Number Needed to Treat (NNT) With FINTEPLA (Fenfluramine) to Achieve a Clinically Meaningful Reduction in Convulsive Seizure Frequency in Patients With Dravet Syndrome: Patient Care and Health Economic Implications

Joseph Sullivan,[1] Dennis Dlugos,[2] Rima Nabbout,[3] Mercedes Maruscak,[4] Gail Farfel,[4] Bradley Galer,[4] Arnold Gammaitoni[4]

[1]University of San Francisco Weill Institute for Neurosciences, CA, USA; [2]Children's Hospital of Philadelphia, PA, USA; [3]Hôpital Universitaire Necker-Enfants Malades, Paris, FR; [4]Zogenix, Inc., Emeryville, CA, USA

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
- Use of number needed to treat (NNT) can assist in translating clinical trial data to clinical practice and can be useful in making decisions based on pharmacoeconomic concerns[3,4]
- Selecting the right endpoints from which to calculate NNTs is critical for them to be useful in informing individual decision-making from both clinical practice and payer perspectives

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)[5-7]:
  - 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 Improvement (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[8]

Methods

- Both 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)[8]**
  - 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 data)
  - Calculated NNT to achieve the resultant degree of MCSF reduction in one treated patient
- Proportion of patients with (1) profound (≥75%) or (2) negligible (<25%) reduction in seizure frequency and improvement in BRIEF®2 Index scores after Year 1 of treatment (Study 1503 data) as defined by Reliable Change Index (RCI) ≥95% certainty relative to a reference population of neurotypically developing healthy volunteers
  - Clinically meaningful changes in BRIEF®2 scores were defined using RCI (≥95% certainty) scores for BRI, ERI, CRI, and GEC as reported in the BRIEF®2 manual; RCI values take into account the standard error of measurement at each testing time and its respective standard deviation and are used to establish confidence intervals at different levels of certainty

Statistical Analysis

- Receiver operator characteristic (ROC) analysis[9,10]
  - 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: 2 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
  - The proportion of patients with clinically meaningful improvement in BRIEF®2 scores (Behavior, Emotion, Cognition, Global) among improvers and non-improvers was assessed by comparing patients with <25% (negligible) vs ≥75% (profound) MCSF reduction; clinically meaningful improvement in everyday executive function was defined using RCI values ≥95% certainty
- NNT calculations (**Table 1**)[11]
  - 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[11]

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
- 58 patients in the open-label extension (OLE) had completed ≥1 year of fenfluramine (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

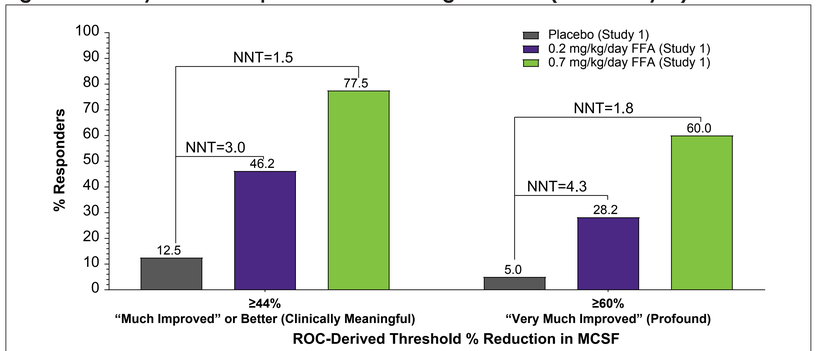
ROC-Derived Thresholds for Clinically Meaningful Change in Seizure Frequency at Week 14 (Table 2; Figure 1)

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]



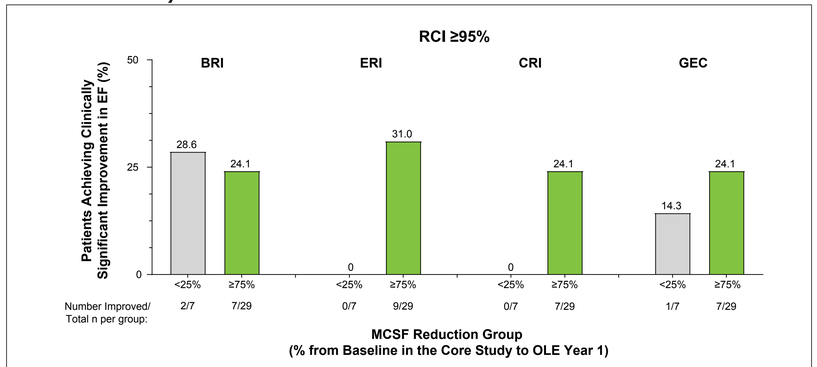
[a]Results for the investigator-rated CGI-I scores were comparable to the caregiver-rated CGI-I scores (see **Table 2**).
CGI-I, Clinical Global Impression of Improvement Scale; FFA, fenfluramine; MCSF, monthly convulsive seizure frequency; NNT, number needed to treat; ROC, receiver operator characteristic.

