

Abuse potential assessment of cannabidiol (CBD) in recreational polydrug users: A randomized, double-blind, controlled trial

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ARTICLE INFO

Article history:

Received 15 June 2018

Revised 27 July 2018

Accepted 30 July 2018

Available online 2 October 2018

Keywords:

Cannabidiol
Abuse potential
Alprazolam
Dronabinol
Epilepsy

ABSTRACT

Rationale: Treatment with a highly purified oral solution of cannabidiol (CBD), derived from the plant *Cannabis sativa* L., demonstrated some evidence of central nervous system (CNS)-related adverse events in patients enrolled in phase 3 trials for treatment of childhood-onset epilepsy. Cannabidiol was categorized as a Schedule 1 substance by the United States Drug Enforcement Administration; therefore, it was important to test CBD for human abuse potential.

Methods: This was a single-dose, randomized, double-blind, double-dummy, placebo- and active-controlled crossover trial. The abuse potential of single oral doses of plant-derived pharmaceutical formulations of highly purified CBD (Epidiolex®; 750 mg, 1500 mg, and 4500 mg) was compared with that of single oral doses of alprazolam (2 mg), dronabinol (10 mg and 30 mg), and placebo in healthy recreational polydrug users. The primary endpoint to assess abuse potential was the maximum effect (E_{max}) on Drug-Liking visual analog scale (VAS). Other measurements included E_{max} on Overall Drug-Liking VAS, Take Drug Again VAS, positive and negative effects, other subjective effects, and Drug Similarity VAS. Cognitive and psychomotor functions were assessed using the Divided Attention Test, the Hopkins Verbal Learning Test—Revised, and the Digit–Symbol Substitution Task. Pharmacokinetic parameters were determined for CBD and its major metabolites. Standard safety measures and adverse events were assessed.

Principal results: Of 95 eligible subjects, 43 qualified for the treatment phase, received at least 1 dose of investigational medicinal product, and were included in safety assessments; 35 subjects were included in the pharmacodynamic analysis. Subjects receiving alprazolam and dronabinol had significantly higher Drug-Liking E_{max} ($P < 0.0001$) compared with those receiving placebo, confirming study validity. Compared with placebo, Drug-Liking was not significantly different for subjects taking 750-mg CBD ($P = 0.51$). Drug-Liking E_{max} values for 1500-mg and 4500-mg CBD were significantly different from placebo ($P = 0.04$ and 0.002 , respectively); however, the mean differences were < 10 points on VAS compared with > 18 -point differences between positive controls and placebo. Alprazolam and dronabinol had significantly higher Drug-Liking, Overall-Liking, and Take Drug Again VAS E_{max} values compared with all doses of CBD ($P \leq 0.004$). In contrast to alprazolam, CBD administration had no observable effect on cognitive/psychomotor tests. Pharmacokinetic parameters for CBD in this trial were consistent with previous studies. The majority of adverse events reported during the trial were of mild or moderate severity; no serious adverse events or deaths were reported.

Conclusion: Administration of a therapeutic dose of CBD (750 mg) showed significantly low abuse potential in a highly sensitive population of polydrug users. Although high and supratherapeutic doses of CBD (1500 mg and 4500 mg, respectively) had detectable subjective effects compared with placebo; the effects were significantly lower than those observed with alprazolam and dronabinol.

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1. Introduction

Of the more than 80 cannabinoid compounds produced by *Cannabis sativa* L., the two major neuroactive components are delta-9 tetrahydrocannabinol (THC), which has euphoric effects, and cannabidiol (CBD), which is thought to lack euphoric effects [1]; THC has agonist activity at neuronal presynaptically localized cannabinoid type 1 (CB₁) receptors, where it acts to inhibit neurotransmitter release, and at cannabinoid type 2 (CB₂) receptors in immune tissues, where it modulates cytokine release and immune cell migration [2]. Cannabidiol has no agonist activity at CB₁ or CB₂ receptors, likely explaining the lack of euphoric effects observed in some studies [1,3]; CBD has antiseizure activity in animal models of Dravet syndrome [4]. A plant-derived pharmaceutical formulation of highly purified CBD in an oral solution is in phase 3 development for the treatment of the childhood-onset epilepsies, Dravet syndrome and Lennox–Gastaut syndrome. This formulation is not approved outside the United States and is approved in the United States for seizures associated with Lennox–Gastaut syndrome or Dravet syndrome in patients aged ≥ 2 years of age. Efficacy in reducing seizure frequency and safety of this CBD formulation have been demonstrated in completed [5–8] and ongoing trials [9,10].

Central nervous system (CNS) adverse reactions that have been reported in at least 10% of patients receiving CBD and greater than placebo in phase 3 trials of CBD include somnolence; fatigue, malaise, and asthenia; and insomnia, sleep disorder, and poor quality sleep [11]. In a study of CBD interactions with smoked marijuana in healthy users of recreational marijuana, CBD pretreatment did not alter the subjective, reinforcing, or cardiovascular effects of smoked marijuana [12]. Secondary analysis of the same study showed that CBD (at doses up to 800 mg) did not produce elevations in any subjective ratings of drug effect relative to placebo [13].

Based on the CNS-related adverse events (AEs) reported in CBD clinical trials and in accordance with US Food and Drug Administration (FDA) guidance [14], a human abuse potential study was conducted to evaluate the abuse potential of therapeutic and supratherapeutic single doses of an oral formulation of CBD. A previous human abuse potential study of CBD evaluated effects in recreational marijuana users [13]; however, as CBD had not demonstrated effects consistent with those of THC, recreational polydrug users were chosen for participation in this study to provide a broader range of drug experiences with which to compare any potentially novel euphoric effects of CBD. This population would also be the most susceptible population to abuse novel drugs with CNS effects and may exhibit a lower risk of false-negative responses than nondrug users who generally do not report liking or self-administration of drugs of abuse [15,16]. Abuse potential was compared with placebo, alprazolam, and the cannabinoid dronabinol, which is a synthetic formulation of THC.

2. Material and methods

This phase 1, single-dose, randomized, double-blind, double-dummy, placebo- and active-controlled crossover trial (Health Canada Control Number 188004) was conducted at a single site in Ontario, Canada (Syneos Health, formerly INC Research at the time of the study) in accordance with the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. The institutional review board (IRB Services, Ontario, Canada) and regulatory authorities (Health Canada, Ontario, Canada) approved the study protocol, and all subjects gave written informed consent before trial initiation.

