Poster #P242

Impact of Fenfluramine on Convulsive Seizure Frequency in Dose-capped Patients With Dravet Syndrome

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QUESTION

- Is fenfluramine (FFA) effective in reducing monthly convulsive seizure frequency (MCSF) in patients with Dravet syndrome (DS) receiving the maximum daily dose (i.e., are dose-capped)?

INVESTIGATION

- A post hoc analysis of median MCSF in patients with Dravet syndrome who completed any of three randomized controlled trials (RCTs) and continued through its open-label extension (OLE), stratified by patient weight and concomitant stiripentol (STP) use
- Median percentage change in MCSF was measured from OLE Month 2 to end-of-study (EOS) vs RCT baseline

RESULTS

RCT Baseline MCSF

Dose-capped	Without Concomitant STP[a] n=60	With Concomitant STP[b] n=23
Mean ± SD	37.6 ± 81.9	34.5 ± 34.6
Median (min, max)	18.4 (3.3, 623.5)	24 (2.7, 162.7)
Not dose-capped	**Without STP n=183**	**With Concomitant STP n=58**
Mean ± SD	57.9 ± 227.4	20.2 ± 32.1
Median (min, max)	16 (2.7, 2700.7)	8 (2.7, 213.3)

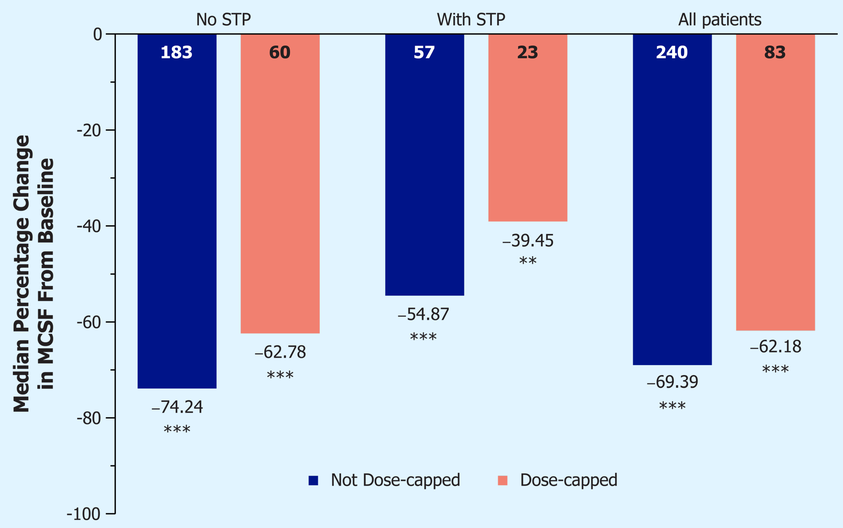
[a]Includes patients ≥37.5 kg at RCT baseline (Studies 1 and 3) treated with 26 mg/d FFA during the OLE.
[b]Includes patients ≥42.5 kg at RCT baseline (Study 2) treated with 17 mg/d FFA during the OLE.

RCT Baseline Demographics and Characteristics

Dose-capped	Without STP[a] n=60	With Concomitant STP[b] n=23	All Patients n=83
Age, y			
Mean ± SD	13.9 ± 2.9	14.9 ± 2.3	14.2 ± 2.8
Median (min, max)	15 (6, 19)	15 (9, 19)	15 (6, 19)
Weight, kg			
Mean ± SD	52.9 ± 12.4	58.8 ± 13.3	54.5 ± 12.8
Median (min, max)	50.5 (36.2, 99.7)	53.0 (43.0, 85.3)	51.2 (36.2, 99.7)
Sex, n (%)			
Male	34 (56.7)	16 (69.6)	50 (60.2)
Not Dose-capped	**n=183**	**n=58**	**n=241**
Age, y			
Mean ± SD	7.5 ± 3.9	6.8 ± 3.4	7.4 ± 3.8
Median (min, max)	7 (2, 18)	7 (2,15)	7 (2, 18)
Weight, kg			
Mean ± SD	26.2 ± 9.8	24.5 ± 8.8	25.8 ± 9.6
Median (min, max)	24.1 (11.5, 70.2)	22.3 (13.2, 43.8)	23.9 (11.5, 70.2)
Sex, n (%)			
Male	93 (50.8)	32 (55.2)	125 (51.9)

[a]Includes patients ≥37.5 kg at RCT baseline (Studies 1 and 3) treated with fenfluramine 26 mg/d during the OLE.
[b]Includes patients ≥42.5 kg at RCT baseline (Study 2) treated with fenfluramine 17 mg/d during the OLE.

