Neuren (NEU) - ASX Announcement **24 June 2016**

Neuren presents at the Rettsyndrome.org 2016 Research Symposium

Melbourne, Australia, 24 June 2016: Neuren Pharmaceuticals (ASX: NEU) today announced that its program to develop trofinetide as a new treatment for Rett syndrome was featured in two presentations at the Rettsyndrome.org 2016 Research Symposium, held near Chicago from 22 June to 24 June.

The Research Symposium opened with a presentation by Daniel Glaze MD, Baylor College of Medicine, titled *"Past, Present and Future: A program to develop and establish trofinetide as a safe and effective treatment for Rett syndrome"*. It was presented on behalf of Dr. Glaze by Dr. Jeff Neul, University of California, San Diego. Dr Glaze and Dr Neul are Principal Investigators in Neuren's Phase 2 clinical trials of trofinetide in Rett syndrome.

Neuren's Vice President Clinical Development, Dr Nancy Jones, also presented a poster titled *"Improving outcome measures for Rett Syndrome clinical trials: Development of CSS/MBA change indexes to assess treatment outcome"*.

The presentation and the poster are attached as appendices to this announcement.

Neuren continues to make good progress with all elements of a comprehensive drug development program required for a New Drug Application (NDA) for trofinetide to treat Rett syndrome:

- Neuren's Phase 2 clinical trial in subjects aged 5 to 15 with Rett syndrome remains on track to be completed by the end of 2016.
- Neuren has agreed with the FDA the construct of the efficacy measure derived from the Motor Behavior Assessment that will be the primary endpoint in a Phase 3 trial.
- The chronic toxicity studies that are required prior to longer term dosing in a Phase 3 trial and to support the filing of a NDA are underway and will be completed in the first half of 2017.
- The optimization of the manufacturing process at commercial scale by third party contract manufacturers is progressing well and will enable drug product from the commercial process to be used in the Phase 3 trial.

Neuren Executive Chairman Richard Treagus commented: "Neuren's partnership with Rettsyndrome.org and the leading clinical experts in Rett syndrome has been instrumental in helping us reach this advanced stage. We are now closely evaluating options that will best support the remaining development and commercialization of trofinetide, while maximising the potential value for Neuren's shareholders."

About trofinetide

Trofinetide is a synthetic analogue of a naturally occurring neurotrophic peptide derived from IGF-1, a growth factor produced by brain cells. In animal models, trofinetide exhibits a wide range of important effects including inhibiting neuroinflammation, normalizing the role of microglia, correcting deficits in synaptic function and regulating oxidative stress response. Trofinetide is being developed both in intravenous and oral formulations for a range of acute and chronic conditions. The oral form of trofinetide is in Phase 2 development in Rett syndrome, Fragile X syndrome and concussion. The intravenous form of trofinetide is in Phase 2 development for moderate to severe traumatic brain injury. Three programs have received Fast Track designation from the US FDA and the Rett syndrome and Fragile X syndrome programs have also received Orphan Drug designation in the United States and the European Union.

About Neuren

Neuren Pharmaceuticals Limited (Neuren) is a biopharmaceutical company developing new therapies for brain injury, neurodevelopmental and neurodegenerative disorders. The novel drugs target chronic conditions as well as acute neurological injuries. Neuren presently has a clinical stage molecule, trofinetide in Phase 2 clinical trials as well as NNZ-2591 in pre-clinical development.

Forward-looking Statements
This ASX-announcement contains forward-looking statements that are subject to risks and uncertainties. Such statements involve known and unknown risks and important factors that may cause the actual results, performance or achievements of Neuren to be materially different from the statements in this announcement.