2.1. Study design

The primary objective of the trial was to evaluate the abuse potential of single doses of 750 mg, 1500 mg, and 4500 mg of the pharmaceutical formulation of highly purified CBD derived from *Cannabis sativa* L. plant

in oral solution (100 mg/mL; Epidiolex®; GW Research Ltd., Cambridge, UK) compared with the single oral doses of alprazolam 2 mg (generic of Xanax®, Sandoz Inc., Princeton, NJ, USA), dronabinol 10 mg and 30 mg (generic of Marinol®, Pharmaceuticals International for PAR Pharmaceuticals, Spring Valley, NY, USA), and placebo (oral solution provided by GW Research Ltd., Cambridge, UK and lactose tablets manufactured at Pointe-Claire, Quebec, Canada) in healthy, recreational polydrug users. The trial also evaluated safety and pharmacokinetics (PK) of CBD, THC, and their major metabolites in healthy, recreational polydrug users.

The overall trial design was consistent with guidelines for the assessment of abuse potential in humans [14–16]. The benzodiazepine alprazolam (Controlled Substances Act Schedule IV [C-IV] drug) was selected as one of the positive controls because of some similarities in pharmacological effects (side effects, such as somnolence; anticonvulsant and anti-anxiety effects) and PK profile to CBD. Although no THC-like effects have been seen with CBD, synthetic THC [dronabinol (C-III)] was also included as a positive control to completely rule out any of these potential effects because CBD is derived from cannabis. Consistent with regulatory guidelines, a therapeutic dose (750 mg), a high therapeutic dose (1500 mg), and a supratherapeutic dose (4500 mg) of CBD were used to evaluate the dose-response of the drug. The 4500-mg supratherapeutic dose (more than 60 mg/kg for a 70 kg adult) was selected as a high single dose of CBD that was tolerated in a previous single-ascending dose study and showed a similar adverse event profile to the maximal dose of 6000 mg even though the C_{max} of CBD increased proportionally (data on file).

The trial design consisted of screening, qualification, treatment, and follow-up phases (Fig. 1). After an outpatient medical screening visit, subjects were randomized to a 7-day, double-blind, crossover qualification phase (QP) to ensure that they could discriminate the subjective effects of the positive control drugs (single doses of 2-mg alprazolam, 20-mg dronabinol) from placebo. During the QP, administration of each drug (alprazolam, dronabinol, and placebo) was separated by approximately 48 h, and a minimum of 8 washout days was required before starting the treatment phase (TP). To qualify for the TP, subjects were required to meet the following criteria in the QP: at least a 15-point difference between placebo and positive controls on the Drug-Liking visual analog scale (VAS), with a maximum effect (E_{max}) of at least 65 points for alprazolam and dronabinol; Drug-Liking E_{max} for placebo between 40 and 60 points, inclusive; acceptable overall response to alprazolam, dronabinol, and placebo on the subjective measures; able to tolerate the control drugs, and general behavior indicating that the subject would be able to complete the trial.

The TP consisted of seven 3-day visits, each separated by a washout period of at least 8 days. Subjects who successfully completed the QP were randomized to 1 of 14 treatment sequences according to two 7 × 7 Williams squares. All subjects received a single dose (after an overnight fast) of each of the following in a randomized, double-blind, crossover manner: CBD 750 mg, CBD 1500 mg, CBD 4500 mg, alprazolam 2 mg, dronabinol 10 mg, dronabinol 30 mg, and placebo (Table S1). Subjects returned for the safety follow-up 8 to 14 days after the last drug administration.

2.2. Study population

Healthy male and female adults between the ages of 18 and 55 years with body mass index (BMI) between 19.0 and 30.0 kg/m² and a weight of ≥ 50 kg at screening were eligible for this trial. Subjects were required to have had ≥ 10 nontherapeutic experiences with CNS depressants, ≥ 10 nontherapeutic experiences with cannabinoids, ≥ 1 nontherapeutic use of another class of drugs of abuse in their lifetime, and ≥ 1 nontherapeutic use of a CNS depressant and a cannabinoid within the 12 weeks before screening. Use of CBD was not thought to be associated with euphoric effects similar to those of THC; therefore, subjects were required to have polydrug experience, in addition to cannabinoids, to provide a broader range of

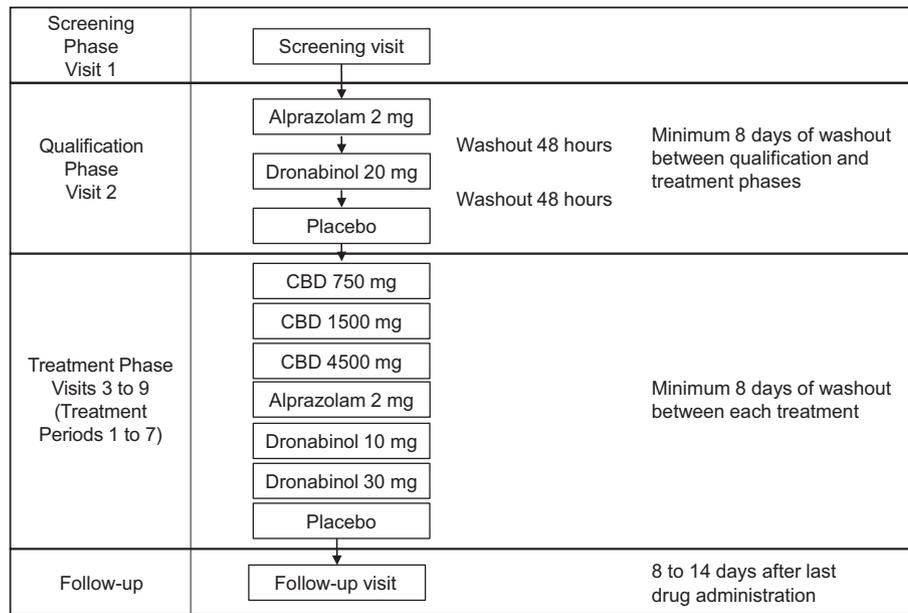


Fig. 1. Study design. The sequence of treatments shown illustrates the overall design and does not represent an actual treatment sequence. CBD, cannabidiol.

experiences with which to evaluate the potentially novel effects of CBD. Female subjects of childbearing potential must have had a negative pregnancy test at screening and before treatment phase and were required to use an effective method of contraception during the trial. All subjects were required to pass the QP. The main exclusion criteria were any history of alcohol or drugs-of-abuse dependence or addiction (as defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition Text Revised [DSM-IV-TR]) [17], current or prior treatment for substance abuse disorders, intravenous use of drugs of abuse within 2 years of screening, or any condition that may affect drug absorption, distribution, metabolism, or excretion. Subjects were required to restrict the use of alcohol, recreational drugs, poppy seeds, grapefruit products, and prescription and over-the-counter medications, including herbal remedies, during the trial.