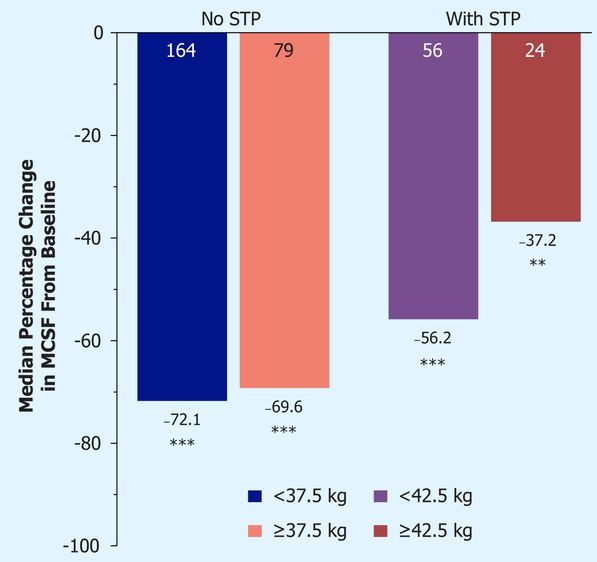
Figure 1. Median Percentage Change in MCSF From RCT Baseline to OLE (Month 2 Through EOS) in Patients Treated With FFA by Dose-capping and Concomitant STP Use



Number within each bar represents the number of patients in the group. Dose-capped patients are a subset of the patients weighing ≥37.5 kg who reached the maximum dose of 26 mg/day (without concomitant STP) or ≥42.5 kg who reached the maximum dose of 17 mg/day (with concomitant STP).
, *P*<0.01; *,*P*<0.0001. *P* values are vs pre-randomization baseline.

Abbreviations: EOS, end-of-study; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NS, not significant; OLE, open-label extension; RCT, randomized controlled trial; SD, standard deviation; STP, stiripentol.

Figure 2. Median Percentage Change in MCSF From RCT Baseline to OLE (Month 2 Through EOS) Following Fenfluramine Treatment by Weight

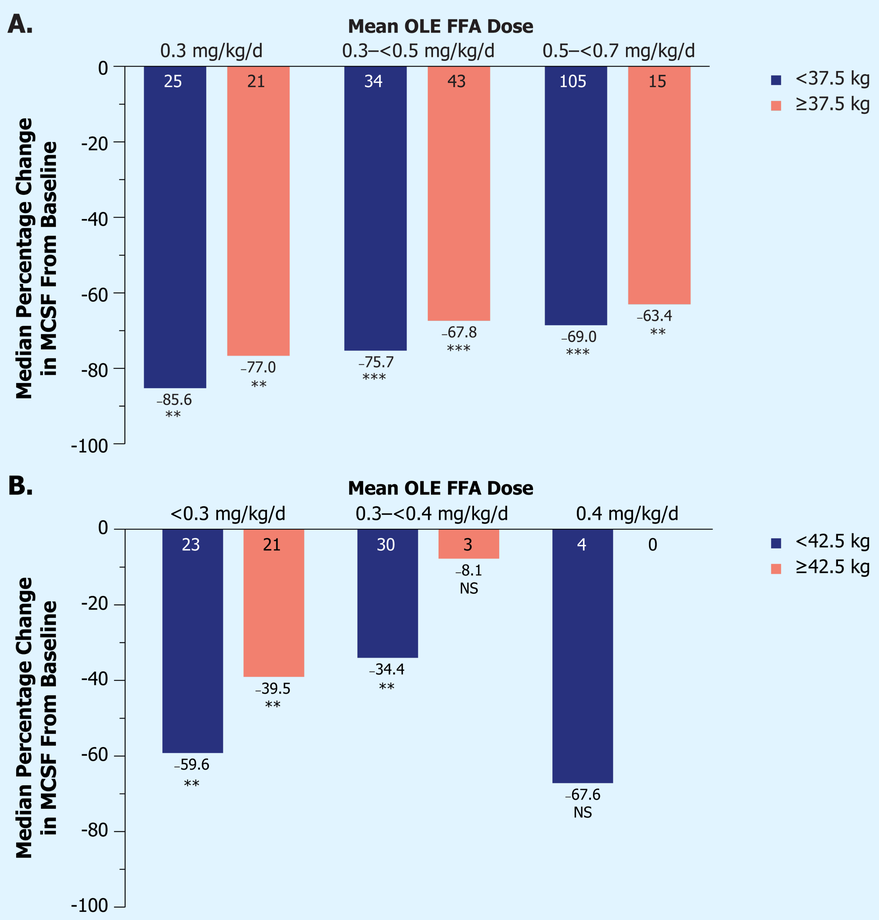


Number within each bar represents the number of patients in the group.
, *P*<0.01; *, *P*<0.0001. *P* values are vs pre-randomization baseline.

