

Improving outcome measures for Rett Syndrome (RTT) clinical trials: the development of RTT-specific anchors for the Clinical Global Impression Scale

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INTRODUCTION

High-quality outcome measures are a critical component of well-designed clinical trials in subjects with Rett Syndrome (RTT). We describe the development of novel anchors specific to RTT signs and symptoms for the Clinical Global Impression Scales (Severity and Improvement). This effort is part of an on-going clinical trial involving adolescent and adult females with RTT, which is the first industry-sponsored, multi-site clinical trial in this clinical population.

- The Clinical Global Impression Scale (CGI) (Guy, 1976) is a measure of global clinical change with strong face validity that has been widely used as an outcome measure in CNS clinical trials, including trials in neurodevelopmental disorders such as autism and Fragile X syndrome.
- The CGI is a 7-point Likert rating scale that reflects expert clinical judgment. It includes independent *severity of illness* (CGI-S) and *improvement* (CGI-I) scales.
- Despite its favorable assay sensitivity in clinical trial settings involving a number of different neuropsychiatric disorders, a disadvantage of the CGI has been its lack of focus on the specific signs and symptoms of the disorder under study (Busner et al. 2009).
- Development of specific anchors for the scale that are keyed to gradations in the signs and symptoms of the disorder being assessed holds promise for enhancing the validity and reliability of the CGI for specific disorders.

Table 1: CGI Scales

Score	CGI-S:	CGI-I:
	<i>Provides an assessment of the patient's symptom severity at the time of assessment, based on the clinician's cumulative experience involving patients with the disorder</i>	<i>Rates improvement since start of the study medication. Score can be used to separate clinical trial subjects into "responders" (CGI-I of 1 or 2) and "non-responders" (CGI-I of 3 to 7)</i>
1	Normal, not at all ill	Very much improved
2	Borderline ill	Much improved
3	Mildly ill	Minimally improved
4	Moderately ill	No change
5	Markedly ill	Minimally worse
6	Severely ill	Much worse
7	Extremely ill	Very much worse

STUDY OVERVIEW

- Double-blind, placebo controlled study of NNZ-2566 ([1-3] IGF-1 analog) versus placebo
- Adolescent and adult females ages 16-45 years old
 - Participants have confirmed RTT and MeCP2 mutation
 - CGI-S severity score of 4 or higher at screening
- Primary outcome: Safety as measured by adverse events
- Secondary outcomes: Efficacy and Pharmacokinetics
 - Global outcomes measured by CGI-S and CGI-I
 - RTT Natural History Motor Behavior Assessment (MBA)
 - RTT Clinical Severity Score (CSS)
 - Aberrant Behavior Checklist
 - Vineland Adaptive Behavior Scale
 - RTT Caregiver Burden Inventory
 - Caregiver Top Three Concerns
 - EEG activity and hand movements
 - Autonomic function: respiration, hyperventilation, apneas, oxygen desaturation
- Clinicaltrials.gov ID: NCT01703533-For complete inclusion/exclusion criteria

