102472. Number needed to treat (NNT) with fenfluramine to achieve a clinically meaningful reduction in convulsive seizure frequency in patients with Dravet syndrome: Health economic implications

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Introduction

- Families of patients with Dravet syndrome experience substantial financial and humanistic burdens[1,2]
  - Unpredictability and severity of seizures disrupt family life and require frequent medical care and expenses
  - Patients experience moderate to severe intellectual disability in adulthood, requiring caregivers to invest time and financial resources into healthcare and other services throughout the patient's lifetime
- Ideal treatment strategies
  - Optimize both reduction in seizure frequency and clinically meaningful improvements in patient quality of life that ease caregiver burden

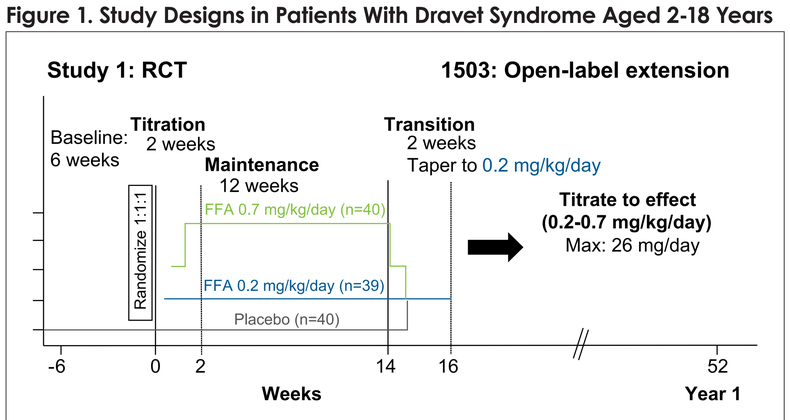
Objectives

- To determine the number needed to treat (NNT) with adjunctive fenfluramine to achieve "clinically meaningful" reductions in monthly convulsive seizure frequency (MCSF)

Methods

Primary Data: Study 1 (NCT02682927/NCT02826863) and Study 1503 (NCT02823145) (Figure 1)[3,4]

Figure 1. Study Designs in Patients With Dravet Syndrome Aged 2-18 Years



FFA, fenfluramine; RCT, randomized controlled trial.

- Fenfluramine (FFA) was administered as ZX008, an oral solution of FFA HCl containing 2.2 mg/mL FFA
- Caregivers recorded numbers/types of seizures in a daily diary; seizure frequency was converted to MCSF (seizure frequency per 28 days)

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)[5,6]**
  - 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, including metrics for ability to regulate and manage behavior, emotion, and cognitive processes such as problem-solving, as well as a summary score incorporating all indexes
  - 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 data)
  - Calculated NNT to achieve the resultant degree of MCSF reduction
- 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 ≥75% reduction in MCSF after Year 1 of the open-label extension (OLE)

Statistical Analysis

- Receiver operator characteristic (ROC) analysis[7]
  - 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 the combined titration and maintenance periods
  - Dependent variable: 3 types of binary CGI-I ratings
    - "Minimally Improved" or better vs "No Change" or worse
    - "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 was defined as the cut point for which specificity ≈ sensitivity[7]
- BRIEF® analysis
  - Raw BRIEF® scores were updated to BRIEF®2 scores and were transformed into T-scores based on age- and sex-specific norms, with lower scores corresponding with better executive functioning
  - 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% (negligible) vs ≥75% (profound) MCSF reduction via 2-sided Mann-Whitney U test
- NNT calculations (**Table 1**)
  - 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[8]

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

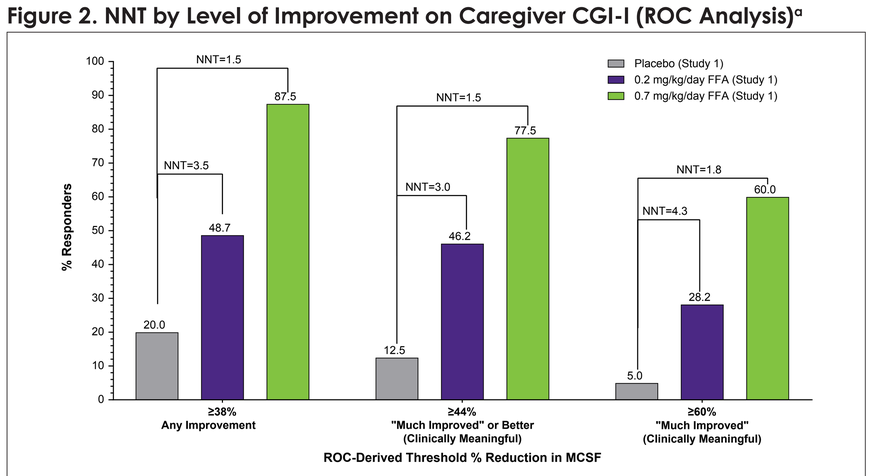
- A ≥44% reduction in MCSF was identified as the cut point for a clinically meaningful change in seizure frequency based on both investigator and caregiver CGI-I ratings of "Much Improved" or better
  - Fenfluramine 0.7 mg/kg/day NNT to achieve this level of response was 2 (**Table 2**; **Figure 2**)
- The cut points for profound reductions in MCSF were ≥67.5% (investigators) and ≥60% (caregivers) based on CGI-I ratings of "Very Much Improved" (**Table 2**; **Figures 2 and 3**)
  - Fenfluramine 0.7 mg/kg/day NNT was 2 to achieve this level of response (**Table 2**)

