NNZ-2566: A Novel, Experimental Treatment for Rett Syndrome

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INTRODUCTION

- ❑ Rett Syndrome (RTT): a rare, genetic disorder characterized by neurodevelopmental, autonomic, and CNS dysfunctions which increase risk of premature mortality and have profound and life-long impacts.
  - Usually caused by mutations in the X-chromosome gene Methyl-CpG-binding Protein 2 (*MECP2*)
  - Occurs almost exclusively in females. Current incidence 1 in 10,000
  - Young girls with RTT have apparently normal early development with onset of regression at 6 -18 months of age
  - Regression includes: developmental arrest and loss of spoken communication, purposeful hand use, and motor skills
- ❑ Currently, no successful or approved drug treatments available to alleviate core symptoms of RTT
- ❑ First industry-sponsored, multi-site clinical trial in RTT

OBJECTIVES

The effects of treatment with orally administered NNZ-2566 (an analog of IGF-1 terminal tripeptide) on symptoms of RTT were examined in a Phase 2, randomized, double-blind, placebo-controlled, dose-escalation study.

1. Primary outcome: Safety as measured by adverse events, ECGs, physical exams and lab values
2. Secondary outcomes:
   - Efficacy using clinician and caregiver measures of RTT symptom severity, associated behavioral symptoms, and physiological abnormalities

STUDY DESIGN

Table 1: Dosing Cohorts of Oral NNZ-2566 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*

- Adolescent and adult females ages 16-45 years
- Met diagnostic criteria for typical RTT and having a *MECP2* mutation
- See www.clinicaltrials.gov (NCT01703533) for complete inclusion/exclusion criteria

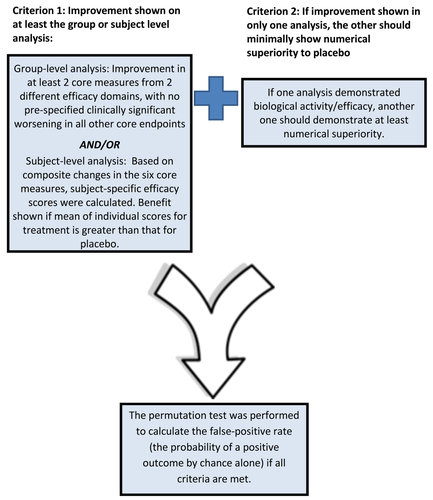
ANALYTICAL METHODS

- Clinical benefit pre-specified by change criteria in 6 core measures comprising 4 efficacy domains (Table 2 & Figure 1)
- Core efficacy analyses were adjusted for baseline.

Table 2: Core Efficacy Measures by Efficacy Domain

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

Figure 1: Pre-Specified Criteria for Biological Activity/Efficacy



RESULTS

Table 3: Participant Demographics (mITT)

	Cohort 0		Cohort 1		Cohort 2		
Characteristic	Placebo (N=4)	35 mg/kg (N=5)	Placebo (N=5)	35 mg/kg (N=13)	Placebo (N=11)	70 mg/kg (N=17)	Total (n=55)
Age, years							
N	4	5	5	13	11	17	55
Mean (SD)	22.4 (4.6)	26.7(8.8)	32.1(9.3)	22.6 (5.6)	27.1(8.4)	24.5(5.9)	25.3(7.1)
Median	22.2	25.4	33.9	20.6	25.2	23.9	24.2
Minimum, Maximum	17.4,27.9	17.6,40.8	18.5,44.2	15.9,31.0	16.3,43.9	17.1,35.9	15.9,44.2
Ethnicity							
Hispanic or Latino	2	0	1	0	0	2	5 (9%)
Not Hispanic or Latino	2	5	4	13	11	15	50 (91%)
Race							
White	3	5	5	10	11	15	49 (89%)
Black or African American	1	0	0	3	0	1	5 (9%)
Asian	0	0	0	0	0	1	1 (2%)

ITT: Intent to Treat-all randomized subjects. *mITT:* Modified Intent to Treat-randomized subjects who received at least one dose of study medication.

Safety:

- Both dose levels of NNZ-2566 well-tolerated
- There were no SAEs attributable to study drug.
- No time- or dose-dependent changes in the safety profile noted.

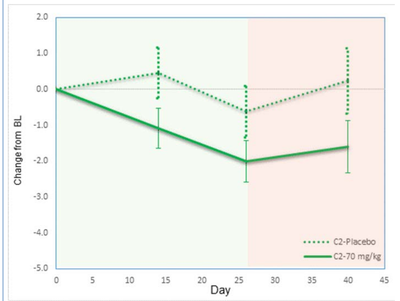
RESULTS

Efficacy

- Clinical benefit (as per pre-specified definition) demonstrated at Day 26 for the 70mg/kg dose in both group- and subject-level analyses (Fig. 2).

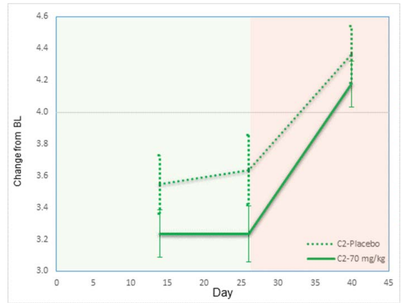
Figure 2: Assessments that met improvement criteria in the 70mg/kg b.i.d.. group (Cohort 2, mITT)

Motor Behavior Assessment Change Index



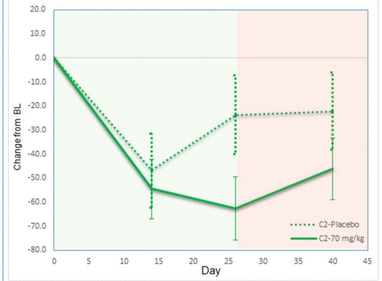
Lsmeans: Adjusted for Baseline when Baseline p<0.1. Data during treatment at Day 14 and Day 26. Post treatment at Day 40. Direction of benefit: decrease in score.

Clinical Global Impression of Improvement



Means. Data during treatment at Day 14 and Day 26. Post treatment at Day 40. Direction of benefit: lower score.

Caregiver Top 3 Concerns



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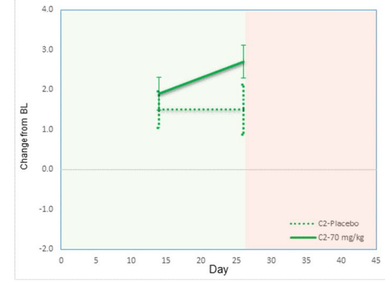
Mean Subject-level Efficacy Score



Means. Data during treatment at Day 14 and Day 26. Direction of benefit: higher score.

- No clinically significant worsening in any pre-specified core outcomes.
- The probability that this was a false-positive outcome based on a permutation test was 0.023.

CONCLUSIONS

- ❑ Overall, this small Phase 2 study met its primary end point.
  - Both dose levels of NNZ-2566 well-tolerated.
  - No time- or dose-dependent changes in safety profile noted.
- ❑ Higher dose exceeded pre-specified criteria for evidence of clinical benefit in the core symptoms of RTT.
- ❑ Results provide initial evidence of effectiveness of NNZ-2566 as a potentially viable treatment for the core signs and symptoms of Rett syndrome and support further trials in this population.

ACKNOWLEDGEMENTS

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