NNZ-2591, a Synthetic IGF-1 Metabolite Analog: Phase 2 Clinical Trial Results for Children and Adolescents With Pitt Hopkins Syndrome

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Unmet Medical Need Associated With Pitt Hopkins Syndrome

Pitt Hopkins syndrome (PTHS) is caused by mutations in *TCF4*

TCF4 plays a role in the **formation, maintenance,** and **function** of **dendrites** and **synapses**

PTHS has broad and severe impacts

Intellectual impairment
Repetitive behavior
Self-injury
Sensory processing differences

Language deficits
Breathing abnormalities
Feeding difficulties

GI dysfunction
(reflux and constipation)

Sleep difficulties
Seizures
Vision impairment (severe myopia)

Motor impairments including hypotonia (low muscle tone), gross and fine motor delays

Walking difficulties

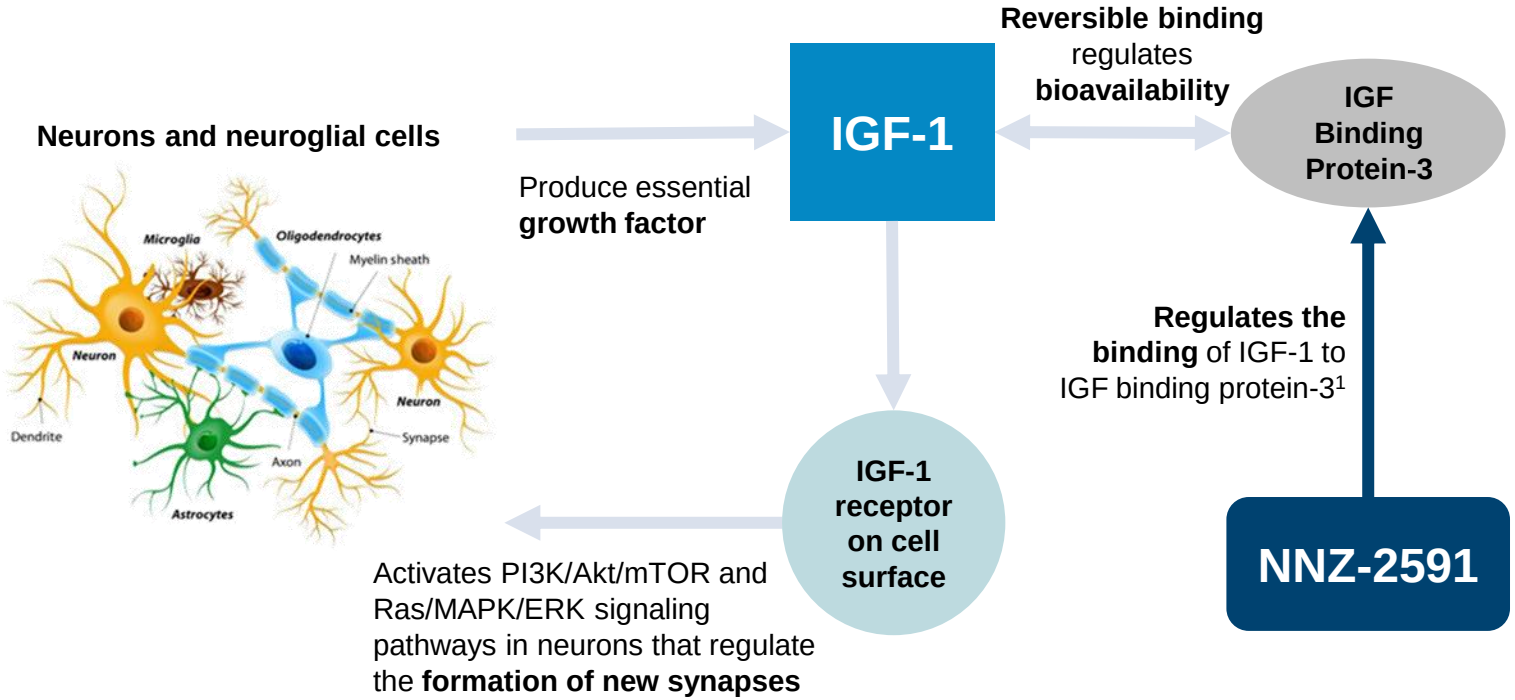
There are no approved treatments for PTHS

- There is **no cure for PTHS**
- Medications help **manage symptoms**, but **do not address the underlying disorder or prevent onset**

TCF4, transcription factor 4; GI, gastrointestinal.

