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The safety, tolerability, and effectiveness of PTL-101, an oral cannabidiol formulation, in pediatric intractable epilepsy: A phase II, open-label, single-center study

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ABSTRACT

Introduction: Several works have reported on the antiepileptic impact of cannabis-based preparations in patients with treatment-resistant epilepsy (TRE). However, current formulations suffer from low bioavailability and side effects. PTL-101, an oral formulation containing highly purified cannabidiol (CBD) embedded in seamless gelatin matrix beadlets was designed to enhance bioavailability and maintain a constant gastrointestinal transit time.
Methods: This phase II, prospective study was open to pediatric patients with TRE on stable antiepileptic drugs' (AEDs) doses, who experienced ≥4 seizures within four weeks of enrolment and with a history of ≥4 AEDs failing to provide seizure control. Following a 4-week observation period, patients began a 2-week dose-titration phase (up to ≤25 mg/kg or 450 mg, the lower of the two), followed by a 10-week maintenance treatment period. Caregivers recorded seizure frequency, type, and severity and ranked their global impressions after 7 and 12 weeks of treatment. Responders were those showing a ≥50% reduction from baseline monthly seizure frequency. Safety assessments monitored vital signs, adverse effects, physical and neurological exams, and laboratory tests.
Results: Sixteen patients (age: 9.1 ± 3.4) enrolled in the study; 11 completed the full treatment program. The average maintenance dose was 13.6 ± 4.2 mg/kg. Patient adherence to treatment regimens was 96.3 ± 9.9%. By the end of the treatment period, 81.9% and 73.4 ± 24.6% ($p < 0.05$) reductions from baseline median seizure count and monthly seizure frequency, respectively, were recorded. Responders' rate was 56%; two patients became fully seizure-free. By study end, 8 (73%) caregivers reported an improved/very much improved condition, and 9 (82%) reported reduced/very much reduced seizure severity. Most commonly reported treatment-related adverse effects were sleep disturbance/insomnia, (4 (25.0%) patients), followed by somnolence, increased seizure frequency, and restlessness (3 patients each (18.8%)). None were serious or severe, and all resolved.
Conclusions: PTL-101 was safe and tolerable for use and demonstrated a potent seizure-reducing effect among pediatric patients with TRE.
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1. Introduction

Epilepsy encompasses a wide range of chronic syndromes characterized by recurrent, unprovoked, and unpredictable seizures. The disease is estimated to affect over 65 million people worldwide, including approximately 0.6% of children under the age of 18 [1], 82% of whom will be under the age of 10 [2]. Treatment-resistant epilepsy (TRE), defined as failure to achieve sustained seizure remission after appropriate calibration of at least two antiepileptic drugs (AEDs), affects approximately 30% of patients with epilepsy [3]. Apart from the severe morbidity and significantly increased mortality among patients with TRE [4,5], early onset comes along with high incidence of cognitive, behavioral, motor, and neurodevelopmental delays [6].

Since ancient times, the *Cannabis sativa* and *Cannabis indica* plants have been exploited for their potent therapeutic effects, including in seizure control [7]. Of their >80 expressed cannabinoids, Δ^9-tetrahydronannabinol (Δ^9-THC) and cannabidiol (CBD) have been characterized as the two major neuroactive components, with the former recently ascribed psychoactive effects and the latter, anticonvulsant and antiepileptiform activity [8–10]. Cannabidiol has been shown to both potentiate the therapeutic effects of Δ^9-THC and also diminish the undesirable effects of THC such as anxiety, panic, sedation, dysphonia, and

