Development of Clinician- and Caregiver-Reported Outcome Measures for Evaluating Pitt Hopkins Syndrome

Cassandra Newsom,[1] Kimberly Goodspeed,[2] Sarah E O'Kelley,[3] Helen K Root,[3] Kimberly Farrand,[4] Larry Glass,[4] Liza Squires,[4] Nancy E Jones[4]

[1]Department of Neurobiology, Heersink School of Medicine, University of Alabama Birmingham, Birmingham, AL, USA; [2]Department of Pediatrics, University of Texas Southwestern Medical Center, Dallas, TX, USA; [3]Department of Psychology, College of Arts and Sciences, University of Alabama Birmingham, Birmingham, AL, USA; [4]Neuren Pharmaceuticals, Camberwell, VIC, AUS

Objective

To describe the development of outcome measures tailored to Pitt Hopkins syndrome (PTHS)

Conclusions

The PTHS-specific Clinical Global Impression (CGI) of Severity, CGI of Improvement, and Caregiver Impression of Change measures captured meaningful and statistically significant changes in key PTHS symptoms in an open-label interventional clinical trial

Developing measures to evaluate PTHS that are meaningful to clinicians and caregivers will advance clinical trials and may support treatment decisions

Background

- Pitt Hopkins syndrome (PTHS) is a rare genetic neurodevelopmental condition caused by sequence variants affecting the *TCF4* gene[1]
- PTHS symptoms are broad and severe with variable presentation; symptoms include severe to profound intellectual impairment, language deficits, motor impairment, respiratory abnormalities, gastrointestinal dysfunction, sleep challenges, sensory processing differences, repetitive behaviors, and self-injury[1]
- There are no validated outcome measures specific to PTHS, making it challenging to assess improvements in clinical trials
- Global impression assessments can capture variable symptoms and are commonly adapted to evaluate heterogeneous neuropsychiatric syndromes[2,3]
- We describe the development and initial use of clinician- and caregiver-reported PTHS-specific global impression assessments in an open-label interventional phase 2 clinical trial of NNZ-2591, an investigative drug that is a synthetic analog of the insulin-like growth factor 1 metabolite cyclic glycine-proline

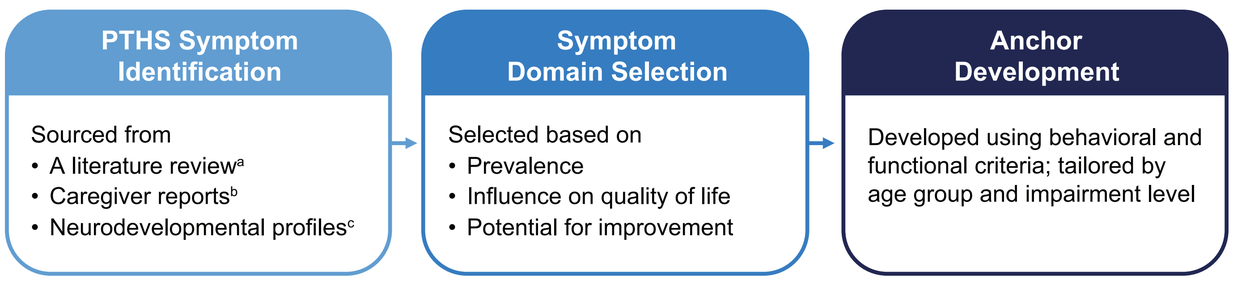
Methods

PTHS-Specific Outcome Measure Development

Clinician-Reported Measures

- Clinician-reported PTHS-specific Clinical Global Impression measures were developed to evaluate PTHS severity (Clinical Global Impression of Severity [CGI-S]) and improvement (Clinical Global Impression of Improvement [CGI-I]; **Figures 1 and 2**)
- CGI-S and CGI-I measure development aligned with the US Food and Drug Administration guidance for developing fit-for-purpose outcome measures[4]
- Clinicians rate PTHS severity (CGI-S) or improvement (CGI-I) vs baseline by providing global and symptom domain scores (**Figure 3**)

Figure 1. PTHS-Specific CGI Measure Development



CGI, Clinical Global Impression; PTHS, Pitt Hopkins syndrome.
[a]Comprehensive literature review, including case studies of children and adolescents with PTHS.
[b]Reports of symptoms from 33 children with PTHS or Pitt Hopkins–like syndrome 1 or 2.
[c]Profiles of 10 children with PTHS based on multiple established assessments.