NNZ-2591 and Regulating IGF-1 in the Brain

- **NNZ-2591** is a **synthetic analog of cyclic glycine-proline**, a peptide that occurs naturally in the brain
- NNZ-2591 is formulated to be **stable**, be **orally bioavailable**, and readily cross the **blood-brain barrier**
- NNZ-2591 can **regulate the amount of IGF-1** that is available to **activate IGF-1 receptors**
- The effects of NNZ-2591 are "state-dependent" – **correcting impairment**, but **not impacting normal cells**



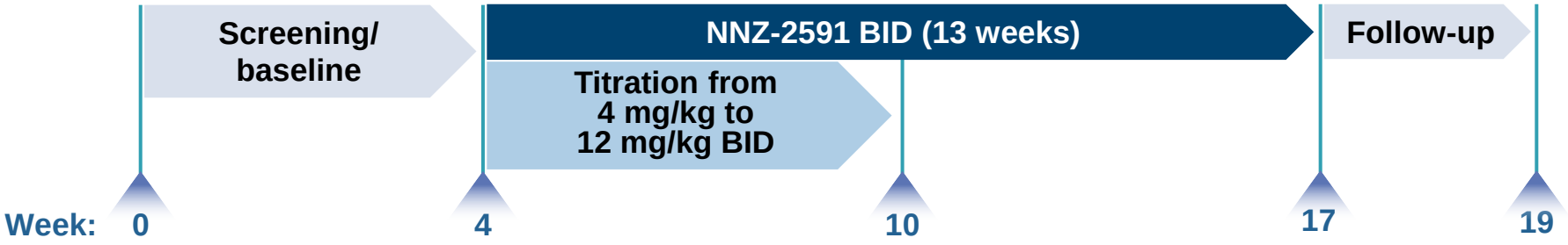
In a **haploinsufficient mouse model of PTHS (*Tcf4* $^{+/-}$)**, NNZ-2591 showed consistent efficacy across **PTHS-relevant domains** (hypoactivity, daily living skills, learning and memory, sociability, repetitive behavior, and motor performance)

IGF, insulin-like growth factor; PTHS, Pitt Hopkins syndrome.

1. Guan J, et al. *Sci Rep.* 2014;4:4388.

Study Design and Endpoints

Objective: To evaluate the safety and effect of treatment of oral liquid NNZ-2591 in children and adolescents with PTHS in a phase 2, 13-week, open-label clinical trial



- **Key eligibility criteria:** Individuals aged 3–17 years with PTHS
- Conducted at **5 US sites**[a]
- **Endpoints:**
  - **Primary:** safety, tolerability, pharmacokinetics
  - **Secondary:** 14 efficacy measures, including 4 specifically designed for PTHS
- **Key Objective:** Select the primary efficacy endpoint(s) for a registration study

4 PTHS-Specific Efficacy Measures

Global: Overall and Domain

Clinical Global Impression of Improvement (CGI-I)
Caregiver Impression of Change (CIC)
Clinical Global Impression of Severity (CGI-S)

Symptom Specific

Caregiver Top 3 Concerns

[a]University of Alabama at Birmingham, Rush University, University of Texas Southwestern, University of California San Francisco, Colorado Children's Hospital.
BID, twice daily; PTHS, Pitt Hopkins syndrome.

The Importance of PTHS-Specific Efficacy Measures

PTHS has **broad and severe impacts** on nearly **every aspect of life,** and presents **heterogeneously** among individuals

To evaluate whether a treatment is effective for PTHS, measures should **globally assess core PTHS symptoms**

Like for many **rare diseases**, there are currently **no well-accepted clinical outcome measures specific to PTHS**

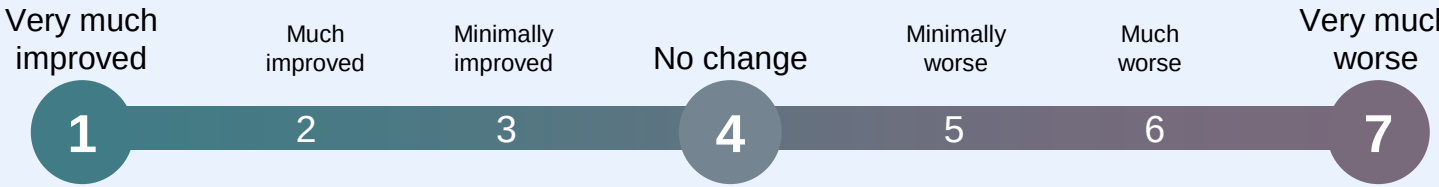
We applied recently developed PTHS-specific efficacy measures to evaluate NNZ-2591 for the treatment of PTHS

PTHS, Pitt Hopkins syndrome.

