# PL31. Number needed to treat (NNT) with fenfluramine to achieve a clinically meaningful reduction in convulsive seizure frequency in patients with Dravet syndrome

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## Introduction

- Assessments of group responses to placebo and active treatment in clinical antiepileptic drug (AED) trials are regulatory requirements, but decisions in clinical practice are made on an individual-patient basis[1,2]
- Use of number needed to treat (NNT) can assist in translating clinical trial data to clinical practice
- Selecting the right endpoints from which to calculate NNTs is critical for them to be useful in informing individual decision-making

## Objectives

- This post hoc analysis used data from phase 3 and long-term extension studies of fenfluramine for the treatment of Dravet syndrome in pediatric patients (NCT02682927/ NCT02826863, NCT02926898, NCT02823145)[3-5]:
  - To determine clinically meaningful changes in monthly convulsive seizure frequency (MCSF) by evaluating the association between seizure reduction and improvement ratings on the Clinical Global Impression of Change (CGI-I) scale as a metric for determining clinically meaningful changes in MCSF
  - To determine the NNT with fenfluramine to achieve "clinically meaningful" MCSF reductions in a pediatric Dravet syndrome population by CGI-I ratings and performance on the Behavior Rating Inventory of Executive Function (BRIEF®2) assessment[6]

## Methods

- Both the CGI-I ratings and BRIEF®2 index score changes were used to define clinically meaningful changes in MCSF
- Statistical approaches were used to determine which degree of change in MCSF correlated with those definitions of clinically meaningful improvement

### Clinical Instruments in the Post Hoc Analysis

- **Investigator and caregiver ratings on the Clinical Global Impression of Improvement (CGI-I) scale**
  - 7-point Likert scale: with responses ranging from 1 ("Very Much Improved") to 7 ("Very Much Worse") relative to Time 0
  - Clinically meaningful response was defined as "Very Much Improved" (score of 1) or "Much Improved" (score of 2)
  - Profound response was defined as "Very Much Improved" (score of 1)
- **Behavior Rating Inventory of Executive Function (BRIEF®; updated to BRIEF®2)[6]**
  - Assessed executive function at pre-randomization baseline and impact of treatment after treatment Year 1 in patients ≥5 years old
  - Validated, standardized psychometric assessment questionnaire for quantifying executive function (Emotion, Behavior, and Cognition).
  - Metrics: Behavior Regulation Index (BRI); Emotion Regulation Index (ERI); Cognitive Regulation Index (CRI); Global Executive Composite (GEC)

### Post Hoc Assessments

- Degree of seizure frequency reduction that was associated with qualitative improvement assessed by CGI-I ratings after 14 weeks of treatment (Study 1 and Study 2 data)
  - Calculated NNT to achieve the resultant degree of MCSF reduction in one treated patient
- Proportion of patients with (1) profound (≥75%) or (2) minimal (<25%) reduction in seizure frequency and ≥10-point improvement in BRIEF®2 Index scores after Year 1 of treatment (Study 1503 data)
  - Calculated NNT to achieve one instance of ≥75% reduction in MCSF after Year 1 of the open-label extension (OLE)

### Statistical Analysis

- Receiver operator characteristic (ROC) analysis[7,8]
  - Anchor-based analysis based on investigator and caregiver ratings on the CGI-I scale
  - Independent variable: percentage change in seizure frequency per 28 days between baseline and end of combined titration and maintenance periods
  - Dependent variable: 3 types of binary CGI-I ratings
    - "Much Improved" or better vs "Minimally Improved" or worse (most consistent with a clinically meaningful change)
    - "Very Much Improved" vs "Much Improved" or worse
  - The threshold for achieving clinically meaningful MCSF reduction was defined as the cut point for which specificity ≈ sensitivity[7]
- BRIEF®2 analysis
  - Reliable Change Index (RCI) was used to determine the magnitude of the change in BRIEF®2 scores that would be outside "normal," defined as a change in T-score that is observed in ≤5% of a large (N=3600) neurotypical normative population (defined as ≥10-point improvement)
  - The proportion of patients with clinically meaningful ≥10-point improvement in BRIEF®2 Index scores (Behavior, Emotion, Cognition, Global) among improvers and non-improvers was assessed by comparing patients with <25% (minimal) vs ≥75% (profound) MCSF reduction via 2-sided Mann-Whitney U test
- NNT calculations (**Table 1**)[9]
  - 1/(Experimental Rate-Control Rate)
  - NNT can be interpreted by relating the effect size of an intervention (Cohen's d) to the number of patients who would need to receive this intervention to achieve a predefined response rate
  - In **Table 1**, Cohen's d is calculated using the difference in seizure frequency between placebo- and fenfluramine-treated groups over pooled standard deviations