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

CGI-I Category	Change in MCSF Cut Point (%)	Sensitivity (%)	Specificity (%)	Correct (%)	% Responders at MCSF Threshold (mg/kg/day FFA)			NNT (mg/kg/day FFA)	
					Placebo	0.2	0.7	0.2	0.7
Investigator Assessment of CGI-I									
Very Much Improved (profound)	**-68**	**82**	**81**	**82**	**5.0**	**25.6**	**52.5**	**5**	**2**
Much Improved or better (clinically meaningful)	**-44**	**76**	**75**	**75**	**12.5**	**46.2**	**77.5**	**3**	**2**
Minimally Improved or better	-37	72	72	72	25.0	51.3	87.5	4	2
Caregiver Assessment of CGI-I									
Very Much Improved (profound)	**-60**	**75**	**77**	**77**	**5.0**	**28.2**	**60.0**	**4**	**2**
Much Improved or better (clinically meaningful)	**-44**	**76**	**74**	**75**	**12.5**	**46.2**	**77.5**	**3**	**2**
Minimally Improved or better	-38	70	67	69	20.0	48.7	87.5	3	1.5

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

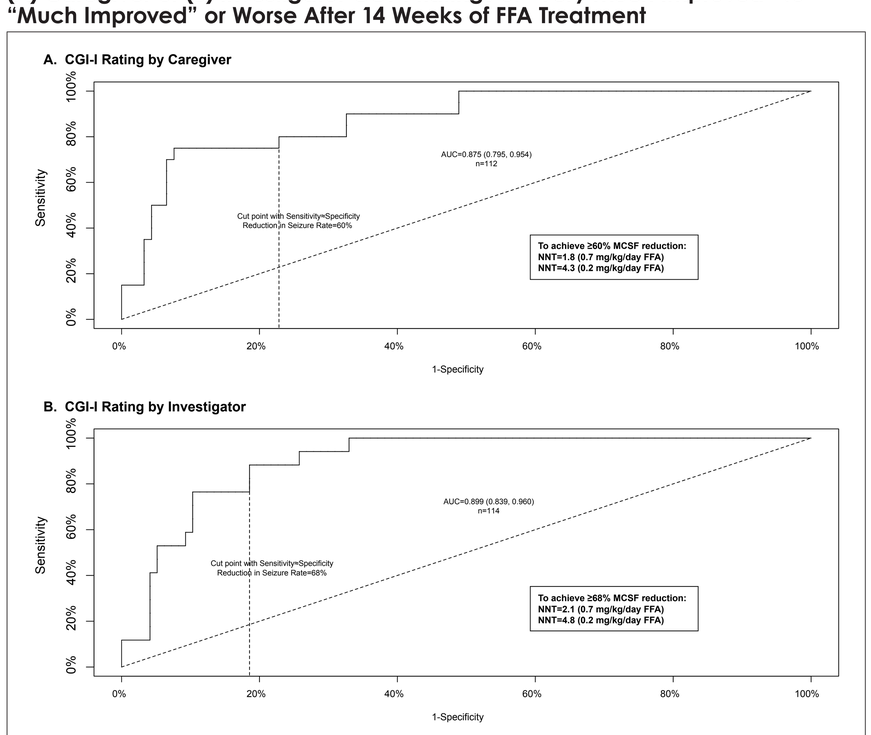
Figure 2. NNT by Level of Improvement on Caregiver CGI-I (ROC Analysis)[a]



[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; OLE, open-label extension; ROC, receiver operator characteristic.

