Non-Seizure and Seizure Benefits Associated With the Use of Fintepla® (Fenfluramine HCl Oral Solution) in a Subgroup of Dravet Syndrome Patients Participating in a Phase 3 Study: Interim Findings of a Survey of Investigators

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INTRODUCTION

- Dravet syndrome (DS) is a rare, treatment-resistant epilepsy syndrome with an age of onset of 1 to 18 months[1-3]
- DS results in developmental delays, behavioral issues, and impairment in cognitive, motor, communication, language, and physical domains[4-8]
- In a recent survey, more than 75% of caregivers reported substantial concerns and challenges with non-seizure comorbidities in DS[8]
- In a recently completed phase 3 study, clinically meaningful improvement was observed in the Behavior Regulation and Emotion Regulation Indices on the Behavior Rating Inventory for Executive Function (BRIEF®2) in the fenfluramine (FFA) treatment group relative to placebo controls ($P<0.02$)

OBJECTIVE

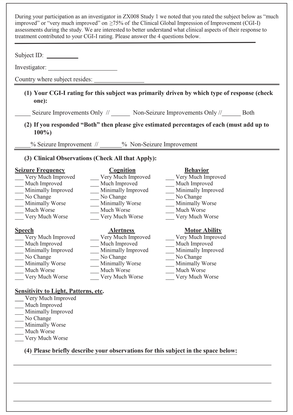
- To examine non-seizure outcomes in a subgroup of 34 children and adolescents who were treated with adjunctive FFA for >14 weeks and rated by investigators as "Much Improved" or "Very Much Improved" during the study

METHODS

Study Design

- Patients who received FFA in studies NCT02682927, NCT02826863, and NCT02823145 and were rated by the investigator as being "Much Improved" or "Very Much Improved" on the Clinical Global Impression of Improvement (CGI-I) scale for at least 75% of the ratings throughout the study were identified
- Investigators were contacted via e-mail and asked to complete a short survey for the identified patients (**Figure 1**). Responses were captured using an electronic data capture system
  - Survey assessed non-seizure and seizure outcomes (using a 7-point Likert Scale) and included an open-ended section for recording clinical observations

Figure 1. Investigator Survey



During your participation as an investigator in ZX008 Study 1 we noted that you rated the subject below as "much improved" or "very much improved" on ≥75% of the Clinical Global Impression of Improvement (CGI-I) assessments during the study. We are interested to better understand what clinical aspects of their response to treatment contributed to your CGI-I rating. Please answer the 4 questions below.

Subject ID: _____

Investigator: _____

Country where subject resides: _____

(1) Your CGI-I rating for this subject was primarily driven by which type of response (check one):

_____ Seizure Improvements Only // _____ Non-Seizure Improvements Only // _____ Both

(2) If you responded "Both" then please give estimated percentages of each (must add up to 100%)

_____% Seizure Improvement // _____% Non-Seizure Improvement

(3) Clinical Observations (Check All that Apply):

Seizure Frequency	Cognition	Behavior
___ Very Much Improved	___ Very Much Improved	___ Very Much Improved
___ Much Improved	___ Much Improved	___ Much Improved
___ Minimally Improved	___ Minimally Improved	___ Minimally Improved
___ No Change	___ No Change	___ No Change
___ Minimally Worse	___ Minimally Worse	___ Minimally Worse
___ Much Worse	___ Much Worse	___ Much Worse
___ Very Much Worse	___ Very Much Worse	___ Very Much Worse

Speech	Alertness	Motor Ability
___ Very Much Improved	___ Very Much Improved	___ Very Much Improved
___ Much Improved	___ Much Improved	___ Much Improved
___ Minimally Improved	___ Minimally Improved	___ Minimally Improved
___ No Change	___ No Change	___ No Change
___ Minimally Worse	___ Minimally Worse	___ Minimally Worse
___ Much Worse	___ Much Worse	___ Much Worse
___ Very Much Worse	___ Very Much Worse	___ Very Much Worse

Sensitivity to Light, Patterns, etc.

