Safety and Effectiveness of Adjunctive Fenfluramine in an Open-Label Extension Study of Children (Under 6 Years Old) With Dravet Syndrome

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Background

- Dravet syndrome (DS) is a rare, drug-resistant developmental and epileptic encephalopathy characterized by frequent convulsive seizures, developmental impairment, and decreased quality of life[1]
- Patients with DS show slowing or regression of psychomotor, behavioral, and neurological development[5,6]
- High convulsive seizure frequency increases risk of premature death, including likelihood of sudden unexpected death in epilepsy (SUDEP)[7]
- Fenfluramine (FFA) is indicated for the treatment of seizures associated with DS in patients ≥2 years in the United States,[8] European Union,[9] United Kingdom,[10] and Japan[11]
- Patients with DS, 2-18 years old, who successfully completed treatment in any of the 3 randomized controlled trials (RCTs) of FFA (NCT02682927,[2,3] NCT02826863,[2,3] and NCT02926898[4]) were eligible to participate in an open-label extension (OLE) study
- Phase 3 studies[2-4] and interim OLE[12] analyses have shown that treatment with FFA is well tolerated and is associated with profound, durable reduction in median monthly convulsive seizure frequency (MCSF) in patients with DS

Objective

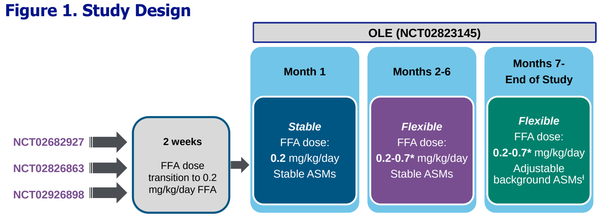
- To describe long-term safety and effectiveness of FFA in patients <6 years old with DS who participated in the OLE study

Methods

Study Design

- Patients with DS, 2-18 years old at enrollment of the initial RCTs were eligible to enroll in the OLE (NCT02823145[12])
- Patients transitioned to a dose of FFA 0.2 mg/kg/day over 2 weeks, and remained at that dose for the first 4 weeks; then, patients titrated based on seizure response and tolerability (**Figure 1**)
  - Maximum FFA dose without stiripentol: 0.7 mg/kg/day, max 26 mg/day
  - Maximum FFA dose with stiripentol: 0.4 mg/kg/day, max 17 mg/day
  - After 6 months of a stable FFA dose, concomitant anti-seizure medications (ASMs) could be reduced; all patients had to remain on ≥1 concomitant ASM
    - No new ASMs could be added
- Patients could remain in the OLE for up to 36 months
- Safety assessments were conducted monthly for 3 months, then every 3 months thereafter
- Echocardiograms were performed at OLE study entry, after 4-6 weeks, then every 3 months to estimate pulmonary arterial pressure and to evaluate cardiac valve function and morphology

Figure 1. Study Design



*Maximum daily dose, 26 mg/day without stiripentol; 17 mg/day with stiripentol.
†Background ASMs could be reduced or withdrawn completely; subjects were required to remain on a minimum of 1 concomitant ASM. No new concomitant ASMs could be added.
ASM, anti-seizure medication; FFA, fenfluramine; OLE, open-label extension.

Endpoints

- Safety analysis was performed on the safety population, defined as all enrolled patients 2 to <6 years old with ≥1 dose FFA during the OLE
  - Number (%) of patients experiencing treatment-emergent adverse events (TEAEs)
- Effectiveness was analyzed in the modified intent-to-treat (mITT) population, defined as enrolled patients 2 to <6 years old with baseline data from the RCT who received ≥1 dose FFA with ≥30 days of valid seizure data during the OLE
  - Change in median MCSF from RCT baseline to overall OLE
- Global functioning was assessed using the Clinical Global Impression-Improvement (CGI-I) scale scores as reported by caregivers and investigators (mITT population)
  - CGI-I takes into consideration overall seizure and non-seizure effectiveness, safety, and tolerability

Analyses

- Demographic information, CGI-I, TEAEs, and MCSF change from baseline were presented using descriptive statistics
- MCSF change from baseline was assessed using Wilcoxon signed-rank test

Results

- As of January 27, 2023, 375 patients were enrolled; 92 patients were 2 to <6 years old and received ≥1 dose of FFA (**Table 1**)

Table 1. Patient Demographics and FFA Exposure in Patients 2 to <6 Years Old

Patients Enrolled	N=92
Age, years	
Mean ± SD	3.5 ± 1.1
Median (min, max)	4 (2, 5)
Sex, n (%)	
Male	51 (55.4)
Female	41 (44.6)
Patients disposition, n (%)	
Completed all study visits	12 (13.0)
Discontinued FFA early or transitioned out of the OLE study	80 (87.0)
Reasons for discontinuation	
Transition to a different OLE or to commercial product	61 (66.3)
Lack of effectiveness	10 (10.9)
Withdrawal by subject	5 (5.4)
Death (SUDEP)[a]	2 (2.2)
Physician decision	1 (1.1)
Other	1 (1.1)
Duration of treatment with FFA in OLE, days	
Mean ± SD	831.4 ± 307.0
Median (min, max)	907.5 (81, 1280)

[a]No deaths were treatment-related.
FFA, fenfluramine; OLE, open-label extension; SD, standard deviation; SUDEP, sudden unexpected death in epilepsy.

