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PII: S0022-3549(21)00413-5
DOI: https://doi.org/10.1016/j.xphs.2021.08.012
Reference: XPHS 2485

To appear in: *Journal of Pharmaceutical Sciences*

Received date: 16 April 2021
Revised date: 10 August 2021
Accepted date: 10 August 2021

Please cite this article as: Orrin Devinsky MD , Kelly Kraft PhD , Lorraine Rusch PhD , Melanie Fein MD , Andrea Leone-Bay PhD , Improved Bioavailability with Dry Powder Cannabidiol Inhalation: A Phase 1 Clinical Study, *Journal of Pharmaceutical Sciences* (2021), doi: https://doi.org/10.1016/j.xphs.2021.08.012

Improved Bioavailability with Dry Powder Cannabidiol Inhalation: A Phase 1 Clinical Study

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Target Journal: *J Pharm Sci*

Word count: 2,230/5,500

Figures and Tables: 6/8

Keywords: bioavailability, clinical pharmacokinetics, inhalation, pulmonary drug delivery, first-pass metabolism

Conflict of Interest Disclosures: O. Devinsky receives grant support from NINDS, NIMH, MURI, CDC and NSF. He has equity and/or compensation from the following companies: Receptor Holdings Inc, Tilray, Qstate Biosciences, Tevard Biosciences, Empatica, Engage (acquired by UCB, Inc.), Papa & Barkley, Rettco, SilverSpike, and California Cannabis Enterprises (CCE), and has received consulting fees from GW Pharma, Cavion (acquired by Jazz Pharmaceuticals) and Zogenix. K. Kraft and A. Leone-Bay are employees of Receptor Life Sciences. L. Rusch is an employee of Cardiovascular Clinical Sciences. M. Fein is an employee of High Point Clinical Trials Center.

Funding/Support: This work was supported by Receptor Life Sciences, Seattle, WA.

Role of the Funder/Sponsor: Receptor Life Sciences (K. Kraft and A. Leone-Bay) was responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Author Contributions: O. Devinsky, A. Leone-Bay, and K. Kraft contributed to the study concept and design. L. Rusch, K. Kraft, and M. Fein acquired, analyzed, or interpreted data. A. Leone-Bay and K. Kraft drafted the manuscript and O. Devinsky, L. Rusch, and M. Fein provided critical review of the manuscript. L. Rusch participated in statistical analyses. A. Leone-Bay obtained funding. O. Devinsky, K. Kraft, and M. Fein provided administrative, technical, or material support, and K. Kraft supervised the study. O. Devinsky, A. Leone-Bay, and K. Kraft had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Abbreviations: 7-COOH-CBD, 7-carboxycannabidiol; AE, adverse event; AIT, Alberta Idealized Throat; AUC, area under the plasma concentration-time curve; $AUC_{last,}$ area under the plasma concentration-time curve to the last measurable concentration; BMI, body mass index; BLQ, below the lower limit of quantitation; CBD, cannabidiol; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; DPI, dry powder inhaler; ECG, electrocardiogram; FDA, Food and Drug Administration; FDKP, fumaryl diketopiperazine; $F_{rel,}$ relative bioavailability; LC-MS/MS, liquid chromatography with tandem mass spectrometry; MedDRA, Medical Dictional for Regulatory Activities; PK, pharmacokinetic; SD, standard deviation; TEAE, treatment-emergent adverse event; THC, Δ^9-tetrahydrocannabinol; T_{max}, time to C_{max}.

ABSTRACT

Oral cannabidiol (CBD) is approved by the Food and Drug Administration (FDA) to treat patients with Dravet and Lennox-Gastaut syndromes, and tuberous sclerosis complex. The therapeutic potential of oral CBD formulations is limited by extensive first-pass hepatic metabolism. Following oral administration, the inactive metabolite blood concentration is ~40-fold higher than CBD. Inhalation bypasses the pharmacokinetic (PK) variability attributed to irregular gastrointestinal absorption and first-pass hepatic metabolism and may efficiently deliver CBD into systemic circulation. This phase 1 study compared the PK of a dry-powder inhaler (DPI) CBD formulation (10 mg; excipient containing 2.1 mg CBD) with an oral CBD solution (Epidiolex®, 50 mg) in healthy participants. Following a single dose of Epidiolex or DPI CBD (n=10 PK evaluable participants each), the maximum CBD concentration for the inhaled powder was 71-fold higher than that of Epidiolex while administering 24-fold less CBD. The mean time to reach maximum concentration was 3.8 minutes for the DPI CBD formulation compared with 122 minutes for Epidiolex. Both Epidiolex and DPI CBD were generally safe and well-tolerated. These data indicate that DPI CBD provided more rapid onset and increased bioavailability than oral CBD and support further investigations on the use of DPI CBD for acute indications.

