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PTL401, a New Formulation Based on Pro-Nano Dispersion Technology, Improves Oral Cannabinoids Bioavailability in Healthy Volunteers

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ABSTRACT

There is a growing clinical interest in developing and commercializing pharmaceutical-grade cannabinoid products, containing primarily tetrahydrocannabinol (THC) and cannabidiol (CBD). The oral bioavailability of THC and CBD is very low due to extensive "first-pass" metabolism. A novel oral THC and CBD formulation, PTL401, utilizing an advanced self-emulsifying oral drug delivery system, was designed to circumvent the "first-pass" effect. In this study, the bioavailability of THC and CBD from the PTL401 capsule was compared with similar doses from a marketed reference oromucosal spray (Sativex®). Fourteen healthy male volunteers received, on separate treatment days, either a single dose of PTL401 or an equivalent dose of the oromucosal spray. Blood samples for pharmacokinetic analyses were collected, and safety and tolerability were assessed. PTL401 yielded 1.6-fold higher plasma C_{max} than the equivalent dose of the oromucosal spray, for both THC and CBD. Their relative bioavailability was also higher (131% and 116% for CBD and THC, respectively). Values of T_{max} were significantly shorter for both CBD and THC (median of 1.3 h for PTL401 vs. 3.5 h for the spray). The pharmacokinetic profiles of the active 11-OH-THC metabolite followed the same pattern as THC for both routes of delivery. No outstanding safety concerns were noted following either administration. We conclude that PTL401 is a safe and effective delivery platform for both CBD and THC. The relatively faster absorption and improved bioavailability, compared to the oromucosal spray, justifies further, larger scale clinical studies with this formulation.

Introduction

There is a growing body of evidence that cannabinoids have a beneficial effect on various clinical conditions such as pain, post-traumatic stress disorder, loss of appetite/anorexia, sleep disorders, symptoms of multiple sclerosis (MS), epilepsy, schizophrenia, and other indications. In addition, the evolving knowledge and expanding research on the role of the endocannabinoid system in disease states have led to intensive research and development of cannabinoids as "formal" medicines.[1-4]

Among the many active components of the cannabis plant extract, the 2 most prominent compounds are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD).[5] THC possesses psychoactive effects and acts primarily through the CB1 and CB2 cannabinoid receptors. The major metabolite of THC is 11-hydroxy-THC (11-OH-THC) which is a potent activator of the CB1 receptors.[6] CBD is nonpsychoactive and probably induces its effects through different mechanisms.[3,7] Apparently CBD alleviates, at least partly, the untoward effects of THC.[8,9] It may therefore seem reasonable to combine both components in the same product. Surprisingly, there is only one commercial product that contains both THC and CBD, Sativex® oromucosal spray, indicated for symptom improvement in adult patients with moderate-to-severe spasticity due to MS.[10] Currently, in fact, there are also very few marketed pharmaceutical oral formulations that contain only THC.

Various modes of cannabinoids administration were tested in animals and humans: smoking, inhalation, oral, sublingual, rectal, ophthalmic, and transdermal.[6] The active ingredients are either

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extracted from their natural source (*Cannabis sativa* plant) or are chemically synthesized. They have been incorporated in vapor, aerosols, oils, cookies, topical creams, and suppositories. Some are produced according to Good Manufacturing Practice standards, but many are prepared under less controlled conditions.

The transformation of cannabinoids from alternative or herbal preparations to regulated prescription drugs is rapidly progressing. The development of such drugs requires well-controlled clinical trials to objectively establish therapeutic efficacy, dose ranges, and safety.[11,12] A pharmaceutical-grade delivery system that would enable efficient and consistent dosing of THC and CBD should also be designed to ensure adequate and reproducible bioavailability, display dose proportionality, and be as convenient as possible to administer, to assure patients adherence to treatment.

