Tolerability and Safety of Fenfluramine and Global Functioning of Patients in a Combined Open-label Extension Study of Children and Adults With Dravet Syndrome or Lennox-Gastaut Syndrome

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Introduction & Objective

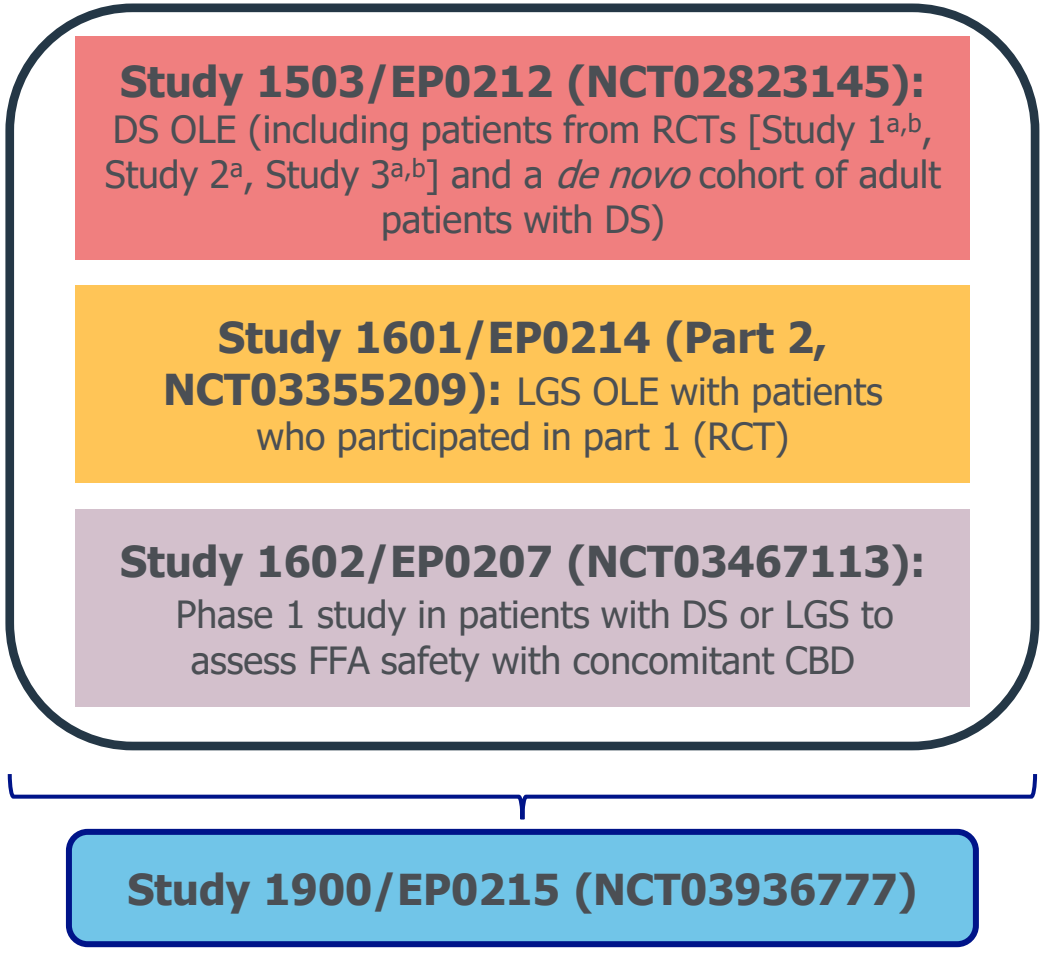
- Dravet and Lennox-Gastaut syndromes (DS, LGS) are rare, lifelong developmental and epileptic encephalopathies (DEEs) characterized by high seizure burden and developmental delay[1-2]
- Fenfluramine (FFA) targets the serotonergic (5-HT) system and sigma-1 receptors[3]
  - Also differs from other antiseizure medications in its minimal risk for CYP450-related drug-drug interactions[4-6]
- Results of DS and LGS randomized controlled trials[7-10] and open-label extension (OLE) studies[11,12] demonstrating FFA safety and efficacy led to the approval of FFA for the management of seizures associated with DS and LGS in patients ≥2 years old in the US[13]