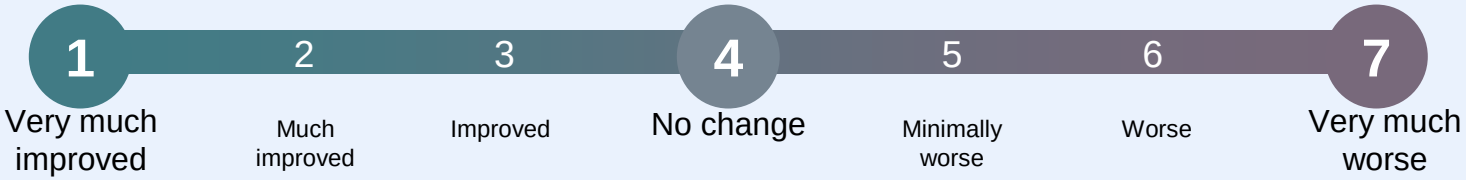
PTHS-Specific Efficacy Measures

Measures of Improvement

Clinician-Rated
Clinical Global Impression of Improvement (CGI-I)



Caregiver-Rated
Caregiver Impression of Change (CIC)

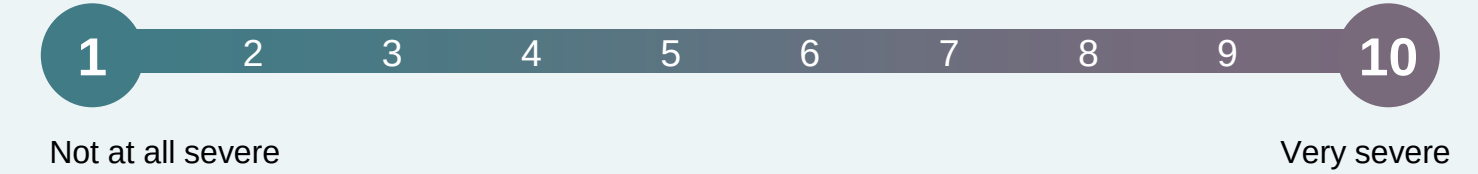


Symptom Change From Baseline

Measures of Severity

Clinician-Rated
Clinical Global Impression of Severity (CGI-S)

Caregiver-Rated
Caregiver Top 3 Concerns Severity

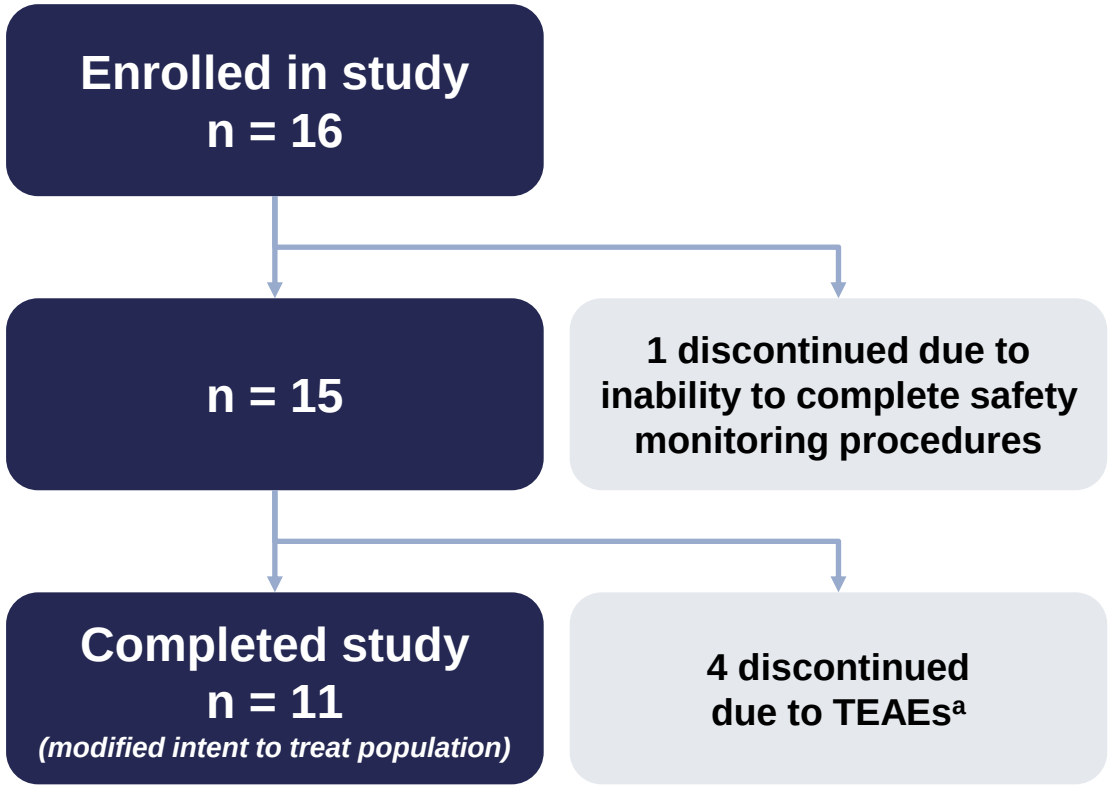


Symptom Severity at Time of Assessment

Clinician raters completed training to calibrate scoring and anchor interpretation (at study initiation and again during the study)

CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; PTHS, Pitt Hopkins syndrome.

