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

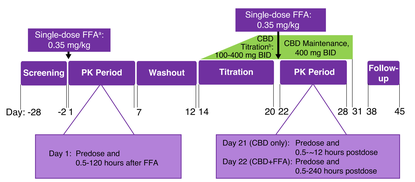
Objectives

- 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

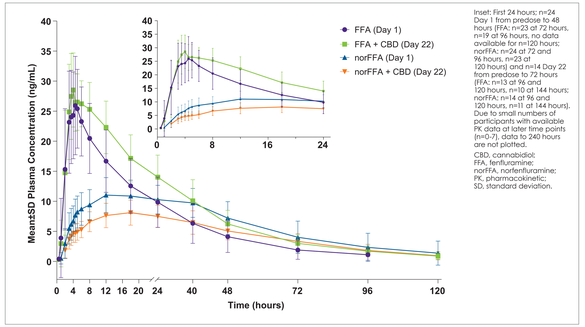
	Safety Population (n=32)	PK Population (n=24)	Completers Population (n=14)
Age (years), mean±SD (range)	32±10 (19-50)	31±10 (19-49)	30±10 (19-49)
Sex, n (%)			
Males	23 (72)	18 (75)	11 (79)
Females	9 (28)	6 (25)	3 (21)
Race, n (%)			
White	14 (44)	9 (38)	5 (36)
Black or African-American	11 (34)	11 (46)	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®[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_{inf} (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)[b]	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

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Disclosures

BB, GMF, GM: Employees, Zogenix, Inc.; Ownership interest, Zogenix, Inc.

SS: Consultant, Zogenix, Inc.

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