STUDY PARTICIPANTS

Figures 1 a and b: Participant Race and Ethnicity

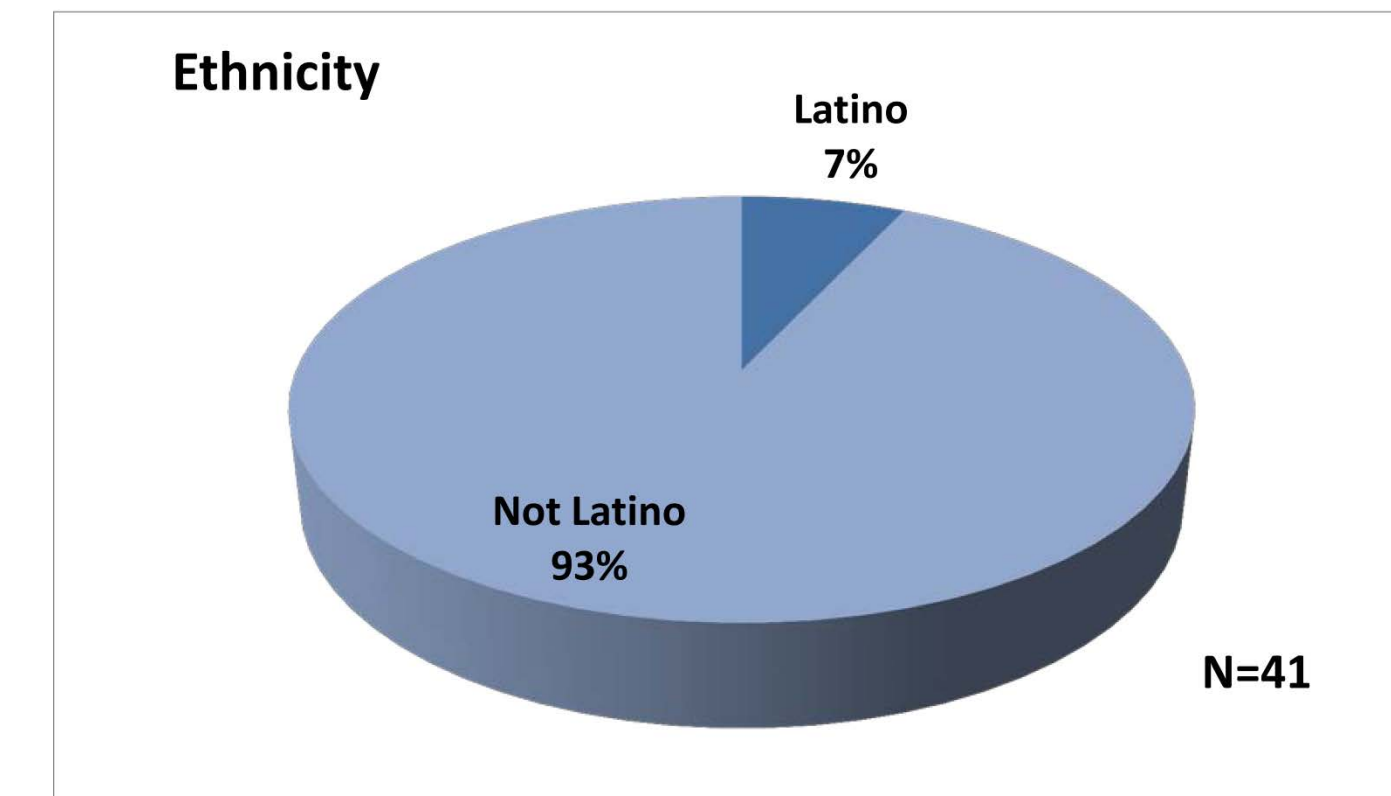