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The Treatment of Rett Syndrome with Trofinetide (NNZ-2566): Past, Present, Future

Daniel Glaze, MD
Baylor College of Medicine

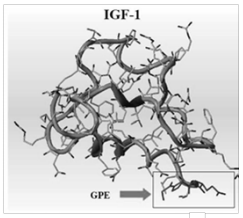
Multicenter Trials of Trofinetide

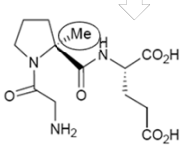
- **Past:** Neu-2566-RETT-001 Phase 2 in Adolescents and Adults with RTT
- **Present:** Neu-2566-Rett 002 Phase 2, Children with RTT
- **Future:** Anticipated Phase 3 Trial, Pediatric and Adult RTT

Sponsor: Neuren Pharmaceuticals
Rett 001 and 002 partially funded by RettSyndrome.org

Trofinetide (NNZ-2566)

- IGF-1 is a naturally occurring growth factor in the brain
- Glypromate (GPE) separates from IGF-1 in the brain
- IGF-1 and GPE maintain and restore equilibrium in the brain



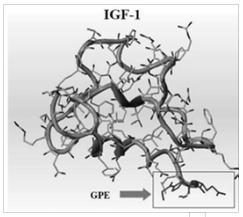


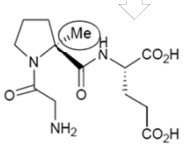
trofinetide

Trofinetide (NNZ-2566)

Trofinetide is a synthetic analogue of GPE

- Able to cross blood brain barrier
- Suitability as an oral medication: 50-60% bioavailable
- Influences processes underlying response to injury and synaptic plasticity



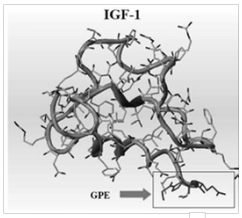


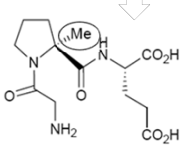
trofinetide

Trofinetide (NNZ-2566)

Trofinetide is a synthetic analogue of GPE

- Potentially targets a range of neurological conditions
- Does not bind to IGF1 receptor
- Provides good brain levels in animal models

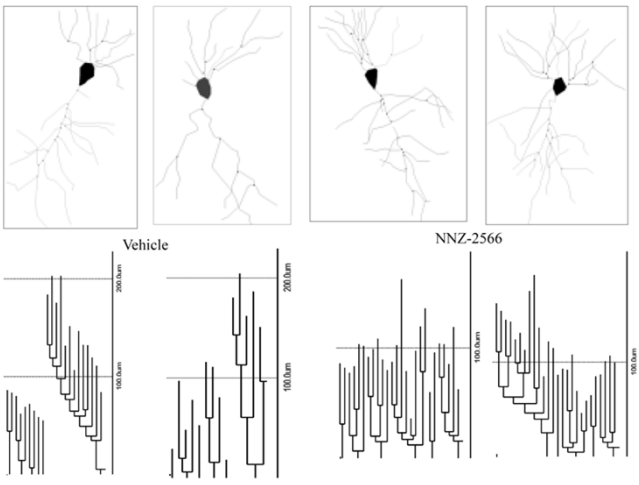




trofinetide

Trofinetide: Effects in *Mecp2* Mouse Model

- Enhanced long-term potentiation
- Increased dendritic length and arborization
- Improved longevity



Trofinetide (NNZ-2566)

- In Sum: These suggest potential application to treat Rett syndrome.
- Oral liquid formulation: good safety profile in adult healthy volunteers and Rett 001

Rett 001 Trial in Adolescents and Adults

- Phase 2, randomized, double-blind, placebo-controlled, dose-escalation clinical trial of trofinetide in RTT
  - Primary Outcome: Safety
  - Secondary Outcomes: Efficacy

Participants

- Females ages 15.9-44.2 yr. (mean 25.3)
- Met diagnostic criteria for typical RTT and *MECP2* mutation
- CGI-S score ≥ 4

