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Synthetic pharmaceutical grade cannabidiol for treatment of refractory infantile spasms: A multicenter phase-2 study

Shaun A. Hussain [a,*], Dennis J. Dlugos [b], M. Roberta Cilio [c,d,e], Neha Parikh [f], Alex Oh [f], Raman Sankar [a,g]

[a] Department of Pediatrics (Division of Neurology), David Geffen School of Medicine and UCLA Mattel Children's Hospital, Los Angeles, CA, United States
[b] University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, PA, United States
[c] Department of Neurology, University of California, San Francisco, San Francisco, CA, United States
[d] Department of Pediatrics, Catholic University of Leuven, Brussels, Belgium
[e] Institute for Experimental and Clinical Research, Catholic University of Leuven, Brussels, Belgium
[f] Insys Development Company, Chandler, AZ, United States
[g] Department of Neurology, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States

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ABSTRACT

Purpose: Limited data suggest that cannabidiol (CBD) may be effective for treatment of refractory infantile spasms (IS). This study was designed to more rigorously evaluate the efficacy and safety of synthetic CBD in the treatment of IS.
Methods: Children six to 36 months of age with IS that failed treatment with both adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) were eligible for enrollment. Children receiving clobazam were excluded. After baseline overnight video-electroencephalography (vEEG) to confirm diagnosis and ascertain hypsarrhythmia, patients were treated with synthetic CBD oral solution (20 mg/kg/day). Overnight video-EEG was repeated after 14 days, and both baseline and repeat video-EEGs were completely de-identified and reviewed in a pairwise fashion by an independent, blinded pediatric electroencephalographer. The primary efficacy endpoint was freedom from spasms and hypsarrhythmia on day 14.
Results: Nine patients were enrolled, comprising an older (median age = 23 months) cohort with long-standing IS (median duration = 13 months) and numerous prior treatment failures (median = 6). One patient responded to therapy and eight patients exhibited neither clinical nor electrographic response.
Conclusions: The immediate but temporary response in a single patient suggests that CBD oral solution is not particularly effective in highly refractory cases, but may, nevertheless, be effective in younger patients with shorter durations of IS. Further study, examining both short- and long-term outcomes, is warranted to further evaluate the efficacy and safety of CBD oral solution in the treatment of IS.

1. Introduction

Infantile spasms (IS) is an often devastating form of epilepsy with onset in the first year of life. Frequently attributed to one of many structural, genetic, or metabolic disorders, IS is usually accompanied by neurodevelopmental arrest [1]. It is characterized by clusters of brief seizures (epileptic spasms) and a spectrum of severe electroencephalographic abnormalities including hypsarrhythmia [2]. A lack of prompt and successful treatment is associated with adverse long-term developmental outcomes [3]. With a cumulative short-term response rate to hormonal therapy and vigabatrin (VGB; when administered sequentially [4–6] or simultaneously [7]) of approximately 66%, and a cumulative risk of IS relapse approaching 50% [8,9], we estimate that first-line therapies yield sustained long-term remission in only one-third of children with IS. With regard to safety, adrenocorticotropic hormone (ACTH) and prednisolone confer a small risk of potentially lethal infection and symptomatic hypertension [10], and VGB carries risk of irreversible peripheral vision loss [11,12] as well as symptomatic reversible brain magnetic resonance imaging (MRI) abnormalities [13–15]. Accordingly, there is substantial need for novel therapies to treat IS, especially in refractory cases.

In the context of the extensive historical use of various cannabis-based products for treatment of epilepsy [16], cannabidiol (CBD) has emerged as a nonpsychoactive [17], safe, and effective therapy for Dravet syndrome [18] and Lennox–Gastaut syndrome [19,20]. In addition, limited data suggest that various formulations of CBD may exhibit efficacy across multiple epilepsy syndromes [21,22], including IS [23]. However, objective scientific enthusiasm for CBD is presently eclipsed by lay reports of incredible treatment success using artisanal CBD-enriched cannabis extracts, leading to widespread "unsupervised" use

* Corresponding author at: UCLA Pediatric Neurology, 10833 Le Conte Ave, Room 22-474, Los Angeles, CA 90095-1752, United States.
E-mail address: shussain@mednet.ucla.edu (S.A. Hussain).