Here we report the long-term safety data and results from global functioning analyses from an interim report of an OLE study in pediatric and adult patients with DS or LGS treated with FFA through July 26, 2024

1. Zuberi SM, et al. *Epilepsia*. 2022;63(6):1349-97. 2. Specchio N, et al. *Epilepsia*. 2022;63(6):1398-442. 3. Martin P, et al. *Int J Mol Sci*. 2021;22(16):8416. 4. Martin P, et al. *Pharmacol Res Perspect*. 2022;10(3):e00958. 5. Martin P, et al. *Pharmacol Res Perspect*. 2022;10(3):e00959. 6. Wirrell EC, et al. *Epilepsia Open*. 2024;9(5):1643-57. 7. Lagae L, et al. *Lancet*. 2019;394(10216):2243-54. 8. Nabbout R, et al. *JAMA Neurol*. 2020;77(3):300-8. 9. Sullivan J, et al. *Epilepsia*. 2023;64(10):2653-66. 10. Knupp K, et al. *JAMA Neurol*. 2022;79(6):554-64. 11. Scheffer IE, et al. *Epilepsia*. 2025;66:1919–32. 12. Knupp KG, et al. *Epilepsia*. 2023;64(1):139-51. 134. UCB, Inc. FINTEPLA® (fenfluramine) oral solution [prescribing information]. Smyrna, GA; April 2025.

Methods: Study Design and Endpoints

Open-label studies



- Patients continued the latest FFA dose from the previous studies; doses could then be flexibly titrated (dose caps applied)
  - All patients were required to be receiving ≥1 concomitant ASM
- The **primary objective** was to assess the **long-term safety and tolerability** of FFA
- A secondary objective was to evaluate patient global functioning using CGI–I global ratings at last visit relative to baseline (entrance into this OLE) by investigator and caregiver
- Endpoints are presented by DEE and by age group, where applicable
- Descriptive statistics were used

[a]Patients receiving any form of CBD were not eligible to participate in the DS RCTs.
[b]Concomitant stiripentol use not permitted in Study 1 and Study 3.
ASM, antiseizure medication; CBD, cannabidiol; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; CGI–I, Clinical Global Impression–Improvement; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; RCT, randomized controlled trial.

Results: Demographics and FFA Exposure

	DS n=265	LGS n=147	All N=412
Age at Visit 1 of this OLE, years			
Mean (SD)	13.4 (6.1)	15.3 (7.7)	14.1 (6.8)
Median (range)	13.0 (3–33)	15.0 (3–37)	13.0 (3–37)
Adult patients (≥18 y), n (%)	72 (27.2)	55 (37.4)	127 (30.8)
Male, n (%)	144 (54.3)	77 (52.4)	221 (53.6)
BMI (kg/m^2), n	261	142	403
Mean (SD)	18.3 (4.4)	18.8 (4.7)	18.4 (4.5)
Median (range)	17.3 (11.5–38.7)	17.6 (10.3–38.5)	17.4 (10.3–38.7)
Region, n (%)			
North America	111 (41.9)	72 (49.0)	183 (44.4)
Europe	140 (52.8)	70 (47.6)	210 (51.0)
Australia	14 (5.3)	5 (3.4)	19 (4.6)
Prior ASMs at Visit 1 of this OLE, number			
Mean (SD)	2.9 (1.2)	3.3 (1.2)	3.1 (1.2)
Median (range)	3.0 (0–7)	3.0 (0–6)	3.0 (0–7)
Study treatment exposure, days			
Median (range)	440.0 (8–1544)	940.0 (123–1445)	729.5 (8–1544)

Overall median exposure (since start of FFA, including feeder studies): 1464.5 days (range, 171–2800)

