CBD-OS FOR THE TREATMENT OF LENNOX-GASTAUT SYNDROME AND DRAVET SYNDROME

FDA ADVISORY COMMITTEE MEETING BRIEFING DOCUMENT

PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUG ADVISORY COMMITTEE

GW RESEARCH LTD

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LIST OF ABBREVIATIONS

4-AP	4-aminopyridine
6-OH-CBD	6-hydroxy-cannabidiol
7-COOH-CBD	7-carboxy-cannabidiol
7-OH-CBD	7-hydroxy-cannabidiol
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AED	Antiepileptic drug
AESI	Adverse events of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ALZ	Alprazolam
ANCOVA	Analysis of covariance
AST	Aspartate aminotransferase
AUC	Area under the concentration-time curve
b.i.d.	Twice daily [Latin: *bis in die*]
CB_1	Cannabinoid receptor type 1
CB_2	Cannabinoid receptor type 2
CBD	Cannabidiol
CBD-OS	Cannabidiol oral solution
CI	Confidence interval
C_{max}	Maximum measured plasma concentration
CMC	Chemistry, manufacturing, and controls
CYP	Cytochrome P450
CYP2C19	Cytochrome P450 2C19
CYP3A4	Cytochrome P450 3A4
DDI	Drug-drug interaction
DILI	Drug-induced liver injury
DRO	Dronabinol
DS	Dravet syndrome
EAP	Expanded access program
eDISH	Evaluation of drug-induced serious hepatoxicity
EEG	Electroencephalogram
EMA	European Medicines Agency
E_{max}	Maximum effect
ESC	Epilepsy Study Consortium
ESM	Ethosuximide
GPR55	G protein-coupled receptor 55
FDA	Food and Drug Administration
G-tube	Gastrostomy tube
GGT	Gamma glutamyltransferase
GW	GW Research Ltd
IND	Investigational new drug
i.p.	Intraperitoneal
ISS	Integrated Summary of Safety
ITT	Intention to treat
IVRS	Interactive voice response system
LGS	Lennox-Gastaut syndrome
LEV	Levetiracetam

LFP	Local field potential
LTG	Lamotrigine
MEA	Multi-electrode array
MES	Maximal electroshock
N-CLB	*N*-desmethylclobazam
NDA	New drug application
NMRI	Naval Medical Research Institute
OLE	Open-label extension
OR	Odds ratio
PB	Phenobarbital
PBO	Placebo
PCDH19	Protocadherin-19
PD	Pharmacodynamics
PK	Pharmacokinetics
POPPK	Population pharmacokinetics
PP	Per Protocol analysis
p.r.n.	As needed [Latin: *pro re nata*]
PT	Preferred term
PZT	Pentylenetetrazole
QTc	The QT interval corrected for heart rate
QTcF	QTc with Fridericia correction
SAE	Serious adverse event
SCN1A	Voltage-gated sodium channel α1 subunit
SD	Standard deviation
SE	Status epilepticus
S/CGIC	Subject/Caregiver Global Impression of Change
SOC	System organ class
STP	Stiripentol
SUDEP	Sudden unexpected death in epilepsy
$t_{½}$	Half-life
TE	Treatment-emergent
THC	Δ^9-tetrahydrocannabinol
t_{max}	Time to maximum plasma concentration
TRPV1	Transient receptor potential channel
UK	United Kingdom
ULN	Upper limit of normal
US	United States
VAS	Visual analogue scale
VNS	Vagus nerve stimulation
VPA	Valproic acid or any prescribed valproate product (valproate semisodium or valproate sodium)

1. EXECUTIVE SUMMARY

Cannabidiol (CBD) oral solution (CBD-OS) is a first-in-class antiepileptic drug (AED) for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older. GW Research, which is a part of GW Pharmaceuticals and operates under Greenwich Biosciences in the United States (US), holds the Investigational New Drug (IND) application for CBD-OS. CBD-OS is composed of crystalline CBD that has been purified from a cannabis extract. Although CBD is a cannabinoid, it shares almost none of the pharmacologic features of the prototypical cannabinoid, Δ^9-tetrahydrocannabinol (THC). In animal models of seizures, CBD is thought to exert its anticonvulsant effect by a reduction in neuronal hyperexcitability and inflammation through modulation of intracellular calcium via the orphan G protein-coupled receptor (GPR55) and the transient receptor potential channel 1 (TRPV1), as well as through modulation of adenosine-mediated signaling (Ryan, Drysdale et al. 2009, Sylantyev, Jensen et al. 2013, French, Koepp et al. 2017).

The Food and Drug Administration (FDA) provided guidance on the development program and reached agreement with GW on key aspects of the clinical studies. In 2013, the FDA authorized multiple physician-initiated expanded access programs (EAPs) for CBD-OS. Subsequently, the GW-sponsored IND for CBD-OS was submitted in 2014. During the course of development, CBD-OS has been granted Orphan Drug Designation and Rare Pediatric Designation for the treatment of LGS and DS and Fast-Track Designation for the treatment of DS.

The clinical development program supporting the safety and efficacy of CBD-OS includes 2 randomized, placebo-controlled studies in LGS – 1 investigating 10 and 20 mg/kg/day CBD-OS (Study 1414) and 1 investigating 20 mg/kg/day CBD-OS (Study 1423) – and a single randomized, placebo-controlled study of 20 mg/kg/day CBD-OS in DS (Study 1332 Part B [1332B]). The design of these studies was discussed with FDA at a pre-IND meeting, after which the protocols were amended to incorporate feedback from the Agency. Endpoints and analyses, including sensitivity analyses for the primary endpoint and missing data imputations, were also agreed upon with the FDA.

Overall, the findings from the three Phase 3 studies demonstrate that, when added to a current AED therapy, CBD-OS reduces seizure frequency in patients with drug-resistant LGS or DS while maintaining a predictable and manageable safety profile.

1.1. BACKGROUND ON LENNOX-GASTAUT SYNDROME AND DRAVET SYNDROME

LGS and DS are rare childhood-onset forms of encephalopathic epilepsy with poor long-term prognoses. Both syndromes are among the most drug-resistant forms of epilepsy, with more than 90% of patients continuing to have uncontrolled seizures daily despite treatment (Ostendorf and Ng 2017). LGS and DS are characterized by multiple seizure types and may progress to status epilepticus (SE), or prolonged seizures lasting more than 5 minutes that require immediate intervention.

While DS is a monogenic disease caused by a voltage-gated sodium channel α1 subunit gene (*SCN1A*) mutation in 75% of patients (Scheffer 2012) and LGS has a more heterogeneous pathophysiology, both typically present similarly during infancy or early childhood, often with multiple seizure types. In addition to epilepsy, the majority of patients with LGS and DS experience severe intellectual and developmental disabilities and behavioral disturbances such as attention deficit hyperactivity disorder (ADHD), anxiety, aggressive behavior, and psychosis. Cognitive impairment is apparent in ≥75% of patients with LGS by 5 years following onset (Camfield 2011), and 50% of DS patients experience severe intellectual impairment (Genton, Velizarova et al. 2011).

Importantly, patients with LGS and DS have an increased risk of death, primarily due to SE and sudden unexpected death in epilepsy (SUDEP). A population-based study of children with LGS showed that all-cause mortality was 14 times greater than in the general population (Autry, Trevathan et al. 2010). An analysis of mortality in the Epilepsy Genetics Research Program demonstrated a DS-specific mortality rate of 15.84 per 1000 patient-years (Cooper, McIntosh et al. 2016). SUDEP was the most common cause of death (59%), equating to a DS-specific SUDEP rate of 9.32 per 1000 patient-years, which is nearly twice the rate for adults with refractory epilepsy. Another review of 177 deaths in DS showed that the majority occurred before the patient reached 10 years of age, in which SUDEP was the leading cause of death (Shmuely, Sisodiya et al. 2016).

In LGS, drop seizures, which include any seizure that causes a fall or head drop, are common and have the greatest clinical impact, often causing physical injury leading to increased morbidity and mortality (van Rijckevorsel 2008, Isojarvi, Lee et al. 2016). Convulsive seizures have the greatest clinical impact in DS and are often accompanied by loss of consciousness and falling. Patients with LGS display a characteristic electroencephalogram (EEG) pattern (Arzimanoglou, French et al. 2009), while patients with DS usually have normal EEG patterns at onset of epilepsy.

Almost all patients with LGS and DS continue to have seizures despite treatment with multiple AEDs, putting them at high risk for injury or death. The primary goal of therapy for LGS and DS is to reduce seizure frequency and severity while limiting the AEs associated with multiple AEDs; however, there remains a significant unmet need for additional therapies for these patients.

1.2. NONCLINICAL FINDINGS

Administration of CBD or 7-hydroxy-cannabidiol (7-OH-CBD; an active metabolite of CBD), when given alone or in combination with other AEDs, reduces seizures in a variety of animal models.

Briefly, anticonvulsant efficacy of CBD was evaluated and confirmed in a series of *in vitro* animal models of epileptiform activity and *in vivo* animal models of acute seizure and epilepsy. The *in vitro* evaluations were performed using the 4-aminopyridine (4-AP) and Mg^{2+}-free models of epileptiform activity which assessed CBD effects using multi-electrode array (MEA) electrophysiological recordings from rat hippocampal slices. The *in vivo* assessments were

conducted in electrically-, audiogenically-, and chemically-induced seizure models in rodents. Specifically, mice were evaluated in the maximal electroshock (MES) and audiogenic models of acute generalized seizure following a single intraperitoneal (i.p.) injection of Purified CBD or its metabolite 7-OH-CBD. Purified CBD was also tested in pentylenetetrazole (PTZ)-induced generalized seizures, pilocarpine-induced temporal lobe seizures, and penicillin-induced partial seizures in rats. In all cases, purified CBD was found to exert significant anticonvulsant effects in each model. The anticonvulsant effect of CBD was further confirmed when co-administered with clinically used AEDs in the models of chemically-induced generalized and temporal lobe seizures mentioned.

CBD also prolonged survival and improved welfare scores in the *SCN1A*$^{-/-}$ mouse model that reproduces the phenotype associated with DS. Evaluations of motor function integrity were conducted to assess any contribution of suppressed motor function to the apparent anticonvulsant effects of CBD. Direct comparisons were made between Purified CBD and standard AEDs in measures of motor coordination and muscle strength. No effect of CBD on motor function was found.

The summary findings for primary pharmacodynamics are:

- CBD showed significant antiepileptiform effects similar to those in clinically used AEDs in 2 *in vitro* models of epileptiform activity.
- CBD showed significant anticonvulsant effects in 5 different *in vivo* rodent models of seizures and a mouse model of DS.
- The anticonvulsant effects of CBD are likely not due to motor suppression.

1.3. CLINICAL PHARMACOLOGY

1.3.1. SINGLE- AND MULTIPLE-DOSE PHARMACOKINETICS

CBD appeared rapidly in plasma after dosing, with little or no lag time and t_{max} of 2.5 to 5.0 hours, independent of dose.

CBD is predominantly cleared by metabolism to an inactive metabolite, 7-carboxy-cannabidiol (7-COOH-CBD), which represents ≥90% (based on area under the concentration-time curve [AUC]) of drug-related components measured in plasma. An active metabolite, 7-OH-CBD, circulates at approximately half the level of CBD, with a further metabolite, 6-hydroxy-cannabidiol (6-OH-CBD), being a minor product (<10% of CBD).

Increases in exposure (maximum measured plasma concentration [C_{max}] and AUC) to CBD and its metabolites were generally less than dose-proportional after single oral doses (1500, 3000, 4500, or 6000 mg CBD-OS), suggesting that absorption is likely to be saturable at high, supra-therapeutic doses. With multiple CBD-OS dosing, steady state is reached rapidly with moderate accumulation of CBD and its metabolites, and there was a near doubling in exposure (C_{max} and AUC) for a doubling in CBD-OS dose (750 and 1500 mg twice daily [b.i.d.]). Dose-related increases in exposure have also been demonstrated in patient studies at clinically relevant doses (10 to 20 mg/kg/day).

The terminal elimination half-life ($t_{½}$) at steady state was estimated to be 56-61 hours in healthy subjects.

Peak-trough ratios following b.i.d. dosing suggest there is very little fluctuation in within-day exposure, ensuring adequate exposure coverage throughout a 24-hour period.

1.3.2. DRUG-DRUG INTERACTION STUDIES

Cytochrome P450 (CYP) 3A4 and CYP2C19 are likely to be the main enzymes responsible for the oxidative metabolism of CBD. Population pharmacokinetic (POPPK) assessment showed no effect of concomitant CYP2C19 inhibitors, CYP3A4 inhibitors and CYP3A4 inducers on plasma exposure to CBD or its major circulating metabolites. In addition, in a POPPK assessment, there was no important effect of other AEDs (clobazam, levetiracetam [LEV], topiramate, valproate [VPA], lamotrigine [LTG], rufinamide) on systemic exposure to CBD.

A drug-drug interaction (DDI) study (Study 1543) in healthy volunteers showed no statistically significant effects of the AEDs clobazam, stiripentol (STP), or VPA on CBD plasma exposures.

Co-administration of CBD with drugs (or their metabolites) that are sensitive substrates of CYP2C19 may result in increased exposures due to this enzyme's inhibition by CBD. In the absence of probe substrate studies, there is also a theoretical potential for CBD to affect CYP3A4 substrates as an inducer or inhibitor of this isoform. Dedicated Phase 1 DDI studies with probe substrates and inhibitor/inducers are ongoing to further quantify risks as a perpetrator and victim of DDIs and thus refine guidance for prescribers. CBD does not affect major renal or hepatic transporters.

Overall, the data tend to suggest that there are no important effects of co-administration of concomitant AEDs, CYP3A4 inducers/inhibitors, or CYP2C19 inhibitors on exposure to CBD or its major circulating metabolites.

1.3.3. OTHER INTRINSIC AND EXTRINSIC FACTORS

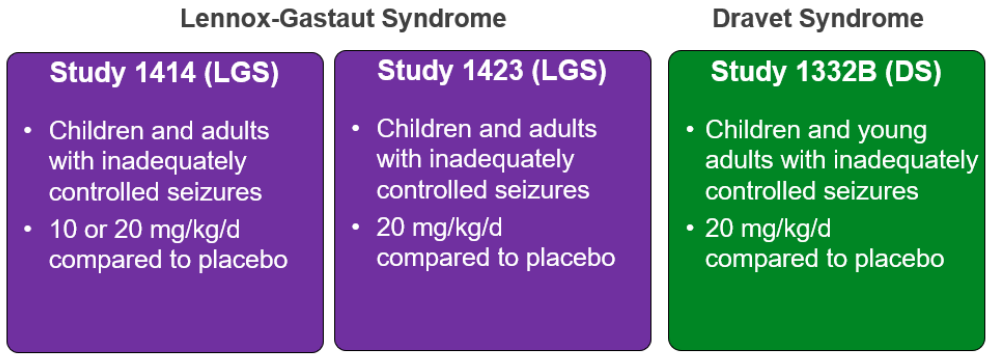
There was no important influence of CYP2C19 genetic variants on CBD exposures when comparing extensive metabolizers with ultra-rapid metabolizers and intermediate metabolizer phenotypes; however, evaluation of the poor metabolizer phenotype is ongoing.

There was no significant effect of age, weight, sex, race, gender, or renal status on the PK of CBD. The major intrinsic and extrinsic factors affecting drug exposure were increased exposure to CBD in hepatic impairment (moderate and severe) and a food interaction with a high fat meal resulting in a >4-fold increase in bioavailability.

1.4. CLINICAL EFFICACY

Evidence of clinical efficacy of CBD-OS comes from Studies 1414 and 1423 in LGS and 1332B in DS (Figure 1). All 3 studies were conducted in patients with inadequately controlled seizures in LGS or DS and investigated CBD-OS 20 mg/kg/day; Study 1414 also investigated 10 mg/kg/day.

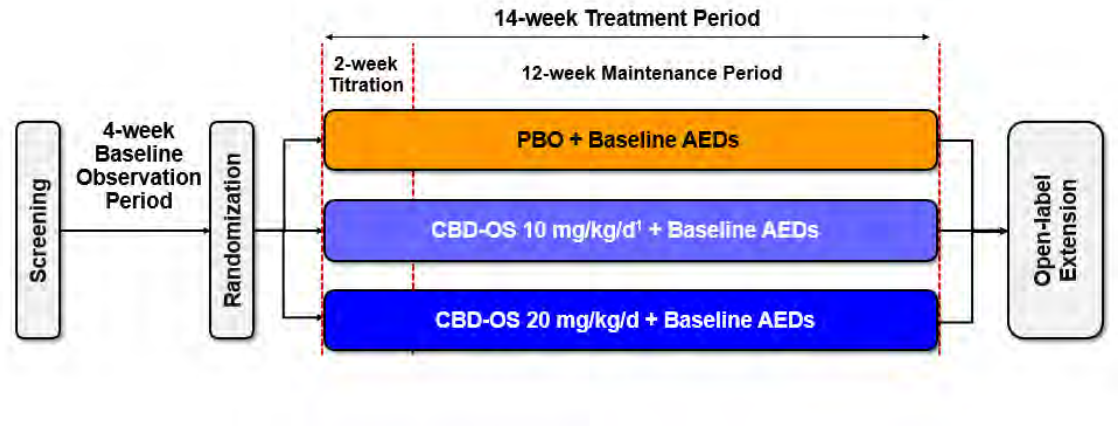
Figure 1: Overview of CBD-OS Phase 3 Studies in LGS and DS



The three Phase 3 studies used the same overall study design, shown in Figure 2. The studies consisted of:

- Screening
- Baseline Observation Period: Following screening, patients were observed for 4 weeks to establish their baseline 4-week seizure rate.
- Randomization: Patients meeting the enrollment criteria were randomized to receive CBD-OS 20 mg/kg/day, CBD-OS 10 mg/kg/day (in Study 1414 only), or placebo in addition to their baseline AEDs.
- Treatment Period: All patients began at a starting dose of 2.5 mg/kg/day and were titrated to the target dose during the first 2 weeks of the 14-week treatment period.
- Maintenance Period: The remaining 12 weeks are referred to as the maintenance period.
- Open-Label Extension (OLE) study: Patients who completed one of the controlled studies could enter the OLE study; all patients in the OLE study were titrated up to 20 mg/kg/day CBD-OS.