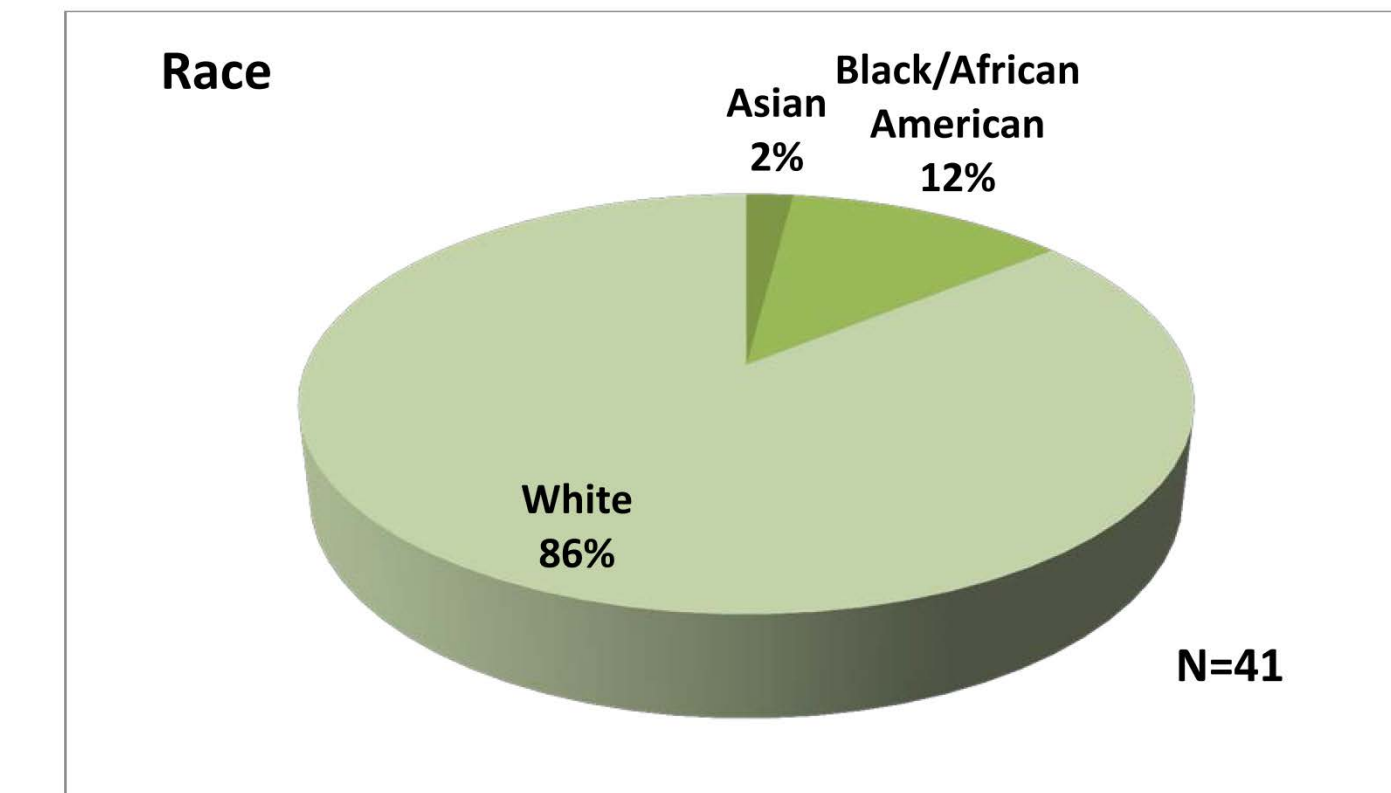
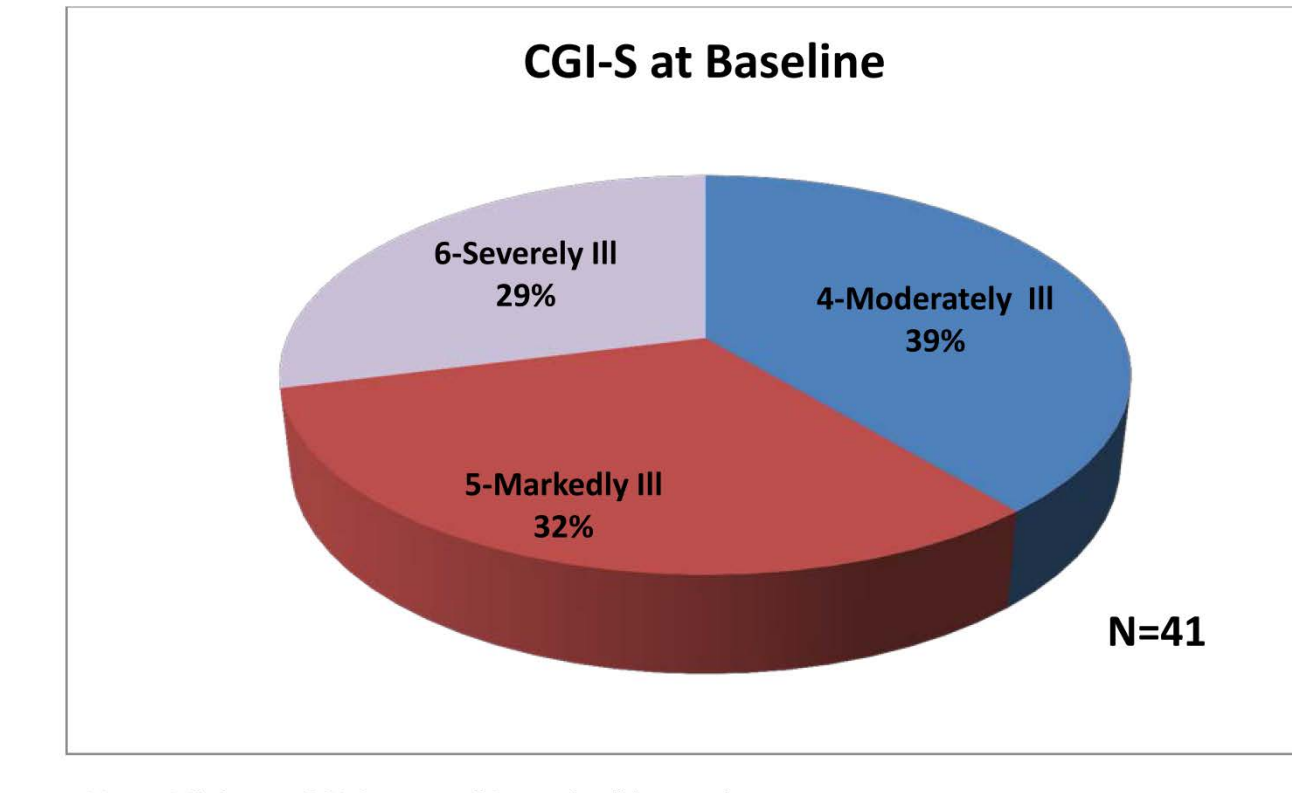


