Post-Hoc Analysis of Fenfluramine for Lennox-Gastaut Syndrome by Baseline Frequency Quartiles of Seizures Associated With a Fall

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Introduction

- In Lennox-Gastaut syndrome (LGS), various factors contribute to severity of disease, including but not limited to high seizure frequency[1]
- Seizures associated with a fall increase the risk of injury and may lead to increased healthcare related costs and decreased quality of life[1]
- Thus, frequency of seizures associated with a fall may be used as a surrogate marker of disease severity
- Fenfluramine (FFA) exerts its antiseizure activity through a serotonergic and positive sigma-1 receptor modulation mechanism[2-5] and is currently approved for the management of seizures associated with LGS in the US for patients ≥2 years old,[6] and as add-on treatment for patients ≥2 years old with seizures associated with LGS in the EU, UK, Japan, and Israel[7-10]
- In a randomized-controlled trial (RCT, NCT03355209), compared with placebo, FFA provided a significantly greater reduction in seizures associated with a fall, as well as generalized tonic-clonic seizures (GTCS)[11]

Objective

- In this post-hoc analysis of the FFA RCT in patients with LGS, baseline frequency of seizures associated with a fall was used as a surrogate marker of disease severity to evaluate efficacy and safety of FFA across a spectrum of patients who participated in that study

Methods

- In the FFA LGS RCT, patients were randomized to FFA 0.2 mg/kg/day or FFA 0.7 mg/kg/day (maximum = 26 mg/day) or placebo[11]
  - After a 2-week titration period, patients were maintained on their randomized dose for an additional 12 weeks
- Various outcomes and endpoints were described by quartiles of baseline frequency of seizures associated with a fall (quartile 1 [Q1], quartile 2 [Q2], quartile 3 [Q3], and quartile 4 [Q4]), including:
  - Baseline characteristics
  - Median change from baseline in frequency of seizures associated with a fall
  - Ratings of clinically meaningful improvement ("Much Improved" or "Very Much Improved") on Clinical Global Impression-Improvement (CGI-I) scale by investigator and caregiver at last visit, and
  - Incidence of treatment-emergent adverse events (TEAEs) occurring in ≥10% of patients grouped by quartiles
- In the FFA LGS RCT, Epilepsy Study Consortium (ESC)-confirmed seizures associated with a fall included the following types: generalized tonic-clonic (GTC), secondarily GTC (focal to bilateral tonic-clonic), tonic, or atonic[11]
- Quartiles of baseline frequency of GTCS (Q1-Q4) were also used to describe median change from baseline in frequency of GTCS
  - Note, for this post-hoc analysis, these were included as part of the ESC-confirmed seizures associated with a fall and reported alone as a separate outcome
- Descriptive statistics were used

Results

Analyses by quartiles of seizures associated with a fall (N=263)

- Quartiles (Q) are described in **Figure 1**

Figure 1. Quartiles (Q) of Baseline Seizures Associated With a Fall per 28 days (N=263)

Q1 (n=65): 2-34	Q2 (n=66): 35-76	Q3 (n=66): 77-175[a]	Q4 (n=66): 177-2943[a]
• Placebo, n=26 • FFA 0.2 mg/kg/day, n=21 • FFA 0.7 mg/kg/day, n=18	• Placebo, n=26 • FFA 0.2 mg/kg/day, n=20 • FFA 0.7 mg/kg/day, n=20	• Placebo, n=14 • FFA 0.2 mg/kg/day, n=25 • FFA 0.7 mg/kg/day, n=27	• Placebo, n=21 • FFA 0.2 mg/kg/day, n=23 • FFA 0.7 mg/kg/day, n=22

[a]Note there were no patients with 176 seizures associated with a fall/28 days at baseline
FFA, fenfluramine.

Overview

QUESTION

Are the efficacy and/or safety of fenfluramine (FFA) in patients with Lennox-Gastaut syndrome (LGS) affected by the disease severity at patient's pre-FFA baseline?

INVESTIGATION

Using baseline frequency of seizures associated with a fall as a surrogate marker of disease severity at FFA initiation, this post-hoc analysis of the FFA LGS randomized-controlled trial (RCT) evaluated efficacy and safety of FFA across a spectrum of patients. Efficacy of reduction in generalized tonic-clonic seizures (GTCS) was also evaluated by quartiles of baseline GTCS frequency per 28 days.