INTRODUCTION

Cannabidiol (CBD) has been used to treat epilepsy and other disorders for millenia;[1] however, it wasn't until the 1970s when the first controlled clinical studies were conducted.[2] Randomized controlled trials of CBD led to FDA approval of Epidiolex®, an oral solution of CBD in sesame oil, to treat refractory epilepsies in patients with Dravet and Lennox-Gastaut syndromes, and tuberous sclerosis complex.[3] CBD has also shown promise in chronic pain, sleep disorders, fibromyalgia, anxiety, migraine, post-traumatic stress disorder, and anxiety disorders.[1]

Within the spectrum of anxiety disorders, panic attack and performance anxiety are increasingly common conditions with potentially debilitating consequences for patients. Both conditions are characterized by sudden onset, a rapid peak of intense fear or discomfort, and physical symptoms such as palpitations and sweating.[4] Acutely, panic attacks and performance anxiety are managed with benzodiazepines. These drugs are associated with tolerability and abuse liability issues, requiring 30–60 minutes for onset of therapeutic effect. Thus, a need remains for an immediate-onset treatment with fewer side effects and improved tolerability.

Studies suggest that CBD has clinical utility as treatment for anxiety disorders. CBD is an indirect agonist of cannabinoid 1 receptors, a known regulator of fear and anxiety responses,[5] and a modulator of 5-hydroxytryptamine receptor 1A, an established anxiolytic target.[6] In both animal and human studies, CBD demonstrated anti-panic and anti-anxiety effects.[7,8] Specifically, single oral doses of CBD significantly reduced anxiety during simulated public speaking tests in both healthy volunteers and in patients with social anxiety disorder.[9-12]

The therapeutic potential of oral CBD, however, is limited by poor bioavailability (4%–20%) due to irregular absorption and extensive first-pass hepatic metabolism.[13] CBD is hepatically metabolized to 7-hydroxy-CBD, which is further converted to the inactive metabolite 7-carboxy-CBD (7-COOH-CBD). Following oral dosing, 7-COOH-CBD is the primary circulating metabolite, with ~40-fold higher blood concentration of the inactive compound than CBD.[3] High oral CBD doses are often required to achieve

therapeutic blood levels, ranging from 5 to 25 mg/kg or 350 to 1750 mg/day. Oral CBD pharmacokinetics (PK) are characterized by variable absorption times (0.5–4 hours) and high inter- and intra-patient variability, with coefficients of variability for the maximum observed plasma concentration (C_{max}) of 88% and area under the plasma concentration-time curve (AUC) of 78%.[13] These PK challenges are compounded by large differences in absorption when administered with food.[3] An alternative route of administration that avoids irregular absorption and first-pass hepatic metabolism, such as inhalation, may address these PK challenges.

Previous studies have reported CBD delivery by inhalation using specialized heated aerosolizers and vaporizers.[14,15] These systems are limited by the complexity of the equipment and the difficulties associated with patient self-administration, especially when the need is acute and rapid. Here, we describe a dry powder inhaler (DPI) CBD formulation administered using a simple, small, breath-powered inhaler. This system is easy to use and provides rapid onset and high bioavailability by avoiding gastrointestinal absorption and first-pass hepatic metabolism. The powder comprises the inhalation excipient, fumaryl diketopiperazine (FDKP), that forms microparticles onto which active pharmaceutical ingredients can be adsorbed and are sized for delivery to the deep lung. Both the excipient and inhaler are components of an FDA-approved inhaled insulin product.[16]

PARTICIPANTS AND METHODS

Study Drug Preparation and Testing

A hemp isolate containing ~99% CBD was used to prepare the CBD inhalation powder by spray drying. CBD (3.9 g) was dissolved in approximately 290 g of 200 proof ethanol. A separate solution of 1,2-distearoyl-sn-glycero-3-phosphocholine (1.5 g) in approximately 50 g of 200 proof ethanol was prepared, then added to the CBD solution. FDKP (9.6 g), approximately 50 g of ethanol, and 98 g of water were added to the CBD mixture. The resulting suspension was spray dried using a Buchi B-290 spray dryer (Buchi Labortechnik AG, Flawil, Switzerland) equipped with an inert loop, a dehumidifier, and a chiller. The Buchi B-290 spray drier was operated at 10% feed rate, 90% aspirator rate, 60 mm nitrogen flow

rate, and an inlet temperature of 150 °C. The resulting powder was analyzed by high performance liquid chromatography to determine percent drug content.

Aerodynamic performance was assessed using the Andersen cascade impactor (ACI; Copley Scientific, Nottingham, UK). CBD inhalation powder (10 mg) was weighed into a cartridge designed for use in the DreamBoat™ inhaler (MannKind Corporation, Westlake Village, CA). Cartridges were placed into a DreamBoat inhaler, and then discharged through the ACI at a flow rate of 28.3 L/min, which corresponds to a 6.5 kPa pressure drop across the inhaler. The total flow volume was 4 L. Results reported include the delivered dose, fine particle fraction (FPF) and fine particle dose (FPD) <5.0 µm, mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD). The results reported are the average of six cartridge discharges.

