38

A Phase 1, Single-Dose, Open-Label Pharmacokinetic Study to Investigate the Drug-Drug Interaction Potential of ZX008 (Fenfluramine HCl Oral Solution) and Cannabidiol

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Introduction

- Adjunctive fenfluramine (FFA, administered as an oral solution of fenfluramine HCl containing 2.2 mg/mL fenfluramine) demonstrated profound efficacy with long-term duration for treatment of children with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS)[1,2]
  - In a pivotal Phase 3 randomized, placebo-controlled clinical study in DS of FFA at doses of 0.7 mg/kg/day and 0.2 mg/kg/day, the placebo-adjusted changes in monthly convulsive seizure frequency from baseline were -62.3% and -32.4%, respectively (P<0.001 and P=0.02)
- FFA has also demonstrated efficacy and durability of seizure reduction in patients with LGS[3]
  - In an open-label, investigator-initiated study in patients with LGS, FFA treatment resulted in a 53% median reduction in seizure frequency
  - Phase 3 studies are underway for FFA treatment of LGS
- Purified cannabidiol (CBD; marketed as Epidiolex® by Greenwich Biosciences, Inc.) was approved for the treatment of DS and LGS by the US Food and Drug Administration in 2018[4-7]
- FFA and CBD are likely to be co-prescribed in the multi-antiepileptic drug treatment regimens typically used to treat LGS and DS because both conditions are pharmacoresistant and usually require polypharmacy
- FFA and CBD have different mechanisms of action,[8,9] increasing the likelihood that both drugs may be used concomitantly to improve management of seizure control
- Both FFA and CBD are metabolized by hepatic cytochrome P450 mixed-function oxidases (CYP450),[5,10,11] suggesting the potential for drug-drug interactions
  - CBD inhibits multiple CYP450 enzymes in vitro (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4),[5] including CYP450s implicated in FFA metabolism (CYP1A2, CYP2B6, and CYP2D6, with possible additional metabolism by CYP2C9, CYP2C19, and CYP3A),[8] suggesting a potential pharmacokinetic (PK) effect of CBD on FFA

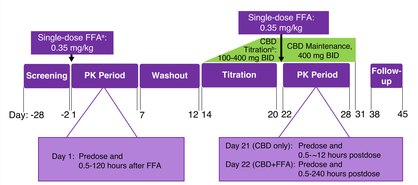
Objectives

- To assess the tolerability and PK profiles of FFA and its major metabolite, norfenfluramine (norFFA), following a single dose of FFA oral solution (0.35 mg/kg), with and without steady-state coadministration of CBD in healthy volunteers
- To determine the effect of FFA on CBD metabolism

Methods

- The study was a Phase 1, single-center (Canada), 1-sequence, single-dose drug-drug interaction study in healthy volunteers (Study 1604; EudraCT Number: 2016-002804-14; conducted by Syneos Health™; Morrisville, NC)
- The study was approved by the Research Ethics Committee and applicable health authorities in Canada
- At study initiation, purified CBD was not yet FDA approved or available in the United States; 5% (20:1) was the lowest tetrahydrocannabinol (THC) content of commercially available products
- CBD was administered with food as CanniMed® Oil 20:1 (20 mg/mL CBD + 1 mg/mL THC; Aurora; Saskatoon, SK, Canada)
- The study enrolled healthy adult recreational drug users with recent cannabis product experience in order to minimize the potential impact by the psychoactive THC component of the CBD product (**Figure 1**)
  - Key inclusion criteria: male or female, body mass index 18-31 kg/m^2, body weight ≥50 kg, age range 19-50 years (inclusive)
  - Key exclusion criteria: illicit drug/alcohol dependence within past 2 years, heavy smoking (≥20 cigarettes/day), history of epilepsy or hypertension (including pulmonary hypertension), cardiovascular disease, or clinically significant hepatic/renal impairment

Figure 1. Study Schematic



[a]FFA (2.2 mg/mL) was administered as 2.5 mg/mL of a FFA HCl oral solution.

[b]Protocol was amended from titration of 100 to 700 mg of CBD BID on Days 14 to 16 due to unacceptable tolerability by participants (maximum tolerated dose: 400-mg CBD and 20-mg THC BID). CBD titration for participants included in the final PK analyses followed 2 schemes:

[1] Day 14-15, 100 mg BID; Day 16, 200 mg BID; Day 17, 300 mg BID; Day 18-19, 500 mg BID; and Day 20, 400 mg BID.

