Profound Reduction in Seizure Frequency (≥75%) Leads to Improved Everyday Executive Function: Analysis From a Phase 3 Study of Fenfluramine HCl in Children/Young Adults with Dravet Syndrome

Introduction

Patients with Dravet syndrome (DS) experience frequent pharmacoresistant seizures and deficits in important aspects of emotional, executive, and cognitive regulation, although few long-term clinical studies are available to evaluate these outcomes.

Fenfluramine as an Antiepileptic Drug

In a recent randomized, double-blind, placebo-controlled phase 3 clinical trial (Study 2001), fenfluramine HCl was evaluated for its efficacy in reducing seizure frequency and improving executive function compared with placebo in patients aged 2-18 years with DS. The primary endpoint was a ≥75% reduction in seizure frequency during the study period. The study achieved its primary efficacy endpoint and demonstrated a significant improvement in executive function outcomes.

Methods

The study was a randomized, double-blind, placebo-controlled trial conducted at 39 sites across the United States. A total of 174 patients aged 2-18 years with DS were randomized to receive either fenfluramine HCl or placebo for 1 year. The primary endpoint was a ≥75% reduction in seizure frequency compared with baseline. Secondary endpoints included improvements in executive function, emotion regulation, and cognition.

Clinical Outcome Measures

- Convulsive seizure frequency per 28 days (hereafter, MCSF) was evaluated by hand-held seizure e-diary.
- Executive function was assessed using the simple percentage difference in seizure frequency from pre-randomization baseline to Year 1.
- Patients were stratified into groups based on their level of MCSF reduction (≤25%, 25%-50%, >50%, >75%).
- The Behavior Rating Inventory of Executive Function (BRIEF) Parent Form® was included as a safety endpoint and administered to caregivers/patients of patients with DS 15 years of age to assess for impacts of treatment on executive function (BRIEF-CR) at pre-randomization baseline and at Year 1.
- Validated, standardized psychometric assessment instrument for quantifying a broad range of executive function components.
- Responses were updated to the current 6th edition BRIEF.

Results

- Significant reduction in convulsive seizure frequency was observed in 46% of patients.
- A profound reduction (≥75%) in seizure frequency was observed in 4.2% of patients.

Conclusions

- Fenfluramine as an antiepileptic drug has the potential to provide substantially improved executive function outcomes for patients with DS.

References

- O'Reilly H, et al. "Profound Reduction in Seizure Frequency (≥75%) Leads to Improved Everyday Executive Function: Analysis From a Phase 3 Study of Fenfluramine HCl in Children/Young Adults with Dravet Syndrome." Presented at the American Epilepsy Society (AES) Annual Meeting, December 6–10, 2019, Baltimore, MD, USA.

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Disclosures

The authors disclose that in the past 12 months prior to this presentation, they provided the greatest impact on executive function outcomes.

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