The bioavailability of cannabinoids varies considerably according to the mode of administration. When smoked or inhaled, exposure depends not only on depth of inhalation, puff duration, and breath-hold but also varies between heavy users and occasional smokers.[6,13] THC, CBD, and many of their metabolites are highly lipophilic and essentially water insoluble.[6] Their solubility/dissolution in the hydrophilic intestinal milieu is low and may interfere with their gastrointestinal (GI) absorption.[14] Indeed, with oral use, absorption of cannabinoids is slow and erratic, sometimes unpredictable, and is affected by gastric pH and food.[6,14-17] The oral bioavailability of cannabinoids is also hampered by their extensive first-pass metabolism.

The use of nanoparticles and nanodispersion systems for oral drug delivery has been gaining interest in the recent years.[18-21] A novel formulation based on self-nanoemulsifying drug delivery technology has been recently developed.[22-25] The base formulation was termed pro-nano-liposphere (PNL) preconcentrate and is ingested as a soft gelatin capsule. When reaching the aqueous phase of the GI tract, the preconcentrate spontaneously forms drug-encapsulated nanolipospheres with a particle diameter of less than 60 nm. This delivery system has been previously adapted to an immunosuppressive agent, cyclosporine A (CsA).[24] CsA-PNL (marketed as Deximune®) was approved for marketing by the European Medicines Agency. No untoward effects related to the delivery system itself, such as gastric irritation, have been reported. As previously described by Elgart at al.,[22] the formed nanoparticles improve solubility of lipophilic drugs, presenting a more than 99% drug load. Furthermore, they also inhibit oxidative metabolism by CYP3A4 and diminish P-gp efflux, thus improving the oral bioavailability and Caco-2 permeability of these types of drugs. Because cannabinoids are also lipophilic compounds with poor oral bioavailability, they were considered suitable candidates for this type of drug delivery system. PTL401 is the proprietary PNL-based formulation of THC and CBD. The isotropic mixture currently contains THC and CBD at a ratio of 1:1, in combination with lipids, low amount of surfactants, and a cosolvent. The particles are composed of a lipid core which ensures solubilization of the cannabinoids and allows their contact with the enterocyte surface (passing the unstirred water layer attached to the cells). Owing to their small size (~30 nm), these nanoparticles may spread over a large surface area and access intervillous spaces of the intestinal brush border. We have previously demonstrated that small particle size is inversely correlated with oral bioavailability.[23] An additional aspect in cannabinoid absorption is the lymphatic route. Novel lipid-based nanoformulations have unique characteristics that make them promising candidates for lymphatic delivery. Thus, first-pass metabolism of compounds with lower bioavailability is avoided.[26] It was demonstrated that the cannabinoids are taken up by chylomicrons, proving that when triggered, they undergo lymphatic absorption[14,27] because the lipid core of the PNL formulation is composed of medium chain triglycerides, that enable an additional absorption rout via the lymphatic system.

The THC/CBD oral formulation is easy to administer and enables flexibility in the doses of cannabinoid that may be loaded with up to 100 mg per capsule of either THC, CBD, or their combination. This may be clinically important because doses required for different indications may vary. The product is also stable in room temperature and does not require special storage conditions.

In the preclinical studies, it has been shown that the nanoparticles loaded with THC or CBD improve oral bioavailability of both molecules. A 4- to 6-fold enhancement in oral CBD and THC uptake was observed in rats treated with PNL, as compared to control orally delivered solution. We assume that the enhanced PK profile of THC and CBD, when incorporated into PNL, is due to increased absorption rather than changes in the elimination.[25]

The objective of the current study was to establish the pharmacokinetic (PK) profile of the PNL-based THC/CBD formulation in humans. The oromucosal spray was chosen as the reference formulation not only because it is the only commercial product containing both THC and CBD but also because it is readily absorbed through the oral mucosa, thus apparently bypassing the first-pass metabolism.[17] We also explored whether production of the THC major metabolite, 11-OH-THC, was affected by the mode of administration.

