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FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

A phase 1, randomized, pharmacokinetic trial of the effect of different meal compositions, whole milk, and alcohol on cannabidiol exposure and safety in healthy subjects

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Abstract

Objective: The pharmacokinetics (PK) and safety of single oral 750-mg doses of a plant-derived pharmaceutical formulation of highly purified cannabidiol (CBD; Epidiolex in the USA and Epidyolex in Europe; 100-mg/mL oral solution) were assessed in healthy adults following a high-fat/calorie meal (n = 15), a low-fat/calorie meal (n = 14), whole milk (n = 15), or alcohol (n = 14), relative to the fasted state (n = 29).

Methods: Blood samples were collected until 96 hours postdose in each period and evaluated by liquid chromatography and tandem mass spectrometry. PK parameters (maximum observed plasma concentration [C_{max}], area under the plasma concentration-time curve from time zero to the last observed quantifiable concentration, area under the concentration-time curve from time zero to infinity [$AUC_{0-\infty}$], and time to maximum plasma concentration [t_{max}]) of CBD and its major metabolites were derived using noncompartmental analysis.

Results: CBD exposure increased by 3.8-fold for $AUC_{0-\infty}$ and 5.2-fold for C_{max} when CBD was administered with a high-fat/calorie meal versus fasted. To a lesser extent, a low-fat/calorie meal enhanced CBD exposure versus fasted with a 2.7-fold increase in $AUC_{0-\infty}$ and a 3.8-fold increase in C_{max}. Similarly, when dosed with whole milk, CBD exposure increased versus fasted by 2.4-fold for $AUC_{0-\infty}$ and 3.1-fold for C_{max}. Modest elevations in CBD exposure occurred when it was dosed with alcohol: 1.6-fold for $AUC_{0-\infty}$ and 1.9-fold for C_{max}. No clinically relevant effect of any test condition on CBD t_{max} or $t_{½}$ versus the fasted state was apparent. The same trend was seen for the CBD metabolites, except that 7-carboxy-cannabidiol t_{max} was considerably longer when CBD was administered with alcohol (14 vs 4 hours fasted). Inter- and intrasubject variability in PK parameters was moderate to high during the trial.

Significance: CBD and metabolite exposures were most affected by a high-fat/calorie meal. CBD exposures also increased with a low-fat/calorie meal, whole milk, or alcohol, but to a lesser extent. CBD was tolerated, and there were no severe or serious adverse events during the trial.

KEYWORDS

alcohol, cannabidiol, cannabinoid, food effect, pharmacokinetics

1 | INTRODUCTION

Highly purified cannabidiol (CBD) oral solution (approved as Epidiolex in the USA and Epidyolex in Europe) has demonstrated efficacy, with an acceptable safety profile, in patients ≥2 years of age with Lennox-Gastaut syndrome or Dravet syndrome in randomized controlled trials.[1–5] Recent nonclinical scientific literature suggests the anticonvulsant effects of CBD are regulated by at least three targets: modulation of intracellular Ca^{2+} via G protein–coupled receptor 55 and desensitization of transient receptor potential vanilloid type 1 channels, and adenosine reuptake.[6–8] Because CBD does not activate the cannabinoid receptors CB_1 and CB_2 at physiological concentrations, CBD is not associated with detectable euphoric effects and has limited propensity for abuse.[9,10]

The pharmacokinetics (PK) of CBD have been described in several recent studies, both in patients with epilepsy and in healthy volunteers.[2,11–14] In one healthy volunteer trial, after single CBD doses of between 1500 and 6000 mg, CBD appeared rapidly in plasma; maximum observed plasma concentration (C_{max}) occurred between 3 and 5 hours postdose, and CBD remained detectable up to 72 hours postdose.[11] In the same trial, when 1500 mg CBD was administered following a US Food and Drug Administration (FDA) standardized high-fat meal, CBD C_{max} increased by 4.85-fold and area under the plasma concentration-time curve from time zero to the last observed quantifiable concentration (AUC_{0-t}) by 4.2-fold. However, this previous trial did not assess whether a low-fat/calorie meal, milk, or alcohol would also increase CBD exposure.

The current trial investigated the extent to which low- and high-fat/calorie meals affect the PK of CBD. In addition, as some patients with the currently approved or proposed indications for CBD may be on milk diets, and the potential for a drug-drug interaction with alcohol may exist, the effects of whole milk and alcohol on CBD PK were also investigated.

Key Points

- CBD exposure increased under all test treatment conditions in this trial when compared to the fasted state
- CBD and metabolite exposures were most affected by a high-fat/calorie meal
- CBD exposures also increased with a low-fat/calorie meal, whole milk, or alcohol, but to a lesser extent
- The 750-mg CBD dose used in this trial was tolerated by healthy adults across test conditions
- There were no serious or severe adverse events in this trial, and no new safety concerns were identified

2 | MATERIALS AND METHODS

2.1 | Trial design

The primary objective of this trial was to investigate the effects of meal types (high fat/calorie or low fat/calorie), whole milk, or alcohol compared to the fasted state on the PK of single doses of CBD in healthy subjects. Secondary objectives were to evaluate the safety and tolerability of CBD in the same population and to evaluate potential changes in the metabolite-to-parent ratio (MR) of 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD) versus CBD in the same population.

