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Article

Safety, Pharmacokinetics and Pharmacodynamics of Spectrum Red Softgels in Healthy Participants

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Abstract

Due to a lack of published pharmacokinetic (PK) and/or pharmacodynamic (PD) data, informed physician and patient decision-making surrounding appropriate dosing of cannabis for medical purposes is limited. This Phase 1, multiple-dose study evaluated the safety, tolerability, PK and PD of Spectrum Red softgels (2.5 mg Δ^9-tetrahydrocannabinol (THC) and <0.25 mg cannabidiol (CBD)). Participants ($n = 41$) were randomized to one of five groups: 5 mg THC and 0.06 mg CBD daily (Treatment A), 10 mg THC and 0.12 mg CBD daily (Treatment B), 15 mg THC and 0.18 mg CBD daily (Treatment C), 20 mg THC and 0.24 mg CBD daily (Treatment D) or placebo. Study medication was administered in divided doses, every 12 h, ~60 min after a standardized meal, for 7 consecutive days. All treatment-emergent adverse events (TEAEs) (65/65) were of mild-to-moderate severity; none was serious. The highest number of TEAEs (30/65) occurred on the first day of treatment. The most common TEAEs included somnolence, lethargy and headache (reported by eight, seven and five participants, respectively). On Day 7, maximum observed plasma concentration of 11-carboxy-THC increased by 2.0- and 2.5-fold as the dose doubled between Treatments A and B and between Treatments B and D, respectively. Mean peak post-treatment ratings of self-reported subjective effects of 'feel any effect' and 'dazed' differed between Treatment D and placebo on Days 1, 3 and 7. Over a week of twice-daily dosing of Spectrum Red softgels, daily doses of THC up to 20 mg and of CBD up to 0.24 mg were generally safe and became better tolerated after the first day of treatment. A prudent approach to improve tolerability with Spectrum Red softgels might involve initial daily doses no higher than 10 mg THC and 0.12 mg CBD in divided doses, with titration upward over time as needed based on tolerability.

Introduction

Cannabis products that are used for medical purposes and that contain varying amounts of two phytocannabinoids, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are available in the market in many countries. THC and THC-like compounds have regulatory approval in specific regions to treat anorexia associated with weight loss in patients with acquired immunodeficiency syndrome, nausea and vomiting associated with cancer chemotherapy, and neuropathic pain but are associated with adverse effects such as dizziness, drowsiness and intoxication (1–3). However, there is a paucity of data on the pharmacokinetics (PK) and pharmacodynamics (PD) of non-pharmaceutical cannabis products

used for medical purposes that contain THC plus other constituents, such as CBD and other phytocannabinoids and terpenes. One study examined the PK and PD of a single dose of a medical cannabis capsule with doses of THC ranging from 5 to 10 mg and concluded that such acute doses were safe and were not associated with cardiovascular or cognitive effects (4). Although this study provides an interesting basis for further investigation, its results are of a limited therapeutic value because of the narrow dose ranges selected and single-dose design. Multiple-dose studies with broad dose ranges are needed to more closely approximate real-world conditions in individuals who consume non-pharmaceutical cannabis products and to more fully inform health-care practitioners on safety and dosing.

Although concurrently measured PK and PD data have not been collected for non-pharmaceutical cannabis used for medical purposes in multiple-dose studies, the broader literature on the PK and PD of THC can help show their expected effects. Bioavailability of oral THC is generally low, estimated to be ∼6% as a result of significant first-pass metabolism by the liver (5, 6) via cytochrome P450 (CYP450) isozymes CYP2C9, CYP2C19 and CYP3A4. THC is hydroxylated to pharmacologically active 11-hydroxy-THC (11-OH-THC) by CYP2C9, and its direct oxidation produces a pharmacologically inactive acid, 11-carboxy-THC (11-COOH-THC) (7). Subjective acute effects of oral THC include increased ratings of subjective 'high', increased hunger and alterations in mood, and at oral doses of 10 mg THC or higher, cognition and psychomotor functions are temporarily impaired (8).

The lack of repeated- or multiple-dose PK and PD data leaves an enormous gap in the literature related to non-pharmaceutical cannabis products for medical purposes that are now sold by hundreds of companies throughout the world. The aim of this study was to provide a thorough evaluation of the safety, tolerability, PK and PD of a standardized oral cannabis product, Spectrum Red softgel, that is used for medical purposes.

Methods

Compliance with ethical standards

This trial was conducted in accordance with consensus ethics principles, International Conference on Harmonization Good Clinical Practice guidelines, the Declaration of Helsinki and local Australian laws and regulations. The protocol was approved by the Alfred Hospital Ethics Committee (Project No. 594/19; approved 16 December 2019). Written informed consent was obtained from each participant before any trial-related procedures were performed.

Participants

Adults aged 18–55 years were eligible for the study if they were in good health as assessed by medical history, physical examination, 12-lead electrocardiogram (ECG) and clinical laboratory investigations; had ≥2 lifetime exposures to THC-containing cannabis products and had a body mass index (BMI) 18–30 kg/m^2. Women of childbearing potential were required to have a negative pregnancy test at screening and at intake to the research facility.

Exclusion criteria included women who were pregnant, lactating, breastfeeding, or planning a pregnancy; women of childbearing potential, or men who were sexually active with women of childbearing potential, who were unwilling or unable to use an acceptable method of contraception; use of tobacco/nicotine-containing products >5 occasions within 1 month of screening or during the study; use of prescription drugs or herbal supplements (except hormonal contraception) within four weeks of screening; use of any over-the-counter drugs, vitamins, or supplements within 72 h prior to study treatment; a positive breath test for ethanol or positive urine drug screen at screening or prior to study treatment; a history of psychosis or schizophrenia, including first-degree relatives; use of any CBD- or THC-containing product within 8 weeks of screening or during the study; and a history of suicidal behavior or current suicidal ideation.

Study design and treatment

This Phase 1, randomized, double-blind, placebo-controlled, multiple-dose trial of Spectrum Red No 2 softgel (labeled 2.5 mg THC and <0.25 mg CBD) was conducted between December 2019 and March 2020 at one site in Australia. Spectrum Red softgels are a cannabis-based product commercially available for medical use in Canada and Australia. Spectrum Red softgels were made with supercritical carbon dioxide extracted cannabis resin in a soft gelatin capsule containing medium-chain triglyceride (MCT), gelatin, glycerin, titanium dioxide, and color (Tweed Inc., Canopy Growth Corporation, Smiths Falls, ON, Canada). Analytical testing of the clinical batch detected the presence of other cannabinoids, including cannabinol and cannabigerol, and a total terpene concentration 0.08%; the measured content of 0.03 mg/softgel CBD was consistent with the labeled content of <0.25 mg/softgel CBD and was used to estimate dosages of CBD.

Participants were randomly assigned to one of five groups in a 1:1:1:1:1 ratio: 5 mg THC and 0.06 mg CBD daily [1 softgel, twice daily (Treatment A)]; 10 mg THC and 0.12 mg CBD daily [2 softgels, twice daily (Treatment B)]; 15 mg THC and 0.18 mg CBD daily [3 softgels, twice daily (Treatment C)]; 20 mg THC and 0.24 mg CBD daily [4 softgels, twice daily (Treatment D)]; or placebo. To create equivalence across treatment groups with respect to total amount of study medication administered, participants in the four active treatment groups received both Spectrum Red softgels plus placebo tablets (total of 6 softgels and tablets, twice daily). Participants in the placebo treatment group received placebo softgels (Tweed Inc., Canopy Growth Corporation, Smiths Falls, ON, Canada) plus placebo tablets, in order to closely mimic the combination of softgels and tablets that participants in the four active treatment groups received, and thus preserve the blind. The placebo softgels were made with MCT oil, gelatin, glycerin, alfalfa extract and beta carotene extract. Analytical testing of placebo softgels confirmed the absence of phytocannabinoids and terpenes.

