Prospective evaluation of non-seizure benefits related to treatment with fenfluramine in pediatric and adult patients with Dravet syndrome

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BACKGROUND

Dravet syndrome (DS) is a developmental and epileptic encephalopathy (DEE) characterized by multiple seizure types, intellectual disability, behavioral problems, psychiatric comorbidities, poor sleep patterns, and progressive gait impairment.

Fenfluramine is approved for the treatment of seizures associated with DS in the United States,[1] European Union,[2] United Kingdom,[3] Japan,[4] and Israel[5] in patients ≥2 years of age. Fenfluramine significantly reduces seizure frequency in patients with DS, and some evidence suggests a beneficial effect on non-seizure parameters.[6] Real-world data (both non-seizure and seizure outcomes) in adults with DS are particularly limited.

Objective

To describe baseline cognition and adaptive behavior in both adult and pediatric patients with DS and the first interim results of fenfluramine-associated treatment effect on seizure frequency.

METHODS

- Prospective evaluation of adult and pediatric patients with a clinical diagnosis of DS and *SCN1A* pathogenic variant treated with fenfluramine between August 2023 through January 2025
- Neuropsychological evaluation was performed once and included baseline (pre-fenfluramine) scores of:

Cognitive score level

Bayley Scales of Infant and Toddler Development (Bayley-IV), or the Wechsler Intelligence Scales (WIS) adapted to age

Adaptive behavior scores

Vineland Adaptive Behavior Scales (VABS-III)

- Seizure frequency was collected from seizure diaries as reported by caregivers; change from baseline (pre-fenfluramine) in frequency of generalized tonic-clonic seizures (GTCS) is reported
- Incidence of valvular heart disease (VHD) or pulmonary arterial hypertension (PAH) while on fenfluramine is reported

RESULTS

Parameters	Adults (n = 5)	Pediatrics (n = 2)
Age at last follow up, mean years (range)	33 (24–46)	6 (5–7)
Female, n (%)	2 (40)	1 (50)
Proved *SCN1A* variant, n (%)	5 (100)	2 (100)
Age at DS diagnosis, median years (range)	22 (9–39)	1.7 (1.4–2)
Number of previously tried ASMs, mean (range)	9.6 (8–12)	3.5 (3–4)
Previous use of sodium-channel blockers, n (%)	5 (100)	0 (0)
Fenfluramine treatment period, mean months (range)	3.23 (<1–6)	13.5 (6–21)
Mean dose of fenfluramine at last follow-up, mg/kg/day (range)	0.138 (0.06–0.22)	0.67 (0.64–0.7)
Number of concomitant ASMs, mean (range) • Patients treated with stiripentol, n (%)	3.5 (3–4) • 5 (100%)	2 (1–3) • 0 (0%)

Table 1. *Baseline characteristics of the adult and pediatic cohort thus far enrolled in the study.* Over the study period, 25 patients (both adult and pediatric) will be enrolled and evaluated at baseline (before fenfluramine treatment start) and at annual visits. Since last follow-up, two adult patients discontinued treatment with fenfluramine due to adverse events (nausea/loss of appetite & weight loss). ASM: Anti-seizure medication, DS: Dravet syndrome.

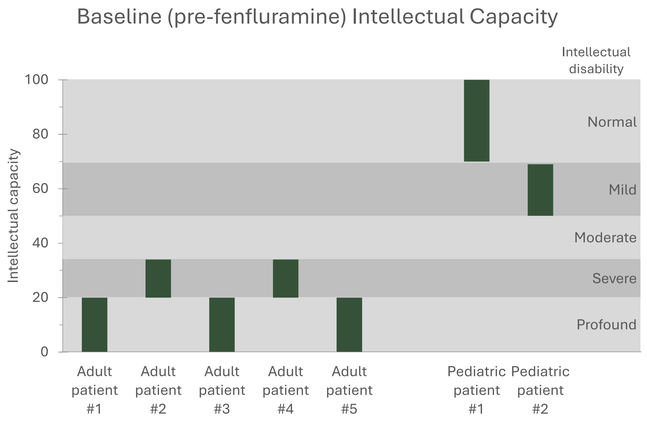

Figure 1. *Intellectual function assessment of patients with DS at baseline.* Patients were evaluated using standarlized neuropsychological assessments to determine intellectual capacity. Normal IQ: >70, Mild ID: 50–69; Moderate ID: 35–49; Severe ID: 20–34; Profound ID: <20. DS: Dravet syndrome, ID: intellectual disability.