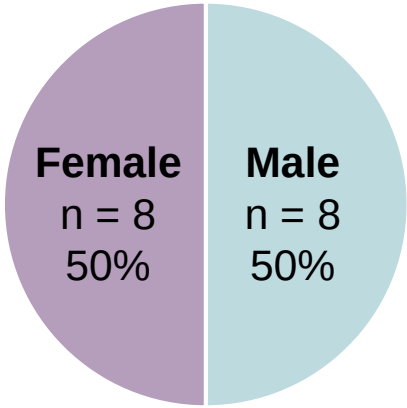
Participant Disposition, Demographics, and Baseline Characteristics



Age

Mean	9.1 years
Median	9.5 years
Range, years	
3–12:	n = 11
13–17:	n = 5

Sex



CGI-S at baseline

Mean (SD)
5.0 (0.69)

CGI-S, Clinical Global Impression – Severity; TEAE, treatment-emergent adverse event.
[a]All were mild or moderate in severity and resolved: 2 due to TEAEs unrelated to NNZ-2591 (COVID-19; mild vomiting, diarrhea, and lethargy); 1 due to moderate constipation, self-injury, abdominal distension, and fatigue; 1 due to mild sleep disorder and constipation.

Safety and Tolerability

NNZ-2591 was safe and well tolerated over 13 weeks of treatment

- All **TEAEs** were **mild to moderate**, most were not drug related
  - **0 serious** TEAEs
  - **4 discontinuations due to TEAEs**; all were **mild or moderate** and **resolved**
    - 2 due to TEAEs unrelated to drug (COVID-19; mild vomiting, diarrhea, and lethargy)
    - 1 due to moderate constipation, self-injury, abdominal distention, and fatigue; all were related to study drug
    - 1 due to mild sleep disorder and constipation; all were related to study drug
- **No meaningful trends in** laboratory values, EKG findings, or other **safety parameters** were observed during treatment

TEAEs in 2 or more participants	N = 16	
	n (%)	Severity
Constipation	3 (19)	2 mild, 1 moderate
Diarrhea	4 (25)	all mild
Vomiting	2 (13)	all mild
Fatigue	4 (25)	3 mild, 1 moderate
Somnolence	2 (13)	all mild
Irritability	2 (13)	all mild
Contusion	2 (13)	all mild
Gastroenteritis-viral	2 (13)	1 mild, 1 moderate
Nasopharyngitis	3 (19)	all mild
Cough	2 (13)	all mild
Rhinorrhea	2 (13)	all mild
Decreased appetite	2 (13)	all mild

EKG, electrocardiogram; TEAE, treatment-emergent adverse event.

Efficacy Endpoint Summary

CGI-I

Mean: **2.6**

Median: 3.0

CIC

Mean: **3.0**

Median 3.0

CGI-I and CIC reflect improvement from baseline

1 – Very much improved
2 – Much improved
3 – Minimally improved
4 – No change
5 – Minimally worse
6 – Much worse
7 – Very much worse

Statistically significant improvements (*P* <.05[a]) in 4/4 PTHS-specific endpoints at end of treatment vs baseline

PTHS-specific efficacy measure (total or overall score)	*P* value[a]	
	Participants who completed study[b] n = 11	All participants, including those who discontinued n = 15
CGI-I	.0039	.0205
CIC	.0234	.0137
CGI-S	.0313	.0078
Top 3 Caregiver Concerns	.0077	.0024