All relevant trial-related documents, including the protocol, were reviewed by a local independent ethics committee. All subjects provided written informed consent for participation in the trial, which was performed in full conformity with the current Declaration of Helsinki,[15] the International Council for Harmonisation guidelines for Good Clinical Practice,[16] and all other applicable regulations. The trial was performed between August 9, 2018 and November 15, 2018 at a Pharmaceutical Research Associates site specializing in clinical pharmacology trials in the Netherlands.

This was a randomized, open-label, three-period, three-way crossover trial. Subjects were randomly assigned to a total of three of the five treatments over three periods according to a partially balanced incomplete block design, in which the reference treatment (administered under fasted condition) was to be given to all 30 subjects and test treatments (administered following a high-fat/calorie meal or low-fat/calorie meal, or with whole milk or alcohol) were each to be given to 15 subjects.

Screening took place between Days −28 to −2, and patients were confined to the trial site from Day −1 (pretreatment) to Day 5 of each of the three treatment periods, with a follow-up visit 7-10 days after the last CBD dose. Baseline assessments were performed on Day −1. In all treatment groups, subjects fasted overnight for at least 10 hours following a light supper on the evening before, then received single oral 750-mg doses of a pharmaceutical formulation of highly purified CBD derived from the *Cannabis sativa* L. plant in oral solution (100 mg/mL; Epidiolex in the USA; Epidyolex in Europe; GW Research) under the assigned treatment conditions on the morning of Day 1 of each period. There was a washout period of at least 14 days between CBD administration per period. Following dosing under the appropriate conditions (Treatments 1-5), the subjects fasted for a period of 4 hours until lunch. During fasting, fluids other than water were not allowed. In addition, water was not allowed from 2 hours predose until 1 hour postdose.

Each subject was to receive a single 750-mg CBD dose (7.5 mL) under three of the following five conditions (all received the reference treatment [fasted]) according to the randomly assigned treatment sequence:

- Treatment 1: Reference; CBD dosed fasted
- Treatment 2: CBD dosed 30 minutes after starting a standardized FDA high-fat/calorie breakfast:
  a. 918 kcal consisting of two fried eggs (in 15 g butter/margarine; approx. 100 g), one portion of bacon (40 g), one portion of fried potatoes (115 g), two slices of toasted whole-wheat bread with 15 g margarine, and one glass of whole milk (240 mL)
  b. For vegetarians, bacon could be replaced by brie (915 kcal total)
- Treatment 3: CBD dosed 30 minutes after the start of a standardized low-fat/calorie breakfast:
  a. 406-427 kcal consisting of two slices of whole-wheat bread (approx. 68 g), one Swedish crisp bread (approx. 15 g), 15 g margarine (40% fat), one portion of cheese (approx. 20 g) or cheese spread (15 g) OR one portion of ham/chicken breast/smoked meat (approx. 15 g), two portions of jam (2 × 15 g) or one portion of jam (15 g) and one portion of apple treacle (15 g), 1-2 mugs of decaffeinated coffee or tea (150-300 mL; without milk/sugar) or one glass (240 mL) of water
- Treatment 4: CBD dosed immediately before (within 5 minutes) intake of 500 mL whole milk
- Treatment 5: CBD dosed immediately before (within 5 minutes) intake of 40 g alcohol diluted in 500 mL still lemonade

2.2 | Inclusion and exclusion criteria

2.2.1 | Trial population

The inclusion criteria specified that the trial population consisted of healthy male and female subjects (aged 18-60 years; body mass index between 18 and 32 kg/m^2; body weight ≥ 50 kg). Female subjects of child-bearing potential were nonpregnant and nonlactating at screening and at each admission to the trial site. Male and female subjects agreed to use effective contraception for the duration of the trial and for 3 months thereafter.

2.3 | Trial assessments

2.3.1 | Materials

Reference and internal standards for CBD, 7-OH-CBD, and 7-COOH-CBD bioanalysis were supplied by GW Pharma and Sigma-Aldrich.

2.3.2 | Plasma sample preparation

At the times specified below, 3-mL blood samples were taken from subjects via either an indwelling intravenous catheter or direct venipuncture. Blood samples were then centrifuged for 10 minutes (1500 *g*) at 4°C directly after collection, after storage for 2 hours on ice, or after 2 hours at room temperature. Plasma samples were then frozen at a nominal −20°C and analyzed after 1 freeze/thaw cycle.

Blood samples for PK analysis were taken at the following time points during each period: predose and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, 48, 72, and 96 hours postdose.

PK parameters evaluated included C_{max}, area under the concentration-time curve from time zero to infinity ($AUC_{0-\infty}$), AUC_{0-t}, time to maximum plasma concentration (t_{max}), $t_{½}$, oral clearance of drug from plasma (CL/F), apparent volume of distribution (V_z/F), and MR for C_{max}, $AUC_{0-\infty}$, and AUC_{0-t}.

CBD and metabolite samples were extracted from plasma by liquid-liquid extraction.

2.3.3 | Bioanalysis and PK assessment

Validated liquid chromatographic–tandem mass spectrometric bioanalytical methods were used to quantify concentrations of CBD, 7-OH-CBD, and 7-COOH-CBD in a sample volume of 50 μL. Sample processing was performed by liquid-liquid extraction. Separation between metabolites was achieved by high-performance liquid chromatography using a Waters Acquity UPLC PEH phenyl column (2.1 × 50 mm, 1.7 μm). The assay range was 1.00-1000 ng/mL for CBD and 7-OH-CBD, and 10.0-10 000 ng/mL for 7-COOH-CBD.