Participants were confined to a research facility and received study medication every 12 h, ∼60 min after a standardized meal (e.g., for breakfast, two cups of cereal; two slices of toast; two servings of butter or margarine; two condiments; 250 mL of milk; and one sugar sachet), for 6 days, plus a single dose in the morning of Day 7. Participants were discharged after a 32 h post-dose blood draw on Day 8 and returned to the research facility on Days 9, 10, 11 and 13 for blood draws and study assessments.

Safety assessments

Safety assessments included laboratory assessments (hematology, biochemistry and urinalysis), monitoring of vital signs and ECGs, suicidality (Columbia-Suicide Severity Rating Scale; C-SSRS) and assessment of treatment-emergent adverse events (TEAEs)/serious adverse events (SAEs).

PK assessments

Blood samples were collected in a 4 mL draw Heparin container prior to the morning dose and 1, 2, 4, 6, 8 and 12 h after the morning

dose on Day 1; pre-morning dose on Days 2–7; prior to the morning dose and 1, 2, 4, 6, 8, 12 and 16 h after the morning dose on Day 7; and 24, 32, 48, 72, 96 and 144 h after the Day 7 morning dose. Immediately following collection, blood samples were placed on wet ice and centrifuged, and plasma was immediately frozen at −80°C until shipment to the bioanalytical laboratory (iC42 Clinical Research and Development, University of Colorado, Aurora, Colorado, USA) on dry ice. Samples were stored at the bioanalytical laboratory at −80°C.

Urine samples were collected prior to the morning dose on Days 1–6, and all urine samples on Day 7 were pooled in two intervals of 00:00–12:00 and 12:00–24:00. Urine samples were frozen on dry ice and then stored in a −80°C freezer until shipment to the bioanalytical laboratory (iC42 Clinical Research and Development, University of Colorado, Aurora, Colorado, USA) on dry ice. Samples were stored at the bioanalytical laboratory at −80°C. All samples (plasma and urine) had undergone one freeze-thaw cycle at the time of analysis.

Analytical methods

Plasma and urine concentrations of THC, CBD and metabolites were quantified using a 2D high-performance liquid chromatography—tandem mass spectrometry (LC/LC–MS-MS) assay developed and validated by iC42 Clinical Research and Development (9), and study samples were analyzed in a United States Clinical Laboratory Improvement Amendments-certified laboratory environment accredited by the College of American Pathologists (Northfield, Illinois, USA). Plasma aliquots of 200 µL of the calibrator, quality control, blank and zero samples were transferred into 1.5 mL low-binding Eppendorf tubes (Eppendorf, Hamburg, Germany). Eight hundred microliters of a protein precipitation solution of 30% water containing 0.2 M ZnSO4/70% methanol (v/v) containing the appropriate isotope-labeled internal standards were added. After vortexing for 10 min and centrifugation (25,000xg, 4°C for 10 min), the supernatants were injected into the LC-LC system (1,260 Infinity HPLC components, Agilent, Santa Clara, California, USA) for online extraction using an extraction column (C8-material, 3.0 5 mm, 2.7 µm particle size, Advanced Materials Technology, Wilmington, Delaware, USA). After 1 min, the analytes were backflushed onto the analytical column (Ascentis Express RP-Amide, 3.0 × 150 mm, 2.7 µm particle size, Supelco, Bellefonte, Pennsylvania, USA) and separated using a gradient of 0.04% formic acid in water (mobile phase A) and acetonitrile: methanol: isopropanol (3:1:1, v/v/v, mobile phase B). Analytes were quantified using an MS/MS detector (series 5,500, Sciex, Concord, Ontario, Canada). MS/MS data were acquired after atmospheric pressure chemical ionization in combination with multiple reaction monitoring in positive-ion mode. Calibration curves were constructed daily from peak area ratios of analytes to the internal standard. Calibrators were fitted using a quadratic equation in combination with 1/x weighting. Calculations were carried out using Sciex MultiQuant (version 3.0.2.). For details, please see Sempio et al. (9).

The assay had been developed and validated following applicable Clinical Laboratory Standards Institute and United States Food and Drug Administration (FDA) guidelines (10, 11). Plasma and urine concentrations of the following, with lower limit of quantification (LLOQ) in parentheses, were analyzed: THC (0.780 ng/mL), 11-OH-THC (3.125 ng/mL), 11-COOH-THC (0.780 ng/mL), CBD (0.780 ng/mL), 7-hydroxy-CBD (7-OH-CBD; 1.560 ng/mL) and 7-carboxy-CBD (7-COOH-CBD; 1.560 ng/mL). All concentrations reported as non-quantifiable were below the LLOQ. Urine concentrations of THC, CBD and metabolites were not normalized to creatinine. Urine samples were not hydrolyzed. The upper limits of quantification were between 100 and 2,000 ng/mL. Inter-day analytical accuracy and imprecision ranged from 90.4 to 111% and from 3.1 to 17.4%, respectively. There were no significant matrix interferences and carry-over. Sample stability exceeding the maximum storage time (at −80°C) and freeze-thaw cycles the study samples were exposed to were established (9). The calibration and quality control strategy during study sample analysis was in compliance with applicable United States FDA guidance (11).

PD assessments

Subjective effects were self-reported using the Drug Effects Questionnaire (DEQ), administered prior to the morning dose and 1, 2, 4, 6, 8 and 12 h after the morning dose on Days 1, 3 and 7. Participants were instructed to rate how they were feeling 'right now' on 6 items specifically related to the study product: 'feel any effect,' 'dislike any of the effects,' 'like any of the effects,' 'feel any good effects,' 'feel any bad effects,' and 'likely to take this study product again.' They also rated how much they were experiencing the following 14 adjectives: 'sick,' 'heart racing,' 'anxious,' 'relaxed,' 'paranoid,' 'tired/drowsy,' 'alert,' 'irritable,' 'energetic,' 'restless,' 'hungry,' 'dazed,' 'distracted' and 'euphoric/happy.' Items were rated on a 100-point visual analog scale, with anchors of 'not at all' and 'extremely.'

Urine drug screens

Urine drug screens (TOX/see rapid immunoassay test; Bio-rad; Hercules, CA, USA) were collected at inpatient discharge on Day 8 and at outpatient visits on Days 9, 10, 11 and 13. Participants with positive screens for 11-COOH-THC (>50 ng/mL) were instructed to not drive a motor vehicle until a subsequent screen was negative. Positive screens were not confirmed with laboratory-based gas or liquid chromatography/mass spectrometry.

Statistical analyses

AEs were tabulated and classified by System Organ Class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (version 22.1). Safety data were summarized using descriptive statistics. PK parameters for THC, CBD and metabolites were calculated using non-compartmental analysis (Phoenix 64 version 8.1, Pharsight, a Certara Company, USA). Individual PK parameters and plasma concentration over time were summarized using descriptive statistics. On Days 1, 3 and 7, post-treatment peak value (E_{max}) for each DEQ item was analyzed using ANOVA, with treatment group as fixed effect and participant as random effect. Least square mean (LSmean) estimates and 95% confidence intervals reported for each treatment group and for each paired difference between groups were adjusted with Tukey multiple comparison tests.

