



A Phase I, Open-Label, Pharmacokinetic Trial to Investigate Possible Drug-Drug Interactions Between Clobazam, Stiripentol, or Valproate and Cannabidiol in Healthy Subjects

Clinical Pharmacology
in Drug Development
2019, 8(8) 1009–1031
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Published by Wiley Periodicals, Inc. on
behalf of The American College of
Clinical Pharmacology
DOI: 10.1002/cpdd.665

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Abstract

GW Pharmaceuticals' formulation of highly purified cannabidiol oral solution is approved in the United States for seizures associated with Lennox-Gastaut and Dravet syndromes in patients aged ≥ 2 years, for which clobazam, stiripentol, and valproate are commonly used antiepileptic drugs. This open-label, fixed-sequence, drug-drug interaction, healthy volunteer trial investigated the impact of cannabidiol on steady-state pharmacokinetics of clobazam (and N-desmethyclobazam), stiripentol, and valproate; the reciprocal effect of clobazam, stiripentol, and valproate on cannabidiol and its major metabolites (7-hydroxy-cannabidiol [7-OH-CBD] and 7-carboxy-cannabidiol [7-COOH-CBD]); and cannabidiol safety and tolerability when coadministered with each antiepileptic drug. Concomitant cannabidiol had little effect on clobazam exposure (maximum concentration [$C_{\max}$] and area under the concentration-time curve [AUC], 1.2-fold), N-desmethyclobazam exposure increased ($C_{\max}$ and AUC, 3.4-fold), stiripentol exposure increased slightly ($C_{\max}$, 1.3-fold; AUC, 1.6-fold), while no clinically relevant effect on valproate exposure was observed. Concomitant clobazam with cannabidiol increased 7-OH-CBD exposure ($C_{\max}$, 1.7-fold; AUC, 1.5-fold), without notable 7-COOH-CBD or cannabidiol increases. Stiripentol decreased 7-OH-CBD exposure by 29% and 7-COOH-CBD exposure by 13%. There was no effect of valproate on cannabidiol or its metabolites. Cannabidiol was moderately well tolerated, with similar incidences of adverse events reported when coadministered with clobazam, stiripentol, or valproate. There were no deaths, serious adverse events, pregnancies, or other clinically significant safety findings.

Keywords

cannabidiol, clobazam, drug-drug interaction, pharmacokinetics, stiripentol, valproate

GW Pharmaceuticals' (GW's) highly purified formulation of cannabidiol oral solution (cannabidiol) was US Food and Drug Administration approved (in the United States) in June 2018 for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients aged ≥ 2 years. In vitro studies and an in vivo generalized seizure model showed that cannabidiol reduced seizure severity,¹ and in recent phase 3 trials, cannabidiol at doses up to 20 mg/kg/day was effective in reducing the frequency of treatment-resistant seizures in patients with DS (where the target patient population included only pediatric patients)² and LGS (where the target patient population included both pediatric and adult patients).^{3,4} These data are supported by results published from a multisite open-label expanded access program of cannabidiol,

first in 214 pediatric and adult patients with treatment-resistant epilepsies,⁵ and most recently in 607 patients.⁶

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Submitted for publication 5 October 2018; accepted 20 January 2019.

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It is important to consider the possibility of drug-drug interactions (DDIs) between cannabidiol and commonly used antiepileptic drugs (AEDs) because it is anticipated that cannabidiol will be used concomitantly with AEDs including clobazam, stiripentol, and valproate, as these drugs are considered first- and second-line treatment options in DS and LGS.⁷⁻⁹ In human liver microsomes, cannabidiol is metabolized by cytochrome P450 (CYP) 2C19 to its active metabolite 7-hydroxy-cannabidiol (7-OH-CBD), and then further metabolized by CYP3A4 to its inactive metabolite 7-carboxy-cannabidiol (7-COOH-CBD).^{10,11} In vitro studies suggest that cannabidiol is a potent inhibitor of both CYP2C19 and CYP3A4 and a weaker CYP2D6 inhibitor¹²⁻¹⁴; however, results from a recent phase 1 healthy volunteer trial demonstrated that cannabidiol has no clinically relevant effects on the activity of CYP3A4 because steady-state administration of cannabidiol did not alter the systemic exposure, terminal half-life, or plasma clearance of the CYP3A4 probe midazolam.¹⁵ Cannabidiol can also be directly conjugated by uridine 5'-diphospho-glucuronosyltransferases (UGTs), particularly UGT1A7, UGT1A9, and UGT2B7.¹⁶ The 3 commonly used AEDs investigated in this trial were clobazam (a 1,5-benzodiazepine), stiripentol (an aromatic alkyl alcohol), and valproate (a fatty acid derivative). Clobazam exhibits nonlinear pharmacokinetics, and its major active metabolite is N-desmethyloclobazam (N-CLB),¹⁷⁻¹⁹ which, at steady state, is present at approximately 8-fold the plasma concentration of parent clobazam.²⁰ In vitro studies have demonstrated that the N-demethylation of CLB to N-CLB is predominantly mediated by CYP3A4 and the subsequent hydroxylation of N-CLB is catalyzed by CYP2C19.²¹ N-CLB is a sensitive CYP2C19 substrate and levels of N-CLB are significantly elevated in subjects who are poor metabolizers for CYP2C19.^{22,23} Stiripentol also exhibits nonlinear pharmacokinetics^{24,25} and is a potent inhibitor of CYP2C19 and CYP3A4.²⁶ Likely as a result of the role of CYP2C19 in the metabolism of N-CLB and the inhibitory effect of stiripentol on CYP2C19 activity, there have been pharmacokinetic (PK) interactions reported between stiripentol and clobazam.²⁷ Valproate is extensively plasma protein bound and the amount of circulating, unbound, pharmacologically active drug as well as the metabolic flux influences the clearance of valproate.²⁸ Valproate is metabolized in the liver via at least 3 routes (reviewed in Ghodke-Puranik et al²⁹): glucuronidation and β -oxidation are the major metabolic pathways, and the main valproate metabolite found in urine is valproate glucuronide formed by multiple UGT enzymes; CYP (CYP2C9, CYP2B6 and CYP2A6)-mediated desaturation and oxidation of val-

proate to form 2-propyl-4-pentenoic acid (4-ene-VPA) and other metabolites are minor metabolic routes. In patients, concomitant administration of cannabidiol with clobazam resulted in an increase in the plasma concentration of N-CLB³⁰⁻³² often associated with increased sedation, a recognized adverse event (AE) noted with clobazam administration for the treatment of LGS.³³ Increases in liver transaminases are more common in patients who are taking cannabidiol with valproate (which is associated with hepatotoxicity³⁴) than in those who are not.³¹ Given that in these patient trials, the majority of patients were on multiple concomitant AEDs, the importance of this phase 1 trial was evident: to understand the potential for PK interactions between cannabidiol and 3 commonly used other AEDs in a healthy population who were not taking other AEDs.

The primary objectives of this phase 1 trial in healthy male and female subjects were:

1. To assess the effect of multiple dose administration of cannabidiol as the perpetrator drug on steady-state plasma concentrations of each of the AED victim drugs:
 - a) Clobazam (and its active metabolite, N-CLB)
 - b) Stiripentol
 - c) Valproate (and its potentially hepatotoxic metabolite,^{35,36} 4-ene-VPA);
2. To assess the effect of multiple dose administration of clobazam, stiripentol, or valproate as perpetrator drugs, on steady-state plasma concentrations of the victim analytes cannabidiol and its metabolites 7-OH-CBD and 7-COOH-CBD.

The secondary objective was to evaluate the safety and tolerability of cannabidiol when given concurrently with each of these 3 AEDs.

Methods

Independent Ethics Committee Approval

The protocol and the informed consent forms were submitted for review and approved by the Independent Ethics Committee of the Foundation Evaluation of Ethics in Biomedical Research, Assen, The Netherlands, before eligibility screening. Written informed consent was obtained from each subject before any trial-related procedures were performed, and additional consent was obtained prior to collection of a blood sample for CYP2C19.

Trial Design

This was an open-label, fixed-sequence, DDI trial carried out between November 4, 2015, and November 18, 2016, at PRA Health Sciences–Early Development

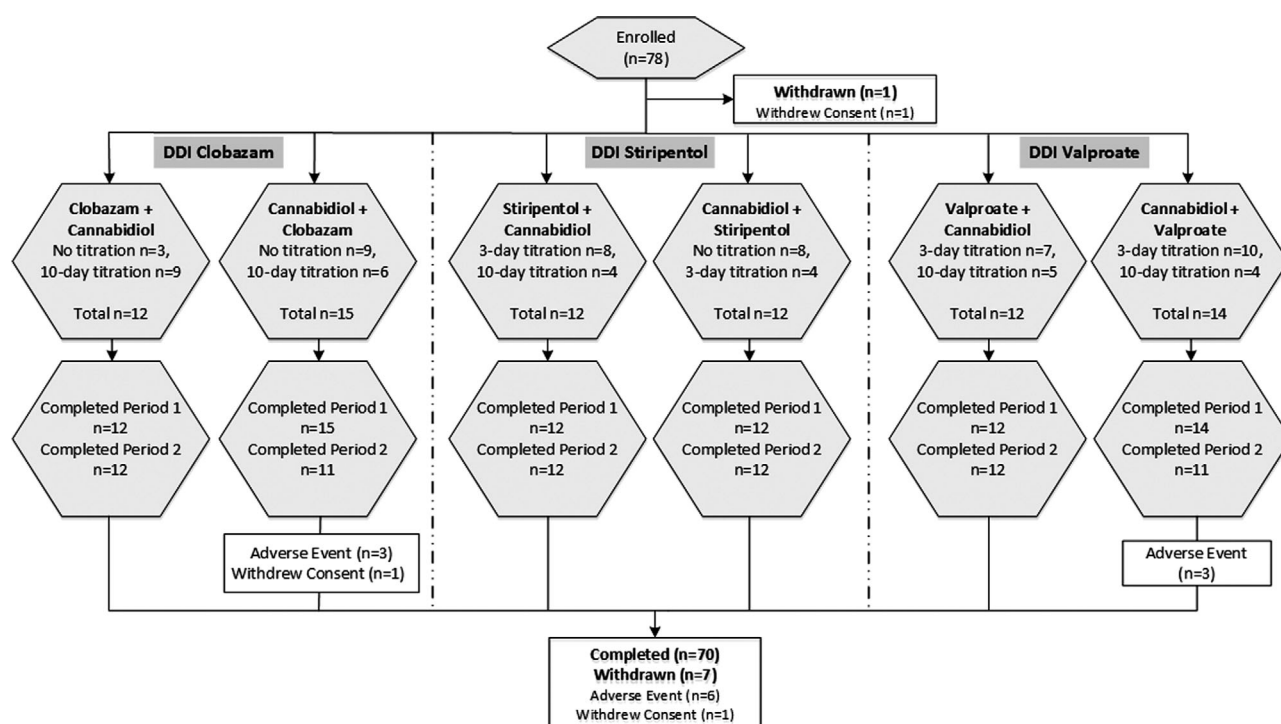


Figure 1. Disposition of subjects. Period 1, victim drug alone; period 2, victim and perpetrator drugs in combination.

Table 1. Summary of Clobazam, Stiripentol, and Valproate Drug-Drug Interactions Investigated in the Trial

Substudy Descriptor	Victim Analytes	Perpetrator Drug
Clobazam + Cannabidiol (n = 12) Cannabidiol + Clobazam (n = 15)	DDI Clobazam Steady-state clobazam (+ N-desmethyclobazam)	Steady-state cannabidiol
	Steady-state cannabidiol (+ 7-OH-CBD and 7-COOH-CBD)	Steady-state clobazam
Stiripentol + Cannabidiol (n = 12) Cannabidiol + Stiripentol (n = 12)	DDI Stiripentol Steady-state stiripentol	Steady-state cannabidiol
	Steady-state cannabidiol (+ 7-OH-CBD and 7-COOH-CBD)	Steady-state stiripentol
Valproate + Cannabidiol (n = 12) Cannabidiol + Valproate (n = 14)	DDI Valproate Steady-state valproate (+ 4-ene-VPA)	Steady-state cannabidiol
	Steady-state cannabidiol (+ 7-OH-CBD and 7-COOH-CBD)	Steady-state valproate

4-ene-VPA, 2-propyl-4-pentenoic acid; 7-OH-CBD, 7-hydroxy-cannabidiol; 7-COOH-CBD, 7-carboxy-cannabidiol; DDI, drug-drug interaction.