Study Design

RC-2018/02 was a single-site, phase 1, open-label study in healthy participants conducted at High Point Clinical Trials Center (High Point, NC) between 6 August 2019 and 9 March 2020. Eligible participants were healthy adults (≥21 and ≤55 years) with a body mass index (BMI) ≥18 and ≤30 kg/m² and weight ≥50 kg. Participants may have used cannabis products more than 10 times in their lives, but current usage was limited to 3 times or less per week and not within 6 days prior to Day −1 (adherence to these criteria were confirmed approximately 1 week prior to Day −1 by plasma CBD concentrations <0.1 ng/mL). Participants who had a medical contraindication to cannabis, history of cigarette or cigar smoking, or any active respiratory conditions (e.g., asthma or chronic obstructive pulmonary disease) were excluded.

Participant screening occurred up to 21 days before administration of the assigned study drug (**Figure 1**). On Day 1, participants fasted for ≥10 hours before study treatment and received a single dose of Epidiolex oral CBD solution (Greenwich Biosciences, Inc., Carlsbad, CA) or dry powder CBD through the DreamBoat inhaler. Follow-up occurred on Day 2.

Study Drug, Device, and Dosing

The DPI CBD formulation contained ~21% CBD by weight. For dosing, 10 mg of powder was filled into single-use cartridges for the DreamBoat inhalation device; each cartridge contained 2.1 mg CBD. Epidiolex oral solution (50 mg CBD) was purchased by the study site from a local pharmacy.

Inhaler instructions for use were adapted from the Afrezza® (insulin human) inhalation powder package insert,[16] and were provided to participants verbally and in pictographic form immediately before dosing. Participants received a DreamBoat inhaler containing a DPI CBD-filled cartridge. While holding the inhaler away from their mouths, participants exhaled fully. Immediately following the exhalation, participants positioned the inhaler in their mouth, keeping their head level and tilting the inhaler slightly downward, and inhaled deeply through the inhaler. After inhaling, participants removed the inhaler from their mouth, held their breath for as long as comfortable, exhaled, and resumed breathing normally.

Study Endpoints and Assessments

The primary objective was to characterize and compare the PK profiles of oral CBD with the DPI CBD formulation. Non-compartmental plasma PK parameters for CBD and 7-COOH-CBD were also assessed. The secondary objective was to evaluate and compare the safety of the oral and inhaled CBD formulations including adverse events (AEs), physical examination findings, vital sign measurements, 12-lead electrocardiogram (ECG) findings, somnolence evaluations, as well as clinical hematology, clinical chemistry, and urinalysis results. Blood samples for PK analyses were collected pre-dose and at 2.5- (DPI CBD formulation only), 5-, 10-, 15-, 30-, and 45-minutes and 1-, 1.5-, 2-, 4-, 8- and 12-hours following dosing. The PK parameters measured included C_{max}, time to reach C_{max} (T_{max}), AUC to the last measurable concentration (AUC_{last}), and relative bioavailability (F_{rel}) of each CBD formulation.

Blood Sample Handling

Blood samples for determination of CBD and 7-COOH CBD concentrations were collected into vacutainer tubes containing di-potassium ethylenediaminetetracetic acid (K_2 EDTA) as an anticoagulant and stored in

an ice water bath for up to 60 minutes before processing. Blood samples were centrifuged at 2200g for 15 minutes at 5 °C. Plasma was separated, divided into four aliquots (CBD primary and backup samples and 7-COOH CBD primary and backup samples), and stored in polypropylene vials at −70 °C in a vertical position until analysis.

CBD and 7-COOH-CBD Extraction and Analysis

CBD and 7-COOH-CBD plasma concentrations were assayed using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) methods by Syneos (Quebec, Canada). For CBD analysis, plasma aliquots of 100 µL were mixed with 150 µL of 2% cystine in water, 100 µL of working standard solution (1.25 ng/mL cannabidiol-d3 in methanol), and 1 mL of 100 mM ammonium formate buffer solution. Hexanes (7 mL) were added, and the tube was shaken on a horizontal shaker for 15 minutes. After centrifugation at 3000 rpm for 5 minutes, the organic layer was removed and evaporated to dryness. The sample was reconstituted in 150 µL of a water/methanol solution (20/80), vortexed for 30 seconds, and centrifuged at 3000 rpm for 5 minutes. The resulting supernatant was analyzed by HPLC-MS/MS using an ACE Excel 2 (Advanced Chromatography Technologies, Aberdeen, Scotland) column (C18, 2 µm particle size, 150×3.0 mm). The compounds were detected by an AB Sciex API 5000 mass spectrometer using electrospray ionization (ESI). The injection volume was 25 µL. Oven temperature was maintained at 25 °C, and the autosampler tray temperature was maintained at 4 °C. Chromatographic separation was achieved using an isocratic method for mobile phase A (water/methanol/acetic acid solution [18/82/0.01]) at a constant flow rate of 0.5 mL/min over a total run time of 11.4 minutes. The linear range of quantitation was 25–25,000 pg/mL.

