Improving Outcome Measures for Trials in Phelan-McDermid Syndrome (PMS): Development of PMS-Specific Clinician and Caregiver Impression-of-Change Measures

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Objective

To develop and evaluate clinician and caregiver-reported outcome assessments specific to Phelan-McDermid syndrome (PMS)

Conclusions

The PMS-specific Clinical Global Impression (CGI) of Severity, CGI of Improvement, PMS Clinician Domain-Specific Rating Scale, and Caregiver Impression of Change (CIC) captured meaningful and statistically significant changes in core PMS symptoms in an interventional clinical trial

Improvements in PMS symptoms were consistent across clinician- and caregiver-reported PMS-specific assessments

Improvements in the PMS-specific CGI and CIC assessments correlated with improvements in other validated assessments, including measures of quality of life, behavior, and communication

Background

- Phelan-McDermid syndrome (PMS) is a rare genetic neurodevelopmental disorder often caused by genetic deletions or abnormalities of the *SHANK3* gene[1]
- PMS symptoms are broad and can be heterogeneous; common symptoms include absent or severely delayed speech, moderate to profound intellectual disability, behavioral differences, hypotonia, and motor deficits[1]
- Currently, there is no widely accepted and validated clinical outcome assessment specific to evaluating PMS[2]
- Global impression assessments are commonly used to evaluate neuropsychiatric syndromes, as they can capture wide-ranging and variable syndrome manifestations[3]
- Herein, we describe the development and initial use of PMS-specific clinician- and caregiver-reported global impression assessments
- The PMS-specific assessments were evaluated in children and adolescents with PMS in a phase 2 clinical trial of NNZ-2591, a synthetic analog of the insulin-like growth factor 1 metabolite cyclic glycine-proline

Methods

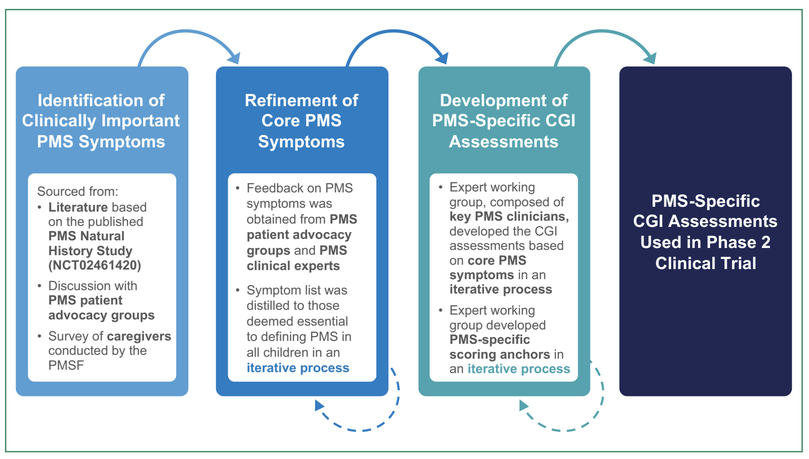
PMS-Specific Assessment Development

Clinician-Reported Assessments

Clinical Global Impression Assessments

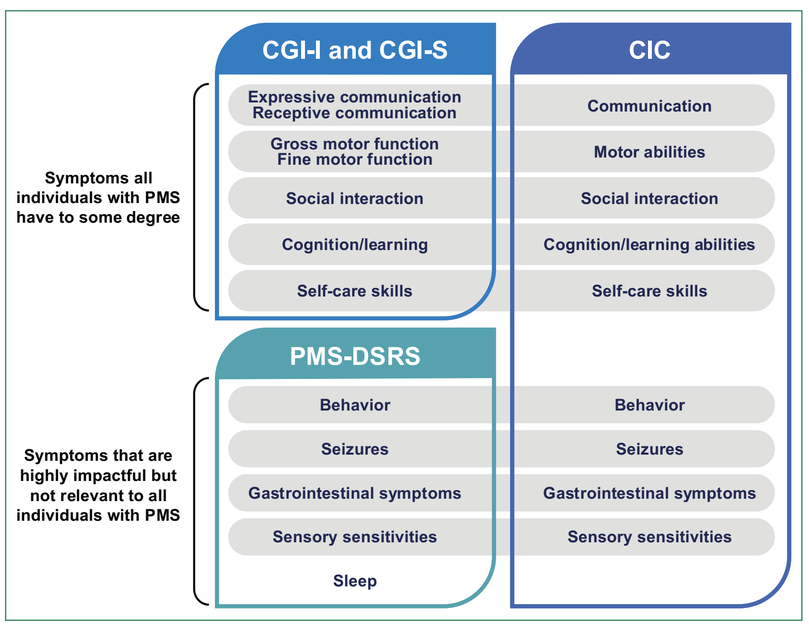
- The PMS-specific Clinical Global Impression (CGI) of Improvement (CGI-I) and CGI of Severity (CGI-S) were developed using an iterative process with feedback from patient advocacy organizations and expert clinicians[4] (**Figure 1**)
- Symptom domains were selected to encompass core PMS symptoms common to all people with PMS that influence daily function and well-being, including symptoms prioritized by caregivers[2] (**Figure 2**)
- The CGI assessments reflect clinicians' perspectives on the severity of illness (CGI-S) and the improvement in symptoms (CGI-I), scored on a 7-point Likert rating scale (**Figure 3**)

