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

Daniel Glaze, MD
Baylor College of Medicine

# Multicenter Trials of Trofinetide

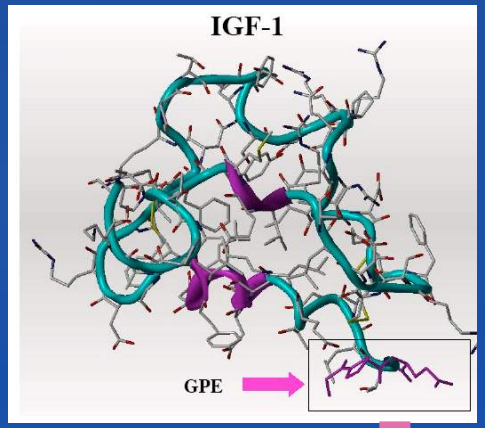
- **Past:** Neu-2566-RETT-001 Phase 2 in Adolescents and Adults with RTT
- **Present:** Neu-2566-Rett 002 Phase 2, Children with RTT
- **Future:** Anticipated Phase 3 Trial, Pediatric and Adult RTT

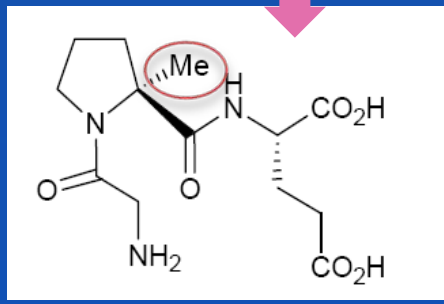
*Sponsor: Neuren Pharmaceuticals*

*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



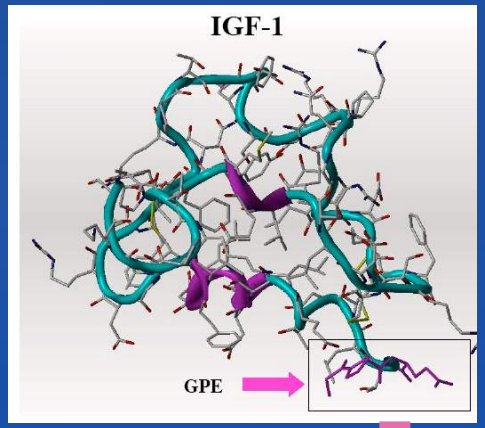



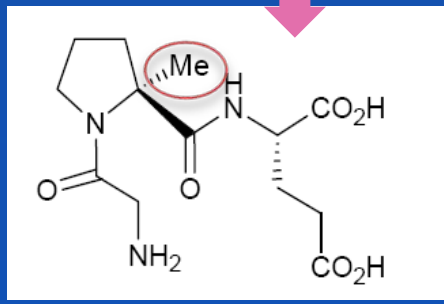

trofinetide

# 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



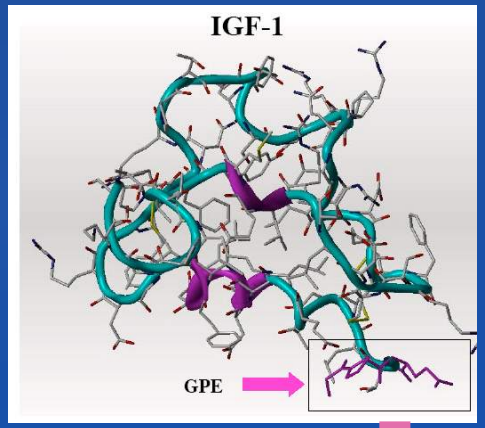



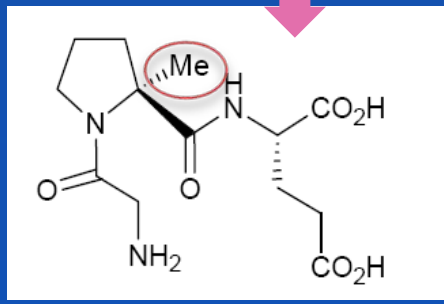

trofinetide

# 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

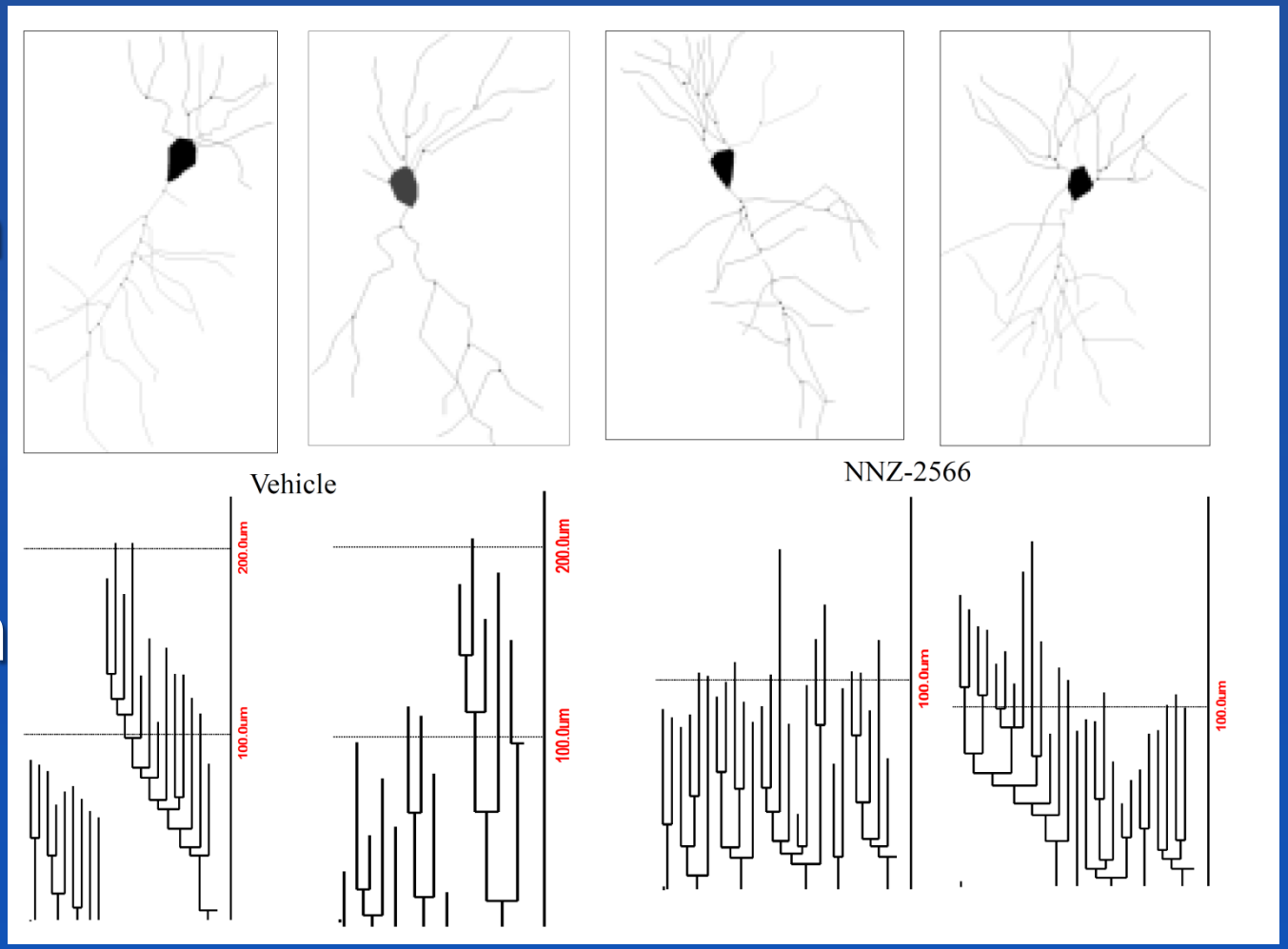



trofinetide

# 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)<br>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)<br>5. Aberrant Behavior Checklist (ABC) |
| *Efficacy Domain 4:* Physiological measures | 6. Modified Apnea Index |

# Pre-Specified Criteria for Efficacy

**Criterion 1: Improvement shown on at least the group or subject level analysis:**

Group-level analysis: Improvement in at least 2 core measures from 2 different efficacy domains, with no pre-specified clinically significant worsening in all other core endpoints

***AND/OR***

Subject-level analysis: Based on composite changes in the six core measures, subject-specific efficacy scores were calculated. Benefit shown if mean of individual scores for treatment is greater than that for placebo.

**Criterion 2: If improvement shown in only one analysis, the other should minimally show numerical superiority to placebo**

If one analysis demonstrated biological activity/efficacy, another one should demonstrate at least numerical superiority.

The permutation test was performed to calculate the false-positive rate (the probability of a positive outcome by chance alone) if all criteria are met.