Figure 2: Phase 3 Study Design



[1]Dose included in LGS Study 1414 only

All 3 pivotal studies used prespecified epilepsy endpoints to evaluate efficacy. Seizure counts were recorded daily during the baseline and treatment period using an interactive voice response

system (IVRS) telephone diary. Compliance of caregivers/patients reporting daily seizures during the study was >90% across the 3 pivotal studies. The primary endpoint for all 3 studies was the percent change from baseline in the prespecified seizure type (drop seizures for the LGS studies and convulsive seizures for the DS study) during the 14-week treatment period. Key secondary endpoints included a responder analysis of the proportion of patients with ≥50% reduction from baseline in prespecified seizure type in all 3 studies, and percent change from baseline in total seizure frequency and the Subject/Caregiver Global Impression of Change (S/CGIC) in the LGS studies, all analyzed during the 14-week treatment period. Endpoints were also analyzed during the 12-week maintenance period, as seizure control requires titration to achieve effect.

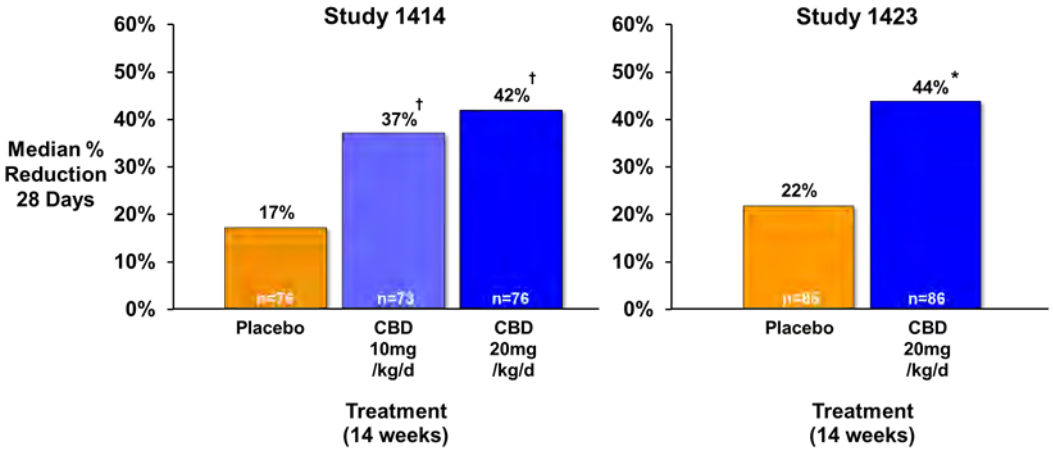
Baseline demographic, disease, and treatment characteristics were generally well balanced between the CBD-OS and placebo groups in all 3 studies. The patient population in the DS study (1332B) was similar to the LGS studies (1414 and 1423), though DS patients were on average younger and experienced a lower number of seizures during the baseline period.

1.4.1. RESULTS FROM LGS STUDIES 1414 AND 1423

Primary Endpoint Results

Both LGS studies met their primary endpoint, showing that CBD-OS had a statistically significant effect compared with placebo in the median percent change from baseline in drop seizure frequency (average per 28 days) during the 14-week treatment period in the intention to treat (ITT) analysis sets (Figure 3). In each study, CBD-OS 20 mg/kg/day was superior to placebo in reducing drop seizure frequency during the treatment period (estimated median difference: -21.57; 95% confidence interval (CI): -34.79, -6.67; p=0.0047 in Study 1414 and estimated median difference: -17.21; 95% CI: -30.32, -4.09; p=0.0135 in Study 1423); CBD-OS 10 mg/kg/day was also superior to placebo in Study 1414 (estimated median difference: -19.19; 95% CI: -31.24, -7.69; p=0.0016). Additional analyses showed efficacy of CBD-OS during the 12-week maintenance period once the target dose was achieved, with both doses of CBD-OS showing numerical superiority to placebo. The robustness of the primary analysis in each study was further supported by a series of prespecified sensitivity analyses, including analyses using the PP analysis set, ANCOVA analyses following rank and logarithmic data transformation, and use of multiple imputations to account for missing data.

Figure 3: Percent Change from Baseline in Drop Seizure Frequency During the 14-Week Treatment Period in LGS Studies 1414 and 1423 (ITT)

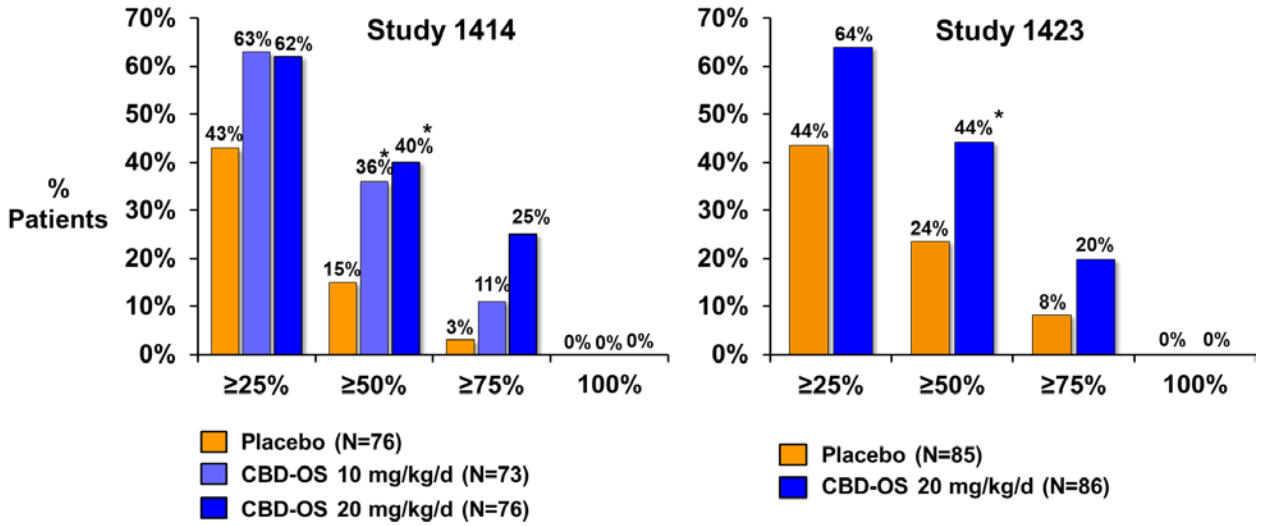


* p-value <0.05, † p-value <0.001

Key Secondary Endpoint Results

For the first key secondary endpoint, proportion of patients who achieved ≥50% reduction from baseline in drop seizure frequency during the treatment period, both studies demonstrated a statistically significant improvement with CBD-OS 20 mg/kg/day vs. placebo (odds ratio [OR]: 3.85; 95% CI: 1.75, 8.47; p=0.0006 in Study 1414 and OR: 2.57; 95% CI: 1.33, 4.97; p=0.0043 in Study 1423) as well as CBD-OS 10 mg/kg/day vs. placebo in Study 1414 (OR: 3.27; 95% CI: 1.47, 7.26; p=0.003) (Figure 4). Additional seizures thresholds of ≥25%, and ≥75% reduction from baseline were also improved with CBD-OS compared with placebo. Similar results were seen in the 12-week maintenance period. No patients achieved drop seizure freedom (100% reduction from baseline) during the overall treatment period; however, 9 patients on CBD-OS were drop seizure free during the maintenance period.

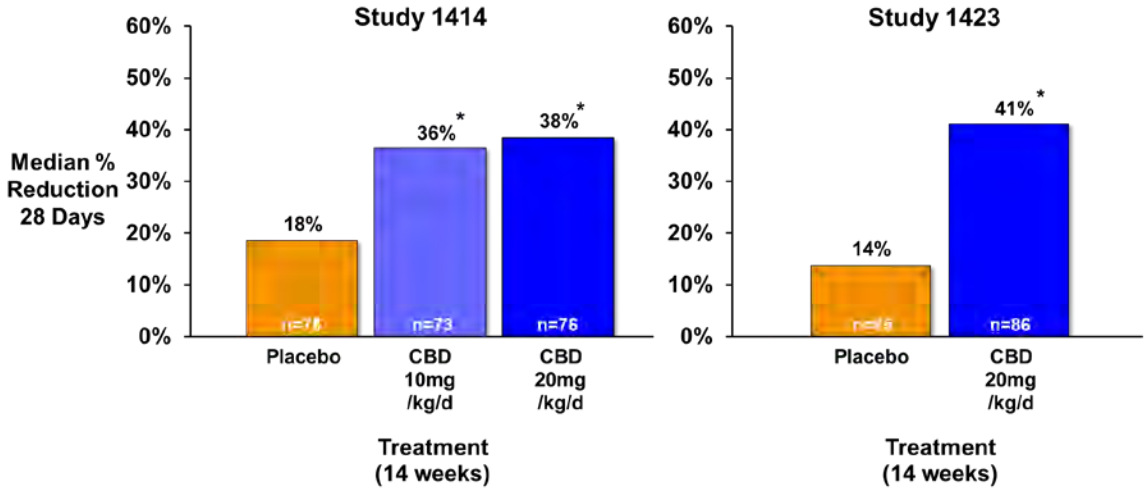
Figure 4: Proportion of Patients with ≥25%, ≥50, ≥75%, and 100% Reduction from Baseline in Drop Seizure Frequency in LGS Studies 1414 and 1423 (ITT)



* p-value <0.05

Both studies also showed statistically significant reductions in total number of seizures with CBD-OS 20 mg/kg/day vs. placebo (estimated median difference: -18.76; 95% CI: -31.80, -4.43; p=0.0091 in Study 1414 and estimated median difference: -21.23; 95% CI: -33.26, -9.37; p=0.0005 in Study 1423) and 10 mg/kg/day vs. placebo (estimated median difference: -19.47; 95% CI: -30.37, -7.47; p=0.0015 in Study 1414) during the treatment period (Figure 5). These results were similar in the 12-week maintenance period.

Figure 5: Percent Change from Baseline in Total Seizure Frequency during the Treatment Period in LGS Studies 1414 and 1423 (ITT)



* p-value <0.05

Additionally, CBD-OS showed superiority to placebo for the third key secondary endpoint, S/CGIC, which reflects the clinical meaningfulness of treatment to patients and caregivers on a

7-point Likert scale. In both studies, the odds of achieving an improvement in overall condition – a score of 5, 6, or 7 on the Likert scale – at the last study visit were statistically significantly higher with CBD-OS 20 mg/kg/day (OR: 1.83; 95% CI: 1.02, 3.30; p=0.044 in Study 1414 and OR: 2.54; 95% CI: 1.45, 4.47; p=0.001 in Study 1423) and 10 mg/kg/day (OR: 2.57; 95% CI: 1.41, 4.66; p=0.002) compared with placebo (Figure 6 and Figure 7).

Figure 6: Subject/Caregiver Global Impression of Change at Last Visit in LGS Study 1414 (ITT)

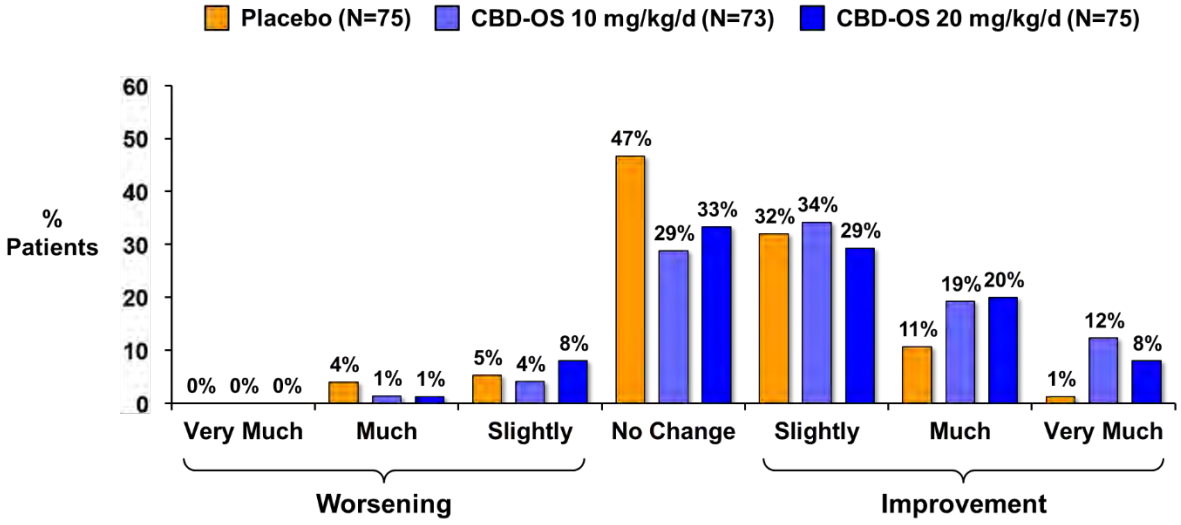
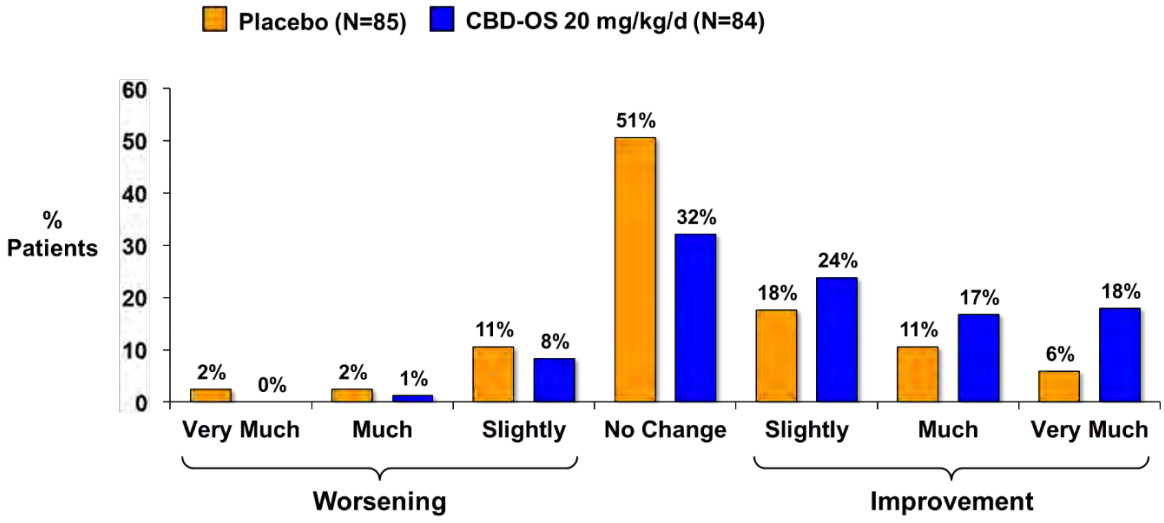


Figure 7: Subject/Caregiver Global Impression of Change at Last Visit in LGS Study 1423 (ITT)



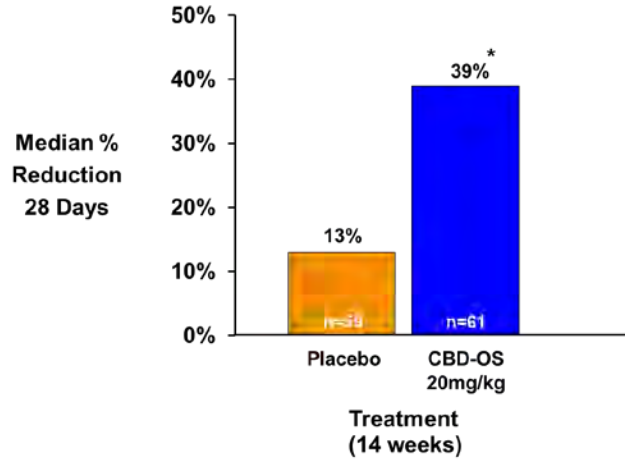
1.4.2. RESULTS FROM DS STUDY 1332B

Primary Endpoint Results

Study 1332B met its primary endpoint, showing that CBD-OS 20 mg/kg/day had a statistically significant effect compared with placebo (estimated median difference: -22.79; 95% CI: −41.06,

−5.43; p=0.0123) in the median percent change from baseline in convulsive seizure frequency (average per 28 days) during the 14-week treatment period in the ITT analysis set (Figure 8). As in the LGS studies, additional analyses showed that efficacy was maximized during the 12-week maintenance period once the target dose was achieved. The robustness of the primary analysis was further supported by a series of prespecified sensitivity analyses, including analyses using the PP analysis set, ANCOVA analyses following rank and logarithmic data transformation, and use of multiple imputations to account for missing data.

Figure 8: Percent Change from Baseline in Convulsive Seizure Frequency During the 14-Week Treatment Period in DS Study 1332B (ITT)

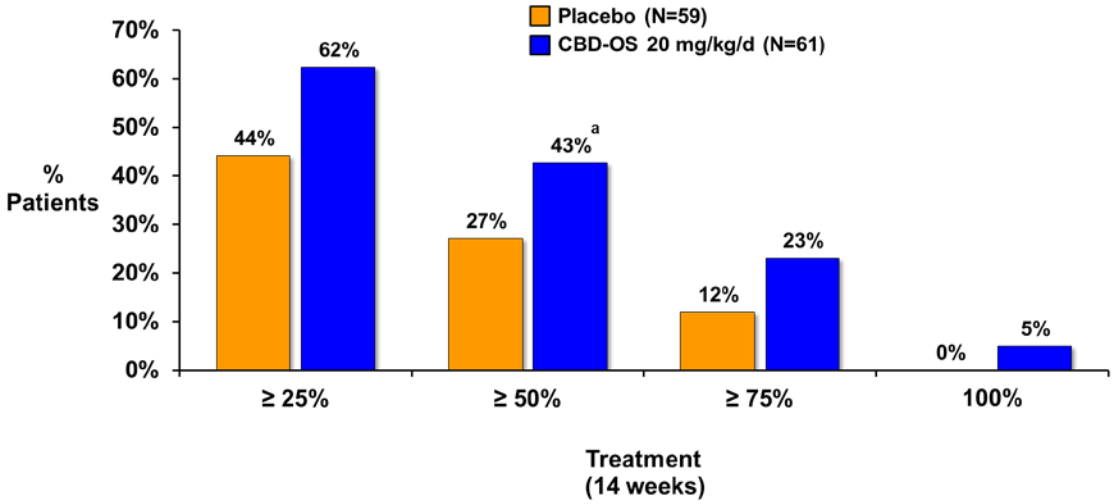


* p-value <0.05

Key Secondary Endpoint Results

On the key secondary endpoint, proportion of patients who achieved ≥50% reduction from baseline in convulsive seizure frequency during the 14-week treatment period, CBD-OS 20 mg/kg/day showed a numerical improvement compared with placebo, but this difference was not statistically significant (OR: 2.00; 95% CI: 0.93, 4.30; p=0.0784) (Figure 9). Additionally, CBD-OS showed consistent reduction from baseline in convulsive seizure frequency at the 25%, 75%, and 100% thresholds. Three patients in the CBD-OS group experienced convulsive seizure-freedom (100% reduction from baseline in seizure frequency) during the treatment period. Similar results were seen in the 12-week maintenance period.