Materials and Methods

The study took place at the Tel Aviv Sourasky Medical Center (TASMC) Clinical Research Center (CRC), Israel, and was conducted according to Good Clinical Practice (GCP) guidelines. The study was approved by the TASMC Institutional Ethics Committee and by the Ministry of Health and registered in ClinicalTrials.gov (https://clinicaltrials.gov/, identifier: NCT03201835). All subjects provided a written informed consent before any study-related procedures were performed.

Study Drugs

The THC incorporated in the investigational formulation was synthesized by THC Pharm GmbH (Frankfurt, Germany), and the CBD was produced by STI Pharmaceuticals (Essex, UK).

The PTL401 formulation was composed of (w/w%): THC (1.2%), CBD (1.1%), polysorbate 20 (13.7%), sorbitan monooleate 80 (13.7%), polyoxyethylene hydrogenated castor oil 40 (13.7%), tricaprin (13.7%), lecithin (8.3%), and ethyl lactate (34.6%). It was manufactured in compliance to Good Manufacturing Practice requirements and was prepared by the preconcentrate preparation method as previously described[24]; the active ingredients were dissolved in a water-miscible organic solvent (approved for oral use) with phospholipids, by gentle heating and mixing. Following addition of surfactants, an oily transparent and homogeneous solution was formed. Particle size and polydispersity index (PDI) of the clinical batches were confirmed by measurement immediately after dispersion of the oily preconcentrate (at 1:9 dilution ratio) in the tested medium that was warmed to 37°C and vortex mixed for 30 s. The tested media used were those recommended for drug dissolution in the GI tract. Because cannabinoid uptake might be affected by food, PTL401 was examined *in vitro* in simulated intestinal fluid for both fasting conditions and fed conditions at pH adjusted to 1.2, 4.5, and 6.8. The particle size and PDI were measured using the Zetasizer Nano ZS ZEN 3600 (Malvern Instruments Ltd., Malvern, UK) equipment.

Subjects

Subjects eligible for participation in the study were males, 18-45 years of age, with a body mass index of 19 to <30 kg/m^2 and weight ranging from 55 to 85 kg, nonusers of any tobacco or nicotine products for a period of at least 6 months before screening, and judged to be healthy based on medical history, physical examination, electrocardiogram (ECG), and safety laboratory tests (complete blood count, clinical chemistry, and urinalysis). Subjects were excluded if they have used cannabis products in the last 30 days, had a history of drug or alcohol abuse, had a positive urine drugs of abuse (including THC) test on screening and on admission before the first treatment, suffered from a clinically significant relevant medical condition (chronic or acute), including psychiatric disorders, or had positive serology for hepatitis A antibodies, hepatitis B surface antigen, or HIV antibodies. Subjects were not allowed to participate if they had a history of recurrent oral aphthae or other pathology of the oral mucosa, were receiving any medications, or had a known hypersensitivity to any drug. Caffeine/xanthines such as coffee, tea, chocolate caffeine containing soft drinks, or energy drinks were not allowed during confinement in the CRC. Alcoholic beverages and other alcohol containing products were not allowed for 48 h before each dose and throughout the blood collection period.

Study Design

The PK of THC and CBD following PNL401 administration was assessed as part of a larger scale single-center, open-label, randomized, comparative crossover single-dose study, that included 2 additional cannabinoid formulations other than the PNL product, not reported in the current paper. The PK profile was compared to the reference Sativex® oromucosal spray (GW Pharma Ltd., Cambridge, UK) in the same subjects. The same statistical model was applied to all treatments.

Fifteen healthy male volunteers were randomized to receive, on separate treatment days, a single dose of either 3 PTL401 soft gelatin capsules containing a total of 10.8-mg THC and 10-mg CBD (each capsule contained 3.6-mg THC and 3.3-mg CBD) or 4 actuations of oromucosal spray (2 under the tongue and 2 inside the cheek, each 100-μL spray contained 2.7-mg THC and 2.5-mg CBD, total per administration: 10.8-mg THC and 10-mg CBD). There was a washout period of 7 days between each dosing event. Eligible subjects were admitted to the CRC in the evening before each study drug administration and remained in-house under medical supervision for 24 h after dosing. Following an overnight fast of at least 10 h, the subjects received a standard meal within 30 min prior to dosing. The subjects were monitored for safety, and adverse events (AEs) were recorded throughout the study duration. An end-of-study/safety follow-up visit took place 7-10 days after the last dose of study treatment. Concomitant medications used by the subjects during the study were recorded.