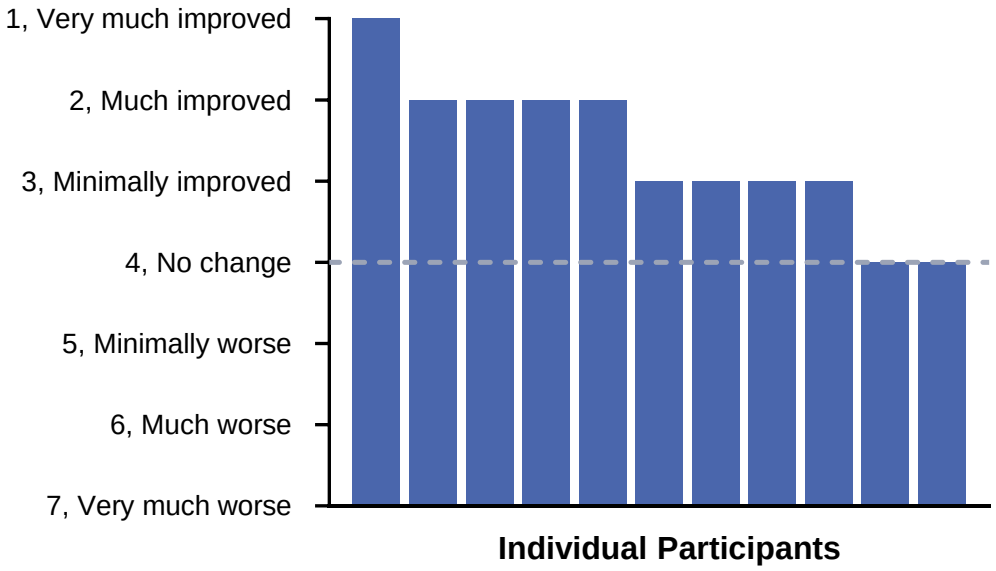
Change from baseline for the measures that were not designed specifically for PTHS were not statistically significant

[a]Wilcoxon signed-rank test.
[b]Modified intent to treat population.
CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression – Improvement; CGI-S, Clinical Global Impression – Severity; PTHS, Pitt Hopkins syndrome.

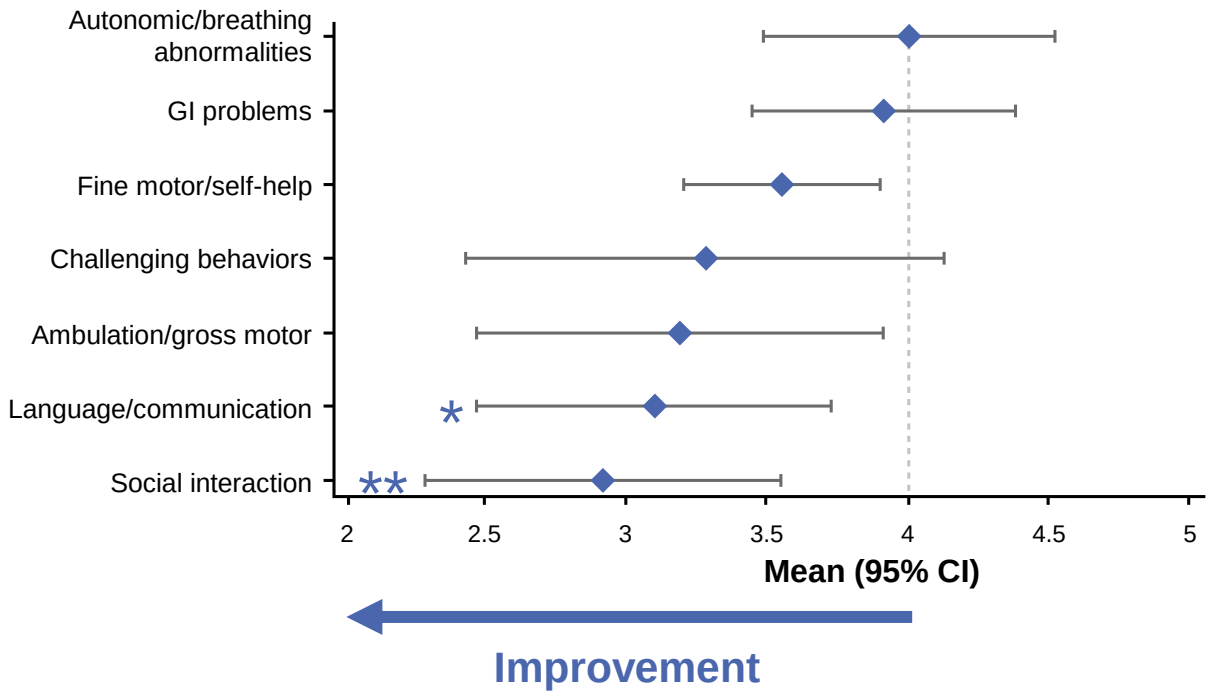
Clinician-Rated PTHS CGI-I Results by Participant and Domain

Mean CGI-I score of 2.6, with improvements in 9 of 11 children after 13 weeks of treatment

CGI-I Overall Score per Participant[a]



CGI-I Domain Scores[a]