Figure 1. PMS-Specific CGI Assessment Development



CGI, Clinical Global Impression; PMS, Phelan-McDermid syndrome; PMSF, Phelan-McDermid Syndrome Foundation.

Figure 2. PMS-Specific Assessment Domains



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

Methods (cont'd)

PMS Clinician Domain-Specific Rating Scale

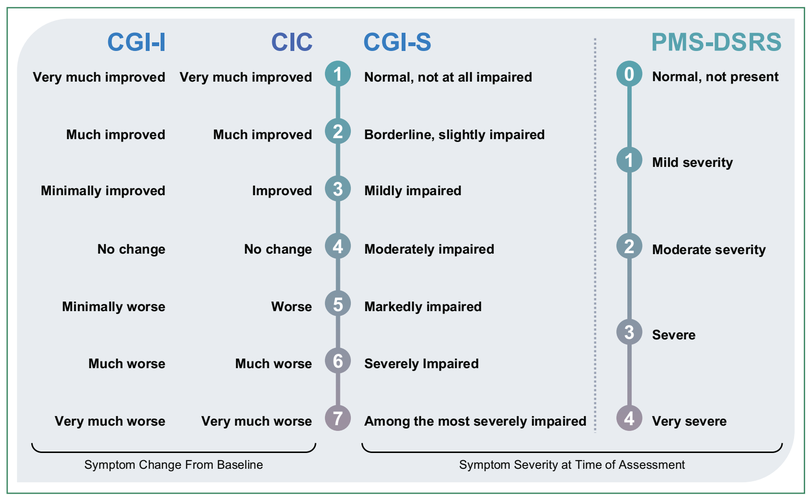
- The PMS Clinician Domain-Specific Rating Scale (PMS-DSRS) was developed to evaluate highly impactful PMS symptoms not included in the CGI assessments that affect some, but not all, individuals with PMS (**Figure 2**)
- The PMS-DSRS reflects clinicians' perspectives on symptom severity; each symptom domain was scored on a 5-point Likert scale. The severity scoring was based on a scale originally developed for congenital myotonic dystrophy type 1 that was adapted for other neurodevelopmental disorders[5]

Caregiver-Reported Assessment

Caregiver Impression of Change

- The PMS-specific Caregiver Impression of Change (CIC) was developed based on an assessment used in the Rett Syndrome Natural History Study and was designed to provide caregivers' global impressions, analogous to the clinician-reported CGI-I
- CIC symptom domains were based on those developed for the CGI assessments, plus 4 other highly impactful symptom domains that may not be relevant for all people with PMS (**Figure 2**)
- The CIC reflects caregivers' perspectives on the change in their child's function and well-being; the overall score and each domain were evaluated on a 7-point Likert scale (**Figure 3**)

Figure 3. PMS-Specific Assessment Rating Scales



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

Clinical Study Design and Participants

- A multisite, open-label, phase 2 clinical trial was conducted to evaluate the safety and tolerability of NNZ-2591; efficacy was assessed as a secondary outcome (NCT05025241)
- After a 4- to 6-week screening and baseline observation period, NNZ-2591 was administered orally twice daily for 13 weeks; doses were titrated up from 4 mg/kg to 12 mg/kg over the first 6 weeks of treatment
- Eligible participants were aged 3–12 years at screening and had a clinical diagnosis of PMS with a disease-causing genetic abnormality of the *SHANK3* gene