Figure 2: Severity Level at Baseline



Note: Minimum CGI-S score of 4 required for study entry.

Table 2: Participant Demographics

Enrollment to date (Randomized)	N=46
Mean Age	26 yrs
Age Range	16 - 44 yrs

METHODS

Utilizing information obtained from the RTT Natural History Study (ClinicalTrials.gov ID: NCT00299312), a classification grid of symptom severity was created, then developed into anchors describing progressive levels of impairment in symptoms. The CGI-I anchors provide examples of sign/symptom change as well as a framework for considering the duration, onset, durability of change, and context of sign/symptom change across these domains.

Table 3: Initial assignment of RTT-CSS severity scores and symptoms to CGI-S rating score

CLINICAL DOMAINS	1	2	3	4	5	6	7
	(CSS =0)	(CSS <5)	(CSS 5-10)	(CSS 10-20)	(CSS 20-25)	(CSS 25-35)	(CSS 35-40)
Language/Communication	Normal	Appropriate. May have unusual features such as perseveration/echolalia. Reading disability/dyslexia	Phrases-sentences. May have conversations or echolalia	Words (<5) Babbles. Makes choices <25-50%	No Words Babbles. Makes choices <25%	Vocalizations Occasionally screams. Makes No Choices or only rarely makes choices	No Words No Vocalizations Screams No Choices
Ambulation	No impairment	Normal, may have slight evidence of dystonia/ataxia/dyspraxia on careful exam	Walks, able to use stairs/run. May ride tricycle or climb	Walks Independently, unable to use stairs or run	Walks with Assistance	Stands With Support or independently May walks with support Sits independently or with support	Cannot sit Doesn't Stand or Walk
Hand Use	Completely normal, no impairment	Normal, may have slight fine motor issues	Bilateral Pincer grasp. May use pen to write but has some fine motor issues like tremor	Reaches for objects, raking grasp or unilateral pincer. May use utensils/cup	Reaches No Grasps	Rarely-Occasionally Reaches Out No Grasp	None
Social (Eye Contact)	Normal	Occasional eye gaze avoidance	Appropriate eye contact, >30 sec	Eye Contact <20 secs	Eye Contact <10 secs	Eye Contact, Inconsistent 5 secs	No eye Contact
Autonomic	None	Minimal	No or minimal breathing abnormalities (<5% of times observed) and Warm, pink extremities	Breathing Dysrhythmia <50% No Cyanosis Cool UE & LE Pink	Breathing Dysrhythmia 50% No Cyanosis Cold UE & LE Pink	Breathing Dysrhythmia, 50%-100%, maybe with Cyanosis Cold UE & LE may be Blue	Breathing Dysrhythmia, Constantly with Cyanosis Cold UE & LE Mottled/Blue
Seizures	None	None or controlled	None, with or without meds	Monthly-Weekly 50-100% of Time	Weekly	Weekly-Daily	Daily
Attentiveness	Entirely normal	Occasional inattention	Attentive to conversation and follows commands		50% of Time	Less than 50% time	0%