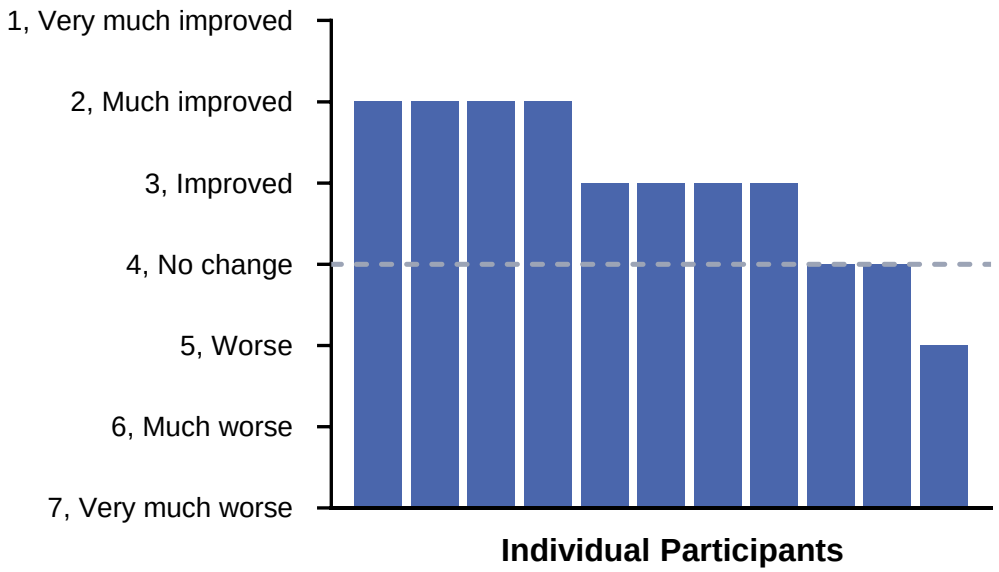


[a]Assessed in the modified intent to treat population (consisting of participants who completed the study) at week 13, the end of treatment.
*P <.05; **P <.01 for observed change relative to baseline vs null median of 4 (no change) based on Wilcoxon signed-rank test.
CGI-I, Clinical Global Impression – Improvement; GI, gastrointestinal; PTHS, Pitt Hopkins syndrome.

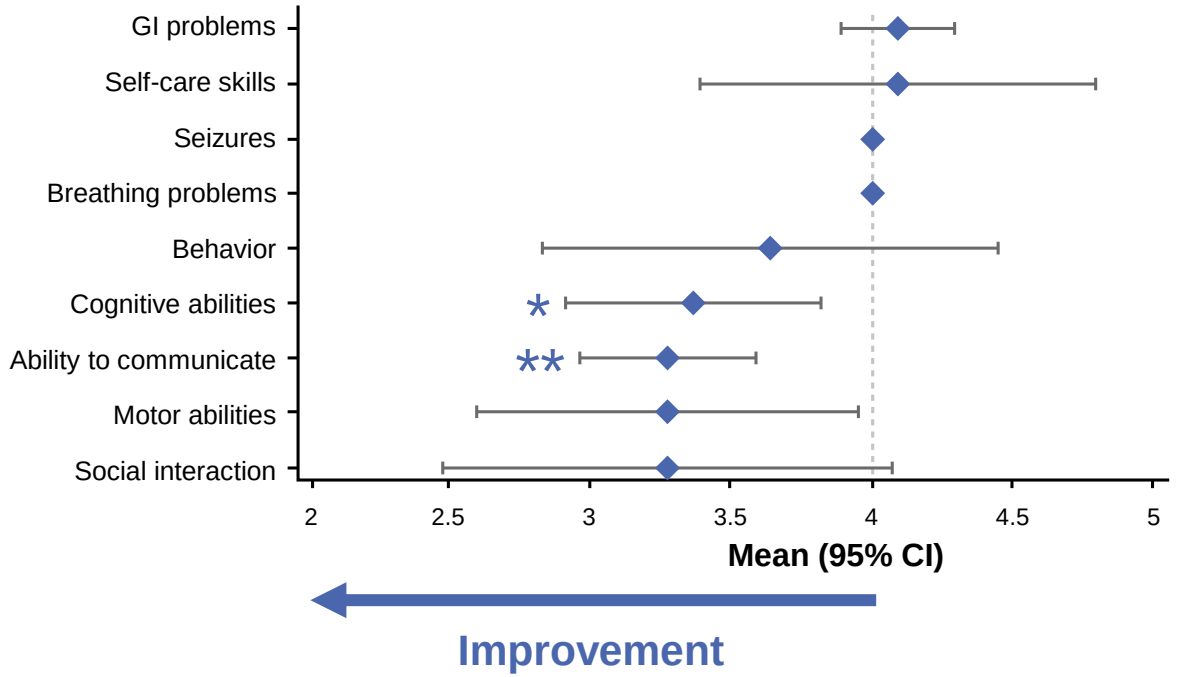
Caregiver-Rated PTHS CIC Results by Participant and Domain

