Poster #302

Analysis of Safety, Tolerability and Clinical Global Impression-Improvement Scale Ratings in Patients With Dravet Syndrome Enrolled as Adults in a Fenfluramine Open-Label Extension Study

Ingrid E Scheffer, MBBS, PhD, FRACP, FRS[1]; Orrin Devinsky, MD[2]; Milka Pringsheim, MD[3]; Katsumi Imai, MD[4]; Elizabeth A Thiele, MD, PhD[5]; Amélie Lothe, PhD[6]; Mélanie Langlois, PhD[6]; Michael D Lock, PhD[7]; Teri Jimenez[8]; Diego Morita, MD[8]; Julia Jacobs, MD, PhD[9]; Antonio Gil-Nagel, MD, PhD[10]; Rocio Sanchez-Carpintero, MD, PhD[11]

[1]University of Melbourne, Austin Hospital and Royal Children's Hospital, Florey and Murdoch Children's Research Institutes, Melbourne, Victoria, Australia; [2]NYU Langone Medical Center, New York, NY, USA; [3]Schön Klinik Vogtareuth, Germany; German Heart Centre Munich, Munich, Germany; PMU Salzburg, Austria; [4]Shizuoka Institute of Epilepsy and Neurological Disorders, Urushiyama, Shizuoka, Japan; [5]Massachusetts General Hospital, Boston, Massachusetts, USA; [6]UCB Pharma S.A., Colombes, France; [7]Independent Statistical Consultant, Haiku, HI, USA; [8]UCB Biosciences, Inc., Morrisville, NC, USA; [9]Alberta Children's Hospital, Calgary, AB, Canada; [10]Hospital Ruber Internacional, Madrid, Spain; [11]Clínica Universidad de Navarra, Av. de Pío XII, 36, 31008, Pamplona, Spain.

Overview

QUESTION

What data from the Dravet syndrome (DS) clinical development program are available to support the use of fenfluramine (FFA) in adult patients?

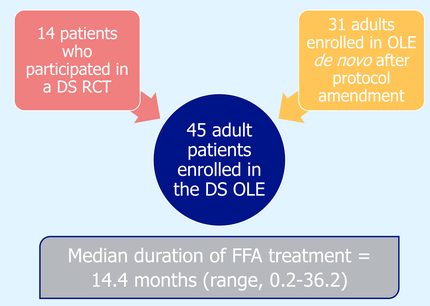
INVESTIGATION

- Patients with DS who enrolled in the open-label extension (OLE) as adults and received at least one dose of FFA were evaluated, including:
  - Patients who participated in a DS randomized controlled trial (RCT) and were 18 years before receiving FFA in the OLE, and
  - Adults who enrolled in the OLE *de novo* (without participating in an RCT)
- Incidence of treatment-emergent adverse events (TEAEs) and ratings on Clinical Global Impression-Improvement (CGI-I) scale as of the last OLE data cut (January 2023) are reported

RESULTS

- Forty-five adult patients were included in the analysis (see **Figure**)
- 24 were female (53.5%) and mean age ± SD was 22.0 ± 4.1 years; *SCN1A+* in 93.2% of patients with known status (n=44)
- 97.8% of patients experienced ≥1 TEAE; TEAEs occurring in ≥15% of patients were decreased appetite, somnolence, upper respiratory tract infection, fatigue, and decreased blood glucose; there were no cases of valvular heart disease or pulmonary arterial hypertension observed
- Clinically meaningful improvement ("very much improved" or "much improved") was reported at last visit by 70.7% and 69.1% of caregivers and investigators, respectively (see **Table**)

Figure. Adult Patients in OLE (N=45) and Duration of FFA Treatment



DS, Dravet syndrome; FFA, fenfluramine; OLE, open-label extension; RCT, randomized controlled trial.

Table. CGI-I Scores at Last Visit as Rated by Caregivers and Investigators

Rating, n (%)	Caregivers (n=41)	Investigators (n=42)
Very much improved	13 (31.7)	12 (28.6)
Much improved	16 (39.0)	17 (40.5)
Minimally improved	6 (14.6)	10 (23.8)
No change	1 (2.4)	2 (4.8)
Minimally worse	2 (4.9)	1 (2.4)
Much worse	0 (0.0)	0 (0.0)
Very much worse	3 (7.3)	0 (0.0)

CGI-I, Clinical Global Impression-Improvement.

CONCLUSIONS

This analysis of FFA use in adult patients for up to 3 years revealed no new or unexpected safety signals and demonstrated clinically meaningful benefit, suggesting the potential use of FFA as an anti-seizure medication in this subpopulation.