Results

Participant characteristics

In total, 41 participants were enrolled and randomly assigned to one of five treatment groups (Treatment A, $n = 9$; Treatment B, $n = 8$; Treatment C, $n = 8$; Treatment D, $n = 8$; placebo and $n = 8$). Participants were, on average, 28.1 years old (SD = 6.0) with a BMI of 22.9 (SD = 3.0). Slightly more than half (58.5%) of participants were female (Treatment A, $n = 4$; Treatment B, $n = 4$; Treatment C, $n = 6$; Treatment D, $n = 5$; placebo and $n = 4$), and the majority were White (80.5%) and not Hispanic or Latino (92.7%). All 41 participants

were included in the safety and intent-to-treat populations. Three participants withdrew from the study: one (Treatment A) withdrew due to TEAEs (see Safety and Tolerability), and two withdrew for other reasons during the outpatient period (one participant in Treatment D discontinued due to COVID-19 restrictions, and one participant in Treatment E discontinued due to a family emergency). The eight participants in the placebo group, along with the one participant who withdrew due to TEAEs, were not included in the PK population ($n = 32$). The two participants who withdrew for other reasons during the outpatient period provided sufficient PK samples to be included in the PK population.

Safety and tolerability

Table I displays all-causality TEAEs. Overall, 65.9% of participants (27/41) experienced at least one TEAE. The most common TEAEs included somnolence, lethargy and headache (reported by 8 [19.5%], 7 [17.1%] and 5 [12.2%] participants, respectively). The number of TEAEs between Treatments A [15], C [15] and D [23] were similar, all of which were higher than the number in the placebo group [9]; however, there were a third as many TEAEs in Treatment B [3] than in the placebo group. More participants in Treatment D [6] reported nervous system disorders than Treatments A [5], B [1] and C [3]. The highest number of TEAEs (30/65; 46.2%) occurred on the first day of treatment (Figure 1).

All TEAEs were of mild [61/65] or moderate [4/65] severity; there were no severe TEAEs. The moderate TEAEs included vascular access site pain and neutropenia (Treatment A), which were likely not related to study drug, and paranoia and nightsweats (Treatment D). There were no SAEs, no life-threatening TEAEs, and no deaths reported. No clinically significant differences were observed between treatment groups with respect to clinical chemistry laboratory assessments, vital signs, physical examinations, ECGs, or suicidality.

One participant from Treatment A experienced six TEAEs, and the TEAEs of dizziness, headache and somnolence resulted in

Table I. All-Causality TEAEs per Treatment Group, by MedDRA SOS and Preferred Term (Safety Population)

		Treatment[a]				
SOC PT [*n* (%) *E*]	Overall ($n = 41$)	A ($n = 9$)	B ($n = 8$)	C ($n = 8$)	D ($n = 8$)	Placebo ($n = 8$)
Participants with at least one TEAE	27 (65.9) 65	6 (66.7) 15	2 (25.0) 3	6 (75.0) 15	7 (87.5) 23	6 (75.0) 9
Nervous system disorders	19 (46.3) 25	5 (55.6) 8	1 (12.5) 1	3 (37.5) 4	6 (75.0) 8	4 (50.0) 4
Somnolence	8 (19.5) 8	1 (11.1) 1	0	1 (12.5) 1	4 (50.0) 4	2 (25.0) 2
Lethargy	7 (17.1) 7	3 (33.3) 3	1 (12.5) 1	1 (12.5) 1	1 (12.5) 1	1 (12.5) 1
Headache	5 (12.2) 5	2 (22.2) 2	0	2 (25.0) 2	0	1 (12.5) 1
Cognitive disorder	1 (2.4) 2	0	0	0	1 (12.5) 2	0
Dizziness	1 (2.4) 1	1 (11.1) 1	0	0	0	0
Paraesthesia	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Sensory disturbance	1 (2.4) 1	1 (11.1%) 1	0	0	0	0
Injury, poisoning and procedural complications	7 (17.1) 7	2 (22.2) 2	0	0	3 (37.5) 3	2 (25.0) 2
Vascular access site inflammation	3 (7.3) 3	0	0	0	2 (25.0) 2	1 (12.5) 1
Vascular access site pain	3 (7.3) 3	2 (22.2) 2	0	0	1 (12.5) 1	0
Vascular access complication	1 (2.4) 1	0	0	0	0	1 (12.5) 1
General disorders and administration site conditions	5 (12.2) 6	1 (11.11) 1	1 (12.5) 1	2 (25.0) 3	1 (12.5) 1	0
Fatigue	5 (12.2) 5	1 (11.1) 1	1 (12.5) 1	2 (25.0) 2	1 (12.5) 1	0
Drug withdrawal syndrome	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Musculoskeletal and connective tissue disorders	5 (12.2) 6	0	0	2 (25.0) 3	2 (25.0) 2	1 (12.5) 1
Back pain	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Muscle spasms	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Muscle tightness	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Muscle twitching	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Myalgia	1 (2.4) 1	0	0	0	0	1 (12.5) 1
Neck pain	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Psychiatric disorders	5 (12.2) 6	1 (11.1) 2	1 (12.5) 1	0	3 (37.5) 3	0
Euphoric mood	3 (7.3) 3	0	1 (12.5) 1	0	2 (25.0) 2	0

(Continued)

Table I. Continued

SOC PT [*n* (%) *E*]	Overall (*n* = 41)	Treatment[a]				
		A (*n* = 9)	B (*n* = 8)	C (*n* = 8)	D (*n* = 8)	Placebo (*n* = 8)
Paranoia	2 (4.9) 2	1 (11.1) 1	0	0	1 (12.5) 1	0
Restlessness	1 (2.4) 1	1 (11.1) 1	0	0	0	0
Reproductive system and breast disorders	3 (7.3) 3	0	0	1 (12.5) 1	2 (25.0) 2	0
Dysmenorrhea	2 (4.9) 2	0	0	1 (12.5) 1	1 (12.5) 1	0
Menstruation delayed	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Respiratory, thoracic and mediastinal disorders	3 (7.3) 3	1 (11.1) 1	0	1 (12.5) 1	0	1 (12.5) 1
Dyspnea	1 (2.4) 1	0	0	0	0	1 (12.5) 1
Epistaxis	1 (2.4) 1	1 (11.1) 1	0	0	0	0
Rhinorrhea	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Gastrointestinal disorders	2 (4.9) 2	0	0	1 (12.5) 1	1 (12.5) 1	0
Dry mouth	2 (4.9) 2	0	0	1 (12.5) 1	1 (12.5) 1	0
Infections and infestations	2 (4.9) 2	0	0	1 (12.5) 1	1 (12.5) 1	0
Respiratory tract infection	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Upper respiratory tract infection	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Skin and subcutaneous disorders	2 (4.9) 2	0	0	0	1 (12.5) 1	1 (12.5) 1
Dermatitis	1 (2.4) 1	0	0	0	0	1 (12.5) 1
Night sweats	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Blood and lymphatic system disorders	1 (2.4) 1	1 (11.1) 1	0	0	0	0
Neutropenia	1 (2.4) 1	1 (11.1) 1	0	0	0	0
Immune system disorders	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Allergy to arthropod bite	1 (2.4) 1	0	0	1 (12.5) 1	0	0
Investigations	1 (2.4) 1	0	0	0	1 (12.5) 1	0
Blood prolactin increased	1 (2.4) 1	0	0	0	1 (12.5) 1	0

E = number of adverse events, MedDRA = Medical Dictionary for Regulatory Activities, *n* = number of participants with events, PT = preferred term.
[a]Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.

withdrawal of study drug and subsequent discontinuation from the study.

Pharmacokinetics

Figure 2 shows the geometric mean plasma concentration-time profiles for THC and its metabolites; Table II summarizes plasma THC concentrations; Table III summarizes the PK parameters for 11-COOH-THC; and Table IV summarizes the urinary PK parameters for 11-COOH-THC.