[2] Day 14-15, 100 mg BID; Day 16, 200 mg BID; Day 17, 300 mg BID; Day 18-20, 400 mg BID.

BID, twice daily; CBD, cannabidiol; FFA, fenfluramine; PK, pharmacokinetic.

Results

Patient Characteristics and Disposition

- Of 32 participants enrolled (safety population), 8 were excluded from the PK population (n=24)
  - Positive drug screen (n=1), withdrawal of consent (n=1), adverse event (n=1)
  - Protocol amendment resulting in scheduling complications (n=5)
- Of 24 evaluable participants in the PK population, 14 completed the study (completers population, n=14); 10 discontinued early
  - Positive drug screen (n=1), withdrawal of consent (n=2), adverse event (n=1)
  - Study termination (n=6) when sponsor determined that an adequate number had completed the study to support the planned analysis

Table 1. Participant Disposition and Baseline Characteristics

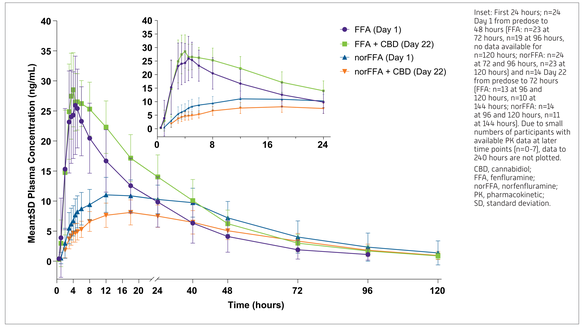
	Safety Population (n=32)	PK Population (n=24)	Completers Population (n=14)
Age (years), mean±SD [range]	32±10 [19-50]	31±10 [19-49]	30±10 [19-49]
Sex, n [%]			
Males	23 [72]	18 [75]	11 [79]
Females	9 [28]	6 [25]	3 [21]
Race, n [%]			
White	14 [44]	9 [38]	5 [36]
Black or African-American	11 [34]	11 [46]	6 [43]
Asian	4 [13]	2 [8]	1 [7]
Other	3 [9]	2 [8]	2 [14]
Height (cm), mean±SD [range]	174±10 [153-190]	175±10 [153-190]	175±10 [153-190]
Weight (kg), mean±SD [range]	76±11 [53-99]	77±11 [60-99]	78±9 [60-89]
BMI (kg/m^2), mean±SD [range]	25±3 [20-30]	25±3 [20-29]	25±3 [20-29]

BMI, body mass index; PK, pharmacokinetic; SD, standard deviation.

Pharmacokinetics

- CBD steady-state mean AUC_{0-12} (1865 ng•h/mL, coadministered with FFA) was comparable to exposures reported for twice-daily (BID) purified CBD (20 mg/kg/day), the maximum approved dose of the FDA-approved product Epidiolex®[8,5,12]
- Based on the lower inhibitory potency of THC than CBD in vitro and lower dose relative to CBD,[13] THC was not expected to interfere with PK study objectives (analysis for THC, 11-OH-THC not shown)

Figure 2. Plasma Concentrations of FFA and norFFA After Administration of FFA in the Presence or Absence of CBD



Inset: First 24 hours; n=24 Day 1 from predose to 48 hours (FFA: n=23 at 72 hours, n=19 at 96 hours, no data available for n=120 hours; norFFA: n=24 at 72 and 96 hours, n=23 at 120 hours) and n=14 Day 22 from predose to 72 hours (FFA: n=13 at 96 and 120 hours, n=10 at 144 hours; norFFA: n=14 at 96 and 120 hours, n=11 at 144 hours). Due to small numbers of participants with available PK data at later time points (n=0-7), data to 240 hours are not plotted.

CBD, cannabidiol; FFA, fenfluramine; norFFA, norfenfluramine; PK, pharmacokinetic; SD, standard deviation.