The precision (coefficient of variation) and accuracy (relative error/mean % different) of the high-performance liquid chromatography method was acceptable for all analytes (≤15% [20% at the lower limit of quantification]). Recovery was 45.4%-48.8% for CBD, 71.3%-77.4% for 7-OH-CBD, and 75.6%-83.5% for 7-COOH-CBD.

Validation and acceptance criteria were based on FDA guidance for industry[17] and European Medicines Agency guidance on bioanalytical method validation.[18]

2.3.4 | Safety assessments

The safety and tolerability of CBD were evaluated by treatment-emergent adverse event (AE) review, vital sign measurements, 12-lead electrocardiograms (ECGs), clinical laboratory evaluations, physical examinations, and Columbia-Suicide Severity Rating Scale (C-SSRS) assessment.

2.4 | Statistical analysis

Descriptive statistics of subject demographics and safety outcomes were based on the safety analysis set (all subjects who received at least one dose of CBD).

The PK population for analysis included all subjects who received at least one dose of CBD and provided enough bioanalytical assessments to calculate reliable estimates of the PK parameters.

PK parameters for CBD and its metabolites were determined by standard noncompartmental analysis using Phoenix WinNonlin (Pharsight) version 8.1. PK values were log-transformed prior to analysis. C_{max}, $AUC_{0-\infty}$, and AUC_{0-t} in each group were analyzed using a linear mixed-effects model. The model included terms for sequence, period, treatment, and subject nested within sequence. The ratio of geometric least squares means, expressed as test/reference for each comparison, and corresponding 90% confidence intervals (CIs) were presented for comparisons for analysis of relative exposure. For t_{max}, nonparametric analysis of the same comparisons was performed using a Wilcoxon signed rank test. The median t_{max} for each treatment and the median of pairwise differences between the treatments (test/reference) was presented along with the approximate 90% CI.

2.4.1 | Sample size

For this exploratory trial, no prospective calculations of statistical power were made.

3 | RESULTS

3.1 | Subject demographics

A total of 30 subjects were enrolled, and 28 subjects completed the trial. Two withdrew prior to the third (final) period and therefore did not have any PK data for that period; one subject did not receive the reference treatment (fasted condition), and one did not receive Treatment 3 (low-fat/calorie meal). All 30 subjects were included in the safety and PK analysis sets, but one subject was excluded from the Treatment 5 (alcohol) PK analysis due to vomiting prior to the t_{max} of CBD.

Demographics information is presented in Table 1.

The only concomitant medication administered during the trial was paracetamol for AEs of headache and common cold in one subject each.

3.2 | Pharmacokinetics

Geometric mean plasma concentrations of CBD and its metabolites under the various test conditions are presented in Figure 1. During the trial, there was no effect of any test treatment on CBD t_{max}. Median CBD t_{max} was between 3 and 5 hours, independent of treatment group (Tables 2 and 3). The same trend was seen for the CBD metabolites, except that the

TABLE 1 Demographics and baseline characteristics; safety analysis set

	Treatment					
	Fasted, n = 29	High-fat/calorie, n = 15	Low-fat/calorie, n = 14	Whole milk, n = 15	Alcohol, n = 15	Overall, n = 30
Demographic	**Number of subjects (%)**					
Sex						
Male	12 (41.4)	9 (60.0)	3 (21.4)	6 (40.0)	6 (40.0)	12 (40.0)
Female	17 (58.6)	6 (40.0)	11 (78.6)	9 (60.0)	9 (60.0)	18 (60.0)
Race						
White	26 (89.7)	13 (86.7)	13 (92.9)	12 (80.0)	13 (86.7)	26 (86.7)
American Indian or Alaska Native	1 (3.4)	1 (6.7)	0	0	1 (6.7)	1 (3.3)
Multiple: American Indian or Alaska Native + black or African American	1 (3.4)	0	0	1 (6.7)	1 (6.7)	1 (3.3)
Multiple: White + Asian	1 (3.4)	0	1 (7.1)	1 (6.7)	0	1 (3.3)
Multiple: White + black or African American	0	1 (6.7)	0	1 (6.7)	0	1 (3.3)
Parameter	**Mean (standard deviation)**					
Age, y	36.6 (14.3)	41.1 (12.4)	38.2 (13.8)	31.7 (12.9)	35.9 (15.9)	36.4 (14.1)
Weight, kg	71.7 (11.0)	71.6 (8.32)	72.9 (13.0)	72.0 (12.8)	73.4 (11.0)	72.3 (11.2)
Height, cm	172 (10.6)	172 (12.7)	169 (7.0)	173 (8.4)	173 (12.5)	172 (10.4)
BMI, kg/m^2	24.3 (3.18)	24.3 (3.06)	25.4 (3.47)	23.9 (3.34)	24.6 (3.40)	24.5 (3.30)

Abbreviations: BMI, body mass index; n, number of subjects exposed.