For Treatment A, all plasma concentrations for THC were below the limit of quantification (BLoQ) on Day 1, and only one sample (at 1 h) was quantifiable for THC on Day 7 (Table II). The majority of plasma THC concentrations from participants in Treatments B, C and D on Days 1 and 7 were BLoQ; the plasma THC concentrations that were quantifiable on Days 1 and 7 were reported between 1 and 4 h post-dose (Table II). Because no participant in Treatments A, B, or D had more than two quantifiable concentrations of THC on either Day 1 or 7, PK parameters for THC were not calculated for these treatment groups. One participant in Treatment C had more than two quantifiable concentrations of THC on Day 1 and therefore had C_{max}, t_{max} and $AUC_{0\text{-}t}$ calculated on Day 1; however, this participant did not have sufficient quantifiable concentrations of THC on Day 7 to allow for PK calculations.

For Treatments A and B, all plasma concentrations for 11-OH-THC on Days 1 and 7 were BLoQ. On Day 1, one participant in Treatment C (4.36 ng/mL) and two in Treatment D (4.07 and 6.07 ng/mL) had quantifiable 11-OH-THC concentrations 2 h post-dose, and on Day 7 there were slightly more quantifiable 11-OH-THC concentrations [i.e., one in Treatment C (4.10 ng/mL) and one in Treatment D (3.66 ng/mL) 1 h post-dose; one in Treatment C (5.68 ng/mL) and three in Treatment D (3.30, 3.95 and 4.14 ng/mL) 2 h post-dose; and one in Treatment D (4.67 ng/mL) 4 h post-dose]. However, because no participant in any treatment group had more than two quantifiable concentrations of 11-OH-THC on either Day 1 or 7, PK parameters for 11-OH-THC were not calculated.

On Day 1, 11-COOH-THC was readily detected in plasma with a median t_{max} of 2 h. On Day 7, the t_{max} for 11-COOH-THC

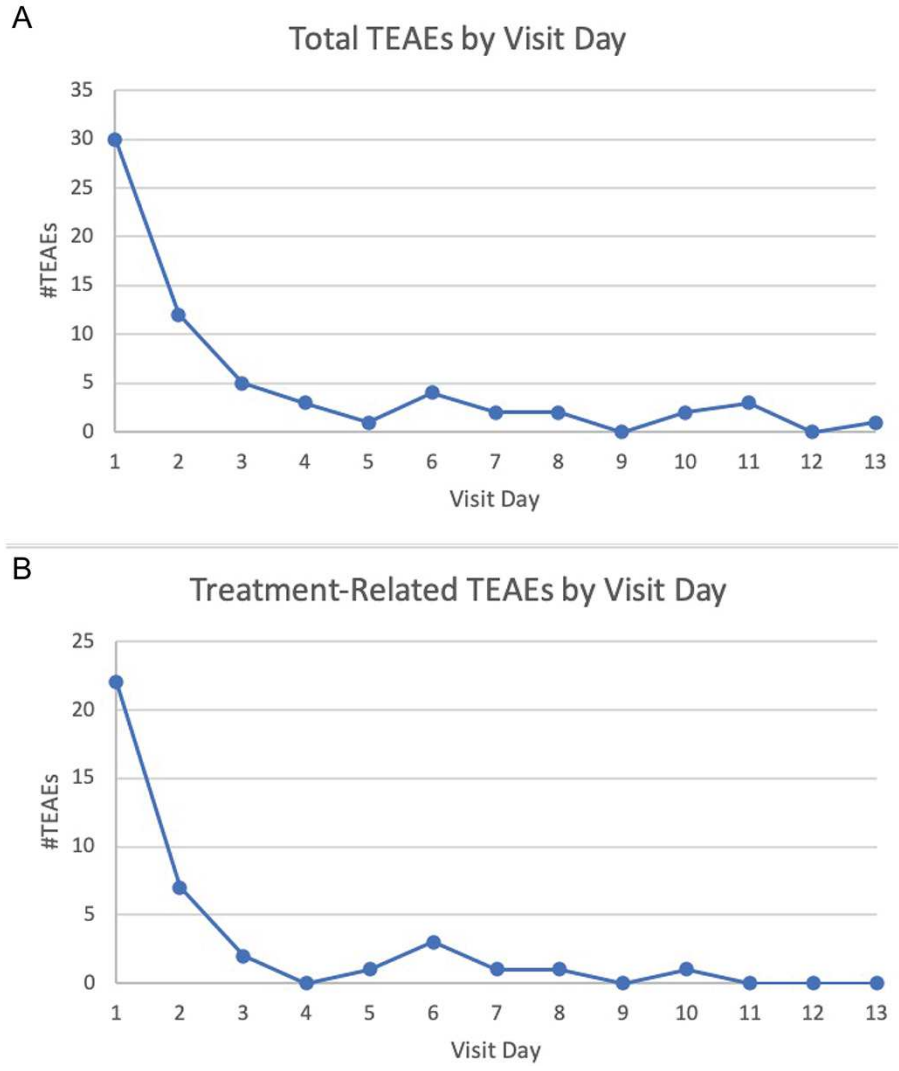

Figure 1. A) Total and B) treatment-related TEAEs by visit day.

was 2–4 h, and the C_{max} increased by 2.0- and 2.5-fold as the dose doubled between Treatments A and B, and Treatments B and D, respectively. A similar apparent increase was observed for 11-COOH-THC $AUC_{0–12}$ on Day 7, where it increased by 2.0- and 2.5-fold as the dose doubled between Treatments A and B, and Treatments B and D, respectively. Overall, apparent clearance (CL/F) slightly decreased with increasing doses of study medication. On Day 7, the accumulation ratio based on area under the curve ($R_{ac(AUC)}$) was 2.3–3.2-fold higher for all treatment groups than the Day 1 values.

Urinary THC concentrations were BLoQ for all treatment groups. Urinary 11-COOH-THC $Fe_{0–24}$ was low (<1%) and consistent for Treatments B, C and D (0.0003) and even lower for Treatment A (0.0001) (Table IV). Renal clearance of 11-COOH-THC was BLoQ for Treatment A and between 0.005 and 0.007 L/h for all other treatment groups.

The only quantifiable CBD concentration (1.36 ng/mL) occurred at 2 h post-dose on Day 7 in Treatment D; all other plasma, and all urine, concentrations of CBD were BLoQ. All plasma and urine concentrations of 7-OH-CBD and 7-COOH-CBD were BLoQ for all participants and timepoints.

Pharmacodynamics

Of the six items that assessed subjective drug effect ratings specifically related to the study product, mean post-treatment peak ratings on three items were higher in Treatment D relative to placebo (Table V). Mean post-treatment peak ratings of 'feel any effect' were higher for Treatment D relative to placebo on Days 1, 3 and 7, with the median time to post-treatment peak ratings occurring between 2 and 3 h on Days 1 (median = 2.8, Q1 = 2.3, Q3 = 4.6), 3 (median = 2.5, Q1 = 1.6, Q3 = 2.6) and 7 (median = 2.5, Q1 = 1.5, Q3 = 3.6). Mean post-treatment peak ratings of 'feel any bad effects' were higher for Treatment D relative to placebo on Day 1 and on Day 7, with the median time to post-treatment peak ratings occurring between 2 and 3 h on both Days 1 (median = 2.7; Q1 = 1.6, Q3 = 5.7) and 7 (median = 2.2; Q1 = 1.5, Q3 = 4.6). Mean post-treatment peak ratings of 'dislike any of the effects' were higher for Treatment D relative to placebo on Day 1, with the median time to post-treatment peak ratings occurring between 2 and 3 h (median = 2.3, Q1 = 1.7, Q3 = 4.8).