For 7-COOH-CBD analysis, plasma aliquots of 100 µL were mixed with 100 µL of 2% cystine in water, 100 µL of working standard solution (1 ng/mL testosterone-2,2,4,6,6-d5 in methanol), and 500 µL of acetonitrile. After centrifugation at 4000 rpm for 5 minutes at 4 °C, the supernatant was removed and diluted with 2 mL of water containing 0.1% phosphoric acid. The sample was loaded onto an activated solid phase extraction cartridge (Oasis MCX [60 mg, 3 mL], Waters Corporation, Milford, MA). The

sample was passed through the cartridge. The cartridge was treated as described: washed with 1 mL 100 mM ammonium formate/2% formic acid and centrifuged at 300 rpm for 2 minutes; washed with 1 mL of a water/methanol (90/10) solution with 1% formic acid, and centrifuged at 300 rpm for 2 minutes, then at 1000 rpm for 2 minutes. The cartridge was loaded with 1 mL of an acetonitrile/methanol (50/50) solution followed by centrifugation at 300 rpm for 2 minutes, and then centrifugation at 1000 rpm for 5 minutes. The resulting eluent was evaporated to dryness, then reconstituted with 100 µL of solvent, centrifuged at 4000 rpm for 5 minutes, then analyzed by HPLC-MS/MS using an Acquity UPLC HSS T3 (Waters Corporation, Milford, MA) column (C18, 1.8 µm particle size, 150×2.1 mm). The compounds were detected by an AB Sciex API 5000 mass spectrometer using ESI. The injection volume was 15 µL. Oven temperature was maintained at 30 °C, and the autosampler tray temperature was maintained at 4 °C. Chromatographic separation was achieved using an isocratic method for mobile phase A (water/methanol [35/65] solution) at a constant flow rate of 0.3 mL/minutes over a total run time of 14 minutes. The linear range of quantitation was 0.25–250 ng/mL.

Statistical Analyses

The planned sample size was 12 participants per group but was not based on statistical calculations. All participants who received the study medication were included in the safety population; those who had at least 1 PK assessment were included in the PK analysis population. For each participant who received DPI CBD formulation, the DreamBoat cartridge was weighed before and after inhalation and participants who did not receive at least 7 mg of the dry-powder formulation (the minimum intended dose) were excluded from the PK population.

From the individual plasma concentrations, PK parameters were estimated using a non-compartmental method via the Phoenix WinNonlin software (version 8.1, Cetara, Princeton, NJ) by Quartesian (Princeton, NJ). Actual sampling times were used to determine PK parameters; theoretical sampling times were used for graphical representation only. During PK analyses, drug concentrations below the lower limit of quantitation (BLQ) of an assay were considered as zero except when they occurred between two

non-BLQ concentrations where they were considered as missing during PK calculations and estimations. Descriptive statistics including mean, standard deviation (SD), percent coefficient of variation (CV%), median, minimum, maximum, geometric mean, geometric standard error, and geometric CV were calculated for each time point by treatment for plasma concentrations of CBD and 7-COOH-CBD. The individual and mean linear and semi-linear plasma concentration-time data of CBD and 7-COOH-CBD are presented graphically. AUC and C_{max} values for the DPI CBD formulation were multiplied by 23.8 (the ratio of oral dose [50 mg] to the nominal DPI CBD dose [2.1 mg]) for a dose-adjusted direct comparison of the two formulations.

Safety data are presented by system organ class, preferred term, and treatment; AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.1. Somnolence was measured by participant-reported responses on the Stanford Sleepiness Scale. Missed samples and non-reportable concentrations (e.g., quantity not sufficient) were treated as if they had not been scheduled for collection. For participants with missing or non-reportable concentrations for 3 or more of the last samples within a particular sampling period or formulation, only the C_{max} and T_{max} were presented, and other PK parameters were not reported.

Oversight

This study was performed in accordance with the Declaration of Helsinki and the protocol was reviewed and approved by the IntegReview Institutional Review Board. All participants in the study provided written informed consent.

RESULTS

Formulations

Inhalation powder comprising CBD and the inhalation excipient FDKP were prepared by spray drying. The drug product had a target drug content of 25% by weight; after preparation, HPLC analysis confirmed 21% CBD content in the powders, representing 84% drug recovery.

The average of 6 determinations of aerodynamic performance testing of the DreamBoat inhaler with 10 mg of CBD inhalation powder showed that the delivered dose was 8.1 mg (81% of the cartridge fill). The MMAD (GSD) was 4.2 (2.3) µm. Approximately half of the delivered dose (3.8 mg, 47%) was recovered on the impactor stages; the remaining powder (4.3 mg, 53%) was captured in the inlet port. A total of 2.8 mg of powder, or 35% of the delivered dose, was recovered on stages 2 through 6 (<5.8 µm). The FPF <5.0 µm was 30%, corresponding to an FPD of 2.4 mg.