Assessments

Pharmacokinetics

Blood samples for THC, 11-OH-THC, and CBD analysis (4 mL each, collected in lithium heparin tubes) were drawn over 24 h after each administration, at the following time points: predose (within 60 min before dosing), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 8, 12, and 24 h postdose. Plasma was separated following centrifugation and sent frozen at −20°C to ABS Laboratories Ltd. (Welwyn Garden City, UK).

Samples (200 mL) and internal standard were extracted by a liquid-liquid extraction procedure and liquid chromatography-tandem mass spectrometry assay (quantification was by peak area ratio). All samples for a given subject were analyzed in duplicates as a single batch. Calibration standards ranging from 0.1 to 100 ng/mL and quality control samples at concentration of 0.3, 5, and 80 ng/mL were used. Values that were below the limits of quantitation were treated as zero.

The PK parameters were calculated using SAS®, version 9.4, software (SAS Institute, Cary, NC). The following parameters were derived from the time-concentration data: maximum plasma concentration (C_{max}), time to reach maximum concentration (T_{max}), terminal elimination rate constant (λ_z), area under the curve to the last measurable concentration ($AUC_{0\text{-}t}$) calculated by the linear trapezoidal rule, the area under the curve to infinite time ($AUC_{0\text{-}inf}$) calculated as: $AUC_{0\text{-}t} + C_{last}/\lambda_z$ (C_{last} being the last measurable concentration) and apparent terminal elimination half-life time ($t_{½}$), defined as $0.693/\lambda_z$.

Safety

AEs were recorded throughout the study period. Vital signs (systolic and diastolic blood pressure, heart rate, and respirations) were measured at screening and monitored during each 24 h in-house session at predose and 1, 4, 12, and 24 h after dosing and at the end-of-study visit. A physical examination was performed before each dosing session, before discharge from the CRC and at the end-of-study visit. An oral examination was performed before the spray administration, before discharge from the clinical research center and at the end-of-study visit. A 12-lead ECG and safety laboratory evaluations were performed at screening and at the end-of-study visit.

Statistical Analysis

The sample size selected was 15 healthy male volunteers. This number was not calculated based on statistical assumptions but was deemed adequate for descriptive statistics. The subjects were randomized using a balanced incomplete block design. Randomization was performed by the study statistician programmed in SAS® V9.4 statistical software (SAS Institute).

The safety analysis set included all subjects who received at least one administration of the study drugs (exposed population), including subjects prematurely withdrawn. The PK analysis set included all subjects with no major deviations related to study drug intake.

Statistical analyses were performed using SAS® V9.4. Baseline values were defined as the last valid value before first study drug administration. All statistical analyses were descriptive in nature. Continuous variables were summarized by count, mean, SD, minimum, median, and maximum and categorical variables by count and proportion. Confidence intervals (CIs), where relevant, are 2 sided with a confidence level of 90%, unless otherwise stated. The number and percentage of subjects with at least 1 AE were

Table 1
Particle Size Measurements of PNL401 at Various Media Simulating Intestinal Fluid (Mean ± SD)

Medium	Size (nm)	PDI
Simulated gastric fluid Fasting conditions pH 1.2	33.70 ± 1.00	0.2 ± 0.0
Simulated gastric fluid Fed conditions pH 4.5	30.80 ± 0.40	0.1 ± 0.0
Simulated intestinal fluid pH 6.8	30.10 ± 1.60	0.2 ± 0.0

Table 2
Baseline Demographic of Participants ($N = 15$)

Demographic	Mean (SD)	Median	Min, Max
Age (y)	30.7 (7.2)	32.4	19.3, 42.8
Body mass index (kg/m^2)	24.8 (2.0)	24.8	21.5, 29.9
Gender *n* (%)	Male 15 (100%)		
Race *n* (%)	Caucasian 15 (100%)		

summarized by drug and overall. A full listing of AEs was also summarized. Vital signs (including change from baseline) were summarized in relation to treatment, with descriptive statistics for the safety population.