Mean post-treatment peak ratings of five of nine items of negative subjective effects were higher for Treatment D relative to placebo: 'heart racing,' 'restless,' and 'distracted' on Day 1;

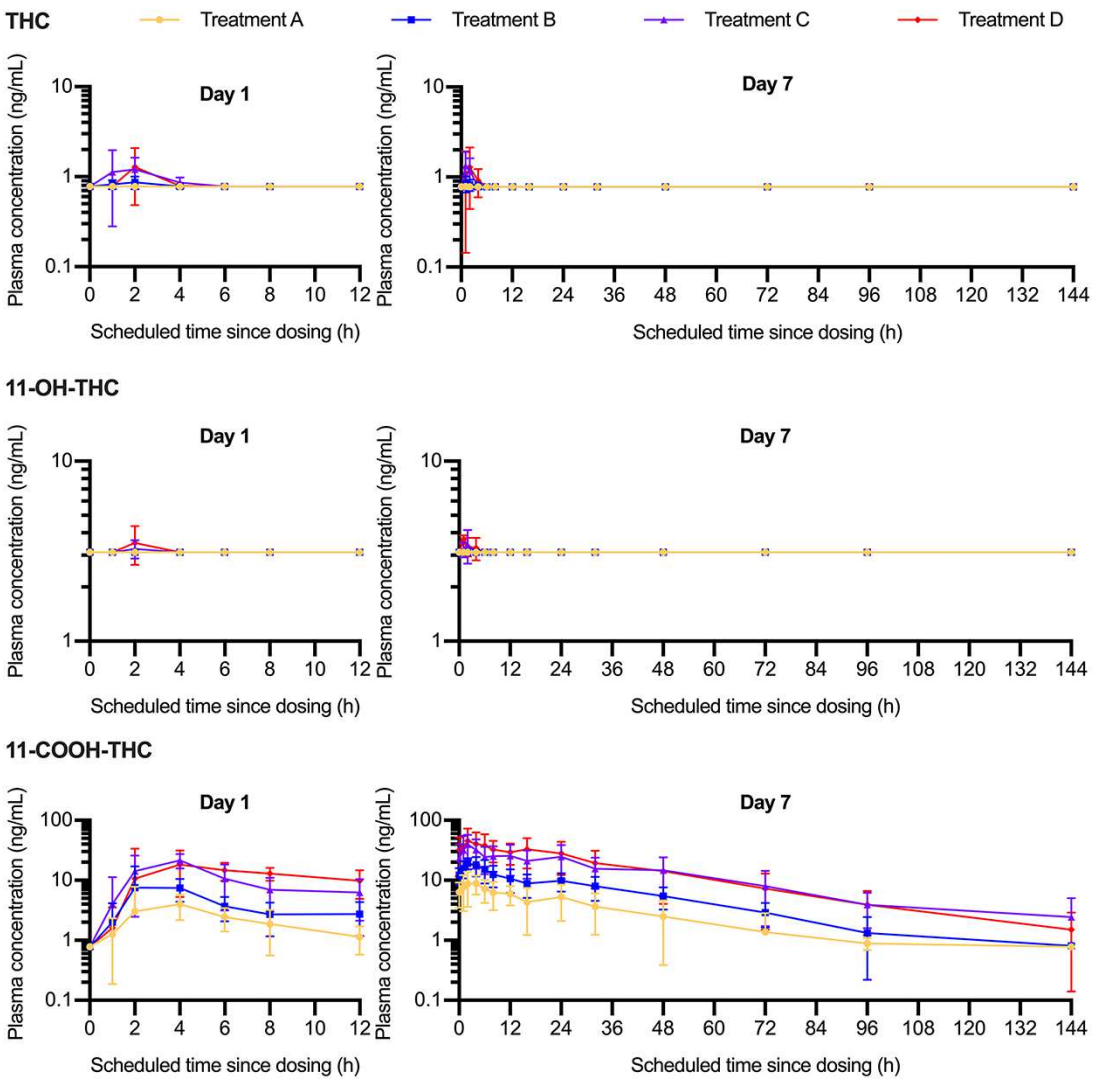

Figure 2. Geometric mean (± standard deviation) plasma concentration-time profiles for THC, 11-hydroxy-tetrahydrocannabinol (11-OH-THC), and 11-carboxy-tetrahydrocannabinol (11-COOH-THC) on Day 1 and Day 7 for Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.

'anxious' on Day 7; and 'dazed' on Days 1, 3 and 7. For these items, post-treatment peak ratings were observed between 1 and 3 h after dosing. Mean post-treatment peak ratings of 'tired/drowsy' were also higher for Treatment D relative to placebo on Days 1, 3 and 7, but higher pre-dose scores on this item for Treatment D vs. placebo (e.g., on Day 7, Treatment D: $M = 25.1$, $SD = 24.2$; placebo: $M = 7.9$, $SD = 8.2$) suggest that differences on this item may simply be due to pre-dose differences between groups.

Mean post-treatment peak ratings of 'anxious' on Day 1, and of 'feel any effect' and 'dazed' on Day 7, were higher for Treatment C relative to placebo. Treatment B did not differentiate from placebo on any DEQ item. Mean post-treatment peak ratings of 'like any of the effects' were lower for Treatment A relative to placebo on Days 1, 3 and Day 7, and mean post-treatment peak ratings of 'likely to take study product again' were lower for Treatment A relative to placebo on Days 3 and 7; however, the negative direction of these differences and the relatively high mean post-treatment peak ratings on these items in the placebo group (Table V) may reflect high placebo responding, rather than true low scores in Treatment A.

Mean post-treatment peak ratings of some negative subjective effects were higher in the highest-dose treatment group (D) relative to the three lower-dose treatment groups (A, B and C). Mean post-treatment peak ratings of 'feel any effect' were higher for Treatment D relative to Treatment A and relative to Treatment B on Days 1, 3 and 7, and ratings of 'dazed' were higher for Treatment D relative to Treatment A on Days 1 and 7 (Table V). Mean post-treatment peak ratings of several other negative subjective effects were higher in Treatment D relative to the three lower dose treatment groups (e.g., 'anxious,' 'restless'), but not uniformly across Days 1, 3 and 7.

No items that assessed positive effects (relaxed, alert, energetic, hungry and euphoric/happy) differentiated active treatment groups from placebo.

Urine drug screens

At least one participant in Treatments C and D had a positive urine drug screen for 11-COOH-THC through 72 h after the final dose of

Table II. Summary of Plasma THC Concentrations by Treatment Group, PK Population

	Treatment A[a] ($n = 8$)		Treatment B[a] ($n = 8$)		Treatment C[a] ($n = 8$)		Treatment D[a] ($n = 8$)	
Timepoint	n BLoQ (n)	Mean (SD)	n BLoQ (n)	Mean (SD)	n BLoQ (n)	Mean (SD)	n BLoQ (n)	Mean (SD)
Day 1								
Pre-dose	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)
1 hours	8 (8)	0 (0)	6 (8)	0.24 (0.45)	5 (8)	0.97 (1.73)	7 (8)	0.10 (0.29)
2 hours	8 (8)	0 (0)	5 (8)	0.39 (0.54)	2 (8)	1.07 (0.73)	3 (7)	1.17 (1.34)
4 hours	8 (8)	0 (0)	8 (8)	0 (0)	5 (8)	0.38 (0.52)	6 (7)	0.13 (0.33)
6 hours	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)
8 hours	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)
12 hours	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	7 (8)	0.13 (0.37)
Day 7								
Pre-dose	8 (8)	0 (0)	7 (7)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)
1 hours	6 (7)	0.12 (0.32)	6 (8)	0.28 (0.53)	2 (8)	1.23 (0.87)	6 (7)	0.80 (2.12)
2 hours	8 (8)	0 (0)	7 (8)	0.15 (0.41)	2 (8)	1.05 (0.75)	3 (8)	1.25 (1.43)
4 hours	8 (8)	0 (0)	7 (8)	0.13 (0.36)	7 (7)	0 (0)	6 (8)	0.38 (0.76)
6 hours	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)
8 hours	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)
12 hours	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)	8 (8)	0 (0)

Timepoints are in relation to the morning dose. Concentrations that were below the BLoQ were assigned as zero for analysis. *n*: number; LLOQ of THC is 0.78 ng/mL.
[a]Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.

