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

N. E. Jones¹, D. G. Glaze², J. L. Neul³, M. Snape⁴, E. Anagnostou⁴, J. Horrigan¹

¹Neuren Pharmaceuticals, Ltd., ²Baylor College of Medicine, ³Autism Therapeutics, ⁴Holland Bloorview Kids Rehab Hospital

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 ongoing 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.

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
- CGI-S severity of 4 or higher at screening
- CGI-I improvement of 3 or higher at baseline

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 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.

STUDY PARTICIPANTS

- Enrollment: 45 adolescent and adult females with RTT participated in the study.
- Baseline Severity: 5
- Improvement: 3

RESULTS

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

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.

ACKNOWLEDGEMENTS

The study is sponsored by Neuren Pharmaceuticals, and funded by Neuren Pharmaceuticals and the International Rett Syndrome Foundation. We acknowledge the participating centers, Baylor College of Medicine (PIs: Drs. Daniel Glaze and Jeffrey Neul), the University of Alabama, Birmingham (PI: Dr. Alan Percy), and Gilette Children’s Specialty Healthcare (PIs: Drs. Timothy Feyma and Art Beisang) and their contributions to the development of CGI calibration vignettes. We also thank the families who have participated in the study.

REFERENCES


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