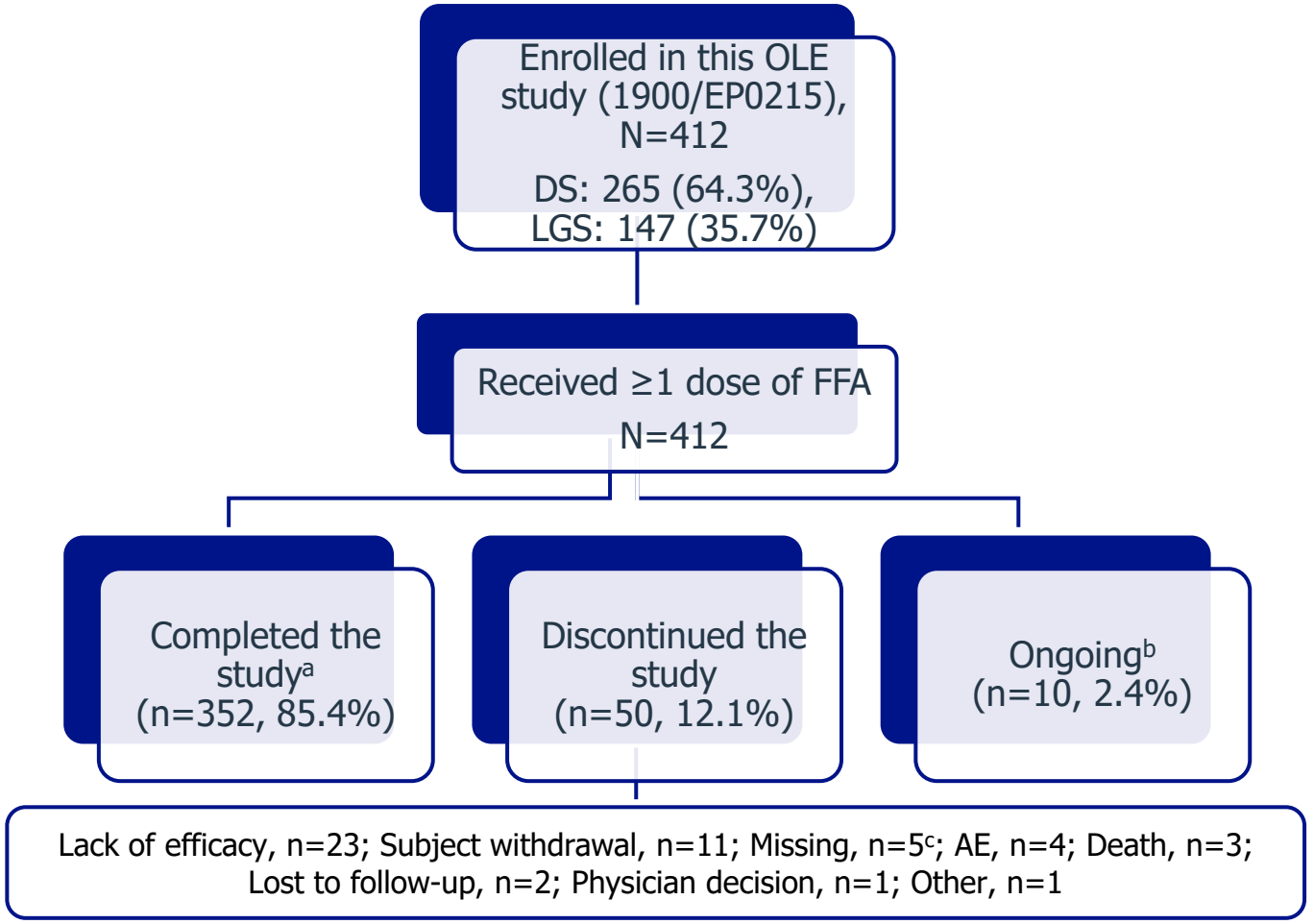
AE, adverse event; ASMs, anti-seizure medications; BMI, body mass index; DS, Dravet syndrome; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension.

Results: CGI–S Scores at Baseline of This OLE Study

	DS N=265		LGS n=147		All N=412	
	Caregiver, n (%)	Investigator, n (%)	Caregiver, n (%)	Investigator, n (%)	Caregiver, n (%)	Investigator, n (%)
1=Normal, not at all ill	21 (7.9)	13 (4.9)	19 (12.9)	16 (10.9)	40 (9.7)	29 (7.0)
2=Borderline ill	17 (6.4)	11 (4.2)	1 (0.7)	3 (2.0)	18 (4.4)	14 (3.4)
3=Mildly ill	31 (11.7)	35 (13.2)	14 (9.5)	17 (11.6)	45 (10.9)	52 (12.6)
4=Moderately ill	52 (19.6)	106 (40.0)	26 (17.7)	35 (23.8)	78 (18.9)	141 (34.2)
5=Markedly ill	74 (27.9)	54 (20.4)	39 (26.5)	46 (31.3)	113 (27.4)	100 (24.3)
6=Severely ill	40 (15.1)	30 (11.3)	33 (22.4)	23 (15.6)	73 (17.7)	53 (12.9)
7=Among the most extremely ill	14 (5.3)	5 (1.9)	8 (5.4)	5 (3.4)	22 (5.3)	10 (2.4)
Missing	16 (6.0)	11 (4.2)	7 (4.8)	2 (1.4)	23 (5.6)	13 (3.2)