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tachycardia [11,12], which has intensified research efforts toward formulation of pure or highly enriched CBD preparations for the treatment of epilepsy and other neurological disorders [8,13]. In the first report of a randomized study assessing pure CBD, two of the four treated patients with epilepsy were seizure-free after a 3-month treatment phase, while placebo-treated patients showed no clinical changes [14]. In a two-phase, placebo-controlled pilot study testing CBD capsules (200–300 mg/day) as an add-on treatment in patients with refractory secondarily generalized epilepsy, treatment proved safe and well tolerated and reportedly brought to almost complete or partial seizure control in 7 of the 8 treated patients [15]. Similarly, in a retrospective, multicenter assessment of 74 pediatric patients with TRE treated with 1–20 mg/kg/day CBD-enriched cannabis oil (CBD:THC ratio of 20:1) for at least three months, a ≥50% reduction in seizure frequency was reported for 52% of the patients [16]. In parallel, reduced seizure frequency and improved behavior and alertness were noted in >50% of patients and improved language, communication, and motor skill in 25%. In a prospective, open-label, multicenter study assessing the impact of addition of oral CBD to antiepileptic regimens in 162 patients with severe TRE, Devinsky et al. [17] reported on reduced seizure frequency over the 12-week treatment period. More recently, Devinksy et al. [18] reported on a double-blind, placebo-controlled trial, in which patients with Dravet syndrome and drug-resistant seizures were treated with either 20 mg/kg/day oral CBD or with a placebo solution for 14 consecutive weeks. Active treatment was associated with 47.6% drop in the median monthly frequency of convulsive seizures, with 43% of the CBD-treated patients showing a ≥50% drop in convulsive seizure frequency and only 27% of the placebo-treated patients showing such responses.

To date, only a small number of cannabis-based drugs, in the form of oromucosal sprays, capsules, or oily solutions, have been approved for marketing or are in advanced stages of development. Current formulations have been associated with adverse events following –recurrent use, including lesions, mouth ulcerations, pain and soreness of the oral mucosa, dry mouth, and distinct aftertaste [19]. In addition, oral, oil-based CBD formulations tested in clinical trials have been associated with low bioavailability and erratic gastrointestinal (GI) uptake and subsequently variable pharmacokinetics [20], which often lead to administration of high doses directly associated with adverse effects and poor patient adherence. An optimal oral dosage form is not yet available because of the substantial “first pass” metabolic effect, which limits the oral bioavailability of cannabinoids to 6% [21,22].

PTL101, an oral CBD formulation, was manufactured using a proprietary gelatin matrix pellet technology developed to provide for oral, high-loading, excipient-free, cannabinoid-based preparations. The gelatin matrix is comprised of a 100% natural and digestible gelatin polymer that is readily soluble at body temperature. Thus, in the aqueous environment of the GI tract, this soluble gelatin polymer promotes dispersion of lipophilic cannabinoids, by producing a microemulsion in situ, which is expected to enhance bioavailability of the active ingredient (s) and to a relatively constant GI-transit time, while avoiding punctual irritation of gastric mucosa. Further, the maximized surface-to-volume ratio contributes to enhance bioavailability of PTL101 as demonstrated in a phase I pharmacokinetics study [23]. This phase II study assessed the safety and efficacy of oral administration of PTL101 as an add-on therapy in the treatment of intractable epilepsy among pediatric patients.

2. Material and methods

This phase II, open-label, single-center study was initiated following protocol approval by the Tel Aviv Sourasky Medical Center's ethics committee and was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonization and Good Clinical Practice guidelines. The trial was registered at clinicaltrials.gov (registration number: NCT02987114). Voluntary, informed consent was provided by the legal guardian of all patients, and patients were allowed to withdraw consent at any point throughout the study.

2.1. CBD capsules

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

2.2. Patient population

Pediatric (ages 2–15, inclusive) patients diagnosed as having TRE on stable doses of 1–4 AEDs for at least 4 weeks prior to study, who suffered from at least four clinically countable seizures (tonic, clonic, tonic–clonic in the form of partial seizures, partial seizures secondarily generalized or primary generalized, complex partial seizures, and drop attacks (tonic/atonic)) within 4 weeks of study entry, and with a history of at least four AEDs, including one trial of a combination of at least two such drugs, without successful seizure control, were eligible for inclusion in the study. Patients with vagal nerve stimulation had to be on a stable setting of for at least 6 months, and those on a special diet (ketogenic, high fat – low carbohydrate), had to be on a stable fat:carbohydrate ratio for at least 8 weeks prior to enrolment. Exclusion criteria included prior or current use of cannabis-based or synthetic cannabinoid preparations within 3 months of the study, unwillingness to abstain for use of cannabis-based or synthetic cannabinoid preparations throughout the study period, neurodegenerative or deteriorated neurological disease, history of psychiatric disorders, heart failure, psychotic/anxiety events, or illicit drug use.