Safety

- No new or unexpected TEAEs were observed (**Table 2**)
- No cases of valvular heart disease or pulmonary arterial hypertension were observed

Table 2. TEAEs Occurring in ≥15% of Patients 2 to <6 Years Old (N=92)

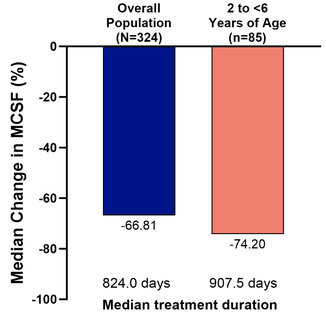
Patients reporting ≥1 TEAE, n (%)	91 (98.9)
Pyrexia	42 (45.7)
Nasopharyngitis	38 (41.3)
Upper respiratory tract infection	24 (26.1)
Ear infection	20 (21.7)
Vomiting	17 (18.5)
Gastroenteritis	17 (18.5)
Viral infection	14 (15.2)

TEAEs, treatment-emergent adverse events.

Effectiveness

- In the mITT population of patients 2 to <6 years old (n=85), median MCSF change from RCT baseline to the duration of the overall OLE was -74.2%, *P*<0.001
  - Change in MCSF was comparable to the overall population (-66.8%, *P*<0.001; **Figure 2**)

Figure 2. Median Percentage Change in MCSF During OLE, Overall Population (mITT, N=324) vs Patients 2 to <6 Years Old (mITT, n=85)

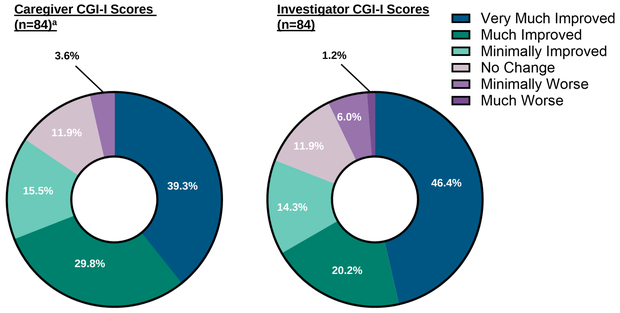


FFA, fenfluramine; MCSF, median convulsive seizure frequency; mITT, modified intent-to-treat; OLE, open-label extension; RCT, randomized controlled trial.

Global functioning

- At last visit, 71/84 (84.5%) caregivers and 68/84 (81.0%) investigators reported improvement on CGI-I (**Figure 3**)
  - Clinically meaningful improvement ("much improved" or "very much improved") was reported by 69.0% and 66.7% of caregivers and investigators, respectively

Figure 3. Caregiver and Investigator CGI-I Ratings in Patients 2 to <6 Years Old at Final Visit (mITT, n=84)



CGI-I scores were assessed in the mITT population (patients 2 to <6 years old with RCT baseline data who received ≥1 dose FFA with ≥30 days of valid seizure data during the OLE).
There were no responses of "very much worse" by caregivers or investigators.
[a]There were no responses of "much worse" (0%) on CGI-I by caregivers.
CGI-I, Clinical Global Impression—Improvement; FFA, fenfluramine; mITT, modified intent-to-treat; OLE, open-label extension; RCT, randomized controlled trial.

Conclusions

- Long-term safety data (median 2.5 years) showed that FFA was well tolerated with an acceptable safety profile in patients with DS 2 to <6 years old
  - No new safety signals or observations of valvular heart disease or pulmonary arterial hypertension up to 3 years
- Patients with DS 2 to <6 years old treated with FFA have sustained reduction in seizure frequency
  - Change in MCSF was similar between patients <6 years old and all patients enrolled in the OLE
- Caregivers and investigators reported clinically meaningful improvement after treatment with FFA, suggesting an improvement in global functioning that may reflect seizure-related and non–seizure-related benefits
- A limitation of this study is possible inclusion bias due to the reduced likelihood of nonresponders to enroll and continue participation in the OLE

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Acknowledgements: UCB Pharma-sponsored. The authors thank the patients and their caregivers in addition to the investigators and their teams who contributed to this trial. The authors acknowledge Tom Grant, PhD (UCB Pharma, Slough, UK), for managing the development of the poster, and Mari Willeman, PhD, and Scott Bergfeld, PhD, of PharmaWrite (Princeton, NJ) for writing assistance, which was funded by UCB Pharma.

