Single-Dose Pharmacokinetics of Oral Cannabidiol Following Administration of PTL101: A New Formulation Based on Gelatin Matrix Pellets Technology

Jacob Atsmon¹, Daphna Heffetz², Lisa Deutsch³, Frederic Deutsch³, and Hagit Sacks²

Abstract
Cannabidiol (CBD) is the main nonpsychoactive component of the cannabis plant. It has been associated with anti-seizure, antioxidant, neuroprotective, anxiolytic, anti-inflammatory, antidepressant, and antipsychotic effects. PTL101 is an oral gelatin matrix pellets technology–based formulation containing highly purified CBD embedded in seamless gelatin matrix beadlets. Study objectives were to evaluate the safety and tolerability of PTL101 containing 10 and 100 mg CBD, following single administrations to healthy volunteers and to compare the pharmacokinetic profiles and relative bioavailability of CBD with Sativex oromucosal spray (the reference product) in a randomized, crossover study design. Administration of PTL101 containing 10 mg CBD, led to a 1.7-fold higher Cmax and 1.3-fold higher AUC compared with the oromucosal spray. Tmax following both modes of delivery was 3–3.5 hours postdosing. CBD exhibited about a 1-hour lag in absorption when delivered via PTL101. A 10-fold increase in the dose resulted in an ~15-fold increase in Cmax and AUC. Bioavailability of CBD in the 10-mg PTL101 dose was 134% relative to the reference spray. PTL101 is a pharmaceutical-grade, user-friendly oral formulation that demonstrated safe and efficient delivery of CBD and therefore could be an attractive candidate for therapeutic indications.

Keywords
cannabidiol, cannabinoids, pharmacokinetics, oral drug delivery

The use of cannabinoids for medical purposes has drawn increasing interest in recent years.¹–³ The cannabis plant contains numerous ingredients with pharmacological activities,⁴ and it is often difficult to isolate particular compounds that exert a unique therapeutic effect on specific medical conditions. Nevertheless, 2 major cannabinoids, cannabidiol (CBD) and delta-9-tertahydrocannabinol (THC) have become the main focus of clinical research and development activity.

Unlike THC, CBD does not possess psychoactive effects. It has low affinity to the CB1 (neuronal) and CB2 (found mainly in the body’s immune system) receptors. Apparently CBD acts on other signaling systems that are involved in its pharmacological activity.⁴ In vitro and in vivo preclinical research has shown that CBD has several potential effects on therapeutic applications: it possesses antiseizure, antioxidant, neuroprotective, anti-inflammatory, analgesic, antitumor, antiemetic, antipsychotic, and antianxiety activities.⁵,⁶ Case reports and randomized clinical trials also suggest that CBD may be effective in treating epilepsy, particularly in children.⁷–¹⁰ In fact, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have granted CBD preparations the “orphan drug” designation for use in the treatment of epilepsy in children (Dravet and Lennox-Gastaut syndromes) and neonatal asphyxia. Moreover, CBD has also been investigated in small-scale clinical trials in patients with psychotic symptoms¹¹,¹² and

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It appears to be safe in humans and animals. Side effects that lead to cases of patient withdrawal from CBD treatment were reported when it was administered at relatively high doses (up to 50 mg/kg/day). The most common ones (occurring in more than 10% of CBD-treated patients) were somnolence, diarrhea, decreased appetite, fatigue, pyrexia, vomiting, lethargy, upper respiratory tract infection, and convulsions. 

One of the main drawbacks in many efficacy clinical trials with cannabinoids is that the available products are not manufactured under conditions of Good Manufacturing Practice that safeguard their quality and reproducibility, because they are not considered regulated medications. Only very few cannabis-based medications manufactured under stricter standards, are currently marketed under regulatory approval. 

Medical cannabis is administered to patients either by smoking, vaporization, or buccal spray or by being consumed orally in the form of oil in soft capsules, oil drops, or cookies. The bioavailability of cannabinoids varies significantly by their mode of administration. The average bioavailability through smoking is in the range of 30%, whereas the oral route is even lower (approximately 5%) due to extensive first-pass metabolism.