Assessments

- Clinicians scored each CGI assessment domain and provided an overall global score. Clinician raters participated in a scoring calibration training and were required to demonstrate reliability with established gold-standard scoring on clinical case vignettes; ratings within score of 1 of the gold-standard score were considered reliable
- Clinicians scored each PMS-DSRS domain; a total severity score was calculated as the sum of the domain scores
- Caregivers scored each CIC domain and provided an overall global score
- The following validated assessments of key symptom areas were also administered:
  - Gastrointestinal health (Gastrointestinal Health Questionnaire [GIHQ])
  - Quality of life (Quality of Life Inventory – Disability [QI-Disability], Impact of Childhood Neurological Disability [ICND] – Overall Quality of Life Rating Scale)
  - Sleep (Child Sleep Habits Questionnaire [CSHQ])
  - Communication (MacArthur-Bates Communicative Development Inventory [MB-CDI], Observer-Reported Communication Ability [ORCA])
  - Behavior (Aberrant Behavior Checklist-2 [ABC-2], Behavior Problems Inventory – Short Form [BPI-SF])
  - Adaptive behavior/self-care (Vineland Adaptive Behavior Scales-3 [VABS-3])

Analyses

- Intra-rater reliability was estimated for the CGI-S by evaluating ratings conducted across screening and baseline visits
- A Wilcoxon signed-rank test was used to evaluate change from baseline vs null median at week 13 in efficacy outcomes
- The relationships between PMS-specific assessments and other outcome assessments were evaluated with Pearson correlations

Results

Participants

- A total of 18 participants enrolled in the phase 2 study of NNZ-2591; participant ages ranged from 4–13 years, two-thirds were male, and most were White (88.9%)
- At baseline, the average PMS severity at screening and baseline visits reflected moderate to marked impairment (mean [SD] CGI-S score of 4.5 [1.0])

Intra-Rater Reliability

- There was 100% agreement between the CGI-S ratings conducted at the screening and baseline visits (correlation coefficient of 1.0), reflecting excellent intra-rater reliability

Assessment Correlations at Baseline

- At baseline (pretreatment), the overall CGI-S demonstrated moderate-to-strong correlations with measures of communication and adaptive behavior/self-care (**Table 1**)
- Both CGI-S communication domains demonstrated strong correlations with other measures of communication
- The CGI-S cognition/learning, self-care, and social interaction domains demonstrated moderate-to-strong correlations with measures of communication and adaptive behavior/self-care

Table 1. Correlation at Baseline of CGI-S Scores With Scores of Other Validated Assessments

	Correlation Coefficient					
CGI-S Domain[a]	MB-CDI Vocabulary[b]	ORCA[c]	VABS-3 ABC[d]	VABS-3 Communication[e]	VABS-3 Socialization[e]	VABS-3 Daily Skills of Living[e]
Overall	–0.85	–0.86	–0.65	–0.72	–0.55	–0.46
Expressive Communication	–0.78	–0.90	–0.52	–0.66	–0.43	–0.27
Receptive Communication	–0.90	–0.72	–0.62	–0.76	–0.48	–0.41
Social Interaction	–0.50	–0.50	–0.58	–0.47	–0.53	–0.56
Self-Care	–0.74	–0.85	–0.59	–0.67	–0.48	–0.42
Cognition/Learning	–0.87	–0.71	–0.64	–0.80	–0.47	–0.44
Gross Motor	–0.13	–0.22	–0.08	–0.20	0.002	0.03
Fine Motor	–0.62	–0.53	–0.41	–0.54	–0.21	–0.31

CGI-S, Clinical Global Impression of Severity; MB-CDI, MacArthur-Bates Communicative Development Inventory; ORCA, Observer-Reported Communication Ability; VABS-3, Vineland Adaptive Behavior Scales-3; VABS-3 ABC, VABS-3 Adaptive Behavior Composite.
[a]Higher scores indicate more impairment or severity. [b]Higher scores indicate greater language development. [c]Higher scores indicate greater communication ability. [d]Higher scores reflect better adaptive behavior/self-care skills. [e]Higher scores reflect better skills.

