

221. Quantifying “Clinically Meaningful Changes” in Seizure Frequency—Data from 3 Phase 3 Studies of ZX008 (Fenfluramine Hydrochloride Oral Solution) in Dravet Syndrome: Do Expectations and Views Change Over Time?

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Introduction

- In clinical antiepileptic drug (AED) trials, a $\geq 50\%$ reduction in seizure frequency is conventionally accepted as clinically meaningful¹
- This threshold is largely empirical and has not been tested in a controlled clinical trial setting
- Quantifying a “clinically meaningful” change is complicated by interpatient variability in seizure type and severity, and by level of seizure reduction achieved with AED treatment
- Anchor- and distribution-based methods have been used in other clinical contexts to quantitate clinically important improvements resulting from therapeutic interventions^{2,3}

Objectives

- To examine the degree of seizure frequency reduction associated with caregiver and investigator Clinical Global Impression of Improvement (CGI-I) ratings of “Much Improved” and “Very Much Improved” in randomized controlled trials (RCTs) of fenfluramine for the treatment of Dravet syndrome

Methods

Primary Data

- Investigators performed a post-hoc analysis of data collected during 2 phase 3 RCTs and a long-term open-label extension (OLE) study of adjunctive fenfluramine (FFA) for the treatment of Dravet syndrome⁴⁻⁶
- FFA was administered BID as an oral solution of FFA HCl containing 2.2 mg/mL
- In Study 1, FFA was administered for 14 weeks at a dose of 0.2 mg/kg/day or 0.7 mg/kg/day (maximum daily dose: 26 mg/day)
- In Study 2, FFA was added to stiripentol (STP)-containing AED regimens for 15 weeks at a dose of 0.4 mg/kg/day (maximum daily dose: 17 mg/day)
- Eligible patients from the RCTs entered the OLE (NCT02823145) at 0.2 mg/kg/day and were titrated to effect (0.2-0.7 mg/kg/day)
- Investigator and caregiver ratings on the Clinical Global Impression of Improvement (CGI-I) scale were reported on a 7-point Likert scale
 - Responses ranged from 1 (“Very Much Improved”) to 7 (“Very Much Worse”) relative to prerandomization baseline
 - Clinically meaningful response was defined as 1 (“Very Much Improved”) or 2 (“Much Improved”)

Statistical Analysis³

- The association between change in monthly convulsive seizure frequency (MCSF) and CGI-I score for individual patients was assessed by receiver operator characteristic (ROC) analysis
 - Independent variable: percent change in seizure frequency per 28 days between baseline and the end of combined titration and maintenance periods at Week 14 or 15
 - 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 clinically meaningful threshold was defined as the cutpoint for which specificity was approximately equal to sensitivity