PK parameters of THC, 11-OH-THC, and CBD were summarized by number of observations, arithmetic and geometric means, SD, standard error, coefficient of variation (CV %), median, minimum, and maximum, for each of the treatments administered. PK calculations were based on individual plasma concentrations of the blood samples. Plasma concentrations below the lower limit of quantification at early time points were treated as zero. Concentrations below the lower limit of quantification appearing in the terminal samples time points were omitted from the analysis. Before the analyses described in the following section, PK parameter values of C_{max}, t_{max}, and AUC_{0-t} were log transformed. For each of the PK parameters C_{max}, t_{max}, AUC_{0-t} individually, and for THC, 11-OH-THC, and CBD, the difference between ways of administration was assessed with a linear mixed-effects model: Parameter = Sequence + subject (Sequence) + Period + way of administration + Error with fixed terms for ways of administration, period, and sequence, and a random term for subject nested within sequence. The adjusted means (least squares means) of the differences between all relevant pairs of ways of administration and 2-sided 90% CI were calculated from the fitted model.

Results

Particle Size Measurement

The results of particle size measurement and PDI following dispersion in the various aqueous media are shown in Table 1. Particle size of PTL401 was approximately 30 nm with PDI of 0.1-0.2 in the mediums tested *in vitro*.

Demographics and Subject Disposition

Of the 15 eligible subjects, one withdrew prematurely due to reasons unrelated to study treatments. All subjects were Caucasian males, with no significant medical history, and were considered healthy based on screening assessments. Demographic characteristics are summarized in Table 2.

Pharmacokinetics

PK data were collected from 14 subjects who completed the study. The individual predose concentrations of THC, CBD, and 11-OH-THC in all subjects, and all treatments were zero. Mean plasma concentrations of THC, CBD, and 11-OH-THC over time are presented in Figure 1. PK parameters, statistical analysis, and relative bioavailability are provided in Tables 3 and 4. Despite substantial interindividual variability, there are several distinctive features that can still emerge from the compiled data. Time to C_{max} (t_{max}) was shorter following PTL401 administration, for both CBD and THC (1.25 vs. 3.5 h). Since the CIs of the ratios did not include 1 (0.3-0.6, Table 4), it could be claimed that PTL401 has significantly shorter t_{max} than the reference spray. The initial peaks following the spray administration were detected 30 min later than those generated after PTL401 ingestion. Following PTL401 administration, it was evident that higher concentrations of CBD and THC were maintained for a longer period of time. C_{max} of both THC and CBD was also approximately 1.6-fold higher when compared to the equivalent doses of the oromucosal spray. The ratio's CIs did not include 1 (Table 3), and therefore, it could be claimed that PTL401 has significantly higher C_{max} levels than the reference spray. The same claim applies to the AUC levels. The relative bioavailability of CBD and THC, calculated from the AUC ratios, was 31% and 16% higher, respectively, following the oral administration. The bioavailability is significantly greater than 100% as the lower confidence limit is greater than 100%. The active 11-OH-THC metabolite concentrations were detected shortly after THC, and the same ratio of AUC and C_{max} was maintained.