For a copy of the poster scan:

or visit:

UCBposters.com/EEC2024
Poster ID: **302**

Introduction

- Dravet syndrome (DS) is a rare, lifelong, treatment-resistant developmental and epileptic encephalopathy (DEE) characterized by high seizure burden and multiple comorbidities[1]
  - High seizure frequency is associated with worsening of comorbidities and a lower quality of life (QOL)[2]
- While DS onset occurs in infancy, it persists into adulthood and there is long-term risk for poor outcomes
  - A survey of caregivers of patients with DS in Europe revealed that only 11% of adults surveyed (n=100) were seizure free[2]
  - In a 10-year, prospective health-related quality of life (HRQoL) study, epilepsy severity was associated with reduced HRQoL in the older patient group (≥16 years old)[3]
  - Additionally, cognitive impairment in older patients contributes to worsened HRQoL[4,5]
- Antiseizure medications (ASMs) that reduce seizure burden and can be used effectively into adulthood are needed
- Fenfluramine (FFA; Fintepla, UCB, Brussels, Belgium) is approved in the US, UK, EU, Israel, and Japan for the treatment of seizures associated with DS in patients ≥2 years of age[6-10]
  - Three randomized controlled trials (RCTs, NCT02682927, NCT02826863, NCT0296898) of FFA use in DS included patients aged 2-18 years[11-13]
  - An interim report of the open-label extension (OLE) study demonstrated sustained clinically meaningful reductions in seizure frequency in 232 patients, mean age 9.1 years, over 256 days (range, 58-634)[14]

Objective

This analysis aims to describe use of FFA in patients who enrolled in the DS OLE study as adults (≥18 years old).

Methods

- Study design for the RCTs[11-13] and OLE[14] have been previously described
  - In the OLE, patients began FFA at 0.2 mg/kg/day; dose could then be titrated based on effectiveness and tolerability after 4 weeks
- In February 2018, a protocol amendment of the OLE study allowed enrollment of adult patients *de novo*
- For this analysis, patients who participated in an RCT and turned 18 years old prior to enrolling in the OLE or who enrolled in the OLE *de novo* (without previous FFA use) as adults were included
- Outcomes of interest included: patient demographics, disposition, incidence of treatment-emergent adverse events (TEAEs), mean daily dosage groups, FFA treatment duration, and proportion of patients rated as demonstrating clinically meaningful improvement on the Clinical Global Impression-Improvement (CGI-I) scale
  - Clinically meaningful improvement includes scores of "much improved" or "very much improved"
- Descriptive statistics were used
- Final data cut date was 27 January 2023

Results

- Forty-five patients were adults (≥18 years old) at OLE enrollment:
  - 14 patients previously participated in a Phase 3 RCT
  - 31 adults enrolled in the OLE without participating in an RCT
- Demographics are described in **Table 1**
  - 11 (24.4%) patients were 18 years old at enrollment and 34 (75.6%) were >18 years old
- Mean daily dose and treatment duration was known in 39 patients; notably 19/39 patients were dose-capped (**Table 1)**
- 33 (73.3%) patients transitioned to another OLE study and 4 (8.9%) patients transitioned to commercial FFA; 2 patients each discontinued due to an adverse event, lack of efficacy, and other (**Table 1)**
- 44 (97.8%) patients experienced at least one TEAE (**Table 2**); 8 patients experienced ≥1 serious TEAE
- There were no deaths among these patients and no cases of valvular heart disease or pulmonary arterial hypertension
- At last visit, 29/41 (70.7%) caregivers and 29/42 (69.1%) investigators reported clinically meaningful improvement on CGI-I (**Figure 1**)

Table 1. Demographics and FFA Characteristics of Patients Enrolled as Adults in the DS OLE

	N=45
Age at enrollment (years)	
Mean ± SD	22.0 ± 4.1
Range	18.0-32.0
Sex, n (%)	
Male	21 (46.7)
Female	24 (53.3)
SCN1A pathogenic variant present, n (%)[a]	41 (93.2)
Weight at baseline (kg)	
Median (range)	58.2 (31.0-113.0)
BMI at baseline (kg)[b]	
Median (range)	21.9 (13.5-38)
Concomitant ASMs (number)	
Median (range)	3.0 (1.0-10.0)
Patient disposition, n (%)	
Completed all study visits	2 (4.4)
Transitioned out of OLE	37 (82.2)
Discontinued FFA early	6 (13.3)
FFA mean daily dose, n (%)[c]	
<0.3 mg/kg/day	22 (48.9)
0.3 to <0.5 mg/kg/day	14 (31.1)
≥0.5 mg/kg/day	3 (6.7)
Dose-capped patients, n (%)[c]	
17 mg while on concomitant STP (n=8)	7 (87.5%)
26 mg without concomitant STP (n=31)	12 (38.7%)
FFA treatment duration/exposure, months	
Median (range)	14.4 (0.2-36.2)

