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1. *Abstract Title*

The Treatment of Rett Syndrome with NNZ-2566 (trofinetide)

2. *Abstract*

Objective

The effects of treatment with an IGF-1 terminal tripeptide analog (NNZ-2566) on symptoms of Rett syndrome (RTT) were examined in a Phase 2, multi-site, randomized, double-blind, placebo-controlled, dose-escalation clinical trial involving adolescent/adult females.

Background

RTT is a genetic syndrome characterized by neurodevelopmental, autonomic, and CNS dysfunctions which increase risk of premature mortality and have profound and life-long impacts. Currently, no successful or approved drug treatments are available to alleviate its core symptoms.

Design/Methods

Participants (n=56) were treated *bid* up to 28 days with placebo, 35mg/kg or 70mg/kg of NNZ-2566. Safety/tolerability were assessed by adverse events, ECGs, physical exams and lab values. Efficacy was evaluated using clinician and caregiver measures of RTT symptom severity, associated behavioral symptoms, and physiological aberrations. Clinical benefit was pre-specified by change criteria in six core measures comprising four efficacy domains. The group analysis required improvement in at least two core measures from two different efficacy domains, with no clinically significant worsening in all other core endpoints. For the individual analysis, based on composite changes in the six core measures, a subject-specific efficacy score was calculated and mean scores compared between treatment and placebo groups.

Results

Both dose levels of NNZ-2566 were well-tolerated. No time- or dose-dependent adverse events were noted. Clinical benefit was demonstrated (p=0.023 by permutation testing) for the 70mg/kg dose in the group- and subject-level analyses. Three of the six core measures demonstrated clinical benefit: MBA Change Index (core RTT symptoms), CGI-I (overall clinical status), and Caregiver Top 3 Concerns (most concerning aspects of RTT identified by caregivers) with no pre-specified clinically significant worsening in any core endpoints.

Conclusions

Overall, NNZ-2566 was well-tolerated. The higher dose exceeded the pre-specified criteria for evidence of biological activity/efficacy in core measures compared with placebo. The clinical benefit was evident in the core symptoms of RTT in both clinician- and caregiver-completed assessments.