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of these products, despite the illegal status of cannabis-derived CBD in most jurisdictions [24] and the widespread misrepresentation of cannabinoid content in such products [25]. Given this background, we set out to rigorously evaluate the efficacy and safety of pharmaceutical-grade synthetic CBD oral solution in a formal phase 2 clinical trial.

2. Methods

2.1. Institutional approvals

This study was accomplished in accordance with Good Clinical Practices, the International Conference on Harmonisation, and the ethical principles of the Declaration of Helsinki. The study protocol and informed consent documents were approved by the institutional review boards for each study site. For all patients, a legal representative (parent) provided written informed consent prior to study procedures. This study was registered at clinicaltrials.gov: NCT02551731.

2.2. Study design

As illustrated in Fig. 1, this was a 14-day study, with optional extension of therapy among patients demonstrating at least partial response. The presence of IS (at least one cluster of at least three electroclinical spasms over a span of not more than 10 min) was confirmed by inpatient overnight video-electroencephalography (VEEG). Eligible patients were treated in an open-label fashion with pharmaceutical-grade synthetic CBD oral solution (300 mg/mL, Insys Development Company, Chandler, AZ) with an initial dosage of 20 mg/kg/day, divided in two daily doses, without titration. Repeat inpatient overnight VEEG was administered on day 14 to establish the primary efficacy endpoint (see below). Whereas nonresponders discontinued therapy, complete responders and partial responders were invited to participate in an extension phase with continued therapy for up to an additional 56 weeks, with optional dose titration to 40 mg/kg/day, at the discretion of the study physician. During the extension phase, patients returned for study visits monthly for five months and quarterly thereafter.

2.3. Patient selection criteria

Infants ages six months to 36 months inclusive were eligible if (1) they had a clinical diagnosis of IS (also known as epileptic spasms according to the 2010 International League Against Epilepsy classification scheme [26]), (2) baseline overnight VEEG demonstrated at least one cluster of electroclinical spasms (three or more spasms in any 10-minute epoch), and (3) the patient had not responded to adequate trials of both ACTH and VGB in the view of the study physician after review of pertinent medical records.

Patients were excluded if (1) they had exposure to any cannabis-derived product within 30 days of screening, (2) a second-line therapy for IS (i.e., topiramate, zonisamide) was commenced within two weeks of screening, or (3) they had received treatment with felbamate (because of side-effect profile), clobazam (because of drug–drug interaction), or the ketogenic diet (given the possibility of late response that might confound the primary efficacy endpoint) within two weeks of screening.

2.4. Study procedures

At screening, patients underwent a medical history, physical examination with vital signs, neurological examination, and clinical laboratory testing (hematology, chemistry, liver function tests, follicle-stimulating hormone, and uric acid) as well as urine cannabinoid screen to confirm lack of recent cannabinoid exposure. Physical and neurological examinations, as well as clinical laboratory examination, were conducted at each study visit. Pharmacokinetic blood samples were obtained for determination of trough plasma CBD and 7-hydroxycannabidiol (7-OH-CBD) concentrations at each visit, except for the first day of dosing and final visit.

Inpatient overnight VEEG was administered during the screening visit and on day 14 using VEEG acquisition systems manufactured by Nihon-Kohden (UCLA) or Xltec (UCSF). Video-electroencephalography studies were interpreted by the investigator (unblinded) and an independent reader (blinded).