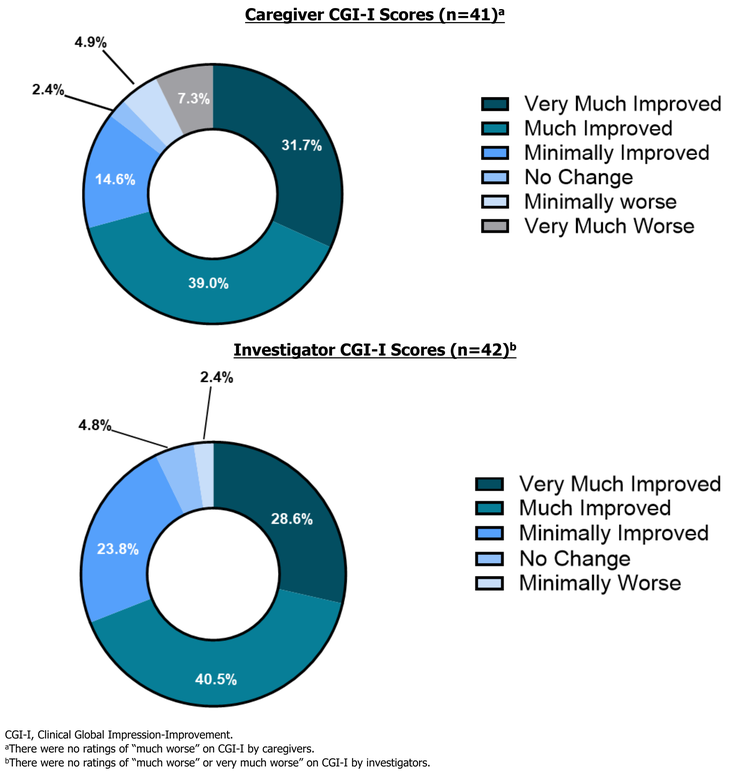
[a]Out of 44 patients, unknown in 1 patient.
[b]Reported for 44 patients; height was not available for one patient.
[c]Dosing and exposure available for 39 patients.
ASMs, anti-seizure medications; BMI, body mass index; DS, Dravet syndrome; FFA, fenfluramine; OLE, open-label extension; SD, standard deviation; STP, stiripentol.

Table 2. Treatment Emergent Adverse Events Occurring in ≥15% of Patients Who Enrolled as Adults in the DS FFA OLE (N=45)

	All N=45
Patients reporting ≥1 TEAE, n (%)	44 (97.8)
TEAEs occurring in ≥15% of patients, n (%)	
Decreased appetite	20 (44.4)
Somnolence	11 (24.4)
Upper respiratory tract infection	10 (22.2)
Fatigue	8 (17.8)
Decreased blood glucose	8 (17.8)

DS, Dravet syndrome; FFA, fenfluramine; OLE, open-label extension; TEAEs, treatment emergent adverse events.

Figure 1. Caregiver and Investigator CGI-I Scores at Last Visit



CGI-I, Clinical Global Impression-Improvement.
[a]There were no ratings of "much worse" on CGI-I by caregivers.
[b]There were no ratings of "much worse" or very much worse" on CGI-I by investigators.

Conclusions

In this analysis of adults with DS treated with FFA for up to 3 years, there were no new or unexpected safety signals observed. Additionally, CGI-I scores from caregivers and investigators demonstrated clinically meaningful benefit which may contribute to positive effects on HRQoL. These data support the use of FFA as an anti-seizure medication in this subpopulation of adults with DS.

References

1. Wirrell EC, et al. *Epilepsia.* 2022;63(7):1761-77.
2. Lagae L, et al. *Dev Med Child Neurol.* 2018;60(1):63-72.
3. Makiello P, et al. *Epilepsia.* 2023;64(4):1012-20.
4. Brunklaus A, et al. *Epilepsia.* 2011;52(8):1476-82.
5. Sinoo C, et al. *Epilepsy Behav.* 2019;90:217-27.
6. UCB Inc. FINTEPLA® (fenfluramine) oral solution [prescribing information]. Smyrna, GA March 2023.
7. Medicines & Healthcare products Regulatory Agency. 2023. https://www.gov.uk/government/publications/orphan-registered-medicinal-products/orphan-register.
8. Zogenix ROI Ltd. Fintepla 2.2 mg/mL oral solution [summary of product characteristics]. Dublin, IE April 2023 .
9. State of Israel Ministry of Health. Registration certificate medical product - Fintepla: registration no. 169-41-36976-99. 2022.
10. UCB Japan Co. LTD. Fintepla Oral Solution 2.2 mg/mL [prescribing information]. Tokyo, Japan September 2022.
11. Lagae L, et al. *Lancet.* 2019;394(10216):2243-54.
12. Nabbout R, et al. *JAMA Neurol.* 2020;77(3):300-8.
13. Sullivan J, et al. *Epilepsia.* 2023;64(10):2653-66.
14. Sullivan J, et al. *Epilepsia.* 2020;61(11):2396-404.