Dosing Cohorts of Oral Trofinetide vs Placebo

Cohort 0			
2:1 Randomization	35mg/kg BID or Placebo	14 Days Treatment	N=9

Cohort 1			
2.1 Randomization	35mg/kg BID or Placebo	28 days treatment	N=18

Cohort 2			
2:1 Randomization	70mg/kg BID or Placebo	28 days of treatment	N=29

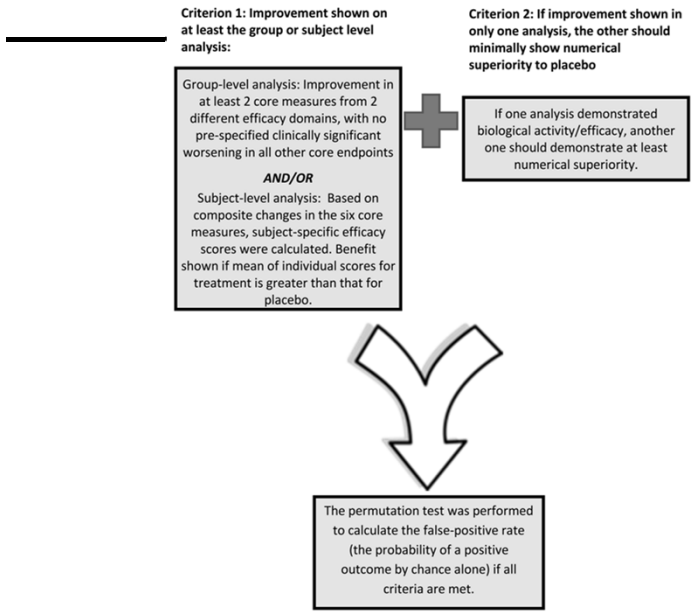
Safety Measures

- Adverse events
- ECGs
- Laboratory blood tests (chemistry, hematology, thyroid, HgA1C)
- Physical exams
- Vitals signs
- Caregiver report/seizure diary

Core Efficacy Measures

Efficacy Domain	***Core Outcome Measure***
Efficacy Domain 1: Clinician-completed syndrome-specific measures	1. Rett Syndrome Motor-Behavior Assessment (MBA) 2. Rett Clinical Severity Scale (CSS)
Efficacy Domain 2: Clinician-completed syndrome-specific global measures	3. Clinical Global Impression of Improvement (CGI-I) scale
Efficacy Domain 3: Caregiver completed syndrome-specific and general measures	4. Caregiver Top 3 Concerns visual analog scale (VAS) 5. Aberrant Behavior Checklist (ABC)
Efficacy Domain 4: Physiological measures	6. Modified Apnea Index

Pre-Specified Criteria for Efficacy



Participant Characteristics (mITT)

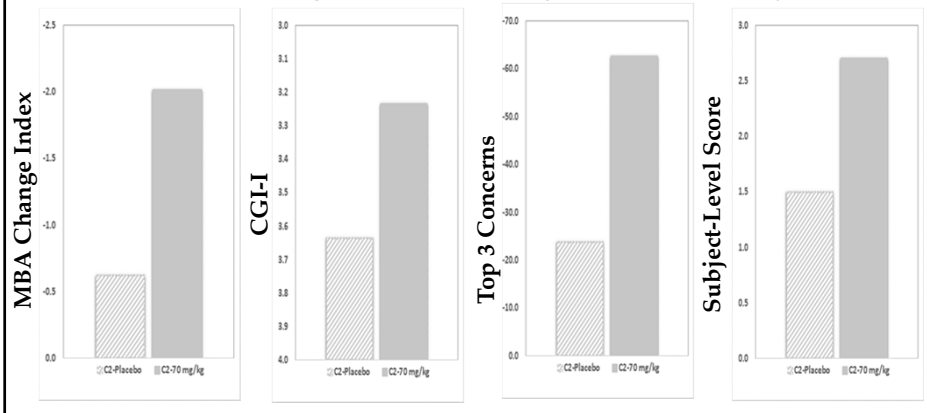
	Placebo (Combined)	35 mg/kg	70 mg/kg
N	20	18	17
Age (yr.)	27.41	23.74	24.52
CSS (mean)	23.7	23.5	24.5
CGI-S (mean)	5.1	4.9	5.2

Results: Safety

- Achieved its primary endpoint - both dose levels of trofinetide were well-tolerated after 28 days of treatment and no safety concerns were identified.
- As measured by adverse events, ECGs, vitals, physical exams and lab values