Table III. Plasma PK Parameters for 11-COOH-THC; PK Population

	Treatment A[a] ($n = 8$)		Treatment B[a] ($n = 8$)		Treatment C[a] ($n = 8$)		Treatment D[a] ($n = 8$)	
PK parameter (unit)	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
11-COOH-THC								
C_{max} (ng/mL)[b]	6.2 (36.9)[e]	10.1 (43.8)	8.7 (72.1)	20.4 (26.5)	22.4 (45.4)	43.6 (47.4)	24.9 (38.1)	51.6 (48.1)
t_{max} (h)[c]	2.0 (2.0–4.0)[e]	4.0 (1.5–8.0)	2.0 (2.0–6.0)	2.0 (1.0–6.0)	3.0 (2.0–4.0)	2.0 (1.0–2.0)	4.0 (2.0–11.9)	2.0 (1.0–12.0)
$AUC_{0–12}$ (h*ng/mL)[b]	28.0 (57.3)[f]	86.0 (39.3)	56 (44.7)[g]	173 (32.8)	128.0 (52.1)[h]	356 (45.1)	195 (13.8)[i]	433 (42.9)
AUC_{0-t} (ng*h/mL)[b]	26.6 (44.0)[e]	269.0 (64.1)	43.8 (66.7)	577.0 (37.8)	124.0 (48.6)	1620.0 (56.6)	136.0 (43.4)	1670.0 (56.9)
$t_{1/2}$ (h)[d]	–	25.6 (9.8)[i]	–	27.5 (3.7)[g]	–	30.7 (8.2)[h]	–	27.6 (3.5)
CL/F (L/h)[b]	–	62.1 (28.1)[i]	–	57.6 (37.5)[g]	–	42.7 (48.9)[h]	–	46.2 (42.8)
$R_{ac(Cmax)}$[b]	–	0.6 (48.1)[e]	–	0.4 (70.6)	–	0.5 (22.8)	–	0.5 (45.3)
$R_{ac(AUC)}$[b]	–	2.3 (38.9)[f]	–	3.2 (23.0)[g]	–	2.9 (16.5)[h]	–	3.0 (29.4)[i]
$(M/P)_{AUC0-t}$[b]	–	BLoQ	–	BLoQ	–	BLoQ	–	BLoQ

$AUC_{0–12}$: area under the plasma concentration-time curve from 0 to the 12 h time point, $AUC_{0–t}$: area under the plasma concentration-time curve from 0 to the last quantifiable concentration, CL/F: oral clearance of drug from plasma, C_{max} maximum observed plasma concentration, (M/P) AUC_{τ} AUCτ Metabolite/AUCτ Parent, $R_{ac(AUC)}$ accumulation ratio based on AUC, $R_{ac(Cmax)}$ accumulation ratio based on C_{max}, t_{max} time to reach C_{max}, 11-COOH-THC 11-carboxy-THC.
[a]Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.
[b]Geometric mean (geometric CV%).
[c]Median (range).
[d]Arithmetic mean (arithmetic CV%).
[e]$n = 5$.
[f]$n = 2$.
[g]$n = 6$.
[h]$n = 7$.
[i]$n = 4$.

study medication (Figure 3). One participant in Treatment C had a positive urine drug screen for 11-COOH-THC 144 h after the final dose.

Discussion

Safety and tolerability

Daily doses of Spectrum Red softgels ranging from 5 mg THC and 0.06 mg CBD to 20 mg THC and 0.24 mg CBD were well tolerated, a finding that is consistent with a systematic review of medical cannabis and cannabinoids that found that nearly 97% of AEs were not serious (12). The most frequently reported TEAEs of somnolence and lethargy are similar to TEAEs commonly reported in studies of Marinol®, an approved oral pharmaceutical THC product (13), and to TEAEs reported in a study of a single dose of a medical cannabis capsule with doses of THC ranging from 5 to 10 mg (4). The number of TEAEs between Treatments A [15], C [15] and D [23] were similar, all of which were higher than the number in the placebo group [9]. However, there were a third as many TEAEs in Treatment B [3] than in the placebo group. This lack of dose dependence in the incidence of TEAEs could be partially explained by the relatively large number of TEAEs [6] reported by the one participant in Treatment A who discontinued study treatment and participation; it could also be explained by unknown individual difference characteristics. For example, although all participants were required to have had at least two lifetime exposures to THC-containing cannabis products,

Table IV. Urine PK Parameters of 11-COOH-THC; PK Population

PK parameter (units)[b]	Treatment A[a] ($n = 8$)	Treatment B[a] ($n = 8$)	Treatment C[a] ($n = 8$)	Treatment D[a] ($n = 8$)
$Ae_{0–12}$ (mg)	BLoQ	0.002 (38.9)[c]	0.002 (39.4)[d]	0.003 (73.0)[e]
$Ae_{12–24}$ (mg)	0.0006 (79.8)[c]	0.002 (76.4)[e]	0.003 (63.1)[e]	0.005 (93.1)
$Ae_{0–24}$ (mg)	0.0006 (79.8)[c]	0.003 (92.3)[e]	0.005 (48.5)[e]	0.007 (111.4)
$fe_{0–12}$	BLoQ	0.0002 (38.9)[c]	0.0001 (39.3)[d]	0.0002 (73.0)[e]
$fe_{12–24}$	0.0001 (79.9)[c]	0.0002 (76.4)[e]	0.0002 (36.1)[e]	0.0003 (93.1)
$fe_{0–24}$	0.0001 (79.9)[c]	0.0003 (92.3)[e]	0.0003 (48.5)[e]	0.0003 (111.3)
C_{LR} (L/h)	BLoQ	0.007 (32.5)[c]	0.005 (42.6)[d]	0.006 (59.8)[e]

All urine PK parameters for THC, CBD and 7-OH-CBD were BLoQ. $Ae_{0–12}$ amount of drug eliminated between 0 and 12 h, $Ae_{12–24}$ amount of drug eliminated between 12 and 24 h, $Ae_{0–24}$ amount of drug eliminated between 0 and 24 h, *BLoQ*, C_{LR} renal clearance, $Fe_{0–12}$ fraction of administered dose excreted in urine between 0 and 12 h, $Fe_{12–24}$ fraction of administered dose excreted in urine between 12 and 24 h, $Fe_{12–24}$ fraction of administered dose excreted in urine between 0 and 24 h, *NE* not estimable.
[a]Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.
[b]Geometric mean (geometric mean CV%).
[c]$n = 3$.
[d]$n = 4$.
[e]$n = 5$.

perhaps different extents of prior experience with THC could have influenced tolerability to study medication.