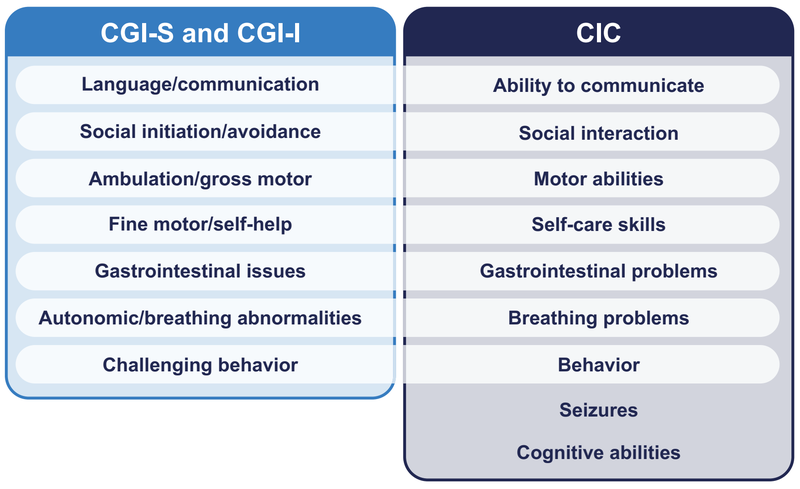
Caregiver-Reported Measure

- A PTHS-specific Caregiver Impression of Change (CIC) measure was developed to capture caregivers' perspectives on change in function and well-being
- The CIC measure was designed to be analogous to the CGI-I measure with the addition of 2 impactful symptom domains, seizures and cognition (**Figure 2**)
- On the CIC measure, caregivers rated global and symptom domain improvements (**Figure 3**)

Calibration and Training

- To calibrate the CGI-S and CGI-I, clinicians with varying levels of experience in managing PTHS rated 7 clinical vignettes representing various PTHS severity levels
  - Ratings were reviewed, and raters provided feedback on measure clarity and applicability
  - Symptom descriptions and anchors were revised to improve measure reliability
- Clinician raters participating in the phase 2 clinical trial underwent training and were required to demonstrate reliability with established gold-standard CGI-I and CGI-S scoring on clinical case vignettes; ratings within 1 point of the gold-standard score were considered reliable

Figure 2. PTHS-Specific Measure Domains

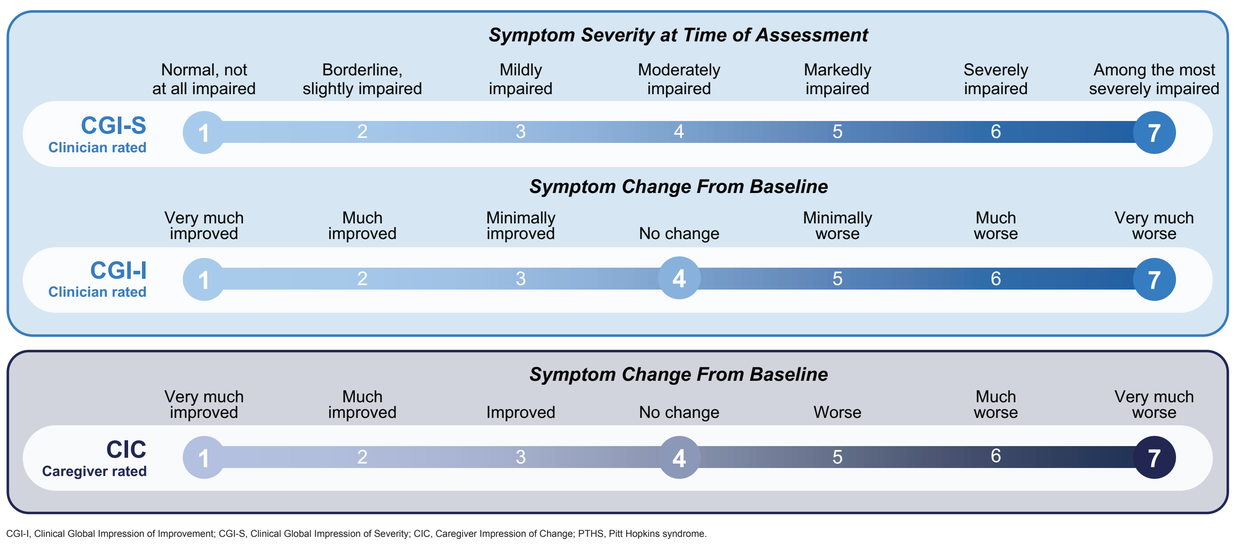


CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; CIC, Caregiver Impression of Change; PTHS, Pitt Hopkins syndrome.