Some of these delivery modalities are either associated with adverse effects following excessive use such as potential carcinogenic effects by smoking or mouth ulcers, dry mouth, aftertaste, and poor and variable absorption leading to overdose. 

The oral administration of cannabinoids has several advantages: it is easier to consume, dose and composition are more tightly controlled, exposure time is longer, and side effects are considerably less intense. 

An optimal oral dosage form having consistent delivery and high bioavailability is not yet available and is therefore warranted. 

Pellets have been used for many years as a multiparticulate dosage system for oral delivery of therapeutic agents. Pellets offer greater flexibility in the design and development of active ingredients placed within a functional coating that provides optimal drug-release properties. They can be filled in capsules, compressed in tablets, or mixed in suspensions. Pellets can be divided into desired dose strengths without formulation or process changes. When administered orally, pellets disperse freely throughout the gastrointestinal tract and have been shown to improve bioavailability and minimize local irritation of the gastrointestinal mucosa. 

PTL101 is an oral CBD formulation, manufactured using a unique proprietary gelatin matrix pellets (beads) technology, tailored to provide an oral, high-loading, flexible, room temperature–stable CBD preparation in a wide range of doses. CBD is bound to gelatin pellets without additional excipients or fill materials. The unique manufacturing process enables the formation of seamless homogenous beads. The pellets are packed in 2-piece acid-resistant capsules and can be administered as such or mixed with food for use in patients who have difficulty swallowing medications. The gelatin matrix is ready soluble at body temperature (within fewer than 30 minutes). In the aqueous environment of the gastrointestinal (GI) tract, the soluble gelatin enables dispersion of the lipophilic cannabidiol by producing a microemulsion in situ. The gelatin matrix pellets were designed to have maximal surface-to-volume ratio and distribute homogenously across the entire GI tract, thus providing a relatively constant GI transit time, while avoiding irritation of the gastric mucosa. Our working assumption was that this technology may improve the bioavailability of CBD. Relatively high bioavailability could result in decreased doses, decreased dosing frequency, and fewer side effects and altogether may encourage higher adherence. Therefore, the objective of the current study was to assess the bioavailability of CBD following administration of PTL101. CBD doses for various therapeutic targets have not yet been regulatory approved and may vary considerably. Therefore, 2 dose formulations were prepared for future clinical evaluation: one containing 10 mg and one containing 100 mg CBD. The pharmacokinetic (PK) profile was compared with the marketed oromucosal spray, which contains both THC (27 mg/mL) and CBD (25 mg/mL). The PK of the oromucosal spray is well established and may serve as a reliable reference to the novel CBD formulations.

Methods 

Materials 

The CBD used was derived from highly purified Cannabis sativa extract (>93% CBD, less than 0.2% THC). The extract was prepared by AiFame-AiLab GmbH, St. Gallen, Switzerland. PTL101 capsules were manufactured by Gelpell AG, St. Gallen, Switzerland.

Study Design and Procedures 

The study took place at the Clinical Research Center of the Tel Aviv Medical Center. It was approved by the hospital’s ethics committee and by the Israeli Ministry of Health prior to study initiation and was conducted in accordance with International Conference on Harmonisation-Good Clinical Practice guidelines and the Declaration of Helsinki. All subjects provided written informed consent before participating in the study. 

This was a single-center, open-label, randomized, comparative crossover single-dose study. In the same
study, 2 additional THC/CBD formulations, unrelated to the PTL101 capsules, were also tested against the reference oromucosal spray. The PK results of these preparations will be published separately.

On different treatment days, 15 healthy male volunteers were randomized to receive a single dose of either a 10-mg PTL101 capsule, a 100-mg PTL101 capsule (manufactured by Gelpell AG, St. Gallen, Switzerland), or 4 actuations of the spray (Sativex, GW Pharma Ltd., Salisbury, Wiltshire, UK), 2 under the tongue and 2 inside the cheek. Each 100-µL spray contains 2.7 mg THC and 2.5 mg CBD; the total dose per administration was 10.8 mg THC and 10 mg CBD. All subjects received all treatments. There was a washout period of 7 days between each dosing. Eligible subjects were admitted to the center in the evening before each study drug administration. Following an overnight fast of at least 10 hours, the subjects received a standard meal within 30 minutes prior to dosing. After receiving the drug, they remained in-house for 24 hours for PK blood collection and safety monitoring. An end-of-study/safety follow-up visit took place 7–10 days after the last study treatment. Adverse events (AEs) and concomitant medications used by the subjects were recorded throughout the duration of the study.