2.3. Study design

Patients participated in a 4-week observation period, during which the legal guardian/caregiver recorded patient seizure frequencies. Those failing to provide a completed seizures' diary (at least 25 days with data) were considered screen failures and were withdrawn from the study. Patients then began a 2-week dose-titration period, in which an initial dose of 50 mg PTL101 was administered in clinic on the morning of the day 1. The subject remained in the clinic for 5–7 h after the first dosing for medical supervision. Throughout the titration period, the legal guardian/caregiver kept a diary of patient epilepsy seizure frequency and type. The legal guardian/caregiver was contacted on days 3, 7, and 10 (±2 days) of treatment during the dose-titration period, to determine the need for dose modifications. Dose elevations (at increments of 50 mg) were implemented in the evenings. When reaching a daily dose of 100 mg or more, drug was administered twice daily (BID), morning and evening, with the higher dose in the evening. A maximum dose of 25 mg/kg per day, or 450 mg/day, the lower of the two, was allowed. Patients were expected to reach a maintenance (stable) dose at the maximum, by the end of this titration period. After reaching a stable dose, defined at the discretion of the investigator as per patient response and adverse effects, patients were treated with the maintenance dose for 10 consecutive weeks, during which the legal guardian recorded all patient seizures and the patient visited the clinic in the first and fifth weeks (Fig. 1). Thereafter, treatment was tapered over a one-week period. The legal guardian/caregiver was contacted by phone during this week to assess the patient's status and again, by phone, during the following week, for a general follow-up.

2.4. Laboratory assessments

Before the observation period, vital signs were recorded, and physical and neurological examinations were performed. Before the first dose (day 1), and at the initiation (day 15) of and midway through (day 50) the maintenance treatment period, vital signs were measured, and

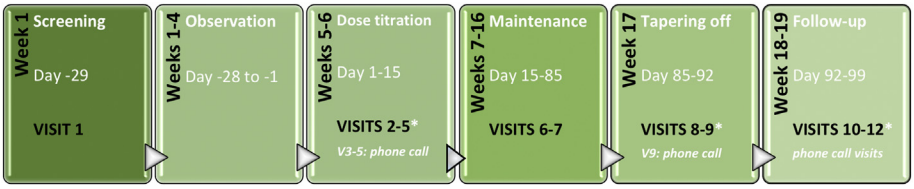

Fig. 1. Study treatment and assessment schedule. Patients were screened up to 29 days before initiation of the study. Eligible patients then participated in a 4-week observation period, during which the legal guardian/caregiver recorded patient seizure frequencies. Patients then began a 2-week dose-titration period (weeks 5–6). Throughout the titration period, the legal guardian/caregiver kept a diary of patient epilepsy seizure frequency and type. The legal guardian/caregiver was contacted on days 3, 7, and 10 of the dose-titration period, to determine the need for dose modifications. Patients were expected to reach a maintenance (stable) dose at the maximum, by the end of this titration period. Patients were then treated with the maintenance dose for 10 consecutive weeks, during which the legal guardian recorded all patient seizures and the patient visited the clinic in the first and fifth weeks. Thereafter, treatment was tapered over a one-week period. The legal guardian/caregiver was contacted by phone during this week to assess the patient's status and again, by phone, during the following week, for a general follow-up.

physical and neurological examinations were performed. In addition, blood and urine samples were collected at the screening and at the end of the treatment period, for performance of a battery of hematology, blood chemistry, and urine analyses. A 12-lead electrocardiogram (ECG) were also performed at these two visits. A standard electroencephalogram (EEG) was performed before drug treatment and once during the last five weeks of the maintenance treatment period.

2.5. Clinical assessments

The legal guardian/caregiver was asked to complete the Caregiver Global Impression of improvement (CGI-I) questionnaires in the middle and at the end of the 10-week maintenance treatment period. The questionnaire used a 5-point rating scale to assess legal guardian/caregiver's global impression of improvement in patient's clinical condition, where "1" indicates Very much improved and "5" indicates Very much worse. At these same time points, the caregiver completed the Caregiver Global Impression of Seizures Severity (CGI-S) questionnaire, which uses a 5-point rating scale to assess legal guardian/caregiver's global impression of seizures severity, where "1" indicates Very much reduced and "5" indicates Very much increased.

