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DAYBUE™ (trofinetide) Clinical Trials in Male Participants

This letter is provided in response to your specific request for information regarding clinical trials of trofinetide conducted in male participants.

Relevant Labeling Information[1]

- DAYBUE is indicated for the treatment of Rett syndrome in adults and pediatric patients 2 years of age and older.

Summary

- The trofinetide clinical development program for Rett syndrome (RTT) does not include data from male patients.
- Male participants were included in **Phase 1 clinical studies** of healthy adult volunteers, a **Phase 2 study in fragile X syndrome** (FXS) and two **Phase 2 clinical studies in traumatic brain injury** (TBI).[2]

Background

RTT is a rare, debilitating neurological disorder that occurs primarily in females.[3] The trofinetide clinical development program does not include data from male patients with RTT.[2] The exclusion of males from the Phase 2 and Phase 3 clinical trials in RTT was based on considerations of study design to reduce variability in the population sample.[4] Males with RTT were not enrolled due to the rarity of cases and difficulties inherent in adding another criterion for stratification.[4]

Male participants were included in Phase 1 clinical studies of healthy adult volunteers, a Phase 2 study in adolescent and adult males with FXS, and two Phase 2 clinical studies in adolescents and adults with TBI. Overall, 326 males have been exposed to trofinetide in clinical trials, including 189 who received trofinetide via IV infusion and 137 who received oral trofinetide.[2]

Phase 1 Studies in Healthy Adult Volunteers

Overall, 120 healthy adult male participants have been exposed to trofinetide in Phase 1 clinical studies. In a Phase 1 study of oral trofinetide in 9 men and 9 women, no between-sex differences in the pharmacokinetics (PK) of trofinetide were observed. No treatment- or dose-related patterns were evident across Phase 1 studies in the incidence of treatment-emergent adverse events (TEAEs).[2]

Phase 2 Study in FXS: NEU-2566-FXS-001

The safety and tolerability of oral trofinetide (35 mg/kg or 70 mg/kg twice daily [BID]) was studied in 72 adolescent and adult males (12–41 years old) with FXS in a Phase 2 randomized, double-blind, placebo-controlled study (Neu-2566-FXS-001).[5] Incidences of TEAEs were generally comparable between the trofinetide and placebo groups. The most common TEAEs overall were upper respiratory tract infection (7%) and diarrhea (6%).[5]

Phase 2 Studies in TBI

The majority of participants in the two randomized, double-blind, placebo-controlled Phase 2 studies assessing trofinetide in participants with TBI were male: 88.1% in Neu-2566-TBI-001/002 (N=251) and 87.1% in Neu-2566-TBI-003 (N=31).[2]

In Neu-2566-TBI-001/002, a dose escalation study of trofinetide administered via IV infusion (1, 3 or 6 mg/kg/h) in participants with moderate to severe TBI (16–72 years old), the incidence of TEAEs and serious TEAEs did not differ meaningfully between trofinetide and placebo, except for serious TEAEs of prolonged electrocardiogram (ECG) QT (trofinetide, 4.2%; placebo, none).[2]

Neu-2566-TBI-003, a study in participants with mild TBI (18–45 years old) treated with orally administered trofinetide (35 mg/kg and 70 mg/kg BID), was stopped early due to slow enrollment. There was no clear relationship of incidence of specific TEAEs to either treatment or dose; the most frequent TEAEs were headache and dizziness.[2]

Pooled Analysis of Double-blind Oral-treatment Studies in Males

In a pooled safety analysis of data from male participants in double-blind studies of oral trofinetide (Neu-2566-FXS-001 and Neu-2566-TBI-003), headache (16.7%), vomiting (6.7%), diarrhea (6.7%) and fatigue (6.7%) were the most frequent TEAEs with trofinetide (N=60) occurring more than placebo (N=35).[6]

References

1. DAYBUE™ (trofinetide) [package insert]. San Diego, CA. Acadia Pharmaceutical Inc. **[Link]**
2. Acadia Pharmaceuticals Inc. Data on File. Trofinetide Investigator's Brochure. February 15, 2024.
3. Neul JL, Kaufmann WE, Glaze DG, et al. Rett syndrome: revised diagnostic criteria and nomenclature. *Ann Neurol.* 2010;68(6):944-950. **[PubMed]**
4. Neul JL, Percy AK, Benke TA, et al. Design and outcome measures of LAVENDER, a phase 3 study of trofinetide for Rett syndrome. *Contemp Clin Trials.* 2022;114:106704. **[PubMed]**
5. Berry-Kravis E, Horrigan JP, Tartaglia N, et al. A Double-Blind, Randomized, Placebo-Controlled Clinical Study of Trofinetide in the Treatment of Fragile X Syndrome. *Pediatr Neurol.* 2020;110:30-41. **[PubMed]**
6. Acadia Pharmaceuticals Inc. Trofinetide Integrated Summary of Safety. 2022.