RESULTS

- Quartiles (Q) of baseline seizures (by seizure type) per 28 days are displayed in the **Table**

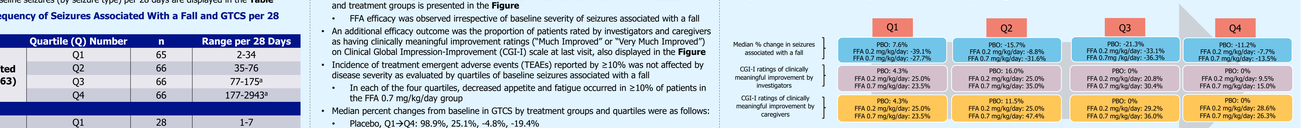
Table. Baseline Frequency of Seizures Associated With a Fall and GTCS per 28 Days by Quartile

Seizure Type	Quartile (Q) Number	n	Range per 28 Days
Seizures Associated With a Fall (N=263)	Q1	65	2-34
	Q2	66	35-76
	Q3	66	77-175[a]
	Q4	66	177-2943[a]
GTCS (N=114)	Q1	28	1-7
	Q2	29	7.3-15
	Q3	28	15.5-30[b]
	Q4	29	32-198[b]

[a]There were no patients with 176 seizures associated with a fall/28 days at baseline. [b]There were no patients with 31 GTCS/28 days at baseline. GTCS, generalized tonic-clonic seizure.

- Median percent change from baseline in frequency of seizures associated with a fall by quartiles and treatment groups is presented in the **Figure**
  - FFA efficacy was observed irrespective of baseline severity of seizures associated with a fall
- An additional efficacy outcome was the proportion of patients rated by investigators and caregivers as having clinically meaningful improvement ratings ("Much Improved" or "Very Much Improved") on Clinical Global Impression-Improvement (CGI-I) scale at last visit, also displayed in the **Figure**
- Incidence of treatment emergent adverse events (TEAEs) reported by ≥10% was not affected by disease severity as evaluated by quartiles of baseline seizures associated with a fall
  - In each of the four quartiles, decreased appetite and fatigue occurred in ≥10% of patients in the FFA 0.7 mg/kg/day group
- Median percent changes from baseline in GTCS by treatment groups and quartiles were as follows:
  - Placebo, Q1→Q4: 98.9%, 25.1%, -4.8%, -19.4%
  - FFA 0.2 mg/kg/day, Q1→Q4: -79.2%, -39.7%, -50.4%, -78.2%
  - FFA 0.7 mg/kg/day, Q1→Q4: -77.4%, -28.5%, -39.9%, -60.2%
  - Both FFA treatment groups were associated with reductions in GTCS from baseline, and a numerically greater reduction in GTCS from baseline compared with placebo

Figure. Change in Seizures Associated With a Fall and Proportion of Patients Rated as Having Clinically Meaningful Improvement at Last Visit by FFA Treatment Group and Quartiles of Baseline Seizures Associated With a Fall



[a]Q1: Placebo, n=26; FFA 0.2 mg/kg/day, n=21; FFA 0.7 mg/kg/day, n=18; **Q2**: Placebo, n=26; FFA 0.2 mg/kg/day, n=20; FFA 0.7 mg/kg/day, n=20; **Q3**: Placebo, n=14; FFA 0.2 mg/kg/day, n=25; FFA 0.7 mg/kg/day, n=27; **Q4**: Placebo, n=21; FFA 0.2 mg/kg/day, n=23; FFA 0.7 mg/kg/day, n=22.
CGI-I, Clinical Global Impression-Improvement; FFA, fenfluramine; PBO, placebo; Q, quartile.

CONCLUSIONS

The results of this post-hoc analysis evaluating FFA use in patients with LGS highlight that FFA can be used safely and effectively across a spectrum of LGS disease severity.