Subjects

Eligible subjects were 18- to 45-year-old healthy men with a body mass index of 19 to 30 kg/m² who had not smoked or used tobacco products for a period of at least 6 months before screening. Exclusion criteria included current or previous history of any significant medical disorders that might potentially increase the risk because of participation in the study; subjects who previously experienced adverse events associated with cannabis exposure or dependence, psychiatric disorders, fasting or recurrent dizziness, epilepsy/seizures, idiosyncratic reactions to any medication, the presence of mouth ulcerations or abnormalities in the oral cavity, and drug or alcohol abuse within the last 2 years. Individuals with a positive urine drugs-of-abuse test were not allowed to participate. Subjects who used prescription or over-the-counter medications, vitamins, and herbal or dietary supplements within 14 days of the first dosing session and/or used any known enzyme-altering agent within 30 days of the first dosing session were also excluded.

All volunteers underwent a screening procedure within 21 days before the first drug administration, in which medical history was documented, physical examination was performed, and an electrocardiogram (ECG) was recorded. Safety laboratory tests — blood chemistry, complete blood count, serology for HIV, hepatitis B, and hepatitis C, and urinalysis — were performed.

Subjects agreed to refrain from caffeine/xanthine-containing products as well as grapefruit and alcoholic beverages during in-house dosing PK periods.

Assessments

Pharmacokinetic Analyses. Blood samples (4 mL each, collected in lithium heparin tubes) were collected for PK analysis at the following times after each drug administration: predose (within 60 minutes before dosing), 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 5, 8, 12, and 24 hours postdose. The PK parameters were calculated using SAS version 9.4 software (SAS Institute, Cary North Carolina). The following parameters were derived from the time–concentration data: maximum plasma concentration (Cmax), time to reach maximum concentration (Tmax), terminal elimination rate constant (λz), area under the curve to the last measurable concentration (AUC0–t), area under the curve to infinite time (AUC0–inf) calculated as AUC0–t + Clast/λz, area under the curve to the last measurable concentration, and apparent terminal elimination half-life time (t1/2), defined as 0.693/λz.

Bioanalytical Methods and Validations. All samples from a given subject were extracted and analyzed in a single batch. The calibration range of the assay was 0.1 to 100 ng/mL. Each batch contained duplicate calibration standards at 0.1, 0.25, 1.0, 2.5, 10.0, 25.0, 50.0, and 100.0 ng/mL and duplicate quality control samples (QCs) at 0.3, 5.0, and 80 ng/mL. Aliquots of human plasma (200 µL) were spiked with CBD-d3 as the internal standard and subjected to liquid/liquid extraction using 450 µL of a 7:1 v/v hexane/ethyl acetate mixture. After mixing and centrifugation, the hexane/ethyl acetate was transferred to a second 96-well plate and evaporated to dryness under nitrogen. The samples were then reconstituted in 120 µL of 1:1 acetonitrile/water. A 50-µL volume was injected on to an Agilent Zorbax SB-C18 2.1 × 50 mm 1.8-µm UPLC column at 40°C using a flow rate of 0.4 mL/min of 0.1% (v/v) formic acid in 70:30 methanol:water. The samples were separated by reverse-phase chromatography using a gradient with 0.1% (v/v) formic acid in 80:20 methanol:acetonitrile on a Jasco XLC system. The samples were ionized using Turboionspray at 5000 V in the positive ion mode on an AB Sciex 4000 triple quadrupole. The multiple reaction ions monitored for CBD and CBD-d3 were m/z 315.4 > 193.2 and 318.4 > 196.2, respectively. All calibration standards and QCs analyzed during the support of this study met the acceptance criteria of accuracy at the lower limit of quantification of within 100% ± 20% and accuracy at all other concentrations of within 100% ± 15%. The interbatch precision (CV%) and accuracy for the QCs from this study were 4.0% and 99.5%, respectively, at 0.3 ng/mL, 3.1% and 98.6%, respectively, at 5.0 ng/mL, and 3.3% and 97.3%, respec-
tively, at 80 ng/mL. The interbatch precision (CV%) and accuracy for the calibration standards from this study were 3.2% and 99.9%, respectively, at 0.10 ng/mL, 3.4% and 100.3%, respectively, at 0.25 ng/mL, 2.5% and 100.0%, respectively, at 1.00 ng/mL, 2.5% and 100.7%, respectively, at 2.50 ng/mL, 2.0% and 101.8%, respectively, at 10.0 ng/mL, 2.3% and 99.4%, respectively, at 25.0 ng/mL, 3.5% and 95.7%, respectively, at 50.0 ng/mL, and 2.3% and 102.7%, respectively, at 100 ng/mL. This method was validated following the FDA guidance for industry and the EMA guideline on bioanalytical method validation.