Figure 9: Proportion of Patients with ≥25%, ≥50, ≥75%, and 100% Reduction from Baseline in Convulsive Seizure Frequency in DS Study 1332B (ITT)

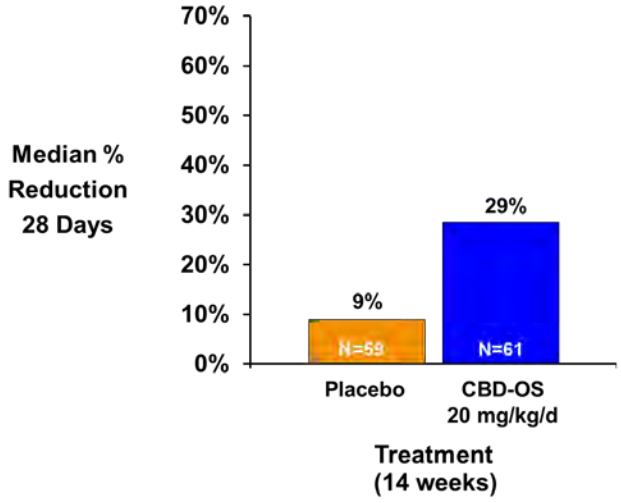


a. p-value=0.0784

Additional Endpoint Results

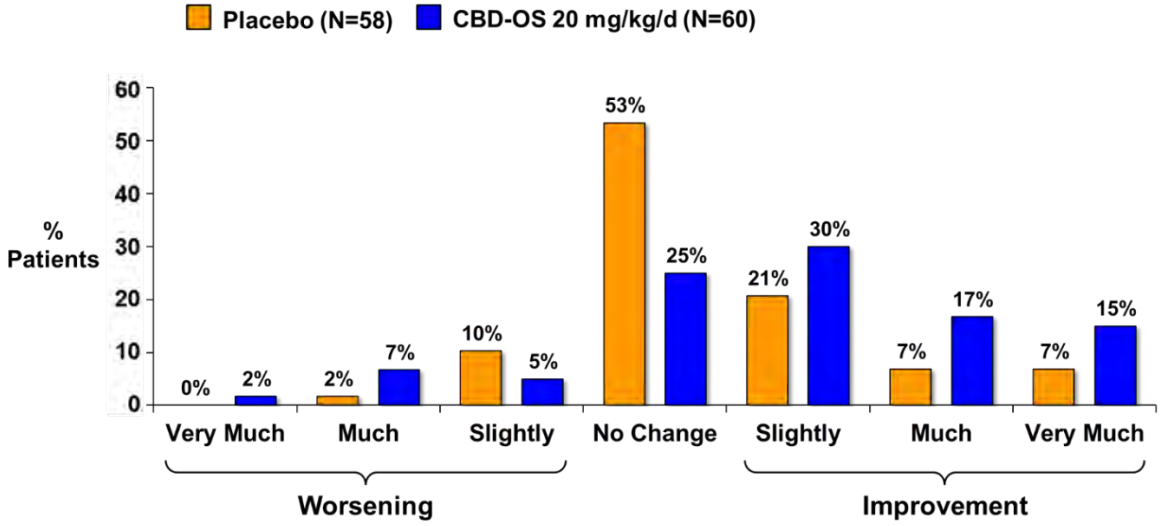
CBD-OS 20 mg/kg/day showed a statistically significant reduction in total number of seizures compared with placebo during the 14-week treatment period (estimated median difference: -9.20; 95% CI: -39.25, -1.17; nominal p-value=0.0335). These results were similar in the 12-week maintenance period.

Figure 10: Percent Change from Baseline in Total Seizure Frequency during the 14-Week Treatment Period in DS Study 1332B (ITT)



Additionally, CBD-OS showed superiority to placebo on the CGIC. The OR for improvement was 2.29, with a 95% CI of 1.17 to 4.47 (nominal p-value=0.0155), in favor of CBD-OS (Figure 11).

Figure 11: Caregiver Global Impression of Change at Last Visit in DS Study 1332B (ITT)



1.5. CLINICAL SAFETY

1.5.1. EXPOSURE

Safety data to support the use of CBD-OS in DS and LGS patients have been collected from 8 completed Phase 1 studies; 3 completed double-blind, placebo-controlled studies in target indications (1 study in DS [Study 1332 Parts A and B] and 2 studies in LGS [Studies 1414 and 1423]); 1 ongoing Phase 3 OLE study; and an EAP. Overall, 1419 unique patients with epilepsy have been exposed to CBD-OS, including 88 patients with DS and 235 patients with LGS who were enrolled in controlled studies. An additional 209 patients with DS[a] and 157 patients with LGS were exposed to CBD-OS in the ongoing long-term OLE study. In the ongoing EAP, 684 patients with refractory epilepsy received CBD-OS, including 64 patients with DS and 97 patients with LGS. Table 1 shows that the total exposure to CBD-OS represents over 1400 patient-years.

Table 1: Patient Years of Exposure to CBD-OS from All Sources

	Controlled Studies		OLE	EAP
	Placebo (N=227)	All CBD-OS (N=323)	CBD-OS (N=644)	CBD-OS (N=684)
Total Patient-years	60.42	78.07	638.15	690.02

1.5.2. OVERVIEW OF ADVERSE EVENTS

In the controlled studies, the overall AE profile was similar between patients with LGS and patients with DS (Table 2). Additionally, patients with LGS and DS have many similar disease characteristics including multiple seizure types, comorbidities, and concomitant medications.

[a] These patients had either received placebo in the completed controlled studies or originated from DS Study 1424 and were not otherwise counted.

Therefore, safety data from patients exposed to CBD-OS were combined for both indications into the All CBD-OS group.

An overview of AEs in the Phase 3 studies is shown in Table 2. For both CBD-OS and placebo groups, most of the AEs were mild to moderate in intensity. The incidence of severe AEs was 13.3% in the All CBD-OS group compared with 4.8% in the placebo group. The 3 most common severe AEs in the All CBD-OS group were somnolence (1.9%), pneumonia (1.5%), and convulsion (1.5%). When comparing by dose group, the overall incidence of AEs was higher in the 20 mg/kg/day group (90.3%) than in the 10 mg/kg/day group (81.3%).

AEs that led to withdrawal from the study were more common in patients taking CBD-OS than in the placebo group (9.3% vs. 1.3%, respectively); increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), and somnolence were the most common reasons for withdrawal in the All CBD-OS group (2.5%, 2.2%, and 1.5%, respectively). However, withdrawal due to these AEs was less common in the 10 mg/kg/day group compared with the 20 mg/kg/day group.

In the Phase 3 studies, 18.6% of the All CBD-OS patients had at least 1 event that was considered serious, compared with 7% of placebo patients. The most common serious adverse events (SAEs) in the All CBD-OS group were SE (5.0%), pneumonia (2.8%), convulsion (2.2%), and AST increased (2.2%).

In the patients exposed to CBD-OS from all sources (controlled studies, OLE, and EAP), there were 20 deaths. However, none of the fatal AEs were considered related to treatment by the reporting Investigator or the Sponsor. In the LGS and DS controlled studies, 1 patient experienced a fatal AE of acute respiratory distress syndrome in the All CBD-OS group, compared with none in the placebo group. Of the 644 patients in the OLE study, 7 had a fatal AE: 5 LGS patients and 2 DS patients. The five LGS deaths were due to: intestinal obstruction, gastrointestinal necrosis, peritonitis and septic shock; pneumonia aspiration and respiratory failure; convulsion; Rett's disorder, respiratory failure, and cardiac arrest; and hypoxic-ischemic encephalopathy. The two DS deaths were due to SUDEP. Both LGS and DS are associated with high epilepsy-related premature mortality. The incidence of mortality across the controlled studies and OLE is consistent with the high mortality rate seen in this patient population. In the EAP, 12 patients had a fatal AE caused by a variety of individual preferred terms (PTs). None of the 12 deaths occurred in the patients with LGS or DS included in the EAP.

Table 2: Overview of AEs in LGS and DS Studies

Patients with any	Pool LGS[a]		Pool DS[b]		Pool LGS/DS	
	Placebo (N=161) n (%)	All CBD-OS (N=235) n (%)	Placebo (N=66) n (%)	All CBD-OS (N=88) n (%)	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)
AEs	114 (70.8)	207 (88.1)	50 (75.8)	77 (87.5)	164 (72.2)	284 (87.9)
Severe	8 (5.0)	31 (13.2)	3 (4.5)	12 (13.6)	11 (4.8)	43 (13.3)
AEs leading to discontinuation	2 (1.2)	19 (8.1)	1 (1.5)	11 (12.5)	3 (1.3)	30 (9.3)
SAEs	12 (7.5)	46 (19.6)	4 (6.1)	14 (15.9)	16 (7.0)	60 (18.6)
Deaths	0 (0)	1 (0.4)	0 (0)	0 (0)	0 (0)	1 (0.3)

[a] Pool LGS includes Study 1414 and 1423; [b] Pool DS includes 1332A and 1332B

Overall, there was a higher incidence of AEs in the All CBD-OS group compared with the placebo group. The most common AEs in the CBD-OS group were somnolence (24.5%), decreased appetite (20.1%), and diarrhea (16.7%) (Table 3).

Table 3: Common Adverse Events in ≥10% of Patients in LGS and DS Studies

PT	Placebo in Controlled Studies (N=227; 60.42 patient-years) n (%)	All CBD-OS in Controlled Studies (N=323; 78.07 patient-years) n (%)
Patients with at least 1 AE	**164 (72.2%)**	**284 (87.9)**
Somnolence	19 (8.4)	79 (24.5)
Decreased appetite	11 (4.8)	65 (20.1)
Diarrhea	20 (8.8)	54 (16.7)
Pyrexia	24 (10.6)	42 (13.0)
Vomiting	26 (11.5)	35 (10.8)
Upper respiratory tract infection	22 (9.7)	32 (9.9)
Fatigue	8 (3.5)	31 (9.6)

1.5.3. ADVERSE EVENTS OF SPECIAL INTEREST

AEs of special interest (AESIs) included transaminases elevations, somnolence/sedation, seizure worsening, SE, falls and injuries, rash, pneumonia, and diarrhea. Details on seizure worsening, falls and injuries, rash, pneumonia, and diarrhea are provided in Section 7.3.

Transaminase Elevations

The incidence of elevated transaminases (ALT or AST >3×upper limit of normal [ULN]) was higher in the CBD-OS groups compared with the placebo group (3.0%, 18.1%, and 0.9% for CBD-OS 10 mg/kg/day, 20 mg/kg/day, and placebo, respectively). An independent review of liver function abnormalities identified in clinical laboratory testing led to the following conclusions:

- ALT and AST elevations may occur with CBD-OS therapy and appear to be due to a direct hepatocellular effect of CBD or its metabolites.

- Risk factors for ALT elevations (a more liver-specific transaminase than AST) include concomitant VPA in 84% of cases, ALT elevation at baseline, and CBD-OS doses of 20 mg/kg/day.
    - In the pivotal studies, CBD-OS 20 mg/kg/day group, 29.2% of patients taking concomitant VPA had ALT >3×ULN compared with 5.0% of patients not taking concomitant VPA.
    - In the pivotal studies, CBD-OS 20 mg/kg/day group, 30% of patients with ALT>ULN at baseline had ALT >3×ULN compared with 12.4% of patients whose ALT was ≤ULN at baseline.
    - The incidence of ALT >3×ULN in the pivotal studies was 16.3% in the 20 mg/kg/day CBD-OS group compared with 1.5% in the 10 mg/kg/day CBD-OS group.
- The onset of ALT elevations is usually within the first 30 days of continuous treatment with CBD-OS but can occur later in patients taking concomitant VPA.
- The ALT elevations were transient and typically resolved within 14 days.
- The ALT elevations reversed with discontinuation or dose adjustment of CBD-OS or concomitant VPA, and often with continued treatment with these drugs.
- No ALT elevations resulted in severe or permanent hepatic damage.
- No Hy's Law cases were seen amongst any of the patients with raised transaminases.
- Liver test monitoring is recommended for patients treated with CBD-OS.

Key characteristics of liver tests in the controlled studies are shown in Table 4.

Table 4: Frequency of Liver Test Elevations in Pivotal Study Patients

Liver Test	Multiple of ULN	Placebo (N=220) *n/N* (%)	CBD-OS 10 mg/kg/day (N=67) *n/N* (%)	CBD-OS 20 mg/kg/day (N=229) *n/N* (%)
ALT	>3×ULN and bilirubin >1.5×ULN	0/220	0/67	0/229
ALT	>3×ULN and bilirubin >2.0×ULN	0/220	0/67	0/229
AT (ALT or AST)	>3×ULN and bilirubin >1.5×ULN	0/219	0/67	0/226
	>3×ULN and bilirubin >2.0×ULN	0/219	0/67	0/226
Bilirubin	>2×ULN	0/220	0/67	0/227
ALP	>ULN	17/181 (9.4)	5/56 (8.9)	13/188 (6.9)
	>1.5×ULN	5/212 (2.4)	1/64 (1.6)	8/222 (3.6)
	>2×ULN	5/219 (2.3)	1/65 (1.5)	3/227 (1.3)
	>3×ULN	3/220 (1.4)	0/67	0/229
INR	>ULN	14/209 (6.7)	6/64 (9.4)	15/222 (6.8)
	>1.5×ULN	0/220	0/67	0/229

ALP: Alkaline phosphatase; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; AT: Aminotransferase; INR: International normalized ratio; ULN: Upper limit of normal

Note: N corresponds to the total number of patients in the treatment group. *n / N* : *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at baseline.

Somnolence/Sedation

Somnolence and sedation were common AEs with CBD-OS. The incidence of AEs of somnolence or sedation or both was 29.4% in the All CBD-OS group compared with 9.3% in the placebo group. Of the 79 patients in the All CBD-OS group with somnolence, 5 (6.3%) had SAEs, and 5 (6.3%) had AEs that led to discontinuation.

Somnolence and sedation tended to occur early in treatment but were also observed at other time points. The events were mostly non-serious, of mild or moderate severity, and did not generally lead to discontinuations. Most events of somnolence or sedation had no action taken regarding CBD-OS and resolved.

Status Epilepticus

Even with treatment, patients with LGS and DS remain at risk for status epilepticus (SE). In the randomized controlled studies, the incidence of SE was 5% in the All CBD-OS group vs. 3% in the placebo group. With the exception of 1 event in the All CBD-OS group, all events in both groups were serious, and 1 patient in the All CBD-OS group had an event that led to discontinuation. Importantly, most patients that experienced a SE event reported a clinically meaningful decrease in seizure frequency. Review of these events support that SE was related to the underlying epilepsy.

1.6. CONCLUSIONS

There is a significant unmet need for patients with drug-resistant LGS and DS who continue to have seizures despite treatment with multiple AEDs. In 3 consecutive Phase 3 studies, CBD-OS

added to other AED therapy met the primary endpoint of reduction in seizure frequency in patients with LGS and DS. Doses of CBD-OS at 10 mg/kg/day and 20 mg/kg/day were superior to placebo at reducing drop seizure frequency, and efficacy was maximized during the 12-week maintenance period once the target dose was achieved in LGS patients. Similar results were also seen in DS patients treated with CBD-OS 20 mg/kg/day; a statically significant reduction in convulsive seizure frequency was observed, and efficacy was maximized during the 12-week maintenance period. Key secondary endpoints including responder analyses, reduction in total seizures, and S/CGIC confirmed the robustness of the CBD-OS treatment effect.

The safety and tolerability profile of CBD-OS is predictable, and the potential risks are manageable through the proposed label and medication guide. Most of the AEs in the clinical studies were mild to moderate in intensity; the most common AEs in the All CBD-OS group included somnolence, decreased appetite, and diarrhea. Elevated transaminases were observed more frequently in CBD-OS patients than placebo, and increased AST and increased ALT were the most common reasons for discontinuing CBD-OS treatment. Therefore, routine liver tests prior to CBD-OS use and periodically during treatment are recommended. In addition, GW will implement a post-marketing enhanced pharmacovigilance program to monitor the safety profile of CBD-OS, with a focus on liver abnormality reports.

Overall, CBD-OS provides a positive benefit-risk for patients with drug-resistant LGS or DS and can satisfy an unmet need by providing an additional treatment option to reduce the number of seizures in LGS and the first indicated treatment option for DS.

2. BACKGROUND ON LENNOX-GASTAUT SYNDROME AND DRAVET SYNDROME

Summary

- LGS and DS are rare, severe forms of epilepsy with onset in early childhood and poor long-term prognoses.
- Almost all patients with LGS and DS continue to have seizures despite treatment with multiple AEDs.
- Large numbers of uncontrolled seizures put patients with LGS and DS at high risk for intellectual and developmental disabilities, serious injury, and premature death.
- Patients with LGS and DS are affected by multiple seizure types; drop seizures are the most clinically meaningful type of seizure in LGS, and convulsive seizures are the most clinically meaningful type of seizure in DS.
- The primary goal of therapy for LGS and DS is to reduce seizure frequency and severity while limiting the AEs associated with multiple AEDs.
- There are currently 6 FDA approved adjunctive treatment options for LGS, and none for DS.
- Patients with LGS and DS typically take 3 or more AEDs in addition to off-label and non-pharmacological treatments, which do not usually provide sufficient seizure control in this population.
- There is a significant unmet medical need for new classes of antiepileptic treatments with different mechanisms of action to add to available therapies to help manage seizure burden in patients with drug-resistant LGS and DS.

2.1. OVERVIEW OF LENNOX-GASTAUT SYNDROME AND DRAVET SYNDROME

LGS and DS are rare, childhood-onset forms of epilepsy. These disorders are 2 of the most drug-resistant forms of epilepsy, with all seizure types extremely resistant to conventional AEDs. LGS and DS are associated with a large number of seizures of multiple seizure types, and the majority of patients also experience severe intellectual and developmental disabilities and neurological disturbances.

While LGS has multiple etiologies, approximately 75% of patients with DS have mutations in the *SCN1A* gene (Scheffer 2012). The onset of LGS is typically between 3 and 5 years of age (Camfield 2011), and the onset of DS usually occurs between 4 and 8 months of age and is often triggered by fever. Based on calculations performed by the Sponsor to support requests filed to FDA in February 2017 for rare pediatric disease designations, the estimated prevalence is 30,000 patients with LGS and approximately 4,100 patients with DS in the US (data on file).