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- Baseline characteristics are reported in **Table 1**

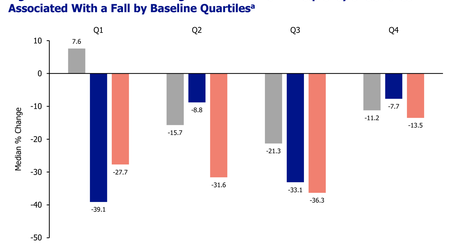
Table 1. Baseline Characteristics by Quartiles of Baseline Frequency of Seizures Associated With a Fall (N=263)

		Quartile 1 n=65	Quartile 2 n=66	Quartile 3 n=66	Quartile 4 n=66
Age, mean (SD), years		14.2 (7.1)	17.2 (7.4)	14.3 (6.9)	9.3 (7.0)
Sex Male, n (%) Female, n (%)		38 (58.5) 27 (41.5)	40 (60.6) 26 (39.4)	38 (57.6) 28 (42.4)	30 (45.5) 36 (54.5)
Baseline weight, n (%) <37.5 kg ≥37.5 kg		25 (38.5) 40 (61.5)	20 (30.3) 46 (69.7)	32 (48.5) 34 (51.5)	47 (71.2) 19 (28.8)
BMI, mean (SD)		19.9 (4.8)	21.3 (5.2)	19.4 (5.7)	18.2 (4.0)[a]
Prior ASMs,[b] median (range)		8 (2-16)	8 (1-20)	8 (1-18)	7 (2-19)
Concomitant ASMs,[c] median (range)		3 (1-4)	3 (1-4)	3 (1-5)	3 (1-4)
Frequency of Seizures Associated With a Fall	Placebo, n	26	26	14	21
	Median (range)	23.8 (2-34)	47.5 (35-76)	105.5 (78-171)	348 (177-1761)
	FFA 0.2 mg/kg/day, n	21	20	25	23
	Median (range)	21.8 (4.1-32)	51.5 (35-75)	118 (77-175)	399 (199.8-2943)
	FFA 0.7 mg/kg/day, n	18	20	27	22
	Median (range)	20 (6.5-31)	56.5 (38-75)	111 (77-173)	460 (183-1803)

[a]BMI in 65 patients.
[b]Prior ASMs are defined as any ASM with a start date prior to the first dose of FFA.
[c]Concomitant ASMs are defined as any ASM with start or stop date after the first dose of FFA.
ASMs, anti-seizure medications; BMI, body mass index; FFA, fenfluramine; SD, standard deviation.

- Median percent changes from baseline in frequency of seizures associated with a fall by quartiles and treatment groups are presented in **Figure 2**
  - FFA efficacy did not appear to be impacted by baseline severity of seizures associated with a fall
  - Numerically greater median percent reductions in seizures associated with a fall were observed in all quartiles when patients were treated with FFA 0.7 mg/kg/day compared with placebo

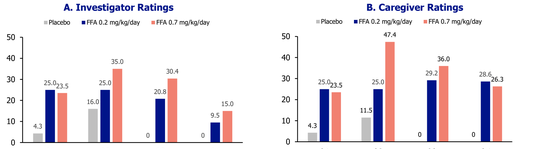
Figure 2. Median Percent Change From Baseline in Frequency of Seizures Associated With a Fall by Baseline Quartiles[a]



[a]Q1 (2-34): Placebo, n=26; FFA 0.2 mg/kg/day, n=21; FFA 0.7 mg/kg/day, n=18; **Q2 (35-76)**: Placebo, n=26; FFA 0.2 mg/kg/day, n=20; FFA 0.7 mg/kg/day, n=20; **Q3 (77-175)**: Placebo, n=14; FFA 0.2 mg/kg/day, n=25; FFA 0.7 mg/kg/day, n=27; **Q4 (177-1943)**: Placebo, n=21; FFA 0.2 mg/kg/day, n=23; FFA 0.7 mg/kg/day, n=22
FFA, fenfluramine; Q, quartile.