Video-electroencephalography studies were rigorously de-identified by (1) removing/recoding timestamps, (2) removing unblinded site electroencephalographer comments, and (3) disabling audio recording. In addition, study personnel were instructed not to administer study medication on camera, and all patients/caregivers and study staff were advised not to make any major changes in appearance (e.g., shaving a beard) that might conceivably be captured on video. These efforts were undertaken to ensure that the independent reader/pediatric electroencephalographer (DJD) was truly blinded to the pretreatment vs posttreatment status of each VEEG study. Push-button events and descriptions of these events (including time of day, but not date) were provided to the external reviewer. The independent reader evaluated each pair of VEEG studies (pre- and posttreatment) together and was specifically asked to determine whether there was a "substantive change" in the burden of hypsarrhythmia and epileptic spasms. For each EEG, the unblinded study physician and the independent reader were asked to independently determine the presence or absence of (1) epileptic spasms, (2) at least

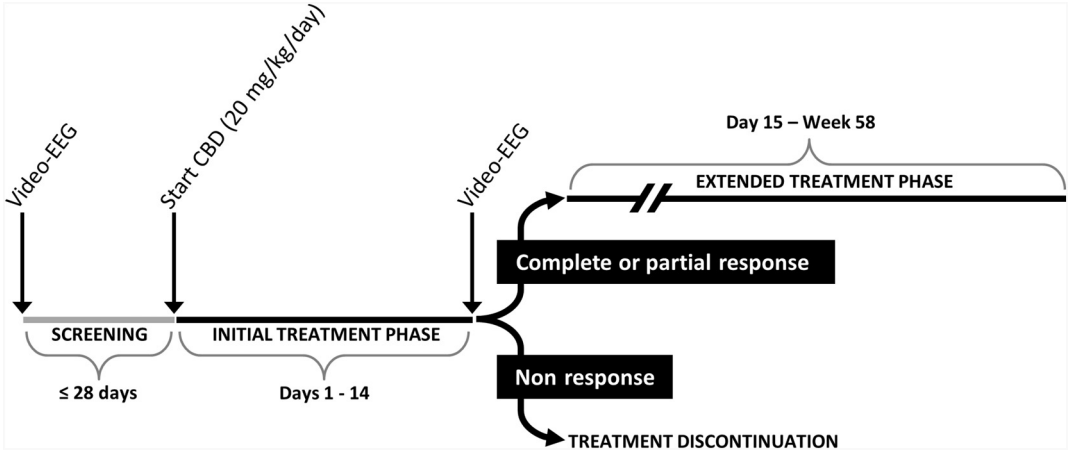

Fig. 1. Study design. BID, twice daily; CBD, cannabidiol. [1]Nonresponse was defined as lack of improvement with respect to both epileptic spasms and hypsarrhythmia, on day 14 (±2 days) video-EEG. [2]Partial response was defined as improvement in epileptic spasms or hypsarrhythmia, on day 14 (±2 days) video-EEG. [3]Complete response was defined as freedom from both epileptic spasms and hypsarrhythmia, on day 14 (±2 days) video-EEG.

one sleep–wake cycle, (3) hypsarrhythmia, (4) high voltage, and (5) multifocal spikes. In addition, both reviewers were asked to quantify the burden of hypsarrhythmia using the Mytinger (BASED) score [27], given the observation that hypsarrhythmia identification suffers from poor interrater reliability [28]. For reference, the Mytinger score ranges from zero (normal) to five (maximum burden of hypsarrhythmia), and scores of four to five indicate presence of hypsarrhythmia. In addition, the independent reader was asked to do an actual count of spasms as seen during the VEEG. The counts were collected for a period of 1 h immediately after the first awakening after 4:00 AM, regardless of clustering.

Hypsarrhythmia was defined as the presence of high-voltage diffuse slow waves and multifocal spikes, observed for at least 1 min continuously during any epoch and/or in at least 10 bursts of any duration. High voltage was defined as nonepileptiform slow waves with voltage consistently greater than 200 μV on a bipolar longitudinal montage. Multifocal spikes were defined as epileptiform discharges localized to at least three nonneighboring channels, arising from both hemispheres.

2.5. Study outcomes

The primary efficacy endpoint was the percentage of patients with freedom from both spasms and hypsarrhythmia on day 14 VEEG as determined by the independent (blinded) reader. Response was classified as "complete response" if neither spasms nor hypsarrhythmia were present; "partial response" if there was "substantive" change on VEEG; or "nonresponse" if there was no change or worsening on VEEG. Secondary efficacy endpoints included change in Mytinger score and scores on the Clinical Global Impression of Improvement Assessment (CGI-I), a simple seven-point Likert scale that varies from one (very much improved) to seven (very much worse).