Sensitivity to Change

- Statistically significant improvements were observed at the end of NNZ-2591 treatment in all PMS-specific clinician- and caregiver-reported global impression assessments (**Table 2**)
- Most participants experienced improvements on the PMS-specific assessments of change, including 16 of 18 participants on the clinician-reported CGI-I, and 15 of 18 participants on the caregiver-reported CIC
- For both PMS-specific clinician-reported measures of symptom severity (CGI-S and PMS-DSRS), 7 of 18 participants had a decrease in symptom severity from baseline to the end of treatment
- Improvements in PMS-specific assessments were supported by significant improvements in validated assessments evaluating quality of life (QI-Disability), gastrointestinal symptoms (GIHQ), sleep (CSHQ), and behavior (ABC-2, BPI-SF) (see poster 93 for detailed results[6])

Table 2. PMS-Specific Efficacy Assessments

	NNZ-2591 N = 18			
Assessment, Overall Score, Mean (SD)	Baseline[a]	Week 13	Change From Baseline	*P* value
CGI-I	—	2.4 (0.9)	—	<.0001***
CGI-S	4.5 (1.0)	4.1 (1.0)	–0.4 (0.5)	.0156*
PMS-DSRS	5.7 (2.1)	4.7 (2.2)	–0.9 (1.7)	.0156*
CIC	—	2.7 (1.0)	—	.0003***

CIC, Caregiver Impression of Change; CGI-I, Clinical Global Impression of Improvement; CGI-S, Clinical Global Impression of Severity; PMS, Phelan-McDermid syndrome; PMS-DSRS, PMS Clinician Domain-Specific Rating Scale.
*P <.05; **P <.01; ***P <.001 for change from baseline (or observed change relative to baseline for CGI-I and CIC) vs null median based on Wilcoxon signed-rank test.
[a]Baseline scores were determined as the average scores from visits during the baseline/screening period for assessments collected at more than 1 visit during the baseline/screening period.

Relationships Between Assessments

- Improvements from baseline to the end of treatment were consistent across CGI-I and CIC symptom domains; communication, cognition and learning, and social interaction had the greatest magnitude of improvements for both assessments (see poster 93 for detailed results[6])
- At the end of treatment, 13 of 18 participants improved on both the clinician-reported CGI-I and caregiver-reported CIC; 2 improved on the CIC with no change on the CGI-I; 2 improved on the CGI-I with no change on the CIC; 1 improved on the CGI-I and worsened on the CIC
- The correlation coefficient between the CGI-I and the CIC overall scores at the end of treatment was 0.29
- At week 13, 16 of 18 participants had CGI-I and CIC scores within 1 point of each other

Refinement of PMS-Specific CGI Assessments

- Following the phase 2 study of NNZ-2591, the PMS-specific CGI assessments were refined for future use based on feedback from study investigators and guidance from expert PMS clinicians
- The refined CGI assessments are undergoing further validation

Disclosures and Acknowledgments

E Berry-Kravis has received funding from Neuren, Acadia, Alcobra, AMO, Asuragen, Avexis, Biogen, BioMarin, Cydan, Engrail, Erydel, Fulcrum, GeneTx, GW, Healx, Ionis, Jaguar, Kisbee, Lumos, Marinus, Mazhi, Moment Biosciences, Neurogene, Neurotrope, Novartis, Orphazyme/Kempharm/Zevra, Ovid, PTC Therapeutics, Retrophin, Roche, Seaside Therapeutics, Taysha, Tetra, Ultragenyx, Yamo, Zynerba, and Vtesse/Sucampo/Mallinckrodt Pharmaceuticals, to consult on trial design or run clinical or laboratory validation trials in genetic neurodevelopmental or neurodegenerative disorders, all of which is directed to Rush University Medical Center (RUMC) in support of rare disease programs. She receives no personal funds and RUMC has no relevant financial interest in any of the commercial entities listed. LV Soorya has served as an advisor for Neuren and Jaguar Gene Therapy, receives royalties from Hogrefe Publishing, and receives consulting fees from Sunnyteens. A Kolevzon has served as an advisor or consultant for Neuren, Acadia, ADNP Kids Research Foundation, Alkermes, Biogen, Clinilabs Drug Development Corporation, David Lynch Foundation, GW Pharmaceuticals, Jaguar Gene Therapy, Klingenstein Third Generation Foundation, Ovid, Ritrova, and Scioto Biosciences. A Thurm has served as an unpaid advisor for Neuren. L Glass, L Squires, and NE Jones are executives at Neuren Pharmaceuticals and may hold Neuren stock or stock options.

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. The Gastrointestinal Health Questionnaire was used with permission from Kathleen J Motil, MD, PhD, from Baylor College of Medicine. Medical writing assistance, funded by Neuren, was provided by Morgan A Gingerich, PhD, of JB Ashtin.

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