- The proportion of patients with CGI-I ratings of clinically meaningful improvement by treatment group and quartile by investigator and caregiver are displayed in **Figure 3A** and **Figure 3B**, respectively
  - FFA groups were associated with higher rates of clinically meaningful improvement compared with placebo; patients in the placebo groups with higher baseline frequency of seizures associated with a fall (Q3 or Q4) demonstrated no clinically meaningful improvements as reported by both investigators and caregivers
  - Investigators and caregivers seemed generally aligned across Q1-Q3; in Q4, caregivers found more patients treated with FFA had clinically meaningful improvement, compared with ratings from investigators
- Incidence of TEAEs reported by ≥10% of patients in either group over the course of the RCT (decreased appetite, somnolence, fatigue, pyrexia, diarrhea, vomiting) by baseline quartiles of seizures associated with a fall are described in **Table 2**
  - In each of the four quartiles, decreased appetite and fatigue occurred in ≥10% of patients in the FFA 0.7 mg/kg/day group

Figure 3. Proportion of Patients Rated as Having Clinically Meaningful Improvement ("Much Improved" or "Very Much Improved") on CGI-I by Treatment Group and Quartiles of Baseline Seizures Associated With a Fall[a]



[a]Q1 (2-34): Placebo, n=26; FFA 0.2 mg/kg/day, n=21; FFA 0.7 mg/kg/day, n=18; **Q2 (35-76)**: Placebo, n=26; FFA 0.2 mg/kg/day, n=20; FFA 0.7 mg/kg/day, n=20; **Q3 (77-175)**: Placebo, n=14; FFA 0.2 mg/kg/day, n=25; FFA 0.7 mg/kg/day, n=27; **Q4 (177-1943)**: Placebo, n=21; FFA 0.2 mg/kg/day, n=23; FFA 0.7 mg/kg/day, n=22.
CGI-I, Clinical Global Impression-Improvement; FFA, fenfluramine; Q, quartile.

Table 2. Incidence of TEAEs Reported by ≥10% of Patients by Baseline Quartiles of Seizures Associated With a Fall[a]

		Q1	Q2	Q3	Q4
Any TEAE	Placebo	21 (80.8)	22 (84.6)	10 (71.4)	17 (81.0)
	FFA 0.2 mg/kg/day	17 (81.0)	16 (80.0)	21 (84.0)	16 (69.6)
	FFA 0.7 mg/kg/day	15 (83.3)	19 (95.0)	23 (85.2)	21 (95.5)
TEAEs Occurring in ≥10% of Patients of Any Group Over the RCT					
Decreased appetite	Placebo	3 (11.5)	5 (19.2)	1 (7.1)	4 (19.0)
	FFA 0.2 mg/kg/day	4 (19.0)	3 (15.0)	9 (36.0)	2 (8.7)
	FFA 0.7 mg/kg/day	8 (44.4)	9 (45.0)	7 (25.9)	8 (36.4)
Somnolence	Placebo	4 (15.4)	4 (15.4)	1 (7.1)	1 (4.8)
	FFA 0.2 mg/kg/day	2 (9.5)	4 (20.0)	2 (8.0)	2 (8.7)
	FFA 0.7 mg/kg/day	2 (11.1)	5 (25.0)	2 (7.4)	6 (27.3)
Fatigue	Placebo	5 (19.2)	4 (15.4)	1 (7.1)	1 (4.8)
	FFA 0.2 mg/kg/day	4 (19.0)	1 (5.0)	2 (8.0)	1 (4.3)
	FFA 0.7 mg/kg/day	3 (16.7)	3 (15.0)	6 (22.2)	4 (18.2)
Pyrexia	Placebo	2 (7.7)	3 (11.5)	2 (14.3)	4 (19.0)
	FFA 0.2 mg/kg/day	4 (19.0)	0	3 (12.0)	4 (17.4)
	FFA 0.7 mg/kg/day	1 (5.6)	4 (20.0)	3 (11.1)	1 (4.5)
Diarrhea	Placebo	0	4 (15.4)	0	0
	FFA 0.2 mg/kg/day	1 (4.8)	6 (30.0)	1 (4.0)	2 (8.7)
	FFA 0.7 mg/kg/day	4 (22.2)	1 (5.0)	5 (18.5)	1 (4.5)
Vomiting	Placebo	0	1 (3.8)	0	4 (19.0)
	FFA 0.2 mg/kg/day	3 (14.3)	4 (20.0)	3 (12.0)	2 (8.7)
	FFA 0.7 mg/kg/day	1 (5.6)	4 (20.0)	2 (7.4)	2 (9.1)

