Impact of fenfluramine on the expected SUDEP mortality rates in patients with Dravet syndrome

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ABSTRACT

Purpose: To assess the impact of fenfluramine (FFA) on the expected mortality incidence, including sudden unexpected death in epilepsy (SUDEP), in persons with Dravet syndrome (DS).

Methods: In this pooled analysis, total time of exposure for persons with DS who were treated with FFA in phase 3 clinical trials, in United States and European Early Access Programs, and in two long-term open-label observational studies in Belgium was calculated. Literature was searched for reports of SUDEP mortality in DS, which were utilized as a comparison. Mortality rates were expressed per 1000 person-years.

Results: A total of 732 persons with DS were treated with FFA, representing a total of 1185.3 person-years of exposure. Three deaths occurred, all in the phase 3 program: one during placebo treatment (probable SUDEP) and two during treatment with FFA (one probable SUDEP and one definite SUDEP). The all-cause and SUDEP mortality rates during treatment with FFA was 1.7 per 1000 person-years (95% CI, 0.4 to 6.7), a value lower than the all-cause estimate of 15.8 per 1000 person-years (95% CI, 9.9 to 25.4) and SUDEP estimate of 9.3 (95% CI, 5.0 to 17.3) reported by Cooper et al. (Epilepsy Res 2016;128:437) for persons with DS receiving standard-of-care.

Conclusion: All-cause and SUDEP mortality rates in DS patients treated with FFA were substantially lower than in literature reports. Further studies are warranted to confirm that FFA reduces SUDEP risk in DS patients and to better understand the potential mechanism(s) by which FFA lowers SUDEP risk.

Clinical Trial Registration: NCT02926898, NCT02682927, NCT02826863, NCT02823145, NCT03780127.

1. Introduction

Dravet syndrome is a rare, severe, treatment-resistant developmental epileptic encephalopathy with onset in the first year of life in otherwise normal infants. The syndrome is characterized initially by heat- or fever-triggered hemi-clonic and generalized convulsive seizures, often prolonged, during the first year of life, with subsequent development of other seizure types [1, 2]. In addition to high seizure burden, children with Dravet syndrome often develop comorbidities, including motor and speech impairment, learning disabilities, and behavioral problems, including autism, and have a decreased quality of life [2, 3]. Pathogenic variants of SCN1A, which encodes the alpha-1 subunit of the
The phase 3 double-blind, placebo-controlled trials of fenfluramine (FFA) added to patients’ anti-epilepsy drug (AED) regimens reported dramatic and sustained reductions in the frequency of major convulsive seizures in patients with Dravet syndrome [15, 16, 17]. These studies also demonstrated up to 80% reduction in GTCS frequency during treatment with FFA [18]. The magnitude and durability of effects of FFA on convulsive seizures, in particular GTCS, suggest that FFA may provide benefit in reducing the incidence of SUDEP in patients with Dravet syndrome. Here we present a post hoc analysis examining all-cause and SUDEP mortality in patients with Dravet syndrome treated with FFA in phase 3 clinical trials, European (EU) and United States (US) Early Access programs (EAPs), and two cohorts of Dravet syndrome patients in Belgium who have been treated with FFA for up to 32 years and compare the findings with the expected incidence of mortality and SUDEP based on published literature.

2. Methods

The incidence of all-cause and SUDEP mortality in persons with Dravet syndrome while treated with FFA was compared to prior published studies of people with Dravet syndrome not treated with FFA. A literature search was conducted to identify published reports of mortality in Dravet syndrome. The search strategy was “Dravet [title] AND (mortality OR death OR SUDEP)”. Titles and abstracts were inspected to identify relevant studies, and the bibliographies of those papers were reviewed for additional reports of mortality studies.

