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

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## Introduction

- Dravet syndrome (DS) is a rare, treatment-resistant, developmental and epileptic encephalopathy characterized by seizure onset within the first year of life and developmental delay[1]
  - Patients with DS experience a high frequency of convulsive seizures, including generalized tonic-clonic seizures (GTCS)
  - GTCS is a leading risk factor for sudden unexpected death in epilepsy[2]
- Fenfluramine (FFA) is approved in the US, EU, UK and Japan, among others, for the treatment of seizures associated with DS in patients ≥2 years old[3-8]
  - Patients treated with FFA without concomitant stiripentol (STP) are titrated from 0.2 mg/kg/d to effect up to the maximum maintenance dose of 0.7 mg/kg/d FFA (absolute maximum daily dose of 26 mg/d)
  - With concomitant STP, patients are titrated from 0.2 mg/kg/d to the maximum dose of 0.4 mg/kg/d FFA (absolute maximum daily dose of 17 mg/d)
- Patients treated with FFA without STP who weigh ≥37.5 kg (~82.5 lb) or treated with FFA and concomitant STP who weigh ≥42.5 kg (~88.2 lb) may not receive a weight-based dose, regardless of effect, due to the absolute maximum daily dose (i.e., are dose-capped)

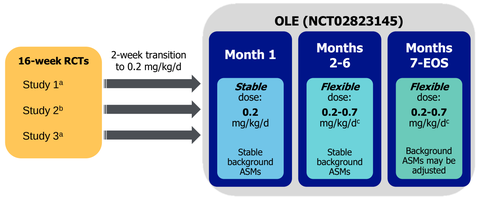
## Objective

- To assess the efficacy of FFA in patients with DS in clinical trials who are dose-capped

## Methods

- Patients with DS who completed any of three randomized controlled trials (RCTs; Studies 1 and 3 [NCT02682927, NCT02826863], or Study 2 [NCT02926898]) were eligible to enroll for up to 36 months in an open-label extension (OLE; NCT02823145; **Figure 1**)

**Figure 1. 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.

- In this post-hoc analysis, median percentage change in monthly convulsive seizure frequency (MCSF), stratified by patient weight and STP use, from RCT baseline to OLE Month 2 through end-of-study (EOS) was assessed
- Convulsive seizures were defined as hemiclonic, tonic, clonic, myoclonic-atonic, focal with observable motor signs, and GTCS
- Patients were considered 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

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## Overview

### QUESTION

- Is fenfluramine effective in reducing monthly convulsive seizure frequency (MCSF) in patients with Dravet syndrome 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; Studies 1, 2, and 3) and continued through its open-label extension (OLE)
  - Analyses were stratified by patient weight and concomitant stiripentol use
- Patients were considered dose-capped if:
  - They were treated without stiripentol, ≥37.5 kg and reached the absolute maximum dose of 26 mg/d fenfluramine
  - They were treated with concomitant stiripentol, ≥42.5 kg, and reached the absolute maximum dose of 17 mg/d fenfluramine
- Median percentage change in MCSF was measured from OLE Month 2 to end-of-study vs RCT baseline

### RESULTS

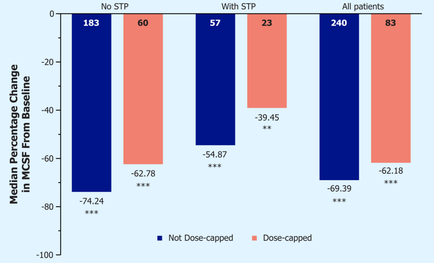
- Patients who were dose-capped had significantly reduced MCSF during the OLE in comparison to RCT baseline
- At all doses of fenfluramine, patients had a similar change in MCSF regardless of weight

**Baseline MCSF**

| Dose-capped | Without STP[a] n=60 | 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** | **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.
MCSF, monthly convulsive seizure frequency per 28 days; OLE, open-label extension; RCT, randomized controlled trial; STP, stiripentol.

**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.
EOS, end-of-study; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; OLE, open-label extension; RCT, randomized controlled trial; STP, stiripentol.

