Improving outcome measures for Rett Syndrome (RTT) clinical trials: Development of CSS/MBA change indexes to assess treatment outcome

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INTRODUCTION

Background: High-quality outcome measures are a critical component of well-designed clinical trials for individuals with Rett syndrome (RTT). We describe the development of two assessments modified for use as outcome measures sensitive to treatment response and specific to RTT.

- The RTT Clinical Severity Scale (CSS) and RTT Motor Behavior Assessment (MBA) have been used to evaluate over 1200 children and adults with RTT and other *MECP2*-related disorders in the NIH-sponsored RTT Natural History Study (RNHS).
- The MBA and CSS have established content validity for their use as clinical assessments of individuals with RTT across the age range and a variety of severity levels and degrees of disability. The MBA has been a primary measure of longitudinal clinical outcome and severity for individuals across the age span since its development in 1990.
- However, experience with their use as outcome measures for treatment trials is limited. We developed a modified scoring rubric for these assessments centering on items with the prospect of reflecting changes in symptom severity over relatively brief treatment periods (Table 1).

Development of CSS and MBA Change Indexes:

- The items for the MBA and CSS change indexes (MBA_{CI} and CSS_{CI}) were determined by expert opinion and were subject to initial review of face validity (Jones et al. 2014). The change indexes comprise items common to the RTT phenotype which were identified by clinical experts as amenable to change.
- The full versions of the CSS and MBA were administered in a Phase 2 trial of trofinetide in adults and adolescents with RTT (NCT01703533). The MBA Total Score, Subscale Scores, MBA_{CI}, CSS Total Score and CSS_{CI} were calculated. The MBA_{CI} and CSS_{CI} were used as core measures of efficacy in the trial.

Objectives:
Preliminary data on their psychometric properties and sensitivity to change were examined based on data from the Phase 2 trial in adults and adolescents. They were also analyzed in the larger RTT Natural History study database. Preliminary data on validation and their use as outcome measures in the Phase 2 trial in adults and adolescents are presented.

Table 1: Summary of Assessments

Assessment	Number/Type of Items	Standard Scoring	Change Index
CSS	• 13 items • Likert scale (0-4 or 0-5) • Items include: ○ 3 areas that are historical/static ○ 3 areas looking at onset and current function ○ 7 areas of current function	• Total Score	Sum of 5 item scores • *Language at the time of exam* • *Nonverbal communication at this visit by exam* • *Respiratory dysfunction at this visit by exam* • *Autonomic symptoms at this visit by exam* • *Epilepsy/seizures at this visit*
MBA	• 37 items • Likert scale (0-4) • Three subscales: ○ Behavioral/Social ○ Orofacial/Respiratory ○ Motor/Physical Scores based on current functioning	• Total Score • Subscale Scores	Sum of 17 item scores • *Aggressive behavior* • *Air-saliva expulsion/drooling* • *Breath holding* • *Bruxism* • *Does not respond to spoken words when addressed by examiners or parents, acts as deaf even to loud noises.* • *Dyskinesias* • *Dystonia* • *Hand clumsiness* • *Hyperventilation* • *Irritability, crying, tantrums* • *Poor eye/social contact* • *Regression of communication skills* • *Seizures* • *Speech disturbance* • *Stereotypic hand washing, clapping, stroking, kneading (when unrestrained)* • *Truncal rocking/shifting wt (voluntary)* • *Vasomotor disturbance*

STUDY DESIGN: PHASE 2 IN ADOLESCENTS AND ADULTS (RETT 001)

Phase 2, randomized, double-blind, placebo-controlled, dose-escalation clinical trial (Glaze et al. 2015)

- Adolescent and adult females ages 16-45 years
- Met diagnostic criteria for typical RTT and MECP2 mutation

Table 2: Dosing Cohorts of Oral Trofinetide vs Placebo

Cohort Number	Dose	Treatment Period	Post-Treatment Follow-Up	Active:Placebo Ratio
0	35 mg/kg b.i.d.	14 days	Day 28	2:1
1	35 mg/kg b.i.d.	28 days	Day 40	2:1
2	70 mg/kg b.i.d.	28 days	Day 40	2:1

* Key assessments occurred on Days 14 and 26

Primary outcome:

Safety as measured by adverse events, ECGs, physical exams and lab values

Secondary outcomes:

- Efficacy using clinician and caregiver measures of RTT symptom severity, associated behavioral symptoms, and physiological abnormalities
- Clinical benefit pre-specified by change criteria in 6 core measures including CSS_{CI} and MBA_{CI}

TRIAL PARTICIPANTS

Table 3: Participant Demographics (mITT)