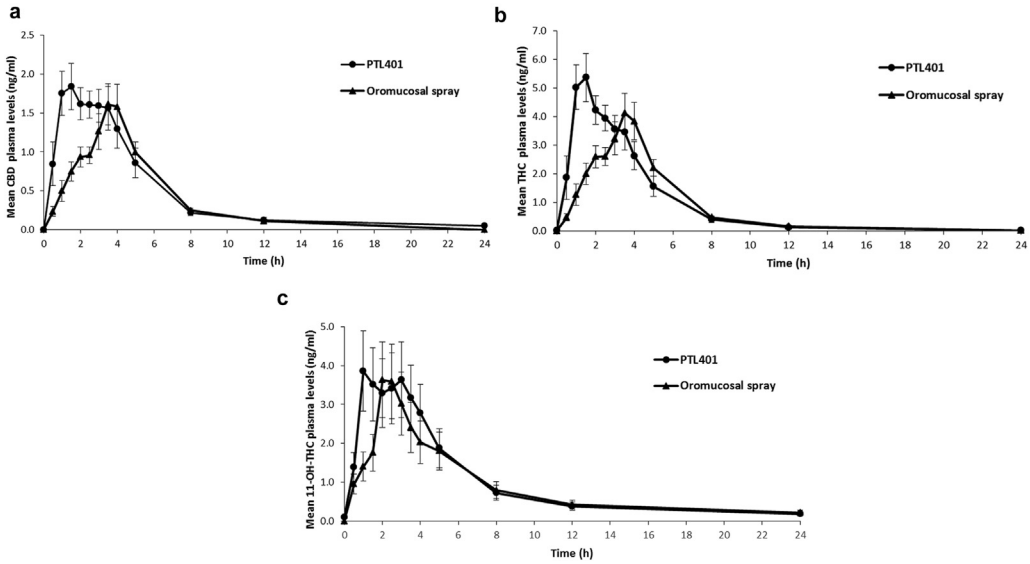

Figure 1. Plasma concentration over time curves for (a) CBD, (b) THC, and (c) 11-OH-THC following a single-dose administration of PTL401 (10-mg CBD, 10.8-mg THC) and oromucosal spray (10-mg CBD, 10.8-mg THC). Mean ± SEM, $N = 14$.

Table 3
PK Parameters of CBD, THC, and 11-OH-THC After Administration of Single Doses of PTL401 (10-mg CBD; 10.8-mg THC) and Reference Oromucosal Spray (10-mg CBD; 10.8-mg THC) ($N = 14$)

Analyte	Treatment	Statistical Variables	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0\text{-}t)}$ (ng/mL × h)	$AUC_{(0\text{-}inf)}$ (ng/mL × h)	λ_Z (h^{-1})	$t_{½}$ (h)
CBD	PTL401	Mean (SD)	2.94 (0.733)	1.64 (1.184)	9.85 (4.465)	10.52 (4.533)	0.29 (0.173)	3.21 (1.617)
		SEM	0.196	0.316	1.193	1.212	0.046	0.432
		Median (range)	2.93 (1.20-4.03)	1.25 (0.50-4.00)	8.90 (2.93-17.96)	9.46 (3.36-18.75)	0.24 (0.12-0.67)	2.94 (1.03-5.79)
		CV%	24.96	72.05	45.33	43.08	59.66	50.31
	Spray	Mean (SD)	2.05 (1.102)	3.18 (1.137)	7.30 (2.857)	7.81 (2.809)	0.33 (0.093)	2.31 (0.719)
		SEM	0.295	0.304	0.763	0.751	0.025	0.192
		Median (range)	1.73 (0.57-4.27)	3.50 (1.00-5.00)	7.35 (3.10-13.51)	7.75 (3.90-14.00)	0.32 (0.17-0.53)	2.21 (1.31-4.01)
		CV%	53.83	35.77	39.13	35.96	28.58	31.14
THC	PTL401	Mean (SD)	7.57 (2.041)	1.50 (1.019)	20.38 (7.253)	20.99 (7.311)	0.41 (0.108)	1.83 (0.621)
		SEM	0.545	0.272	1.938	1.954	0.029	0.166
		Median (range)	7.70 (3.75-10.60)	1.25 (0.50-4.00)	21.31 (8.36-30.66)	21.71 (9.99-31.38)	0.41 (0.20-0.61)	1.69 (1.13-3.49)
		CV%	26.95	67.94	35.59	34.82	26.21	33.97
	Spray	Mean (SD)	5.21 (2.640)	3.25 (0.826)	17.54 (6.633)	18.01 (6.676)	0.39 (0.103)	1.93 (0.776)
		SEM	0.705	0.221	1.773	1.784	0.028	0.207
		Median (range)	4.27 (1.82-9.70)	3.50 (1.50-4.00)	17.39 (7.49-31.49)	17.87 (8.28-32.29)	0.39 (0.16-0.61)	1.79 (1.13-4.38)
		CV%	50.65	25.42	37.82	37.06	26.21	40.33
11-OH-THC	PTL401	Mean (SD)	6.59 (3.478)	2.21 (1.014)	32.07 (21.690)	33.63 (22.583)	0.19 (0.054)	3.92 (1.031)
		SEM	0.93	0.271	5.797	6.036	0.014	0.276
		Median (range)	5.64 (3.38-16.90)	2.00 (1.00-4.00)	28.94 (15.60-101.43)	29.76 (16.64-105.34)	0.17 (0.11-0.30)	4.07 (2.35-6.06)
		CV%	52.76	45.78	67.63	67.16	28.4	26.31
	Spray	Mean (SD)	4.71 (3.449)	3.43 (1.138)	28.28 (19.862)	30.04 (21.042)	0.19 (0.057)	4.04 (1.094)
		SEM	0.922	0.304	5.308	5.624	0.015	0.292
		Median (range)	3.98 (1.87-15.00)	3.50 (1.50-5.00)	27.04 (9.21-80.93)	28.60 (10.11-85.45)	0.16 (0.12-0.30)	4.24 (2.34-5.65)
		CV%	73.27	33.16	70.23	70.04	30.67	27.10