**Table 1. NNT Interpretation[9]**

| NNT | Cohen's d[a] | Effect Size |
|---|---|---|
| 1 | – | Perfect[b] |
| 3 | 0.8 for NNT=2.3 | Large |
| 4 | 0.5 for NNT=3.6 | Medium |
| 9 | 0.2 for NNT=8.96 | Small |

[a]Cohen's d is an effect size metric that expresses differences among treatment groups in units of standard deviation (ie, difference in seizure frequency between placebo- and fenfluramine-treated groups over pooled standard deviations).
[b]NNT of 1 occurs only if an intervention has a rate of 100% for the outcome measured compared to a rate of 0% for the comparator intervention (ie, treatment vs placebo).

## Results

### Patients at Times of Analysis

- Of 119 total patients in Study 1 with MCSF data at Visit 12 (~Week 14), corresponding CGI-I data were available for 112 caregivers and 114 investigators
- 53 patients in the OLE had completed ≥1 year of FFA and had both pre-randomization baseline and Year 1 BRIEF®2 data when this analysis was performed

### Clinically Meaningful Change in Seizure Frequency Based on CGI-I Ratings

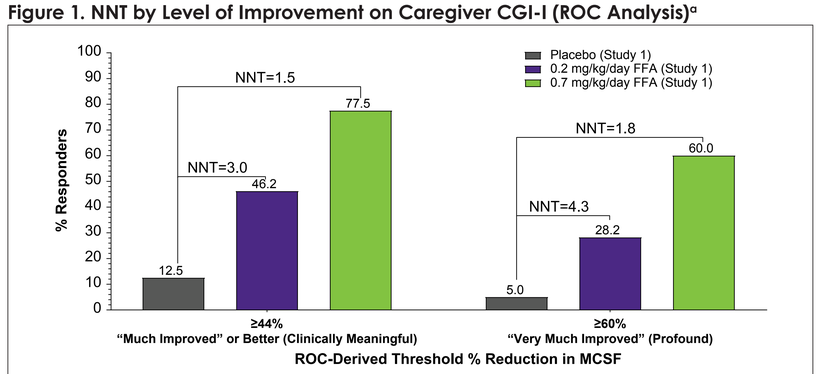
### ROC-Derived Thresholds for Clinically Meaningful Change in Seizure Frequency at Week 14 (Table 2; Figure 1)

**Table 2. NNT Analysis Using ROC-Derived MCSF Cut Points at Week 14**

| CGI-I Category | Change in MCSF Cut Point (%) | % Responders at MCSF Threshold (mg/kg/day FFA) | | |
|---|---|---|---|---|
| | | Placebo | 0.2 | 0.7 |
| **Investigator Assessment of CGI-I** | | | | |
| Very Much Improved (profound) | -68 | 5.0 | 25.6 | 52.5 |
| Much Improved or better (clinically meaningful) | -44 | 12.5 | 46.2 | 77.5 |
| **Caregiver Assessment of CGI-I** | | | | |
| Very Much Improved (profound) | -60 | 5.0 | 28.2 | 60.0 |
| Much Improved or better (clinically meaningful) | -44 | 12.5 | 46.2 | 77.5 |

CGI-I, Clinical Global Impression of Improvement; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NNT, number needed to treat; ROC, receiver operator characteristic.

**Figure 1. NNT by Level of Improvement on Caregiver CGI-I (ROC Analysis)[a]**



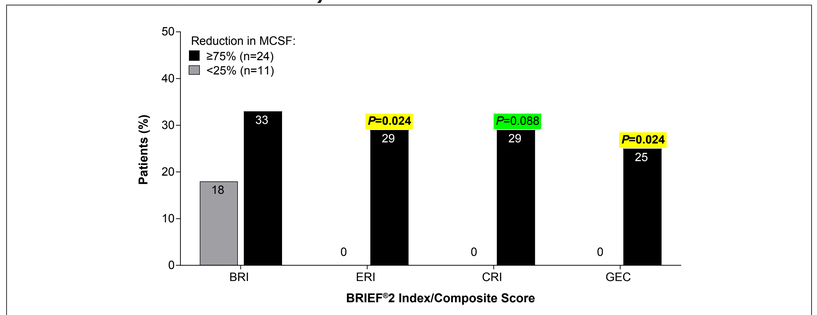

[a]Results for the investigator-rated CGI-I scores were comparable to the caregiver-rated CGI-I scores (see **Table 2**).
CGI-I, Clinical Global Impression of Improvement Scale; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NNT, number needed to treat; ROC, receiver operator characteristic.