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

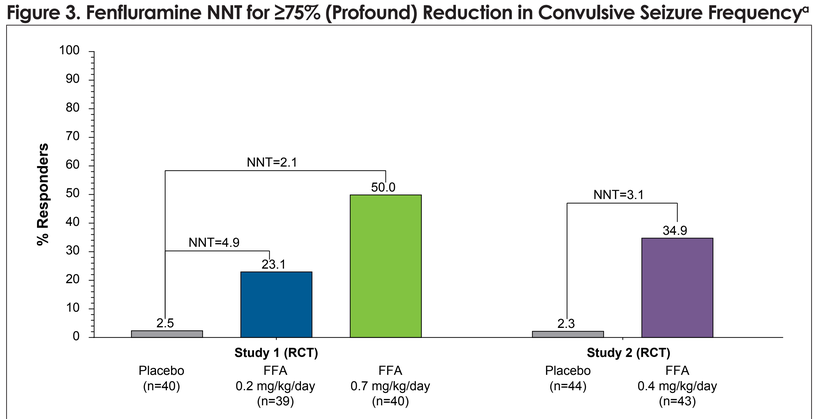
- In a pooled analysis of active and placebo subjects at Year 1, more patients (n=29/58; 50%) achieved profound (≥75%) vs minimal (<25%) levels of MCSF reduction (n=7/58; 12%)
- Proportionately more patients in the profound (≥75%) responder group experienced clinically meaningful improvement in ERI, CRI, and GEC 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),[7] NNT of 3 was found at the ≥75% responder level (**Figure 3**)

Figure 2. Proportion of Patients With Significant, Clinically Meaningful Improvement (defined by RCI ≥95% certainty) in BRIEF®2[a] Index/Composite Scores (Pre-Randomization Baseline to Year 1)



BRI, Behavior Regulation Index; BRIEF®2, Behavior Rating Inventory of Executive Function; CRI, Cognitive Regulation Index; EF, executive function; ERI, Emotion Regulation Index; GEC, Global Executive Composite score; MCSF, monthly convulsive seizure frequency; OLE, open-label extension; 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.[11]
FFA, fenfluramine; NNT, number needed to treat; RCT, randomized clinical trial.

Conclusions

- NNTs based on clinically meaningful endpoints provide complementary information to group mean changes often reported in clinical trials for understanding the efficiency of a treatment to achieve this level of improvement
- For every 2 to 3 patients with Dravet syndrome treated with fenfluramine compared with placebo, 1 patient achieved ≥50% or ≥75% MCSF reduction (large treatment effect size; Cohen's d≈0.8)
- NNT results for FFA compare favorably to similar studies of other therapies in Dravet syndrome (NNT of 4 to 6 for ≥50% response)[12-14] and other forms of refractory epilepsy (NNT of 8 to 20 for ≥50% response in a systematic review of 70 RCTs)[15]
- Published average annual healthcare utilization costs for DS are ~$27,276 plus ≥$80,000 (indirect)[2]
- An NNT=2 to achieve clinically meaningful outcomes may have important positive health economic implications for both payers and patients/caregivers vs currently available treatment options

References

1. Jensen MP, et al. *Epilepsy Behav.* 2017;70(Pt A):104-9.
2. Whittington MD, et al. *Epilepsy Behav.* 2018;80:109-13.
3. Mohanraj R, Brodie MJ. *Seizure.* 2003;12(7):413-43.
4. Perucca E. *Pharm World Sci.* 1997;19(5):217-22.
5. Lagae L, et al. *Lancet.* 2019;394(10216):2243-54.
6. Sullivan J, et al. *Epilepsia.* 2020;61(11):2396-404.
7. Nabbout R, et al. *JAMA Neurol.* 2020;77(3):300-08.
8. Bishop K, et al. American Epilepsy Society 2019.
9. Farrar JT, et al. *J Pain.* 2010;11(12):109-18.
10. Terluin B, et al. *J Clin Epidemiol.* 2017;83:90-100.
11. Citrome L. *Innov Clin Neurosci.* 2014;11(5-6):26-30.
12. Devinsky O, et al. *N Engl J Med.* 2017;376(21):2011-20.
13. Miller I, et al. *JAMA Neurol.* 2020;77(5):613-21.
14. Moretz D. Salem, OR: Oregon State University College of Pharmacy; 2019 January.
15. Costa J, et al. *Epilepsia.* 2011;52:1280-91.

Acknowledgments

This study was funded by Zogenix, Inc (Emeryville, CA). Zogenix thanks all of the patients, their families, and the investigators involved in this study. Medical writing and editorial assistance were provided by Danielle Ippolito, PhD, CMPP, MWC, and Dolores Matthews, ELS, of PharmaWrite, LLC (Princeton, NJ, USA), and were funded by Zogenix, Inc.

Disclosures

JS: Contracted Research with Stoke, Marinus, Zogenix, and Biopharm. Consultant/advisor: Dravet Syndrome Foundation, Epygenix, Encoded, and Neurocrine; Stock options: Epygenix; Reviewer: Epilepsy Study Consortium; Travel support: Zogenix; **DD:** Salary support: NIH, Pennsylvania Department of Health, Pediatric Epilepsy Research Foundation, Epilepsy Study Consortium; Research support (institution): Aquestive, BioPharm, Brain Sentinel, Encoded, Greenwich, INSYS, Neurelis, Q-State, SK Life Science, UCB, USL, Zogenix; Travel support (protocol development/investigator meetings): Biogen, BioMarin, Marinus, Ovid/Takeda, Pfizer, Ultragenyx, Xenon, Zogenix; Honoraria/travel support (CME/educational): American Academy of Neurology, American Epilepsy Society, Child Neurology Society, Chinese Pediatric Society, Ecuador Neurology Project, Epilepsy Foundation of America, Epilepsy Foundation of North Carolina, Medscape, Miller Medical Communications, Ministry of Health of the United Arab Emirates, Seoul National University, Wake Forest University School of Medicine; **MM, GF, BG, AG:** Employees, Zogenix, Inc; Ownership interest, Zogenix, Inc; **RN:** Research funding, Eisai, GW Pharma, Novartis, Shire, and Zogenix; Consultant/ advisor, Eisai, Biogen, GW Pharma, Novartis, Shire, Zogenix; Speaker, Advicenne, Eisai, BioMarin, GW Pharma, Novartis, Zogenix.

Presented at Academy of Managed Care Pharmacy (AMCP) 2021 Virtual, April 12-16