SEM, standard error of the mean; C_{max}, maximum observed plasma concentration; t_{max}, time to C_{max}; $t_{½}$, terminal elimination half-life; $AUC_{0\text{-}t}$, area under the plasma concentration-time curve from time zero to the last measurable concentration; $AUC_{0\text{-}inf}$, area under the plasma concentration-time curve from time zero to infinity; λ_Z, terminal elimination rate constant.

Safety and Tolerability

A summary of treatment-emergent AEs (TEAEs) is presented in Table 5. All TEAEs were mild in severity and resolved spontaneously without treatment or sequel. Headache was the most frequently reported AE and its causality was considered as "possibly related to study drug" in one subject (7.1%) after receiving PTL401 and 2 subjects (14.2%) after receiving the spray. A very mild elevation in creatine kinase levels was noted in one subject who received the spray. The possible causality could not be ruled out. No clinically significant findings were noted on physical examination, vital signs, ECG recordings, and other safety laboratory tests.

Discussion

The PK parameters of the oromucosal spray, derived from this study, resemble available data from previous reports.[28-30]

The proposed mechanism, by which PTL401 displays a substantially more favorable PK profile than expected from oral exposure of cannabinoids, has been described in the Introduction. THC undergoes extensive and rapid metabolism by the cytochrome P450 system (CYP2C9 and CYP3A4), to an equipotent 11-OH-THC derivative which is further transformed to the inactive 11-nor-9-carboxy-THC (THC-COOH).[17,31] The total production of the active 11-OH-THC metabolite, as expressed by its AUC, was apparently higher following PTL401 administration, consistent with the higher THC levels. 11-OH-THC is the most important psychotropic metabolite of Δ^9-THC, with a similar spectrum of actions or maybe even more potent than THC.[6] It is noteworthy that its elimination half-life was 2-fold longer than THC following both administrations.

As anticipated from the preclinical data, the total amount of the THC and CBD that was actually absorbed through the GI mucosa was higher than expected from oral administrations.[25] The formation of nanoparticles was tested in 3 mediums that are commonly used for simulating the GI tract. Particle size of PTL401 was about 30 nm in all the mediums tested, indicating that there was no effect of pH on the cannabinoids' nanoparticle formation, and therefore, the formulation can probably be administered under

Table 4
Statistical Analysis of the PK Parameters of CBD, THC, and 11-OH-THC ($N = 14$)