CGI–S, Clinical Global Impression–Severity; Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open-label extension.

Results: Disposition



[a]Completed means completed 36 months of treatment (24 months in Denmark) or transitioned to commercial fenfluramine.
[b]Ten patients were either ongoing in the cardiovascular safety follow-up period or final disposition was not yet available.
[c]Five patients with "missing" disposition data were incorrectly reported as having completed the study but had not completed 36 months of treatment (or 24 months in Denmark), so have no reported reason for discontinuation.
AE, adverse event; DS, Dravet syndrome; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension.

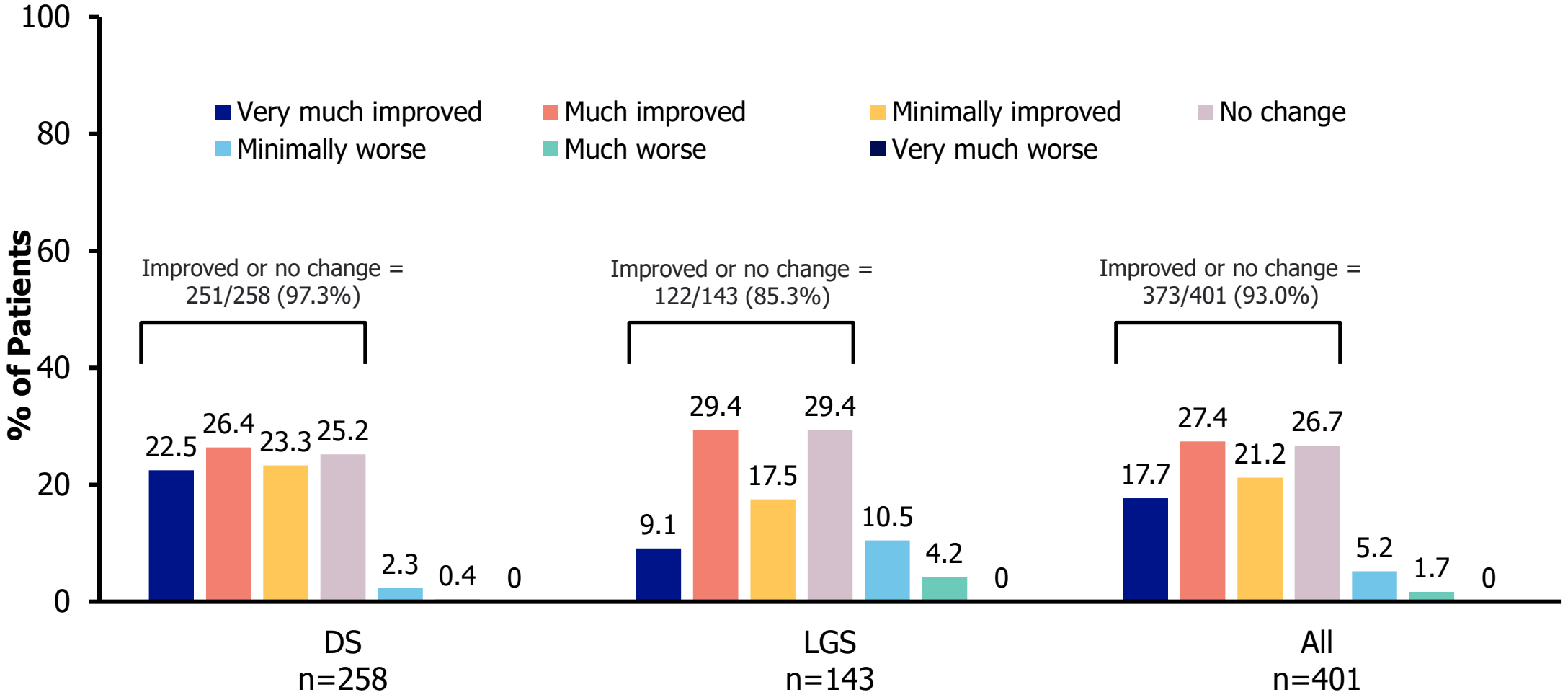
Results: Safety Summary

	DS n=265	LGS n=147	All N=412
Patients with any TEAE, n (%)	183 (69.1)	128 (87.1)	311 (75.5)
Patients with serious TEAEs, n (%)	29 (10.9)	38 (25.9)	67 (16.3)
Patients with TEAEs leading to study discontinuation, n (%)	0 (0.0)	4 (2.7)	4 (1.0)
Patients with treatment-related TEAEs[a], n (%)	29 (10.9)	22 (15.0)	51 (12.4)
Patients with treatment-related serious TEAEs[a], n (%)	1 (0.4)	4 (2.7)	5 (1.2)
Deaths[b], n (%)	1 (0.4)	2 (1.4)	3 (0.7)
TEAEs reported in ≥10% of all patients, n (%)			
Coronavirus infection	43 (16.2)	42 (28.6)	85 (20.6)
Seizure	26 (9.8)	37 (25.2)	63 (15.3)
Pyrexia	39 (14.7)	15 (10.2)	54 (13.1)
Nasopharyngitis	34 (12.8)	15 (10.2)	49 (11.9)

- No evidence of a clinically significant effect of FFA on ECG parameters (QTcF) was observed
- No patients with VHD[c,d]
- No patients with PAH (PASP >35 mmHg)

[a]Treatment-related is based on the investigator's assessment.
[b]3 deaths were attributed to cardiac arrest, left ventricular dysfunction, and status epilepticus; none were deemed by the investigator to be related to fenfluramine.
[c]Per the agreement with the FDA, VHD is defined as mild, moderate or severe aortic regurgitation (AR) or moderate or severe mitral regurgitation (MR), with additional characteristics and/or physical signs or symptoms attributable to VHD (eg, valve thickening, restricted valve motion).