LGS and DS are characterized by the presence of multiple seizure types. All seizure types may progress to SE, of either convulsive or nonconvulsive type.

LGS and DS are extremely resistant to treatment during childhood, and patients continue to have uncontrolled seizures throughout their lifetime. Cognitive impairment is apparent in ≥75% of all LGS patients by 5 years post-onset, and behavioral and psychiatric comorbidities (including ADHD and aggressive behavior) are common (Camfield 2011). Only 10% of LGS patients live independently as adults – 90% require a caregiver or are institutionalized. Similarly, long-term seizure outcomes in DS are poor, with a long-term study reporting 84% of DS patients still having seizures in adulthood (Akiyama, Kobayashi et al. 2010, Takayama, Fujiwara et al. 2014). Significant developmental delay is apparent from the second year onwards, and associated neuropsychological disturbances, such as ADHD, are common. Intellectual impairment affects nearly all patients and is severe in 50% of cases. Dependency in adulthood is a nearly constant feature of DS due to the chronic significant disability (Genton, Velizarova et al. 2011).

Children and adolescents with LGS and DS have an increased risk of death. A population-based study of children with epilepsy showed that all-cause mortality was 14 times greater among patients with LGS than in the general population (Autry, Trevathan et al. 2010). Neurological comorbidity including prolonged seizures and SE are correlated with mortality and, in particular, SUDEP. SUDEP and SE are the most common causes of death in DS, with drowning and accidental death following seizures being other common causes. Dravet syndrome is associated with many risk factors for SUDEP, including frequent generalized tonic-clonic seizures, early seizure onset, polytherapy, and developmental delay (Sillanpaa and Shinnar 2010, Hesdorffer, Tomson et al. 2011). A recent review of 177 unique cases of death in DS highlighted that 73% of the deaths occurred before the patient reached 10 years of age, with the cause being SUDEP in 49% of cases, and SE in 32% of cases (Shmuely, Sisodiya et al. 2016). Longitudinal follow-up (median 17 years) of 100 unrelated DS patients enrolled into the Epilepsy Genetics Research Program reported 17 deaths with a median patient age of 7 years, equating to a DS-specific mortality rate of 15.84 per 1000 patient-years (Cooper, McIntosh et al. 2016). SUDEP was the most common cause of death (59%), equating to a DS-specific SUDEP rate of 9.32 per 1000 patient-years, which is nearly twice the rate for adults with drug-resistant epilepsy.

2.2. CURRENT TREATMENT OPTIONS

Treatment of severe encephalopathic epilepsies involves life-long therapy with multiple AEDs. Most patients require regular office visits and laboratory testing to monitor efficacy and safety to avoid toxicity to vital organ systems.

There are currently no AEDs approved in the US for the treatment of DS. There are 6 approved treatments as adjunctive therapy for LGS in the US: felbamate, LTG, topiramate, rufinamide, clonazepam, and clobazam.

Table 5 provides an overview of treatment options in LGS and DS. In clinical practice, VPA is often used for both LGS and DS to prevent the initial recurrence of convulsive seizures, and benzodiazepines (e.g., diazepam, midazolam, clonazepam, or clobazam) are frequently co-administered to limit the duration of prolonged seizures. Second-line and later options in DS

typically include STP (an investigational medicine in the US), topiramate, ketogenic diet, LEV, bromides, and vagus nerve stimulation (VNS), while in LGS, LTG, rufinamide, lacosamide, and felbamate are additionally used.

Table 5: Treatment Options in LGS and DS

Line of Treatment	LGS	DS
1st line	VPA, LEV, or LTG	VPA
2nd line	+ topiramate or clobazam	+ clobazam
3rd line	+ rufinamide, lacosamide, zonisamide, or perampanel	+ STP or topiramate
4th line	felbamate	-

In most cases, the relief provided by polytherapy is insufficient (Arzimanoglou, French et al. 2009, Chiron and Dulac 2011), with drug-resistant epilepsy noted to be as high as 90% in LGS (Ostendorf and Ng 2017). Patients with DS may be prone to seizure exacerbation with sodium channel blockers such as carbamazepine, oxcarbazepine, LTG, phenytoin, and vigabatrin (Wirrell, Laux et al. 2017). Many of the drugs that are used to treat LGS or DS carry a substantial AE burden, with some of the AEs being potentially fatal (Goldenberg 2010). Despite these risks, the continued use of these medications indicates the importance of reducing the frequency of seizures to the patients, caregivers, and the prescribing neurologists.

Patients with LGS and DS need additional options to treat the large number of seizures and multiple seizure types that persist despite treatment with existing therapy. Additional therapies are needed to further reduce the incidence of seizures.

3. PRODUCT DESCRIPTION

Summary

- CBD-OS is proposed to be indicated for the adjunctive treatment of seizures associated with LGS and DS in patients 2 years of age and older at a dose of 10 to 20 mg/kg/day.
- The mechanisms of action of CBD are believed to be novel when compared to current AEDs; CBD is thought to exert its anticonvulsant effect by reducing neuronal hyperexcitability via TRPV1, GPR55, and adenosine modulation and inflammation.
- Nonclinical data support the anticonvulsant effect of CBD.

3.1. PROPOSED INDICATION AND DOSING REGIMEN

The proposed indication for CBD-OS is for the adjunctive treatment of seizures associated with LGS or DS in patients 2 years of age and older.

CBD-OS should be taken twice daily with food, starting at a dose of 2.5 mg/kg (5 mg/kg/day) for 1 week, and increasing to a therapeutic dose of 5 mg/kg (10 mg/kg/day) after the first week. Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg (5 mg/kg/day) to 10 mg/kg twice daily (20 mg/kg/day).

CBD-OS is supplied in bottles as a clear, colorless to yellow solution. Each bottle contains 100 mL of solution comprising 100 mg/mL CBD with the excipients sesame oil (a lipid-based solvent which has an acceptable safety profile and stability); sucralose (a sweetener) and strawberry flavoring for palatability; and 7.9% (w/v) anhydrous ethanol (a co-solvent for sucralose).

3.2. MECHANISM OF ACTION

As with many AEDs, the precise mechanisms by which CBD exerts its anticonvulsant effect in humans are unknown. Based upon preclinical findings, CBD-OS has a novel, multi-modal mechanism of action that targets neuronal excitability unrelated to sodium channels and is structurally unrelated to any other AED.

In preclinical models, CBD reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 and modulation of adenosine-mediated signaling (Ryan, Drysdale et al. 2009, Sylantyev, Jensen et al. 2013, Iannotti, Hill et al. 2014, French, Koepp et al. 2017).

CBD does not exert its anticonvulsant effects through interaction with cannabinoid receptors (Ibeas Bih, Chen et al. 2015). Although CBD is a cannabinoid, it has negligible affinity or activity *in vitro* at either cannabinoid receptors, CB_1 or CB_2, and is negative in the tetrad test, an accepted bioassay for CB_1 agonism (McPartland, Duncan et al. 2015).

3.3. NONCLINICAL STUDIES

Antiepileptic properties of Purified CBD have been demonstrated *in vitro* with the 4-AP and the Mg^{2+}-free models of epileptiform activity in MEA recordings from rat hippocampal slices. Translation of the *in vitro* research to *in vivo* efficacy was demonstrated in rodent acute seizure models targeting a range of seizure types in order to address the considerable variation in seizure types seen in clinical patients:

- Purified CBD, 7-OH-CBD, and 7-COOH-CBD in the MES model of generalized seizure in mice
- Purified CBD in the audiogenic seizure in mice
- Purified CBD in chemically-induced models of generalized, temporal lobe, or partial seizures in rats
- Co-administration of Purified CBD with an AED in chemically-induced models or generalized and temporal lobe seizures in rats

The exact mechanism of anticonvulsant efficacy of CBD is not yet fully elucidated. *In vitro* studies suggest the anticonvulsant property is at least partly due to the modulation of intracellular Ca^{2+} (particularly related to CBD activity at GPR55 and TRP channels). Additionally, information from the literature suggests a role for adenosine reuptake.

3.4. *IN VITRO* - ANTIEPILEPTIFORM ACTIVITY

3.4.1. PURIFIED CBD IN TWO *IN VITRO* MODELS OF EPILEPTIFORM ACTIVITY

The effects of Purified CBD (0.01 to 100 μM) were investigated in the 4-AP and the Mg^{2+}-free *in vitro* models of epileptiform activity using MEA recordings of rat hippocampal slices.

Overall, data from these *in vitro* studies demonstrated CBD to have therapeutic potential in the control of epilepsy and provided enough evidence to take this plant-derived cannabinoid into well established *in vivo* models of seizure (Jones, Hill et al. 2010).

CBD (≥10 nM) exerted significant anti-epileptiform effects on both 4-AP and Mg^{2+}-free epileptiform local field potential (LFP) in acute hippocampus slices. The effects were concentration-related and region-dependent. The magnitude of CBD effects on LFP amplitude and duration were comparable to the clinically used AEDs, felbamate and phenobarbital (PB) (Hill, Jones et al. 2010).

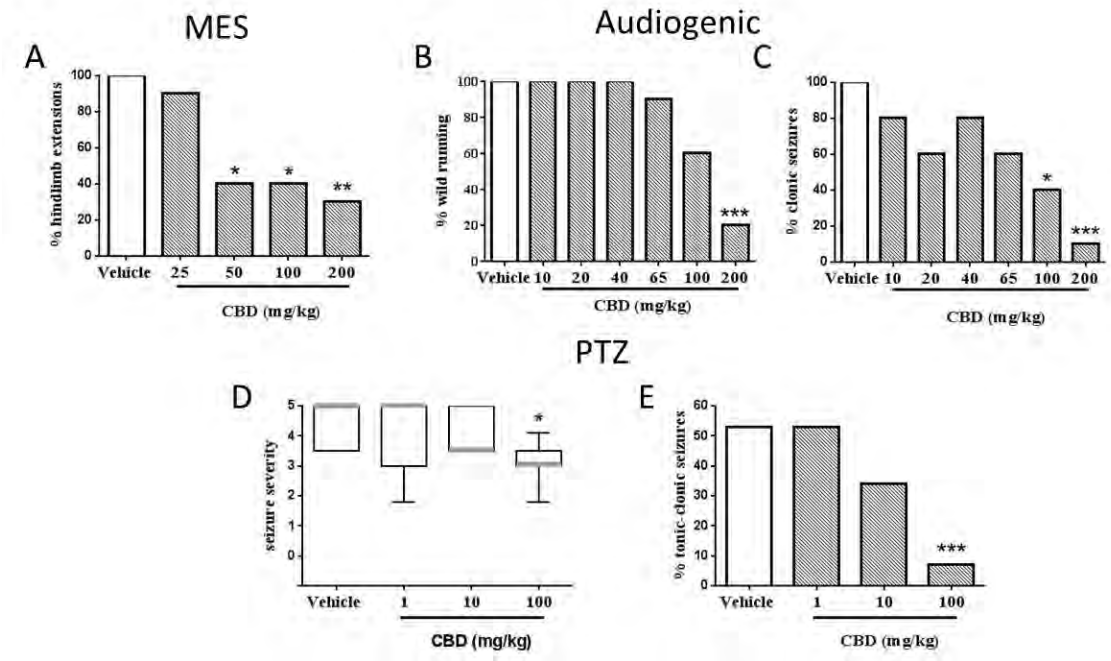
3.5. *IN VIVO* - ANTICONVULSANT ACTIVITY IN SEIZURE MODELS

3.5.1. SUMMARY OF RESULTS FROM *IN VIVO* SEIZURE MODELS

Overall, Purified CBD showed anticonvulsant effects in 5 well-established models of seizure. In mice, Purified CBD demonstrated efficacy in the MES model of generalized seizure and the audiogenic seizure test. In rats, Purified CBD reduced mortality, decreased seizure severity, or decreased the incidence of the most severe seizures in the PTZ-induced seizure model. Furthermore, Purified CBD reduced mortality or decreased the incidence of the most severe

seizures in the pilocarpine- and penicillin-induced seizure models. Representative data are pictured in Figure 12 and Figure 13. When co-administered with AEDs, CBD retained its anticonvulsant effects and was well tolerated. The interaction between CBD and VPA was additive or synergistic in the PTZ model when the lowest dose of VPA (100 mg/kg) was administered (Jones, Hill et al. 2014).

Figure 12: Representative Data of the Effects of CBD in Acute Models of Generalized Seizure

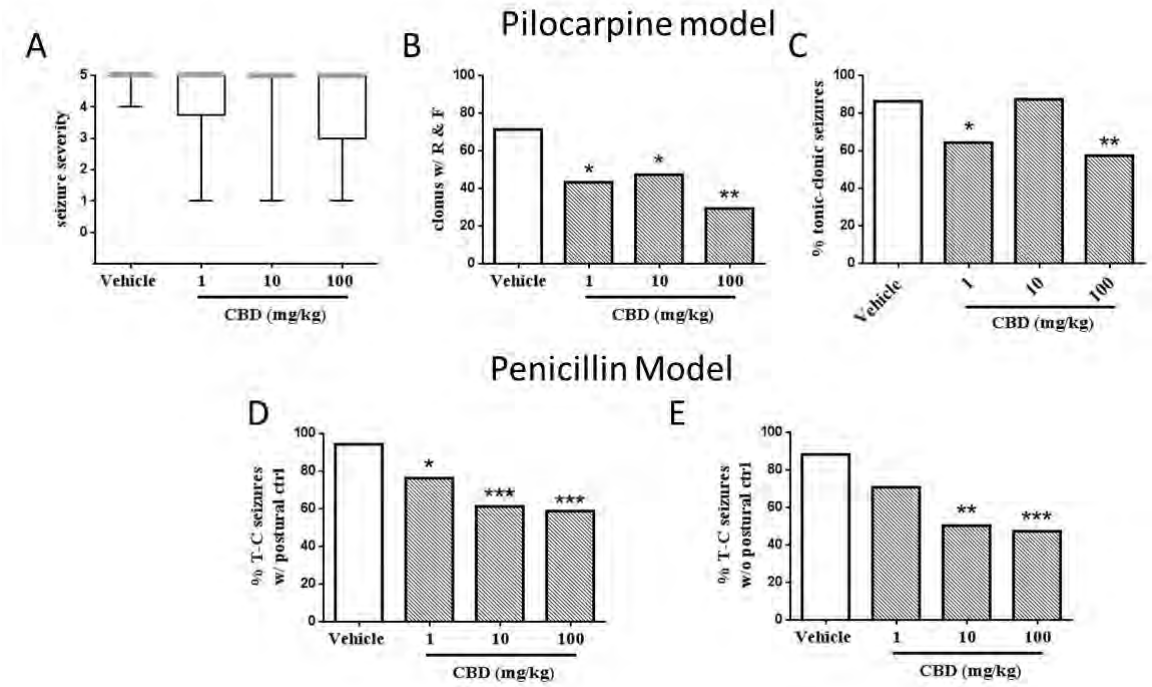


*p<0.05. **p<0.01. ***p<0.001. Data are presented as differences from vehicle group. n≥14 per group. Differences between groups in the percentage of animals that develop different seizures states were assessed using a nonparametric binomial test. Differences between seizure severity values were assessed using one-way analysis of variance with a *post hoc* Tukey's test.

For Panel D, the median seizure severity is indicated by a thick grey horizontal line, the 25th and 75th percentiles are indicated by the black box, and the 10th and 90th percentiles are indicated by the whiskers.

Data published in Jones, Hill et al. (2015) (Panel A) and Jones, Glyn et al. (2012) (Panels D and E).

Figure 13: Representative Data of the Effects of CBD in Acute Models of Temporal Lobe and Partial Seizures



*p<0.05. **p<0.01. ***p<0.001. Data are presented as differences from vehicle group. n ≥ 14 per group. Differences between groups in the percentage of animals that develop different seizures states were assessed using a nonparametric binomial test. Differences between seizure severity values were assessed using one-way analysis of variance with a *post hoc* Tukey's test.
ctrl = control; R & F = rearing and falling; T-C = tonic-clonic.
For Panel A, the median seizure severity is indicated by a thick grey horizontal line, the 25th and 75th percentiles are indicated by the black box, and the 10th and 90th percentiles are indicated by the whiskers.
Data published in Jones, Glyn et al. (2012).

3.5.2. MAXIMAL ELECTROSHOCK MODEL OF GENERALIZED SEIZURE IN MICE

3.5.2.1. PURIFIED CBD

Male Institute for Cancer Research mice (10/group) were given 0 (1:1:18 ethanol:Kolliphor EL:saline), 25, 50, 100, or 200 mg/kg Purified CBD. The MES seizures were induced by a current of 30 mA delivered at 100 Hz for 200 ms via ear clamps. Seizure behavior was observed for 10 seconds during electroshock.

Purified CBD had no significant anticonvulsant effect on animals displaying forelimb extension; however, 200 mg/kg Purified CBD significantly reduced seizure severity. In the main measure of seizure behavior, Purified CBD had a significant anticonvulsant effect on animals displaying hindlimb extension, with significantly fewer animals exhibiting hindlimb extensions as compared to the vehicle group (100%, 40%, 40%, or 30% in groups given 0, 50, 100, or 200 mg/kg CBD, respectively) (Jones, Hill et al. 2015).

3.5.2.2. PURIFIED CBD OR 7-OH-CBD

Male Naval Medical Research Institute (NMRI) mice (12/group) were given an i.p. injection of 0 (vehicle; 10% ethanol and 20% Kolliphor HS 15 in physiological saline), 0 (neutral vehicle; 0.2% hydroxypropyl methylcellulose in physiological saline), 2 mg/kg diazepam (positive control), 200 mg/kg Purified CBD, or 150 or 200 mg/kg 7-OH-CBD. Seizures were induced by an electrical shock stimulus via corneal electrodes. The number of tonic convulsions and mortality rate were assessed.

Eleven of the 12 mice in the neutral vehicle group displayed tonic convulsions, and there were no differences in effects on seizures for the 2 vehicle substances. Both Purified CBD and 7-OH-CBD markedly decreased the number of mice showing tonic convulsions (−91% and −100% for both doses, respectively).

3.5.2.3. 7-COOH-CBD

NMRI mice (12/group) were given an i.p. injection of either vehicle (1:1:18 of ethanol/ Kolliphor EL/physiological saline), 2 mg/kg diazepam (positive control), 200 mg/kg Purified CBD, or 50, 100, 150 or 200 mg/kg 7-COOH-CBD. Seizures were induced by an electrical shock stimulus via corneal electrodes. The number of animals showing tonic convulsions were assessed. Eleven of the 12 mice in the vehicle group displayed tonic convulsions. Both purified CBD and diazepam significantly reduced the number of mice showing tonic convulsions (-91% $p<0.001$ and -82% $p<0.001$ for both doses respectively). 7-COOH-CBD did not change the number of mice showing tonic convulsions at any dose tested as compared with vehicle controls.