Table 2. Primary PK Parameters for FFA and norFFA After FFA ± CBD Administration

PK Parameters	FFA 0.35 mg/kg Day 1		FFA 0.35 mg/kg + CBD 400 mg BID Day 22	
	FFA			
	n		n	
Median T_{max} [h] [range]	24	4.5 [2.0-50.0]	14	4.0 [2.0-8.0]
Mean C_{max} [ng/mL] [% CV]	24	28.6 [29.9]	14	30.8 [21.3]
Mean AUC_{inf} [ng•h/mL] [% CV]	24	673.1 [44.7]	14	934.5 [29.2]
Mean $t_{1/2}$ [h] [range]	24	19.4 [9.4-36.9]	14	24.6 [14.1-36.5]
GMR[a] C_{max} [90% CI]	14	NC	--	109.6 [103.0-116.7]
GMR[a] AUC_{0-t} [90% CI]	14	NC	--	158.8 [147.9-170.4]
	norFFA			
	n		n	
Median T_{max} [h] [range]	24	18.0 [12.0-36.0]	14	18.0 [11.9-35.9]
Mean C_{max} [ng/mL] [% CV]	24	11.7 [24.7]	14	8.3 [24.9]
Mean AUC_{inf} [ng•h/mL] [% CV]	24	798.4 [60.1]	14	542.3 [32.3]
Mean $t_{1/2}$ [h] [range]	24	29.0 [17.8-97.5]	14	29.3 [16.2-48.1]
GMR[a] C_{max} [90% CI]	14	NC	--	66.7 [61.5-72.2]
GMR[a] AUC_{0-t} [90% CI]	14	NC	--	78.3 [70.3-87.1]

[a]GMR for CBD/FFA or norFFA.

% CV, percent coefficient of variation; AUC_{0-t}, area under the concentration-time curve from time 0 to time t; AUC_{inf}, area under the curve from time 0 (dosing) extrapolated to infinity; BID, twice daily; CBD, cannabidiol; CI, confidence interval; C_{max}, maximum observed concentration in plasma; FFA, fenfluramine; GMR, geometric mean ratio; NC, not calculated; norFFA, norfenfluramine; PK, pharmacokinetic; $t_{1/2}$, elimination half-life; T_{max}, time to maximum observed concentration in plasma.

Table 3. Key CBD PK Parameters for CBD ± FFA

PK Parameters	CBD 400 mg BID Day 21		CBD 400 mg BID + FFA 0.35 mg/kg Day 22	
	n		n	
Median T_{max} [h] [range]	14	3.0 [2.0-6.0]	14	4.3 [3.0-6.0]
Mean C_{trough} [ng/mL] [% CV]	14	48.3 [37.0]	14	79.4 [79.4]
Mean C_{max} [ng/mL] [% CV]	14	391.6 [35.0]	14	445.6 [38.3]
Mean AUC_{0-12} [ng•h/mL] [% CV][1]	12	1733 [27.9]	12	1865 [31.4]
GMR[a] C_{max} [90% CI]	14	NC	--	113.4 [94.0-136.8]
GMR[a] AUC_{0-12} [90% CI]	14	NC	--	102.6 [91.3-115.3]

[a]GMR for CBD/FFA.

% CV, percent coefficient of variation; AUC_{0-12}, area under the concentration-time curve from time 0 (dosing) to 12 hours postdose; CBD, cannabidiol; CI, confidence interval; C_{max}, maximum observed concentration in plasma; C_{trough}, trough concentration in plasma; FFA, fenfluramine; GMR, geometric mean ratio; NC, not calculated; PK, pharmacokinetic; T_{max}, time to maximum observed concentration in plasma.

Safety

- The maximum-tolerated dose of CBD was 400 mg BID
  - Treatment-emergent adverse events (TEAEs) were reported in 29% to 34% of participants after single-dose FFA and 54% to 100% of participants when dosing with CBD alone (safety population) (**Table 4**)
  - Most TEAEs were mild (78%) or moderate (22%) in severity
  - 1 severe and serious case of drug-induced psychosis was considered to be related to 100-mg BID CBD
- 5 patients (16%) experienced TEAEs leading to study drug discontinuation:
  - Visual impairment and dizziness
  - Nausea, headache, and decreased appetite
  - Presyncope
  - Elevated liver enzymes (γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase)
  - Agitation