# Participant Characteristics (mITT)

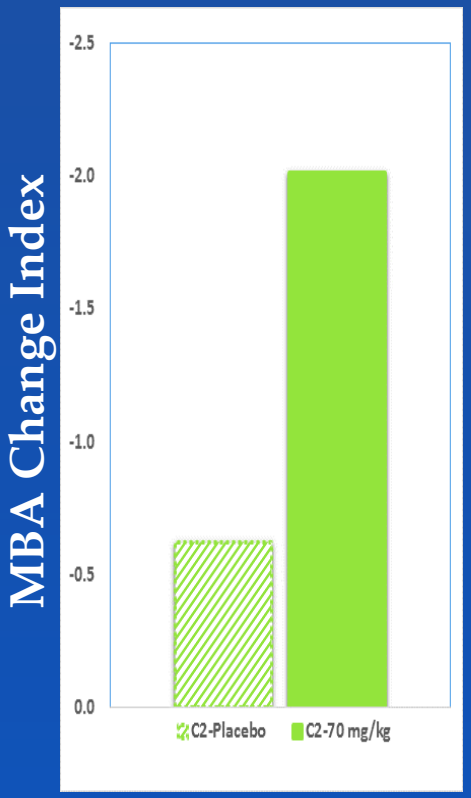
| | Placebo (Combined) | 35 mg/kg | 70 mg/kg |
|---|---|---|---|
| **N** | 20 | 18 | 17 |
| | | | |
| **Age (yr.)** | 27.41 | 23.74 | 24.52 |
| | | | |
| **CSS (mean)** | 23.7 | 23.5 | 24.5 |
| | | | |
| **CGI-S (mean)** | 5.1 | 4.9 | 5.2 |

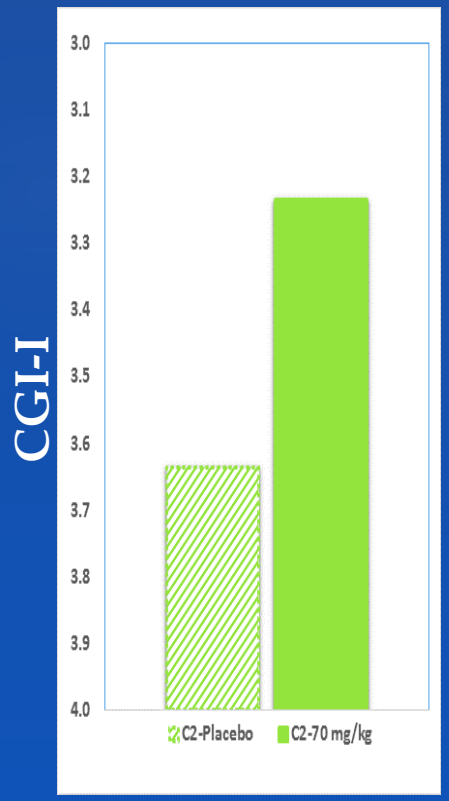
# Results: Safety

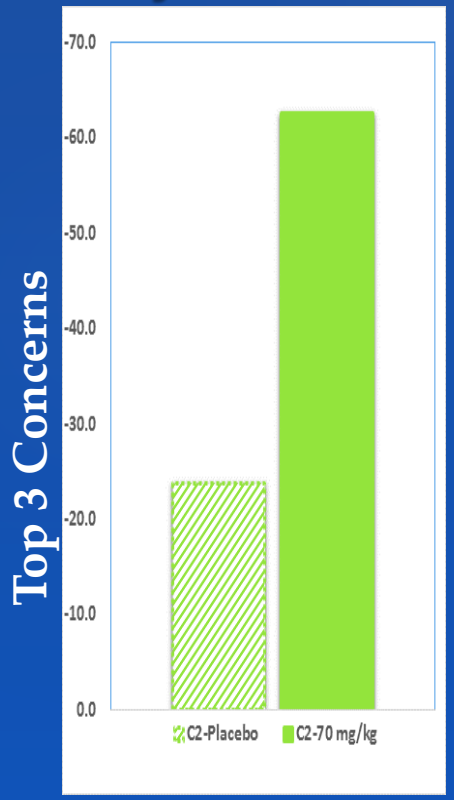
- Achieved its primary endpoint - both dose levels of trofinetide were well-tolerated after 28 days of treatment and no safety concerns were identified.
- As measured by adverse events, ECGs, vitals, physical exams and lab values