Study Population

In the oral CBD group, 10 of the 11 enrolled participants completed the study; 1 participant discontinued the study for personal reasons before receiving the study treatment. In the DPI CBD group, all 12 enrolled participants completed the study; 2 participants did not receive the minimum intended dose following inhalation and were excluded from the PK analyses. Most participants were male (20 [87%]) and either Black/African American (14 [61%]) or White (8 [35%]) **(Table 1)**. The mean (SD) age was 36 (8) years in the oral CBD group and 30 (7) years in the inhaled CBD group.

Pharmacokinetics

The dose-adjusted mean AUC for oral CBD was 20.0 hr*ng/mL and for inhaled CBD was 182.5 hr*ng/mL **(Figure 2, Table 2)**. Dose adjusted mean C_{max} was 6.3 ng/mL in the oral CBD group and 447 ng/mL in the inhaled CBD group. Compared with oral CBD administration, inhalation increased CBD bioavailability (AUC) by 9.1-fold and increased peak CBD by 71-fold. The mean (SD) T_{max} for CBD was 121.8 minutes (128.4 minutes) for the oral CBD group and 3.8 minutes (1.3 minutes) for the inhaled CBD group.

After oral administration, AUC of the metabolite 7-COOH-CBD was 60-fold higher than CBD AUC; after inhalation, 7-COOH-CBD AUC was only 2.4-fold higher than CBD AUC **(Figure 3, Table 2)**. Inhalation of dry powder CBD yielded a 25-fold reduction in the inactive metabolite-to-parent ratio compared with oral CBD administration.

Safety

Participants who received oral CBD reported no treatment-emergent AEs (TEAEs). A dry, throat-clearing cough following inhalation was reported in 3 of 12 participants who received the DPI CBD formulation; the events were not considered an AE, were transient in nature and resolved in all cases. One participant who received DPI CBD experienced laboratory abnormalities (alanine aminotransferase, aspartate aminotransferase, and blood creatinine phosphokinase increased) that were deemed by the investigator to be related to the participant's vigorous exercise before receiving the study drug **(Table 3)**. All AEs were mild in intensity and no participant discontinued the study due to a TEAE. No clinically meaningful changes in physical examinations, clinical hematology, urinalysis, ECG, or vital signs were observed in the oral or DPI CBD groups. Neither oral nor DPI CBD affected participant-reported somnolence **(Table 3)**.

DISCUSSION

The current phase 1 study provides the first direct PK characterization of oral CBD versus a DPI CBD formulation in healthy adult participants. CBD has demonstrated therapeutic efficacy in a variety of indications including neuropsychiatric[17,18] and seizure disorders.[19-21] CBD can be administered orally,[22] through the pulmonary system,[14,23] as well as other routes, highlighting the need for comparative studies to determine the optimal administration route for each indication. Current oral CBD formulations are limited by low bioavailability with high variability in absorption as well as extensive first-pass hepatic metabolism.[22,24]

Repeated aerodynamic performance testing of the DreamBoat inhaler with 10 mg of CBD inhalation powder delivered an average of approximately 80% of the cartridge dose. Nearly half of the delivered

dose was recovered on the impactor stages; the remainder was captured in the inlet port. One third was of the powder was recovered on stages 2 through 6. The reported FPF <5.0 µm was 30% is in line with the published literature, which shows that the FPF of commercially available dry powder inhalers, ranging from 10% to 50% of the label claim.[25]

Administration of CBD as a dry powder via the DreamBoat inhaler resulted in a more rapid and consistent response compared with oral CBD (mean time to C_{max} of 4 minutes inhaled versus 2 hours oral). Although the DPI CBD formulation contained a much lower dose than oral CBD, the DPI resulted in a peak CBD concentration nearly 3-fold higher than oral CBD. When adjusted for dose, the maximum CBD concentration was 71-fold greater and overall exposure was 9-fold greater for DPI CBD compared with oral CBD. Drug absorption with DPI CBD was more rapid and robust than oral CBD, consistent with direct delivery to the deep lung, because the DPI formulation avoids the erratic absorption and first-pass hepatic metabolism of oral administration.[23]

Following hepatic metabolism of oral CBD, many metabolites circulate systemically, with 7-COOH-CBD most abundant.[26] In this study, the DPI CBD formulation resulted in a 25-fold reduction in the ratio of the inactive metabolite 7-COOH-CBD to CBD compared with the oral formulation. These data support the finding that inhalation of CBD formulated as a dry powder is a more efficient administration route than oral delivery. Following inhalation, a larger fraction of the active parent CBD circulates in the blood compared with the inactive metabolite. Additionally, these data show that inhalation delivery has the potential to reduce the concerns of hepatotoxicity associated with oral CBD administration. CBD absorbed from the gastrointestinal tract goes directly to the liver, while CBD absorbed through the lung bypasses first-pass hepatic metabolism.