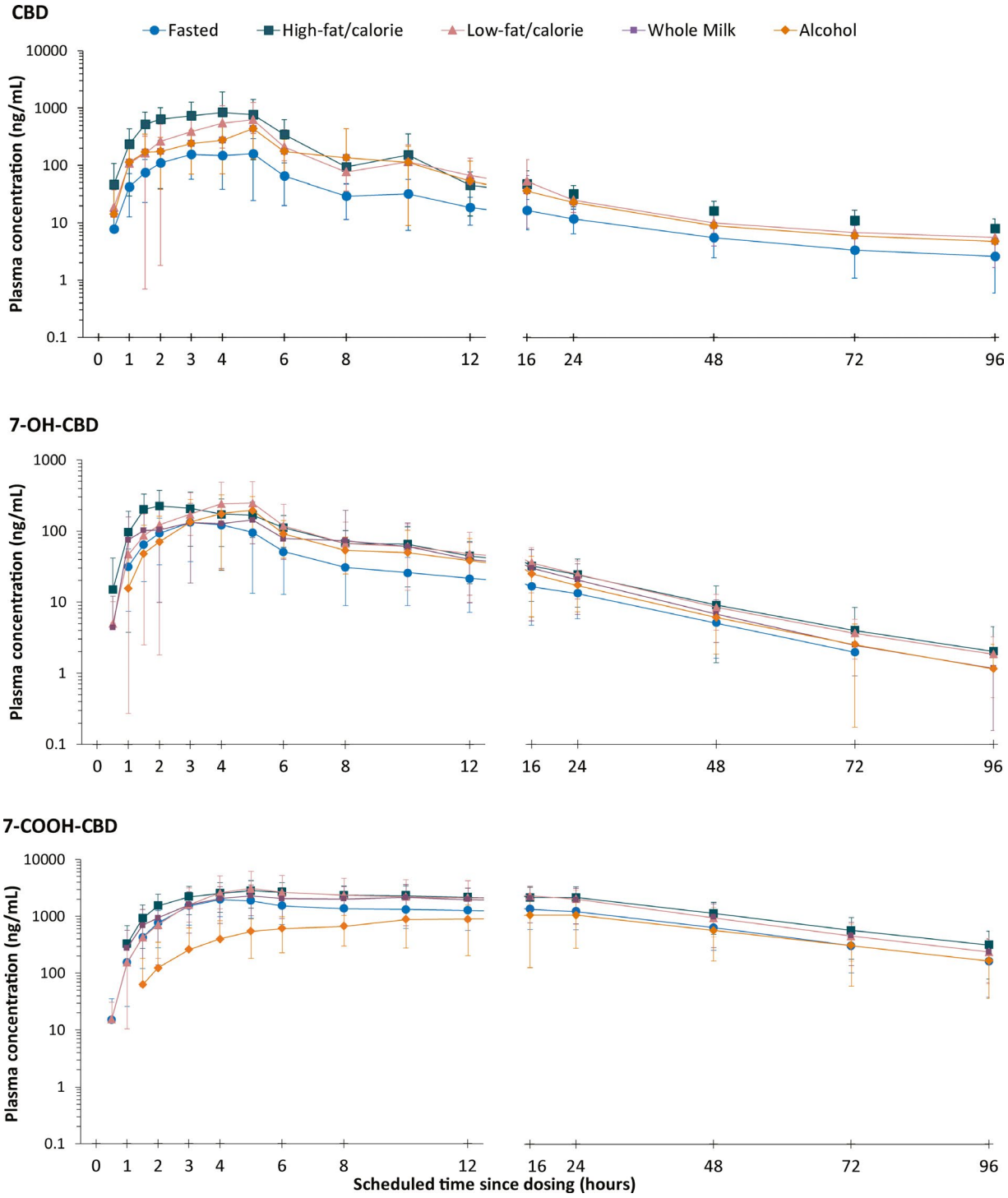

FIGURE 1 Geometric mean (±standard deviation) plasma concentration-time profiles for cannabidiol (CBD), 7-hydroxy-cannabidiol (7-OH-CBD), and 7-carboxy-cannabidiol (7-COOH-CBD) after a single oral 750-mg CBD dose under fasted conditions or with various meal types (high-fat/calorie or low-fat/calorie), whole milk, or alcohol (semilogarithmic); pharmacokinetic analysis set

t_{max} of 7-COOH-CBD was considerably longer when CBD was administered with alcohol (14 hours vs 4 hours fasted). CBD apparent $t_{½}$ was similar for all treatments; the arithmetic mean was between 34 and 41 hours. The apparent $t_{½}$ of 7-OH-CBD and 7-COOH-CBD was also similar for all treatments. Arithmetic mean $t_{½}$ was between 18 and 20 hours for 7-OH-CBD and between 23 and 28 hours for 7-COOH-CBD.