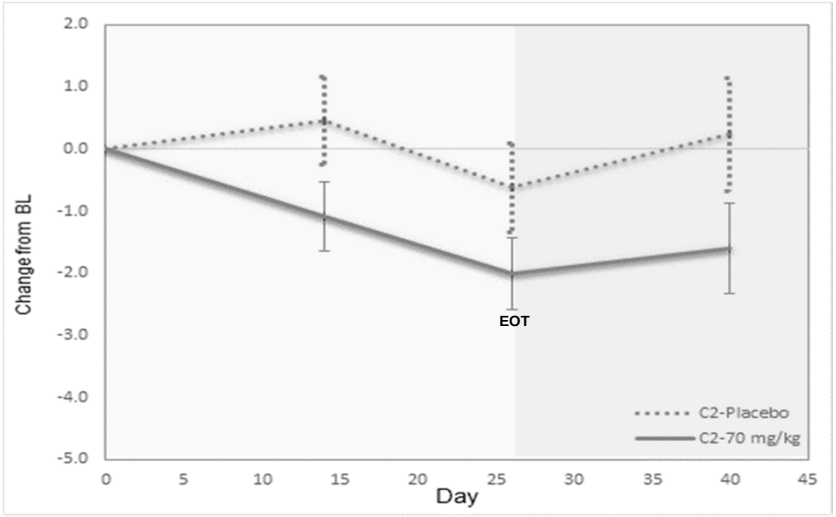
RESULTS: 70mg/kg b.i.d. Dose of Trofinetide Demonstrates Evidence of Efficacy

Higher dose exceeded the pre-specified criteria for improvement in core efficacy measures compared with placebo on group and subject level analysis



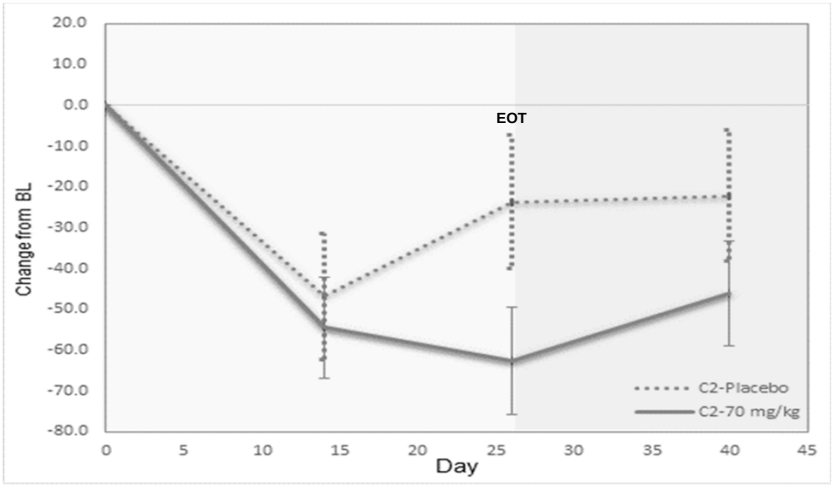
Least Squares mean change from baseline to Day 26 (Direction of benefit = Up)
*modified intent to treat group

Motor Behavior Assessment-Change Index:70mg/kg b.i.d. group



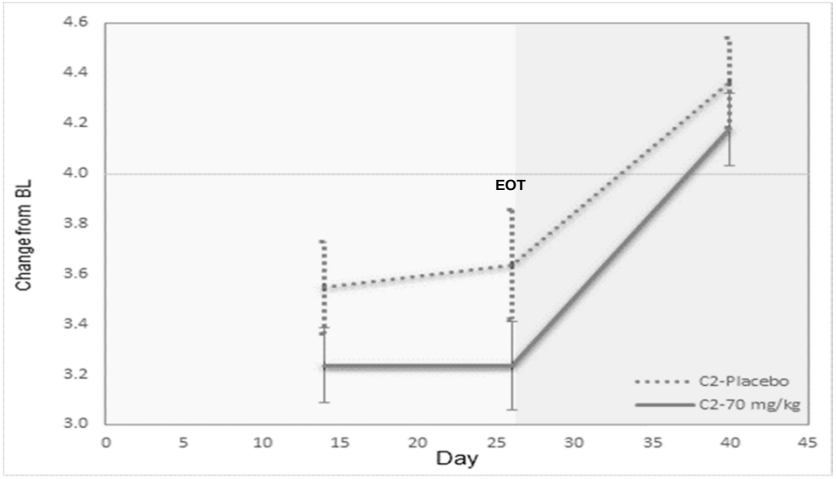
Direction of benefit: decrease in score. Lsmeans: Adjusted for Baseline when Baseline p<0.1. End of treatment=EOT