Pharmacokinetics

Quantifiable concentrations of THC and 11-OH-THC were infrequent on both Days 1 and 7, and those concentrations that were quantifiable were observed between 1 and 4 h post-dose. The timing of quantifiable plasma THC concentrations is similar to the timing in previous studies, in which peak plasma concentrations of THC were detected ∼1–5 h after oral administration (5, 8). Furthermore, the infrequent quantifiable concentrations of THC observed in this study echo findings from a systematic review that concluded that oral THC has a variable PK profile (14). Although quantifiable concentrations of THC and 11-OH-THC were sporadic, there was moderate accumulation of plasma 11-COOH-THC, and some participants in the two higher-dose treatment groups had urine drug screens that were positive for 11-COOH-THC for several days after the final dose of study medication; these results suggest accumulation of THC and metabolites in tissue and relatively slow urinary excretion. Given the low dosages of CBD administered in this study, there was an almost uniform lack of quantifiable exposure to CBD or its metabolites. Nonetheless, a potential area for future study is whether CBD, other phytocannabinoids or terpenes contained in the studied non-pharmaceutical cannabis product used for medical purposes influenced the PKs of THC. Some studies have shown that CBD may delay the time to reach peak plasma concentrations of THC, while other studies have shown that combining CBD with THC may lead to an increased peak concentration of plasma THC, and others have shown no significant effect of CBD on the PKs of THC (see review by Freeman et al.) (15). As much is still unknown regarding the effect of phytocannabinoids other than CBD and of terpenes on the PKs of THC, more studies are needed to directly examine the interaction of different constituents of cannabis products used for medical purposes on PKs.

Pharmacodynamics

Treatment D differentiated from placebo on several effects related to the study medication and several negative subjective effects. Specifically, mean peak post-treatment ratings of 'feel any effect' and 'dazed' differed between Treatment D and placebo on Days 1, 3 and 7, and ratings of 'feel any bad effects' differed between Treatment D and placebo on Days 1 and 7; other subjective effects differed between Treatment D and placebo only on Day 1 (i.e., 'dislike any of the effects, 'heart racing', 'restless' and 'distracted') or Day 7 (i.e., 'anxious'). Across these subjective effects, post-treatment peak ratings occurred between 1 and 3 h. Additionally, Treatment D differentiated from the three lower-dose treatment groups on some subjective effects on either Day 1 or 7 (e.g., 'anxious' and 'restless'), but there was not a clear relation between dose and PD that was consistent across subjective effects or days. Due to the small number of participants in each group and the wide variability surrounding estimates of between-group differences, these PD results should be interpreted with caution. Nonetheless, the relatively consistent finding across subjective effects that Treatment D differentiated from placebo, while the three lower-dose treatment groups did not, is similar to results from prior studies that have shown that subjective effects are typically observed at higher doses of THC (8).

Clinical implications

THC and THC-like compounds have regulatory approval in specific regions to treat anorexia associated with weight loss in patients with acquired immunodeficiency syndrome, nausea and vomiting associated with cancer chemotherapy and neuropathic pain. These compounds are also being evaluated as potential treatments for various other conditions, including chronic pain, acute pain, sleep and opioid sparing (16). The synthesis of this study's safety, tolerability, PK and PD data supports a 'start low and go slow' approach with initial doses of Spectrum Red softgels similar to those in Treatments A and B and titration upward over time based on tolerability. However, similar studies with individuals with various medical conditions are needed before formal condition-specific dosing guidelines can be issued. Because the number of TEAEs was highest on the first day of treatment and lower on subsequent treatment days, individuals who consume Spectrum Red softgels for medical purposes might experience improved tolerability after the first day of treatment.

Trial limitations

This study is limited by its focus on healthy adults; future studies are needed to characterize the safety, tolerability, PK and PD of Spectrum Red softgels in patient populations and in diverse populations with respect to age and other demographic characteristics. Sample sizes in each treatment group were small, yielding imprecise estimates of between-group differences in PD. Although several indications for THC and THC-like compounds relate to conditions of very low BMI,