2.6. Statistical analyses

All statistical analyses and data presentations, including tabulations and listings, were performed using the SAS® version 9.4 software. All statistical tests were two-sided. The required significance level of findings was 5%. Adherence during maintenance was calculated as [# of doses taken] / [2 * # of days during the period]. Repeated measures analysis of covariance was performed in order to analyze the mean change from the observation period, and the mean percent change from the observation period, these are modeled as a function of time with the observation period seizure frequency as a covariate. LSmeans (model estimated means) per period were extracted from the models and are presented with level of significance and 95% confidence intervals. Nominal p-values are presented.

2.7. Primary study endpoints

Safety: incidence of treatment-related adverse events. *Efficacy*: percent change in mean countable monthly seizure frequency during the treatment period as compared to the observation period.

The analyses presented were performed on the overall frequency of all seizure types.

3. Results

A total of 16 patients of a mean of age of 9.1 ± 3.4, and mean age at diagnosis of 3.0 ± 3.3, were enrolled in the study. Eleven of these patients were female. While most patients presented no clinically significant neurological abnormalities at screening, 10 patients showed clinically significant abnormal EEG signals before initiation of the observation period. Eleven patients completed the study; two patients were discontinued because of worsening of seizures, one because of lack of compliance, one because of mild adverse events probably related to treatment (increased intensity of drop attacks, aggression, increased restlessness, insomnia, difficulty eating/drinking), and one withdrew consent. A portion of the seizure frequency diary of one patient was lost, excluding this patient from the treatment period 3 analysis.

A total of 1985 PTL-101 administrations were registered in the course of this study. Patient adherence to treatment regimens, as determined from capsule counts and review of diaries, was 96.3 ± 9.9%. The average maintenance phase starting dose was 15.4 ± 5.1 mg/kg, and the

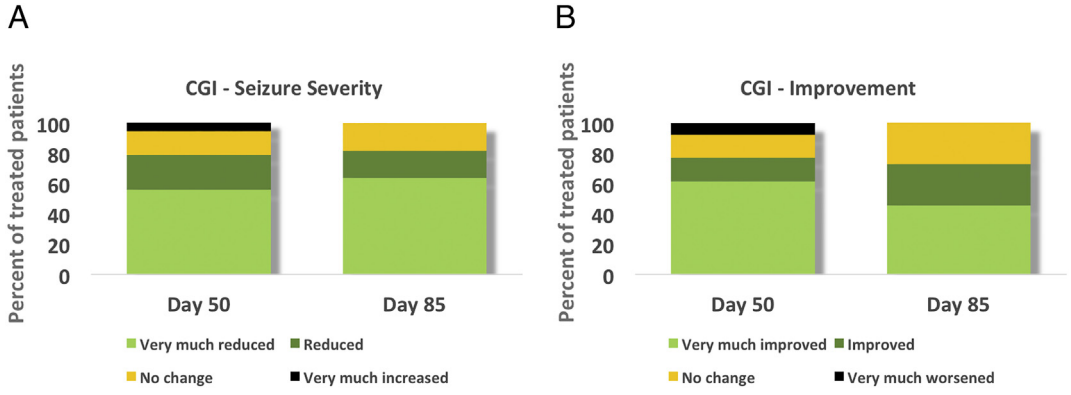

Fig. 2. PTL-101 efficacy. (A) Caregiver Global Impression of Seizure Severity (CGI-S) and (B) Caregiver Global Impression of Improvement (CGI-I) scores, as rated by each patient's legal guardian/caregiver in the middle (day 50) and at the end (day 85) of the 10-week maintenance treatment period. The CGI-I questionnaire used a 5-point rating scale, where "1" indicates Very much improved and "5" indicates Very much worse. The CGI-S questionnaire used a 5-point rating scale, where "1" indicates Very much reduced and "5" indicates Very much increased.

Table 1
Seizure count – percent change from baseline.