3.5.3. AUDIOGENIC SEIZURE IN MICE

3.5.3.1. PURIFIED CBD

Male mice susceptible to audio-induced seizures (DBA/2, 10/group) were given 0 (1:1:18 ethanol:Kolliphor EL:saline), 10, 20, 40, 65, 100, or 200 mg/kg Purified CBD. Doses were administered via i.p. injection 60 minutes before mice were individually placed in a Plexiglas jar mounted with an electric bell. Upon activating the bell (tone of 110 to 120 dB), the latencies to wild runnings and clonic and tonic seizures were measured. The number of deaths was also recorded. The bell was activated until death occurred or for a maximum of 60 seconds.

Purified CBD demonstrated clear and dose dependent anticonvulsant activity. The number of wild runnings decreased by 80% at 200 mg/kg, and clonic convulsions decreased by 60% and 90% at 100 and 200 mg/kg, respectively. Furthermore, Purified CBD decreased tonic convulsions and did not increase mortality compared with the vehicle group.

3.5.4. CHEMICALLY-INDUCED SEIZURES

Purified CBD was tested in 3 models of chemically-induced seizures when administered alone. CBD showed anticonvulsant effects in all models (generalized, temporal lobe, and partial seizures). Since the intended clinical use for CBD-OS is as an adjunctive treatment to existing AED treatment, a known anticonvulsant dose of Purified CBD was co-administered with standard AEDs and evaluated in models of generalized and temporal lobe seizures. The co-administered AEDs were selected based on high prescription rate in treatment of all seizure

types and reported efficacy in the nonclinical seizure models used. The objectives of co-administration assessments were to ascertain whether Purified CBD retains anticonvulsant effects, is well-tolerated, and has any beneficial (additive or synergistic) interactions with AEDs.

3.5.4.1. PURIFIED CBD IN THE ACUTE PENTYLENETETRAZOLE-INDUCED MODEL OF GENERALIZED SEIZURE IN RATS

Adult male Wistar Kyoto rats (15/group) received i.p. injections of 0 (vehicle, 1:1:18 ethanol:Kolliphor EL:saline), 1, 10, or 100 mg/kg Purified CBD before seizure induction by 80 mg/kg PTZ (i.p.) administered 60 minutes later. Behavior was recorded for 30 minutes.

Purified CBD at 100 mg/kg significantly reduced mortality and seizure severity compared to vehicle-treated animals (Jones, Glyn et al. 2012). In contrast, animals treated with 100 mg/kg Purified CBD had a significantly reduced median score of 3.5 (forelimb clonus with a tonic component and righting reflex preserved). The reduction in seizure severity and mortality was associated with a marked decrease in the mean number of occurrences and percentage of animals that developed tonic-clonic seizures of 0.1±0.1 and 7%, respectively, at 100 mg/kg Purified CBD compared to 0.7±0.2 and 53%, respectively, in the vehicle group. In addition, Purified CBD (100 mg/kg) significantly reduced the mean number of occurrences and percentage of animals that showed fully developed tonic-clonic seizures with 0.1±0.1 and 7%, respectively, compared to 0.5±0.1 and 53%, respectively, in vehicle control animals. There was no effect at ≤10 mg/kg Purified CBD.

3.5.4.2. CBD IN THE ACUTE PENTYLENETETRAZOLE-INDUCED MODEL OF GENERALIZED SEIZURE IN RATS

Adult male Wistar Kyoto rats (15/group) were given i.p. injections of 0 (vehicle, 1:1:18 ethanol:Kolliphor EL:saline), 40, 80, 120, or 150 mg/kg CBD (with 0.67, 1.33, 2.00, or 5.6 mg/kg THC, respectively). Administration was 60 minutes before seizure induction by 85 mg/kg PTZ. Behavior was recorded for 30 minutes.

Mortality was reduced at 80 and 120 mg/kg, and the incidence of the most severe seizures was reduced at 120 mg/kg. At 150 mg/kg CBD, mortality and seizure severity were significantly reduced and the onset time to seizure and proportion of seizure-free animals were significantly increased.

3.5.4.3. PURIFIED CBD CO-ADMINISTERED WITH ETHOSUXIMIDE IN THE ACUTE PENTYLENETETRAZOLE-INDUCED MODEL OF GENERALIZED SEIZURE IN RATS

Co-administration of Purified CBD with ethosuximide (ESM) was investigated in the acute PTZ-induced rat model of generalized seizure. Doses of ESM were selected to produce approximately 100%, 70%, and 30% maximal anticonvulsant effect when administered alone.

CBD alone (comparing 100 mg/kg Purified CBD co-administered with ESM vehicle to CBD vehicle co-administered with ESM vehicle) significantly decreased mortality and produced a decrease in median seizure severity similar in magnitude to other studies evaluating CBD administered alone. When given alone, ESM was anticonvulsant in measures of latency to

seizure, seizure severity, and mortality, with a tendency towards an all-or-nothing response (Jones, Hill et al. 2014).

No additive, synergistic, or antagonistic effects were observed for co-administration of Purified CBD and ESM.

3.5.4.4. PURIFIED CBD CO-ADMINISTERED WITH VALPROIC ACID (SODIUM VALPROATE) IN ACUTE PENTYLENETETRAZOLE-INDUCED MODEL OF GENERALIZED SEIZURE AND ACUTE PILOCARPINE-INDUCED MODEL OF TEMPORAL LOBE SEIZURE IN RATS

Co-administration of Purified CBD with VPA was investigated in the acute PTZ and pilocarpine rat models of generalized and temp oral lobe seizure, respectively. Doses of VPA were selected to produce approximately 100%, 70%, and 30% maximal anticonvulsant effect when administered alone.

Anticonvulsant effects observed with co-administration were similar to other studies evaluating CBD administered alone in these same models (Jones, Glyn et al. 2012, Jones, Hill et al. 2014). Prior to seizure induction in either model, there were no adverse effects associated with CBD, while ≥250 mg/kg VPA produced clear adverse effects including stilt-like walking, wet dog shakes, and occasional and apparently involuntary jerking movements.

CBD produced no negative interactions with VPA. The interaction between CBD and VPA was additive or synergistic in the PTZ model when the lowest dose of VPA (100 mg/kg) was administered.

3.5.4.5. PURIFIED CBD IN THE ACUTE PILOCARPINE-INDUCED MODEL OF TEMPORAL LOBE SEIZURE IN RATS

Adult male Wistar Kyoto rats (≥14/group) received i.p. injections of 0 (vehicle, 1:1:18 ethanol:Kolliphor EL:saline), 1, 10, or 100 mg/kg Purified CBD. After 15 minutes, animals received an i.p. injection of the muscarinic receptor antagonist methylscopolamine to minimize peripheral pilocarpine-induced side effects. Forty-five minutes later, animals were given an i.p. injection of 380 mg/kg pilocarpine to induce seizures. Behavior was recorded for 60 minutes.

There were no group differences in mortality, overall severity, or the percentage of seizure-free animals (Jones, Glyn et al. 2012). Purified CBD exhibited modest anticonvulsant effects, significantly lowering the incidence of the most severe seizures. Specifically, the percentage of rats showing bilateral forelimb clonus with rearing and falling decreased from 71% in the vehicle group to 43%, 47%, and 29% in the 1, 10, and 100 mg/kg Purified CBD groups, respectively. Furthermore, the percentage of rats showing tonic-clonic seizures decreased from 86% in the vehicle group to 64% and 57% for 1 and 100 mg/kg Purified CBD, respectively. There was no effect on percentage of rats showing tonic-clonic seizures at 10 mg/kg Purified CBD.

3.5.4.6. PURIFIED CBD CO-ADMINISTERED WITH PHENOBARBITAL IN THE ACUTE PILOCARPINE MODEL OF TEMPORAL LOBE SEIZURE IN RATS

Co-administration of Purified CBD with PB was investigated in the acute pilocarpine rat model of temporal lobe seizure. Doses of PB were selected to produce approximately 100%, 70%, and 30% maximal anticonvulsant effect when administered alone.

In contrast with another study using the acute pilocarpine rat model of temporal lobe seizure, Purified CBD alone did not show significant anticonvulsant effects (Jones, Hill et al. 2014). Phenobarbital had significant anticonvulsant actions in most measures (seizure severity, mortality, proportion of seizure-free animals, and incidence of tonic-clonic seizures).

No additive or synergistic effects were observed for co-administration of Purified CBD and PB.

3.5.4.7. PURIFIED CBD IN THE PENICILLIN-INDUCED MODEL OF PARTIAL SEIZURE IN RATS

Adult male Wistar Kyoto rats (≥17/group) were given i.p. injections of 0 (vehicle, 1:1:18 ethanol:Kolliphor EL:saline), 1, 10, or 100 mg/kg CBD. After 60 minutes, 525 IU penicillin (in 1.5 µL distilled water) was administered via intracerebroventricular infusion into the right lateral cerebral ventricle to induce partial seizures. Behavior was recorded for 120 minutes.

Purified CBD at ≥10 mg/kg caused significant 2-fold reductions in mortality (Jones, Glyn et al. 2012). Animals given 100 mg/kg CBD had reduced seizure severity scores. CBD did not significantly affect the percentage of seizure-free animals. CBD markedly decreased the percentage of animals that developed the most severe seizure state (i.e., tonic-clonic seizures without postural control) from 88% in the vehicle group to 71%, 50%, and 47% in groups given 1, 10, and 100 mg/kg Purified CBD, respectively.

3.5.4.8. PURIFIED CBD IN PILOCARPINE INDUCED STATUS EPILEPTICUS IN RATS

Adult Male Wistar Kyoto rats of > postnatal day 21 (four groups of ≥12/group) were administered either Purified CBD (10 mg/kg 1 hour prior to seizure induction), the positive control PB (30 mg/kg 30 minutes prior to seizure induction), or their respective vehicles (CBD: polyoxyl 15 hydroxystearate (Kolliphor HS) 50 mg/kg; glycerol anhydrous 20 mg/mL; EDTA 1mg/mL; ascorbic acid 2 mg/mL; monothioglycerol 2 mg/mL; water qs to 1 mL; PB: 0.9% NaCl) intravenously via the tail vein. Methylscopolamine was administered subcutaneously to all animals 45 minutes before spontaneous recurrent seizures were induced using pilocarpine via i.p. injection. Behavior was recorded for 1 hour following seizure induction, and severity was scored using the modified Racine scale.

Both CBD ($p=0.0318$) and PB ($p<0.0001$) significantly reduced the maximum seizure severity compared to their respective vehicle treated group.

3.5.5. MOTOR FUNCTION COMPARISONS WITH STANDARD ANTIEPILEPTIC DRUGS

The effects of Purified CBD on motor coordination and muscle strength were evaluated in 2 studies. Anticonvulsant efficacy is not likely due to the suppression of motor function as CBD did not induce significant effects on coordination, balance, fine motor control, or muscle tone at doses in excess of those required for anticonvulsant activity. Such disruptions in motor function were observed with clinically-used AEDs.

3.5.5.1. EFFECTS OF PURIFIED CBD AND STANDARD ANTIEPILEPTIC DRUGS ON THE ACCELERATING ROTAROD TEST OF MOTOR FUNCTION

Male Wistar Kyoto rats (10 to 12/group) were given an i.p. injection of 0 (vehicle; 2:1:17 Kolliphor EL:ethanol:saline) or 200 mg/kg CBD. Effects were compared to those in rats given a single injection of saline or a known AED (40 mg/kg PB; 250 mg/kg VPA; 175 mg/kg ESM). Animals were evaluated based on time to fall from an accelerating rotarod apparatus.

Purified CBD had no effect on the latency of time to fall (Jones, Glyn et al. 2012). Mean time to fall (± standard error of the mean) was 118±14 and 135±17 seconds for vehicle and CBD groups, respectively. Of the 3 AEDs assessed, only PB had a significant deleterious effect on motor performance (Jones, Hill et al. 2014).

3.5.5.2. EFFECTS OF PURIFIED CBD AND STANDARD ANTIEPILEPTIC DRUGS ON THE STATIC BEAM, GRIP STRENGTH, AND INCLINED SCREEN ASSAYS

Male Wistar Kyoto rats (10/group) were given a single i.p. injection of 0 (vehicle; 2:1:17 Kolliphor EL:ethanol:saline), 50, 100, or 200 mg/kg Purified CBD. Effects were compared to those in rats given a single injection of known AEDs (saline; 25, 40, or 50 mg/kg PB; 125, 250, or 350 mg/kg VPA; 90, 175, or 300 mg/kg mg/kg ESM).

Purified CBD did not induce significant negative effects on coordination, balance, fine motor control, or muscle tone and did not induce functional neurotoxicity (Jones, Glyn et al. 2012). The standard AEDs induced significant deficits in these tests at efficacious anticonvulsant doses (Jones, Hill et al. 2014).

3.5.5.3. EFFECTS OF PURIFIED CBD ON THE SURVIVABILITY OF SCN1A KNOCK OUT MICE

The effect of Purified CBD treatment on the survivability and welfare scores of a genetically altered mouse model of DS ($Na_v1.1$ knockout on a C129S background) was examined. Mice (homozygous knockouts *SCN1A*$^{-/-}$ and wildtype littermates $^{+/+}$) were injected subcutaneously twice daily with either Purified CBD (100 mg/kg), clobazam (20 mg/kg) or vehicle (2:1:17 ethanol/Kolliphor/0.9 % saline) from postnatal day 8 onwards until postnatal 5 or death (whichever was earlier).

Purified CBD significantly prolonged the survival of *SCN1A*$^{-/-}$ mice compared to vehicle treated animals (p=0.006) or clobazam (p=0.0004) (Patra, McNeish et al. 2017). Furthermore, Purified

CBD treatment significantly delayed worsening of welfare scores compared to both vehicle ($p<0.05$) and clobazam treated animals ($p<0.05$).

4. REGULATORY AND DEVELOPMENT HISTORY

Summary

- The IND for CBD-OS was submitted in 2014, and CBD-OS has been granted Orphan Drug Designation and Rare Pediatric Designation for the treatment of LGS and DS and Fast-Track Designation for the treatment of DS.
- Efficacy of CBD-OS was assessed in 3 Phase 3 studies: 2 in LGS (Study 1414 and 1423) and 1 in DS (Study 1332B).
- Long-term exposure was examined in an OLE study (1415) and a large EAP.

4.1. REGULATORY HISTORY

FDA provided extensive guidance during the development program of CBD-OS and agreements were reached with GW on key aspects of the clinical studies. These interactions were especially critical as the accelerated program coincided with emerging data from the EAP, which demonstrated proof of concept. Table 6 lists the key regulatory milestones during CBD-OS development. In 2013, the FDA authorized a number of physician-initiated EAPs for CBD-OS. Subsequently, GW submitted the IND for CBD-OS on 31 March 2014 and began clinical studies in DS and LGS on 22 Oct 2014.

CBD-OS received Orphan Drug Designation for CBD as a treatment for DS in November 2013 and for LGS in February 2014. CBD-OS was also granted Fast-Track Designation for DS in June 2014 and Rare Pediatric Designation for DS and LGS in April 2017.

At the pre-IND meeting in March 2014, FDA reviewed and discussed the available chemistry, manufacturing, and controls (CMC) and nonclinical information as well as design elements for proposed initial human study in DS.

At the pre-NDA meeting in July 2016, FDA agreed with the Sponsor's plan to provide a single study in DS supported by 2 studies in LGS. In addition, FDA agreed with the proposed nonclinical, Phase 1, and abuse liability packages and agreed on rolling submission for the NDA.

GW completed the CBD-OS NDA to the FDA on October 27, 2017 to request marketing approval in the US.

On February 21, 2018, the integrated summary of safety (ISS) 120-day safety update was submitted to the FDA. The ISS 120-day safety update included an updated analysis of the overall safety profile of CBD-OS from the ongoing OLE study (1415). These data are included in the safety analyses in this document.

Table 6: Key Regulatory Milestones During CBD-OS Development

Date	Description
04 May 2013	First physician-initiated EAP
14 Nov 2013	Granted Orphan Designation – DS
27 Feb 2014	Granted Orphan Designation – LGS
11 Feb 2014	Pre-IND Meeting
31 Mar 2014	IND Submission
02 Jun 2014	Granted Fast-track development – DS
19 Jul 2016	Pre-NDA meeting – agreement with the plan to provide a single study in DS supported by 2 studies in LGS and the proposed nonclinical, Phase 1, and abuse liability packages; general agreement on rolling submission, ISS, and 120-day safety update plans
20 Apr 2017	Grant of rare pediatric designation for CBD – LGS and DS
02 May 2017	Grant rolling review
27 October 2017	CBD-OS NDA submission completed
21 February 2018	CBD-OS 120-day safety update submitted

4.2. CLINICAL DEVELOPMENT PROGRAM

The efficacy of CBD-OS was assessed in 2 randomized, placebo-controlled studies in LGS – 1 investigating 10 and 20 mg/kg/day CBD-OS (Study 1414) and 1 investigating 20 mg/kg/day CBD-OS (Study 1423) – and a single randomized, placebo-controlled study of 20 mg/kg/day CBD-OS in DS (Study 1332B). A total of 516 patients were randomized into these now completed pivotal studies, comprising 396 patients with LGS (Studies 1414 and 1423) and 120 patients with DS (Study 1332B).

Dose selection for the 3 randomized controlled studies was based upon findings in a single randomized, placebo-controlled dose-ranging safety and PK study of 5, 10, and 20 mg/kg/day CBD-OS in children with DS (Study 1332 Part A [1332A]). More details on dose selection can be found in Section 5.2.

Patients who completed one of the controlled studies were eligible to enter an OLE study (Study 1415) that had a primary objective of monitoring long-term safety. Long-term exposure was also assessed within an EAP for patients with drug-resistant epilepsies including those with LGS or DS who were not candidates for the controlled studies.

Phase 1 and 2 clinical pharmacology studies were conducted in healthy subjects and specific populations to evaluate possible factors which may affect the PK characteristics of CBD, as well as to evaluate potential DDIs with AEDs commonly used in LGS and DS (VPA, clobazam, and STP).

