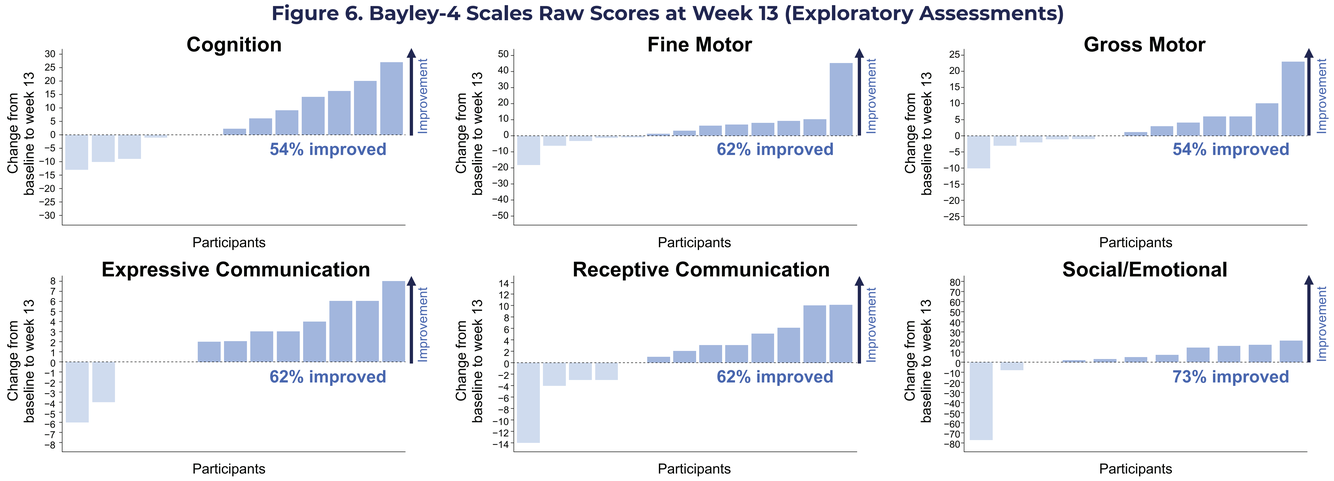
Figure 5. AS-Specific CGI-I and CIC Scores Among Children (Subgroup Aged 4–12 Years) at Week 13



AS, Angelman syndrome; CGI-I, Clinical Global Impression of Improvement; CIC, Caregiver Impression of Change.
Modified intent-to-treat population.
P value was determined using the Wilcoxon signed-rank test.
[a]Results are reported for all children (aged 4–12 years) in the modified intent-to-treat population.

- Over 50% of participants showed improvement in raw scores on all Bayley-4 subscales, demonstrating improvements across multiple domains of AS including cognition, motor skills, communication, and social/emotional signs (Figure 6)

Figure 6. Bayley-4 Scales Raw Scores at Week 13 (Exploratory Assessments)



Outcomes are reported for the modified intent-to-treat population for participants with nonmissing values.