Safety Assessments. Adverse events were recorded throughout the study period. Vital signs (blood pressure, heart rate, and respiratory rate) were measured predose and 1, 4, 12, and 24 hours after each dosing. A physical examination was performed before each dosing and prior to discharge from the research unit. An oral examination was performed during the session, in which the spray was administered predose and before discharge from the research center.

Statistical Analysis. The sample size of 15 volunteers was not calculated based on statistical assumptions, but was considered adequate for the descriptive statistics required for the study. The subjects were randomized using a balanced incomplete block design using SAS V9.4 statistical software (SAS Institute, Cary, North Carolina).

Statistical analyses were performed using SAS V9.4 (SAS Institute, Cary, North Carolina). Baseline values were defined as the last valid value prior to first study drug administration. All statistical analyses were descriptive in nature. Continuous variables were summarized by a count, mean, standard deviation, minimum, median, and maximum and categorical variables by a count and proportion. Confidence intervals, where relevant, were 2-sided with a confidence level of 90%, unless otherwise stated.

Safety Analysis. The safety analysis set included all subjects who were dosed at least once.

Pharmacokinetic Analysis. The PK analysis set included all subjects with no major deviations related to study drug intake. Pharmacokinetic parameters of CBD were summarized by number of observations, arithmetic and geometric means, standard deviation (SD), standard error (SE), coefficient of variation (CV %), median, minimum, and maximum for each of the treatments administered. Pharmacokinetic calculations were based on individual plasma concentrations of the blood sampling. Samples with plasma concentrations below the lower limit of quantification (LLOQ) at early times were treated as zero. Plasma concentrations below the LLOQ appearing in the terminal samples were omitted from the analysis. The PK parameters described above were estimated for each subject based on plasma CBD concentrations. Prior to analyses described below, PK parameter values of C\text{max}, T\text{max}, and AUC\text{t} were log-transformed. For each of the PK parameters C\text{max}, T\text{max}, and AUC\text{t} individually, 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 (LS means) of the differences between all relevant pairs of ways of administration and 2-sided 90% confidence intervals were calculated from the fitted model.

Results

Subject Disposition and Demographics
Of the 15 subjects enrolled in the study, 13 received all 3 administrations, 1 received 2 treatments, and 1 subject was dosed only once — for reasons unrelated to adverse events. The demographic characteristics of the subjects enrolled in the study are described in Table 1.

Safety
In general, all formulations were considered safe and tolerable. No AE was considered serious, and none resulted in withdrawal of a subject from the trial. Headache was the most frequently reported AE (14%–21%). All AEs resolved spontaneously without sequel. No clinically significant abnormalities in vital signs, ECG recordings, physical findings, or safety laboratory tests were noted.

Pharmacokinetics
Pharmacokinetic parameters were derived from data compiled per administration (ie, n in Tables 2 and 3 represents the number of subjects who received the same formulation). Mean plasma CBD concentrations-versus-time curves, administered either as a PTL101-10-mg capsule or equivalent dose as the oromucosal spray, are presented in Figure 1. Comparison of PTL101-10 mg to PTL101-100 mg is presented in Figure 2. PK parameters, statistical data, and relative bioavailability data are summarized in Tables 2 and

<table>
<thead>
<tr>
<th>Table 1. Demographic Characteristics</th>
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<tr>
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<tr>
<td>Age (y), mean (range)</td>
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<tr>
<td>BMI (kg/m²), mean (range)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
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<td>History of tobacco use, n (%)</td>
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</table>