3.2.1 | CBD exposure

Administration of CBD following a high-fat/calorie meal, low-fat/calorie meal, or whole milk resulted in increased exposure of CBD versus the fasted group, an effect that was most pronounced with the high-fat/calorie meal. Administration of CBD with alcohol resulted in modest increases in exposure

TABLE 2 PK parameters for CBD, 7-OH-CBD, and 7-COOH-CBD following single oral 750-mg CBD doses under fasted conditions or with various meal types (high-fat/calorie or low-fat/calorie), whole milk, or alcohol; PK analysis set

Parameter	Fasted, n = 29	High-fat/calorie, n = 15	Low-fat/calorie, n = 14	Whole milk, n = 15	Alcohol, n = 14
	Geometric mean (geometric CV%)				
CBD					
AUC_{0-t}, h·ng/mL	1077 (49.6)	4584 (47.9)	3202 (35.6)	2450 (39.6)	1676 (59.1)
$AUC_{0-\infty}$, h·ng/mL	1190 (48.9)	4870 (46.8)	3394 (35.0)	2588 (40.6)	1782 (57.8)
C_{max}, ng/mL	187 (52.2)	1050 (56.0)	722 (41.8)	527 (51.2)	354 (59.9)
t_{max}[a]	4.00 (2.00-5.00)	3.00 (1.50-6.00)	4.51 (2.00-10.00)	5.00 (1.50-12.00)	5.00 (3.00-10.02)
$t_{½}$, h[b]	39.7 (36.0)	41.3 (16.6)	39.4 (24.3)	36.5 (21.4)	34.0 (22.4)
CL/F, L/h	630 (48.9)	154 (46.8)	221 (35.0)	290 (40.6)	421 (57.8)
V_z/F, L	33 820 (50.3)	9050 (51.5)	12 212 (44.9)	14 966 (24.3)	20 056 (53.9)
7-OH-CBD					
AUC_{0-t}, h·ng/mL	977 (63.5)	2016 (47.8)	2021 (43.2)	1472 (60.6)	1442 (57.1)
$AUC_{0-\infty}$, h·ng/mL	1042 (58.6)	2074 (48.3)	2074 (43.0)	1518 (58.7)	1504 (52.5)
C_{max}, ng/mL	1310 (62.8)	2790 (39.9)	2800 (44.2)	180 (59.1)	216 (65.0)
t_{max}[a]	3.00 (2.00-5.00)	2.00 (1.50-5.00)	4.01 (2.00-5.00)	5.00 (1.50-12.00)	5.00 (3.00-10.02)
$t_{½}$, h[b]	20.2 (31.0)	19.3 (22.9)	20.1 (20.4)	17.9 (25.7)	19.4 (26.3)
MR_{AUC0-t}	0.907 (35.9)	0.440 (44.3)	0.631 (34.9)	0.601 (39.5)	0.861 (36.5)
$MR_{AUC0-\infty}$	0.876 (34.4)	0.426 (42.2)	0.611 (33.6)	0.587 (37.6)	0.844 (34.5)
MR_{Cmax}	0.703 (46.5)	0.266 (54.1)	0.388 (26.7)	0.342 (47.8)	0.609 (46.5)
7-COOH-CBD					
AUC_{0-t}, h·ng/mL	54 427 (61.5)	95 910 (52.0)	89 204 (47.3)	78 304 (69.1)	39 389 (76.1)
$AUC_{0-\infty}$, h·ng/mL	59 272 (63.2)	105 116 (54.7)	95 677 (49.0)	84 510 (69.5)	44 683 (76.7)
C_{max}, ng/mL	1903 (55.2)	2919 (39.9)	2978 (42.5)	2424 (62.1)	831 (84.9)
t_{max}[a]	4.00 (3.00-12.00)	5.00 (3.00-10.00)	5.00 (4.00-16.00)	5.00 (3.00-24.00)	14.0 (4.00-24.02)
$t_{½}$, h[b]	25.0 (29.2)	25.6 (23.3)	23.2 (22.2)	23.9 (18.2)	28.0 (25.6)
MR_{AUC0-t}	50.5 (44.2)	20.9 (55.8)	27.9 (42.0)	32.0 (61.2)	23.5 (55.5)
$MR_{AUC0-\infty}$	49.8 (43.9)	21.6 (54.3)	28.2 (41.9)	32.7 (61.2)	25.1 (52.4)
MR_{Cmax}	10.2 (54.0)	2.78 (64.1)	4.12 (32.7)	4.60 (67.6)	2.35 (87.9)

Abbreviations: 7-COOH-CBD, 7-carboxy-cannabidiol; 7-OH-CBD, 7-hydroxy-cannabidiol; $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the last observed quantifiable concentration; CBD, cannabidiol; CL/F, oral clearance of drug from plasma; C_{max}, maximum observed plasma concentration; CV%, coefficient of variation; MR, metabolite-to-parent ratio; n, number of subjects exposed; PK, pharmacokinetic; $t_{½}$, terminal (elimination) half-life; t_{max}, time to maximum plasma concentration; V_z/F, apparent volume of distribution.

[a]Median (min-max).

[b]Arithmetic mean (CV%).

of CBD versus the fasted group. In all cases, the 90% CI for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} of CBD did not include 1 (Tables 2 and 3, and Figure 2).

3.2.2 | 7-OH-CBD exposure

Administration of CBD following a high-fat/calorie meal, low-fat/calorie meal, or whole milk resulted in increased exposure of 7-OH-CBD versus the fasted group. In all cases, the 90% CI for AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} did not include 1 (Tables 2 and 3, and Figure 2).