2.3. Pharmacodynamic assessments

Pharmacodynamic (PD) assessments were done using the proprietary validated computerized software (Code of Federal Regulations Part 11 compliant) PsychometRx™ (Syneos Health, formerly INC Research, Toronto, Ontario, Canada). Participants rated subjective effects of the study drugs on 100-point VAS, which were either bipolar or unipolar, depending on the nature of the effect being measured (Table S2). The primary endpoint to assess abuse potential was E_{\max} on the Drug-Liking VAS, presented on a bipolar 0 to 100 scale. Secondary endpoints included subjective measures of end-of-day/next-day global effects (Overall Drug-Liking VAS and Take Drug Again VAS); positive effects (Good Effects VAS, High VAS, Stoned VAS); negative effects (Bad Effects VAS); sedative/stimulant effects (Alertness/Drowsiness VAS); and Drug Similarity VAS (at the 12-hour postdose time point only). Cognitive and psychomotor functions were assessed using the Divided Attention Test (DAT), Hopkins Verbal Learning Test—Revised (HVLTR), and Digit Symbol Substitution Task (DSST). All subjects underwent a scripted training and practice regimen before completing the computerized measures. Subjective PD assessments were conducted predose (for measures not referring to the drug) and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, and 24 h post dose, whereas cognitive and motor assessments were conducted predose and at 1, 2, 3, 6, 8, 12, and 24 h post dose. Measures were administered as described previously [18,19].

2.4. PK assessments

Serial blood samples were obtained up to 24 h after dose administration to measure exposure to CBD and assess PK parameters for CBD and metabolites. Descriptive statistics were calculated and presented for plasma concentrations of CBD, its major metabolites, THC, and THC metabolites. The PK parameters were calculated using noncompartmental methods. The PK endpoints were time to maximum observed plasma concentration (T_{\max}), maximum observed plasma concentration (C_{\max}), area under the plasma concentration-time curve from zero to the last measurable concentration ($AUC_{0-\text{last}}$), and area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$).

2.5. Safety assessments

Safety assessments included recording of the incidence, frequency, and severity of AEs; and regular assessments of vital signs, clinical laboratory assessments (hematology, biochemistry, urinalysis), 12-lead electrocardiogram (ECG), physical examinations, “Since Last Visit” Columbia–Suicide Severity Rating Scale (C-SSRS), and continuous cardiac and pulse oximetry monitoring (up to at least 12 h after each drug administration) via telemetry.

2.6. Data analyses

Sample size was determined using a power calculation method for crossover studies [20,21], with a 2-sided significance level of 0.05. A sample size of 35 subjects was expected to have >80% power to detect a 15-point difference in E_{\max} scores on Drug-Liking VAS between alprazolam or dronabinol and CBD, using an estimated standard deviation (SD) of ≈ 17 (pooled between-subject SD from placebo). Randomized subjects who completed all treatment periods in TP and who had at least one Drug-Liking VAS observation around T_{\max} for each treatment in the trial were included in the PD analyses. The PK analyses were conducted for all randomized subjects who received any investigational medicinal product (IMP) in the TP and had at least one postdose PK sample. All subjects who received at least one dose of any IMP in the TP were included in the safety analyses. All statistical analyses were performed using SAS (version 9.3 or higher). During the TP, PD values at each time point were summarized according to the treatment received,

using descriptive statistics and presented graphically. A mixed-effects model for a crossover trial was used to compare the primary and secondary PD endpoints between treatments. The model included treatment, period, sequence, and first-order carryover effect as fixed effects, and subject nested within treatment sequence as a random effect. Baseline (predose) measurement (where applicable) and sex were included as covariates. For each parameter, the above mixed-effects model was first used, and the residuals from the model were investigated for normality using the Shapiro–Wilk *W*-test. Nonparametric tests were used where assumptions for parametric testing were not met, overall treatment effect was assessed using the Friedman test, and pairwise comparisons were assessed using paired *t* test, *z* test, or sign test, depending on the distribution of the residuals. Depending on the type of test used, treatment differences were presented as the difference in least squares means (95% confidence intervals) for parametric tests or median values (first quartile [Q1], third quartile [Q3]) for nonparametric tests.

3. Results

3.1. Subject disposition and baseline characteristics

A total of 95 eligible subjects were randomized to receive single oral doses of alprazolam, dronabinol, and placebo during the QP (Fig. S1). Of these, 43 subjects qualified for the TP and were randomly assigned to 1 of 14 treatment sequences. There were 52 subjects that were not randomized to the TP of the study. Forty-two of these subjects failed to meet qualification criteria (outlined in Section 2.1). The vast majority (38) had either inadequate or inconsistent responses to positive control drugs and/or placebo, and 4 had disqualifying AEs or were noncompliant. An additional 10 subjects did not enter the treatment phase for other reasons (withdrawal by subject [*n* = 3], noncompliance with study drug [*n* = 2], safety reasons [*n* = 1], administrative reasons [*n* = 1], and other reasons [*n* = 3]). All 43 randomized subjects received ≥ 1 dose of IMP and were included in the safety assessments. Of the 8 subjects who withdrew during the TP, 5 subjects withdrew because of safety reasons, 2 subjects withdrew voluntarily, and 1 subject was withdrawn for noncompliance. Thirty-five subjects completed the trial and were included in PD analysis. Of 43 subjects, 41 subjects were included in PK analyses; two subjects were not included in the evaluation because they did not receive any CBD treatment and had no evaluable postdose PK samples.

The subjects in the safety population were primarily male and white (*n* = 31, 72.1%, for both) with mean (SD) age of 37.7 (8.9) years and mean BMI (SD) of 25.9 (2.7) kg/m². All 43 subjects had a history of recreational use of cannabinoids and CNS depressants. All subjects had lifetime experience with at least one other drug class, with the following specific drug exposures: opioids (90.7%), stimulants (79.1%), hallucinogens (48.8%), and dissociative anesthetics (16.3%) (Table S3).

3.2. Effect on subjective PD measures

3.2.1. Qualification phase

Among the subjects who were randomized and completed the trial (i.e., those included in the PD analysis), the median (minimum, maximum) peak Drug-Liking VAS score for placebo was 50 (50, 53) in the QP, which is in the neutral range (40–60, inclusive). Subjects receiving alprazolam 2 mg and dronabinol 20 mg had substantially higher median (minimum, maximum) scores of 89 (65, 100) and 100 (75, 100), respectively.

3.2.2. Bipolar Drug-Liking VAS (primary endpoint)

The mean Drug-Liking scores for placebo over the 12-hour postdose period were in the neutral range (50 on the bipolar VAS) at all time points. The mean score for alprazolam 2 mg reached a maximum of 69.2 at 2 h post dose and a maximum of 65.7 at 6 h post dose for

dronabinol 10 mg. The largest increase in mean Drug-Liking VAS scores of 74.9 at 5 h post dose was observed with dronabinol 30 mg (Fig. 2A). Mean Drug-Liking scores for CBD remained within the neutral zone at all time points, with transient marginal increases up to 56.5 and 58.0 observed at 2 h post dose with CBD 1500 mg and 4500 mg, respectively (Fig. 2A).