Disclosures: IES: served on scientific advisory boards for BioMarin, Chiesi, Eisai, Encoded Therapeutics, GlaxoSmithKline, Knopp Biosciences, Nutricia, Rogcon, Takeda Pharmaceuticals, UCB, Xenon Pharmaceuticals; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, Liva Nova and Eisai; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin and Eisai; has served as an investigator for Anavex Life Sciences, Cerebral Therapeutics, Cerecin Inc, Cereval Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenyx, ES-Therapeutics, GW Pharma (now Jazz Pharmaceuticals), Marinus, Neurocrine BioSciences, Ovid Therapeutics, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceutical, Zogenix (now a part of UCB) and Zynerba; and has consulted for Atheneum Partners, Care Beyond Diagnosis, Epilepsy Consortium, Ovid Therapeutics, UCB and Zynerba Pharmaceuticals; and is a Non-Executive Director of Bellberry Ltd. and a Director of the Australian Academy of Health and Medical Sciences and the Australian Council of Learned Academies Limited. **RN:** Research funding from Eisai, GW Pharma (now Jazz Pharmaceuticals), Novartis, Shire, UCB, and Zogenix Inc (now a part of UCB Pharma); consultant/advisor for Eisai, Biogen, GW Pharma (now Jazz Pharmaceuticals), Novartis, Shire, and Zogenix Inc (now a part of UCB Pharma); speaker for Advicenne, Eisai, BioMarin, GW Pharma (now Jazz Pharmaceuticals), Novartis, and Zogenix Inc (now a part of UCB Pharma). **LL:** Has received grants, and is a consultant and/or speaker for Zogenix (now a part of UCB), LivaNova, UCB Pharma, Shire, Eisai, Novartis, Takeda/Ovid, NEL, and Epihunter. **OD:** Grant support from National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Mental Health (NIMH), Multidisciplinary University Research Initiative (MURI), Centers for Disease Control and Prevention (CDC), and National Science Foundation (NSF); equity and/or compensation from Tilray, Receptor Life Sciences, QstateBiosciences, Hitch Biosciences, TevardBiosciences, Regel Biosciences, Script Biosciences, ActioBiosciences, Empatica, SilverSpike, and California Cannabis Enterprises (CCE); consulting fees from Zogenix (now a part of UCB), Ultragenyx, BridgeBio, GeneMedicine, and Marinus; patents for the use of cannabidiol in treating neurological disorders (owned by GW Pharmaceuticals, now Jazz Pharmaceuticals) for which he has waived any financial interests; other patents in molecular biology; managing partner of the PhiFundVentures. **SA:** Personal fees: Arvelle. Biocodex, GW Pharma (now Jazz Pharmaceuticals), and Xenon; personal fees and nonfinancial support: Biomarin, GW Pharma (now Jazz Pharmaceuticals), and Nutricia; Personal fees/Grants: Eisai and UCB Pharma for work as an investigator; Research support: Zogenix (now a part of UCB). **EAT:** Paid consultant, Zogenix (now a part of UCB Pharma), GW Pharma (now Jazz Pharmaceuticals), Upsher Smith, Aquestive; Research funding, GW Pharma (now Jazz Pharmaceuticals); Clinical trial site PI, GW Pharma (now Jazz Pharmaceuticals), Zogenix (now a part of UCB Pharma). **ECW:** Consulting fees from Acadia, Amicus, Neurocrine and Encoded Therapeutics. She also receives income from Epilepsy.com for serving as Co-Editor in Chief. **TP:** Research funding, Zogenix (now a part of UCB); Consultant and Speaker, Desitin, Eisai, Takeda, UCB Pharma, Zogenix (now a part of UCB). **NS:** Served on scientific advisory boards for GW Pharma (now Jazz Pharmaceuticals), BioMarin, Arvelle, Marinus and Takeda; has received speaker honoraria from Eisai, Biomarin, Livanova, Sanofi; and has served as an investigator for Zogenix (now a part of UCB), Marinus, Biomarin, UCB and Roche. **MP:** Investigator for FINTEPLA®. Consultant/advisor/speaker for Zogenix (now a part of UCB). Travel support by GW Pharma (now Jazz Pharmaceuticals). Investigator/advisory board for Takeda. **KI:** FINTEPLA® Investigator; MHLW Research program on rare and intractable diseases, Grant number JPMH23FC1013. **MLock:** Consultant/advisor Zogenix (now a part of UCB). **MLanglois, PH, SP, AL:** Employment/Stock Ownership: UCB Pharma. **JS:** Research grants, Stoke, Marinus, Zogenix (now a part of UCB), Biopharm; Consultant/Advisor, Dravet Syndrome Foundation, Epygenix, Encoded, GW Pharma (now Jazz Pharmaceuticals), Asceneuron, Longboard Pharmaceuticals, Knopp Biosciences, Neurocrine; Stock options, Epygenix; Travel support, Zogenix (now a part of UCB); Reviewer, Epilepsy Study Consortium.

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Presented at the 53rd Child Neurology Society (CNS) Congress | San Diego, CA | November 11-14
Previously Presented at the International Child Neurology Conference 2024 | Cape Town, South Africa | May 6-10, 2024