[a]Q1 (2-34): Placebo, n=26; FFA 0.2 mg/kg/day, n=21; FFA 0.7 mg/kg/day, n=18; **Q2 (35-76)**: Placebo, n=26; FFA 0.2 mg/kg/day, n=20; FFA 0.7 mg/kg/day, n=20; **Q3 (77-175)**: Placebo, n=14; FFA 0.2 mg/kg/day, n=25; FFA 0.7 mg/kg/day, n=27; **Q4 (177-1943)**: Placebo, n=21; FFA 0.2 mg/kg/day, n=23; FFA 0.7 mg/kg/day, n=22.
FFA, fenfluramine; Q, quartile; RCT, randomized-controlled trial; TEAEs, treatment-emergent adverse events.

Analysis by quartiles of GTCS (N=114)

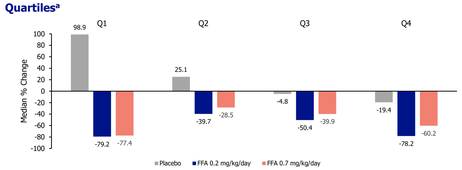
- Quartiles of baseline GTCS per 28 days and baseline GTCS by RCT treatment group are described in **Table 3**
- In all quartiles, both FFA treatment groups were associated with reductions in GTCS from baseline, and a numerically greater reduction in GTCS from baseline compared with placebo (**Figure 4**)
  - The greatest reduction in GTCS from baseline was observed in the first quartile of FFA treatment groups

Table 3. Baseline GTCS Frequencies by RCT Treatment Group (N=114)

	Quartile 1 (1-7) n=28	Quartile 2 (7.3-15) n=29	Quartile 3 (15.5-30)[a] n=28	Quartile 4 (32-198)[a] n=29
Placebo, n	6	11	11	10
Median (range)	1.5 (1-6)	13 (8-15)	23 (16-29)	50 (34-132)
FFA 0.2 mg/kg/day, n	13	10	8	7
Median (range)	3 (1-7)	10 (7.3-15)	20 (16-29)	63 (32-91)
FFA 0.7 mg/kg/day, n	9	8	9	12
Median (range)	4 (1-6)	11.5 (9-15)	21.8 (17-30)	83 (32-198)

[a]Note there were no patients with 31 GTCS/28 days at baseline.
FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; RCT, randomized-controlled trial.

Figure 4. Median Percent Change From Baseline in Frequency of GTCS by Baseline GTCS Quartiles[a]



[a]Q1 (1-7): placebo, n=6, FFA 0.2 mg/kg/day, n=13, FFA 0.7 mg/kg/day, n=9; **Q2 (7.3-15)**, placebo, n=11, FFA 0.2 mg/kg/day, n=10, FFA 0.7 mg/kg/day, n=8; **Q3 (15.5-30)**, placebo, n=11, FFA 0.2 mg/kg/day, n=8, FFA 0.7 mg/kg/day, n=9; **Q4 (32-198)**, placebo, n=10, FFA 0.2 mg/kg/day, n=7, FFA 0.7 mg/kg/day, n=12.
FFA, fenfluramine; GTCS, generalized tonic-clonic seizures; Q, quartile.

Conclusions

In this post-hoc analysis evaluating use of FFA by quartiles of baseline seizure frequency in patients with LGS, greater median percent reductions in seizures associated with a fall were observed in all quartiles when patients were treated with FFA 0.7 mg/kg/day compared with placebo. A greater reduction in GTCS from baseline compared with placebo was observed in all FFA treatment groups throughout all quartiles of baseline GTCS frequency. Additionally, baseline disease severity did not impact FFA effectiveness as evaluated by CGI-I scores or safety and tolerability as described by rates of TEAEs. These results support the use of FFA across the spectrum of LGS disease severity.