The study population for this analysis comes from four sources: patients participating in the international phase 3 Dravet syndrome clinical trials, patients treated in US and EU EAPs, and two cohorts of patients who participated in a long-term open-label study of FFA spanning 32 years [19–21]. The protocol for each study, including the US EAP and the open-label cohort studies, was reviewed and approved by the appropriate ethics committee. All patients or their caregivers provided written informed consent prior to participation in these studies. The EU EAP was not conducted as a clinical trial; therefore, consent was not required. Screening and enrollment for Studies 1 and 3 began in January 2016. Study 1 was completed in August 2017, and Study 3 was completed in August 2020. Study 2 started enrolling patients in January 2017 and was completed in June 2018. Patients enrolled in the open-label extension (OLE) study at the completion of their double-blind treatment. They enrolled in June 2016, and the most recent interim data analysis was performed on October 14, 2019. The US EAP started enrollment in November 2019, and its final data are from August 20, 2020; the EU EAP began enrollment in December 2018, with the most recent data as of July 31, 2020. The first patient in the Belgian long-term open-label cohort study began treatment in April 1988, and the most recent data summary for this ongoing study was from August 2020.

The phase 3 double-blind studies (Study 1, Study 2, Study 3) enrolled patients aged 2 to 18 years who had a clinical diagnosis of Dravet syndrome, and for whom seizures had not been adequately controlled by their current AEDs or other therapies [15–17]. Each study began with a six-week observation period to establish baseline convulsive seizure frequency; patients who met seizure eligibility requirements were then randomized to treatment with placebo or FFA added to their current anti-epilepsy therapy regimen. In Studies 1 and 3, which excluded patients treated with concomitant stiripentol, patients were randomized 1:1:1 to placebo, FFA 0.2 mg/kg/day, or FFA 0.7 mg/kg/day, with a maximum absolute dose of 26 mg/day. The first cohort of 18 patients in Study 2 participated in a drug-drug interaction protocol and enrolled in the OLE study without randomization. The remaining patients in Study 2, who were required to be treated concomitantly with stiripentol, were randomized 1:1 to placebo or FFA 0.4 mg/kg/day, with a maximum absolute dose of 17 mg/day. Studies 1 and 3 began with a two-week titration period followed by a 12-week maintenance period. In Study 2, titration occurred over three weeks and was followed by a 12-week maintenance period. At the end of each core study, each patient underwent down-titration (or dummy down-titration) to an FFA dose of 0.2 mg/kg/day before entering the OLE study. All patients entering the OLE started FFA at 0.2 mg/kg/day for the first four weeks; thereafter, doses could be titrated based on efficacy and tolerability up to the maximum doses described above. In addition, adult patients (>18 years of age) were allowed to directly enroll into the OLE. Both the US and EU EAPs were compassionate use programs that were open to patients with Dravet syndrome who were not eligible for inclusion in any of the phase 3 clinical trials. The FFA treatment regimen was as described above for the phase 3 program OLE study. Finally, the FFA dosing strategy for patients in the Belgian cohorts was similar to the one employed in the OLE study.

2.1. Analysis

The outcomes of interest were all-cause and SUDEP mortality. Investigators in each of the studies included in this analysis reported all treatment-emergent adverse events to Zogenix. Deaths that were deemed by study investigators to be due to SUDEP were further classified by study authors using the definitions described by Nashef et al. [22], based on the case narratives.

The primary analysis was the calculation of all-cause and SUDEP mortality rates during treatment with FFA. To do this, total person-years of observation during treatment with FFA was determined by summing FFA treatment time for all patients in the four populations included in this analysis. In addition, mortality rates were calculated for patients in the phase 3 program for periods before treatment with FFA was initiated. For this estimate, total patient-years of observation with no exposure to FFA was determined by summing all patients’ time in baseline plus all time spent during randomized controlled trials for those who received placebo. Mortality rates were expressed as deaths per 1000 patient-years of observation, with 95% CIs calculated using conventional methods.

No formal statistical comparisons with historical mortality estimates were conducted. Because of the post hoc nature of this study and the small number of deaths that occurred, no statistical testing of mortality rates with and without FFA treatment was performed. However, estimates of all-cause mortality and SUDEP rates prior to initiation of FFA treatment were used as a “check” to determine if there was an inherent difference in death rates in the patient population coming into these trials, as described in previously published reports.