The oral and inhaled dry powder CBD formulations were generally safe and well-tolerated following a single administration. A few patients who received the DPI CBD formulation experienced a dry, throat-clearing cough following inhalation, not considered an AE by the investigator, that was transient and resolved; this was observed in other studies using the FDKP excipient in patients naïve to dry-powder

inhalers.[16] Although one participant in the DPI CBD group experienced mild laboratory abnormalities, these were considered unrelated to the study treatment because the participant had engaged in strenuous weight lifting immediately prior to the study and the elevations were expected post exercise. Participants in this study reported that neither the oral nor DPI CBD formulations impacted somnolence as measured by the participant-reported Stanford Sleepiness Scale. Two participants who received the DPI formulation did not inhale properly and the powder did not discharge completely from the inhaler; to prevent this issue, additional inhaler instruction and training will be provided in future studies.

Other studies have evaluated inhaled CBD administration by vaporization via the Volcano Vaporizer®. In this system, vaporized CBD is collected into balloons and participants are instructed to inhale from the balloons 6–10 times over the course of 10 minutes to receive a full dose. Participants receiving 100 mg vaporized CBD achieved a median peak concentration of 105 ng/mL, and participants receiving 400 mg vaporized CBD achieved a median peak concentration of 526 ng/mL.[14,15] An indirect comparison of the findings from this phase 1 study showed that 2.1 mg CBD formulated as a dry powder and administered in a single inhalation resulted in an 8.6- and 6.8-fold greater dose-adjusted C_{max} compared with the data reported for 100 mg and 400 mg vaporized CBD, respectively. The DPI CBD formulation administered via the DreamBoat inhalation device is simple to use and provided the effective dose in less than 1 minute in one breath. Vaporized CBD requires multiple inhalations over more than 10 minutes. Additionally, vaporizers heat the CBD, which has the potential to thermally convert CBD to tetrahydrocannabinol or other compounds, potentially reducing efficacy.

In summary, a DPI CBD formulation containing 2.1 mg CBD self-administered using the DreamBoat inhaler resulted in rapid and consistent delivery of CBD with increased peak concentrations compared with 50 mg of oral CBD. The DPI CBD formulation avoids erratic absorption and bypasses first-pass hepatic metabolism, resulting in reduced concentrations of an inactive circulating metabolite and enhanced CBD bioavailability compared with oral administration. These results support further

development of DPI CBD for acute indications that require rapid administration of controlled-dose inhalation powders, such as pain, opioid craving, anxiety, and behavioral disorders.

ACKNOWLEDGMENTS

Medical writing support was provided by Apurva Davé, PhD, and Kendall Foote, PhD, of Medical Expressions (Chicago, IL) and was funded by Receptor Life Sciences.

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TABLES

Table 1. Baseline demographics and characteristics for all enrolled participants

Parameter	**Oral CBD n=11[a]**	**DPI CBD n=12[b]**
Age, mean (SD), years	35.6 (8.3)	29.7 (7.1)
Male, n (%)	9 (82)	11 (92)
Not Hispanic or Latino, n (%)	11 (100)	10 (83)
Race, n (%) Black or African American White	 5 (46) 5 (46)	 9 (75) 3 (25)
Weight, mean (SD), kg	75.6 (13.3)	78 (9.8)
Height, mean (SD), cm	176.6 (9.7)	177.0 (7.2)
BMI, mean (SD), (kg/m^2)	24.1 (2.1)	24.9 (2.7)

[a] Includes 1 participant who discontinued the study before receiving the study drug.
[b] Includes 2 participants who did not receive the full CBD dose following inhalation.
BMI, body mass index; CBD, cannabidiol; DPI, dry powder inhaler; SD, standard deviation.

Table 2. Pharmacokinetics of oral and inhaled CBD[a] and 7-COOH-CBD metabolite[b] (PK analysis population)

Parameter	Oral CBD n=10	DPI CBD n=10
Nominal CBD dose, mg	50	2.1
	CBD	
AUC_{last}, mean (SD), hr*ng/mL	20.05 (9.09)	7.66 (3.75)
AUC, dose-adjusted, mean, hr*ng/mL	20.0	182.5
AUC_{last}, median (range), hr*ng/mL	20.26 (7.16 – 33.30)	6.79 (1.34 – 14.24)
F_{rel} (oral vs inhaled)	N/A	9.1-fold higher
$C_{max,}$ mean (SD), ng/mL	6.30 (3.73)	18.78 (9.89)
C_{max}, dose-adjusted, mean, ng/mL	6.3	447.1
C_{max} (oral vs inhaled)	NA	71-fold higher
$C_{max,}$ median (range), ng/mL	5.91 (1.74 – 13.37)	16.25 (3.56 – 33.92)
$T_{max,}$ mean (SD), minutes	121.8 (128.4)	3.8 (1.3)
T_{max}, median (range), minutes	90 (45–480)	2.5 (2.5–5.0)
	7-COOH-CBD	
AUC_{last} for metabolite[c], mean (SD), hr*ng/mL	1202.72 (605.62)	18.11 (10.10)
AUC_{last} for metabolite[c], median (range), hr*ng/mL	1270.33 (419.06 – 2107.06)	15.08 (3.92 – 39.97)
Metabolite-to-parent ratio of AUC_{last}	60	2.4
Metabolite-to-parent ratio (oral vs inhaled)	N/A	25-fold lower
$C_{max,}$ mean (SD), ng/mL	161 (83.6)	2.3 (1.5)
$C_{max,}$ median (range), ng/mL	172.13 (54.38 – 301.07)	1.94 (0.55 – 5.84)
$T_{max,}$ mean (SD), hours	3.2 (3.2)	2.6 (3.3)
T_{max}, median (range), hours	2.0 (2.0–12.0)	1.5 (1.0–12.0)