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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

KGK: Research grants, Zogenix (now a part of UCB Pharma), Stoke, Encoded Therapeutics; consulting fees from Biomarin, Epygenix, and Biocodex; and other support as a Data and Safety Monitoring Board member, Jazz Pharmaceuticals and Epygenix. **RN:** Research funding from Eisai, GW Pharma (now Jazz Pharmaceuticals), Novartis, Shire, UCB, and Zogenix Inc (now a part of UCB); consultant/advisor for Eisai, Biogen, GW Pharma (now Jazz Pharmaceuticals), Novartis, Shire, and Zogenix Inc (now a part of UCB); speaker for Advicenne, Eisai, BioMarin, GW Pharma (now Jazz Pharmaceuticals), Novartis, and Zogenix Inc (now a part of UCB). **IEGS:** 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, Ceroxal Therapeutics, Eisai, Encoded Therapeutics, EpiMinder Inc, Epygenix, 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 Alfasigma Partners, Care Beyond Diagnosis, Epilepsy Consortium, Ovid Therapeutics, UCB and Zynerba Pharmaceuticals, Stoke Therapeutics, Praxis; and is a Non-Executive Director of Bellberry Ltd. and a Director of the Australian Academy of Health and Medical Sciences. **JS:** Research grants: Stoke, Marinus, Zogenix (now a part of UCB), Biopharm; Consultant/Advisor: Ovavet Syndrome Foundation, Epygenix, Encoded, GW Pharma (now Jazz Pharmaceuticals), Accelerate, Longboard Pharmaceuticals, Knopp Biosciences, Neurocrine; Stock options: Epygenix; Travel support: Zogenix (now a part of UCB); Reviewer: Epilepsy Study Consortium. **SMZ:** Research support from Epilepsy Research UK, Dravet Syndrome UK, and Zogenix (now a part of UCB), and has served as consultant/speaker and advisory board member for GW Pharma (now Jazz Pharmaceuticals), Encoded Therapeutics, Stoke Therapeutics, Eisai, UCB, Jaguar Gene Therapy, Arvelle, and Zogenix (now a part of UCB). **KCN:** Provided consulting or participated in advisory boards for Zogenix/UCB, Takeda, Biocodex, and the Epilepsy Study Consortium, Inc. She has participated in educational/CME presentations supported by Efficient CME, Miller Medical Communications, LLC, and the Med Learning Group. **LL:** Received grants and is a consultant and/or speaker for Zogenix (now a part of UCB), LivaNova, UCB, Shire, Eisai, Novartis, Takeda/Ovid, NEL, and Epihunter. **RG:** Research grants from Zogenix (now a part of UCB) during the conduct of the study; served as speaker/consultant for Zogenix (now a part of UCB) outside the submitted work, has served as an investigator for studies with Biocodex, UCB, Angelini, and Eisai, and has served as speaker and advisory board member for Biocodex, Novartis, BioMarin, and GW Pharma (now Jazz Pharmaceuticals). **JW:** Served as an advisor or consultant for GlaxoSmithKline; Eisai; GW Pharmaceuticals (now Jazz Pharmaceuticals); Lundbeck; Neurelis, Inc.; NeuroNexo; Supernus Pharmaceuticals; and Upsher-Smith Laboratories; served as a speaker or a member of a speakers bureau for Cyberonics; Eisai; Lundbeck; Mallinckrodt; Neurelis, Inc.; Supernus Pharmaceuticals; and Upsher-Smith Laboratories and has received research support from Cyberonics; Eisai; Lundbeck; Mallinckrodt; Neurelis, Inc.; Supernus Pharmaceuticals; and Upsher-Smith Laboratories; and Zogenix (now a part of UCB). **BC:** Received research funding from Brabant; has been an advisor to and has received research grants and fees from Zogenix (now a part of UCB Pharma); and holds a patent for ZX008 for the treatment of Dravet syndrome and infantile epilepsies, assigned to KU Leuven University/Antwerp University Hospital and licensed to Zogenix (now a part of UCB Pharma). **PH, ML, JA, AL:** Employees of UCB with stock ownership. **AGN:** Served on speakers bureau, advisory boards, or committees for Angelini Pharma, Bial, Biocodex, Eisai, Esteve, GW Pharma (now Jazz Pharmaceuticals), Ols 4 Cure, Pharvaris, PTC Therapeutics, Rapport Therapeutics, Stoke, UCB Pharma, and Zogenix (now a part of UCB Pharma). Has received research support from Biogen, Jazz Pharmaceuticals, PTC Therapeutics, and UCB Pharma.

American Epilepsy Society 78th Annual Meeting
Los Angeles, CA, USA | December 6–10, 2024