BMI, body mass index.
Table 2. Summary of Plasma Pharmacokinetic Parameters of CBD (n = 14)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUC0–t (ng·h/mL)</th>
<th>AUC0–inf (ng·h/mL)</th>
<th>T1/2 (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTL101-10 mg</td>
<td>3.22 (1.277)</td>
<td>3.00 (2.00–4.00)</td>
<td>9.64 (3.987)</td>
<td>10.31 (4.137)</td>
<td>2.95 (2.576)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>39.62%</td>
<td>22.67%</td>
<td>41.37%</td>
<td>40.14</td>
<td>87.38%</td>
</tr>
<tr>
<td>PTL101-100 mg</td>
<td>47.44 (20.137)</td>
<td>3.50 (1.50–5.00)</td>
<td>149.54 (34.335)</td>
<td>153.04 (34.698)</td>
<td>3.59 (0.256)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>42.35%</td>
<td>31.79%</td>
<td>22.96%</td>
<td>22.67%</td>
<td>7.13%</td>
</tr>
<tr>
<td>Oromucosal spray</td>
<td>2.05 (1.102)</td>
<td>3.50 (1.00–5.00)</td>
<td>7.30 (2.857)</td>
<td>7.81 (2.809)</td>
<td>2.31 (0.719)</td>
</tr>
<tr>
<td>CV (%)</td>
<td>53.83%</td>
<td>35.77%</td>
<td>39.13%</td>
<td>35.96%</td>
<td>31.14%</td>
</tr>
</tbody>
</table>

Data are presented as the arithmetic mean (SD), with the exception of Tmax, for which the median (range) is presented. CV, coefficient of variance (%).

Table 3. Statistical Analysis of the Pharmacokinetic Parameters of CBD (n = 14)

<table>
<thead>
<tr>
<th></th>
<th>Cmax (ng/mL)</th>
<th>Tmax (h)</th>
<th>AUC0–t (ng·h/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTL101-10 mg</td>
<td>2.97</td>
<td>2.97</td>
<td>8.89</td>
</tr>
<tr>
<td></td>
<td>(2.50–3.54)</td>
<td>(2.35–3.75)</td>
<td>(7.49–10.55)</td>
</tr>
<tr>
<td>PTL101-100 mg</td>
<td>43.42</td>
<td>3.45</td>
<td>144.77</td>
</tr>
<tr>
<td></td>
<td>(36.47–51.69)</td>
<td>(2.73–4.36)</td>
<td>(121.76–172.14)</td>
</tr>
<tr>
<td>Oromucosal spray</td>
<td>1.80</td>
<td>2.92</td>
<td>6.65</td>
</tr>
<tr>
<td></td>
<td>(1.51–2.15)</td>
<td>(2.31–3.69)</td>
<td>(5.59–7.91)</td>
</tr>
<tr>
<td>Ratio (90%CI)</td>
<td>1.65</td>
<td>1.02</td>
<td>1.34</td>
</tr>
<tr>
<td>PTL101-10 mg/oromucosal spray</td>
<td>(1.32–2.06)</td>
<td>(0.75–1.38)</td>
<td>(1.13–1.59)</td>
</tr>
<tr>
<td>PTL101-100 mg/oromucosal spray</td>
<td>24.07</td>
<td>1.18</td>
<td>21.78</td>
</tr>
<tr>
<td></td>
<td>(19.30–30.04)</td>
<td>(0.88–1.60)</td>
<td>(18.45–25.72)</td>
</tr>
<tr>
<td>Relative bioavailability (90%CI)</td>
<td>133.8</td>
<td>1.58</td>
<td>134%</td>
</tr>
<tr>
<td>PTL101-10 mg/oromucosal spray</td>
<td>(112.8–158.5)</td>
<td>(112.8–158.5)</td>
<td>(112.8–158.5)</td>
</tr>
</tbody>
</table>

Adjusted/least-squares mean (90%CI). CI, confidence interval.