To evaluate safety, patients were screened for treatment-emergent adverse events (TEAEs) at all follow-up visits, and study personnel spoke to patients' parents or guardians by phone or via email each day for the first five days of the treatment protocol. In addition, clinical laboratory evaluation (specified above) was conducted at all study visits. The Medical Dictionary for Regulatory Activities (Version 18.1) was used to classify all adverse events with respect to system organ class and preferred term.

2.6. Statistical methods

The primary and secondary endpoints for were summarized by descriptive statistics. Exact 95% confidence intervals were presented. Comparison of observed response rate with expected response rate without treatment (i.e., 2% over 14 days, based on two cohort studies that approximate natural history [29,30]) was accomplished with the two-sided, one-sample binomial probability test. Statistical calculations were facilitated with the STATA software (Statacorp, version 14, College Station, Texas, USA).

3. Results

3.1. Subjects

Baseline clinical and demographic characteristics of the study population are presented in Table 1. Thirteen patients were screened, and nine patients were enrolled in the study. The nine children enrolled in the study comprised a relatively older cohort with long duration of IS and numerous treatment failures. All patients had spasms that failed prior trials of ACTH and VGB, and seven patients had spasms that failed prednisolone as well. One patient (#3) had spasms that failed treatment with a community-sourced CBD extract, with reported discontinuation more than 30 days prior to study entry, and with no cannabinoids detected in urine at screening. Seven patients completed 14 days of treatment and returned for repeat VEEG; two patients withdrew from the study prior to returning for day 14 VEEG.

3.2. Efficacy

The burden of spasms and hypsarrhythmia at baseline and day 14, as interpreted by the unblinded site investigator as well as the blinded independent reader, is summarized in Table 2. One patient (#5) was classified as a complete responder based on outcome at day 14. In comparison with the estimated rate of spontaneous resolution without treatment (2%), the observed response rate of 11% (1/9) was not statistically distinct ($P = 0.17$).

At baseline, the parent of patient #5 reported 2–3 clusters of spasms per day, with approximately 40 spasms per cluster. On baseline overnight VEEG (18.4 h duration), there were two clusters of spasms (50 spasms over 12 min and 49 spasms over 8 min, respectively, according to the unblinded site investigator). The blinded independent reader reported that both spasms and hypsarrhythmia were present. After administration of the first dose of CBD, the parent reported no spasms on days 1 through 5, a single cluster of 25 spasms over 5 min on day 6, and none through day 14. On day 14 VEEG, the blinded independent reader reported an absence of both spasms and hypsarrhythmia, and specifically endorsed a substantial reduction in the burden of spasms and hypsarrhythmia. Representative samples of the baseline and day 14 VEEG tracings are presented in Fig. 2. The patient continued CBD at the same dosage (20 mg/kg/day), and the parent reported a relapse of spasms on day 18. Thereafter, the parent reported one to two clusters of spasms per week. Following a study protocol amendment allowing dose escalation, CBD oral solution was titrated to 40 mg/kg/day beginning day 70, without qualitative benefit. The site investigator and the parent both endorsed an impression of "very much improved" or "much improved" in comparison with baseline on all CGI-I measurements. Subsequent reintroduction of VGB accompanied renewed freedom from spasms, and at most recent follow-up at age 22 months, the patient was seizure-free while receiving combination therapy with CBD (as part of a long-term safety study), VGB, and topiramate.

Table 1
Baseline characteristics of the study population.