Figure 3. Median Percentage Change in MCSF From RCT Baseline to OLE (Month 2 Through EOS) by Weight and OLE Mean Daily FFA Dose in:

A. Patients Treated With Fenfluramine Without Concomitant STP;

B. Patients Treated With Fenfluramine With Concomitant STP

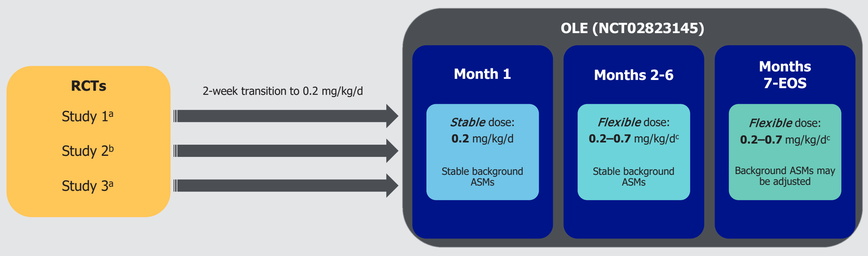


Number within each bar represents the number of patients in the group.
, *P*<0.01; *, *P*<0.0001. *P* values are vs pre-randomization baseline.

METHODS

- Patients with DS who completed any of three RCTs (Studies 1 and 3 [NCT02682927, NCT02826863], or Study 2 [NCT02926898]) were eligible to enroll for up to 36 months in an OLE (NCT02823145; **Figure 4**)
- In this post hoc analysis, median percentage change in MCSF, stratified by patient weight and STP use, from RCT baseline to OLE Month 2 through EOS was assessed
- Convulsive seizures were defined as hemiclonic, tonic, clonic, myoclonic-atonic, focal with observable motor signs, and generalized tonic-clonic
- Patients were dose-capped if they were treated with FFA and:
  - Without STP, weighed ≥37.5 kg at RCT baseline, and were treated with the maximum daily dose (26 mg/d) of FFA during the OLE
  - With concomitant STP, weighed ≥42.5 kg at RCT baseline, and were treated with the maximum daily dose (17 mg/d) of FFA during the OLE
- Within-group percent change from baseline is based on a Wilcoxon signed-rank test
- All *P* values are considered nominal due to the post hoc nature of this analysis

Figure 4. OLE Study Design



[a]Patients were treated without concomitant STP. [b]Patients were treated with concomitant STP. [c]Patients treated with concomitant STP had a maximum dose of 0.4 mg/kg/d; the maximum daily dose for patients without concomitant STP was 26 mg/d and the maximum daily dose for patients with concomitant STP was 17 mg/d.
ASM, antiseizure medication; EOS, end-of-study; OLE, open-label extension; RCT, randomized controlled trial.

CONCLUSIONS

- Patients with DS treated with FFA may be limited to a dose lower than the maximum daily maintenance dose based on their weight
  - Patients treated without concomitant STP who are ≥37.5 kg and patients treated with concomitant STP who are ≥42.5 kg may receive a dose lower than patients who are not dose-capped
- This post hoc analysis suggests that FFA treatment, regardless of concomitant STP use, results in effective reduction in the frequency of convulsive seizures in patients who received a capped daily dose
  - This reduction is consistent with the reduction seen in patients who are not dose-capped
- These data suggest that a fixed-dose treatment regimen is appropriate for achieving clinical response with FFA in treating patients:
  - Without concomitant STP who weigh ≥37.5 kg, receiving 26 mg/d FFA
  - With concomitant STP who weigh ≥42.5 kg, receiving 17 mg/d FFA
- The weight-based approach is recommended for patients treated with FFA without concomitant STP who weigh <37.5 kg and with concomitant STP who weigh <42.5 kg

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Disclosures for all authors can be found in the full poster at the QR code.

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