[d]Three patients presented with mild AR during the study without any other clinical or anatomical abnormality attributable to valve disease, which is not classified as VHD.
ECG, electrocardiogram; FFA, fenfluramine; PAH, pulmonary arterial hypertension; PASP, pulmonary arterial systolic pressure; QTcF, QT interval corrected for heart rate using Fridericia's formula; TEAE, treatment emergent adverse event; VHD, valvular heart disease.

Results: CGI–I Ratings at Last On-Treatment Visit - *Caregiver*



DS, Dravet syndrome; CGI–I, Clinical Global Impression–Improvement; LGS, Lennox-Gastaut syndrome.

Results: CGI–I Ratings at Last On-Treatment Visit - *Investigator*

CGI–I, Clinical Global Impression–Improvement; DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Within each DEE, ratings of improved/no change by caregiver and investigator were similar between age groups

Conclusions

- In this OLE study (after a median 729 days of FFA exposure; mean[SD] FFA daily dose 0.5[0.2] mg/kg/day), long-term use of fenfluramine in pediatric and adult patients with DS or LGS was well tolerated
- TEAEs were consistent with the known safety profile of fenfluramine
  - No new safety signals were identified and no cases of VHD or PAH were observed[a]
- CGI–I ratings by both caregivers and investigators suggest that pediatric and adult patients with DS or LGS treated with long-term fenfluramine (up to 4+ years) had a sustained clinical benefit
- Data from this OLE study support the continued clinical benefit of fenfluramine and its positive benefit/risk profile observed in prior studies[1-6]

[a]Cases of VHD/PAH have been reported with postmarketing use of fenfluramine.

DS, Dravet syndrome; CGI–I, Clinical Global Impression–Improvement; FFA, fenfluramine; LGS, Lennox-Gastaut syndrome; OLE, open-label extension; PAH, pulmonary arterial hypertension; VHD, valvular heart disease.