Analyte	Treatment	C_{max} (ng/mL)	T_{max} (h)	$AUC_{(0\text{-}t)}$ (ng/mL × h)
Adjusted/least-squares means (90% CI)				
CBD	PTL401	2.84 (2.39-3.39)	1.31 (1.04-1.65)	8.72 (7.34-10.37)
	Spray	1.80 (1.51-2.15)	2.92 (2.31-3.69)	6.65 (5.59-7.91)
THC	PTL401	7.33 (6.32-8.50)	1.30 (1.03-1.65)	19.26 (16.74-22.16)
	Spray	4.73 (4.07-5.50)	3.17 (2.49-4.04)	16.67 (14.48-19.19)
11-OH-THC	PTL401	5.98 (4.45-8.03)	2.02 (1.66-2.45)	28.35 (20.61-38.99)
	Spray	4.07 (3.03-5.48)	3.24 (2.66-3.95)	23.87 (17.35-32.84)
Ratio to oromucosal spray (90% CI)				
CBD	PTL401	1.58 (1.26-1.97)	0.45 (0.33-0.61)	1.31 (1.11-1.55)
THC	PTL401	1.55 (1.25-1.92)	0.41 (0.30-0.56)	1.16 (1.03-1.30)
11-OH-THC	PTL401	1.47 (1.20-1.79)	0.62 (0.47-0.82)	1.19 (1.04-1.35)
Relative bioavailability PTL401/oromucosal spray (%) (90% CI)				
CBD	131% (111.0%-155.1%)			
THC	116% (102.6%-130.2%)			

Table 5
Summary of TEAEs ($N = 14$)

Type of TEAE	PTL401		Oromucosal Spray	
	No. of Events	No. of Subjects	No. of Events	No. of Subjects
Any TEAE	4	3	3	3
Mild	4	3	3	3
Moderate	0	0	0	0
Severe	0	0	0	0
Serious	0	0	0	0
Death	0	0	0	0
Possible causality	1[a]	1	3[b]	3
Leading to discontinuation	0	0	0	0

[a] Mild headache.
[b] Mild headache ($n = 2$), mild elevation of creatine phosphokinase ($n = 1$).

either fasting or fed conditions, although the former has not been tested in this study. The novel formulation offers both increased solubility in aqueous phase of poorly soluble mixture of THC and CBD and formation of homogenous nanodispersion, as indicated by the relatively low PDI value, 0.1-0.2.

The main limitations of this study were the small sample size of healthy young male volunteers and, as noted in many other PK cannabis trials, the substantial interindividual variability in PK parameters.[6,15-17,29] Obviously, the target population is of various age groups, includes women, is not healthy, and probably uses concomitant medications—some of which may affect the PKs of cannabinoids. Nevertheless, it appears that the bioavailability of the PNL formulation is at least within the same ranges of the oromucosal spray and, based on the current results, are possibly even higher.

Both the investigational and the reference formulations were well tolerated and safe, following a single dose. Since the compounds were administered only once to a small group of healthy, young, male volunteers, potentially undesirable effects emerging after repeated treatments[32] might have been masked. The positive PK results support further clinical investigations of PTL401 for specific patient populations and therapeutic indications.

One of the shortcomings of repeated oromucosal sprays is the undesirable local effect induced by the excipients: oral discomfort or pain, dry mouth, glossodynia, and mouth ulceration. This may compromise patient adherence, especially when long-term treatment is required.[33,34] These local reactions were not apparent in the current study. An oral formulation, which assures substantial and rapid absorption of the active components without causing local discomfort, may be an attractive alternative to patients who prefer this mode of administration.

Conclusions

The self-nanoemulsifying oral drug delivery system of PTL401 is a safe, effective, and convenient delivery platform for both CBD and THC. Despite the study limitations, this formulation appears to possess several advantages over of the reference oromucosal spray: a faster rate of absorption, improved bioavailability, and lack of potential application site type reactions following chronic administration. PTL401 may offer a quicker onset of action and probably decreased dosing frequency, thus contributing to patient adherence. A subsequent larger scale clinical development program in which CBD and THC doses are adapted for various therapeutic indications is currently being launched.

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