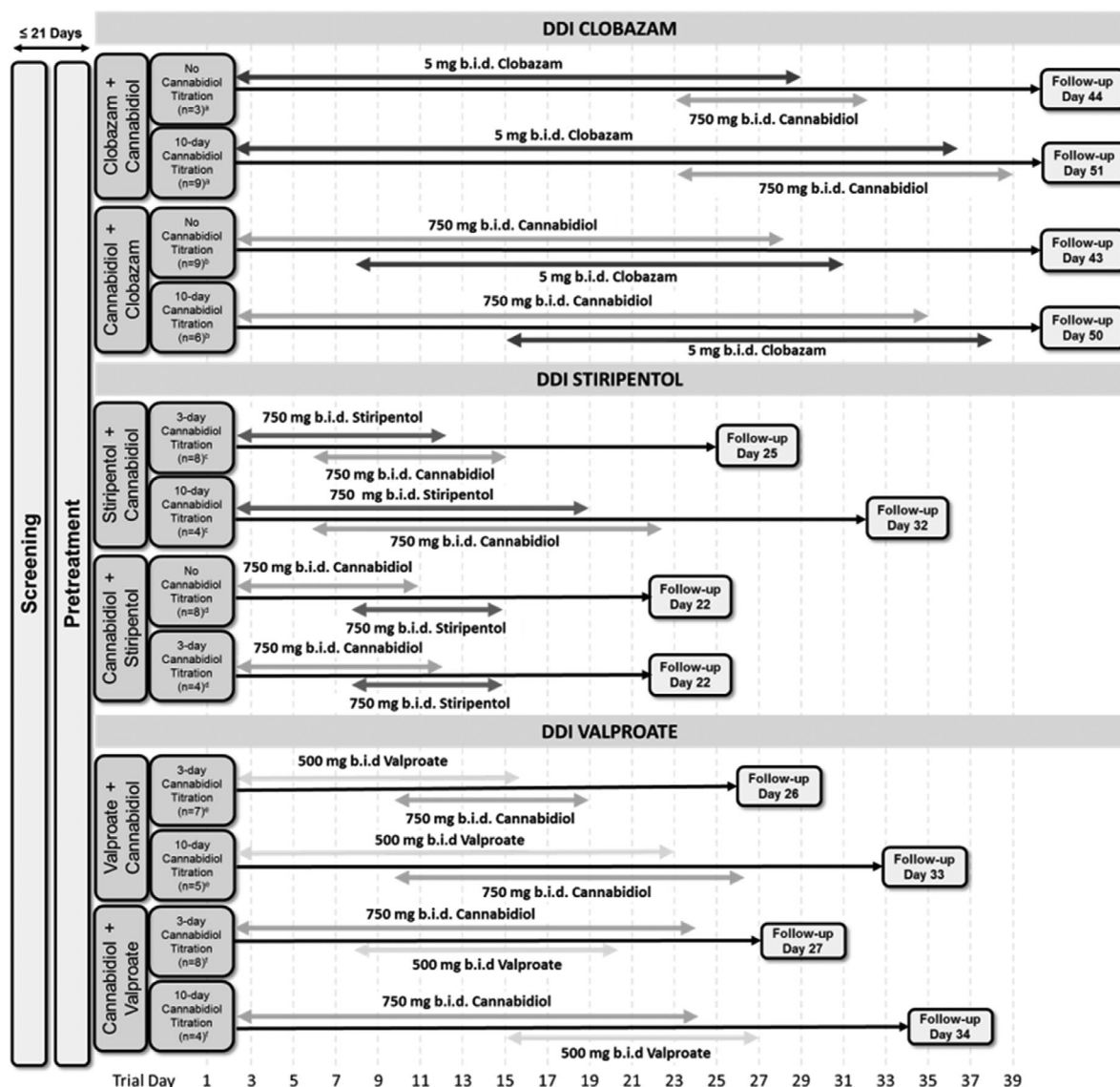
Services clinical sites in Groningen and Zuidlaren, The Netherlands.

The trial enrolled a total of 78 healthy subjects overall (of which 1 subject withdrew prior to receiving treatment) to investigate the potential DDIs between GW's formulation of cannabidiol oral solution (Epidiolex® in the United States) and clobazam, stiripentol, and valproate (Figure 1 and Table 1).

A summary of the treatment duration and dosing regimens for each group is given in Figure 2. All subjects were admitted to the clinical research unit during first-dose administration and, where applicable, for the cannabidiol titration periods. Subjects were instructed

on how to self-administer the cannabidiol and/or their assigned concomitant AED and, between visits to the clinical research unit, doses were administered at home. PK sampling was performed at the clinical research unit at serial time points between predose and up to 72 hours after dosing.

The trial was placed on temporary hold after the occurrence of a number of nonserious cases of rash AEs that had no associated systemic symptoms. Formal investigation, coordinated by GW, did not reveal a definitive cause for the rash, and no link to the investigational medicinal product (IMP) was established. The trial design was subsequently amended to include a titration



^a During Period 1, (clobazam alone), all subjects were dosed with a 1-day clobazam titration.

^b During Period 2 (clobazam + cannabidiol), all subjects were dosed without a clobazam titration.

^c During Period 1, (stiripentol alone), all subjects were dosed with a 1-day stiripentol titration.

^d During Period 2, (stiripentol + cannabidiol), all subjects were dosed without a stiripentol titration period.

^e During Period 1, (valproate alone), all subjects were dosed with a 5-day valproate titration period.

^f During Period 2 (cannabidiol + valproate), all subjects were dosed with a 5-day valproate titration period.

Figure 2. Treatment schema for DDI clobazam, DDI stiripentol, and DDI valproate. Period 1, victim drug alone; period 2, victim and perpetrator drugs in combination. DDI, drug-drug interaction.

period for cannabidiol administration over 3 days, and then extended to 10 days, to align with completed and ongoing studies where incidences of rash had been low. In addition, instead of being given prefilled syringes that were administered up to 1 week after being prepared, subjects were given a bottle of cannabidiol and a syringe and instructed to withdraw the correct dose immediately before administration.

The main criteria for inclusion in the trial were that subjects had to be healthy, male or female, and between 18 and 55 years old (inclusive) with a body mass index between 18.0 and 32.0 kg/m² (inclusive). Criteria for exclusion from trial participation included a history of alcohol or drug addiction, current or recent (within the previous 3 months) use of medicinal or recreational cannabis, and significantly impaired hepatic function.

Samples for analysis of CYP2C19 genotype status were collected from all subjects who signed the informed consent form.

Sample Size

For this exploratory trial, no prospective calculations of statistical power were made for any of the AED + cannabidiol or cannabidiol + AED treatment regimens. The sample size was selected to provide information on the safety, tolerability, and a general indication of the effect of cannabidiol on steady-state plasma concentrations of clobazam (and N-CLB), stiripentol, or valproate (and 4-ene-VPA), and the effect of clobazam, stiripentol, or valproate on steady-state plasma concentrations of cannabidiol.

Investigational Medicinal Products

Cannabidiol

GW's pharmaceutical formulation of highly purified cannabidiol derived from *Cannabis sativa* L. plant in oral solution is manufactured to Current Good Manufacturing Practice standards (100 mg/mL; GW Research Ltd, Cambridge, UK). As shown in Figure 2, the target dose and regimen was 750 mg twice daily (bid), which is equivalent to the highest dose used in recent phase 3 trials in DS and LGS.²⁻⁴ Cannabidiol was administered with no titration, 3-day titration, or 10-day titration, depending on whether the subjects were dosed before or after the trial was temporarily halted and protocol amended.

Clobazam

Clobazam was manufactured by De Collegiale Bereider (Oldenzaal, The Netherlands) and presented as a single 5-mg oral tablet. The target dose and regimen was 5 mg bid. This 10 mg/day dose is at the low end of the starting dose suggested in the clobazam prescribing information. The target dose was therefore selected to anticipate a possible increase in exposure with concomitant cannabidiol through inhibition of the CYP enzymes 2C19 and 3A4. When clobazam was administered alone, as the victim drug, the subjects were given a single morning 5-mg dose on days 1 and 5 mg bid thereafter, including 7 to 14 days of dosing concomitant with cannabidiol, and a final single morning dose on the final day of treatment. When clobazam was administered as the perpetrator drug, subjects went straight into bid dosing on the first day of period 2 with 21 days of dosing concomitant with cannabidiol and a single morning dose on the last day of treatment.

Stiripentol

Stiripentol (registered as Diacomit in Europe) was manufactured by Biocodex Benelux NV (Brussels,

Belgium) and presented as 250- and 500-mg oral capsules. The target dose and regimen was 750 mg bid, which is at the low end of the therapeutic range for stiripentol. In the absence of DDI data from clinical trials to date, an interaction of cannabidiol with stiripentol at both the perpetrator and victim level could not be excluded because of the common CYP enzyme (CYP2C19 and CYP3A4) involvement. When stiripentol was administered alone, as the victim drug, the subjects were given a single morning 750-mg dose on day 1 and 750 mg bid thereafter, including 7 to 14 days of dosing concomitant with cannabidiol, with a final single morning dose on the final day of treatment. When stiripentol was administered as the perpetrator drug, subjects went straight into bid dosing on the first day of period 2 with 5 days of dosing concomitant with cannabidiol and a single morning dose on the last day of treatment.

Valproate

Valproate (valproate sodium, registered as Depakine Enteric in the Netherlands) was manufactured by Sanofi Aventis Netherlands B.V. and presented as 300- and 500-mg oral tablets (enteric coated). The target dose and regimen of 500 mg bid in this trial is standard for epilepsy and in the low therapeutic range to enable good tolerability and to avoid possible hepatic impairment should there have been increased valproate exposure from any possible interaction. When valproate was administered alone, as the victim drug, the subjects were given a single morning 300-mg dose on day 1 and completed a 5-day titration to 500 mg bid, followed by 7 to 14 days of dosing concomitant with cannabidiol, with a final single morning dose on the final day of valproate treatment. When valproate was administered as the perpetrator drug, subjects went straight into bid dosing on the first day of period 2, had 10 days of concomitant dosing with cannabidiol and a single morning dose of valproate on the last day of treatment.

Cannabidiol and AED administration

For each part of the trial, the first dose was administered on day 1 and the 6 groups were treated following specific treatment regimens as summarized in Figure 2. For once daily dosing, each IMP was to be taken between 8:00 AM and 11:00 AM (morning dose). For bid dosing, the morning dose of the IMP was to be taken between 8:00 AM and 11:00 AM and the evening dose was to be taken 12 hours later. Dosing for each individual subject was to be at around the same time (± 1 hour) on each dosing day and was to occur 30 minutes after the start of a meal. In every case, the final dose of IMP was a morning dose.