Compared with placebo, Drug-Liking VAS E_{max} values were significantly higher for alprazolam 2 mg and for both dronabinol 10 mg and dronabinol 30 mg, confirming the study's validity (Table 1). The Drug-Liking VAS E_{max} value for CBD 750 mg was not significantly different from placebo (Table 1). Drug-Liking E_{max} values for CBD 1500 mg and 4500 mg were significantly greater than placebo (*P* = 0.04 and 0.002, respectively); however, the differences were less than 10 points compared with the more than 18-point differences between positive controls and placebo (Table 1). Administration of all 3 doses of CBD showed significantly lower Drug-Liking VAS E_{max} scores compared with alprazolam 2 mg and both doses of dronabinol (Table 1).

3.2.3. Maximum effect on Overall Drug-Liking VAS and Take Drug Again VAS

Overall Drug-Liking E_{max} scores and Take Drug Again VAS for alprazolam 2 mg and both doses of dronabinol were significantly higher compared with those for placebo. In contrast, the values for CBD were not significantly different from placebo on Overall Drug-Liking VAS, and only administration of CBD 1500 mg and 4500 mg showed significantly higher Take Drug Again VAS E_{max} scores compared with that from placebo. Administration of all 3 doses of CBD showed significantly lower scores than all positive control doses on both Overall Drug-Liking VAS and Take Drug Again VAS (Table 1 and Fig. 2B, C).

3.2.4. Measures of positive effects

Mean Good Effects VAS scores for all doses of CBD over time were slightly higher than placebo and lasted for 4 to 6 h (Fig. 3A). Mean scores for all positive controls increased markedly and remained relatively high for at least 12 h post dose (Fig. 3A). All three positive control treatments demonstrated significantly higher E_{max} values compared with placebo on Good Effects VAS, Feeling High VAS, and Feeling Stoned VAS (Fig. 3A, B, and C; Table S4). Treatment with CBD 750 mg showed no difference compared with placebo on all three positive effect scales. Although CBD 1500 mg administration showed significant differences from placebo on some of the endpoints, and CBD 4500 mg showed significant differences from placebo on the majority of endpoints, the magnitude of the differences was lower than those of positive controls (Table S4). With a few exceptions, all three doses of CBD demonstrated significantly lower positive effects than positive controls (Table S4).

3.2.5. Measures of negative effects

Subjects receiving alprazolam 2 mg and dronabinol 30 mg reported significantly higher Bad Effects VAS E_{max} scores compared with placebo. There were no significant differences in Bad Effects between placebo and any CBD dose or dronabinol 10 mg. With the exception of a few sporadic significant differences between CBD 750 mg and 1500 mg and alprazolam 2 mg or dronabinol 30 mg, the majority of differences were not significant (Table S4).

3.2.6. Measures of sedative/stimulant effects and Drug Similarity

Subjects receiving placebo and all doses of CBD reported a small decrease in mean Alertness/Drowsiness VAS scores during 1 to 4 h post dose; however, the values remained in the neutral range (40–60, inclusive), indicating the subjects felt neither drowsy nor alert (Fig. 4). Dronabinol doses were associated with a more substantial decrease in mean Alertness/Drowsiness VAS scores (indicating an increase in drowsiness) later during the time course with the maximum decrease reported at 6 h post dose (Fig. 4). Administration of alprazolam 2 mg was associated with the lowest scores (i.e., greatest increase in drowsiness), with peak effects observed at 3 h post dose (Fig. 4). Compared

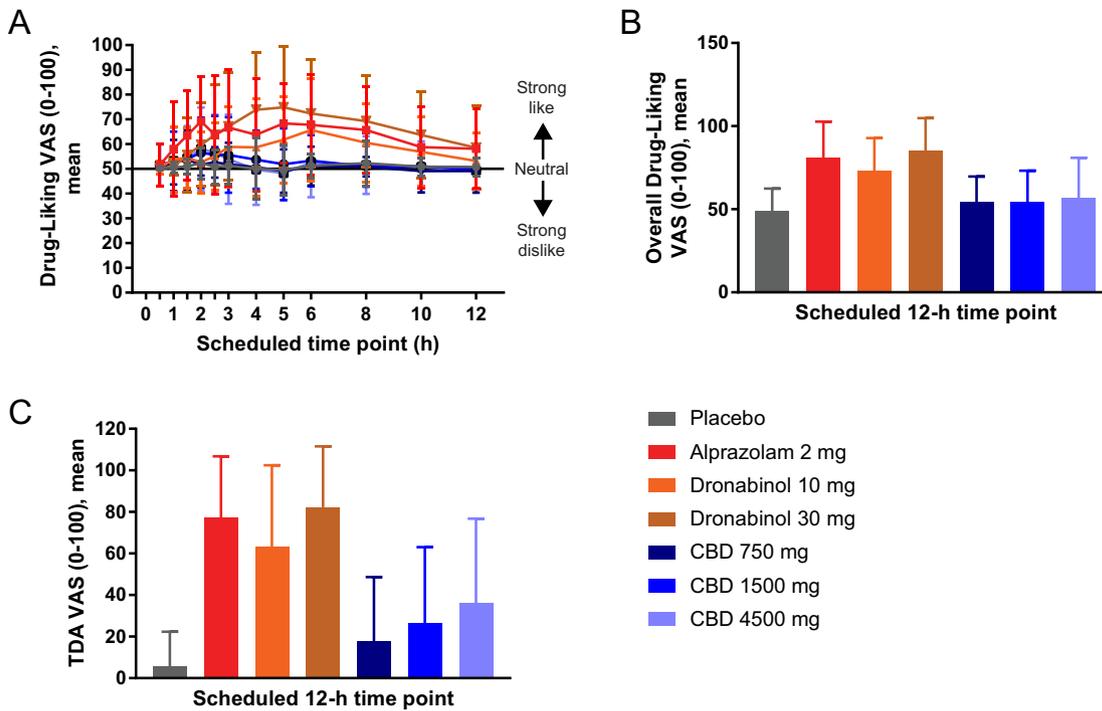


Fig. 2. Drug-Liking, Overall Drug-Liking, and Take Drug Again VAS scores for CBD, alprazolam, dronabinol, and placebo. (A) Time-response profiles of Drug-Liking VAS scores (mean \pm standard deviation), (B) Overall Drug-Liking VAS scores (mean \pm standard deviation), (C) E_{max} values (mean \pm standard deviation) for Take Drug Again. CBD, cannabidiol; E_{max} , maximum effects; TDA, Take Drug Again; VAS, visual analog scale.

with placebo, alprazolam 2 mg, all doses of dronabinol, and CBD showed a significantly lower minimum effect (E_{min}) on Alertness/Drowsiness VAS (Table S4). All doses of CBD showed significantly lower effects

compared with the positive controls, except for two differences in comparisons between dronabinol 10 mg and CBD 1500 mg and dronabinol 10 mg and CBD 4500 mg (Table S4). The median "Placebo" Similarity

Table 1

Comparisons of mean or median differences in E_{max} values for key subjective PD measures.