Patient	Age (months)/Sex	Duration of IS (months)	Etiology	Failed ACTH	Failed VGB	Other prior treatment failures	Coadministered treatments at study entry
1	19/M	18	Unknown	Y	Y	FBM, PER, B6, LEV, PHB, TPM, PRED	TPM
2	23/M	9	HIE	Y	Y	ZNS, PRED, PHB, LEV	LEV
3	27/F	24	Unknown	Y	Y	PRED, leucovorin, LEV, VPA, CLB, MM	None
4	23/F	8	Unknown	Y	Y	LEV, CLN, B6	LEV, CLN, B6
5	14/F	10	Focal PMG, heterotopia	Y	Y	PRED, TPM	TPM
6	15/M	11	Unknown	Y	Y	LEV, CLN, TPM, KETO, VPA, ZNS	LEV, CLN
7	20/F	13	Unknown	Y	Y	PRED, ZNS	ZNS
8	36/F	33	TSC	Y	Y	LEV, LTG, PRED, OXC	VGB, LEV, LTG
9	30/F	29	Unknown	Y	Y	B6, PRED, TPM, KETO, VPA	VGB, VPA

ACTH, adrenocorticotropic hormone; B6, vitamin B6 (pyridoxine); CLB, clobazam; CLN, clonazepam; FBM, felbamate; HIE, hypoxic ischemic encephalopathy; IS, infantile spasm; KETO, ketogenic diet; LEV, levetiracetam; LTG, lamotrigine; MM, medical marijuana; OXC, oxcarbazepine; PER, perampanel; PHB, phenobarbital; PMG, polymicrogyria; PRED, prednisolone; TPM, topiramate; TSC, tuberous sclerosis complex; VGB, vigabatrin; VPA, valproic acid; ZNS, zonisamide.

Table 2
Response to cannabidiol oral solution.

Patient	Unblinded VEEG reader						Blinded independent VEEG reader						Response	Relapse
	Day 0 VEEG			Day 14 VEEG			Day 0 VEEG			Day 14 VEEG				
	S	H	M	S	H	M	S	H	M	S	H	M		
1	Y	Y	5	Y	Y	5	Y	Y	5	Y	Y	5	N	–
2	Y	N	3	Y	N	3	N	N	3	N	N	3	N	–
3	Y	Y	5	Y	Y	5	Y	Y	5	Y	Y	5	N	–
4	Y	Y	5	Y	Y	5	Y	Y	5	Y	Y	5	N	–
5	Y	N	3	N	N	3	Y	Y	4	N	N	3	Y	Y
6[a]	Y	Y	5	–	–	–	–	–	–	–	–	–	N	–
7[b]	Y	N	5	–	–	–	–	–	–	–	–	–	N	–
8	Y	N	3	Y	N	3	N	N	3	N	Y	4	N	–
9[c]	Y	N	3	Y	N	3	–	–	–	–	–	–	N	–

H, hypsarrhythmia; M, Mytinger (BASED) score; S, spasms; VEEG, video-electroencephalogram.
[a] Patient #001-ICSBD09 dropped out of the study after 14 days (lack of efficacy) of treatment and did not return for day 14 repeat VEEG.
[b] Patient #001-ICSBD10 dropped out of the study after five days (lack of efficacy) and did not return for 14 repeat VEEG.
[c] Neither day 0 nor day 14 VEEG for patient #005-ISCBD01 was reviewed by the blinded independent reader.

The remaining eight patients were classified as nonresponders; there were no partial responders. Among them, parents of patients #6 and #7 reported increased burden of spasms, though neither patient returned for day 14 VEEG. Parents of patient #6 declined to return citing the impression of nonresponse and a family emergency. The parents of patient #7 withdrew from the study after early CBD discontinuation. Patient #8 began CBD immediately following a taper of VGB and exhibited electrographic deterioration (emergence of hypsarrhythmia on blinded VEEG review).

3.3. Safety and tolerability

There were five subjects with at least one TEAE, and nine total TEAEs. Parents of patients #3, #4, and #5 reported upper respiratory infections, with associated irritability and increased seizure frequency reported in patient #4. The parent of patient #6 reported increased seizure frequency and sedation (possibly confounded by the use of rescue clonazepam). The parent of patient #7 reported increased seizure frequency and elected to discontinue therapy and withdraw from the study on day 6.