3.2.3 | 7-COOH-CBD exposure

Administration of CBD following a high-fat/calorie meal, low-fat/calorie meal, or whole milk resulted in increased exposure of 7-COOH-CBD versus the fasted group, whereas administration of CBD with alcohol resulted in decreased

TABLE 3 Statistical analysis of PK parameters following administration of 750-mg CBD under fasted conditions compared with various meal types (high-fat/calorie or low-fat/calorie), whole milk, or alcohol; PK analysis set

Comparison	Ratio of geometric least squares means (90% CI)			
	AUC_{0-t},[a] h·ng/mL	$AUC_{0-\infty}$,[a] h·ng/mL	C_{max},[a] ng/mL	t_{max},[b] h
CBD				
High-fat/calorie vs fasted	3.99 (3.37, 4.73)	3.84 (3.24, 4.55)	5.22 (4.25, 6.41)	−0.50 (−1.00, 0.50)
Low-fat/calorie vs fasted	2.86 (2.41, 3.40)	2.72 (2.29, 3.24)	3.76 (3.05, 4.63)	0.54 (0.00, 1.50)
Whole milk vs fasted	2.47 (2.08, 2.92)	2.37 (2.00, 2.81)	3.08 (2.51, 3.78)	1.00 (0.00, 2.00)
Alcohol vs fasted	1.63 (1.37, 1.94)	1.57 (1.32, 1.87)	1.93 (1.57, 2.38)	1.00 (0.00, 1.51)
7-OH-CBD				
High-fat/calorie vs fasted	2.01 (1.70, 2.38)	1.93 (1.65, 2.27)	1.95 (1.60, 2.38)	−1.00 (−1.50, −0.25)
Low-fat/calorie vs fasted	2.02 (1.70, 2.39)	1.94 (1.65, 2.28)	2.15 (1.75, 2.63)	0.50 (−0.50, 1.50)
Whole milk vs fasted	1.51 (1.28, 1.79)	1.47 (1.25, 1.72)	1.40 (1.14, 1.70)	1.00 (0.00, 2.50)
Alcohol vs fasted	1.63 (1.38, 1.94)	1.60 (1.36, 1.89)	1.79 (1.46, 2.19)	1.00 (0.50, 2.00)
7-COOH-CBD				
High-fat/calorie vs fasted	1.65 (1.41, 1.92)	1.64 (1.41, 1.90)	1.41 (1.17, 1.70)	0.50 (0.00, 2.00)
Low-fat/calorie vs fasted	1.71 (1.47, 2.00)	1.70 (1.45, 1.98)	1.59 (1.31, 1.93)	0.96 (0.00, 2.93)
Whole milk vs fasted	1.43 (1.22, 1.66)	1.42 (1.22, 1.66)	1.31 (1.09, 1.58)	1.00 (0.50, 3.00)
Alcohol vs fasted	0.81 (0.70, 0.95)	0.85 (0.73, 0.99)	0.48 (0.39, 0.58)	9.51 (3.52, 11.53)

Abbreviations: 7-COOH-CBD, 7-carboxy-cannabidiol; 7-OH-CBD, 7-hydroxy-cannabidiol; ANOVA, analysis of variance; $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the last observed quantifiable concentration; CBD, cannabidiol; CI, confidence interval; C_{max}, maximum observed plasma concentration; PK, pharmacokinetic; t_{max}, time to maximum plasma concentration.

[a]AUC and C_{max}: an ANOVA was performed on AUC_{0-t}, $AUC_{0-\infty}$, and C_{max} using the SAS procedure for mixed effect models. The PK parameters were natural logarithm transformed prior to the analysis. The ANOVA model included fixed effects for treatment and period, and a random effect for subject.

[b]t_{max}: nonparametric Wilcoxon signed rank test/Hodges-Lehmann. Median, median of the difference, and approximate 90% CI for the difference are presented.

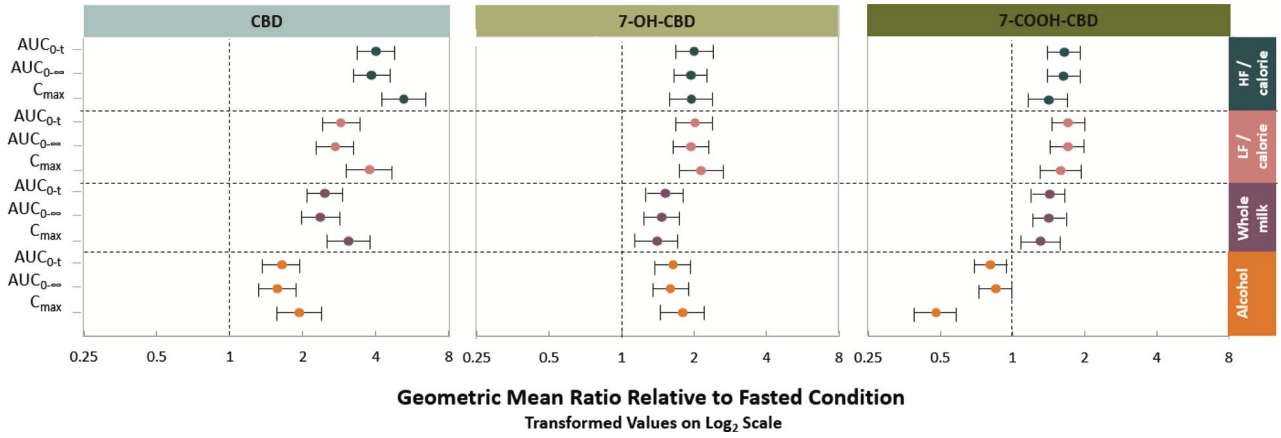

FIGURE 2 Forest plot of geometric least square mean ratios and 90% confidence intervals showing the effects of a high-fat (HF)/calorie meal, low-fat (LF)/calorie meal, whole milk, and alcohol on exposure to cannabidiol (CBD), 7-hydroxy-cannabidiol (7-OH-CBD), and 7-carboxy-cannabidiol (7-COOH-CBD) compared with CBD administered in the fasted state. Transformed values on log scale (base 2). $AUC_{0-\infty}$, area under the concentration-time curve from time zero to infinity; AUC_{0-t}, area under the plasma concentration-time curve from time zero to the last observed quantifiable concentration; C_{max}, maximum observed plasma concentration