Table 2. Demographics and Baseline Characteristics (Safety Set and PK Set)

		DDI Clobazam		DDI Stiripentol		DDI Valproate	
		Clobazam + Cannabidiol (n = 12)	Cannabidiol + Clobazam (n = 15)	Stiripentol + Cannabidiol (n = 12)	Cannabidiol + Stiripentol (n = 12)	Valproate + Cannabidiol (n = 12)	Cannabidiol + Valproate (n = 14)
Characteristic		Number of Subjects (%)					
Sex	Male	11 (91.7)	9 (60.0)	7 (58.3)	8 (66.7)	6 (50)	9 (64.3)
	Female	1 (8.3)	6 (40.0)	5 (41.7)	4 (33.3)	6 (50)	5 (35.7)
Race	Multiple	3 ^a (25.0)	1 ^b (6.7%)	0	0	1 ^b (8.3)	0
	White	8 (66.7)	12 (80.0)	8 (66.7)	11 (91.7)	10 (83.3)	13 (92.9)
	Asian	0	1 (6.7)	2 (16.7)	0	0	0
	Black or African American	1 (8.3)	1 (6.7)	2 (16.7)	1 (8.3)	1 (8.3)	1 (7.1)
CYP2C19 phenotype ^c	Poor metabolizer	0	0	0	0	1 (8.3)	0
	Intermediate metabolizer	1 (8.3)	3 (20.0)	1 (8.3)	2 (16.6)	3 (25.0)	1 (7.1)
	Extensive metabolizer	5 (41.7)	6 (40.0)	5 (41.7)	5 (41.7)	5 (41.7)	8 (57.1)
	Ultrarapid metabolizer	6 (50.0)	4 (26.7)	5 (41.7)	5 (41.7)	2 (16.6)	5 (35.7)
	Undetermined metabolizer	0	2 (13.3)	1 (8.3)	0	1 (8.3)	0
		Mean (SD)					
Age (years)		27.3 (10.9)	27.7 (8.2)	35.1 (12.6)	35.1 (12.9)	26.2 (4.0)	29.9 (10.5)
Weight (kg)		81.96 (13.63)	74.77 (13.00)	71.25 (13.28)	81.13 (14.35)	77.33 (13.41)	74.48 (12.28)
Height (cm)		179.2 (6.2)	173.4 (8.3)	171.6 (8.8)	177.4 (10.8)	176.2 (9.2)	178.8 (12.1)
BMI (kg/m ²)		25.61 (4.54)	24.81 (3.52)	24.13 (3.63)	25.71 (3.52)	24.89 (3.78)	23.21 (2.22)

BMI, body mass index; CYP2C19, cytochrome P450 2C19; DDI, drug-drug interaction; PK, pharmacokinetic; SD, standard deviation.

^aTwo subjects, black or African American + white; 1 subject, black or African American + American Indian or Alaska Native.

^bWhite + Asian.

^cInferred metabolic status for CYP2C19 genotypes was assigned based on functional classification of the specific alleles carried by each subject.⁴¹ Extensive metabolizer genotype: CYP2C19 *1/*1 - no mutations or variant alleles within CYP2C19 detected; intermediate metabolizer genotypes: CYP2C19 *1/*2 or CYP2C19 *1 + *34; poor metabolizer genotype: CYP2C19 *2/*2; ultrarapid metabolizer genotype: CYP2C19 *1/*1 + *17 or CYP2C19 *1/*1 + *17/*17; undetermined metabolizer genotype: CYP2C19 *1/*2 + *17.

Materials

Reference and internal standards for 7-OH-CBD, 7-COOH-CBD, delta-9-tetrahydrocannabinol (THC), 11-hydroxy-delta-9-tetrahydrocannabinol (11-OH-THC), 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (11-COOH-THC), clobazam, N-CLB, stiripentol, valproate, and 4-ene-VPA bioanalysis were supplied as solids or certified solutions by GW Pharma Ltd (Cambridge, UK), Alsachim (Illkirch-Graffenstaden, France), Cerilliant (Round Rock, Texas), Sigma-Aldrich (St Louis, Missouri), or BDG Synthesis (Palo Alto, California).

Pharmacokinetic Sample Collection

Blood samples were taken via an indwelling intravenous catheter or by direct venipuncture at protocol-defined time points, detailed in Table 2. Cannabidiol and metabolite samples were extracted from plasma by protein precipitation with isopropyl alcohol and acetonitrile. Because THC is present as an impurity

in cannabidiol (not more than 0.10% [w/w]), THC and metabolite levels were also analyzed and samples were extracted by liquid-liquid extraction. AED and metabolite (as applicable) samples were extracted by protein precipitation.

Bioanalysis

Using validated high-performance liquid chromatography with tandem mass spectrometry detection and quantitation methods, plasma concentrations of cannabidiol and its major metabolites were determined at LGC (Fordham, UK).

Plasma concentrations of THC and its metabolites clobazam (and N-CLB), stiripentol, and valproate (and 4-ene-VPA) were determined at Covance Laboratories Ltd (Harrogate, UK).

Details of the extraction methods, internal standards, high-performance liquid chromatography and tandem mass spectrometry settings, m/z monitoring,

limits of sensitivity, and precision and accuracy for all analytes are provided in Table S1.

In summary, the lower limit of quantification for each analyte was 2.00 ng/mL for cannabidiol, 0.250 ng/mL for 7-OH-CBD and 7-COOH-CBD, 0.125 ng/mL for THC, 0.250 ng/mL for 11-OH-THC and 11-COOH-THC, 1 ng/mL for clobazam and N-CLB, 20.0 ng/mL for stiripentol, 500 ng/mL for valproate, and 3000 ng/mL for 4-ene-VPA. All analyte calibration curves were created using weighted least squares linear or quadratic regression. There were no significant interfering peaks observed at the retention times for any of the analytes, indicating adequate selectivity of the methods.

The precision (coefficient of variation) and accuracy (relative error [RE%]/mean % different [Bias%]) of the high-performance liquid chromatography method was determined by analysis of the plasma samples, and were acceptable for all analytes ($\leq 15\%$ [20% at the lower limit of quantification]).

CYP2C19 Genotype Analysis

Blood samples for genetic analysis were collected on day -1 of the trial from subjects who had provided additional written, informed consent. DNA was extracted and the sequence of CYP2C19 analyzed by Sanger sequencing at Sheffield Diagnostic Genetics Service (Sheffield, UK). Predicted CYP2C19 metabolic status was assigned to each subject based on carriage of specific CYP2C19 alleles with known function³⁷: carriers of 2 CYP2C19 wild-type alleles were classified as extensive metabolizers, carriers of at least 1 allele conferring increased function were classified as ultrarapid metabolizers, carriers of 1 dysfunctional allele were classified as poor metabolizers and heterozygous carriers were classified as intermediate metabolizers.³⁸ If subjects carried alleles of unknown function, they were classified as undetermined metabolizers.

Safety Analyses

Safety and tolerability assessment was based on the number, type, and severity of AEs, clinical laboratory tests, vital signs, 12-lead electrocardiogram (ECG), physical examination, and Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire.

AEs were recorded from the moment informed consent was completed by the subject until completion of the follow-up visit. Any clinically significant observations in the results of clinical laboratory tests, ECGs, vital signs, or physical examinations were recorded as AEs. A treatment-emergent AE was defined as any event not present before (the first) administration of the IMP, or any event already present that worsened in either severity or frequency following exposure to the

IMP. An AE that occurred before (the first) administration of the IMP was considered a pretreatment AE.

Statistical Methods

The safety set was defined as all subjects who received at least 1 dose of cannabidiol, clobazam, stiripentol, or valproate. Subject disposition, demographics and baseline characteristics, medical history, AEs, clinical laboratory tests (biochemistry, hematology, urinalysis), vital signs (supine systolic and diastolic blood pressure, pulse rate, body temperature, respiratory rate), ECG, physical examination findings, and results from the C-SSRS were summarized and listed.

The PK set was defined as all subjects who received at least 1 dose of cannabidiol, clobazam, stiripentol or valproate, and provided sufficient evaluable time points to calculate reliable estimates of the PK parameters. For cannabidiol (and 7-OH-CBD, 7-COOH-CBD), clobazam (and N-CLB), stiripentol, and valproate (and 4-ene-VPA), the following PK parameters were estimated by noncompartmental methods using Phoenix WinNonlin Version 6.3 (Certara, Princeton, New Jersey): maximum observed plasma concentration ($C_{\max}$), time to attain maximum observed plasma concentration, and area under the plasma concentration-time curve over a dosing interval, where tau is the dosing interval (AUC_{τ}).

Descriptive statistics (n, mean, geometric mean, standard deviation, geometric coefficient of variation, median, minimum, and maximum) were used to summarize the calculated PK parameters by group, "victim"/"perpetrator," drug name, and analyte.

A linear mixed-effects model appropriate for this fixed-sequence design was used to compare the victim drug PK ($C_{\max}$ and AUC_{τ}) after multiple dosing alone, with the victim drug PK combined with multiple dosing with the perpetrator drug; using treatment (alone or combined) as a fixed factor and subject as a random factor. Point estimates and 90% confidence intervals (CIs) for the ratios of the treatment geometric means (treatment ratio [TR]) were provided, and a lack of interaction was concluded if the 90%CIs included 1.00.

Results

Disposition

Seventy-eight (100%) subjects were enrolled; however, 1 subject withdrew consent before receiving either trial drug. Seventy-seven (98.7%) subjects were administered cannabidiol and/or AED and included in the safety and PK analysis sets. Seventy subjects completed the trial, and 7 subjects were withdrawn—6 were due to an AE and 1 withdrew consent to participate. Seventy-seven subjects completed period 1 (AED or

cannabidiol alone), and 70 subjects completed period 2 (AED + cannabidiol or cannabidiol + AED). Figure 1 shows the disposition for all subjects enrolled in the trial.

Demographics and Baseline Characteristics

A summary of the demographic and baseline characteristics recorded on entry into the trial is presented in Table 2. There were more male subjects than female subjects in all groups except for the valproate + cannabidiol cohort, which had an equal number of male and female subjects. The majority of subjects (62; 80.5%) enrolled in the trial and $\geq 66.7\%$ in each cohort were white. Overall, 7 (9.1%) subjects were black or African American, 5 (6.5%) subjects were multiple race, and 3 (3.9%) subjects were Asian. Age was similar across the 6 subject groups: mean age ranged from 26.2 to 35.1 years. The mean body mass index across groups ranged from 23.21 to 25.71 kg/m².

The frequencies of CYP2C19 inferred metabolic status within each cohort of subjects are shown in Table 2. Overall, the frequencies of the CYP2C19 phenotypes were ranked as extensive metabolizers (34 of 77) > ultrarapid metabolizers (27 of 77) > intermediate metabolizers (11 of 77) > poor metabolizers (1 of 77), and 4 subjects were undetermined metabolizers. Given the low number of subjects with the CYP2C19 poor metabolizer phenotype, it was not possible to draw any conclusions regarding the impact of the impact of genotype status on the PK data.

Pharmacokinetics

Arithmetic mean ($\pm$ standard deviation) steady-state plasma concentrations of each of the victim analytes alone or in the presence of steady-state administration of perpetrator drugs are shown in Figure 3. Table 3 summarizes the steady-state PK parameters, and Figure 4 summarizes the treatment effect (for individual subjects and geometric mean ratios) for each victim analyte in every cohort.

Drug-Drug Interaction Clobazam

Clobazam (Victim) + Cannabidiol (Perpetrator). Following repeated concomitant dosing of cannabidiol (750 mg bid) with clobazam (5 mg bid) for 7 days (no titration) and 14 days (10-day titration), there was a slight increase in the exposure of clobazam with the point estimate for the TR for $C_{\max}$ of 1.20 (90%CI, 1.05–1.38) and for AUC_{τ} of 1.21 (90%CI, 1.05–1.39). There was an increase in systemic exposure to N-CLB, whereby the geometric mean $C_{\max}$ increased 3.39-fold (90%CI, 2.61–4.39) and AUC_{τ} increased 3.38-fold (90%CI, 2.62–4.36). Individual subject data revealed that these increases in exposure parameters were observed in all 13 subjects in this group (Figure 4A(i)).

Cannabidiol (Victim) + Clobazam (Perpetrator). Following 21 days of concomitant administration of 5 mg of clobazam bid with 750 mg of cannabidiol bid, there was a slight increase in cannabidiol exposure (TR for cannabidiol $C_{\max}$ and AUC_{τ} : 1.34 [90%CI, 0.93–1.95] and 1.30 [90%CI, 1.00–1.70] respectively) and for 7-COOH-CBD ($C_{\max}$ TR 1.35 [90%CI, 1.12–1.63] and AUC_{τ} TR 1.31 [90%CI, 1.04–1.64]). For cannabidiol and 7-COOH-CBD, increases in exposure parameters were observed in between 7 (58.3%) and 9 (75%) subjects in each group (Figure 3A(ii)). The TR point estimate for $C_{\max}$ of 7-OH-CBD increased by 1.73-fold (90%CI, 1.36–2.20) and AUC_{τ} increased with a TR of 1.47 (90%CI, 1.26–1.70). For both parameters, an increase was observed in all subjects when clobazam was added to cannabidiol (Figure 4A(ii)).