### CONCLUSIONS

- Fenfluramine is effective in reducing convulsive seizure frequency in patients with DS, regardless of dose-capping due to the absolute maximum daily dose and patient weight

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## Results

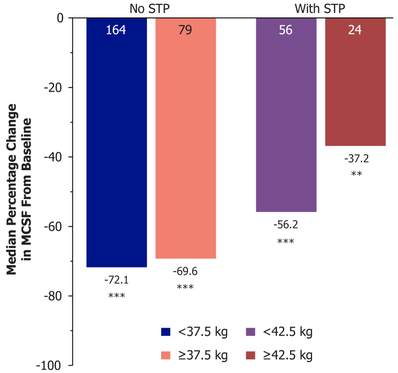
- A total of 324 patients with DS (2-18 years at RCT baseline) enrolled and received at least 1 dose of FFA during the OLE (**Table 1**)
- Of patients without concomitant STP ≥37.5 kg (n=79) or with concomitant STP ≥42.5 kg (n=24), 83/103 (80.6%) were treated at the maximum recommended dose (i.e., dose capped)

**Table 1. RCT Baseline Demographics and Characteristics**

| Dose-capped patients | Without STP[a] n=60 | 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) |
| **Gender, n (%)** | | | |
| Male | 34 (56.7) | 16 (69.6) | 50 (60.2) |
| Female | 26 (43.3) | 7 (30.4) | 33 (39.8) |
| **Non-dose-capped patients** | **Without STP n=183** | **Concomitant STP n=58** | **All Patients 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) |
| **Gender, n (%)** | | | |
| Male | 93 (50.8) | 32 (55.2) | 125 (51.9) |
| Female | 90 (49.2) | 26 (44.8) | 116 (48.1) |

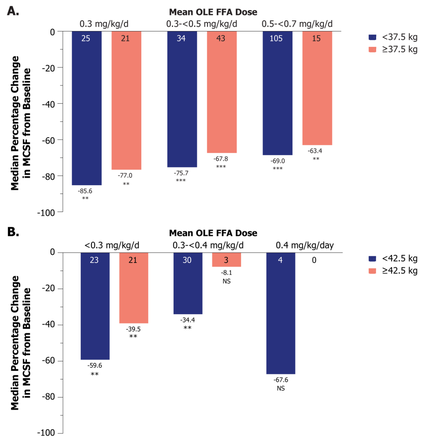
[a]Includes patients ≥37.5 kg at RCT baseline (Studies 1 and 3) treated with 26 mg/d FFA during the OLE.
[b]Includes patients ≥42.5 kg at RCT baseline (Study 2) treated with 17 mg/d FFA during the OLE.
OLE, open-label extension; RCT, randomized controlled trial; STP, stiripentol.

**Figure 2. Median Percentage Change in MCSF From RCT Baseline to OLE (Month 2 through EOS) Following FFA 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.
EOS, end-of-study; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; OLE, open-label extension; RCT, randomized controlled trial; STP, stiripentol.

**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 Without Concomitant STP and B. 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.
EOS, end-of-study; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NS, not significant; OLE, open-label extension; RCT, randomized controlled trial; STP, stiripentol.

## Conclusions

- Patients with DS who are 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 below the patient's effective dose
- 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, 26 mg/d FFA
  - With concomitant STP who weigh ≥42.5 kg, 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

**References**

1. Wirrell EC, et al. *Epilepsia*. 2022;63(7):1761-1777.
2. Harden C, et al. *Neurology*. 2017;88(17):1674-80.
3. UCB, Inc. FINTEPLA® (fenfluramine) oral solution [prescribing information]. Smyrna, GA March 2023.
4. UCB. Fintepla 2.2 mg/mL oral solution [summary of product characteristics]. Bruxelles, BE: UCB;2024.
5. UCB Pharma. Fintepla® (fenfluramine hydrochloride) 2.2 mg/ml oral solution [Australian product information]. Malvern, Australia: UCB Pharma; November 28 2024.
6. UCB Pharma LTD. Fintepla 2.2 mg/ml oral solution [summary of product characteristics]. Slough, Berkshire: UCB Pharma LTD; April 2024.
7. UCB Pharma S.A. 2024. https://israeldrugs.health.gov.il/#!/medDetails/169%2041%2036976%2099.
8. Nippon Shinyaku Co. Ltd. 2022. https://www.nippon-shinyaku.co.jp/file/download.php?file_id=6593.

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