Clinical Trial Study Design, Participants, and Assessments

- NNZ-2591 was evaluated for treating PTHS in a multisite, 13-week, open-label, phase 2 clinical trial (NCT05025332)
  - Safety and tolerability were primary endpoints
  - Efficacy assessments, including the CGI-S, CGI-I, and CIC, were secondary endpoints
- Eligible participants were required to have a clinical PTHS diagnosis with a documented disease-causing genetic etiology, be aged 3–17 years, and weigh ≥ 12 kg at screening
- Following a 4–6-week screening/baseline observation period, NNZ-2591 was orally administered twice daily for 13 weeks; doses were up-titrated from 4 mg/kg to 8 mg/kg to 12 mg/kg over the first 6 weeks of treatment

Figure 3. PTHS-Specific Measure Scoring



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

Analyses

- Intra-rater reliability on the CGI-S was estimated by evaluating the intraclass correlation coefficient between ratings conducted at screening and baseline visits based on covariance parameters estimated from a restricted maximum likelihood mixed model
- A Wilcoxon signed-rank test was used to evaluate change from baseline at week 13 in PTHS-specific efficacy outcomes; statistical tests were nominal and there was no type I error control

Results

Participants

- Of the 16 participants enrolled in the clinical trial, 11 completed the study; among enrolled participants, half were female, the median (range) age was 9.5 (3–16) years, and most were White (69%)
- The average PTHS severity at screening and baseline visits reflected marked impairment among all enrolled participants and those who completed the study (mean [SD] CGI-S scores of 5.0 [0.7] and 5.1 [0.7], respectively)

Intra-Rater Reliability

- CGI-S ratings at screening and baseline visits were consistent for all 16 enrolled participants (intraclass correlation coefficient, 0.9) and the 11 who completed the study (intraclass correlation coefficient, 1.0)

Sensitivity to Change

- Measures appeared sensitive to change, with significant improvements observed after 13 weeks of NNZ-2591 treatment on the overall CGI-S, CGI-I, and CIC measures (**Table 1**)
- Among the participants who completed the study, 9 of 11 improved on the CGI-I measure and 8 of 11 improved on the CIC measure at week 13; 7 of 11 participants improved on both the CGI-I and CIC
- On the CGI-S measure, 6 of 11 participants had 1-point reductions in severity at week 13

Future Directions

- Additional analyses to support the validity of the PTHS-specific assessments are planned

Table 1. Sensitivity of PTHS-Specific Efficacy Measures to Change

	NNZ-2591			
	Participants Who Completed the Study n = 11			
Measure, Overall Score	Baseline	Week 13	Change From Baseline	*P* Value
CGI-S				
Mean (SD)	5.1 (0.7)	4.5 (0.5)	–0.5 (0.5)	—
Median (range)	5.0 (4, 6)	5.0 (4, 5)	–1.0 (–1, 0)	.0313
CGI-I				
Mean (SD)	—	2.6 (0.9)	—	—
Median (range)	—	3.0 (1, 4)	—	.0039
CIC				
Mean (SD)	—	3.0 (1.0)	—	—
Median (range)	—	3.0 (2, 5)	—	.0234

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

Disclosures and Acknowledgments

Neuren participated in the study design; study research; collection, analysis, and interpretation of data; and writing, reviewing, and approving this poster for submission. All authors had access to the data and participated in the development, review, and approval of the poster. Neuren funded the research for this study. Medical writing assistance, funded by Neuren, was provided by Morgan A Gingerich, PhD, of JB Ashtin.

CN has served as an advisor and clinical trial investigator for Neuren Pharmaceuticals. KG is a current employee of Ultragenyx. She has served as a clinical trial investigator for Neuren Pharmaceuticals, and as a consultant or advisor for AllStripes, Astellas Gene Therapy, Jaguar Gene Therapy, and COMBINEDBrain. SEO has no disclosures to report. HKR has no disclosures to report. KF is a consultant for Neuren Pharmaceuticals. LG, LS, and NEJ are executives at Neuren Pharmaceuticals and may hold Neuren stock or stock options.

Presented at the 54th Child Neurology Society Annual Meeting, October 8–11, 2025, Charlotte, NC, USA

References

1. Zollino M, et al. *Clin Genet*. 2019;95:462–78.
2. Kolevzon A, et al. *J Neurodev Disord*. 2021;13:3.
3. Neul J, et al. *J Child Neurol*. 2015;30:1743–8.
4. Food and Drug Administration. Patient-Focused Drug Development: Selecting, Developing, or Modifying Fit-for-Purpose Clinical Outcome Assessments [draft guidance]. 2022. Accessed August 27, 2025. https://www.fda.gov/regulatory-information/search-fda-guidancedocuments/

neuren pharmaceuticals