___ Very Much Improved
___ Much Improved
___ Minimally Improved
___ No Change
___ Minimally Worse
___ Much Worse
___ Very Much Worse

(4) Please briefly describe your observations for this subject in the space below:

_____

_____

_____

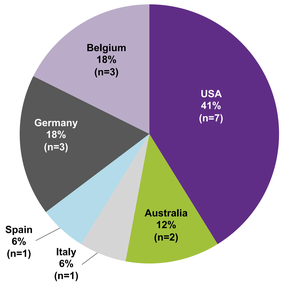
_____

RESULTS

Investigators and Patients

- As of November 1, 2018, 17 of 34 surveys had been completed by investigators
- The 17 patients included in this analysis are from 11 study sites covering 6 countries (**Figure 2**)

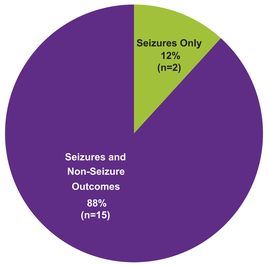
Figure 2. Geographic Distribution of Study Patients (N=17)



The Distribution of Non–Seizure- and Seizure-Related Outcomes Contributing to Investigator Ratings of "Much Improved" or "Very Much Improved"

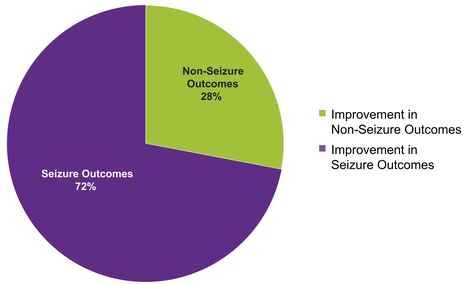
- When asked if their reasoning for rating their patients "Much Improved" or "Very Much Improved" was based on non-seizure improvements only, seizure improvements only, or both, most investigators cited both (88%; n=15/17 patients) (**Figure 3**)

Figure 3. Primary Drivers for Investigator Ratings of "Much Improved" or "Very Much Improved" on CGI-I



- Investigators who responded "both" were then asked to assign a relative weighting as to the contribution of non–seizure- and seizure-related outcomes (**Figure 4**)

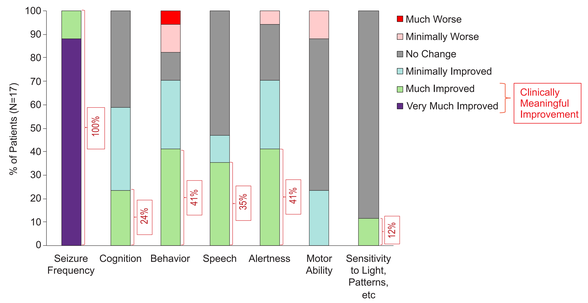
Figure 4. Relative Contribution of Non–Seizure- and Seizure-Related Outcomes When Both Were Drivers for Investigator Ratings of "Much Improved" or "Very Much Improved" (n=15)



CGI-I After FFA Treatment

- Between 12% (n=2) and 41% (n=7) of patients showed clinically meaningful improvement in non–seizure-related outcomes except motor ability (**Figure 5**)
  - One patient (6%) showed a rating of "Much Worse" for behavior

Figure 5. Investigator Global Ratings of Non-Seizure and Seizure Outcomes*



*No investigator noted "Very Much Worse" for any outcomes.

- When asked to briefly describe their clinical observations of the patient, improvements in behavior, speech, cognition, alertness, and learning ability were noted by the majority of investigators (n=12 patients; 71%) (**Table 1**)

Table 1. Clinical Observations of Improvements in Non–Seizure-Related Outcomes After Treatment With FFA

Non–Seizure-Related Outcome	Clinical Observations
Learning	• Marked decrease in school days missed secondary to seizures • Total IQ (evaluated with standardized scale) improved • Better able to learn/more curious at home • Started reading during the study
Behavior	• Less hyperactivity, sitting for longer periods • Increased ability to manipulate environment with decreased perseveration behavior • Improvements in behavior noted by school teacher and nurse • Better self-control • More interaction and own will
Alertness	• More alert during day • More alert and engaged
Cognition/Executive Function	• Noted subjective improvements in speech/cognition • Much better attention and improvement in speech • School noted improvement in cognition

IQ, intelligence quotient.

CONCLUSIONS

- Both non–seizure- and seizure-related outcomes contributed to the investigators rating their patients as "Much Improved" or "Very Much Improved" on CGI-I
- Approximately 25%-40% of the patients in this subset analysis had clinically meaningful improvements in cognition, behavior, speech, and alertness
- FFA may be an important new treatment option for DS to effectively manage seizure and non-seizure outcomes and improve patient quality of life

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DISCLOSURES

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