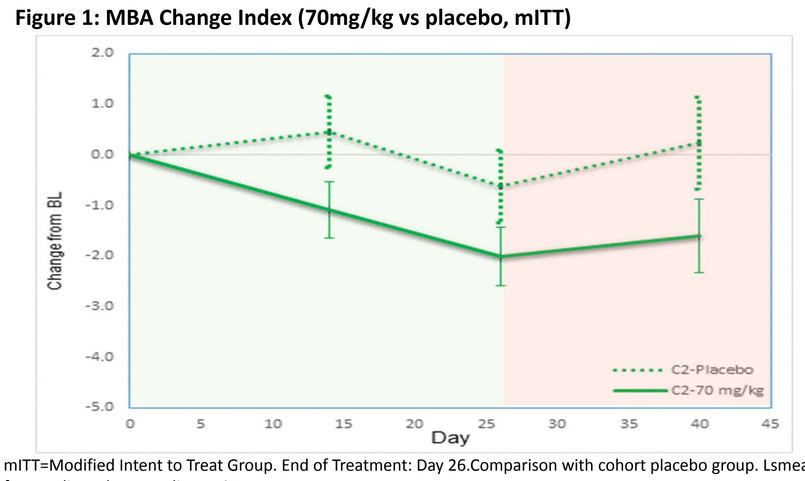
	Placebo (Combined)	35 mg/kg	70 mg/kg
N	20	18	17
Age (yr.)	27.41	23.74	24.52
CSS (mean)	23.7	23.5	24.5
CGI-S (mean)	5.1	4.9	5.2
MBA (mean)	47.7	50.3	49.8

mITT=Modified Intent to Treat Group, n=55

TRIAL RESULTS: SENSITIVITY TO CHANGE OF MBA_{CI} and CSS_{CI}

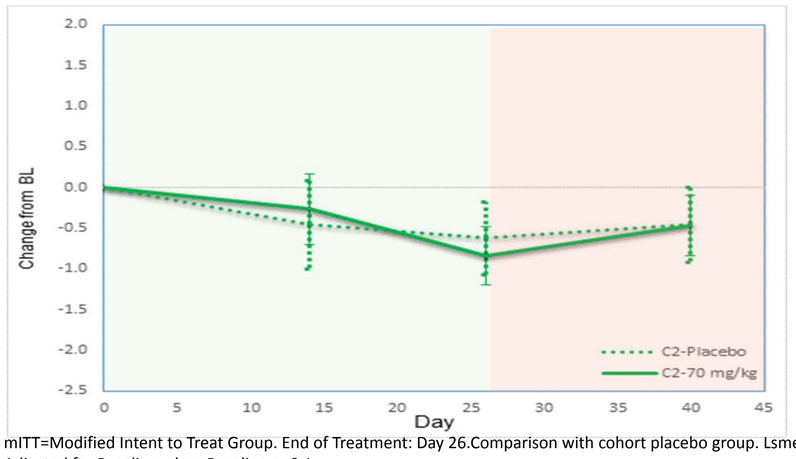
- The MBA_{CI} demonstrated sensitivity to change: the 70mg/kg treatment group showed improvement over placebo based on pre-specified criteria (Fig 1).
- Although the CSS_{CI} changed in the direction of improvement, this was not better than placebo (Fig 2).
- Major symptom areas measured by the MBA_{CI} contributing to the observed clinical benefit in the 70 mg/kg group included: communication, behavior, seizures, breathing abnormalities, hand movements/use, motor/muscular dysfunction

Figure 1: MBA Change Index (70mg/kg vs placebo, mITT)



mITT=Modified Intent to Treat Group. End of Treatment: Day 26.Comparison with cohort placebo group. Lsmeans: Adjusted for Baseline when Baseline p<0.1

Figure 2: CSS Change Index (70mg/kg vs placebo, mITT)



mITT=Modified Intent to Treat Group. End of Treatment: Day 26.Comparison with cohort placebo group. Lsmeans: Adjusted for Baseline when Baseline p<0.1

PRELIMINARY PSYCHOMETRIC ANALYSIS

- Generally the CSS and MBA (total scores) have good to very good internal consistency (RNHS Data: CSS Cronbach's alpha=0.64, n=4900; MBA Cronbach's alpha=0.836, n=5859)

Correlation of Standard Total Score with Change Index Score for CSS and MBA

- CSS_{CI} was moderately correlated with the CSS total (Pearson correlations, Rett 001 data r=0.565, n=55; RNHS data, r=0.665, n=6029)
- The MBA_{CI} score was strongly correlated to the MBA total score (Pearson correlations, Rett 001 data r=0.813, n=55; RNHS data, r=0.875, n=6029).

Internal consistency of change indexes based on Rett 001 Data

- Internal consistency for CSS_{CI} was very weak, with Cronbach's alphas 0.35 or less across all visits.
- Internal consistency for the 17-item MBA_{CI} was moderately weak (Cronbach's alpha 0.505 at baseline), but it could be improved when shorter versions of the scoring index were derived

SUMMARY/FUTURE RESEARCH

- The development of a novel scoring rubric targeted at items with greater dynamic range drawn from essential items of the MBA and CSS holds promise for the improvement of outcome measures for RTT clinical trials, in a manner that is attentive to the natural history of RTT.
- The CSS remains an excellent measure for assessing overall severity but based on the preliminary data from the Phase 2 trial in adults and adolescents, the CSS_{CI} did not demonstrate properties that would make it an appropriate outcome measure for treatment trials. It did not show sensitivity to change and items that would be amenable to change demonstrated poor internal consistency as a collective index.
- The MBA_{CI} shows promise as a useful measure for assessing treatment change in trials for RTT. The analysis of internal consistency suggests that a shorter version of the MBA_{CI} may have stronger psychometric properties which should be considered along with clinical importance and relevance of the items.
- Validation and development of the measure is on-going. Data on younger children is being collected as part of the currently on-going clinical trial of trofinetide in the pediatric population with RTT ages 5-15, NCT02715115. Additional analyses are planned with RNHS study data.

References:

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