3.4. Pharmacokinetic data

The dose-normalized trough concentration of CBD ranged from approximately 3 to 5 ng/mL/mg/kg across all visits, with less than 50% accumulation of CBD and 7-OH-CBD. In an underpowered analysis, complete response was not associated with CBD or 7-OH-CBD concentrations on day 14. The CBD concentrations observed in this study were comparable with those observed in a larger pediatric pharmacokinetic study, which evaluated a similar formulation of pharmaceutical-grade synthetic CBD administered to patients in a fasted state [31].

4. Discussion

With the use of blinded VEEG before and after treatment, this is the first study to rigorously evaluate the efficacy of CBD in the treatment of IS. The lack of enduring response suggests that CBD is not highly effective in the treatment of refractory IS. Response in a single patient could have been coincidental, or perhaps incomplete. It is conceivable that clinically obvious epileptic spasms at baseline became both subtle (so as to escape detection by parents) and infrequent (so as to escape detection on day 14 VEEG). On the other hand, the immediate—albeit temporary—response in one patient also suggests that CBD might exhibit more substantial efficacy among patients with less treatment-refractory seizures. It is noteworthy that the sole responder was arguably the least refractory among the cohort. She was the youngest patient at trial entry and exhibited just four prior treatment failures, though all patients had spasms that failed first-line treatments. If efficacious, response to CBD might be more robust in a younger cohort, with shorter duration of IS and fewer prior treatment failures.

This study presented an opportunity to evaluate the reliability of VEEG assessment to identify spasms and hypsarrhythmia using both

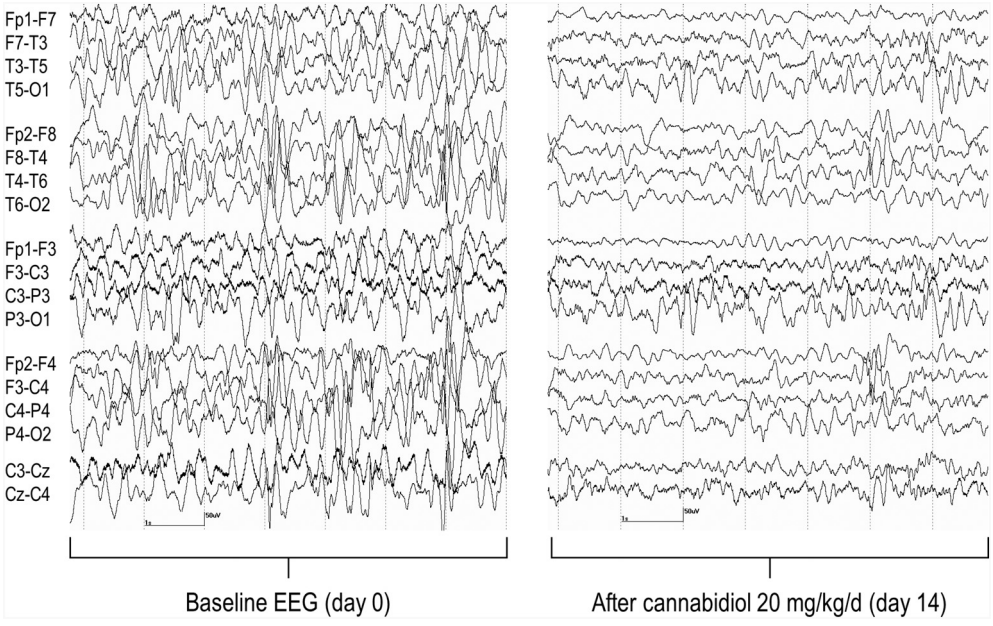

Fig. 2. Interictal EEG before and after cannabidiol treatment (patient #5). These brief EEG clips are estimated to be representative of the overnight EEG recordings from which they were abstracted. Of note, the site investigator and the blinded independent reviewer agreed that the posttreatment study exhibited a lack of hypsarrhythmia (Mytinger score = 3). However, there was disagreement as to the presence of hypsarrhythmia on the baseline study: The site investigator determined that the pretreatment study did not exhibit hypsarrhythmia (Mytinger score = 3), and the blinded independent reviewer determined that it did exhibit hypsarrhythmia (Mytinger score = 4).