Treatments	Drug-Liking VAS LS mean difference ^a (SE)	ODL VAS Mean (SE) or median difference (Q1–Q3)	TDA VAS LS mean difference ^b (SE)
<i>Positive controls vs. placebo (trial validity)</i>			
Alprazolam 2 mg – Placebo	24.2 (3.06) ^c	36.5 (3.98) ^{c,d}	75.4 (6.92) ^c
Dronabinol 10 mg – Placebo	18.6 (3.07) ^c	25.0 (4.45) ^{c,d}	52.9 (6.99) ^c
Dronabinol 30 mg – Placebo	32.3 (3.06) ^c	36.7 (4.29) ^{c,d}	75.1 (7.01) ^c
<i>CBD vs. placebo (absolute abuse potential)</i>			
CBD 750 mg – Placebo	2.0 (3.07)	0 (–1.0–5.0) ^e	6.7 (7.01)
CBD 1500 mg – Placebo	6.4 (3.05) ^f	0 (–1.0–11.0) ^e	15.1 (6.94) ^f
CBD 4500 mg – Placebo	9.5 (3.05) ^f	9.4 (5.44) ^g	29.6 (6.93) ^c
<i>CBD vs. positive controls (relative abuse potential)</i>			
CBD 750 mg – Alprazolam 2 mg	–22.2 (3.05) ^c	–32.0 (3.19) ^{c,d}	–68.7 (6.96) ^c
CBD 1500 mg – Alprazolam 2 mg	–17.9 (3.06) ^c	–30.1 (3.61) ^{c,g}	–60.3 (6.93) ^c
CBD 4500 mg – Alprazolam 2 mg	–14.8 (3.07) ^c	–27.1 (4.10) ^{c,d}	–45.8 (6.99) ^c
CBD 750 mg – Dronabinol 10 mg	–16.6 (3.06) ^c	–20.5 (3.84) ^{c,d}	–46.2 (6.95) ^c
CBD 1500 mg – Dronabinol 10 mg	–12.3 (3.06) ^c	–18.5 (4.34) ^{c,g}	–37.8 (6.93) ^c
CBD 4500 mg – Dronabinol 10 mg	–9.2 (3.08) ^f	–15.6 (5.11) ^{f,g}	–23.3 (7.07) ^f
CBD 750 mg – Dronabinol 30 mg	–30.2 (3.08) ^c	–32.3 (3.75) ^{c,d}	–68.5 (7.04) ^c
CBD 1500 mg – Dronabinol 30 mg	–25.9 (3.06) ^c	–30.3 (3.72) ^{c,d}	–60.0 (6.97) ^c
CBD 4500 mg – Dronabinol 30 mg	–22.8 (3.06) ^c	–27.3 (5.25) ^{c,d}	–45.5 (6.95) ^c

CBD, cannabidiol; E_{max} , maximum effect; LS, least squares; ODL, Overall Drug-Liking; PD, pharmacodynamic; Q1, first quartile; Q3, third quartile; SE, standard error; TDA, Take Drug Again; VAS, visual analog scale.

^a For Drug-Liking, the LS means were estimated from a mixed-effects model, in which treatment, period, and treatment sequence were fixed effects, sex was a covariate, and subject nested within sequence as a random effect. Treatment effect was significant ($P < 0.0001$), while period ($P = 0.2243$), treatment sequence ($P = 0.4552$), and sex ($P = 0.8615$) were not significant; carryover effect was not significant at the 25% level and dropped from the model.

^b For Take Drug Again, the LS means were estimated from a mixed-effects model, in which treatment, period, and treatment sequence were fixed effects, sex was a covariate, and subject nested within sequence as a random effect. Treatment effect was significant ($P < 0.0001$), while period ($P = 0.2645$), treatment sequence ($P = 0.8338$), and sex ($P = 0.5153$) were not significant; first-order carryover effect was significant at the 25% level ($P = 0.1945$) and included in the model.

^c $P \leq 0.0001$.

^d The paired z test was used to assess the difference between 2 treatments; mean difference was presented.

^e The sign test was used to assess the difference between 2 treatments; median difference was presented.

^f $P < 0.05$.

^g The paired t -test was used to assess the difference between 2 treatments; mean difference was presented.

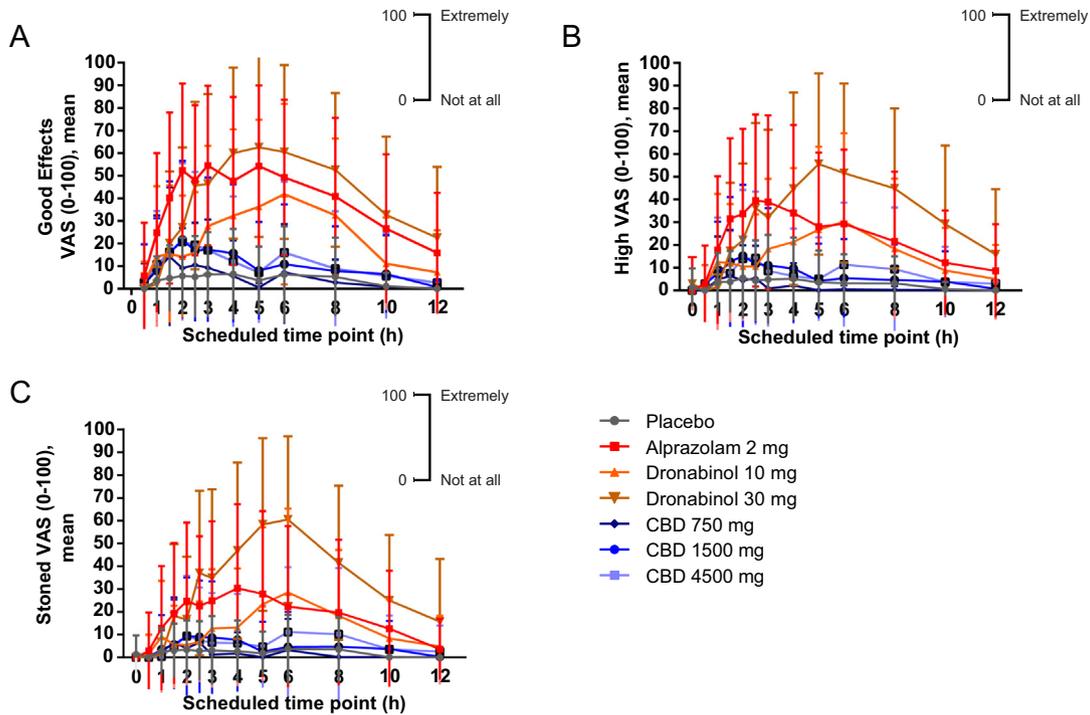


Fig. 3. Time-response profiles for positive effects of CBD, alprazolam, dronabinol, and placebo. (A) Good Effects VAS scores (mean \pm standard deviation), (B) High VAS scores (mean \pm standard deviation), (C) Stoned VAS scores (mean \pm standard deviation). CBD, cannabidiol; VAS, visual analog scale.