Mean CIC score of 3.0, with improvements in 8 of 11 children after 13 weeks of treatment

CIC Overall Score per Participant[a]



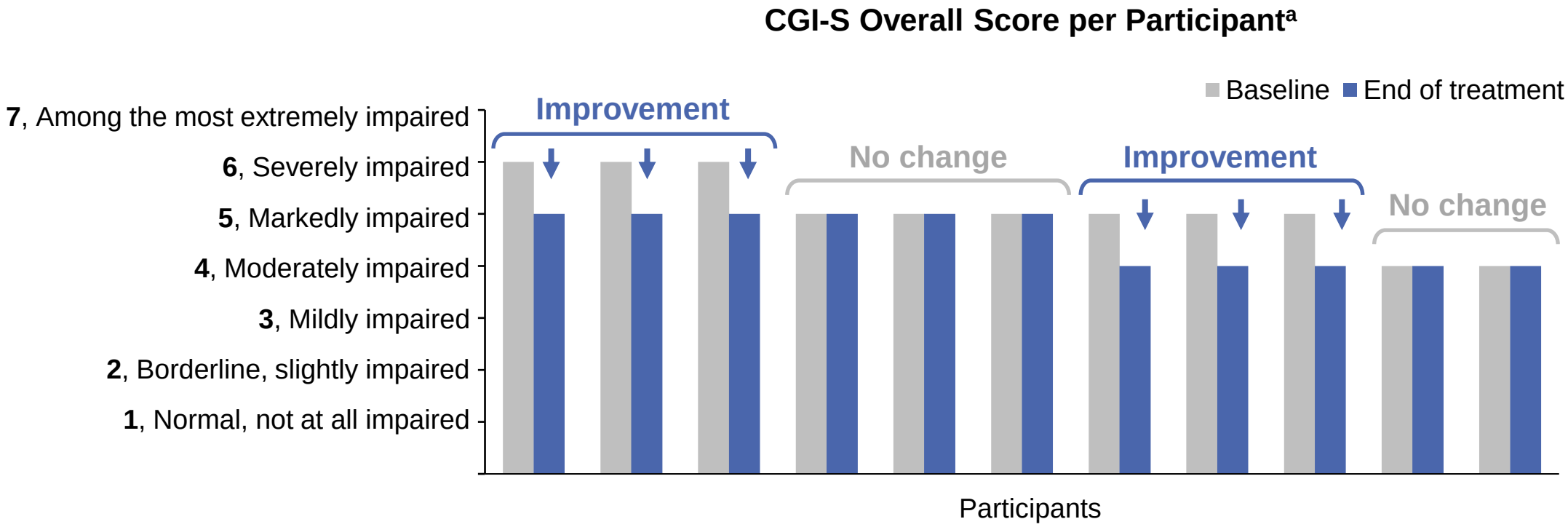
CIC Domain Scores[a]



[a]Assessed in the modified intent to treat population (consisting of participants who completed the study) at week 13, the end of treatment.
*P <.05; **P <.01 for observed change relative to baseline vs null median of 4 (no change) based on Wilcoxon signed-rank test.
CIC, Caregiver Impression of Change; GI, gastrointestinal; PTHS, Pitt Hopkins syndrome.