Subject #	Seizure count (% change from observation period)			
	Treatment period 1 (wks 1–4)	Treatment period 2 (wks 5–8)	Treatment period 3 (wks 9–12)	Entire treatment period (wks 1–12)
01-01	−60.1	−66.4	−67.4	−64.6
01-02	−89.2	−91.4	−93.5	−91.4
01-03	0.0	−22.2	−14.2	−12.1
01-04	−60.0	−100.0	−100.0	−86.7
01-05	54.2	–	–	–
01-06	−79.7	−95.3	−96.7	−90.6
01-08	−40.0	−68.0	−69.1	−59.0
01-09	537.5	–	–	–
01-11	−77.2	−79.4	−81.9	−79.5
01-12	−10.7	−55.4		
01-14	−90.6	−100	−62.3	−84.3
01-16	−92.8	−92.5	−100	−95.1
01-18	−65.7	−79.2	−68.4	−71.1
N	13	11	10	10
Mean (SD) [95% CI]	−5.7 (168.8) [−107.7; 96.3]	−77.3 (23.5) [−93.0; −61.5]	−75.4 (26.1) [−94.0; −56.7]	−73.4 (24.6) [−91.1; −55.8]
Median [95% CI]	−60.1 [−89.2; 0.0]	−79.4 [−95.3; −55.4]	−75.5 [−100; −62.3]	−81.9 [−91.4; −59.0]

average dose for the 10-week maintenance phase was 13.6 ± 4.2 mg/kg.

Overall, a mean 73.4 ± 24.6% and a median 81.9% reduction in monthly seizure frequency was achieved during the 12-week treatment period, with the largest reductions recorded during treatment periods 2 and 3 (mean: 77.3 ± 23.5% and 75.4 ± 26.1%, respectively; median: 79.4% and 75.5%, respectively) (Table 1). The per period LSmean (model estimated) change and percent change from observation period in seizure counts are presented in Table 2. LSmean counts in all three treatment periods were significantly lower than during the observation period ($p < 0.0001$), and LSmean percent change in monthly seizure counts was significantly lower than in both segments of the maintenance phase as compared to the observation phase ($p = 0.0286$ and 0.0413, respectively). Status epilepticus was only reported for a single patient, who suffered from 2 events during the observation period, 3 during treatment period 1 (wks 1–4), and 2 during treatment periods 2 (wks 5–8) and 3 (wks 9–12). No significant gender-related differences in reduction in seizure frequency were noted (Wilcoxon test: $p = 0.3619$). During the titration phase, 8 (50%) patients were considered responders (i.e., had ≥50% reduction in their seizures), while an additional two became responders during the first half of the maintenance phase (Table 3). By the end of the treatment period, 9 patients (56.3%) were considered responders. Two patients were seizure-free at the second and third treatment periods. These measures reflected caregiver overall impressions of seizure severity and overall improvement, with 9 (82%) reporting reduced or very much reduced seizure severity and 8 (73%) ranking the condition as either improved or very much improved by the end of the study (Fig. 2).

Of the 1985 PTL-101 administrations, 36 (1.8%) were associated with at least one treatment-related adverse event, reported by eleven patients (68.8%) (Table 4). None were serious or severe, and all fully resolved. The most common effect possibly or probably related to study treatment was nervousness and sleep disturbances, each reported by 4 (25.0%) patients, followed by somnolence and increased epileptic seizures, each reported by three patients (18.8%). Weakness was reported by two patients. Aside from one patient with high urine leukocyte counts at the end of the treatment phase, who showed no other urine or clinical abnormalities, all blood and urine test results were within clinically acceptable ranges at the end of the maintenance treatment period.

Table 3
Number of responders by treatment period.

Study period	% (n)	95% CI
Treatment period 1 (wks 1–4)	50.0 (8)	[28.0%; 72.0%]
Treatment period 2 (wks 5–8)	62.5 (10)	[38.6%; 81.5%]
Treatment period 3 (wks 9–12)	56.3 (9)	[33.2%; 76.9%]
Entire treatment period (wks 1–12)	56.3 (9)	[33.2%; 76.9%]

4. Discussion

The centuries-old appreciation of the potent therapeutic properties and favorable safety profile of the Cannabis plant family has brought to a recent surge in research efforts to leverage it toward treatment of epilepsy, particularly, refractory epilepsy. Recent efforts to both regulate cannabinoid-based pharmaceuticals and to conduct well-controlled clinical trials have generated promising reports on the marked seizure-reducing effect of CBD preparations [14–18]. This prospective, open-label study, assessing the novel PTL-01 oral CBD formulation, demonstrated a marked beneficial therapeutic effect of a 12-week treatment period on seizure frequencies among patients with TRE. A mean 73.4% and median 81.9% reduction from baseline monthly seizure frequencies was observed, with two patients already fully seizure-free within 5 weeks of treatment, while an additional eight patients reported a >50% reduction in seizure frequency during this period. These clinical measures translated to meaningful improvements in the condition, as expressed by caregivers' global impressions of significant overall improvements and of marked reductions in seizure severity. Despite the predefined dose limitation and consequently relatively low PTL-101 doses administered in this study, its therapeutic impact was similar to those reported for other oral CBD preparations. More specifically, in their most recently published work, Devinsky et al. [18] documented a 43% responder rate, a 47.6% reduction in median monthly frequency of convulsive seizures, and an improvement in at least one CGI category among 62% of patients with Dravet syndrome on a 14-week oral CBD treatment regimen.