Table 4: CGI Severity Anchor Example

Score	Description of Anchors
5. Markedly ill	Markedly ill would describe another large proportion of individuals eligible for the RETT-001 study. This level of severity is characterized by breathing dysrhythmia which is observed 50% of the time, but there is no distinct cyanosis. She has cool, but pink upper and lower extremities. Seizures occur weekly. The individual walks with assistance, and can reach for objects but not grasp. Social and communication skills are impaired. The individual babbles but uses no words functionally, and makes choices < 25% of the time. She may be attentive 50% of the time and typically makes eye contact for less than 10 seconds.

Table 5: Examples of Anchors from the CGI-I

Score	Description of Anchors	Score	Description of Anchors
2-Much Improved	Much Improved may denote moderate improvement in a single symptom area, especially if seen across settings. Likewise, moderate improvements in several areas, even if confined to one setting, may warrant a rating of "Much improved." Durability of the change should be taken into account.	3-Minimally Improved	Minimally Improved indicates modest improvements, especially if confined to one setting. Trivial changes or changes that are possibly present or require guesswork usually would be scored as 4 (the level below this one).

RESULTS

Table 6: Example Calibration Vignettes with CGI-S and CGI-I Scores

Visit	CGI Score	Descriptor
Baseline	Severity: 5	She is 29yo who walks without trouble initiating and without retropulsion. She screams and vocalizes; she does not make consonant sounds. She reaches out for objects but cannot grasp or hold on to any object for more than a few seconds. She makes infrequent eye contact for 5-10 seconds, although she is very attentive to particular shows on TV. She has minimal breath holding and no hyperventilation. Her hands and feet are pink and cool. She has no seizures and is stable on her seizure medications.
Day 14	Severity: 5 Improvement: 3	No negative symptoms or events reported. Caretaker reports she is more attentive and seems to do certain things faster and more frequently, such as urinating and giving high-fives. She is observed to hold her eye gaze longer and walk with a little more fluidity.

FUTURE RESEARCH/IMPLICATIONS

The rating scheme captures clinically relevant gradations in severity and improvement of RTT-related signs and symptoms, offering the prospect of more consistent and relevant administration across research sites and studies. This report describes early development of this novel format for the CGI in the context of a clinical trial involving adolescent and adult females with RTT. Future analyses with the full pool of subjects will examine the psychometric properties and feasibility of this RTT-specific version of the CGI scales in the context of this clinical trial.

REFERENCES

- Busner J, Targum SD, and Miller DS (2009). The Clinical Global Impressions scale: errors in understanding and use. *Comprehensive Psychiatry* 50:257-262.
- Guy W (1976). Clinical global impressions. In: Guy W, editor. ECDEU assessment manual for psychopharmacology (Revised). Rockville, Maryland, National Institute of Mental Health: 217-221.

Copies of the CGI-S and CGI-I RTT anchors can be obtained by emailing: Nancy Jones, PhD at njones@neurenpharma.com

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