Figure 3. ROC Curve: Percentage Change in Seizure Frequency Relative to (A) Caregiver or (B) Investigator CGI-I Ratings of "Very Much Improved" vs "Much Improved" or Worse After 14 Weeks of FFA Treatment



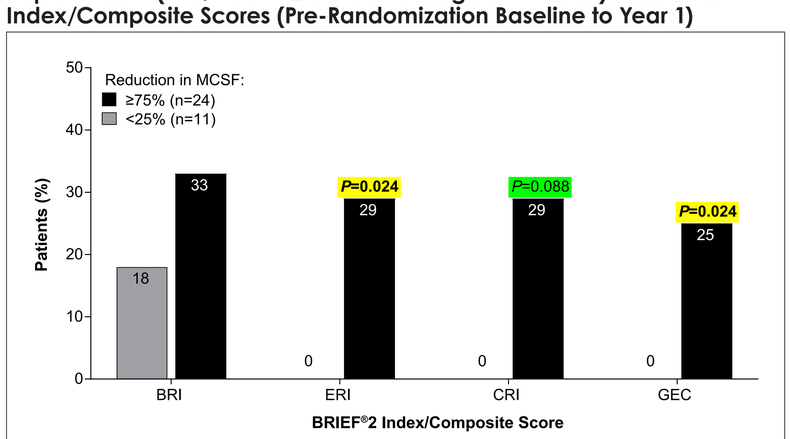
AUC, area under the curve; CGI-I, Clinical Global Impression of Improvement; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NNT, number needed to treat; ROC, receiver operator characteristic.

Profound Reduction (≥75%) in Seizure Frequency and Clinically Meaningful Improvement in Executive Function

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 4**)
- 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 1504, with adjunctive FFA in patients taking stiripentol),[9] NNT of 3 was found at the ≥75% responder level (**Figure 5**)

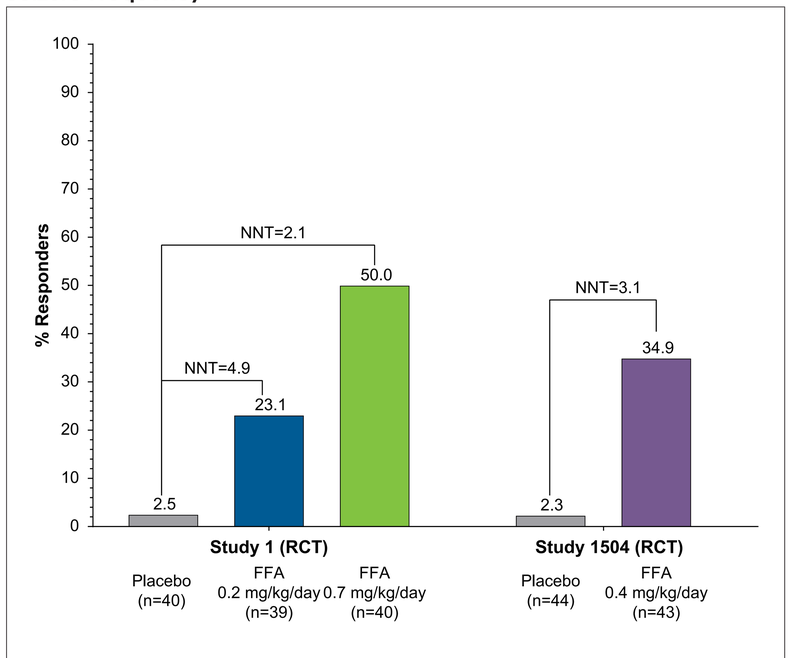
Figure 4. Proportion of Patients With Significant, Clinically Meaningful Improvement (>95% RCI = ≥10-Point Change in T-Scores) in BRIEF®2[a] Index/Composite Scores (Pre-Randomization Baseline to Year 1)



[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; NNT, number needed to treat; NS, not statistically significant; RCI, Reliable Change Index.

Figure 5. Fenfluramine NNT for ≥75% (Profound) Reduction in Convulsive Seizure Frequency[a]



[a]For purposes of comparison, data from the second pivotal RCT (Study 1504) are presented.[9]

FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NNT, number needed to treat; OLE, open-label extension; RCT, randomized controlled trial.

Conclusions

- Fenfluramine treatment (0.7 mg/kg/day) resulted in an NNT of 2 (large effect size) to achieve both clinically meaningful (≥50%) and profound (≥75%) reductions in convulsive seizure frequency
  - A profound (≥75%) reduction was also associated with clinically meaningful improvement in executive functions after 1 year of treatment
- These NNT results are superior to other studies in both Dravet syndrome and other forms of epilepsy where antiepileptic drugs typically have demonstrated NNT of 5 to 6 for ≥50% response[10-13]
- Treatment with an NNT of 2 likely translates into fewer non-responders and lower associated costs of uncontrolled epilepsy, which include additional healthcare resource utilization (eg, doctor visits, emergency room visits, adjustment of treatment regimen)

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