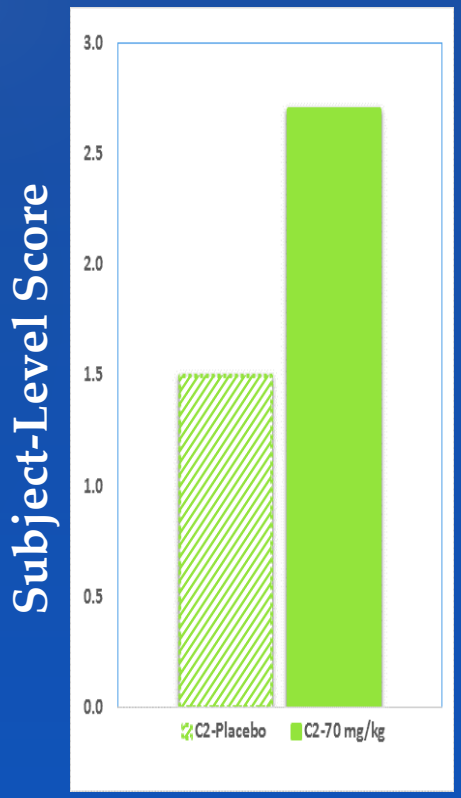
# RESULTS: 70mg/kg b.i.d. Dose of Trofinetide Demonstrates Evidence of Efficacy