### Clinically Meaningful Change in Seizure Frequency Based on Improvement in Executive Functions

### Comparison of Profound (≥75%) vs Minimal (<25%) MCSF Reduction and BRIEF® Scores at Year 1

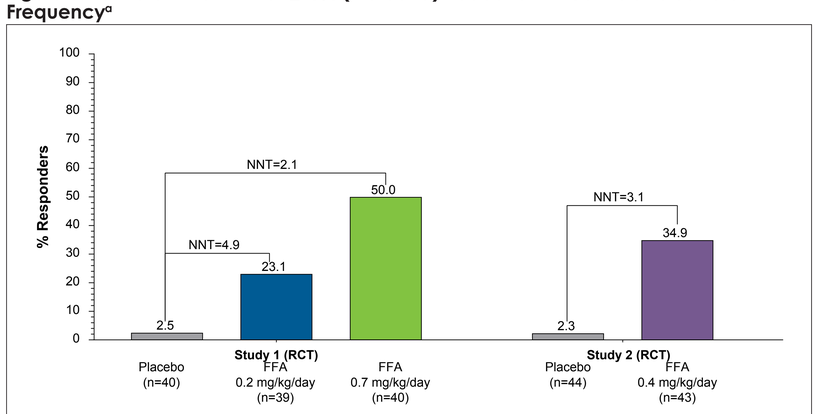
- In a pooled analysis of active and placebo subjects at Year 1, more patients (n=24/53; 45%) achieved profound (≥75%) vs minimal (<25%) levels of MCSF reduction (n=11/53; 21%)
- A significantly higher percentage of patients in the profound (≥75%) responder group experienced significant, clinically meaningful improvement in ERI and GEC scores, with a trend toward improvement in CRI scores (**Figure 2**)
- Profound (≥75%) MCSF reduction corresponded with NNT of 2 to achieve these levels for patients receiving fenfluramine 0.7 mg/kg/day. In a second RCT (Study 2, with adjunctive FFA in patients taking stiripentol),[5] NNT of 3 was found at the ≥75% responder level (**Figure 3**)

**Figure 2. Proportion of Patients With Significant, Clinically Meaningful Improvement (>95% RCI = ≥10-Point Change in T-Scores) in BRIEF®2[a] Index/Composite Scores (Pre-Randomization Baseline to Year 1)**




[a]Test statistics were not corrected for ties. Grouping variable: change in MCSF <25% vs ≥75%.
BRI, Behavior Regulation Index; CRI, Cognitive Regulation Index; ERI, Emotion Regulation Index; GEC, Global Executive Composite score; MCSF, monthly convulsive seizure frequency; RCI, Reliable Change Index.

**Figure 3. Fenfluramine NNT for ≥75% (Profound) Reduction in Convulsive Seizure Frequency[a]**




[a]For purposes of comparison, data from the second pivotal RCT (Study 2) are presented.[5]
FFA, fenfluramine; NNT, number needed to treat; RCT, randomized controlled trial.

## Conclusions

- NNTs based on clinically meaningful endpoints provide complementary information to group mean changes often reported in clinical trials in understanding the efficiency of a treatment to achieve this level of results
- For every 2 to 3 patients with Dravet syndrome treated with fenfluramine, 1 patient achieved ≥50% or ≥75% MCSF reduction compared with placebo (large treatment effect size; Cohen's d≈0.8)
- FFA's NNT results compare favorably to similar studies of other therapies in Dravet syndrome (NNT of 4 to 6 for ≥50% response)[10-12] and other forms of refractory epilepsy (NNT of 8 to 20 for ≥50% response in a systematic review of 70 RCTs)[13]
- Lower NNTs for a given treatment translate into fewer non-responders and lower associated burden on patients and their families

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