[a] For CBD, the LLOQ was 25 pg/mL; linearity was 25-25,000 pg/mL.
[b] For 7-COOH-CBD metabolite, the LLOQ was 0.25 pg/mL; linearity was 0.25-250 pg/mL.
[c] 7-COOH-CBD is the metabolite of CBD measured in this study.

AUC, area under the plasma concentration-time curve; AUC_{last}, area under the plasma concentration-time curve to the last measurable concentration; CBD, cannabidiol; C_{max}, maximum observed plasma concentration; DPI, dry powder inhaler; F_{rel}, relative bioavailability of the oral to inhaled formulations; LLOQ, lower limit of quantitation; SD, standard deviation; T_{max}, time to C_{max}.

Table 3. Summary of treatment-emergent adverse events (Safety Population)

Parameter	Oral CBD n=10[a]	DPI CBD n=12[b]
≥1 TEAE, n participants (%)	0	1
ALT increased	0	1 (8)
AST increased	0	1 (8)
Blood creatine phosphokinase increased	0	1 (8)
≥1 SAE, n participants (%)	0	0
Stanford Sleepiness Scale, mean CFB (SD)		
30 min post dose	−0.6 (1.3)	0.4 (0.8)
1 h post dose	−0.5 (1.4)	0.4 (1.1)
4 h post dose	−1.1 (1.2)	0.1 (0.7)
8 h post dose	−0.8 (1.4)	0.1 (1.5)
12 h post dose	−1.1 (1.2)	−0.4 (0.7)

[a] One participant who discontinued the study before receiving the study drug was excluded from the safety population.
[b] Includes two participants who did not receive at least 7 mg of DPI CBD dose following inhalation.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBD, cannabidiol; CFB, change from baseline; DPI, dry powder inhaler; SAE, serious adverse event; SD, standard deviation; TEAE, treatment-emergent adverse event.

FIGURES

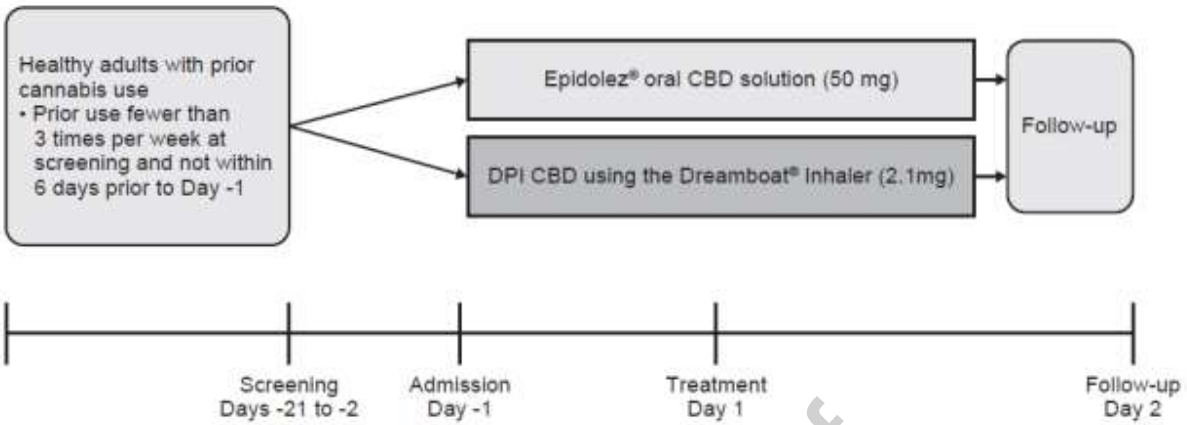

Figure 1. Study design

CBD, cannabidiol; DPI, dry powder inhaler.