Caregiver Top 3 Concerns: 70mg/kg b.i.d. group



Direction of benefit: decrease in score. Lsmeans: Adjusted for Baseline when Baseline p<0.1. End of treatment=EOT

Clinical Global Impression of Improvement:70mg/kg b.i.d. group



Direction of benefit: decrease in score. Lsmeans: Adjusted for Baseline when Baseline p<0.1. End of treatment=EOT

Conclusion

- Oral trofinetide safe and well tolerated
- Higher dose exceeded pre-specified criteria for evidence of clinical benefit in the core symptoms of RTT.
- Results provide initial evidence of effectiveness of trofinetide as a potentially viable treatment for the core signs and symptoms of Rett syndrome and support further trials in this population.
- Provide support for development of RTT specific outcome measures that are sensitive to change in treatment trials

Current Study: Rett 002

- Phase 2, randomized, double-blind, placebo-controlled, clinical trial of trofinetide in RTT
- Outcomes
  - Primary: Safety/PK
  - Secondary: Efficacy
- Blinded treatment with trofinetide or placebo as a strawberry flavored liquid medication
- Randomized to placebo, 50 mg/kg, 100 mg/kg or 200 mg/kg of trofinetide twice daily

Inclusion / Exclusion Criteria

- Dx of classical Rett with MECP2 mutation
- Females 5 to 15 years-old
- Weight at screening 15-100 kg
- At least moderate overall severity in clinical symptoms (CGI-S ≥ 4, CSS 10-36)
- Medication and behavioral therapies stable
- Stable pattern of seizure activity
- Is able to swallow a liquid medication or take medication through a G-tube.
- Patients may be excluded if they have clinically significant medical problems/results from labs or are on excluded medications

Efficacy Assessments

Clinician Completed Measures

- Motor Behavior Assessment; Clinical Global Impression (Severity and Improvement – Anchored with Training on RTT Cases); Clinician Rated Concerns-VAS, Clinical Severity Scale (screening)

Caregiver Completed Measures

- Caregiver Top Three Concerns-VAS; Rett Syndrome Behavior Questionnaire; Rett Caregiver Burden Inventory; Caregiver Diary

Physiological/Functional Measures

- Heart Rate and Respiratory Rate Variability

Study Timeline and Current Progress

- 11 week study with 8 study visits
- Target Enrollment: 64
- Target Completion: Q4 2016
- Planned Study Sites: 12
- Enrolling Study Sites:
  - University of Alabama, Birmingham (Alabama)
  - Baylor College of Medicine (Houston, TX)
  - Boston Children's Hospital (Massachusetts)
  - Greenwood Genetic Center (South Carolina)
  - Rush Medical Center (Chicago, IL)
  - University of California, San Francisco
  - Vanderbilt University (Nashville, TN)

- Other sites in start up
- Study info and new sites opened on the website:

www.Rettstudy.org

What is next?

- Received meaningful guidance on the development program and outcome measures from FDA
- Reached agreement with FDA on the construct of the primary outcome measure considered acceptable for use in pivotal registration trial
- Subject to the results from the Rett 002 pediatric trial, a single pivotal Phase 3 study is planned for 2017

Trials of Trofinetide in RTT: Contributions to Progress in the Field

- Development and validation of RTT-Specific outcome measures will be an important component to support clinical trials development
- Development of RTT-specific measures relevant to assessing treatment outcome in trials
  - Clinical Global Impression Scales (Neul et al. 2015)
  - Rett Caregiver Burden Inventory (Lane et al. In preparation)
  - CSS Change Index and MBA Change Index (see poster in Thursday's session)

Acknowledgements

- Rett 002 Study Sites and PIs
- Drs. A. Percy, J. Neul, D. Glaze
- Rettsyndrome.org
- Neuren
  - Larry Glass
  - Nancy Jones, PhD
- Special thanks to the participating families