Stiripentol

Stiripentol (Victim) + Cannabidiol (Perpetrator). Following repeated concomitant dosing of cannabidiol (750 mg bid) with stiripentol (750 mg bid) for 7 days (3-day titration) and 14 days (10-day titration), there was a slight increase in exposure to stiripentol with point estimates for $C_{\max}$ and AUC_{τ} TR of 1.28 (90%CI, 1.08–1.52) and 1.55 (90%CI, 1.42–1.69), respectively. While AUC_{τ} increased in all subjects, $C_{\max}$ increased in 10 of 13 subjects (Figure 4B(i)).

Cannabidiol (Victim) + Stiripentol (Perpetrator). Four days' concomitant administration of 750 mg of stiripentol bid with 750 mg of cannabidiol bid had no important effect on the exposure to cannabidiol ($C_{\max}$ TR 1.13 [90%CI, 0.96–1.33] and AUC_{τ} TR 1.03 [90%CI, 0.94–1.14]); however, there were minor decreases in the exposure of 7-OH-CBD ($C_{\max}$ TR 0.71 [90%CI, 0.51, 0.99] and AUC_{τ} TR 0.72 [90%CI, 0.61–0.85]) and 7-COOH-CBD ($C_{\max}$ TR 0.87 [90%CI, 0.80–0.96] AUC_{τ} TR 0.87 [90%CI, 0.81–0.94]) (Figure 4B(ii)).

Valproate

Valproate (victim) + Cannabidiol (perpetrator). There was no effect of 7 (3-day titration) or 14 days' (10-day titration) concomitant administration of 750 mg of cannabidiol bid with 500 mg of valproate bid on the exposure to valproate; the point estimates for the geometric mean $C_{\max}$ and AUC_{τ} TRs were 1.01 (90%CI, 0.95–1.07) and 0.99 [90%CI, 0.90–1.09]), respectively. There was no obvious increase in $C_{\max}$ and AUC_{τ} in any subjects (Figure 4C(i)). For the 4-ene-VPA metabolite, all plasma concentrations were below the limit of quantification, probably reflecting the lack of sensitivity of the assay (data not shown).

Cannabidiol (victim) + Valproate (perpetrator). Following up to 10 days of concomitant administration of 500 mg of valproate bid and 750 mg of cannabidiol

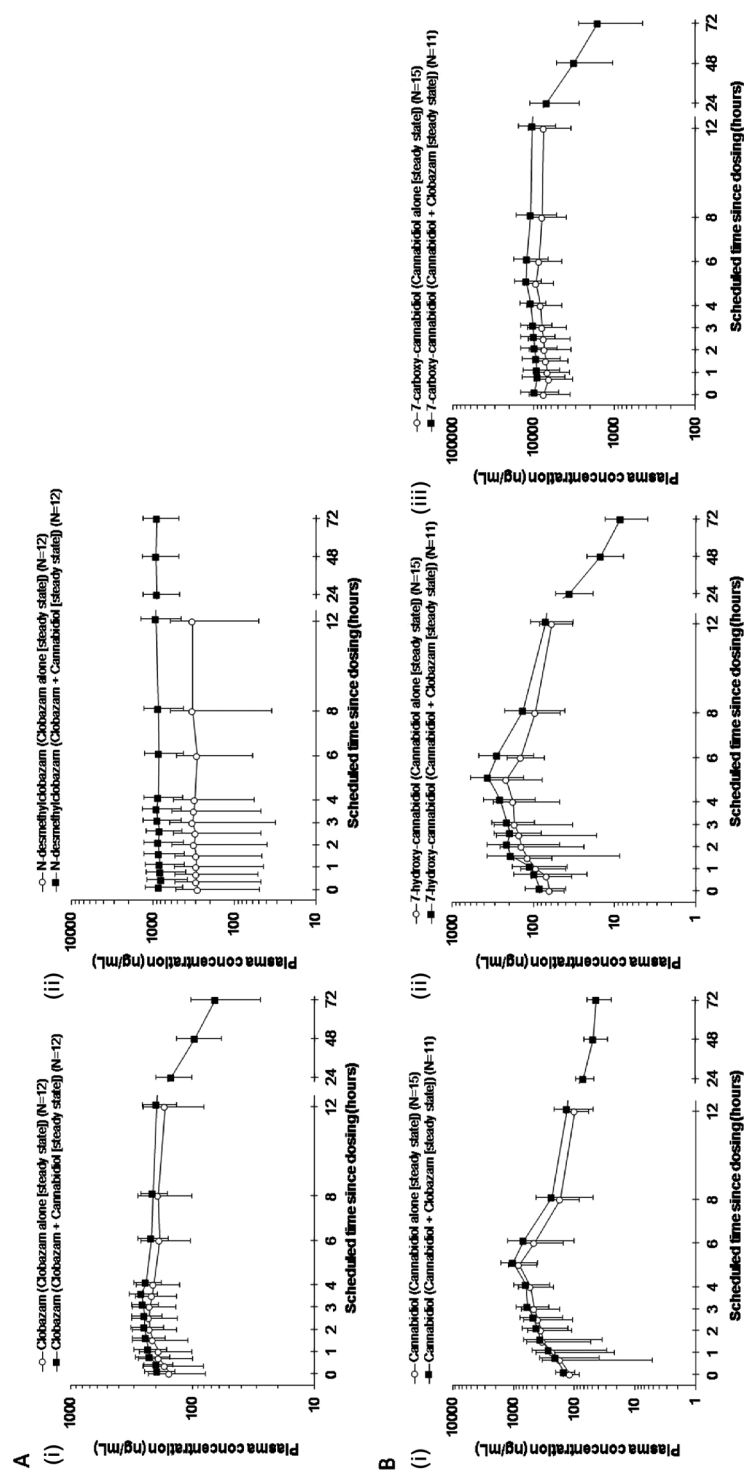


Figure 3. (A) DDI clobazam. The effect of concomitant administration of 750 mg of cannabidiol bid on plasma concentrations of (i) clobazam and (ii) N-desmethyloclobazam (arithmetic mean $\pm$ SD [lower tail is not shown if greater than mean value]). (B) The effect of concomitant administration of 5 mg of clobazam bid on plasma concentrations of (i) cannabidiol, (ii) 7-OH-CBD, and (iii) 7-COOH-CBD (arithmetic mean $\pm$ SD [lower tail is not shown if greater than mean value]). (C) DDI stiripentol. The effect of concomitant administration of 750 mg of cannabidiol bid on plasma concentrations of (i) stiripentol (arithmetic mean $\pm$ SD [lower tail is not shown if greater than mean value]). (D) The effect of concomitant administration of 750 mg of stiripentol bid on plasma concentrations of (i) cannabidiol, (ii) 7-OH-CBD, and (iii) 7-COOH-CBD (arithmetic mean $\pm$ SD [lower tail is not shown if greater than mean value]). (E) DDI valproate. The effect of concomitant administration of 750 mg of cannabidiol bid on plasma concentrations of (i) valproate (arithmetic mean $\pm$ SD [lower tail is not shown if greater than mean value]). (F) The effect of concomitant administration of 750 mg of valproate, on plasma concentrations of (i) cannabidiol, (ii) 7-OH-CBD, and (iii) 7-COOH-CBD (arithmetic mean $\pm$ SD [lower tail is not shown if greater than mean value]). 7-OH-CBD, 7-hydroxy-cannabidiol; 7-COOH-CBD, 7-carboxy-cannabidiol; CI, confidence interval; DDI, drug-drug interaction; SD, standard deviation.

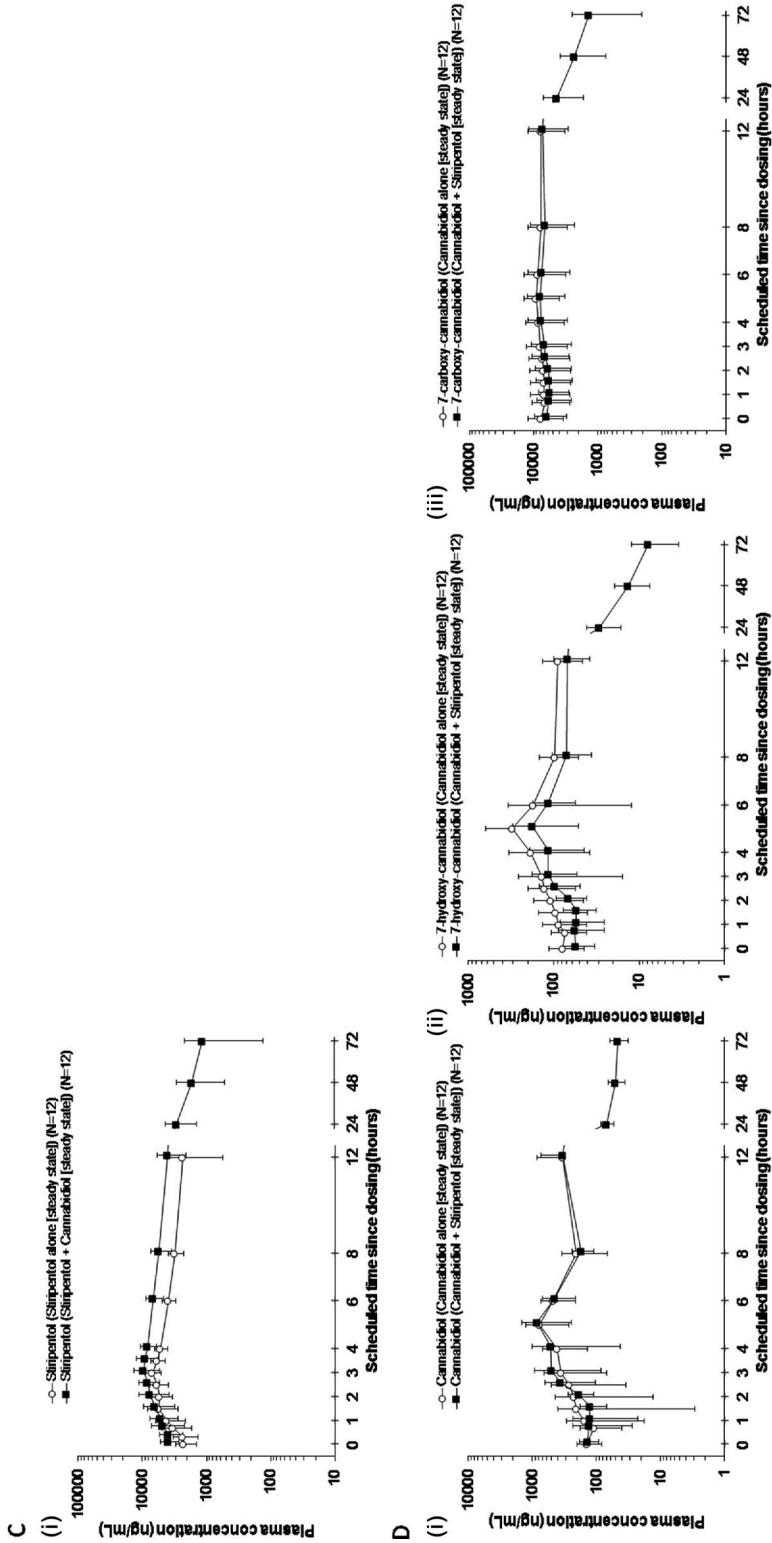


Figure 3. Continued.

