Poster #P207

A Stratified Analysis of Efficacy and Safety of Fenfluramine in Patients With Dravet Syndrome

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QUESTION

What baseline characteristics affect the safety and/or efficacy of add-on fenfluramine (FFA) treatment in patients with Dravet syndrome (DS) in randomized controlled trials (RCTs)?

INVESTIGATION

Patients from 3 RCTs were stratified by age at FFA initiation, number of previously attempted antiseizure medications (ASMs), and *SCN1A* status. Efficacy endpoints were median percentage change in monthly convulsive seizure frequency (MCSF), median longest interval of convulsive seizure-free days, and proportion of patients with clinically meaningful improvement on Clinical Global Impression–Improvement (CGI–I) scores. Safety endpoints were assessed as proportions of patients with treatment emergent adverse events (TEAEs) by dose group.

RESULTS

Baseline Characteristics, Combined From Patients Enrolled in Three RCTs (N=348)

	Placebo (n=132)	FFA 0.2 mg/kg/d Without STP (n=85)	FFA 0.4 mg/kg/d With STP (n=43)	FFA 0.7 mg/kg/d Without STP (n=88)	Total FFA (n=216)
Sex, n (%) female	57 (43.2)	39 (45.9)	20 (46.5)	45 (51.1)	104 (48.2)
Age group, n (%)					
<4 years	15 (11.4)	9 (10.6)	7 (16.3)	13 (14.8)	29 (13.4)
≥4 years	117 (88.6)	76 (89.4)	36 (83.7)	75 (85.2)	187 (86.6)
Race, n (%)					
White	96 (72.7)	70 (82.4)	23 (53.5)	67 (76.1)	160 (74.1)
Asian	12 (9.1)	7 (8.2)	2 (4.7)	9 (10.2)	18 (8.3)
Other or Unknown	10 (7.6)	6 (7.1)	5 (11.6)	7 (8.0)	18 (8.3)
Not reported[a]	14 (10.6)	2 (2.4)	13 (30.2)	5 (5.7)	20 (9.3)
***SCN1A*+, n (%)**	113 (85.6)	72 (84.7)	37 (86.0)	77 (87.5)	186 (86.1)
Number of previously attempted ASMs, n (%)[b]					
1–3	32 (24.2)	7 (8.2)	22 (51.2)	13 (14.8)	42 (19.4)
4–6	54 (40.9)	29 (34.1)	21 (48.8)	28 (31.8)	78 (36.1)
7+	46 (34.8)	49 (57.6)	0	47 (53.4)	96 (44.4)
Number of concomitant ASMs, n (%)					
1–3	101 (76.5)	69 (81.2)	20 (46.5)	78 (88.6)	167 (77.3)
4–6	31 (23.5)	15 (17.6)	23 (53.5)	10 (11.4)	48 (22.2)
Baseline MCSF					
Mean ± SD	30.1 ± 36.2	58.3 ± 175.5	27.9 ± 36.9	67.5 ± 288.1	56.0 ± 214.7
Median (Range)	14.8 (2.7, 229.3)	17.5 (4, 1464)	14.0 (2.7, 213.3)	16.9 (2.7, 2700.7)	16.3 (2.7, 2700.7)

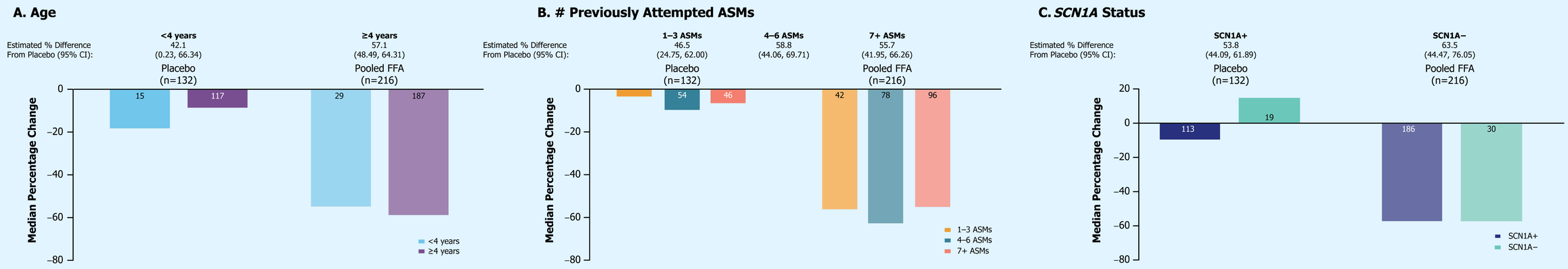
[a]Not reported or missing: privacy laws in some regions and countries preclude disclosure of certain personal information.
[b]Previously attempted ASMs do not include concomitant ASMs.