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)

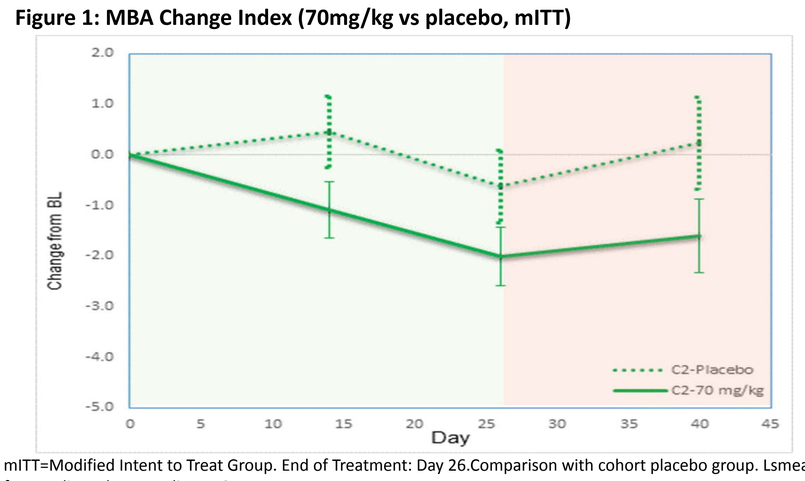
	Placebo (Combined)	35 mg/kg	70 mg/kg
N	20	18	17
Age (yr.)	27.41	23.74	24.52
CSS (mean)	23.7	23.5	24.5
CGI-S (mean)	5.1	4.9	5.2
MBA (mean)	47.7	50.3	49.8

mITT=Modified Intent to Treat Group, n=55

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

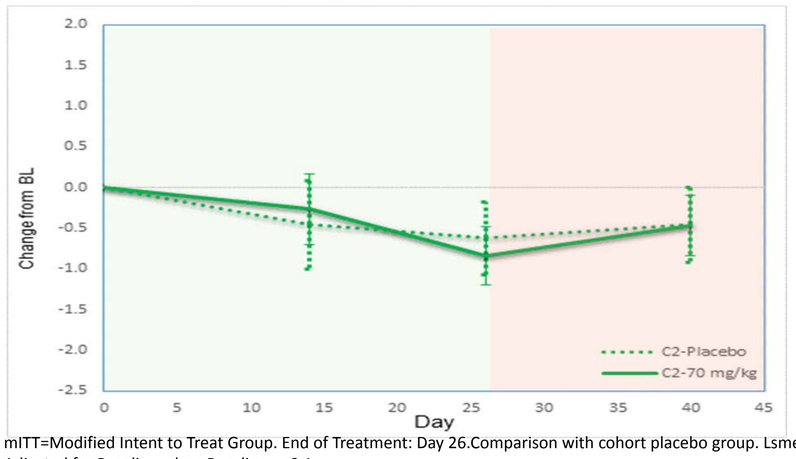
- The MBA_{CI} demonstrated sensitivity to change: the 70mg/kg treatment group showed improvement over placebo based on pre-specified criteria (Fig 1).
- Although the CSS_{CI} changed in the direction of improvement, this was not better than placebo (Fig 2).
- Major symptom areas measured by the MBA_{CI} 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:

Glaze D.G., Neul JL, Percy A., Feyma T., Beisang A., Yaroshinsky A., Stoms G., Imas O., Jordan K.G., Stein P.K., Glass L., Jones NE, Horrigan J. (2015). NNZ-2566: A novel, experimental treatment for Rett syndrome. *Neurology*. 85 (4): e46. Emerging Science Conference Paper.

Jones, N., Neul, J.L., Percy, A., Glaze, D.G., Lane, J., Feyma, T., Beisang, A., Snape, M., Horrigan, J. (2014). Improving outcome measures for Rett Syndrome (RTT) clinical trials: Development of the RTT Caregiver Inventory and CSS/MBA Change Indices. Poster Presentation. International Rett Syndrome Foundation Research Symposium. June 24-26.

ACKNOWLEDGEMENTS

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