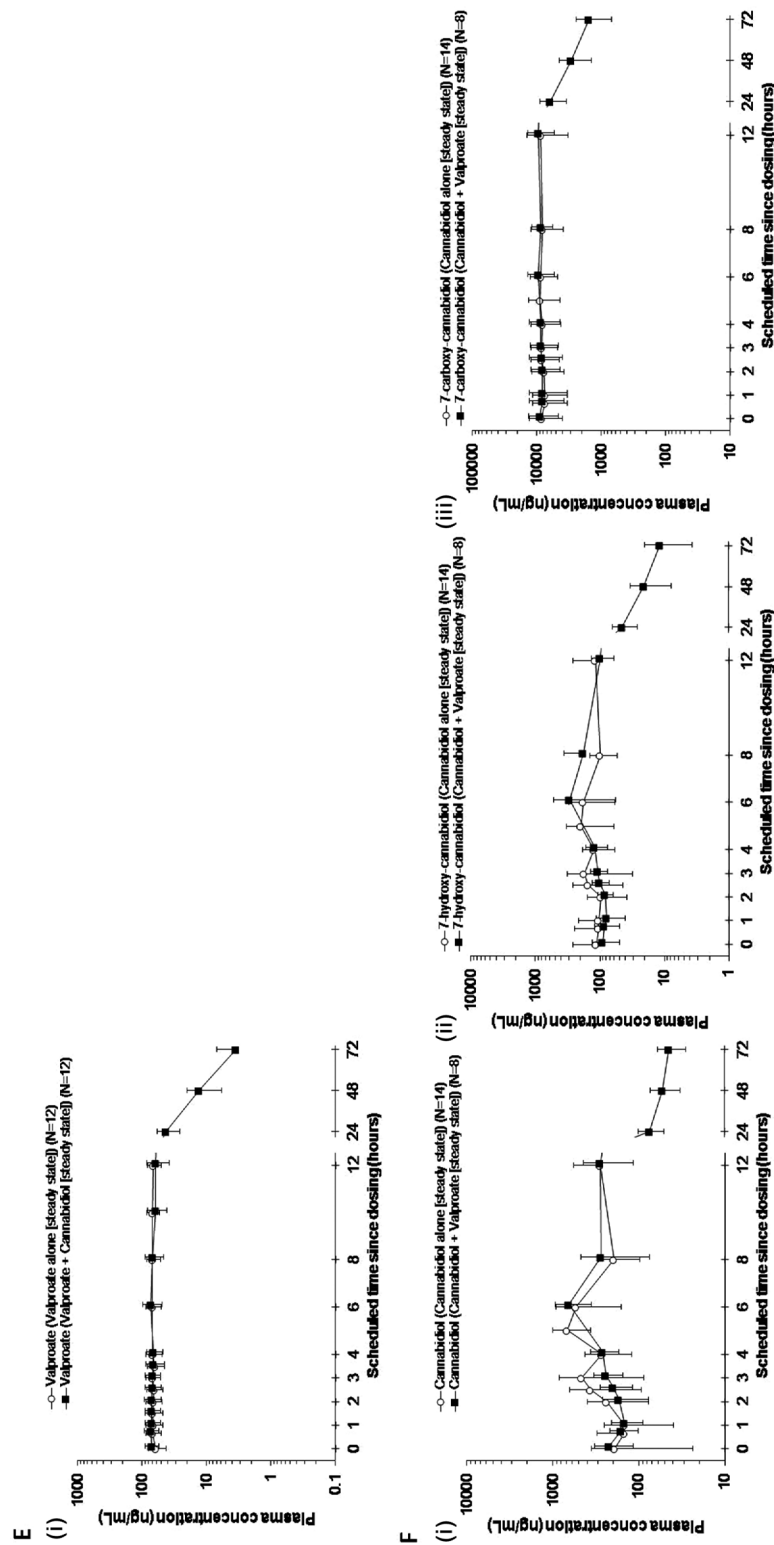


Figure 3. Continued.

Table 3. PK Parameters for All Victim Analytes Throughout the Trial (PK Set)**A: PK Parameters for All Victim Analytes in DDI Clobazam**

Parameter		Clobazam (Victim) + Cannabidiol (Perpetrator)		Cannabidiol (Victim) + Clobazam (Perpetrator)	
		Clobazam Alone	Clobazam + Cannabidiol	Cannabidiol Alone	Cannabidiol + Clobazam
n		12	12	15	11
Analyte		Clobazam		Cannabidiol	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)	239 (90.0)	278 (65.3)	935 (347)	1230 (502)
	Geometric mean (CV%)	225 (38.1)	271 (26.0)	840 (61.1)	1130 (46.9)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)	2310 (1020)	2660 (688)	3720 (1060)	4750 (1410)
	Geometric mean (CV%)	2130 (42.8)	2570 (26.9)	3500 (42.6)	4570 (30.6)
Analyte		N-desmethyclobazam		7-OH-CBD	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)	343 (299)	947 (470)	247 (129)	405 (199)
	Geometric mean (CV%)	239 (125)	811 (70.6)	221 (50.6)	362 (53.7)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)	3720 (3160)	10 400 (5220)	1420 (658)	2020 (889)
	Geometric mean (CV%)	2620 (124)	8860 (71.1)	1310 (41.5)	1860 (45.1)
Analyte				7-COOH-CBD	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)			9510 (3930)	13 300 (5240)
	Geometric mean (CV%)			8900 (37.5)	12 500 (40.1)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)			94 400 (45 200)	128 000 (57 100)
	Geometric mean (CV%)			86 700 (42.8)	117 000 (47.7)

B: PK Parameters for all Victim Analytes in DDI Stiripentol

Parameter		Stiripentol (Victim) + Cannabidiol (Perpetrator)		Cannabidiol (Victim) + Stiripentol (Perpetrator)	
		Stiripentol Alone	Stiripentol + Cannabidiol	Cannabidiol Alone	Cannabidiol + Stiripentol
n		12	12	12	12
Analyte		Stiripentol		Cannabidiol	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)	7800 (1970)	10 300 (4050)	969 (515)	1060 (504)
	Geometric mean (CV%)	7540 (29.0)	9650 (36.7)	852 (57.3)	966 (47.2)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)	46 900 (11 500)	73 900 (25 400)	3880 (1260)	4040 (1460)
	Geometric mean (CV%)	45 700 (23.6)	70 700 (31.0)	3690 (34.2)	3810 (36.1)
Analyte				7-OH-CBD	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)			313 (286)	191 (113)
	Geometric mean (CV%)			234 (88.5)	166 (57.4)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)			1550 (922)	1070 (467)
	Geometric mean (CV%)			1370 (51.3)	986 (45.4)
Analyte				7-COOH-CBD	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)			9700 (5250)	8570 (4690)
	Geometric mean (CV%)			8660 (51.0)	7560 (55.0)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)			93 800 (55 400)	83 000 (49 900)
	Geometric mean (CV%)			82 800 (52.8)	72 200 (57.2)
n		12	12	14	8
Analyte		Valproate		Cannabidiol	
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)	86.4 (16.6)	87.5 (19.1)	895 (322)	660 (278)
	Geometric mean (CV%)	84.9 (19.7)	85.7 (21.4)	838 (39.8)	588 (62.4)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)	813 (162)	814 (221)	3740 (1110)	3660 (1280)
	Geometric mean (CV%)	798 (19.8)	787 (27.3)	3560 (35.8)	3420 (44.1)

Continue

Table 3. Continued

C: PK Parameters for All Victim Analytes in DDI Valproate

Parameter		Valproate (Victim) + Cannabidiol (Perpetrator)		Cannabidiol (Victim) + Valproate (Perpetrator)	
		Valproate Alone	Valproate + Cannabidiol	Cannabidiol Alone	Cannabidiol + Valproate
Analyte		7-OH-CBD			
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)			283 (188)	265 (228)
	Geometric mean (CV%)			236 (66.4)	194 (101.0)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)			1550 (842)	1660 (1060)
	Geometric mean (CV%)			1370 (54.1)	1430 (62.5)
Analyte		7-COOH-CBD			
$C_{\max}$ (ng/mL)	Arithmetic mean (SD)			10 100 (5200)	9990 (4190)
	Geometric mean (CV%)			9090 (48.5)	9320 (40.2)
AUC_{τ} (ng · h/mL)	Arithmetic mean (SD)			100 000 (51 400)	107 000 (46 600)
	Geometric mean (CV%)			90 100 (49.3)	98 800 (42.2)

7-OH-CBD, 7-hydroxy-cannabidiol; 7-COOH-CBD, 7-carboxy-cannabidiol; AUC_{τ} , area under the plasma concentration–time curve over a dosing interval, where τ is the dosing interval; $C_{\max}$, maximum concentration; CV%, coefficient of variation; DDI, drug-drug interaction; PK, pharmacokinetic; SD, standard deviation.

bid, there were no important changes of note in the overall exposure to cannabidiol, with $C_{\max}$ TR of 0.74 (90%CI, 0.58–0.93) and AUC_{τ} TR 1.05 (90%CI, 0.90–1.78). There were also no obvious effects on the exposure to the active metabolite 7-OH-CBD with $C_{\max}$ TR 0.97 (90%CI, 0.67–1.41) and AUC_{τ} TR 1.22 (90%CI, 0.96–1.55) or to 7-COOH-CBD with $C_{\max}$ TR 1.25-fold (90%CI, 1.07–1.45) and AUC_{τ} TR 1.22 (90%CI, 0.96–1.55) (Figure 4C(ii)).

Delta-9-tetrahydrocannabinol exposure. As expected, THC, 11-OH-THC, and 11-COOH-THC plasma concentrations were low or below the level of quantification throughout the trial and therefore the steady-state mean THC exposure ($C_{\max}$) was consistently low across cohorts (data not shown).

Safety

Summary of Treatment-Emergent AEs. All medications were moderately well tolerated when coadministered in the trial. Six subjects were withdrawn due to AEs; 3 when clobazam was added to steady-state cannabidiol and 3 when valproate was added to steady-state cannabidiol. There were a few differences in the reporting of individual preferred terms between treatment with victim drugs alone (during period 1) compared with concurrent administration with victim and perpetrator drugs (during period 2). AEs that were reported in ≥ 2 subjects in at least 1 treatment period are summarized in Table 4.

There were no serious AEs, deaths, or pregnancies during the trial. While most subjects reported AEs of mild severity, 8 (10.4%) subjects reported moder-

ate AEs, and 2 (2.6%) subjects reported severe AEs; both severe events were rashes (papular rash without mucosal involvement) in the cannabidiol (victim) + clobazam (perpetrator) combined treatment period (no cannabidiol titration) and are discussed below.

There were 3 withdrawals due to AEs in subjects in the cannabidiol (victim) + clobazam (perpetrator) subgroup: a moderate AE of AV block first degree was recorded for 1 (8.3%) subject that occurred while receiving cannabidiol alone (no titration) and 2 severe AEs of rash papular (without mucosal involvement) were reported in 2 (16.7%) subjects during the first 2 days of receiving cannabidiol (no titration) + clobazam.

In the cannabidiol (victim) + valproate (perpetrator) cohort there were 3 withdrawals due to AEs of rashes reported on day 2 of receiving cannabidiol (with the rapid 3-day titration) + valproate; 1 case of moderate generalized erythema, 1 case of moderate papular rash, and 1 case of moderate follicular rash, which all resolved after cannabidiol and valproate were discontinued. None of the rashes had any mucosal involvement.

Adverse Events of Special Interest

Rash. Early in the trial, 9 (11.7%) subjects overall experienced AEs containing rash in the preferred term. All but 1 rash were, in the investigator's opinion, considered to be treatment related; 2 were severe, 4 were moderate, and 3 were mild in severity. Five subjects were withdrawn as a result of rash AEs (2 severe and 3 moderate), as noted above. Details of the rashes, including severity of the AE and action taken, as well as details of treatment administered and whether any cannabidiol titration period was included, are provided in Table 5.