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



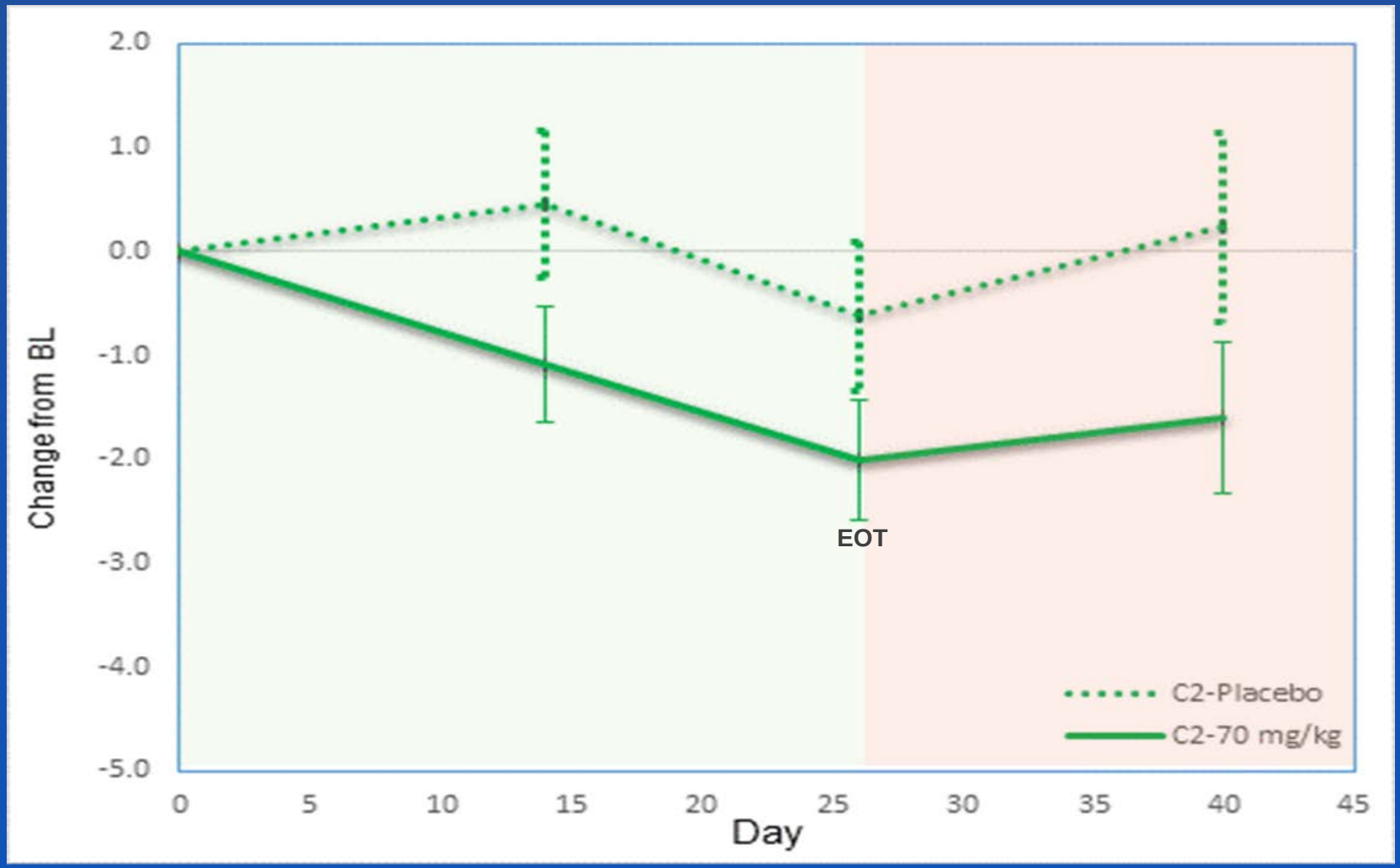



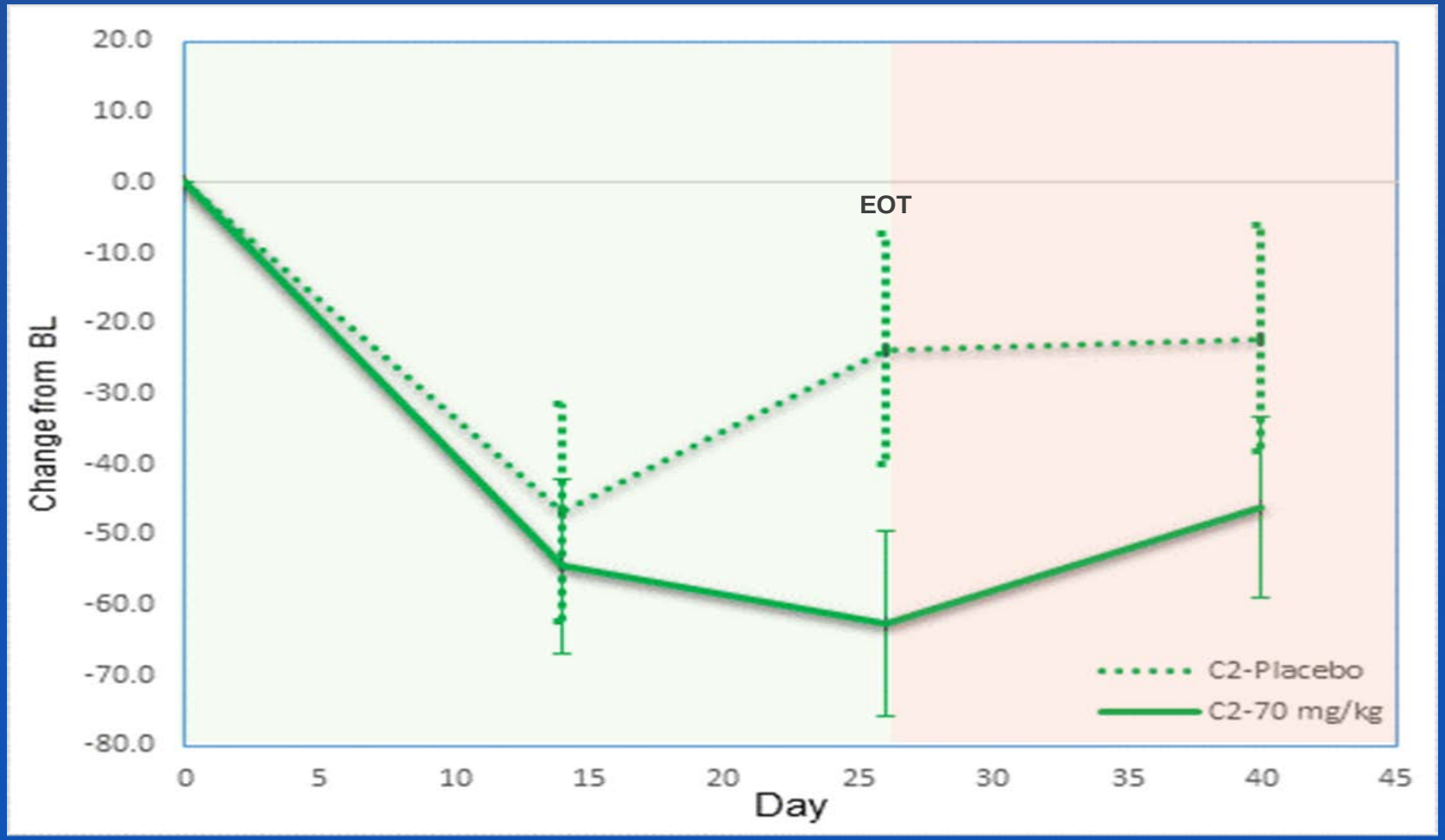

Least Squares mean change from baseline to Day 26 (Direction of benefit = Up)
*modified intent to treat group