PTL-101 was remarkably well tolerated, eliciting only mild or moderate, and mostly short-lived treatment-related adverse effects. PTL-101 most commonly provoked sleep disturbances and nervousness, which seems to clash with the commonly observed hypnotic effect of antiepileptic agents, both reported here and by others [15,17]. In contrast, eating disorders and GI disorders often reported in association with high-content CBD formulation [16–18] were each reported by only one patient on PTL-101 treatment. In addition, there were no findings of elevated liver enzymes at the tested treatment period, a common effect previously reported following CBD therapy, suggested to be the result of interactions with concomitantly administered AEDs [24]. Importantly, there was no evidence of any psychotropic effect, likely

Table 2
LSmean seizure count – change and percent change from baseline.

Treatment period	Change from observation period						Percent change from observation period					
	LSmean	DF	t value	p value	Lower 95% CL	Upper 95% CL	LSmean	DF	t value	p value	Lower 95% CL	Upper 95% CL
1 (wks 1–4)	−76.3	19	−11.3	<0.0001	−90.4	−62.1	−6.3	19	−0.2	0.8369	−69.0	56.5
2 (wks 5–8)	−100.6	19	−13.7	<0.0001	−115.9	−85.2	−77.1	19	−2.4	0.0286	−145.3	−9.0
3 (wks 9–12)	−93.5	19	−12.2	<0.0001	−109.6	−77.4	−74.8	19	−2.2	0.0413	−146.3	−3.3

Table 4
Treatment-related[a] adverse events.

Adverse event	Number of patients (%)
Nervousness	4 (25)
Insomnia	4 (25)
Sleepiness	3 (18.8)
Worsening of seizures	3 (18.8)
Weakness	2 (12.5)
Aggression	2 (12.5)
Eating disorders	1 (6.3)
Temporary amnesia	1 (6.3)
Emotional lability	1 (6.3)
Diarrhea	1 (6.3)
Difficulties in language retrieval	1 (6.3)
Sensory hypersensitivity	1 (6.3)
Tics	1 (6.3)
Nocturia	1 (6.3)
Increased slapping head on bed	1 (6.3)

[a] Probably or possibly related.

because of absence of THC in the PTL101 preparation. The one patient suffering from status epilepticus events showed no increase in frequency as compared to his pretreatment period. Cases of low efficacy and seizure worsening following treatment of intractable pediatric epilepsy with CBD were reported by others [18,25] and similarly resulted in study withdrawal. Negative or absence of reaction to treatment is not rare for children with intractable epilepsy.

This study has several limitations, including the small sample size, lack of a control placebo group, and relatively short duration of treatment. In addition, CBD levels were not monitored. At the same time, while the predefined dose limit was greater than in other studies, the lower doses administered here were still highly effective.

5. Conclusions

This work demonstrated the potent seizure-reducing effect of relatively low PTL-101 doses among pediatric patients with TRE over a 12-week period. The convenient drug form fostered patient adherence, which brought to a high responder rate and considerable overall improvements. Moreover, the novel formulation was associated with a safety profile superior to those of standard oral CBD preparations, with no reports of psychotropic effects or other severe adverse effects. Additional controlled and blinded studies, with larger patient cohorts, will be necessary to further establish the effectiveness of PTL-101, including its long-term efficacy and safety.

Compliance with ethics guidelines

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the legal guardians of all individual participants included in the study.

Declaration of Competing Interest

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published. Editorial assistance in the preparation of this article was provided by Dr. Yehudit Posen of PSW Ltd. Support for this assistance was funded by Phytotech Therapeutics Ltd. The authors thank all study participants for their involvement in the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.yebeh.2019.07.007.

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