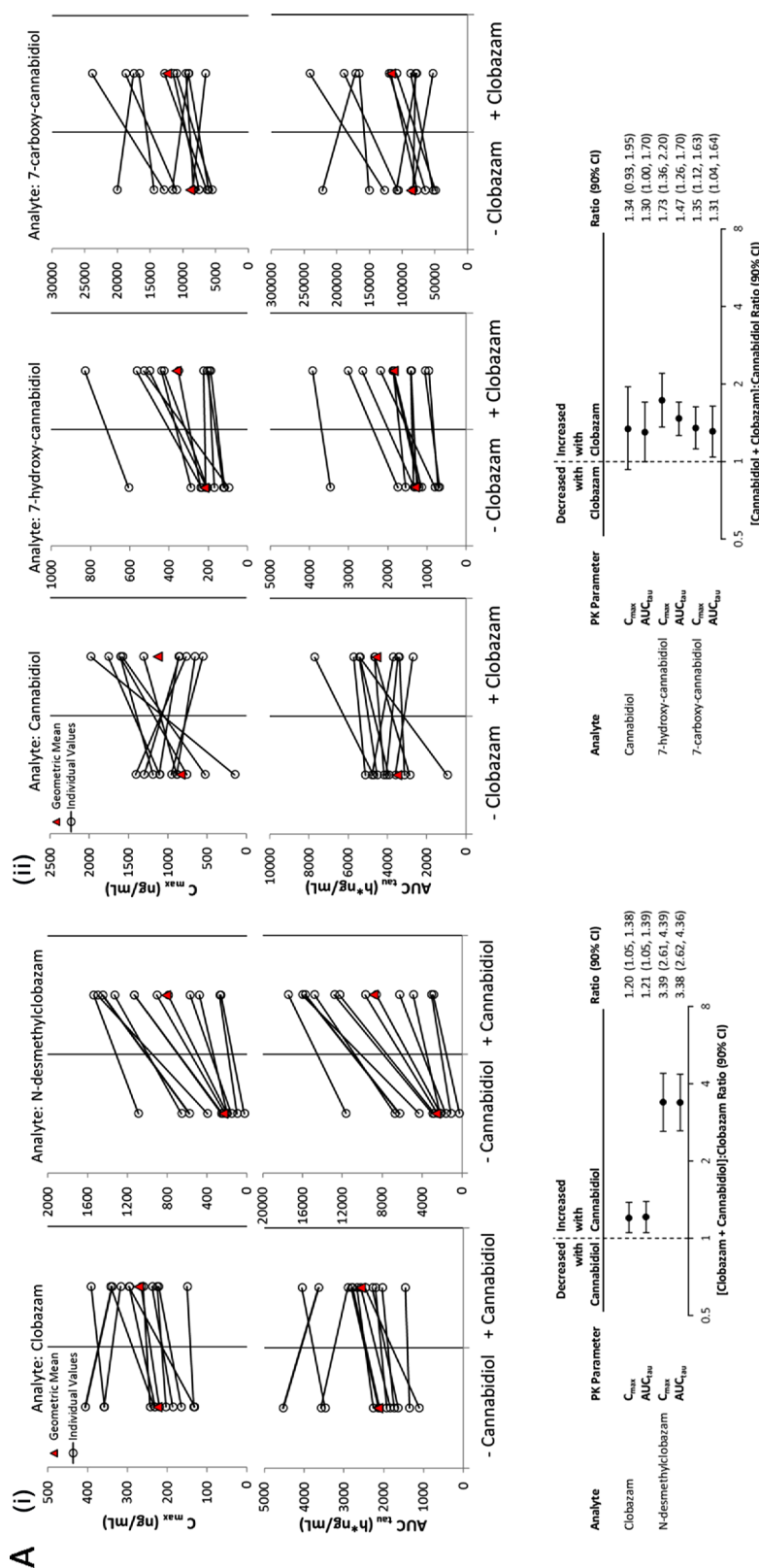


Figure 4. (A) DDI clobazam. (i) The effect of concomitant administration of 750 mg of cannabidiol bid on individual and geometric mean steady-state exposure (top panel: C_{max} ; middle panel: AUC_{tau} ; bottom panel: treatment ratios with 90% confidence intervals [CIs]) to clobazam and N-CLB. (ii) The effect of concomitant administration of 5 mg of clobazam bid, on individual and geometric mean steady-state exposure (top panel: C_{max} ; middle panel: AUC_{tau} ; bottom panel: treatment ratios with 90%CI) to cannabidiol, 7-OH-CBD, and 7-COOH-CBD. (B) DDI stiripentol. (i) The effect of concomitant administration of 750 mg of cannabidiol bid on individual and geometric mean steady-state exposure (top panel: C_{max} ; middle panel: AUC_{tau} ; bottom panel: treatment ratios with 90%CI) to stiripentol. (ii) The effect of concomitant administration of 750 mg of stiripentol bid, on individual and geometric mean steady-state exposure (top panel: C_{max} ; middle panel: AUC_{tau} ; bottom panel: treatment ratios with 90%CI) to cannabidiol, 7-OH-CBD, and 7-COOH-CBD. (C) DDI valproate. (i) The effect of concomitant administration of 750 mg of cannabidiol bid on individual and geometric mean steady-state exposure (top panel: C_{max} ; middle panel: AUC_{tau} ; bottom panel: treatment ratios with 90%CI) to valproate. (ii) The effect of concomitant administration of 750 mg of valproate bid on individual and geometric mean steady-state exposure (top panel: C_{max} ; middle panel: AUC_{tau} ; bottom panel: treatment ratios with 90%CI) to cannabidiol, 7-OH-CBD, and 7-COOH-CBD. 7-OH-CBD, 7-hydroxy-cannabidiol; 7-COOH-CBD, 7-carboxy-cannabidiol; AUC_{tau} , area under the plasma concentration–time curve over a dosing interval, where tau is the dosing interval; CI, confidence interval; C_{max} , maximum concentration; DDI, drug–drug interaction; N-CLB, N-desmethyloclobazam; SD, standard deviation.

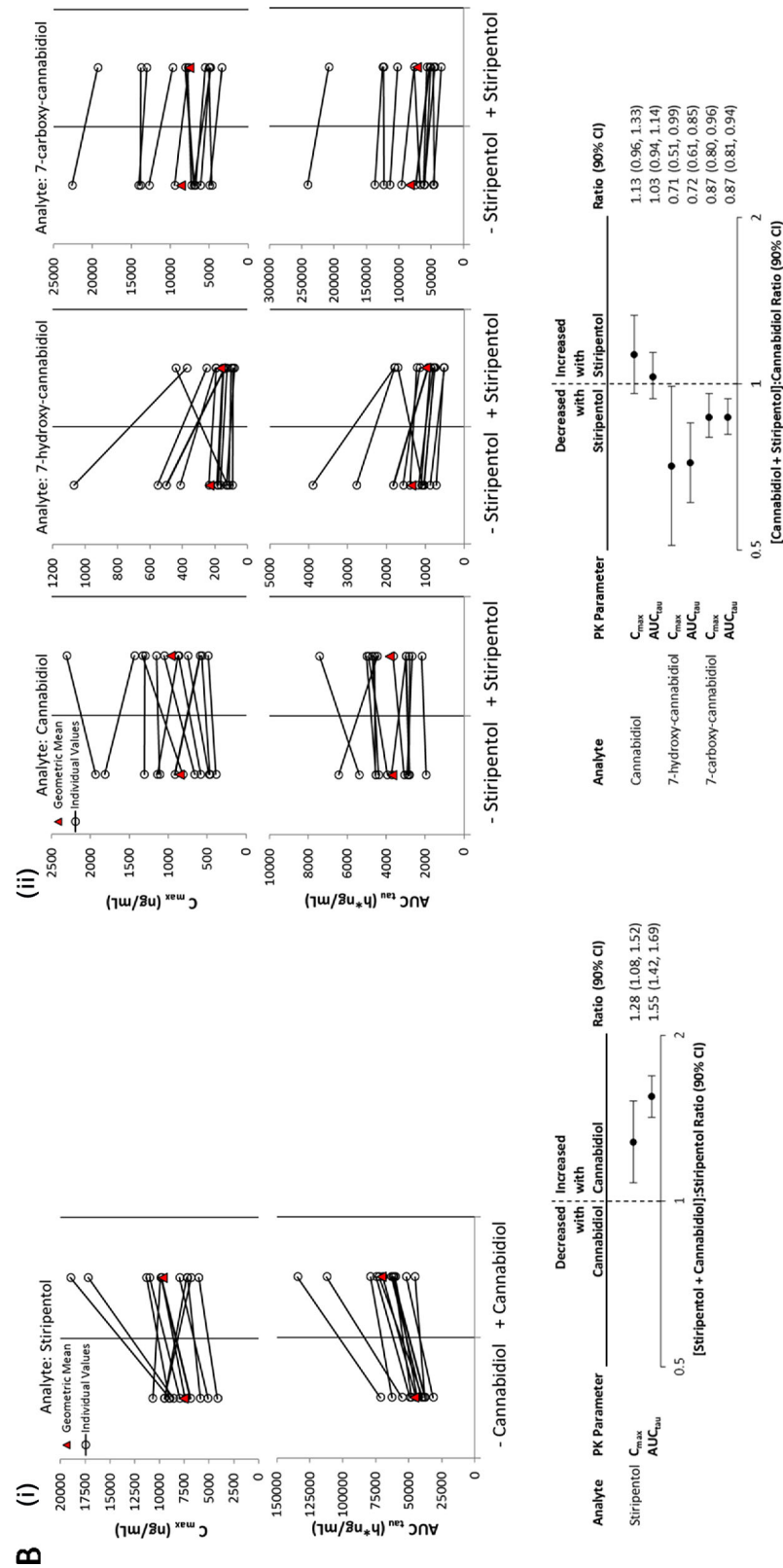


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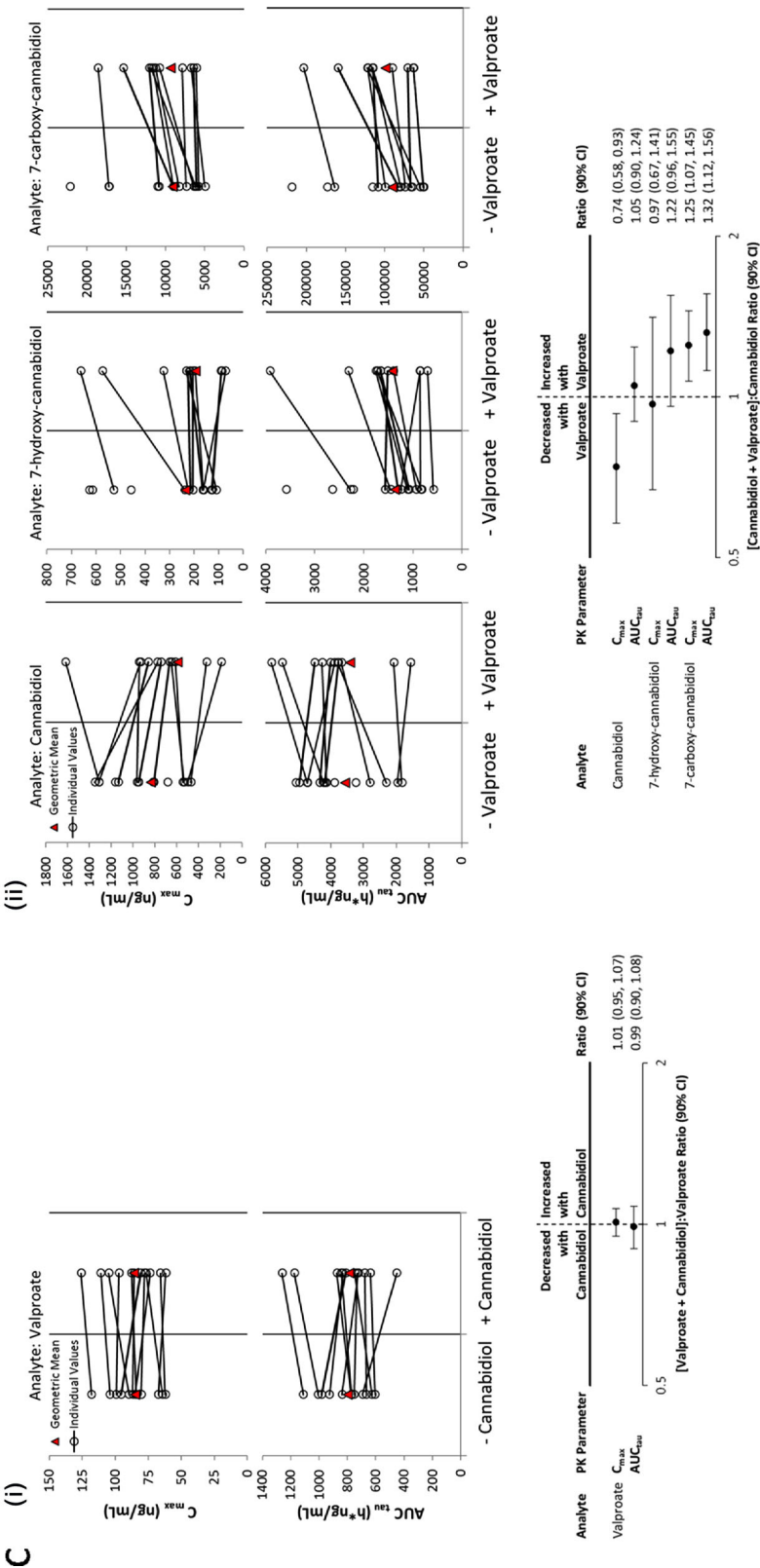


Figure 4. Continued.