TABLE 4 Adverse events experienced by >1 subject per treatment group, by MedDRA preferred term; safety analysis set

System organ class MedDRA preferred term	Fasted, n = 29[a]	High-fat/calorie, n= 15[a]	Low-fat/calorie, n = 14[a]	Whole milk, n = 15[a]	Alcohol, n = 15[a]	Total, n = 30[a]
	Number of subjects (%)[b]					
Subjects experiencing any TEAEs	14 (48.3)	6 (40.0)	8 (57.1)	8 (53.3)	12 (80.0)	27 (90.0)
Nervous system disorders	5 (17.2)	3 (20.0)	5 (35.7)	3 (20.0)	11 (73.3)	18 (60.0)
Headache	4 (13.8)	1 (6.7)	3 (21.4)	1 (6.7)	8 (53.3)	13 (43.3)
Somnolence	2 (6.9)	3 (20.0)	3 (21.4)	1 (6.7)	1 (6.7)	5 (16.7)
Dizziness	0	0	0	0	3 (20.0)	3 (10.0)
General disorders and administration site conditions	3 (10.3)	2 (13.3)	2 (14.3)	1 (6.7)	7 (46.7)	13 (43.3)
Fatigue	0	0	1 (7.1)	1 (6.7)	2 (13.3)	4 (13.3)
Catheter site hematoma	3 (10.3)	0	0	0	1 (6.7)	3 (10.0)
Catheter site inflammation	0	1 (6.7)	1 (7.1)	0	1 (6.7)	2 (6.7)
Catheter site pain	0	0	0	0	2 (13.3)	2 (6.7)
Gastrointestinal disorders	6 (20.7)	3 (20.0)	2 (14.3)	3 (20.0)	6 (40.0)	12 (40.0)
Diarrhea	3 (10.3)	1 (6.7)	1 (7.1)	1 (6.7)	3 (20.0)	5 (16.7)
Nausea	1 (3.4)	1 (6.7)	1 (7.1)	1 (6.7)	2 (13.3)	4 (13.3)
Respiratory, thoracic, and mediastinal disorders	2 (6.9)	0	1 (7.1)	0	1 (6.7)	4 (13.3)
Dysphonia	1 (3.4)	0	0	0	1 (6.7)	2 (6.7)

Abbreviations: MedDRA, medical dictionary for regulatory activities; TEAE, treatment-emergent adverse event.

[a]Number of subjects exposed.

[b]Number of subjects who experienced the TEAE.

exposure of 7-COOH-CBD versus the fasted group (Tables 2 and 3, and Figure 2).

3.2.4 | Metabolite-to-parent ratios

Because metabolites can confer pharmacological activity and possible toxicity beyond that of the parent drug, calculating the MR is a useful and straightforward metric for determining relative exposure. Changes in MR in a bioavailability study might reflect effects of the test conditions on CBD absorption or the biotransformation pathway(s) for the metabolites.

In all treatment groups, 7-COOH-CBD was the most abundant circulating product in plasma, followed by CBD, then 7-OH-CBD.

The 7-OH-CBD $MR_{AUC0\text{-}t}$ ranged from 0.440 in the high-fat/calorie group to 0.861 in the alcohol group for the test treatments, with highest overall $MR_{AUC0\text{-}t}$ of 0.907 in the fasted group. $MR_{AUC0\text{-}\infty}$ and MR_{Cmax} values followed the same trend of being highest in the fasted group and lowest in the high-fat/calorie group (Table 2).

The 7-COOH-CBD $MR_{AUC0\text{-}t}$ ranged from 20.9 in the high-fat/calorie group to 32.0 in the whole milk group for the test treatments, with highest overall $MR_{AUC0\text{-}t}$ of 50.5 in the fasted group. $MR_{AUC0\text{-}\infty}$ values followed the same trend of being highest in the fasted group and were lowest in the high-fat/calorie group, whereas MR_{Cmax} values were lowest in the alcohol group and highest in the fasted group (Table 2).

3.2.5 | Other PK parameters

Reflecting the increase in bioavailability, apparent clearance of CBD was reduced in all test treatment groups relative to the fasted group (Table 2). The same trend was seen with V_z/F, which was reduced in all test treatment groups relative to the fasted group (Table 2). Inter- and intrasubject variability in PK parameters was moderate to high during the trial (Table 2).

3.3 | Safety

A single oral 750-mg dose of CBD was tolerated by healthy adults across all treatment groups. Overall, 27 (90%) subjects experienced at least one AE during the trial (Table 4). Most AEs were mild in severity; only two (13%) subjects experienced moderate AEs after administration with alcohol. There were no severe or serious AEs, deaths, or early withdrawals

due to AEs. Two subjects withdrew prior to completing the final period due to personal reasons.