1. Lagae L, et al. *Lancet*. 2019;394(10216):2243-54. 2. Nabbout R, et al. *JAMA Neurol*. 2020;77(3):300-8. 3. Sullivan J, et al. *Epilepsia*. 2023;64(10):2653-66. 4. Knupp K, et al. *JAMA Neurol*. 2022;79(6):554-64. 5. Scheffer IE, et al. *Epilepsia*. 2025;66:1919–32. 6. Knupp KG, et al. *Epilepsia*. 2023;64(1):139-51.

Appendix/Supplementary Slides

Additional Author Disclosures

- **A-SS:** Research support from Zogenix (now a part of UCB); consultant for Brabant and Zogenix (now a part of UCB).
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- **BG:** Received consultancy fees from GW Pharma, Ovid/Takeda, and Zogenix (now part of UCB), and has been a principal investigator for GW Research Ltd and Zogenix (now part of UCB)
- **EAT:** Paid consultant for Biocodex, GW Pharma (now Jazz Pharmaceuticals), LivaNova, Nobelpharma, Noema Pharma, Stoke Therapeutics, and Zogenix (now part of UCB); has received research funding from Biocodex and GW Pharma (now Jazz Pharmaceuticals); served as clinical tral site PI for GW Pharma (now Jazz Pharmaceuticals), Neurelis, SK Life Sciences, Stoke Therapeutics, and Zogenix (now part of UCB).
- **RS-C:** Received honoraria and/or research funds from Biocodex, Jazz Pharmaceuticals, and Zogenix (now part of UCB).
- **NS:** Served on scientific advisory boards for Arvelle, BioMarin, GW Pharma (now Jazz Pharmaceuticals), Marinus and Takeda; received speaker honoraria from Eisai, Biomarin, Livanova, and Sanofi; served as an investigator for Biomarin, Marinus, Roche, and UCB.
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- **ND, A-LS, ML:** Employees of UCB with stock ownership.
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Disposition by DEE

	DS n=265	LGS n=147	All N=412
Ongoing[a], n (%)	2 (0.8)	8 (5.4)	10 (2.4)
Completed[b], n (%)	255 (96.2)	97 (66.0)	352 (85.4)
Discontinued, n (%)	8 (3.0)	42 (28.6)	50 (12.1)
Reason for discontinuation, n (%)			
Lack of efficacy	4 (1.5)	19 (12.9)	23 (15.6)
Patient withdrawal	2 (0.8)	9 (6.1)	11 (2.7)
Missing[c]	1 (0.4)	4 (2.7)	5 (1.2)
Adverse event	0 (0.0)	4 (2.7)	4 (1.0)
Death	1 (0.4)	2 (1.4)	3 (0.7)
Lost to follow-up	0 (0.0)	2 (1.4)	2 (0.5)
Physician decision	0 (0.0)	1 (0.7)	1 (0.2)
Other	0 (0.0)	1 (0.7)	1 (0.2)

[a]Ten patients are either ongoing in the cardiovascular safety follow-up period or final disposition was not yet available.
[b]Completed means completed 36 months of treatment (24 months in Denmark) or transitioned to commercial fenfluramine.
[c]Five patients with "missing" disposition data were incorrectly reported as having completed the study but had not completed 36 months of treatment (or 24 months in Denmark) so have no reported reason for discontinuation.
DEE, developmental and epileptic encephalopathy; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome.

Treatment-Emergent Adverse Events (TEAEs) by Age Group

	Age 2 to <18 yo n=285	Age ≥18 yo n=127	All Patients N=412
Any TEAE, n (%)	214 (75.1)	97 (76.4)	311 (75.5)
Coronavirus infection	50 (17.5)	35 (27.6)	85 (20.6)
Seizure	45 (15.8)	18 (14.2)	63 (15.3)
Pyrexia	39 (13.7)	15 (11.8)	54 (13.1)
Nasopharyngitis	37 (13.0)	12 (9.4)	49 (11.9)
Diarrhea	17 (6.0)	13 (10.2)	30 (7.3)
Decreased appetite	17 (6.0)	8 (6.3)	25 (6.1)
Upper respiratory tract infection	14 (4.9)	10 (7.9)	24 (5.8)
Somnolence	10 (3.5)	11 (8.7)	21 (5.1)

yo, years old.