Table 4. TEAEs Occurring in ≥10% of Participants in Any Treatment Arm

	FFA 0.35 mg/kg (n=32)[a]	FFA 0.35 mg/kg + CBD 400 mg BID (n=14)	CBD 400 mg BID[b] (n=15)
Any TEAE, n [%]	11 [34]	4 [29]	15 [100]
Headache	4 [13]	0	4 [27]
Nausea	1 [3]	0	3 [20]
Chest discomfort	0	0	2 [13]
Decreased appetite	0	0	3 [20]
Dyspepsia	0	1 [7]	2 [13]
Dizziness	0	1 [7]	4 [27]
Euphoric mood	0	1 [7]	6 [40]
Fatigue	0	1 [7]	9 [60]
γ-Glutamyltransferase increased	0	0	2 [13]
Hunger	0	1 [7]	2 [13]

[a]Includes participants who dropped out due to dose-limiting toxicities during CBD titration and who were excluded from the PK population after protocol amendment resulted in scheduling complications; PK data available for n=24 of the total dosed (safety) population.

[b]TEAEs occurred in lower proportions of patients at the 100-mg (n=17), 200-mg (n=24), and 300-mg (n=17) BID CBD titration doses than for the 400-mg BID CBD maintenance dose (n=15).

The following TEAEs occurred in ≥10% of participants at higher titration doses:

- 450-mg BID CBD titration dose (n=5): any TEAE [100%]; ataxia [20%], dizziness [40%], euphoric mood [100%], gait disturbance [20%], hyperhidrosis [20%], nausea [40%], pallor [40%], and somnolence [20%].
- 500-mg BID CBD titration dose (n=7): any TEAE [100%]; abdominal discomfort [14%], chest discomfort [14%], claustrophobia [14%], dissociation [14%], dizziness [43%], dry mouth [57%], euphoric mood [100%], fatigue [43%], feeling abnormal [14%], headache [14%], hypoaesthesia [14%], lethargy [14%], nausea [43%], palpitations [14%], paraesthesia [14%], photophobia [29%], restlessness [29%], somnolence [43%], tachycardia [14%], vertigo [14%], and vomiting [29%].

CBD, cannabidiol; FFA, fenfluramine; TEAE, treatment-emergent adverse event.

Conclusions

- Coadministration of FFA and CBD resulted in:
  - Increases in FFA C_{max} and AUC_{0-t} of approximately 10% and 60%, respectively
  - Decreases in norFFA C_{max} and AUC_{0-t} of approximately 30% and 20%, respectively
- These effects of CBD on FFA and norFFA PK are unlikely to require dose adjustments when coadministered
- FFA had no significant effect on the PK parameters of CBD, THC, or 11-OH-THC
  - CBD mean C_{max} and AUC_{0-12} ratios were approximately 1.1 and 1.0, respectively, when coadministered with FFA vs administered alone
- CBD exposures in Study 1604 were comparable to CBD steady-state reported in FDA-approved labeling for the maximum dose of Epidiolex®[5]
- CBD was generally well tolerated at doses up to 400-mg CBD and 20-mg THC BID, as was the combination of single-dose FFA (0.35 mg/kg/day) and CBD

References

1. Lagae L, et al. *Lancet*. In press.
2. Nabbout R, et al. AES [poster 3.461]. November 30–December 4, 2018; New Orleans, LA.
3. Lagae L, et al. *Epilepsia*. 2018; Aug 25 [Epub ahead of print].
4. Devinsky O, et al. *N Engl J Med*. 2017;376(21):2011-20.
5. EPIDIOLEX® (cannabidiol) oral solution, CV [prescribing information]. Carlsbad, CA: Greenwich Biosciences, Inc.; September 2018.
6. Thiele EA, et al. *Lancet*. 2018;391(10125):1085-96.
7. Devinsky O, et al. *N Engl J Med*. 2018;378(20):1888-97.
8. Kaplan JS, et al. *Proc Natl Acad Sci U S A*. 2017; Oct 5 [Epub ahead of print].
9. Martin P, et al. AES [poster 2.032]. December 1-5, 2017; Washington, DC.
10. Boyd B, et al. *Int J Clin Pharmacol Ther*. 2019;57(1):11-9.
11. Morrison G, et al. *Clin Pharmacol Drug Dev*. 2019; Feb 21 [Epub ahead of print].
12. US Food and Drug Administration. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000TOC.cfm.
13. Stout SM, Cimino NM. *Drug Metab Rev*. 2014;46(1):86-95.

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Disclosures

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SS: Consultant, Zogenix, Inc.

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