conventional criteria as well as the Mytinger (BASED) score. As illustrated in Table 2, there were notable discrepancies between the impressions of the unblinded site investigator and the blinded independent reader. This is somewhat expected, as the consistent identification of epileptic spasms is generally known to be challenging. For patients #2 and #8, the blinded independent reader did not identify spasms on either pre- or posttreatment studies. In contrast, the site investigator identified several clusters of spasms (both pre- and posttreatment) for both patients. In addition, for patient #8, whereas the site investigator did not identify hypsarrhythmia on either study (both Mytinger score 3), the blinded independent reader agreed that the pretreatment study did not exhibit hypsarrhythmia (Mytinger score 3) but identified hypsarrhythmia (Mytinger score 4) on the posttreatment study, signaling interval electrographic deterioration. Lastly, for patient #5, although both reviewers completely agreed on the characterization of the posttreatment study, the blinded reviewer identified pretreatment hypsarrhythmia (Mytinger score 4), whereas the unblinded site investigator identified lack of hypsarrhythmia (Mytinger score 3). Overall, as in two prior studies [27,28], the identification of spasms and hypsarrhythmia by the investigator and the independent reader varied, while the use of the Mytinger score resulted in substantially greater—albeit still imperfect—consistency across raters. These results suggest that blinded review of VEEG is critical in determining outcomes in IS studies and that the broader implementation of the Mytinger score can mitigate electroencephalographer bias and augment the external validity of reported hypsarrhythmia outcomes. The development and validation of robust and unbiased measures of disease burden in IS represents an enduring challenge for both clinical trials and routine clinical care.

Importantly, this study is distinguished from other clinical trials of CBD by the exclusion of patients treated with clobazam. As CBD is a potent inhibitor of CYP450 3A4 [32] and CYP450 2C19 [33], plasma levels of clobazam and its active metabolite, N-desmethylclobazam (N-CLB), often rise substantially upon CBD treatment [34]. In patients who are treated with CBD and clobazam, elevated plasma levels of clobazam and N-CLB may yield higher rates of both response (i.e., reduction in seizure frequency) and adverse effects (e.g., sedation). Indeed, with reference to the only published randomized controlled trials evaluating CBD for the treatment of Dravet syndrome [18] and Lennox–Gastaut syndrome [19,20], there is concern that positive response to CBD could be attributed, at least in part, to the clobazam–CBD interaction [35]. Although we controlled for the potential impact of clobazam on response and TEAEs, we did not account for the potential impact of fasted vs fed state. Several contemporary reports have identified a food effect such that CBD administration with a high-fat meal is associated with an approximate 5- to 10-fold rise in peak serum CBD concentration [36,37]. Future studies of CBD for treatment of IS should specifically dictate that CBD administration be carried out with, or without, food.

5. Conclusions

In summary, this phase-2 study suggests that CBD may be an effective treatment for IS and warrants further study with examination of both short- and long-term outcomes. The use of a larger study population and a cohort with less treatment-refractory seizures, with a control group and continued implementation of blinded VEEG assessment, is essential to establish efficacy and safety.

Declaration of competing interest

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Neha Parikh and Dr. Oh are employees of Insys Development Company.

Dr. Sankar serves on scientific advisory boards or serves on the speaker's bureau for and has received honoraria and funding for travel from Eisai, UCB Pharma, Sunovion, Supernus, Greenwich Biosciences, LivaNova, and on the advisory boards for Aquestive Therapeutics, West Therapeutic Development, Insys Development Company, and Zogenix; receives royalties from the publication of *Pediatric Neurology, 3rd ed.* (Demos Publishing, 2008) and *Epilepsy: Mechanisms, Models, and Translational Perspectives* (CRC Press, 2011); serves on speakers' bureaus for and has received speaker honoraria from Eisai, UCB, GlaxoSmithKline, Cyberonics, Supernus, and Lundbeck. He has received research support from SK Life Sciences and Insys Development Company, Inc.

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