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

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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 (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 (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: 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

<table>
<thead>
<tr>
<th>Cohort 0</th>
<th>2:1 Randomization</th>
<th>35mg/kg BID or Placebo</th>
<th>14 Days Treatment</th>
<th>N=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1</td>
<td>2.1 Randomization</td>
<td>35mg/kg BID or Placebo</td>
<td>28 days treatment</td>
<td>N=18</td>
</tr>
<tr>
<td>Cohort 2</td>
<td>2:1 Randomization</td>
<td>70mg/kg BID or Placebo</td>
<td>28 days of treatment</td>
<td>N=29</td>
</tr>
</tbody>
</table>
Safety Measures

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

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

<table>
<thead>
<tr>
<th></th>
<th>Placebo (Combined)</th>
<th>35 mg/kg</th>
<th>70 mg/kg</th>
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</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>20</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td><strong>Age (yr.)</strong></td>
<td>27.41</td>
<td>23.74</td>
<td>24.52</td>
</tr>
<tr>
<td><strong>CSS (mean)</strong></td>
<td>23.7</td>
<td>23.5</td>
<td>24.5</td>
</tr>
<tr>
<td><strong>CGI-S (mean)</strong></td>
<td>5.1</td>
<td>4.9</td>
<td>5.2</td>
</tr>
</tbody>
</table>
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
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- Rettsyndrome.org
- Neuren
  - Larry Glass
  - Nancy Jones, PhD
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