3. Results

The literature search yielded 84 distinct publications; of these, one was a review article and eight presented population mortality data [7, 11, 23–29]. Studies identified by this search and through inspection of bibliographies are summarized in Table 1. Although each study
We have chosen to use their all-cause mortality rate of 15.8 per 1000 person-years reported Kaplan-Meier survival analysis to estimate mortality rates [7, 11].

**Abbreviations:** EAP, early access program; FFA, fenfluramine.

### Demographic and baseline characteristics.

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<td>Akiyama et al.</td>
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<td>Dravet syndrome</td>
<td>26</td>
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**Table 1**

**Literature reports of mortality in Dravet syndrome.**

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**Table 2**

**Demographic and baseline characteristics.**

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<th>Treatment</th>
<th>N</th>
<th>MF</th>
<th>Age, years, median (min, 25%, 75%, max)</th>
<th>Years of Observation, mean</th>
<th>Person-years of Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>FFA</td>
<td>366</td>
<td>197:169</td>
<td>9 (2, 5, 13, 19)</td>
<td>1.75</td>
<td>602.8</td>
</tr>
<tr>
<td>US EAP</td>
<td>FFA</td>
<td>134</td>
<td>68:66</td>
<td>8(1, 4, 14, 32)</td>
<td>0.68</td>
<td>90.9</td>
</tr>
<tr>
<td>EU EAP</td>
<td>FFA</td>
<td>191</td>
<td>98:93</td>
<td>9 (2, 5, 15, 47)</td>
<td>0.74</td>
<td>141.8</td>
</tr>
<tr>
<td>Belgium</td>
<td>FFA</td>
<td>41</td>
<td>21:20</td>
<td>5(1, 2, 11, 29)</td>
<td>8.53</td>
<td>349.9</td>
</tr>
<tr>
<td>Total</td>
<td>FFA</td>
<td>732</td>
<td>384:348</td>
<td>8 (&lt;1, 5, 14, 47)</td>
<td>1.62</td>
<td>1185.3</td>
</tr>
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**Abbreviations:** EAP, early access program; FFA, fenfluramine.

1. Age is age at study entry, except for the EU EAP, in which age is age at cutoff date for this analysis.
The pathophysiology of SUDEP is not well understood, but research suggests that multiple factors may be involved. Major risk factors for SUDEP include the presence and frequency of GTCS, followed by failure to adequately control seizures [12, 34]. It appears likely that the substantial reduction in convulsive seizure frequency, including GTCS frequency, coupled with significantly prolonged periods of seizure freedom reported in the clinical trials of FFA are the major contributors to the reduction in all-cause and SUDEP mortality reported here [15-17, 35].

Severe peri-ictal respiratory dysfunction is common in Dravet syndrome patients [36] and may also contribute to elevated SUDEP rates. Results of experiments using the DBA/1 mouse model of SUDEP offer some support for a role of FFA. The DBA/1 mice are susceptible to tonic seizures caused by several stimuli that are typically followed by respiratory arrest and death in the post-ictal period [37]. FFA, which acts in part by stimulating neuronal release of serotonin and inhibiting its reuptake, has also been shown to block seizure-induced respiratory arrest in the DBA/1 mouse model of SUDEP at doses without anticonvulsant activity [37]. In the DBA/1 mouse, drugs that enhance serotonin transmission inhibit mortality, and drugs that antagonize serotonin enhance death [37]. Further support for the role of serotonin in SUDEP comes from the observation that 5-hydroxytryptophan, a precursor for serotonin synthesis, reduced seizure-induced respiratory arrest in DBA/1 mice [38]. In the DBA/1 model, FFA prevented death via a specific serotonin receptor, 5HT4, presumably in the brainstem [39].

These results suggest that FFA may protect against SUDEP independent of its anticonvulsant activity in Dravet syndrome patients. FFA also acts as a positive modulator of the sigma 1 receptor [40], and there may be a synergistic interaction between sigma-1 and serotonin receptors, increasing serotonergic neuronal firing [41]. This interaction may contribute to the low mortality and SUDEP incidence observed in the present study.