TEAEs From 3 RCTs Combined From Patients Enrolled in Three Pivotal Trials (N=348)

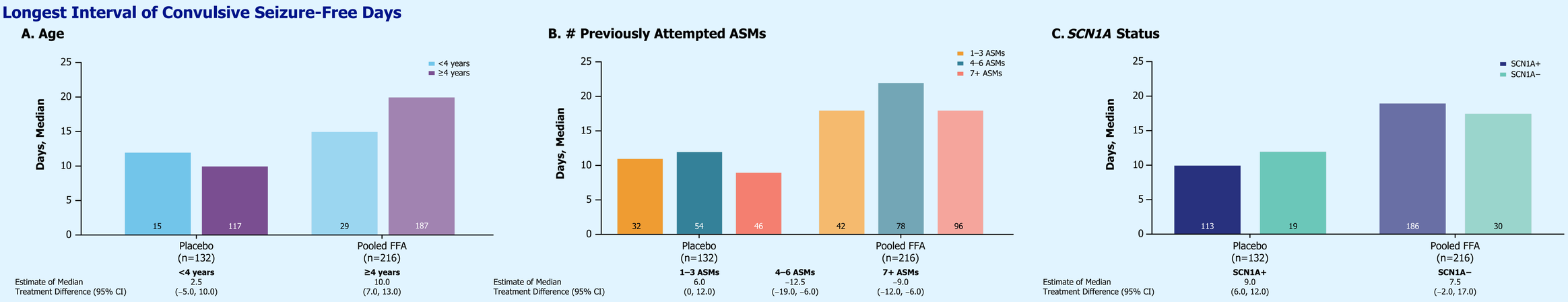
	Placebo (n=132)	FFA 0.2 mg/kg/d Without STP (n=85)	FFA 0.4 mg/kg/d With STP (n=43)	FFA 0.7 mg/kg/d Without STP (n=88)	Total FFA (n=216)
Patients with ≥1 TEAE, n (%)[a]	108 (81.8)	79 (92.9)	42 (97.7)	82 (93.2)	203 (94.0)
Days to onset of earliest occurrence of common TEAEs, mean ± SD[b]	41.0 ± 38.4	30.1 ±31.2	26.2 ± 27.6	24.1 ± 29.9	26.9 ± 29.8
Patients with ≥1 serious TEAE, n (%)	12 (9.1)	8 (9.4)	6 (14.0)	8 (9.1)	22 (10.2)
Patients with any TEAE resulting in discontinuation of treatment, n (%)	2 (1.5)	1 (1.2)	2 (4.7)	7 (8.0)	10 (4.6)
Patients with any TEAE resulting in death, n (%)	1 (0.8)	0	0	0	0

[a]Listed TEAEs occurred in ≥10% of any treatment group.
[b]Common TEAEs are those occurring with a frequency of at least 5% across all subjects.