VAS score at 12 h post dose was 100 with placebo and 59 and 48 with CBD 750 mg and 1500 mg, respectively (Fig. S2). Cannabidiol 4500 mg and positive control treatments were associated with median scores of 0 on the Placebo Similarity VAS (Fig. S2). Alprazolam 2 mg scored the highest, 100, on the Benzodiazepine Similarity VAS, whereas dronabinol had high scores on the THC Similarity VAS (75 and 100 for 10 mg and 30 mg doses, respectively) (Fig. S2). No CBD doses were rated as being similar to any drugs of abuse included in the assessments, with median scores \leq 5.0 on all Drug Similarity scales (Fig. S2).

3.2.7. Measure of cognitive and psychomotor effects

When completing the DAT, no dose of CBD had significant effects on manual tracking, as measured by the subject's ability to keep the target on the moving road or percentage of time over road compared with placebo (Fig. 5). The effect of dronabinol 10 mg was also similar to placebo, whereas dronabinol 30 mg was associated with a slight decrease (<10%) in performance starting at 3 h post dose and continuing up to 6 h post dose (Fig. 5). Following administration of alprazolam 2 mg, an approximately 20% decrease in manual tracking performance was observed, starting at 1 h post dose and continuing to 6 h post dose (Fig.

5). A similar pattern of results was observed on other cognitive and motor assessments (Table S5).

3.3. Measure of PK parameters

Plasma CBD concentration increased relatively slowly, with mean peak concentrations observed at 6 h post dose (Fig. S3). Mean C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ values for CBD increased with an increase in dose from 750 mg to 1500 mg, but the values decreased slightly at 4500 mg compared with 1500 mg (Table 2), indicating a potential saturation in absorption (i.e., less than dose-proportional increases). However, the percentage coefficient of variation (% CV) was relatively high for C_{max} and AUC, particularly at the highest dose of CBD. Median T_{max} ranged from 4 to 6 h across the 3 CBD doses (Table 2). Mean C_{max} , $AUC_{(0-last)}$, and $AUC_{(0-\infty)}$ for the three CBD metabolites (6-OH-CBD, 7-COOH-CBD, and 7-OH-CBD) also showed less than dose-proportional increases between CBD 1500 mg and 4500 mg (Table S6). Peak and overall exposure to THC and its metabolites were relatively low, with C_{max} less than 0.6 ng/mL for THC and 11-OH-THC and less than 5 ng/mL for 11-COOH-THC (data not shown). Median T_{max} for THC and

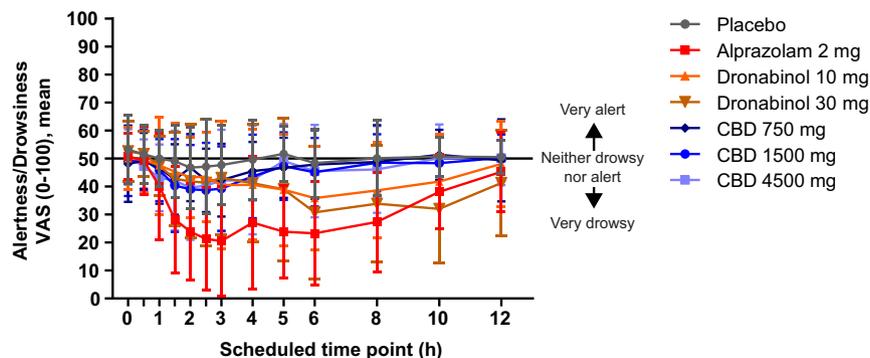


Fig. 4. Time-response profile for sedative/stimulant effects of CBD, alprazolam, dronabinol, and placebo. Alertness/Drowsiness VAS score (mean \pm standard deviation). CBD, cannabidiol; VAS, visual analog scale.

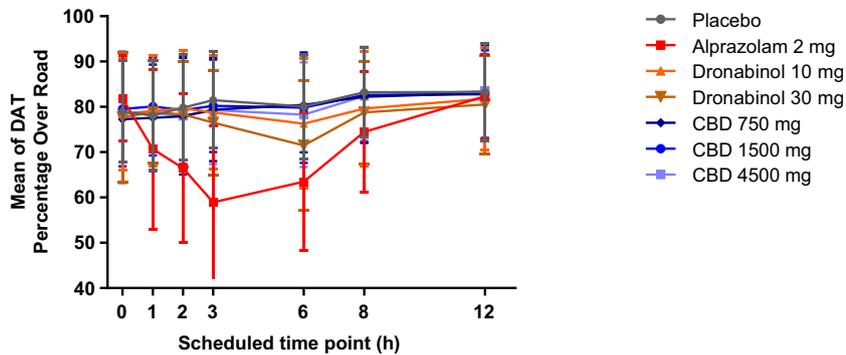


Fig. 5. Time-response profile for cognitive and psychomotor effects of CBD, alprazolam, dronabinol, and placebo. Divided Attention Test – Percentage Over Road values (mean \pm standard deviation). CBD, cannabidiol; DAT, Divided Attention Test.

metabolites ranged from approximately 4 to 6 h post dose (data not shown).

3.4. Safety

All subjects who received alprazolam and most who received dronabinol (dronabinol 30 mg, 97.5%; dronabinol 10 mg, 71.8%) reported ≥ 1 AE, whereas 47.4% to 65.0% of subjects reported ≥ 1 AE following CBD doses (Table 3). Somnolence was the most commonly reported AE with all treatments, except dronabinol 30 mg, for which euphoric mood was the most commonly reported AE (Table 3). There were no serious AEs, and all AEs were moderate or mild in severity, except for one subject whose pregnancy was reported as a severe event (after receiving alprazolam) that was unrelated to study treatment. There were no deaths reported in the study. Five subjects discontinued because of the AEs: 2 with dronabinol 30 mg (arrhythmia supraventricular, $n = 1$; chest discomfort, $n = 1$; both considered treatment-related), 1 with CBD 1500 mg (aspartate aminotransferase [AST] increased and blood creatine phosphokinase [CPK] increased; AST increase was considered treatment-related), and 2 with CBD 4500 mg (ECG QT interval prolonged, $n = 1$; hypersensitivity, $n = 1$; hypersensitivity was considered treatment related).

The incidence of potentially abuse-related AEs was highest following dronabinol doses. Euphoric mood was reported in 12 subjects (30.8%) with dronabinol 10 mg and in 25 (62.5%) with dronabinol 30 mg, whereas with CBD 750 mg, 1500 mg, and 4500 mg, euphoric mood was reported in 2 (5.3%), 2 (5.1%), and 3 (7.5%) subjects, respectively, and by 3 subjects (7.5%) with alprazolam (Table 3). Euphoric mood was not reported with placebo. The incidence of somnolence was highest in subjects who received alprazolam (87.5%), followed by dronabinol doses (35.9% and 55.0%), and was lower with CBD doses (4500 mg, 30.0%; 1500 mg, 30.8%; 750 mg, 23.7%) and placebo (21.6%).