Clinician-Rated PTHS CGI-S Results

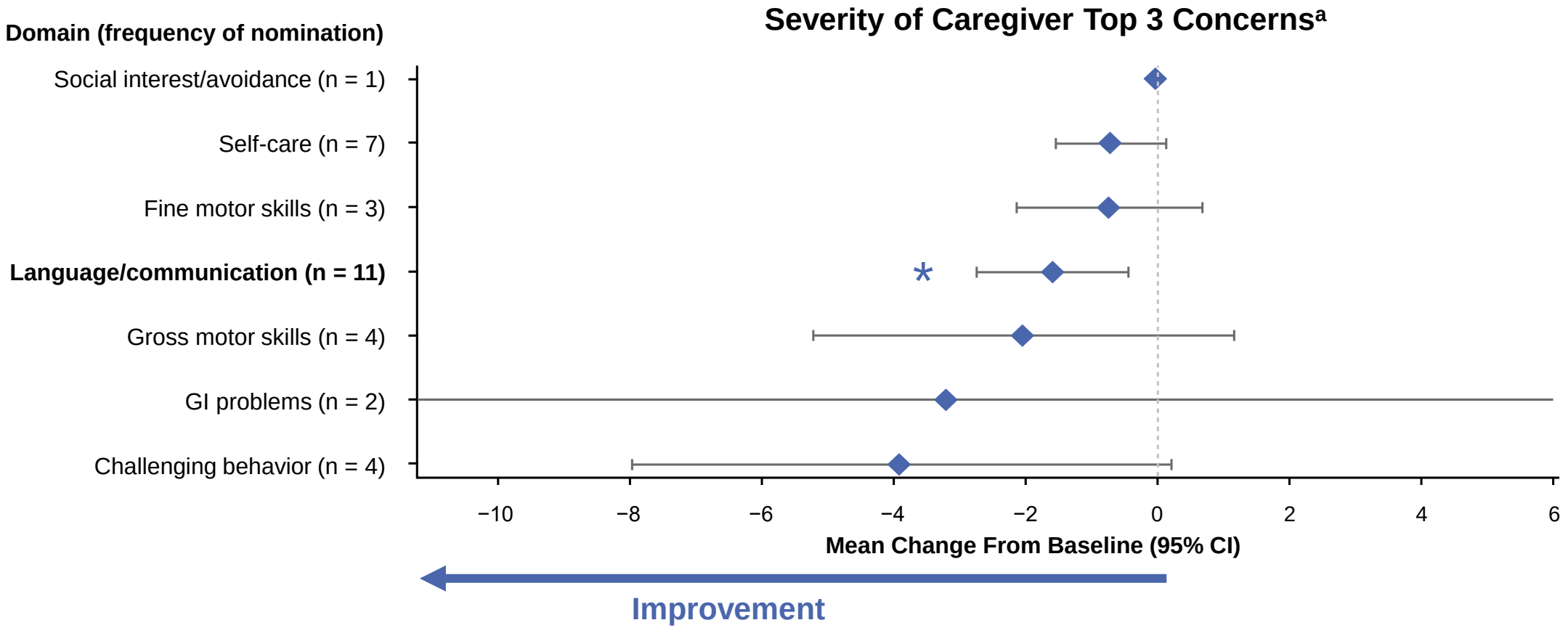
6 of 11 children improved by 1 point on the overall CGI-S score after 13 weeks of treatment



[a]Assessed in the modified intent to treat population (consisting of participants who completed the study) at week 13, the end of treatment.
CGI-S, Clinical Global Impression – Severity; PTHS, Pitt Hopkins syndrome.

Caregiver Top 3 Concerns Results by Domain

Improvement was observed in the most common caregiver concern of language/communication after 13 weeks of treatment



[a]Assessed in the modified intent to treat population (consisting of participants who completed the study) at week 13, the end of treatment.
*P <.05 for observed change from baseline vs null median based on Wilcoxon signed-rank test.
The most commonly selected symptom domain (language/communication) is bolded.
GI, gastrointestinal; PTHS, Pitt Hopkins syndrome.

Clinician and Caregiver Comments at the Time of Rating

Clinicians

*"Increased **babbling** and jargoning….More **inflections** with **eye contact** and **consonant sounds** rather than just noises."*

***"Decreased** frequency and intensity of **smacking** and **hairpulling**."*

*"Supported stepping increased over last few months…Now taking **steps without trainer** with parent support."*

*"Improved **expressive communication**: 2 additional words, uses AAC device to ask for food. Increase vocalization."*

*"**Less breath holding**. More **opinionated.** More **social** interest."*

*"Able to **match items/pictures**…moved from 4 pictures to 6 pictures."*

*"Improved **motor skills**. Better motor **coordination** getting in car."*

Caregivers

*"Is now able to **explore environment**… can move towards people to **initiate contact** and… can seek out whatever … wants to **play** with."*

*"Can seem to **hold** on to things for **longer periods** without letting go."*

*"**Stability** when walking improved."*

*"**Listen** to conversation + follow some discussions, able to **understand** when we're talking about…"*

*"Far **less hyper** and easily able to **concentrate better**… is able to concentrate and **master tasks** that … has been working on for years (getting in and out of car independently, catching a ball)."*

*"More **intentional movements**… been more **gentle** with almost all interactions."*

*"Almost **constant babbling** and even has said "hi" and "more.""*

*"More **calm** and **attentive**, especially looking at faces and eyes."*

AAC, augmentative and alternative communication.

Conclusions

NNZ-2591 was **safe and well tolerated** in participants with PTHS, with no meaningful trends in laboratory values or other safety parameters

Statistically significant improvements from baseline were demonstrated in **all 4 PTHS-specific efficacy measures**, including **2 clinician-assessed measures** and **2 caregiver-assessed measures**

Changes from baseline for the **measures** that were **not designed specifically for PTHS** were **not statistically significant**

Improvements were seen in clinically important aspects of PTHS, including **communication, social interaction, cognition,** and **motor abilities**

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