This study is limited by its post hoc design, the short overall observation time, and the pooling of heterogeneous groups of patients from different settings (i.e., clinical trial, open-label studies, clinical practice); however, the endpoint for this analysis is mortality, which is easily identified regardless of the setting in which the patients were treated. The majority of the patients in the present analysis participated in the phase 3 development studies, and therefore, their observation time was limited by study designs. The short observation time is mitigated in part by the large number of patients included in this analysis. The small number of deaths precluded firm conclusions regarding incidence rates of deaths, including SUDEP, before and during treatment with FFA in the phase 3 development program. Although it is well established that there is a high incidence of SUDEP in Dravet syndrome, the magnitude of the increase has not been established despite multiple studies; therefore, the
selection of a single historical study for comparison may weaken our conclusions. About half of the patients were subjects in structured clinical trials that required a centrally adjudicated diagnosis of Dravet syndrome and a minimum seizure frequency for enrollment. The other patient groups may have had greater diagnostic uncertainty and variable underlying seizure rates prior to treatment; however, all investigators participating in the EAPs and in the original Belgian cohorts were expert pediatric epileptologists and were also investigators in the phase 3 studies of FFA, which may have minimized such differences. Participation in clinical trials may have influenced the level of attention that patients received, possibly altering overall risk of mortality and SUDEP.

5. Conclusion

This post hoc analysis suggests that DS patients treated with FFA experienced a substantially lower rate of all-cause and SUDEP-related mortality compared with a historical natural history cohort. Further studies are warranted to understand if this effect may be due to sustained, profound reduction in GTCS, FFA’s pharmacology, or a combination of both.

Data sharing policy

Zogenix is currently in the process of developing a data sharing plan and process.

Funding

This study was funded by Zogenix, Inc.

Ethical publication statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Author contributions

JHC and BSG are designated as co-first authors to reflect their important contributions to this manuscript. JHC, BSG, and ARG made substantial contributions to the conception or design of the work, drafting of manuscript content, and analysis and interpretation of data. BSG was instrumental in suggesting the analysis of SUDEP rates in patients with Dravet syndrome treated with fenfluramine and comparing the results to published values. BC, A-SS, and ML made substantial contributions to acquisition of data. AG-N, OD, BC, LL, A-SS, ED, EW, SK, AA, ML, and ARG contributed to drafting of the manuscript for content and to analysis or interpretation of data.

Declaration of Competing Interest

Dr. Cross has acted as an investigator for studies with GW Pharma, Zogenix, Vitafo, and Marinus. She has been a speaker and has served on advisory boards for GW Pharma, Zogenix, and Nutricia; all remuneration has been paid to her department. She endorses a handcart at UCL Great Ormond Street Institute of Child Health, as well as grants from NIH, EPSRC, GOSH Charity, ERUK, and the Waterloo Foundation. Her research is supported by the National Institute of Health Research (NIHR) Biomedical Research centre at Great Ormond Street Hospital. Dr. Wirrell has received consulting fees from Encoded, Biocodex, and BioMarin.

Dr. Donner has received honoraria from Eisai, UCB, and Pendopharm.

Dr. Devinsky reports research funding from Novartis, PTC Therapeutics, Zogenix, and Greenwich Pharmaceuticals; and equity interest in Retco, Pairnomix, Tilray, Papa & Barkley, California Cannabis Enterprises, Tevard Biosciences, Regal Biosciences, Script Biosciences, Silver Spike Capital, and Silver Spike SPAC.

Dr. Lagae has received research grants from Zogenix; has served as consultant for Brabant, LivaNova, Ovid, UCB Pharma, and Zogenix; and has served as speaker for Eisai and Shire. Dr. Lagae has a patent for ZX008. Dr. Lagae and the KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by the KU Leuven University/Antwerp University Hospital.

Dr. Ceulemans has received research funding from Brabant and Zogenix and has served as consultant for Brabant and Zogenix. Dr. Ceulemans has a patent for ZX008. Dr. Ceulemans and the KU Leuven University/Antwerp University Hospital may benefit financially from a royalty arrangement that is related to this research if Zogenix is successful in marketing its product, fenfluramine. The terms of this arrangement have been reviewed and approved by the KU Leuven University/Antwerp University Hospital.

Dr. Schoonjans has received an educational grant from Zogenix, Inc.

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Supplementary materials

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References