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



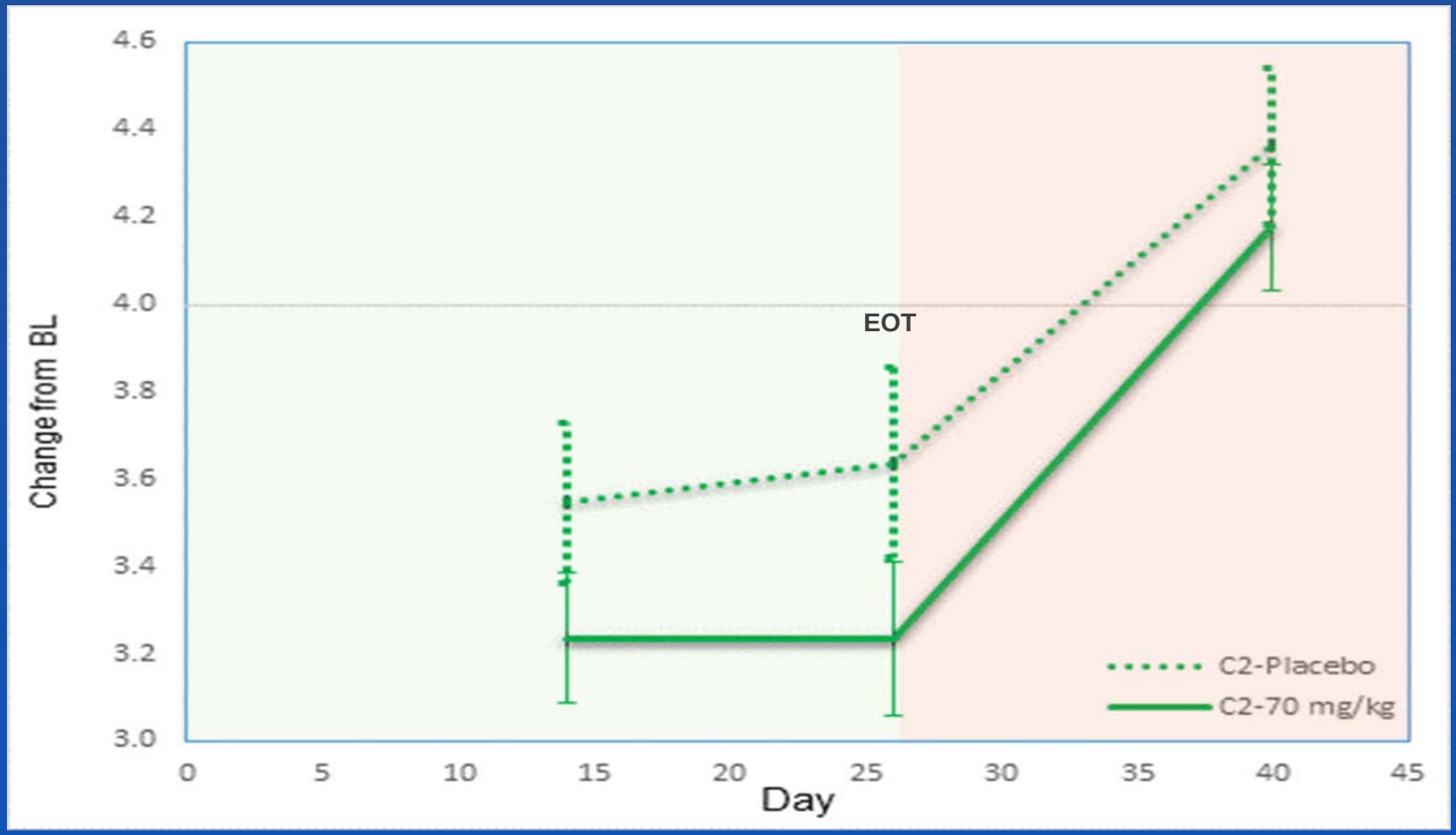

Direction of benefit: decrease in score. Lsmeans: Adjusted for Baseline when Baseline p<0.1. End of treatment=EOT

# **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