Table V. Peak Post-Treatment Value on DEQ; Intent-to-Treat Population

	Treatment[a]														
	Day 1					Day 3					Day 7				
DEQ, LSmean (SE)	Placebo ($n=8$)	A ($n=9$)	B ($n=8$)	C ($n=8$)	D ($n=8$)	Placebo ($n=8$)	A ($n=8$)	B ($n=8$)	C ($n=8$)	D ($n=8$)	Placebo ($n=8$)	A ($n=8$)	B ($n=8$)	C ($n=8$)	D ($n=8$)
Feel any effect	29.8 (9.0)[b]	21.4 (8.5)[c,d]	28.9 (9.0)[e]	53.6 (9.0)[c]	63.8 (9.0)[b,d,e]	19.3 (9.0)[b]	26.7 (8.5)[d]	24.9 (9.0)[e]	47.5 (9.0)	65.9 (9.0)[d,e,b]	12.5 (9.0)[f,b]	11.6 (8.8)[c,d]	30.3 (9.0)[g,e]	55.9 (9.0)[c,f,g]	69.8 (9.0)[b,d,e]
Dislike any of the effects	2.4 (7.6)[b]	17.7 (7.2)[d]	3.6 (7.6)[e]	22.6 (7.6)	40.6 (7.6)[b,d,e]	1.9 (7.6)	22.2 (7.2)	6.3 (7.6)	22.8 (7.6)	17.0 (7.6)	1.3 (7.6)	16.2 (7.4)	4.0 (7.6)	13.3 (7.6)	19.8 (7.6)
Like any of the effects	52.3 (10.5)[h]	21.1 (9.9)[h,c,d]	34.8 (10.5)	58.1 (10.5)[c]	53.1 (10.5)[d]	52.5 (10.5)[h]	13.3 (9.9)[c,d,h]	41.1 (10.5)	46.5 (10.5)[c]	61.3 (10.5)[d]	45.1 (10.5)[h]	10.9 (10.2)[h,c,d]	30.0 (10.5)	48.3 (10.5)[c]	41.9 (10.5)[d]
Good effects	37.1 (10.0)	17.0 (9.4)[d]	40.3 (10.0)	42.1 (10.0)	64.9 (10.0)[d]	37.0 (10.0)	15.6 (9.4)[d]	38.5 (10.0)	34.0 (10.0)[j]	63.9 (10.0)[d,j]	30.5 (10.0)	10.9 (9.8)[c,d]	22.6 (10.0)	48.5 (10.0)[c]	48.5 (10.0)[d]
Bad effects	2.3 (7.9)[b]	15.2 (7.4)	2.0 (7.9)[e]	20.8 (7.9)	36.9 (7.9)[b,e]	4.9 (7.9)	15.6 (7.4)	2.3 (7.9)	19.3 (7.9)	18.3 (7.9)	0.8 (7.9)[b]	14.2 (7.6)	3.3 (7.9)	16.0 (7.9)	23.3 (7.9)[b]
Take study product again	77.0 (11.2)	64.6 (10.6)	69.4 (11.2)	59.3 (11.2)	64.1 (11.2)	77.5 (11.2)[h]	42.1 (10.6)[h]	69.6 (11.2)	47.9 (11.2)	65.8 (11.2)	74.6 (11.2)[h]	41.0 (10.8)[h,i]	81.4 (11.2)[i]	59.5 (11.2)	59.3 (11.2)
Sick	0.5 (4.6)	4.6 (4.3)	0.1 (4.6)	12.5 (4.6)	7.9 (4.6)	0.3 (4.6)	3.8 (4.3)	0.3 (4.6)[g]	14.5 (4.6)[g]	3.6 (4.6)	0.0 (4.6)	2.9 (4.4)	0.3 (4.6)	12.1 (4.6)	6.3 (4.6)
Heart racing	0.3 (4.5)[b]	8.2 (4.2)	0.4 (4.5)[e]	11.3 (4.5)	18.4 (4.5)[b,e]	0.0 (4.5)	7.1 (4.2)	0.3 (4.5)	7.8 (4.5)	11.6 (4.5)	0.1 (4.5)	5.9 (4.3)	0.1 (4.5)	7.8 (4.5)	8.5 (4.5)
Anxious	4.1 (5.3)[f,b]	9.4 (5.0)	0.3 (5.3)[g,e]	21.6 (5.3)[g,f]	21.0 (5.3)[b,e]	2.6 (5.3)	8.9 (5.0)	0.1 (5.3)	8.3 (5.3)	11.8 (5.3)	0.0 (5.3)[b]	6.4 (5.2)	2.9 (5.3)	7.8 (5.3)	17.4 (5.3)[b]
Relaxed	70.37 (9.9)	61.1 (9.3)	64.5 (9.9)	59.1 (9.9)	87.1 (9.9)	58.4 (9.9)	56.7 (9.3)	59.0 (9.9)	58.5 (9.9)	69.6 (9.9)	55.9 (9.9)	37.6 (9.6)[d]	52.8 (9.9)	63.4 (9.9)	68.8 (9.9)[d]
Paranoid	0.5 (5.9)	9.9 (5.6)	6.0 (5.9)	10.9 (5.9)	11.5 (5.9)	0.3 (5.9)	9.3 (5.6)	0.4 (5.9)	10.8 (5.9)	7.5 (5.9)	0.1 (5.9)	6.0 (5.8)	12.4 (5.9)	8.4 (5.9)	8.5 (5.9)
Tired/drowsy	44.0 (9.1)[b]	51.8 (8.6)[d]	56.9 (9.1)[e]	60.1 (9.1)[j]	89.0 (9.1)[b,d,e,j]	32.6 (9.1)[h,f,b]	63.4 (8.6)[h]	52.6 (9.1)	58.5 (9.1)[f]	74.4 (9.1)[b]	33.0 (9.1)[b]	25.5 (8.8)[c,d]	41.8 (9.1)[e]	54.0 (9.1)[c]	71.3 (9.1)[b,d,e]
Alert	53.5 (10.2)	43.6 (9.6)	43.6 (10.2)	40.4 (10.2)	51.0 (10.2)	51.8 (10.2)	27.9 (9.6)	38.8 (10.2)	41.4 (10.2)	43.8 (10.2)	48.5 (10.2)	29.0 (9.8)	34.0 (10.2)	30.9 (10.2)	34.3 (10.2)
Irritable	4.1 (7.0)	14.4 (6.6)	1.0 (7.0)	12.4 (7.0)	10.1 (7.0)	6.4 (7.0)	11.8 (6.6)	6.5 (7.0)	11.5 (7.0)	8.4 (7.0)	5.0 (7.0)	11.4 (6.7)	3.3 (7.0)	11.5 (7.0)	6.4 (7.0)
Energetic	44.0 (9.3)	37.2 (8.8)	33.1 (9.3)	39.9 (9.3)	33.9 (9.3)	42.4 (9.3)	27.9 (8.8)	27.4 (9.3)	39.1 (9.3)	31.4 (9.3)	43.5 (9.3)	29.0 (9.0)	27.4 (9.3)	32.8 (9.3)	24.4 (9.3)
Restless	17.6 (7.3)[b]	18.6 (6.9)[d]	19.5 (7.3)	13.0 (7.3)[j]	39.4 (7.3)[b,j,d]	8.0 (7.3)	18.6 (6.9)	17.5 (7.3)	8.5 (7.3)	14.9 (7.3)	12.3 (7.3)	17.4 (7.1)	11.8 (7.3)	15.4 (7.3)	12.1 (7.3)
Hungry	54.8 (9.8)	40.8 (9.3)[i]	73.8 (9.8)[i,g]	40.0 (9.8)[g]	55.8 (9.8)	40.9 (9.8)	38.6 (9.3)	62.6 (9.8)[g]	33.3 (9.8)[g,j]	61.3 (9.8)[j]	43.8 (9.8)	36.3 (9.7)	42.8 (9.8)	40.9 (9.8)	45.1 (9.8)
Dazed	9.8 (9.9)[b]	23.0 (9.3)[d]	23.4 (9.9)[e]	31.0 (9.9)	56.8 (9.9)[b,d,e]	4.0 (9.9)[b]	28.9 (9.3)	30.1 (9.9)	31.6 (9.9)	54.4 (9.9)[b]	2.3 (9.9)[b,f]	19.4 (9.5)[d]	26.9 (9.9)	32.4 (9.9)[f]	50.4 (9.9)[b,d]
Distracted	12.6 (8.7)[b]	20.3 (8.2)[d]	16.0 (8.7)[e]	25.0 (8.7)	47.3 (8.7)[b,d,e]	7.9 (8.7)[b]	23.3 (8.2)[d]	14.1 (8.7)[e]	19.0 (8.7)[j]	51.6 (8.7)[b,d,e,j]	7.8 (8.7)[b]	15.8 (8.5)[d]	23.0 (8.7)	17.6 (8.7)[j]	46.4 (8.7)[b,d,j]
Euphoric/ happy	48.6 (9.2)	28.7 (8.7)	48.6 (9.2)	43.9 (9.2)	40.1 (9.2)	39.1 (9.2)	22.9 (8.7)[d]	38.0 (9.2)	44.1 (9.2)	57.0 (9.2)[d]	38.9 (9.2)	26.3 (8.9)	37.9 (9.2)	49.6 (9.2)	37.6 (9.2)

SE standard error.
[a]Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.
[b]D vs Placebo ($P<0.05$).
[c]A vs C ($P<0.05$).
[d]A vs D ($P<0.05$).
[e]B vs D ($P<0.05$).
[f]C vs Placebo ($P<0.05$).
[g]B vs C ($P<0.05$).
[h]A vs Placebo ($P<0.05$).
[i]A vs B ($P<0.05$).
[j]C vs D ($P<0.05$).

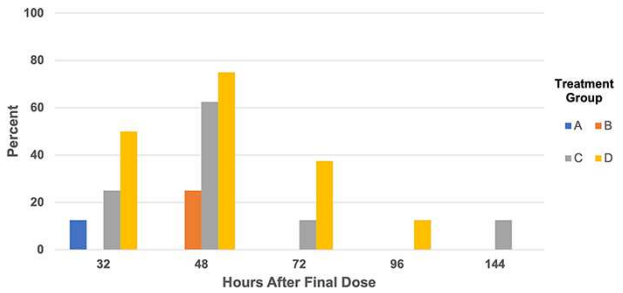

Figure 3. Percentage of urine drug screens positive for 11-carboxy-tetrahydrocannabinol (11-COOH-THC) (>50 ng/mL) in each treatment group. Treatment A: 5 mg total THC and 0.06 mg CBD daily; B: 10 mg total THC and 0.12 mg total CBD daily; C: 15 mg total THC and 0.18 mg total CBD daily; D: 20 mg total THC and 0.24 mg total CBD daily.

the study did not evaluate individuals with extreme BMI. This study did not examine CYP450 genetic polymorphisms, which could influence the therapeutic and adverse effects of cannabinoids and thus impact dosing recommendations (17, 18).

Conclusion

Over a week of twice-daily dosing, daily doses of THC up to 20 mg and of CBD up to 0.24 mg were generally safe and became better tolerated after the first day of treatment. Quantifiable plasma THC concentrations were sporadic; yet, accumulation of its metabolite 11-COOH-THC in plasma was moderate with a dose-related increase in exposure observed. A prudent approach to improve tolerability with Spectrum Red softgels might involve initial daily doses no higher than 10 mg total THC and 0.12 mg total CBD in divided doses, with titration upward over time as needed based on tolerability.

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