Additional Cardiovascular Safety Content

	All N=412
Patients with Trace, Mild, Moderate or Severe Mitral Regurgitation (MR)	
Baseline	40/412 (9.7%)
Any Post Baseline	92/395 (23.3%)
Patients with Trace, Mild, Moderate or Severe Aortic Regurgitation (AR)	
Baseline	5/412 (1.2%)
Any Post Baseline	9/395 (2.3%)

6/92 patients had mild MR, no patient had moderate or severe MR and, therefore, no cases of mitral valvulopathy

6/9 patients had trace AR; 3 of the 9 patients had mild AR, considered aortic valvulopathy (but not VHD)

- 2 of these patients had mild AR at baseline which persisted throughout the study
- 1 patient (with trace AR at baseline) had a single instance of transient mild AR at Mo18

CGI–I at Last Visit by Age Group (Caregiver)

	DS n=265		LGS n=147		All N=412	
Age group	**2 to <18 yo n=192**	**≥18 yo n=72**	**2 to <18 yo n=91**	**≥18 yo n=55**	**2 to <18 yo n=283**	**≥18 yo n=127**
1=Very much improved	44/188 (23.4%)	14/70 (20.0%)	7/91 (7.7%)	6/52 (11.5%)	51/279 (18.3%)	20/122 (16.4%)
2=Much improved	44/188 (23.4%)	24/70 (34.3%)	27/91 (29.7%)	15/52 (28.8%)	71/279 (25.4%)	39/122 (32.0%)
3=Minimally improved	47/188 (25.0%)	13/70 (18.6%)	16/91 (17.6%)	9/52 (17.3%)	63/279 (22.6%)	22/122 (18.0%)
4=No change	47/188 (25.0%)	18/70 (25.7%)	29/91 (31.9%)	13/52 (25.0%)	76/279 (27.2%)	31/122 (25.4%)
5=Minimally worse	5/188 (2.7%)	1/70 (1.4%)	9/91 (9.9%)	6/52 (11.5%)	14/279 (5.0%)	7/122 (5.7%)
6=Much worse	1/188 (0.5%)	0/70	3/91 (3.3%)	3/52 (5.8%)	4/279 (1.4%)	3/122 (2.5%)
7=Very much worse	0/188	0/70	0/91	0/52	0/279	0/122
Improved or no change	182/188 (96.8%)	69/70 (98.6%)	79/91 (86.8%)	43/52 (82.7%)	261/279 (93.5%)	112/122 (91.8%)

Improved or no change

CGI–I, Clinical Global Impression–Improvement scale; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; yo, years old.

CGI–I at Last Visit by Age Group (Investigator)

	DS n=265		LGS n=147		All N=412	
Age group	**2 to <18 yo n=192**	**≥18 yo n=72**	**2 to <18 yo n=91**	**≥18 yo n=55**	**2 to <18 yo n=283**	**≥18 yo n=127**
1=Very much improved	22/188 (11.7%)	4/70 (5.7%)	2/91 (2.2%)	4/52 (7.7%)	24/279 (8.6%)	8/122 (6.6%)
2=Much improved	47/188 (25.0%)	20/70 (28.6%)	28/91 (30.8%)	13/52 (25.0%)	75/279 (26.9%)	33/122 (27.0%)
3=Minimally improved	55/188 (29.3%)	16/70 (22.9%)	19/91 (20.9%)	13/52 (25.0%)	74/279 (26.5%)	29/122 (23.8%)
4=No change	58/188 (30.9%)	29/70 (41.4%)	33/91 (36.3%)	13/52 (25.0%)	91/279 (32.6%)	42/122 (34.4%)
5=Minimally worse	4/188 (2.1%)	0/70	7/91 (7.7%)	8/52 (15.4%)	11/279 (3.9%)	8/122 (6.6%)
6=Much worse	2/188 (1.1%)	1/70 (1.4%)	2/91 (2.2%)	0/52	4/279 (1.4%)	1/122 (0.8%)
7=Very much worse	0/188	0/70	0/91	1/52 (1.9%)	0/279	1/122 (0.8%)
Improved or no change	182/188 (96.8%)	69/70 (98.6%)	82/91 (90.1%)	43/52 (82.7%)	264/279 (94.6%)	112/122 (91.8%)

Improved or no change

CGI–I, Clinical Global Impression–Improvement scale; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; yo, years old.