Table 4. PK Parameters and Treatment Ratios for All Victim Analytes (Antiepileptic Drugs or Cannabidiol) Throughout the Trial

Arm 1 (AED + Cannabidiol)

Parameter	AED First Dose Alone	AED Steady State Alone	AED Steady State + Cannabidiol First Dose	AED Steady State + Cannabidiol Steady State	Treatment Ratio ^d [90%CI]
Clobazam + Cannabidiol (Group 1)					
n	12	12	12	12	12
Clobazam					
C _{max} (ng/mL) ^a	71.4 (20.4)	225 (38.1)	238 (33.4)	271 (26.0)	1.20 [1.05–1.38]
AUC _{tau} (ng · h/mL) ^a	518 (22.2)	2130 (42.8)	2250 (35.6)	2570 (26.9)	1.21 [1.05–1.39]
t _{max} (hours) ^b	3.00 (0.67–3.50)	2.50 (1.00–4.00)	2.25 (0.67–12.00)	3.25 (0.67–4.00)	
N-CLB					
C _{max} (ng/mL) ^a	11.8 (38.7)	239 (125.3)	332 (103.3)	811 (70.6)	3.39 [2.61–4.39]
AUC _{tau} (ng · h/mL) ^a	60.4 (38.6)	2620 (124.4)	3120 (82.8)	8860 (71.1)	3.38 [2.62–4.36]
t _{max} (hours) ^b	23.92 (23.92–23.92)	6.00 (0.33–12.00)	12.00 (0.00–12.00)	10.00 (0.00–12.00)	
Stiripentol + Cannabidiol (Group 3)					
n	12	12	12	12	12
Stiripentol					
C _{max} (ng/mL) ^a	3730 (39.5)	7540 (29.0)	7630 (38.3)	9650 (36.7)	1.28 [1.08–1.52]
AUC _{tau} (ng · h/mL) ^a	14800 (27.8)	45700 (23.6)	51300 (25.9)	70700 (31.0)	1.55 [1.42–1.69]
t _{max} (hours) ^b	3.00 (1.50–4.00)	3.00 (1.50–4.00)	3.50 (2.50–12.00)	3.00 (2.00–6.00)	
Valproate + Cannabidiol (Group 5)					
n	12	12	12	12	12
Valproate					
C _{max} (ng/mL) ^a		84.9 (19.7)	91.1 (24.6)	85.7 (21.4)	1.01 [0.95–1.07]
AUC _{tau} (ng · h/mL) ^a		798 (19.8)	891 (29.3)	787 (27.3)	0.99 [0.90–1.08]
t _{max} (hours) ^b		6.00 (0–12.00)	6.01 (0–8.00)	2.75 (0–8.00)	

Arm 2 (Cannabidiol + AED)

Parameter	Cannabidiol First Dose Alone		Cannabidiol Steady State Alone	Cannabidiol Steady State + AED First Dose	Cannabidiol Steady State + AED Steady State	Treatment Ratio ^f [90%CI]
	750 mg (No Titration)	250 mg (With Titration)				
Cannabidiol + Clobazam (Group 2)						
n	9	6	15	14	11	
Cannabidiol						
C _{max} (ng/mL) ^a	779 (30.3)	314 (51.0)	840 (61.1)	989 (51.7)	1130 (46.9)	1.34 [0.93–1.95]
AUC _{tau} (ng · h/mL) ^a	2510 (40.3)	821 (34.7)	3500 (42.6)	3600 (28.6)	4560 (30.6)	1.30 [1.00–1.70]
t _{max} (hours) ^b	5.00 (3.00–6.00)	4.50 (3.00–5.00)	5.00 (1.50–6.00)	5.00 (3.00–6.00)	5.00 (2.93–6.00)	
7-OH-CBD						
C _{max} (ng/mL) ^a	221 (86.2)	76.8 (53.0)	221 (50.6)	274 (78.8)	362 (53.7)	1.73 [1.36–2.20]
AUC _{tau} (ng · h/mL) ^a	1058 (75.2)	278 (44.3)	1310 (41.5)	1370 (48.5)	1860 (45.1)	1.47 [1.26–1.70]
t _{max} (hours) ^b	3.00 (1.50–6.00)	4.50 (2.00–5.00)	4.00 (1.50–6.00)	5.00 (1.00–6.00)	5.00 (1.50–6.00)	
7-COOH-CBD						
C _{max} (ng/mL) ^a	2770 (58.5)	1320 (38.5)	8900 (37.5)	8930 (40.3)	12500 (40.1)	1.35 [1.12–1.63]
AUC _{tau} (ng · h/mL) ^a	21000 (63.6)	8760 (34.6)	86700 (42.8)	86000 (43.6)	117000 (47.7)	1.31 [1.04–1.64]
t _{max} (hours) ^b	6.00 (4.00–12.05)	5.00 (3.00–12.00)	5.00 (3.98–12.00)	5.00 (0.00–12.00)	5.18 (4.00–8.00)	

Continue

Table 4. Continued

	Cannabidiol First Dose Alone		Cannabidiol Steady State Alone	Cannabidiol Steady State + AED First Dose	Cannabidiol Steady State + AED Steady State	Treatment Ratio ^f [90%CI]
	750 mg (No Titration)	250 mg (With Titration)				
Cannabidiol + Stiripentol (Group 4)						
n	8	4	12	12	12	
Cannabidiol						
C _{max} (ng/mL) ^a	738 (51.1)	279 (46.1)	852 (57.3)	1260 (35.2)	966 (47.2)	1.13 [0.96–1.33]
AUC _{tau} (ng · h/mL) ^a	2720 (45.0)	655 (35.6)	3690 (34.2)	4430 (20.2)	3810 (36.1)	1.03 [0.94–1.14]
t _{max} (hours) ^b	5.00 (5.00–6.00)	4.50 (2.00–5.00)	5.00 (1.50–12.00)	5.00 (0.00–12.00)	5.00 (3.00–12.00)	
7-OH-CBD						
C _{max} (ng/mL) ^a	204 (61.3)	70.6 (54.3)	234 (88.5)	299 (66.6)	166 (57.4)	0.71 [0.51–0.99]
AUC _{tau} (ng · h/mL) ^a	974 (56.1)	270 (51.5)	1370 (51.3)	1530 (40.7)	986 (45.4)	0.72 [0.61–0.85]
t _{max} (hours) ^b	5.50 (5.00–6.00)	3.50 (2.00–5.00)	4.50 (1.50–12.00)	5.00 (0.00–12.00)	5.00 (3.00–12.00)	
7-COOH-CBD						
C _{max} (ng/mL) ^a	2500 (60.1)	1220 (61.9)	8660 (51.0)	8815 (53.0)	7560 (55.0)	0.87 [0.80–0.96]
AUC _{tau} (ng · h/mL) ^a	17900 (74.5)	7790 (55.6)	82800 (52.8)	86100 (50.4)	72200 (57.2)	0.87 [0.81–0.94]
t _{max} (hours) ^b	6.00 (5.00–12.03)	4.50 (2.50–5.00)	5.00 (2.00–12.00)	5.00 (0.00–12.00)	5.00 (0.00–12.00)	
Parameter	Cannabidiol First Dose Alone		Cannabidiol Steady State Alone	Cannabidiol Steady State + AED First Dose	Cannabidiol Steady State + AED Steady State	Treatment Ratio ^f [90%CI]
	750 mg (No Titration)	250 mg (With Titration)				
Cannabidiol + Valproate (Group 6)						
n	0	14	14	14	8	
Cannabidiol						
C _{max} (ng/mL) ^a		257 (74.2)	838 (39.8)	976 (47.1)	588 (62.4)	0.74 [0.58–0.93]
AUC _{tau} (ng · h/mL) ^a		679 (42.5)	3560 (35.8)	4040 (35.9)	3420 (44.1)	1.05 [0.90–1.24]
t _{max} (hours) ^b		5.00 (3.00–5.98)	5.00 (3.00–12.00)	5.00 (3.00–6.00)	6.00 (4.00–12.00)	
7-OH-CBD						
C _{max} (ng/mL) ^a		69.0 (60.4)	236 (66.4)	285 (66.9)	194 (101.0)	0.97 [0.67–1.41]
AUC _{tau} (ng · h/mL) ^a		271 (42.8)	1370 (54.1)	1510 (55.2)	1430 (62.5)	1.22 [0.96–1.55]
t _{max} (hours) ^b		5.00 (2.00–6.00)	5.00 (2.00–12.00)	5.00 (3.00–6.00)	6.00 (3.00–12.00)	
7-COOH-CBD						
C _{max} (ng/mL) ^a		1090 (44.9)	9090 (48.5)	9450 (47.2)	9320 (40.2)	1.25 [1.07–1.45]
AUC _{tau} (ng · h/mL) ^a		7550 (47.4)	90100 (49.3)	93400 (52.5)	98800 (42.2)	1.32 [1.12–1.56]
t _{max} (hours) ^b		5.00 (3.00–6.00)	5.00 (0–12.00)	5.00 (3.00–12.00)	10.00 (2.50–12.00)	

AED, antiepileptic drug; 7-OH-CBD, 7-hydroxy-cannabidiol; 7-COOH-CBD, 7-carboxy-cannabidiol; AUC_{tau}, area under the plasma concentration–time curve over a dosing interval, where tau is the dosing interval; CI, confidence interval; C_{max}, maximum concentration; CV%, coefficient of variation; N-CLB, N-desmethyloclobazam; PK, pharmacokinetic; t_{max}, time to maximum concentration.

^aGeometric mean (intra + intersubject CV%).

^bMedian (range).

^cGeometric mean ratio (CV%).

^dGeometric least squares means ratios for AED steady state + cannabidiol steady state: AED steady state alone.

^ePerpetrator effect on victim was explored using a mixed effect (analysis of variance) model with treatment as fixed factor, and subject as a random factor.

^fGeometric least squares means ratios for cannabidiol steady state + AED steady state: cannabidiol steady state alone.

The trial was put on temporary hold by the sponsor, and the etiology of the rash-related treatment-emergent AEs was investigated, leading to 2 protocol amendments (including the addition of titration periods for cannabidiol [initially 3 days, then increased to 10 days] and change in process for syringe filling and use). No

new cases of rash were reported after these changes were implemented in the second amendment.

Atrioventricular Block. One subject experienced a moderate AE of first-degree atrioventricular block (PR interval prolongation of 149–152 milliseconds relative to baseline) on day 8 while taking cannabidiol alone (no

Table 5. Summary of Rashes (by MedDRA Preferred Term) Reported During the Trial

MedDRA Preferred Term	Subgroup	Cannabidiol Titration?	Treatment When AE Reported	Severity	Drugs Withdrawn?	Treatment Related?
Rash papular	Cannabidiol + Clobazam	None	Concomitant	Severe	Yes	Yes
Rash papular	Cannabidiol + Clobazam	None	Concomitant	Severe	Yes	Yes
Rash erythematous	Stiripentol + Cannabidiol	3 days	Concomitant	Mild	No	Yes
Rash erythematous	Cannabidiol + Stiripentol	None	Concomitant	Mild	No	Yes
Rash papular	Valproate + Cannabidiol	3 days	Concomitant	Mild	No	No
Rash macular	Valproate + Cannabidiol	3 days	Concomitant	Moderate	No	Yes
Generalized erythema	Cannabidiol + Valproate	3 days	Concomitant	Moderate	Yes	Yes
Rash papular	Cannabidiol + Valproate	3 days	Concomitant	Moderate	Yes	Yes
Rash follicular	Cannabidiol + Valproate	3 days	Concomitant	Moderate	Yes	Yes

titration). Cannabidiol was discontinued, and the subject was withdrawn. Although the PR interval had returned to baseline value 50 minutes later, the AE was classified as ongoing at the follow-up visit (1 week later), when the PR interval was 153 milliseconds above baseline.