5. CLINICAL PHARMACOLOGY

Summary

- CBD follows dose-dependent PK and undergoes rapid and extensive biotransformation.
- CBD has a long half-life enabling stable plasma coverage with convenient twice-daily dosing, which reduces peak trough variability.
- Single doses of CBD-OS up to 6000 mg have been generally well tolerated, equating to a dose of over 85 mg/kg for a 70 kg adult, which demonstrates a large safety margin to prevent serious effects of overdoses.
- CBD-OS should be taken with food to maximize plasma exposure to drug while reducing variability.
- PK was unaffected in patients with renal impairment. Slow titration is recommended in patients with moderate or severe hepatic impairment due to increased drug exposure.
- POPPK analysis supports the use of a simplified titration regimen: a starting dose of 5 mg/kg/day followed by weekly dose escalation to reach a target dose of 10 or 20 mg/kg/day.
- There were no clinically important effects of other commonly co-administered AEDs on CBD exposure.
- CBD may increase exposure to substrate drugs that are predominately metabolized by CYP2C19. Based on *in vitro* data, CBD could potentially affect sensitive substrates of CYP3A4 as an inducer or inhibitor of this enzyme.

The clinical pharmacology characteristics of CBD and its metabolites were investigated in both healthy volunteers and patients in a range of settings, resulting in a comprehensive understanding of the PK profiles (Table 7). In addition to these clinical pharmacology studies, the Phase 3 studies (1414 and 1423 in LGS and 1332B in DS) provided PK data in patients with LGS and DS. Study 1541, examining the QT effect, is detailed in Section 7.8.

Table 7: Overview of Clinical Pharmacology Studies

Study	Subjects[a]	Description	Dose(s)[b]
1544	Healthy	SAD and MD safety, tolerability and PK	SAD CBD-OS: 1500, 3000, 4500 and 6000 mg MD CBD-OS: 750 and 1500 mg b.i.d. Matched placebo for MD and SAD arms
		FE (high fat meal) (single-dose)	CBD-OS: 1500 mg
1539	Healthy and hepatic impaired	Effect of hepatic impairment (mild, moderate, and severe) (single-dose)	CBD-OS: 200 mg
1540	Healthy and renal impaired	Effect of renal impairment (mild, moderate, and severe) (single-dose)	CBD-OS: 200 mg
1541	Healthy	Thorough QT	CBD-OS: 750 mg and 4500 mg
1543	Healthy	Interaction between CBD-OS and clobazam, STP and VPA (MD)	CBD-OS: 1500 mg daily (750 mg b.i.d.) Clobazam: 10 mg daily (5 mg b.i.d.) STP: 1500 mg daily (750 mg b.i.d.) VPA: 1000 mg daily (500 mg b.i.d.)
1428	Epilepsy	Interaction between clobazam and CBD-OS (MD)	CBD-OS: 20 mg/kg/day (10 mg/kg b.i.d.) Clobazam: stable dose (doses above 20 mg/day excluded from the study) Matched placebo

b.i.d., twice daily; FE, food effect; max., maximum; OLE, open-label extension; MD, multiple dose; SAD, single ascending dose.
[a] All studies included male and female subjects/patients.
[b] CBD-OS doses were administered orally.

5.1. PHARMACOKINETICS

The PK profiles of CBD and its metabolites were consistent across the CBD-OS clinical pharmacology program, with few notable differences observed between the studies. The main conclusions were as follows:

- CBD displays dose- and time-dependent PK.
- CBD appears rapidly in plasma with little or no lag time and a t_{max} of approximately 3 hours (range 2.5-5 hours) at steady state.
- CBD C_{max} and AUC tended to increase in a less than dose-proportional manner; however, over the therapeutic dose range (10-20 mg/kg/day), PK was only marginally less than dose-proportional.
- CBD is highly bound (>94%) to plasma proteins (predominantly albumin) and has a high apparent volume of distribution (range: 20963-42849 L).
- CBD is rapidly and extensively metabolized *in vitro* and *in vivo*. The major circulating product detected in plasma of healthy volunteers and patients was 7-COOH-CBD

followed by parent drug CBD, and then 7-OH-CBD. 6-OH-CBD was a minor systemic metabolite.

- Systemic exposure to the impurity (THC) was generally low or <LLOQ at clinically relevant doses.
- Accumulation after multiple b.i.d. dosing of CBD-OS was moderate, with a CBD $t_{½}$ of 60 hours (range 56-61 hours).
- Despite the long terminal $t_{½}$, steady state was reached within 2-4 days for parent drug CBD, based on trough values, likely reflecting that the terminal elimination was only a minor contributor to drug clearance.
- At steady state, peak-to-trough ratios were low, indicating therapeutic concentrations are maintained over the dosing interval.
- Exposure-response analysis demonstrated that the probability of being a responder (>50% reduction in drop seizures) increased with exposure to CBD and its metabolites.
- The dose of CBD-OS does not require adjustment by sex, race, or age (pediatric or adult populations).

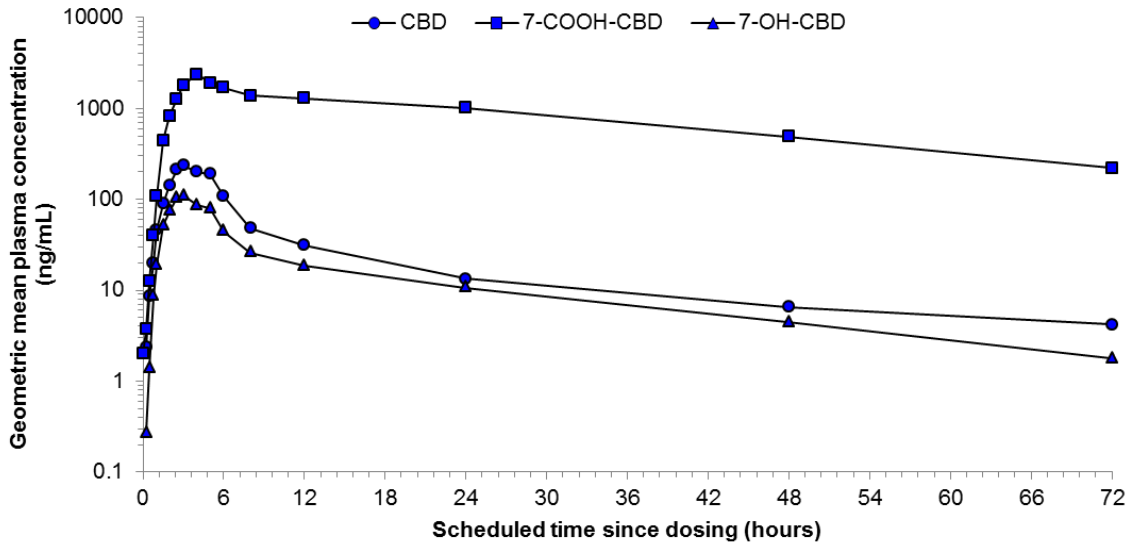
5.1.1. PK STUDY IN HEALTHY INDIVIDUALS (STUDY 1544)

Single and Multiple Dose Administration

Study 1544 evaluated the PK following single and multiple doses of CBD-OS as well as the effect of food on absorption. Participants received single oral doses of 1500, 3000, 4500, or 6000 mg CBD-OS, which was >4 times the recommended upper therapeutic dose (20 mg/kg/day CBD-OS), or matching placebo under fasting conditions. Multiple b.i.d. doses of 750 and 1500 mg (>2 times the recommended upper therapeutic dose), were also given under fasting conditions for 7 days.

CBD rapidly appeared in plasma after single oral doses, and median t_{max} was approximately 4-5 hours, independent of dose. CBD plasma concentrations declined in a multiphasic manner, presumably related to distribution from the central compartment; overall, a biphasic model best described the PK of CBD (Figure 14).

Figure 14: Geometric Mean PK Plasma Concentration-Time Profiles Following Administration of 1500 mg CBD-OS Under Fasted Conditions (Study 1544, FE Arm)



Increases in exposure (C_{max} and AUC) to CBD and its metabolites were generally less than dose-proportional after single oral doses ranging from 1500 to 6000 mg. With multiple CBD-OS doses, there was evidence of moderate accumulation of CBD and its metabolites, and steady state for CBD (based on trough values) was observed after 2-3 days. At steady state, there was a near doubling in exposure (C_{max} and AUC) for a doubling in CBD-OS dose (750 and 1500 mg). Within-day effects were observed for CBD and its metabolites, which likely reflects both accumulation and the differences in prandial state between morning, following overnight fasting, and evening administration.

Food Effect

The effect of a high fat meal on the PK of a single 1500 mg CBD-OS dose was also assessed in this randomized 2-period crossover, incorporating 12 randomly selected subjects (mean age 25 years) from the single ascending dose arm of Study 1544. There was a 10-day washout between periods.

The findings showed that concomitant administration of CBD-OS with a high fat meal resulted in a predictable increase in CBD exposure (C_{max} and AUC), while reducing the total-subject variability compared with the fasted state. In the fed (compared with the fasted) state, there were marked increases in CBD C_{max} of 4.85-fold (90% CI: 4.01-5.87) and area under the concentration-time curve from administration/time zero to the last time point ($AUC_{(0-t)}$) of 4.2-fold (90% CI: 3.63-4.85). The extent of the food effect was also reflected in the exposure to the CBD metabolites. There was no obvious effect of food on CBD or metabolite $t_{max.}$

Subjects in this study were administered a high fat breakfast, so the design represents the most extreme case scenario in terms of increases in exposure due to food intake. Nonetheless, in order

to reduce potential for fluctuation due to the prandial state and to maintain adequate systemic exposure to drug, the label states that CBD-OS should be taken with food.

5.1.2. PHARMACOKINETICS IN LGS AND DS STUDIES

The PK characteristics of CBD in patients (Phase 3 LGS and DS studies) were derived by POPPK modelling. Exposure-response relationships and the potential effects of various extrinsic and intrinsic factors on the PK of CBD are discussed in Section 5.1.4.

5.1.3. SPECIAL POPULATIONS

Studies 1539 and 1540 were conducted to assess the PK of CBD in subjects with hepatic and renal impairment, respectively. Results of Study 1539 showed no effects on CBD or metabolite exposures following administration of a single dose of CBD-OS 200 mg in patients with mild hepatic impairment. There was an increase in exposure to CBD and its active metabolite, 7-OH-CBD, in subjects with moderate and severe hepatic impairment compared to subjects with normal hepatic function ($AUC_{0-\infty}$ increases for total CBD were 2.45- and 5.15-fold for moderate and severe hepatic impairment, respectively). Therefore, the CBD-OS label recommends that patients with moderate or severe hepatic impairment should be titrated slowly to their maintenance dose, and a reduction of the maintenance dose may be necessary; for patients with severe hepatic impairment, a lower starting dose is recommended.

In Study 1540, there were no effects on the C_{max} or AUC of CBD following administration of a single dose of CBD-OS 200 mg in patients with mild, moderate, or severe renal impairment when compared to patients with normal renal function.

5.1.4. POPULATION PHARMACOKINETIC STUDIES

A joint POPPK model was built for CBD and 2 major circulating metabolites (7-OH-CBD and 7-COOH-CBD) based on the data collected in healthy adult subjects from Study 1544. CBD disposition kinetics were described by a 2-compartment linear model. One compartment linear disposition was used to describe 7-OH-CBD and 7-COOH-CBD observations. CBD absorption was adequately described by zero-order kinetics with a short lag time, where the absorption duration increased with CBD-OS dose, and the bioavailable fraction decreased with increasing CBD-OS doses, resulting in a less than dose proportional increase in AUC.

Individual exposure metrics of CBD, 7-OH-CBD, and 7-COOH-CBD in patients with LGS were derived from Studies 1414 and 1423 using the joint POPPK model described above. None of the investigated covariates, including intrinsic factors such as weight, age, ketogenic diet, race, or sex, had a clinically relevant effect on any PK model parameter. There was a positive correlation between the derived AUC of all 3 analytes at Visit 8 (Week 14 of CBD-OS treatment) and the probability of a subject being a drop seizure responder, i.e., having a reduction in drop seizures ≥50%. There were also significant positive correlations between the derived AUCs of the analytes at Visit 8 and the occurrence of ALT >2×ULN, AST >2×ULN (except 7-COOH-CBD), loss of appetite, and somnolence.

Individual exposure metrics of CBD, 7-OH-CBD, and 7-COOH-CBD in patients with DS were also derived from Study 1332A using the joint POPPK model described above. Findings in DS

patients were broadly similar to those in LGS patients; however, the analysis was performed using fewer patients (27 patients compared with 216 patients in the LGS analysis), so the LGS analysis was better powered to show any PK-efficacy and PK safety correlations.

Based on the DS POPPK model, using modeling and simulation, a simplified alternative titration regimen for CBD-OS was explored. In the alternative scheme, a starting dose of 5 mg/kg/day CBD-OS with weekly increases of 5 mg/kg/day until attainment of a maintenance dose of 10 or 20 mg/kg/day was explored. The plasma concentration-time profiles of CBD, 7-OH-CBD, and 7-COOH-CBD were simulated to compare the original titration of CBD-OS used in the Phase 3 studies (see Table 11 in Section 6.1.1) with the alternative one. The simulations suggest that after the initial phase where therapeutic exposures are achieved rapidly for both titration schemes, there is a slower rate of increase to steady state in exposure to CBD and metabolites with the alternative titration scheme when targeting 20 mg/kg/day. This slowed rate of increased exposure may provide the potential clinical outcome of better tolerability (i.e., loss of appetite and increases in AST) as well as delayed efficacy (i.e., postbaseline seizure frequency) over the titration period only. These simulations support the clinical use of a starting dose of 5 mg/kg/day followed by weekly dose escalation to reach a target dose of 10 or 20 mg/kg/day.

5.1.5. POTENTIAL FOR DRUG-DRUG INTERACTION

The Sponsor conducted 3 formal DDI studies to investigate potential effects of CBD-OS on common AEDs that interact with enzymes involved with CBD metabolism, and to investigate the potential effects of common AEDs on CBD-OS. A summary of these studies is as follows:

- Study 1428: Concomitant dosing of CBD-OS (21 days on a maintenance dose of 20 mg/kg/day) with clobazam (patients' usual dose) had no effect on clobazam exposures in patients with epilepsy who received CBD-OS 20 mg/kg/day (n=16) day or placebo (n=4) for 33 days.
- Study 1543: Open-label, fixed sequence study showed no clinically relevant effects of steady state CBD (750 mg BID or placebo) on the PK profiles of steady clobazam, STP or VPA, and vice versa (effect of AEDs on CBD PK), in 6 parallel groups of approximately 12 healthy subjects.
- Study 1447: Ongoing study to assess the long-term safety and tolerability of CBD-OS in the presence of STP or VPA in patients with epilepsy.

A healthy subject study showed no statistically significant effects on CBD plasma exposures when AEDs (clobazam, STP, and VPA) were combined with CBD-OS, and *N*-desmethyl metabolite of clobazam, N-CLB, was elevated 3.39-fold for C_{max} and 3.38-fold for AUC when the two drugs were combined.

Table 8 summarizes the DDIs between CBD-OS (750 mg b.i.d. in healthy subjects and 20 mg/kg/day in patients) and other AEDs. Overall, only a single potentially clinically important DDI has been identified for use of CBD-OS as an adjunctive treatment of seizures. Combination of CBD-OS with clobazam leads to elevated levels of the active metabolites N-CLB and

7-OH-CBD. The proposed labeling for CBD-OS recommends dose reduction for concomitant medications that are sensitive to CYP2C19 substrates, in particular, clobazam.

Table 8: Drug-drug Interactions Between CBD-OS and Concomitant Antiepileptic Drugs Leading to >2-Fold Change in Exposure

Concomitant AED	Influence of AED on CBD-OS	Influence of CBD-OS on AED
Clobazam	No effect	No effect
LTG	No effect	No data
LEV	No effect	No effect
Rufinamide	No effect	No data
Topiramate	No effect	No effect
VPA	No effect	No effect
STP[a]	No effect	No effect

[a] STP has not been approved by the FDA.

Due to the theoretical potential for DDIs based on *in vitro* data, the following studies have been initiated or planned to further quantify the potential for CYP-mediated DDIs and refine guidance for prescribers:

- Study 17028 (ongoing): A Phase 1, open-label, fixed sequence crossover study to investigate the effect of CBD on the CYP3A4 probe midazolam in healthy subjects.
- Study 17074 (in set up): A Phase 1, open-label, fixed-sequence study to investigate a possible PK drug-drug interaction between rifampicin and CBD in healthy subjects.
- Study 17075 (in set up): A Phase 1, randomized, open-label, 2 arm single sequence study to investigate possible PK drug-drug interactions between itraconazole or fluconazole and CBD in healthy subjects.

5.2. DOSE-SELECTION RATIONALE FOR PHASE 3 STUDIES

Dose selection for the 3 pivotal studies was based upon by nonclinical pharmacology studies as well as findings in a single randomized, placebo-controlled dose-ranging safety and PK study of 5, 10, and 20 mg/kg/day CBD-OS in children with DS (Study 1332A). Following assessment of the safety and PK data from this study, an independent data safety monitoring committee recommended 20 mg/kg/day as the dose of CBD-OS to use in all subsequent studies.

The titration regimen used in Studies 1332B, 1423, and 1414 (detailed in Section 6.1.1) was selected to safely achieve a 20 mg/kg/day target dose within a titration period of 2 weeks. The demonstration of efficacy of the 10 mg/kg/day dose in Study 1414 and the PK similarity between the proposed dosing schedule and the dosing used in the controlled studies support the simplification of the titration of CBD-OS.

5.3. PROPOSED TITRATION SCHEDULE

For clinical use, the Sponsor is recommending a starting daily dose of 5 mg/kg/day for 1 week, then increasing the dose to 10 mg/kg/day. Rather than taking 4 steps to reach 10 mg/kg/day, the proposed dosing regimen consists of 2 steps. Additionally, with the proposed dosing regimen, there will be fewer weight-based dosing changes which should reduce the possibility of dosing measurement errors. The proposed dosing regimen has been used in the EAP.

6. CLINICAL EFFICACY

Summary

- CBD-OS was studied in a series of 3 placebo-controlled multicenter studies that used the same 14-week design to assess the efficacy of CBD-OS added to current AED therapy.
- Studies 1414 and 1423 were conducted in LGS patients and Study 1332B was conducted in DS patients; all 3 studies examined 20 mg/kg/day CBD-OS, and 10 mg/kg/day CBD-OS was also examined in Study 1414.
- The patient population in each of the 3 studies were drug resistant, had failed multiple previous AEDs, and had experienced a high seizure frequency despite ongoing treatment with multiple AEDs.
- In all 3 studies, CBD-OS added to other AED therapy met the primary endpoint of reduction in seizure frequency during the 14-week treatment period in patients with drug-resistant LGS and DS.
- In the LGS studies, the first key secondary endpoint showed a statistically significant improvement in the proportion of patients with ≥50% reduction from baseline in drop seizures; the numerical improvement using convulsive seizures for this key secondary endpoint in Study 1332B was not statistically-significant.
- The LGS studies also met the other 2 key secondary endpoints: percent reduction in total seizures during the treatment period and S/CGIC at last visit.