Table 2
Pharmacokinetic parameters of CBD.

PK parameter	CBD 750 mg (N = 38)	CBD 1500 mg (N = 39)	CBD 4500 mg (N = 40)
C_{max} , ng/mL	336.2 (46.7)	524.5 (64.9)	426.9 (112.8)
Mean (% CV)			
T_{max} , h	5.11 (2.18–8.23)	6.13 (3.13–8.17)	4.07 (2.15–12.20)
Median (range)			
$AUC_{(0-last)}$, h·ng/mL	1586.7 (52.0)	2649.6 (70.1)	2338.6 (109.6)
Mean (% CV)			
$AUC_{(0-\infty)}$, h·ng/mL	1683.3 (46.7)	2713 (64.0)	2290.3 (104.1)
Mean (% CV)	(n = 34)	(n = 27)	(n = 31)

$AUC_{(0-last)}$, area under the plasma concentration-time curve from time zero to the last measurable concentration; $AUC_{(0-\infty)}$, area under the plasma concentration-time curve from time zero to infinity; CBD, cannabidiol; C_{max} , maximum plasma concentration; % CV, percentage coefficient of variation; N, number of subjects in the PK population for a given treatment; n, number of values included in the calculation of summary statistics; T_{max} , time to maximum observed plasma concentration.

There were no relevant changes or clear trends in hematology, biochemistry, or urinalysis parameters over time. The majority of median/mean values were within the normal range, except for alanine aminotransferase, AST, and blood CPK, which were elevated at some visits, likely due to the few subjects with AEs of elevated AST and CPK. Cannabidiol was not associated with changes in vital signs compared with placebo. Alprazolam was associated with small decreases in blood pressure, and dronabinol was associated with increased heart rate. Mean ECG parameters were within normal limits across the study, and no subjects who received CBD had abnormal ECG parameters considered clinically significant. One subject discontinued CBD 4500 mg because of an AE of prolonged QT interval; this AE was mild and considered unrelated to study treatment. There were no relevant findings from physical examinations and no changes in C-SSRS from baseline to other visits.

4. Discussion

In this trial, the abuse potential of a pharmaceutical formulation of highly purified CBD was compared with that of placebo and positive controls alprazolam and dronabinol. Subjects who had a history of using multiple classes of drugs of abuse were selected for the trial to ensure that they were able to distinguish between placebo and the active controls and to report any potential novel abuse-related effects of CBD. As expected, compared with placebo, both alprazolam and dronabinol were associated with significant abuse-related effects, including the primary endpoint of Drug-Liking VAS E_{max} , thereby supporting validity of the trial.

The therapeutic dose of CBD (750 mg) did not elicit a significant abuse-related subjective response compared with placebo. Although the primary endpoint of Drug-Liking E_{max} for higher doses of CBD was statistically greater than placebo and some sporadic significant differences were observed on secondary endpoints, the magnitude of difference between CBD doses and placebo was substantially smaller than that observed with positive controls and may be of little clinical significance. Furthermore, the slight increase in reported Drug-Liking and positive subjective effects at higher doses were transient and subsided within 2 to 3 h of administration. Subjects did not report feeling significant bad effects even at higher doses of CBD compared with placebo. The relative lack of increase in Drug-Liking VAS E_{max} scores despite the increase in CBD dose up to 4500 mg indicated that further dose escalation most likely would not result in greater abuse-related effects of CBD. This may in part be related to an apparent saturation in absorption between the 2 highest doses, whereby PK parameters such as C_{max} and AUC did not increase, despite a threefold increase in dose.

Dronabinol (THC) has been associated with significant abuse potential in previous human abuse potential studies [22–24]. Although derived from *Cannabis sativa*, CBD did not show a profile of abuse-related effects similar to that of dronabinol. The difference in abuse potential between dronabinol (synthetic THC) and CBD can likely be

Table 3
Summary of AEs.

	Treatment group						
	Placebo (N = 37)	Alprazolam (N = 40)	Dronabinol 10 mg (N = 39)	Dronabinol 30 mg (N = 40)	CBD 750 mg (N = 38)	CBD 1500 mg (N = 39)	CBD 4500 mg (N = 40)
Any AE, n (%)	16 (43.2)	40 (100)	28 (71.8)	39 (97.5)	18 (47.4)	25 (64.1)	26 (65.0)
Somnolence, n (%)	8 (21.6)	35 (87.5)	14 (35.9)	22 (55.0)	9 (23.7)	12 (30.8)	12 (30.0)
Diarrhea, n (%)	0	0	2 (5.1)	0	1 (2.6)	4 (10.3)	8 (20.0)
Headache, n (%)	3 (8.1)	2 (5.0)	5 (12.8)	4 (10.0)	5 (13.2)	8 (20.5)	4 (10.0)
Abdominal pain, n (%)	0	0	2 (5.1)	1 (2.5)	0	1 (2.6)	4 (10.0)
Nausea, n (%)	4 (10.8)	1 (2.5)	7 (17.9)	7 (17.5)	2 (5.3)	4 (10.3)	3 (7.5)
Euphoric mood, n (%)	0	3 (7.5)	12 (30.8)	25 (62.5)	2 (5.3)	2 (5.1)	3 (7.5)
Fatigue, n (%)	2 (5.4)	7 (17.5)	3 (7.7)	5 (12.5)	2 (5.3)	2 (5.1)	2 (5.0)
Abdominal discomfort, n (%)	1 (2.7)	0	0	0	1 (2.6)	1 (2.6)	2 (5.0)
Feeling of relaxation, n (%)	1 (2.7)	5 (12.5)	0	2 (5.0)	0	1 (2.6)	2 (5.0)
Feeling abnormal, n (%)	1 (2.7)	1 (2.5)	1 (2.6)	2 (5.0)	0	0	2 (5.0)
Feeling cold, n (%)	0	0	0	0	0	0	2 (5.0)
Dry mouth, n (%)	0	0	3 (7.7)	8 (20.0)	1 (2.6)	1 (2.6)	1 (2.5)
Dizziness, n (%)	0	4 (10.0)	2 (5.1)	3 (7.5)	0	0	1 (2.5)
Sinus tachycardia, n (%)	0	1 (2.5)	4 (10.3)	10 (25.0)	0	2 (5.1)	0
Electrocardiogram T wave inversion, n (%)	0	2 (5.0)	1 (2.6)	1 (2.5)	0	0	0

AE, adverse event; CBD, cannabidiol.

explained by their different mechanisms of action. Unlike THC, which has agonist action at endocannabinoid receptors CB₁ and CB₂, CBD has no agonist activity at these receptors [2]. Instead, CBD has shown activity at a number of targets, including glycine receptors and the G-protein-coupled receptor GPR55, which are thought to not be associated with euphoric effects [1]. Furthermore, in discrimination studies in rhesus monkeys, CBD did not substitute for a THC discriminative stimulus, indicating the lack of action by CBD at CB₁ receptors [25]. The minimal effects of CBD in this study are similar to those reported by Babalonis et al. [13]. Although that study showed few significant effects of CBD, a lower range of doses were used (200, 400, and 800 mg) compared with the present study. Consistent with Babalonis et al., the CBD dose of 750 mg used in the present study showed few significant effects, whereas some statistically significant differences from placebo emerged at the higher dose range (twofold and sixfold higher doses of 1500 mg and 4500 mg). In contrast to polydrug users in the present study, Babalonis et al. reported data from marijuana users, who may not have been as sensitive to the potentially novel (non-THC-like) effects of CBD.