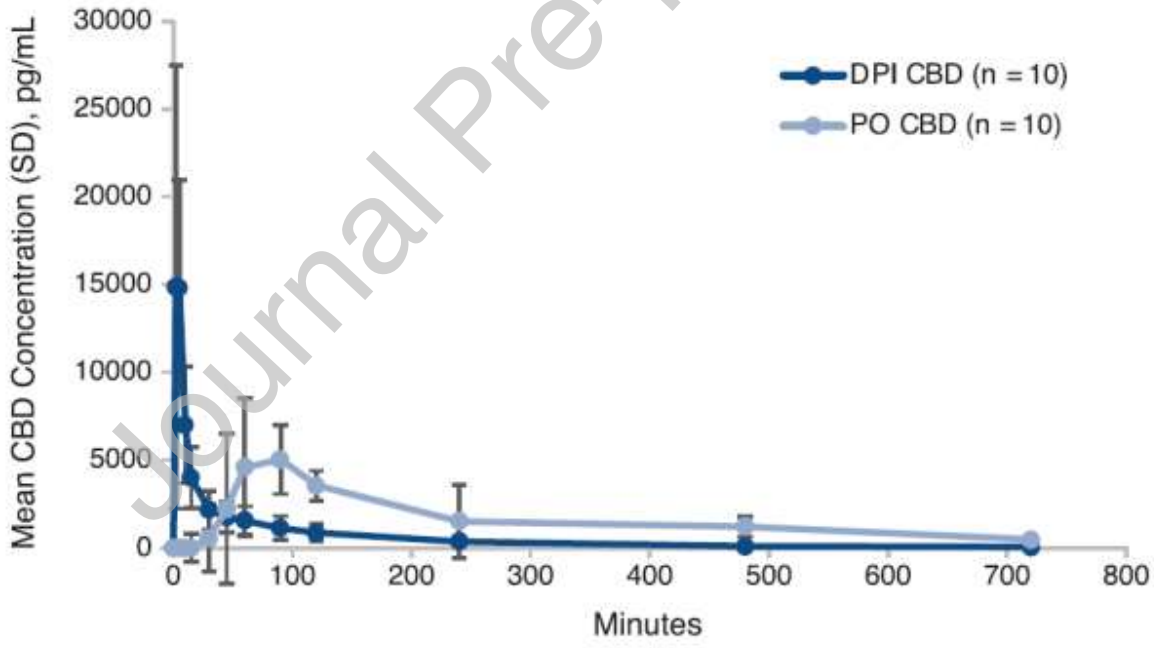

Figure 2. Concentration-time profile of CBD following oral CBD and DPI CBD administration (PK analysis population)

CBD, cannabidiol; DPI, dry powder inhaler; PO, per os (by mouth); SD, standard deviation.

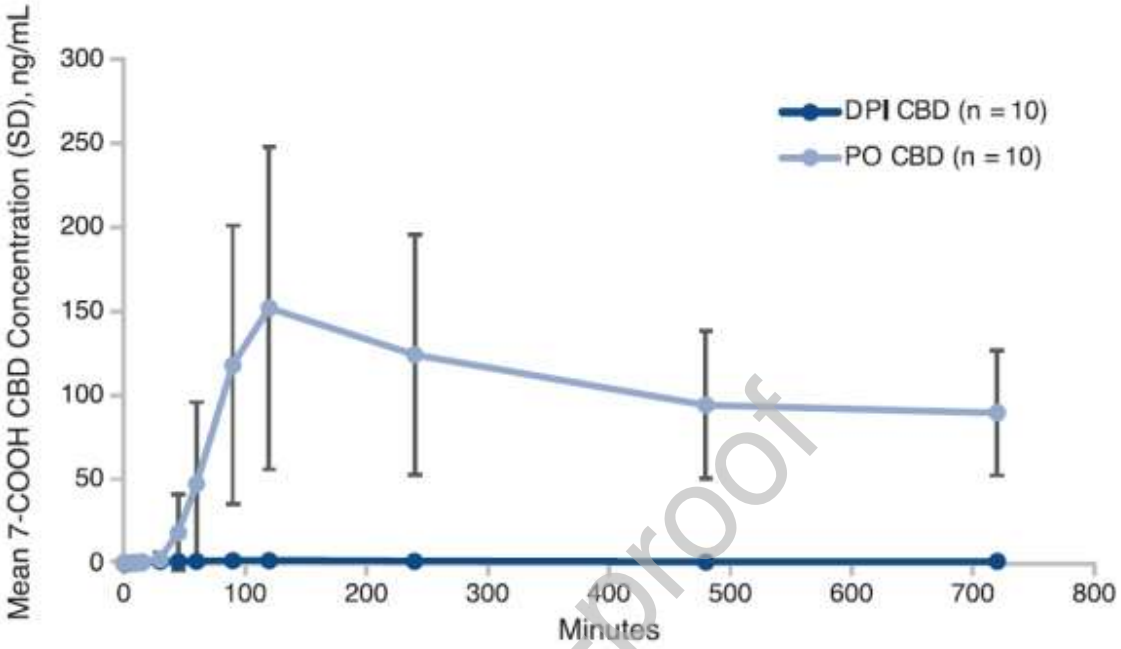

Figure 3. Concentration-time profile for 7-COOH-CBD following oral CBD and DPI CBD administration (PK analysis population)Andrea Leone Bay

7-COOH CBD, 7-carboxycannabidiol; CBD, cannabidiol; DPI, dry powder inhaler; PO, per os (by mouth); SD, standard deviation.