The clinical development program supporting the efficacy of CBD-OS comprises 2 randomized, placebo-controlled studies in LGS and one in DS. In LGS, Study 1414 investigated 10 and 20 mg/kg/day CBD-OS, and Study 1423 investigated 20 mg/kg/day CBD-OS. Study 1332 was a two-part randomized, placebo-controlled study of 20 mg/kg/day CBD-OS in DS. Part A of Study 1332 investigated the dose-ranging safety and PK of CBD-OS at 3 doses (5, 10, and 20 mg/kg/day) in children with DS and is discussed in Section 5.1.2. Part B of Study 1332 assessed the efficacy of 20 mg/kg/day CBD-OS in children with DS and is detailed in this section. Table 9 shows an overview of the pivotal efficacy studies.

Additionally, an OLE study, 1415, and an EAP conducted under physician-sponsored INDs evaluated the persistence of efficacy or tolerance effects of CBD-OS. Study 1415 is an ongoing multisite study for patients with LGS or DS who had previously completed Study 1414, 1423, 1332 [Parts A and B] or 1424. The ongoing EAP comprises physician-initiated emergency, individual, and intermediate INDs in the US; state-initiated intermediate INDs in the US; and a Compassionate Access Scheme in New South Wales, Australia. Table 10 shows an overview of these supportive studies.

Table 9: Overview of Pivotal Phase 3 Studies in LGS or DS

	Study 1414	Study 1423	Study 1332B
Study Design	4-week baseline period, 14-week treatment period (2 weeks of titration and 12 weeks of maintenance), optional OLE or taper (10% per day)		
Description	Adjunct to existing AEDs in patients with LGS who had inadequately controlled drop seizures		Adjunct to existing AEDs in patients with DS who had inadequately controlled convulsive seizures
Patient Population	2-55 years with a clinical diagnosis of LGS, ≥2 drop seizures each week during the 28-day baseline period despite taking ≥1 AED at a stable dose for ≥4 weeks		2-18 years with a clinical diagnosis of DS, ≥4 convulsive seizures during the 28-day baseline period despite taking ≥1 AED at a stable dose for ≥4 weeks
Randomization Stratification Groups	2 to <6 years, 6 to <12 years, 12 to <18 years, and 18 to <56 years		2 to <6 years, 6 to <13 years, 13 to <19 years
Primary Endpoint	Percent change from baseline in drop seizure (atonic, tonic, or tonic-clonic seizure that led or may have led to a fall or injury) frequency		Percent change from baseline in convulsive seizure (tonic-clonic, tonic, clonic, or atonic seizure) frequency
Key Secondary Endpoints	1. Proportion of patients with a ≥50% reduction from baseline in drop seizure frequency during the treatment period 2. Percent change from baseline in total seizure frequency during the treatment period 3. S/CGIC at last visit		1. Proportion of patients with a ≥50% reduction from baseline in convulsive seizure frequency during the treatment period
Doses	CBD-OS 10 mg/kg/d: 73 CBD-OS 20 mg/kg/d: 76 PBO: 76	CBD-OS 20 mg/kg/d: 86 PBO: 85	CBD-OS 20 mg/kg/d: 61 PBO: 59
Regions	US, UK, France, Spain	US, Netherlands, Poland	US, UK, France, Poland
Number of Patients	Planned: 150 Randomized: 225	Planned: 100 Randomized: 171	Planned: 100 Randomized: 120

Abbreviations: AED, antiepileptic drug; CBD-OS, cannabidiol oral solution; DS, Dravet syndrome; LGS, Lennox-Gastaut syndrome; OLE, open label extension; PBO, placebo; S/CGIC, Subject/Caregiver Global Impression of Change.

Table 10: Overview of Supportive Studies in LGS or DS

	Study 1415	EAP
Study Design	Open-label, 2-week titration period, treatment up to 3 years in the US, France, or Poland and up to 1 year in the UK, Spain, The Netherlands, or Israel	Open-label, 5-8-week titration period, patients remain on treatment until approval
Description	Adjunct to existing AEDs in patients with DS or LGS who completed the treatment period of a randomized controlled study with CBD-OS	Adjunct to existing AEDs in patients with drug-resistant epilepsies, including DS and LGS
Patient Population	Patients (2-55 years) with a clinical diagnosis of LGS or DS, taking ≥1 AED at a stable dose, and who completed Study 1414, 1423, 1332 (A or B) or 1424 (study ongoing)	Patients with drug resistant epilepsy taking ≥1 AEDs at a stable dose
Efficacy Endpoints	• Percent change from baseline in drop (LGS only), convulsive (DS and combined DS + LGS), and total (DS, LGS, and combined DS + LGS) seizure frequencies • Number of patients seizure free from drop (LGS only), convulsive (DS and combined DS + LGS), and total (DS, LGS, and combined DS + LGS) seizures	• Percent change from baseline in convulsive and total seizure frequencies for DS, LGS, and combined DS + LGS • Proportions of patients with ≥ 50%, ≥ 75% or 100% reductions from baseline in convulsive and total seizure frequencies for DS, LGS, and combined DS + LGS
Regions	US, UK, France, Poland, Spain, The Netherlands, Israel	US, Australia[a]
Number of Patients	CBD-OS: 630	CBD-OS (all patients): 684 CBD-OS (DS/LGS): 161

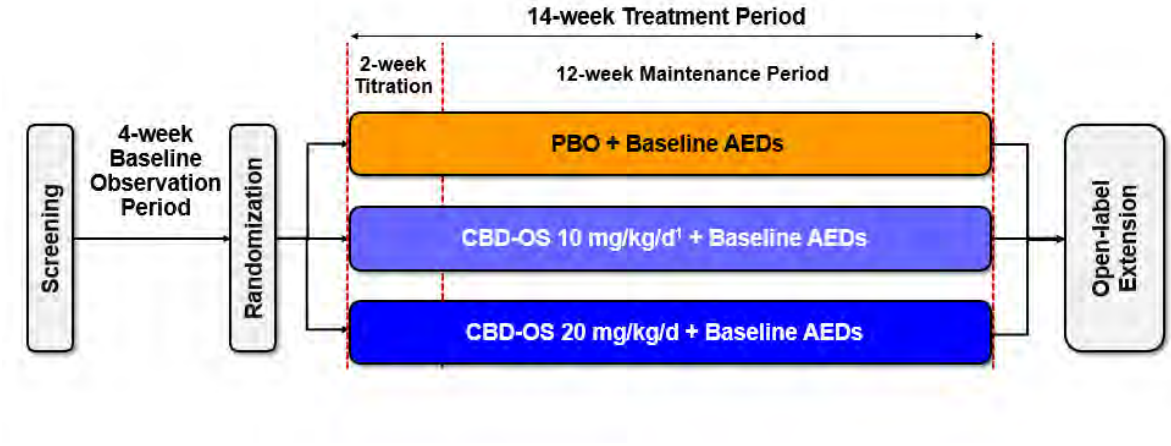
Abbreviations: AED, antiepileptic drug; CBD-OS, cannabidiol oral solution; DS, Dravet syndrome; EAP, expanded access program; LGS, Lennox-Gastaut syndrome.
a. The efficacy dataset excluded Australia as the Australian compassionate access scheme included only very severely ill patients with uncountable seizures.

6.1. PHASE 3 STUDY DESIGN

The pivotal study design was identical for the 2 indications (LGS and DS) and was similar to study designs used as the basis of approval for recently approved AEDs for LGS (The Felbamate Study Group in Lennox-Gastaut Syndrome 1993, Motte, Trevathan et al. 1997, Sachdeo, Glauser et al. 1999, Glauser, Kluger et al. 2008, Ng, Conry et al. 2011). The study design incorporated guidance and advice issued by the FDA, the European Medicines Agency (EMA), and a series of expert advisory panels.

The 3 pivotal studies were double-blind, randomized, placebo-controlled, multicenter studies designed to evaluate the efficacy and safety of CBD for adjunctive treatment of seizures in patients with DS or LGS (Figure 15). All pivotal studies (Studies 1414, 1423, and 1332B) consisted of a 4-week baseline period, followed by a 14-week treatment period. The treatment period included 2 weeks of titration (dose escalation) followed by 12 weeks of maintenance (stable dosing). All pivotal studies were designed to evaluate 20 mg/kg/day CBD-OS vs. placebo as adjunctive therapy, with Study 1414 (LGS) also including a 10 mg/kg/day CBD-OS dose arm to evaluate the effectiveness of half the dose.

Figure 15: Phase 3 Study Design



[1]Dose included in LGS Study 1414 only

Randomization was stratified by four age groups for the LGS studies (2 to <6, 6 to <12, 12 to <18, and 18 to <56 years) and 3 age groups for the DS study (2 to <6, 6 to <13, and 13 to <19 years). Seizure counts were recorded daily using the IVRS telephone diary during the baseline and treatment period. All patients who completed the treatment period were eligible to enroll in the OLE study (Study 1415). While the primary objective of the OLE study was safety monitoring of CBD-OS, the study also continued to collect seizure data, thereby permitting the continued surveillance of efficacy outcomes over a greater period of time.

6.1.1. STUDY TREATMENT

Patients were initiated at a dose of 1.25 mg/kg twice daily (2.5 mg/kg/day), which was increased at increments of 1.25 mg/kg twice daily (2.5 mg/kg/day) every other day over the first week and increments of 2.5 mg/kg twice daily (5 mg/kg/day) every other day, as shown in Table 11. The study drug was presented as an oral solution containing 100 mg/mL CBD in the excipients sesame oil and anhydrous ethanol (79 mg/mL) with added sweetener (0.5 mg/mL sucralose) and strawberry flavoring (0.2 mg/mL); the matched placebo comprised only the excipients.

The proposed dosing regimen was simplified from the clinical studies to reduce the potential for dosing errors; both dosing regimens produced similar exposures in PK modeling (see Section 5.2 for more details).

Table 11: Dose Escalation Schedule

Time	Single Dose (Twice Daily) mg/kg	Daily Dose mg/kg
Day 1-2	1.25	2.5
Day 3-4	2.5	5
Day 5-6	3.75	7.5
Day 7-8	5	10
Day 9-10	7.5	15
Day 11 and later	10	20

Note: The proposed label recommends a less complicated dosing regimen adapted from the dosing regimen used in the EAP (i.e., weekly dose increments of 5 mg/kg/day, starting with a dose of 5 mg/kg/day in Week 1 and increasing up to 20 mg /kg/day by Week 4, depending on individual clinical response and tolerability) (Section 3.1).

6.1.2. INCLUSION AND EXCLUSION CRITERIA

For enrollment in the LGS studies (1414 and 1423), patients had to be aged 2-55 years (inclusive), with a clinical diagnosis of LGS. This included written documentation of having met electroencephalographic diagnostic criteria (slow [<3.0 Hz] spike-and-wave pattern) during the patient's history and evidence of more than 1 type of generalized seizure, including drop seizures, for at least 6 months. Patients had to have documented failures on more than 1 AED and had to have experienced at least 2 drop seizures each week of the 4-week baseline period. A drop seizure was defined as an attack or spell (atonic, tonic, or tonic-clonic seizure) involving the entire body, trunk or head that led or could have led to a fall, injury, slumping in a chair, or hitting the patient's head on a surface.

For enrollment in the DS study (1332B), patients had to be aged 2-18 years (inclusive), with a clinical diagnosis of DS confirmed by a committee of independent experts from the Epilepsy Study Consortium (ESC) and had to have experienced 4 or more convulsive seizures during the 4-week baseline period. A convulsive seizure was defined as a tonic, clonic, tonic-clonic, or atonic seizure.

A full list of inclusion and exclusion criteria can be found in Appendix 10.1.

6.1.3. CONCOMITANT ANTI-EPILEPTIC DRUG ADMINISTRATION

All 3 pivotal studies included patients who were taking 1 or more AEDs which had been maintained at a stable dose for at least 4 weeks prior to screening. All medications or nonpharmacological interventions for epilepsy (including ketogenic diet and VNS) were to remain stable throughout the study. Patients were ineligible if they had used recreational or medicinal cannabis, or synthetic cannabinoid-based medications, within 3 months prior to screening and were to abstain from taking them during the study. Concomitant AED use during the studies is shown in Table 14 of Section 6.2.2.

6.1.4. EFFICACY ENDPOINTS

Seizure counts were recorded daily during the baseline and treatment period using an IVRS telephone diary. The primary endpoint was the percent change from baseline in drop seizure frequency for the LGS studies (1414 and 1423), and convulsive seizure frequency for the DS study (1332B) during the treatment period. Convulsive seizures are accurately identified by caregivers (Akman, Montenegro et al. 2009) and are the most common observable motor component in both LGS and DS. The incidence of drop seizures was selected for the primary endpoint for Study 1414 and 1423 to be consistent with other recent pharmacotherapy studies in LGS (e.g., clobazam), whereas the traditional endpoint for epilepsy studies (convulsive seizures) was chosen for DS. The treatment period was defined as Day 1 until the earliest of: Day 99 or the day of last dose during the treatment period. Hence, for patients who withdrew during the study, seizure frequency was calculated using seizure data up until their date of last dose.

Percentage change from baseline in drop/convulsive seizures was calculated as follows:

$$\left(\frac{Frequency\ during\ the\ treatment\ period - Frequency\ during\ baseline}{Frequency\ during\ baseline}\right) x\ 100$$

The frequency during each period was based on 28-day averages and calculated as follows:

$$\left(\frac{Number\ of\ seizures\ in\ the\ period}{Number\ of\ reported\ days\ in\ IVRS\ in\ the\ period}\right)\ x\ 28$$

Studies 1414 and 1423 in LGS included the following 3 key secondary endpoints, which were protected for type 1 error (see Section 6.1.5 for more details). Study 1332B included only the 50% responder rate as a key secondary endpoint.

- Proportion of patients who achieved at least a 50% reduction from baseline in either drop seizure frequency (LGS) or convulsive seizure frequency (DS)
- Percent change from baseline in total seizure frequency during the treatment period
- S/CGIC at last visit

The S/CGIC comprised the following question, to be rated on a 7-point scale:

> **SGIC:** *"Since you started treatment, please assess the status of your overall condition (comparing your condition now to your condition before treatment) using the scale below."*
> **CGIC:** *"Since the patient started treatment, please assess the status of the patient's overall condition (comparing their condition now to their condition before treatment) using the scale below."*

The prespecified categories for analyses were: "Very Much Improved"; "Much Improved"; "Slightly Improved"; "No Change"; "Slightly Worse"; "Much Worse"; "Very Much Worse".

These endpoints were selected to estimate of the effect of treatment on a patient's entire seizure burden, provide evidence of efficacy in multiple seizure types, and provide valuable information on the clinical meaningfulness of the therapy.

6.1.5. STATISTICAL ANALYSES

Eligibility for the studies was based on seizure count and could be confirmed only at the end of the 4-week baseline period. Coupled with rapid recruitment toward the end of each study (in part due to patients awaiting US Drug Enforcement Administration [DEA] licensing of study sites), this resulted in greater randomization than was planned (Study 1423: 171 randomized vs. 100 planned; Study 1414: 225 randomized vs. 150 planned). Importantly, blinding was maintained throughout the duration of the study, and no blinded or unblinded sample size reassessments were performed.

The primary population for all efficacy analyses was the ITT population, which comprised all randomized patients who received at least 1 dose of investigational product and had post-randomization efficacy data. For all 3 pivotal studies, every patient that was randomized was dosed and provided post-randomization seizure data. The ITT designation was therefore maintained, and all patients were included in the primary analyses.

In all 3 pivotal studies, the primary endpoint was analyzed using a Wilcoxon rank-sum test with an estimate of the median difference between CBD-OS and placebo, together with estimated

95% CIs, being calculated using the Hodges-Lehmann approach. Pre-specified sensitivity analyses of the primary endpoint included repeat analysis using the PP analysis set, analysis over the maintenance period alone, analyses accounting for missing values with alternative methodologies, and parametric analyses.

The LGS studies (1414 and 1423) had multiple key secondary endpoints that were tested in a hierarchical manner. In Study 1414, the primary endpoint was first tested for 20 mg/kg/day CBD-OS vs. placebo, followed by 10 mg/kg/day CBD-OS vs. placebo. All key secondary endpoints for 20 mg/kg/day CBD-OS vs. placebo were then tested in hierarchical order, followed by all key endpoints for 10 mg/kg/day CBD-OS vs. placebo in hierarchical order. In Study 1423, the primary endpoint was tested, followed by all key secondary endpoints in hierarchical order. The hierarchy of key secondary endpoints was as follows:

1. Proportion of patients who achieved ≥50% reduction from baseline in drop seizure frequency during the treatment period
2. Percent change from baseline in number of total seizures (average per 28 days) during the treatment period
3. Change from baseline in S/CGIC score at the last visit

The null hypothesis of an endpoint had to be rejected at the level of 0.05 (2-sided) to test the hypothesis of the subsequent endpoint in the sequence at the level of 0.05 (2-sided). If a null hypothesis was not rejected, then testing was to be stopped and subsequent analyses declared not statistically significant. The null hypotheses for the primary and key secondary endpoints were all rejected in both LGS studies; accordingly, all key secondary endpoints were formally analyzed.

The DS study (1332B) had a single key secondary endpoint, proportion of patients who achieved ≥50% reduction from baseline in convulsive seizure frequency during the treatment period, which was formally tested following the primary endpoint being met.

6.2. STUDY POPULATION

6.2.1. SUBJECT DISPOSITION

Patient disposition was similar across the 3 pivotal studies (Table 12). There were a greater number of withdrawals from the 20 mg/kg/day CBD-OS group compared with placebo in each study. The most common reason for withdrawal across the 20 mg/kg/day CBD-OS groups was AEs (5-13% of patients), which in most cases related to transaminase elevations (see Section 7.3.1). The proportion of patients who were withdrawn due to AEs was lower in the 10 mg/kg/day CBD-OS group in Study 1414 (1%), which was similar to the placebo groups across the 3 studies (1-2%).