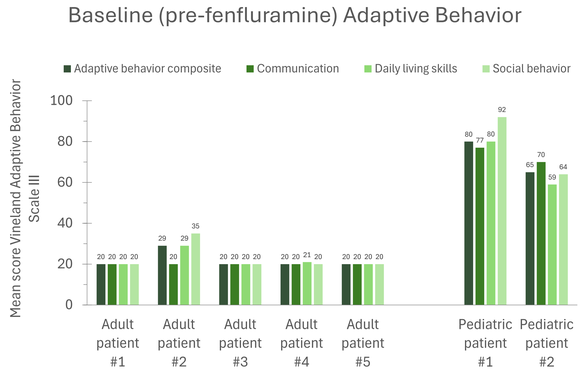

Figure 2. *Adaptive Behavior, measured by Vineland Adaptive Behavior Scale III, in patients with DS at baseline.* Higher scores indicate better adaptive behavior and are classified as follows: "High" (domain and ABC Standard Scores of 130–140), "moderately high" (domain and ABC Standard Scores of 115–129), "adequate" (domain and ABC Standard Scores of 86–114), "moderately low" (domain and ABC Standard Scores of 71–85), and "low" (domain and ABC Standard Scores of 20–70). ABC: adaptive behavior composite, DS: Dravet syndrome.

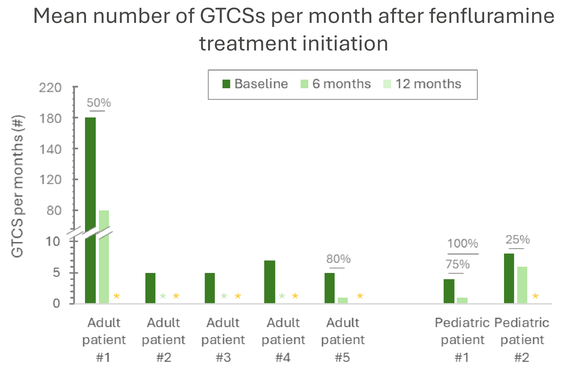

Figure 3. *The mean number of GTCSs per month after fenfluramine treatment initiation.* % represents percentage reduction from baseline. At 6 months, a marked reduction of monthly GTCS was observed in both pediatric and adult patients.
* 6-month treatment not yet reached; * 12-month treatment not yet reached. Pediatric patient #1 reached seizure freedom at 12 months. GTCS: generalized tonic-clonic seizures.

CONCLUSIONS

The interim results from this small prospective cohort of adult and pediatric patients with DS suggest the following:

Intellectual capacity

- Baseline intellectual capacity in the cohort of adult patients (n=5) was in the severe–profound range
- Baseline intellectual capacity in the 2 pediatric patients was in the normal–mild range

Vineland adaptive behavior

- Baseline value for all parameters in adult patients in the range of 20–35
- Baseline values for all parameters in pediatric patients in the range of 65–90

GTCS

- Reduced GTCS frequency within 6 months of fenfluramine added to standard of care treatment was observed; reduction was noted in both adult and pediatric patients

VHD/PAH

- No cases of VHD or PAH were observed after fenfluramine treatment initiated

PATIENT IMPACT

- **Data suggest that DS is associated with gradual decline in intellectual capacity over the disease course**
- **DS incrementally reduces Vineland adaptive behavior over time**
- **GTCS reduction is observed in adult and pediatric patients with fenfluramine treatment**

LIMITATIONS & FUTURE STEPS

- Limitations
  - The small cohort and treatment of the most severe adult patients might lead to selection bias limiting the overall conclusions
- Yearly neuropsychological evaluation will determine if fenfluramine might improve intellectual capacity and/or adaptive behavior

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