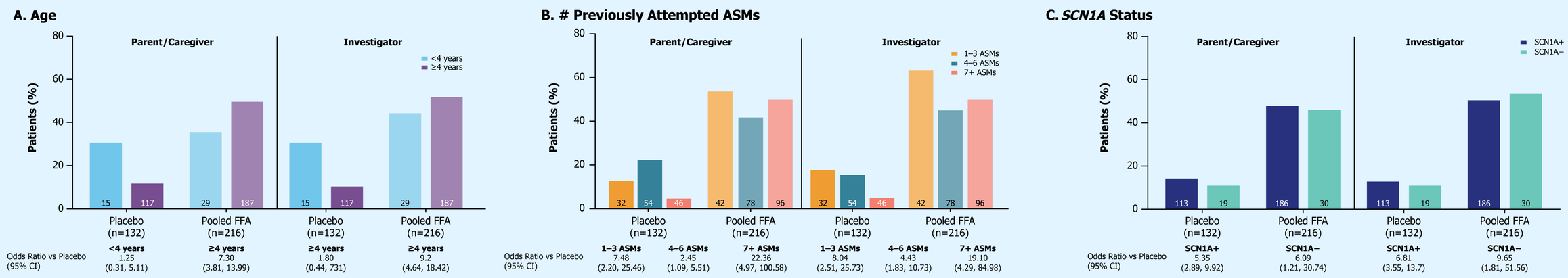
Percent Change in MCSF



Longest Interval of Convulsive Seizure-Free Days



Clinically Meaningful Improvement on CGI–I Scores (Much Improved or Very Much Improved)



95% CI based on Hodges-Lehman estimator of treatment difference.
Clinically meaningful improvement: "Much Improved" or "Very Much Improved" on CGI–I.

Abbreviations: ASM, antiseizure medication; CGI–I, Clinical Global Impression–Improvement Scale; CI, confidence interval; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; RCTs, randomized controlled trials; SD, standard deviation; STP, stiripentol; TEAEs, treatment emergent adverse events.

METHODS

- Patient data from 3 RCTs (NCT02682927, NCT02826863, NCT02926898)[1-3] were pooled by dose group and stratified by baseline characteristics of age, number of previously attempted ASMs, and *SCN1A* status
  - Concomitant STP was an exclusion criterion in NCT02682927 and NCT02826863 and an inclusion criterion in NCT02926898[1-3]
- Safety (analyzed by dose group):
  - TEAEs
- Efficacy endpoints (analyzed by dose group and stratified by baseline characteristic):
  - Change in MCSF
  - Longest interval between seizure-free days
  - Global functioning as measured by clinically meaningful change in CGI–I scores evaluated by investigators or parents/caregivers (Much Improved or Very Much Improved)

Statistics:

- Change in MCSF:
  - *P* values were obtained from an ANCOVA model: factors, treatment group and age group (<6 years, ≥6 years), study as an additional factor for the Overall group; covariate, log baseline convulsive seizure frequency; response, log convulsive seizure frequency (Titration and Maintenance)
  - The estimate of % difference vs placebo was obtained by the least-squares means (LS Means) on the log scale as follows: 100 x [1 − exp(LS Mean active − LS Mean placebo)]
- The interval between seizure-free days:
  - The estimate of median treatment difference with confidence intervals was based on Hodges-Lehman estimator of treatment difference; *P* values were obtained from Wilcoxon rank test comparing overall FFA groups with placebo
- Clinically meaningful change in CGI–I:
  - The Odds Ratio for FFA-treated patients vs placebo (95% CI) was assessed; *P* values were obtained from Cochran-Mantel-Haenszel test controlling for age group
- All hypothesis tests are post hoc in nature; *P* values are considered nominal due to the post hoc nature of the analysis

CONCLUSIONS

- FFA was generally well tolerated; the most common TEAEs were decreased appetite, fatigue, and pyrexia (see QR code for full poster)
- FFA is associated with improved global functioning (seizure and non-seizure) outcomes relative to placebo, regardless of age, number of previously attempted ASMs, or *SCN1A* status in patients with DS
- Results should be interpreted with caution due to limitations of sample size and short treatment duration (2–3 weeks titration plus 12 weeks maintenance); additional studies are needed long-term
- Inferential analyses of stratified groups in larger populations may provide a better understanding of the increased benefits seen in different DS sub-populations and synergies with concomitant medications

References

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.

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