Results

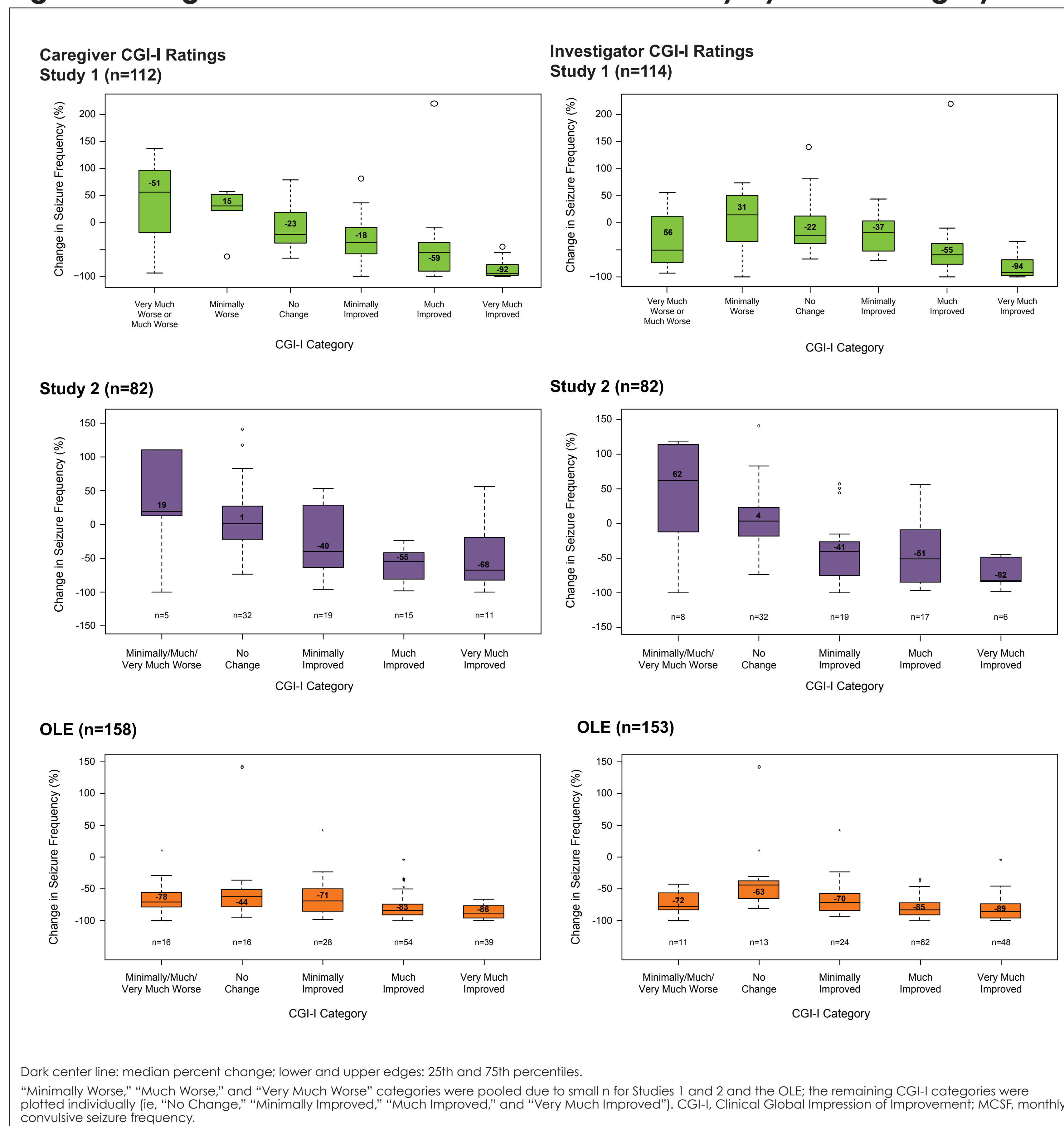
Patients

- Of 206 patients in the RCTs, CGI-I rating assessments at baseline and Week 14 or 15 were available from a total of 114 investigators and 112 caregivers in Study 1 and from 82 investigators and caregivers in Study 2
- Of 330 patients in the OLE, CGI-I rating assessments were available from 153 caregivers and 158 investigators

Associations Between CGI-I and Percent Reduction in MCSF

- The relationship between percent reduction in seizure frequency and caregivers’ and investigators’ CGI-I ratings appeared to be more linear in the RCTs vs the OLE (**Figure**)

Figure. Change in MCSF from baseline to end of study by CGI-I category



ROC-Derived Analyses for Clinically Meaningful Reduction in MCSF

- ROC analysis identified cutpoints of $\geq 44\%$ and $\geq 37.5\%$ in the RCTs vs $\geq 78\%$ - 80% in the OLE as the threshold for a “clinically meaningful change” for caregiver and investigator CGI-I ratings (**Table**)

Table. Receiver Operator Characteristic Analysis

| CGI-I Category | Change in MCSF Cutpoint (%) | | |
|---|-----------------------------|---------|-----|
| | Study 1 | Study 2 | OLE |
| Caregiver | | | |
| Very Much Improved | -60 | -50 | -84 |
| Much Improved or better (clinically meaningful) | -44 | -37.5 | -80 |
| Minimally Improved or better | -38 | -19.5 | -77 |
| Investigator | | | |
| Very Much Improved | -67.5 | -40 | -82 |
| Much Improved or better (clinically meaningful) | -44 | -37.5 | -78 |
| Minimally Improved or better | -36.5 | -20 | -76 |

Red, bold text indicates clinically meaningful change; CGI-I, Clinical Global Impression of Improvement; MCSF, monthly convulsive seizure frequency; OLE, open-label extension.

Conclusions

- Major differences were found in cutpoints between the 2 RCTs and the OLE, suggesting that both caregiver and investigator views regarding MCSF reduction and ratings of “Much Improved” or “Very Much Improved” may change over long periods of time
 - Cutpoints for “clinically meaningful change” were $\geq 44\%$ and $\geq 37.5\%$ MCSF reduction in the RCTs vs $\geq 78\%$ - 80% MCSF reduction in the OLE
 - This difference may be related to changing expectations of drug effect on the part of caregivers and investigators
 - For example, a treatment that can provide a high degree of seizure frequency reduction for long periods of time may change expectations for the amount of efficacy deemed to be “Much Improved” or better
 - Other factors may include non-seizure effects, tolerability, and differences between OLE and RCT study designs
 - In addition, with strong improvements predominating, the extremely narrow distribution of change in seizure frequency in the OLE severely limits the statistical power to detect any (pairwise) associations involving this quantity⁷
- Another explanation for this discrepancy may be changes in response to the medication
 - Delayed or new improvements seen over time, such as in comorbidities
 - Improvement in or resolution of side effects over time

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