In the fasted group, 14 (48%) subjects experienced at least one AE versus six (40%) in the high-fat/calorie group, eight (57%) in the low-fat/calorie group, eight (53%) in the whole milk group, and 12 (80%) in the alcohol group.

The most common AEs were headache, experienced by 13 (43%) subjects overall, and somnolence and diarrhea, affecting five (17%) subjects overall each. More subjects were affected by headache while taking CBD with alcohol (eight [53%] subjects) versus the other treatment groups (7%-21% subjects affected).

Another notable AE was an increased incidence of dizziness in subjects while taking CBD with alcohol, affecting three (20%) subjects versus zero subjects in the other treatment groups.

There were no clinically significant laboratory, physical examination, vital sign, or ECG findings during the trial. There was no evidence of suicidal behavior or ideation as measured by the C-SSRS.

4 | DISCUSSION

This trial in healthy subjects explored the effects of meal composition, whole milk, and alcohol on the PK of CBD and its major metabolites, 7-OH-CBD and 7-COOH-CBD.

4.1 | CBD and metabolite PK

Time for CBD to reach maximum plasma concentration was unaffected by any test treatment; median t_{max} was 3 to 5 hours in all treatment groups. This result is consistent with an earlier phase 1 trial in healthy subjects in which a single 1500-mg dose of the same CBD formulation administered with a standardized high-fat meal had no effect on t_{max}.[11]

After a single 750-mg CBD dose, all test treatments increased CBD exposure (AUC and C_{max}) compared with the fasted state. The largest increases occurred when CBD was administered following a high-fat/calorie meal. An almost identical food effect was reported in the earlier phase 1 trial in healthy subjects when a 1500-mg dose of the same CBD formulation was administered with a standardized high-fat meal.[11]

In the current trial, similar but less notable effects on CBD exposure were seen with a low-fat/calorie meal and whole milk. This is the first trial to explore the PK of CBD under these dietary conditions.

Administration of CBD with alcohol caused a modest increase in CBD exposure; none of the treatment ratios was >2.0. There are no previous studies investigating the effects of alcohol on CBD exposure, although evidence suggests that alcohol may increase[19,20] or have no effect[21,22] on Δ^9-tetrahydrocannabiniol absorption.

As 7-OH-CBD is an active metabolite and 7-COOH-CBD is highly abundant,[11] understanding changes in the MR with reference to extrinsic factors such as food is important. Although most treatments also increased exposure to both CBD metabolites within this trial, increases in exposure were greatest for parent CBD, as supported by the $MR_{AUC0\text{-}t}$, $MR_{AUC0\text{-}\infty}$, and MR_{Cmax}, which were all reduced compared to administration of CBD in the fasted condition. These findings suggest that metabolic transformation of CBD was not affected by different food types or milk. By contrast, exposure to 7-COOH-CBD in the alcohol group was considerably lower than in any other group, despite an increase in CBD exposure in this treatment group. The reason for decreased exposure 7-COOH-CBD relative to other test treatment conditions when CBD was given with alcohol is unknown, but may be due to inhibition of the biotransformation pathway leading to 7-COOH-CBD.

In terms of the effect of a high-fat meal on the PK of the CBD metabolites, the current trial data are consistent with an earlier food effect trial in which concentrations of the same metabolites were measured.[11]

The high variability in the PK of CBD and its metabolites in this trial is common with other cannabinoids.[11–14,23,24] During validation of the bioanalytical method to quantify CBD and metabolite plasma concentrations, recovery of CBD was low at 45.4%-48.8%; however, recovery levels were consistent across the assay range and sufficient to achieve adequate method sensitivity.

Although this trial was designed to explore extreme scenarios in terms of food intake—strict overnight fasting conditions versus extreme dietary conditions—real-life patients are likely to be taking food of various composition throughout the day and their prandial status may vary. Given that a significant food effect has been demonstrated for CBD, particularly with high-fat meals, this extrinsic variable may be considered on a case by case basis in clinical practice to reduce variability in exposure to CBD and its metabolites.

4.2 | Safety

A single dose of 750 mg CBD was tolerated across all five treatment conditions. There were no deaths, or severe or serious AEs, and no AEs led to withdrawal. There were no clinically significant laboratory, physical examination, vital sign, or ECG findings during the trial. There was no evidence of suicidal behavior or ideation.

5 | CONCLUSION

Cannabidiol exposure increased under all test treatment conditions in this trial when compared to the fasted state.

Compared to fasting, CBD and metabolite exposures increased most with a high-fat/calorie meal, followed by a lower fat meal, whole milk, and to a lesser extent, alcohol (except for 7-COOH-CBD, which decreased, relative to the other test treatment conditions, with alcohol). Inter- and intrasubject variability in PK parameters was moderate to high during the trial. The 750-mg CBD dose used in this trial was tolerated across test conditions. There were no serious or severe AEs in this trial, and no new safety concerns were identified.

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CONFLICT OF INTERESTS

J.C., D.C., B.T., J.B., and G.M. are employees of GW Research. J.C., B.T., and G.M. own share options in GW Pharmaceuticals. This trial was sponsored by GW Research. 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.

DATA AVAILABILITY STATEMENT

The sponsor is adhering to current US and EU requirements so will not make individual deidentified participant data available; however, the protocol and statistical analysis plan will be made available upon request to the corresponding author.

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