FULL-LENGTH ARTICLE NPub.org/dfre04

Double-blind, randomized, placebo-controlled study of trofinetide in pediatric Rett syndrome

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Study objective and summary result

This study investigated the safety and efficacy of trofinetide as a treatment for pediatric Rett syndrome (RTT). The results demonstrated that trofinetide appears to be safe and well-tolerated and yields significant symptom improvements in key efficacy measures relative to placebo in pediatric patients with RTT.

Classification of evidence

Class I.

What is known and what this paper adds

A previous phase 2 clinical trial of trofinetide as a treatment for RTT provided evidence of safety, tolerability, and symptom improvement in adolescents and adults. This study provides further support to the safety and efficacy profile of trofinetide.

Participants and setting

This study enrolled 82 female patients with RTT (mean age, 9.73 ± 3.43 years; age range, 5–15 years) at 12 centers in the US. These patients carried a pathogenic *MECP2* variant and were in the postregression stage. Enrollment began in March 2016, and the study concluded in January 2017.

Design, size, and duration

This phase 2 trial began with a 14-day single-blind period in which all participants received placebo treatment. This was followed by a randomized double-blind treatment period of 42 days, during which participants were assigned to placebo BID (n = 24) or trofinetide at 50 mg/kg BID (n = 15), 100 mg/kg BID (n = 16), or 200 mg/kg BID (n = 27). The study drug was taken as a liquid either orally or through a gastrostomy tube. The safety assessments included adverse event (AE)-monitoring, laboratory tests, and physical examinations. Blood samples were also collected for the evaluation of pharmacokinetics. Efficacy assessments included various RTT-specific outcomes measures.

Primary outcome measures

The primary outcome of the study included the safety findings observed throughout the treatment period.

Table AE rates during the double-blind period by treatment group

Treatment group	No. (%) of participants reporting at least 1 AE
Placebo BID	14 (58%)
50 mg/kg BID trofinetide	8 (53%)
100 mg/kg BID trofinetide	11 (69%)
200 mg/kg BID trofinetide	19 (70%)
Total	52 (63%)

Main results and the role of chance

Only 4 serious AEs occurred, and none were study drug–related. Trofinetide at 200 mg/kg BID was associated with significant improvement relative to placebo on 3 RTT-specific assessments: the Rett Syndrome Behaviour Questionnaire – total score (p = 0.042), RTT-Clinician Domain Specific Concerns-Visual Analog Scale (p = 0.025), and Clinical Global Impression Scale-Improvement (p = 0.029).

Bias, confounding, and other reasons for caution

This study had a small sample size and a short duration.

Generalizability to other populations

It is expected that these results will be generalizable across patients with a clinical diagnosis of RTT.

Study funding/potential competing interests

This study was funded by Neuren Pharmaceuticals and Rettsyndrome.org. Some authors report serving as investigators on other clinical trials, including other Neuren-sponsored trials; consulting for healthcare companies; receiving research support from healthcare companies; and being employees and corporate officers of healthcare companies, including Neuren. Go to Neurology.org/N for full disclosures.

Trial registration number

NCT02715115 on ClinicalTrials.gov.

A draft of the short-form article was written by M. Dalefield, a writer with Editage, a division of Cactus Communications. The authors of the full-length article and the journal editors edited and approved the final version.