Acknowledgements

UCB Pharma-sponsored. The authors acknowledge Tom Grant, PhD (UCB Pharma, Slough, UK), for managing the development of the poster, and Sandra M Aguero, PharmD, BCPS, and Scott Bergfeld, PhD, of PharmaWrite, LLC (Princeton, NJ, USA), for writing and editorial 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, Cerecin; has received speaker honoraria from GlaxoSmithKline, UCB, BioMarin, Biocodex, Chiesi, Liva Nova, Nutricia, Zuellig Pharma, Stoke Therapeutics, Eisai, Akumentis; has received funding for travel from UCB, Biocodex, GlaxoSmithKline, Biomarin, Encoded Therapeutics, Stoke Therapeutics and Eisai; has served as an investigator for Anavex Life Sciences, Cerevel Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenyx, ES-Therapeutics, GW Pharma (now Jazz Pharmaceuticals), Marinus, Neurocrine BioSciences, Ovid Therapeutics, SK Life Science, Takeda Pharmaceuticals, UCB, Ultragenyx, Xenon Pharmaceuticals, Zogenix (now a part of UCB Pharma) and Zynerba; and has consulted for Care Beyond Diagnosis, Epilepsy Consortium, Atheneum Partners, Ovid Therapeutics, UCB, Zynerba Pharmaceuticals, BioMarin, Encoded Therapeutics and Biohaven Pharmaceuticals; and is a Non-Executive Director of Bellberry Ltd and a Director of the Australian Academy of Health and Medical Sciences and the Royal Society (Australia). She may accrue future revenue on pending patent WO61/010176 (filed: 2008): Therapeutic Compound; has a patent for *SCN1A* testing held by Bionomics Inc and licensed to various diagnostic companies; has a patent molecular diagnostic/theranostic target for benign familial infantile epilepsy (BFIE) [PRRT2] 2011904493 & 2012900190 and PCT/AU2012/001321 (TECH ID:2012-009).

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, Qstate Biosciences, Hitch Biosciences, Tevard Biosciences, Regel Biosciences, Script Biosciences, Actio Biosciences, Empatica, SilverSpike, and California Cannabis Enterprises (CCE); consulting fees from Zogenix (now a part of UCB Pharma), 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 PhiFund Ventures.

MP: Investigator for FINTEPLA®; Consultant/advisor/speaker for Zogenix (now a part of UCB Pharma); 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.

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).

AL, ML, TJ, DM: Employment/Stock Ownership, UCB Pharma.

MDL: Consultant, UCB Pharma.

JJ: Served on scientific advisory boards for Takeda Pharmaceuticals, ANAVEX Life Science, EISAI, Zogenix (now a part of UCB Pharma), Jazz Pharmaceuticals, Neurocrine & Sunovion; investigator for Anavex Life Sciences, Takeda, Eisai, GW Pharma (now Jazz Pharmaceuticals), Neurocrine, UCB and Zogenix (now part of UCB Pharma); received educational grants from UCB, Jazz Pharmaceuticals, Eisai, LivaNova, Pendopharm, Paladine, Persyst, Natus, Epilog, Medtronic, Dixie, Adtec, Renishaw.

AGN: Served on speakers bureau and advisory boards for Angelini Pharma, Bial, Biocodex, Eisai, Esteve, GW Pharma (now Jazz Pharmaceuticals), PTC Therapeutics, Rapport Therapeutics, Stoke, UCB Pharma, and Zogenix (now a part of UCB).

RSC: Received honoraria and/or research funds from Biocodex, GW Pharma (now Jazz Pharmaceuticals), Jazz Pharmaceuticals and Zogenix (now a part of UCB Pharma).

For a copy of this poster, use your smartphone to scan the QR code, download from the website below, or contact UCB**Cares**®

Website: UCBposters.com/EEC2024; Poster ID: **302**

Phone: +32 2 559 92 00

Email: UCBCares@ucb.com

Presented at the 15th European Epilepsy Congress | Rome, Italy | 7-11 September 2024