Feeling Drunk. AEs of feeling drunk were experienced by 2 subjects while taking stiripentol (victim) + cannabidiol (10-day titration; perpetrator) and 1 while taking cannabidiol (no titration; victim) + stiripentol (perpetrator). Each event was considered mild in severity and resolved with no action taken with cannabidiol.

Menstrual Discomfort. An AE of menstrual discomfort was reported by 1 subject on day 8 of taking cannabidiol (no titration; victim) + stiripentol (perpetrator), which was mild in severity and resolved on the same day it appeared with no action taken.

Other Safety Parameters. There were individual fluctuations in clinical laboratory parameters, body weight, and vital signs, but none of these were considered to be clinically significant or were reported as AEs. The results of the C-SSRS identified no treatment-emergent suicidal ideation or behavior in subjects in any group during the trial.

Discussion

The primary purpose of this trial was to assess the effect of multiple-dose administration of cannabidiol on steady-state plasma concentrations of clobazam (and N-CLB), stiripentol or valproate (and 4-ene-VPA), and to assess the effect of multiple-dose administration of clobazam, stiripentol, or valproate on steady-state plasma concentrations of cannabidiol in healthy male and female subjects.

Pharmacokinetics

Drug-Drug Interactions. PK observations following concomitant administration of cannabidiol and clobazam were indicative of a bidirectional DDI, whereby increases in the active metabolites of both

compounds were observed when administered as the victim drug. While the trial was not powered to demonstrate statistical changes, the changes observed in plasma levels of N-CLB were considered clinically important, as they may be associated with increased risk of clobazam-related AEs. While there were only slight increases in parent clobazam levels, the increases observed for N-CLB plasma exposure are likely mediated by inhibition of CYP2C19. These findings are consistent with those from a noncomparative, investigator-led trial in children with refractory epilepsies, which reported a nonsignificant mean increase in clobazam and a significant increase in the active metabolite N-CLB (of $500\% \pm 300\%$) after 4 weeks of cannabidiol treatment (20 mg/kg/day) compared with pretreatment. It was suggested that these observations were probably related to CYP2C19 inhibition by cannabidiol.^{30,32} N-CLB is the active metabolite of clobazam and is estimated to have between 20% to 100% of the anti-ictal potency of the parent clobazam,³⁹ but while N-CLB plasma levels were increased in patients also treated with cannabidiol and associated with increased sedation,³¹ they were not correlated with seizure reduction in patients.⁴⁰ The mechanism for the observed increase in the exposure of the active 7-OH-CBD metabolite is not fully understood but may result from inhibition of UGTs and/or other minor CYP enzymes by the coadministered clobazam. The observed increase in 7-OH-CBD exposure when clobazam was coadministered with cannabidiol in this trial has the potential to act in synergy with cannabidiol since 7-OH-CBD also shows significant anticonvulsant activity in animal models of epilepsy.^{11,32}

The increase in stiripentol exposure by 28% to 55% between steady-state administration of stiripentol alone and following concomitant treatment with cannabidiol may be related to CYP2C19 inhibition by cannabidiol. Although in 2 subjects there was a doubling in stiripentol plasma exposure with coadministration of cannabidiol, this could not be

attributed to differences in CYP2C19 phenotypes (1 ultrarapid metabolizer and 1 intermediate metabolizer phenotype), and there were no AEs reported for these subjects that were not also reported in subjects with lower stiripentol exposure. Coadministration with stiripentol did not affect cannabidiol exposure; however, stiripentol reduced 7-OH-CBD and 7-COOH-CBD exposure by 29% and 13%, respectively. The mechanism for this reduction is not known. Stiripentol is an inhibitor of both CYP3A4 and CYP2C19, both of which are implicated in the metabolism of cannabidiol¹⁰; however, this did not translate to any increase in cannabidiol when administered in combination. There was no effect of cannabidiol on the PK of valproate or of valproate on the PK of cannabidiol or 7-OH-CBD; however, there was a slight increase in 7-COOH-CBD exposure by 25% to 32%. Due to the moderate nature of these interactions, the effects of cannabidiol on stiripentol, and of stiripentol or valproate on cannabidiol metabolites, are unlikely to be clinically relevant.

Safety

The dose of 750 mg of cannabidiol bid in this trial of healthy male and female volunteers is approximately 20 mg/kg/day for a 75-kg adult, which was effective in drop and convulsive seizures in 3 phase 3 randomized trials of LGS and DS.²⁻⁴ Most subjects attained the target dose and completed the trial.

Cannabidiol was moderately well tolerated at doses up to 750 mg bid when coadministered with clobazam, stiripentol, or valproate. There were 6 (7.8%) discontinuations for AEs among the safety set of 77 subjects. Furthermore, there were no serious AEs, pregnancies, or deaths reported.

There was no clear pattern of difference between cannabidiol as the perpetrator (adding cannabidiol to the other AEDs) or as the victim (when adding other AEDs to cannabidiol). The numbers in this trial were small, and differences between groups in the incidence of AEs other than rash were small. The overall incidence of AEs was similar between subjects who had taken cannabidiol alone or in combination with any of the 3 AEDs.

With the exception of the higher incidence of rashes, the AE profile when cannabidiol was administered in combination with clobazam, stiripentol, or valproate is highly consistent with another cannabidiol trial in healthy volunteers⁴¹ and in recent phase 3 trials.²⁻⁴ In this healthy volunteer DDI trial, most AEs were mild, with 8 subjects reporting moderate and 2 reporting severe AEs.

Adverse events that led to discontinuation of cannabidiol and withdrawal from the trial were mostly (5 of 6) due to rashes and occurred when subjects were

either taking clobazam concomitantly with steady-state cannabidiol (2 subjects) or valproate concomitantly with steady-state cannabidiol (3 subjects); all of these rashes leading to withdrawal were reported in subjects who had not been titrated up to the 750 mg of cannabidiol bid dose or in those with a rapid 3-day titration period, rather than the 10-day cannabidiol titration that was introduced into the updated trial design. Rashes were also reported previously in the pivotal phase 3 randomized controlled trials of cannabidiol for severe refractory epilepsies, although at an incidence consistently <10%.²⁻⁴ A smaller dose-ranging study did report a higher incidence of rash (5 of 27; 18.5%), but all resolved, had no mucosal involvement, and included contact dermatitis.³²

Overall in this trial (including those described above), 9 (11.7%) subjects experienced AEs related to rashes; all were reported while subjects were in period 2 (AED + cannabidiol or cannabidiol + AED) of the trial and affected at least 1 subject in each group, apart from subjects in taking clobazam + cannabidiol. All but 1 rash were, in the investigator's opinion, considered to be treatment related; 2 were severe, 4 were moderate, and 3 were mild in severity. The rashes were varied; 3 were reported as generalized, none had mucosal involvement, and all but 1 of the rashes (AE of erythematous rash reported in the stiripentol + cannabidiol cohort where resolution could not be confirmed because further follow-up was not possible) are known to have resolved. The rash incidence rate in this trial was higher than previously reported in the clinical development program, and the etiology is unclear. These rashes occurred when the trial was partially completed, and thorough investigations (including an environmental assessment, subject and family histories, and clinical laboratory tests) did not uncover an alternative cause. The protocol was amended to include titration of cannabidiol over 3 days, and, when reports of rash continued, then extended to 10 days. In addition, instead of being given prefilled syringes that were administered up to 1 week after being prepared, subjects were given a bottle of cannabidiol and a syringe and were instructed to withdraw the correct dose immediately before administration. Rashes were not reported in any subject after the implementation of these protocol amendments.

Despite the PK DDI between cannabidiol and clobazam (resulting in an increase in N-CLB specifically; N-CLB, C_{max} , and AUC_{tau} TRs were approximately 3.40), there was no apparent effect on the rate or severity of AEs or any other safety parameter in this group. In recent phase 3 trials in patients with LGS and DS the concomitant administration of cannabidiol with clobazam was associated with a higher incidence of somnolence and sedation, and therefore monitoring for these AEs is recommended.^{3,4,32} Indeed,

dose reduction may be considered for clobazam when administered with cannabidiol if AEs associated with clobazam are reported, depending on the benefit-risk assessment.

There was 1 abnormal treatment-emergent ECG finding of asymptomatic atrioventricular conduction delay (nonspecific) that was reported as an AE of first-degree atrioventricular block leading to discontinuation of cannabidiol and withdrawal of the subject from the trial. Otherwise, the assessment of ECGs, vital signs, and most laboratory measurements did not show any consistent differences between the treatment groups or any significant trends. There was no treatment-emergent suicidal ideation or behavior in any group as assessed by the C-SSRS.

Conclusion

A bidirectional DDI was noted when clobazam was coadministered with cannabidiol, resulting in increased exposure to the active metabolites of both drugs. Although there was only a slight increase in clobazam levels, the 3.4-fold increase in N-CLB plasma exposure suggests that dose reduction may be considered for clobazam when administered with cannabidiol, depending on the benefit-risk assessment. The precise mechanism leading to the 47% to 73% increase in the active metabolite of cannabidiol, 7-OH-CBD, when clobazam was added concomitantly to steady-state cannabidiol is not fully understood.

No clinically relevant changes were observed in the PK of cannabidiol when coadministered with either stiripentol or valproate. Cannabidiol coadministration resulted in a slight increase in stiripentol exposure, but this is unlikely to be clinically relevant. Cannabidiol had no relevant effect on the PK of valproate; although a limitation of the study is that only total valproate levels were analyzed when it would have been interesting to measure free valproate because valproate is highly protein bound.²⁸ There has been a recent report of stiripentol given concomitantly with clobazam and cannabidiol where there was no observed increase in N-CLB.³² These data tend to support a CYP2C19-mediated effect of cannabidiol on N-CLB as stiripentol is a potent inhibitor of CYP2C19 and therefore maximally inhibited when stiripentol was administered concomitantly. Consequently, based on PK alone, dose adjustments are not likely to be necessary when cannabidiol is given concomitantly with stiripentol or valproate, and the increased N-CLB exposures may not occur if clobazam is also coadministered with stiripentol or other CYP2C19 inhibitors.

Overall, safety profiles were similar across and between the groups with the exception of rash, which occurred in groups with no titration or with a

rapid titration of cannabidiol dose. Cannabidiol was moderately well tolerated when coadministered with clobazam, stiripentol, or valproate. The majority of AEs were rated as mild or moderate with 2 severe treatment-related AEs; both rashes (rash papular) reported in 2 subjects taking clobazam concomitant with steady-state cannabidiol (without cannabidiol titration). Six subjects had cannabidiol discontinued due to AEs (5 subjects due to rashes and 1 subject due to AV block first degree). These rashes did not recur in further subjects after revisions were made to the protocol. There were no deaths, serious AEs, or pregnancies. There were no clinically significant safety findings for vital signs, ECG parameters (other than the 1 described above), body weight, suicidal behavior, or depressive symptoms.

Acknowledgments

The authors thank the trial participants, their families, and the trial sites that participated in this trial, as well as Sue Ditton, BSc, of GW Research Ltd for her contributions as the clinical study manager.

GW is adhering to current United States and European Union 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.

Declaration of Conflicting Interests

G.B. has consulted for, conducted studies funded by, or received honoraria from GW Research Ltd; K.S. is a consultant of Greenwich Biosciences, Inc; and J.C. and G.M. are employees of GW Research Ltd. Greenwich Biosciences, Inc is the US affiliate of GW Research Ltd.

Funding

This study was sponsored by GW Research Ltd, Cambridge, UK.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.