3. There was substantial variability among the dosed subjects. Mean CBD Cmax following PTL101 administration was 1.7-fold higher for the 10-mg dose and 24.1-fold higher for the 100-mg dose, compared with the reference spray. Tmax occurred 3–3.5 hours following all administrations, although plasma levels for the oral PTL101 drugs were detected later (lag of ~1.0 hour) than the oromucosal spray (0.5 hours). There was an apparent 1.3-fold increase in mean AUC0–24h of the PTL101-10 mg and 21.8-fold increase following the 100-mg dose, compared with the reference product. Thus, a dose-related increase between the 2 strengths of the oral formulations appears to exist. A 10-fold increase in the dose resulted in ~15-fold increase in mean Cmax and AUC (Tables 2 and 3). It is noteworthy that CBD was still detectable in the plasma 12 hours after PTL101-10 mg and the spray administrations and 24 hours after administration of the 100-mg PTL101 formulation. The elimination half-life of CBD was similar between the 10-mg PTL101 dose and the spray (mean of 2.3 vs 2.9, respectively, and median value of approximately 2 hours for both). It was longer following the higher, 100-mg, oral dose (mean and median of 3.6 hours). Bioavailability of the PTL101 (10 mg CBD dose) relative to the reference drug was 134% (Table 3).

Discussion

The PTL101 formulation demonstrated a considerably sound safety profile at the tested doses. Based on the descriptive statistics derived from the time–concentration data, several observations appear to stand out as significant despite the small sample size and interindividual variability. First, the bioavailability of the CBD 10-mg capsule appears to be higher than the same dose of the oromucosal spray (134%; 90%CI, 113%–159%). Second, exposure to CBD increased in a dose-proportional manner. A 10-fold increase in the dose resulted in a ~15-fold increase in mean Cmax and AUC (Tables 2 and 3). This observation may need to be confirmed in a larger-scale pharmacokinetic study with additional interim doses within a wider range (eg, 10, 50, 100, 150, and 200 mg). The observed variability among the dosed subjects is similar to that previously reported in case of oral cannabinoid delivery administered with or without food.21,22,34 Plasma CBD levels peaked following both modes of delivery 3–3.5 hours postdosing. CBD
Figure 1. Plasma concentration-over-time curves for CBD from subjects who received a single dose of PTL101 (containing 10 mg CBD) and oromucosal spray (at a total dose of 10 mg CBD). Mean ± SEM, n = 14.

Figure 2. Plasma concentration-over-time curves for CBD from subjects who received a single dose of PTL101-10 and PTL101-100 (containing 10 and 100 mg CBD, respectively). Mean ± SEM, n = 14.

exhibited a ∼1-hour lag in absorption when delivered via PTL101 (Figure 1) as expected from the acid-resistance capsule used for encapsulating the PTL101’s beads.

$C_{\text{max}}$, $T_{\text{max}}$, and AUC$_{0\text{–}t}$ of CBD from the spray in our study (1.79 ng/mL, 3.18 hours, and 6.77 ng·h/mL, respectively) were in the same range as the values in a previous PK study with a similar dose.$^{23}$

The elimination of cannabinoids from plasma has been previously reported to be biexponential, with an initial half-life of 1–6 hours and a terminal elimination half-life ranging from 24 to 36 hours or longer. The graphs in our study follow a similar pattern. Cannabinoids are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination.
half-life. In our study the drugs were administered under fed conditions that are recommended for consumption of PTL101. Food may have an effect on the rate and extent of absorption.

CBD bioavailability following a single administration of the test formulation was substantially higher than the reference. Indeed, the results from the small sample size of healthy young male volunteers do not necessarily reflect the target population, which may also include women and patients (young and elderly) with various comorbidities using concomitant medications and chronic administration. Nevertheless, we can assume that PTL101 is a reasonable candidate for oral use in patients, allowing lower doses that will potentially decrease the occurrence of adverse reactions and increase adherence, especially when a high dose and chronic use of CBD are required to attain an optimal therapeutic effect.

Declaration of Conflicting Interests
Jacob Atsmon, MD, has no conflicts to disclose. Daphna Heffetz, PhD, and Hagit Sacks, PhD, are employees of PhytoTech Therapeutics. Lisa Deutsch, PhD, has no conflicts to disclose. Frederic Deutsch, has no conflicts to disclose.

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