Several antiepileptic drugs (AEDs) approved by the FDA have shown significant effects in human abuse potential studies, including pregabalin (C-V) [26] and ezogabine (C-V) [27], which have shown similar abuse potential to diazepam and alprazolam, respectively, in individuals with a history of recreational use of sedatives. Another AED, lacosamide (C-V), showed significant but transient euphoric effects at a higher dose (800 mg), although effects were lower compared with alprazolam; the lower therapeutic dose (200 mg) was similar to placebo [28]. An abuse potential study with brivaracetam (C-V) in users of recreational CNS depressants showed significant increases in subjective abuse potential measures compared with placebo, and effects similar to alprazolam at supratherapeutic doses but not the therapeutic dose [29]. In contrast, CBD showed significantly lower effects than alprazolam and dronabinol on various measures of abuse potential and was not rated as similar to any other drugs of abuse. The magnitude of Drug-Liking scores reported for CBD by recreational polydrug users were similar to those reported for eslicarbazepine (not controlled) in recreational sedative users [30].

In contrast to alprazolam and, to a lesser extent, dronabinol, CBD did not impair cognition or motor control at any dose tested and was generally better tolerated than either alprazolam or dronabinol, based on overall incidence of AEs. Subject discontinuations were few and did not follow a specific pattern (i.e., noninformative). Of the subjects who discontinued the study because of AEs, elevations in liver enzymes

noted in two subjects may have been related to muscle enzyme necrosis rather than a liver abnormality associated with concomitant elevations in CPK level. Elevations of liver enzymes similar to those reported in some patients receiving highly purified CBD oral solution for severe, refractory epilepsies in other clinical trials were not observed in this study [5,6], though single dose administration may not show these elevations. One subject discontinued CBD treatment after a supratherapeutic (4500 mg) dose because of an AE of elongated ECG QT interval, but this was considered unrelated to study treatment by the investigator, and it should be noted that therapeutic and supratherapeutic doses of CBD had no effect on QT interval or other ECG parameters in a previous safety study in healthy volunteers [31]. Safety data in the present study further supported PD results and showed a relatively low incidence of potentially abuse-related AEs, such as euphoric mood, with CBD. Although euphoric mood was reported with CBD with the same incidence as alprazolam but lower than with dronabinol, there were no reports with placebo, suggesting a weak signal for euphoria with CBD.

Limitations of the present study include testing abuse potential in a highly susceptible population of polydrug users; findings need to be confirmed with real-world data in more general populations of individuals who abuse prescription drugs. Although efforts were made to recruit female subjects, the majority of subjects in this study were male. However, sex was included as a covariate in the mixed-effects model and was found to be statistically significant only on HVLT-R endpoints, and not the primary subjective measures of abuse potential. Because this CBD formulation is being developed for pediatric indications, this abuse potential study in adult recreational drug users may not necessarily be generalized to children with seizure disorders. Although potential abuse or misuse in this population with severe and debilitating epilepsy can only be confirmed by postmarketing data, it may reasonably be expected to be less than the general population. Because of its low abuse potential, CBD is less likely to be diverted from patients. In addition, because clear signals of psychoactive effects (e.g., sedation, stimulation, etc.) were not observed in previous studies of CBD, selection of an ideal comparator was difficult. Administering CBD with a high fat meal has been shown to increase drug exposure in adult patients with refractory epilepsy [32]; therefore, it is possible that administration of CBD after overnight fasting in this study could affect CBD exposure in subjects. However, apparent saturation in absorption between CBD 1500 mg and 4500 mg suggests that maximum exposure to CBD was achieved in this study. While the apparent saturation in absorption limits our ability to draw conclusions on patients who may have higher absorption, particularly given the relatively wide variability in PK

parameters such as AUC, the saturation in this range is consistent with our unpublished experience with CBD PK. Although this study was not designed to assess PK–PD correlations, future research may be needed to formally evaluate the impact of plasma levels of CBD on PD responses. Other limitations include use of the single-dose design and subjective measurements of drug effects alone, instead of in combination with direct measurements of reinforcing effects, such as self-administration. Assessment of the subjective effects of single doses allows one to make conclusions on the “recreational” abuse potential of a drug but does not assess its reinforcing or dependence (physical or psychological) potential. However, the trial was conducted in accordance with the human abuse potential study guidelines, and data presented are generally consistent with other human abuse potential studies of CBD and preclinical data [13,14,33].

5. Conclusion

The results of this trial support that CBD is associated with minimal abuse potential and low cognitive/psychomotor impairment over a range of doses up to a supratherapeutic dose of 4500 mg in a highly sensitive population of recreational polydrug users. These findings are consistent with the published literature, which indicates few euphoric effects of the active ingredient CBD in multiple different trial populations.

Disclosures

All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship. Kerri Schoedel, Isabella Szeto, Beatrice Setnik, Edward Sellers, Naama Levy-Cooperman, and Catherine Mills have consulted for, conducted studies funded by, or received honoraria from GW Pharmaceuticals. Tilden Etges is a senior pharmacovigilance advisor to GW Research Ltd. and owns stock options in the company. Kenneth Sommerville was an employee at Greenwich Biosciences at the time of this trial and is presently a senior consultant of Greenwich Biosciences and owns stock options in GW and stock in other pharmaceutical companies. Findings reported in this study are specific to GW Pharmaceuticals' formulation of cannabidiol and cannot be extrapolated to other cannabidiol products.

Funding

This study was sponsored by GW Research Ltd.

Author contributions

All authors provided substantial contributions to the conception or design of the work or the acquisition, analysis, or interpretation of data for the work; drafted the work or revised it critically for important intellectual content; and provided final approval of the version to be published.

Acknowledgments

The authors would like to thank the study participants, their families, and the study site that participated in this trial, as well as Dobromir Pavlov, PhD, of Greenwich Biosciences, Inc., for his support as the clinical study manager. Medical writing and editorial support was provided to authors by Ritu Pathak, PhD, Jeremy Kennard, PhD, and Dena McWain of Ashfield Healthcare Communications, Middletown, CT and was funded by Greenwich Biosciences, Inc.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.yebeh.2018.07.027>.

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