Table 12: Disposition of Patients in Phase 3 Studies (ITT)

Parameter	Study 1414 (LGS)			Study 1423 (LGS)[a]		Study 1332B (DS)[b]	
	Placebo (N=76)	CBD-OS 10 mg/kg (N=73)	CBD-OS 20 mg/kg (N=76)	Placebo (N=85)	CBD-OS 20 mg/kg (N=86)	Placebo (N=59)	CBD-OS 20 mg/kg (N=61)
Patient Disposition [n (%)]							
Completed treatment period	74 (97.4)	71 (97.3)	67 (88.2)	84 (98.8)	72 (83.7)	56 (94.9)	52 (85.2)
Entered OLE	73 (96.1)	71 (97.3)	66 (86.8)	84 (98.8)	72 (83.7)	56 (94.9)	49 (80.3)
Withdrawn from treatment period	2 (2.6)	2 (2.7)	9 (11.8)	1 (1.2)	14 (16.3)	3 (5.1)	9 (14.8)
Primary Reason for Withdrawal [n (%)]							
Adverse event	1 (1.3)	1 (1.4)	4 (5.3)	1 (1.2)	8 (9.3)	1 (1.7)	8 (13.1)
Met withdrawal criteria	0	0	1 (1.3)	0	4 (4.7)	0	0
Protocol deviation	0	0	1 (1.3)	0	0	0	0
Withdrawal by patient or parent/guardian	1 (1.3)	0	2 (2.6)	0	0	1 (1.7)	0
Withdrawn by investigator	0	1 (1.4)	1 (1.3)	0	0	0	1 (1.6)
Lost to follow-up	0	0	0	0	0	1 (1.7)	0
Other[c]	0	0	0	0	2 (2.3)	0	0

[a] Study 1423 data from safety analysis set table. The safety analysis set matched the ITT analysis set in this study with the exception of 2 patients (randomized to different treatment arms) who received each other's study medication; both patients completed the study and entered the OLE.
[b] Study 1332B data from safety analysis set table; however, the safety analysis set matched the ITT analysis set in this study.
[c] Other reasons for withdrawal included administration of investigational product via G-tube (1 patient) and noncompliance in investigational product dosing.

6.2.2. DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Baseline demographic, disease, and treatment characteristics were generally well balanced between the CBD-OS and placebo groups across all 3 studies. Overall, there was a similar proportion of male and female patients, the majority were White/Caucasian, and the mean age was 15.3-16.0 years across the treatment arms in Studies 1414 and 1423, and 9.7-9.8 years across the treatment arms in Study 1332B. Key demographic characteristics are shown in Table 13.

Table 13: Key Demographic Characteristics in Phase 3 Studies (ITT)

Demographic Characteristic	Study 1414 (LGS)			Study 1423 (LGS)		Study 1332B (DS)	
	Placebo (N=76)	CBD-OS 10 mg/kg (N=73)	CBD-OS 20 mg/kg (N=76)	Placebo (N=85)	CBD-OS 20 mg/kg (N=86)	Placebo (N=59)	CBD-OS 20 mg/kg (N=61)
Age (years)							
Mean	15.3	15.4	16.0	15.3	15.5	9.8	9.7
SD	9.3	9.5	10.8	9.8	8.7	4.9	4.7
Sex [n (%)]							
Female	32 (42.1)	33 (45.2)	31 (40.8)	42 (49.4)	41 (47.7)	32 (54.2)	26 (42.6)
Male	44 (57.9)	40 (54.8)	45 (59.2)	43 (50.6)	45 (52.3)	27 (45.8)	35 (57.4)
Race [n (%)]							
White/Caucasian	69 (90.8)	62 (84.9)	67 (88.2)	79 (92.9)	75 (87.2)	50 (84.7)	44 (72.1)
Other	7 (9.2)	10 (13.7)	9 (11.8)	6 (7.1)	11 (12.8)	3 (5.1)	6 (9.8)
Not Available[a]	0	1 (1.4)	0	NA	NA	6 (10.2)	11 (18.0)
Region [n (%)]							
USA	62 (81.6)	60 (82.2)	59 (77.6)	66 (77.6)	62 (72.1)	37 (62.7)	35 (57.4)
Rest of World	14 (18.4)	13 (17.8)	17 (22.4)	19 (22.4)	24 (27.9)	22 (37.3)	26 (42.6)
Weight at Baseline (kg)							
Mean	45.7	44.3	41.0	43.0	42.7	35.1	33.8
SD	23.2	26.2	20.6	23.0	22.6	18.3	16.6
Height at Baseline (cm)							
Mean	142.2	140.4	142.3	141.6	140.0	131.1	132.2
SD	24.2	23.1	23.4	24.5	25.1	24.4	26.3
Body Mass Index at Baseline (kg/m^2)							
Mean	21.4	20.9	19.0	19.8	21.0	19.1	18.3
SD	7.0	7.6	5.7	5.7	10.0	4.7	4.5

[a] Not available as per country-specific data protection law.

Table 14 shows key baseline disease and treatment characteristics in the 3 pivotal studies.

In Studies 1414 and 1423, the most common current seizure type reported during the baseline period in each study was tonic (76-80%); the median drop seizure frequency (average per 28 days) during this time was 85.0 in Study 1414 (range: 8.7-7494.0) and 73.8 in Study 1423 (range: 10.3-3174.6). Median frequencies of drop seizures, convulsive seizures, and total seizures in the 20 mg/kg/day CBD-OS treatment group were all slightly higher in Study 1414 compared with Study 1423. Notably, median frequencies of convulsive seizures and total seizures were higher in the LGS studies compared with the DS study.

In Study 1332B, the most common current seizure type reported during the baseline period was generalized tonic-clonic (89%). Patients in this study were drug-resistant, experiencing a median 13 convulsive seizures per 28 days (range: 3.7-1716.7) during the baseline period despite a high AED burden. Twenty percent of patients were on a ketogenic diet or VNS. All but 4 patients (97%) suffered from intellectual impairment, development delay or learning disability, which for the majority (84%) was assessed as moderate, severe, or profound.

In each study, the median number of AEDs currently being taken was 3; the most commonly used were clobazam and VPA. The median number of AEDs no longer taken was slightly higher in the LGS studies (6 per treatment group) compared with the DS study (4 per treatment group), which may be due to the older patient population in the LGS studies, or the reduced treatment

options available in DS. The high median numbers of prior and current AEDs, together with the high number of baseline seizures demonstrates that the patients in the 3 pivotal studies were particularly treatment resistant. The proportions of patients using LTG or rufinamide were higher in the LGS studies compared with the DS study, which is consistent with reports that these AEDs are thought to act primarily on sodium channels, and they can worsen seizures in DS (Guerrini, Genton et al. 1998, Mueller, Boor et al. 2011). STP, which is authorized in the EU, Japan, and Canada for the treatment of generalized tonic-clonic seizures in patients with DS, was used exclusively by patients in the DS study.

Table 14: Key Baseline Disease and Treatment Characteristics in Phase 3 Studies (ITT)

Baseline Characteristic	Study 1414 (LGS)			Study 1423 (LGS)		Study 1332B (DS)	
	Placebo (N=76)	CBD-OS 10 mg/kg (N=73)	CBD-OS 20 mg/kg (N=76)	Placebo (N=85)	CBD-OS 20 mg/kg (N=86)	Placebo (N=59)	CBD-OS 20 mg/kg (N=61)
Drop Seizure Frequency (Average per 28 Days) during the Baseline Period							
Median	80.3	86.9	85.5	74.7	71.4	NA	NA
Q1; Q3	47.8; 148.0	40.6; 190.0	38.3; 161.5	47.3; 144.0	27.0; 156.0	NA	NA
Min; Max	8.7; 1278.3	14.0; 7494.0	13.0; 1092.0	11.2; 3174.6	10.3; 855.9	NA	NA
Convulsive Seizure Frequency (Average per 28 Days) during the Baseline Period							
Median	102.8	102.9	108.5	99.8	87.0	14.9	12.4
Q1; Q3	59.9; 184.3	48.0; 262.0	60.9; 185.4	51.2; 189.0	38.0; 209.2	7.0; 36.0	6.2; 28.0
Min; Max	11.0; 1430.0	14.0; 7494.0	13.0; 1274.9	11.2; 4058.1	10.3; 1434.0	3.7; 718.0	3.9; 1716.7
Total Seizure Frequency (Average per 28 Days) during the Baseline Period							
Median	180.6	165.0	174.3	176.7	144.6	41.5	24.0
Q1; Q3	90.4; 431.3	81.3; 359.0	82.7; 392.4	68.6; 359.5	72.0; 385.7	12.0; 367.0	10.4; 141.0
Min; Max	11.0; 3017.2	14.0; 13607.0	13.0; 4591.0	11.2; 4357.4	15.0; 2829.0	4.0; 3170.0	4.1; 2712.5
AEDs No Longer Taken							
Median	6	6	6	6	6	4	4
Min; Max	1; 22	0; 21	1; 18	0; 28	1; 18	0; 14	0; 26
AEDs Currently Taken							
Median	3	3	3	3	3	3	3
Min; Max	1; 5	1; 5	0; 5	1; 4	1; 5	1; 5	1; 5
AEDs Currently Taken [n (%)][a]							
Clobazam	37 (48.7)	37 (50.7)	36 (47.4)	42 (49.4)	42 (48.8)	38 (64.4)	40 (65.6)
VPA[b]	30 (39.5)	27 (37.0)	28 (36.8)	33 (38.8)	36 (41.9)	34 (57.6)	37 (60.7)
LEV	23 (30.3)	22 (30.1)	24 (31.6)	35 (41.2)	23 (26.7)	17 (28.8)	16 (26.2)
LTG	25 (32.9)	22 (30.1)	20 (26.3)	31 (36.5)	33 (38.4)	2 (3.4)	1 (1.6)
Rufinamide	20 (26.3)	19 (26.0)	26 (34.2)	21 (24.7)	25 (29.1)	1 (1.7)	4 (6.6)
STP[c]	0	0	0	0	0	21 (35.6)	30 (49.2)

[a] For 1332B source data for the number (%) of patients taking VPA, LEV, LTG and rufinamide is Table 6.3B; for this study the safety analysis set matched the ITT analysis set.
[b] VPA includes ergenyl chrono for all studies.
[c] Not approved in the US
Note: Baseline period included all seizure data prior to Day 1.

6.3. STUDY 1414 AND 1423 RESULTS (LGS)

6.3.1. PRIMARY ENDPOINT: PERCENT CHANGE FROM BASELINE IN DROP SEIZURE FREQUENCY DURING THE 14-WEEK TREATMENT PERIOD IN LGS STUDIES 1414 AND 1423

The predefined primary endpoint for the study in LGS was the percent change from baseline in drop seizure frequency (average per 28 days) during the 14-week treatment period. In each study, CBD-OS 20 mg/kg/day was superior to placebo in reducing drop seizure frequency during the treatment period (p=0.0047 in Study 1414 and p=0.0135 in Study 1423); CBD-OS 10 mg/kg/day was also superior to placebo (p=0.0016) in Study 1414 (Table 15 and Figure 3). Placebo responses were in the range of those reported in previous LGS studies (VanStraten, 2012).

Table 15: Percent Change from Baseline in Drop Seizure Frequency during the 14-Week Treatment Period in LGS Studies 1414 and 1423 (ITT Analysis Set)

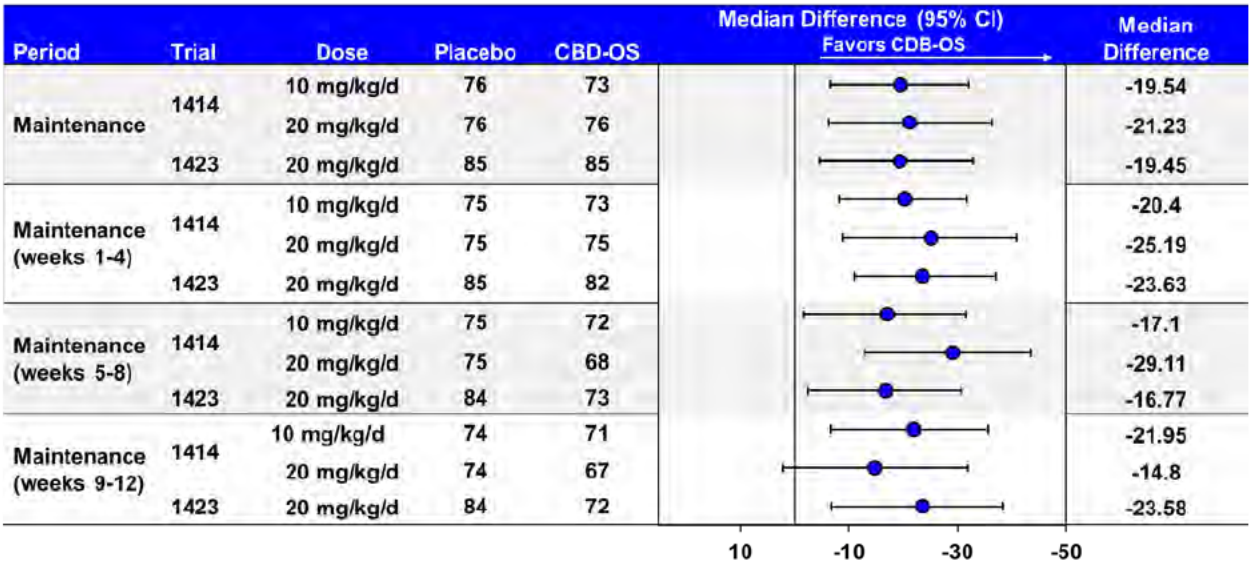
Variable Statistics	Study 1414			Study 1423	
	Placebo (N=76)	CBD-OS 10 mg/kg/day (N=73)	CBD-OS 20 mg/kg/day (N=76)	Placebo (N=85)	CBD-OS 20 mg/kg/day (N=86)
Drop Seizure Frequency (Average per 28 Days) during the Baseline Period					
Median	80.25	86.90	85.53	74.67	71.43
Q1; Q3	47.8; 148.0	40.6; 190.0	38.3; 161.5	47.3; 144.0	27.0; 156.0
Percent Change from Baseline in Drop Seizure Frequency (Average per 28 Days) during the Treatment Period					
Median	-17.17	-37.16	-41.86	-21.80	-43.90
Q1; Q3	-37.1; 0.9	-63.8; -5.6	-72.4; -1.3	-45.7; 1.7	-69.6; -1.9
Estimated Treatment Difference vs. Placebo					
Median difference	NA	-19.19	-21.57	NA	-17.21
95% CI	NA	-31.24, -7.69	-34.79, -6.67	NA	-30.32, -4.09
P-value	NA	0.0016	0.0047	NA	0.0135

Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.
Note: Estimated median difference and 95% CI calculated using the Hodges-Lehmann approach; p-value calculated from a Wilcoxon rank-sum test.

6.3.1.1. PERCENT CHANGE FROM BASELINE IN DROP SEIZURE FREQUENCY DURING THE MAINTENANCE PERIOD (12 WEEKS)

In each study, the maintenance period was defined as Day 15 to Day 99 (or the day of last dose up to and including the end of treatment visit, if earlier). CBD-OS at 20 mg/kg/day and 10 mg/kg/day were numerically superior to placebo in reducing drop seizure frequency during the maintenance period, and each 4-week block thereof (Figure 16).

Figure 16: Percent Change from Baseline in Drop Seizure Frequency During the Maintenance Period in LGS Studies 1414 and 1423 (ITT)

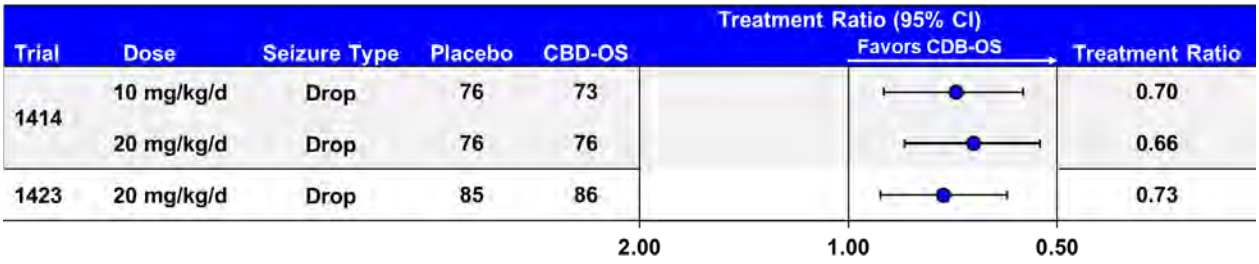


6.3.1.2. SENSITIVITY ANALYSES

The robustness of the primary analysis in each study was supported by a series of post-hoc sensitivity analyses, including analyses that accounted for missing values in various ways.

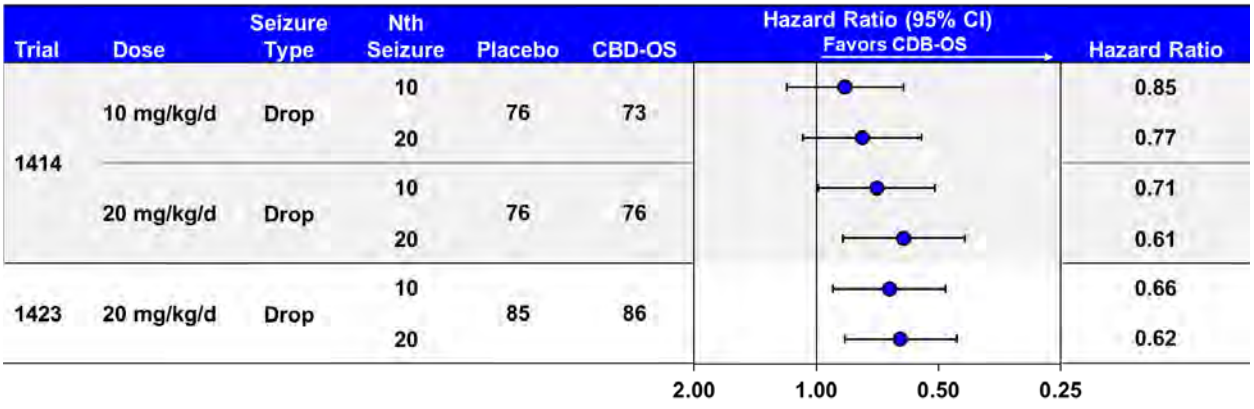
The primary endpoint analysis in each study was a non-parametric Wilcoxon rank-sum test. However, using a non-parametric approach does not allow for flexible modelling techniques using covariates. In order to support effect modifier analyses with a clinically meaningful measure of effect size, a statistical modelling approach was proposed using negative binomial regression. Negative binomial regression analyses of convulsive, drop, and total seizure counts across the LGS studies showed the treatment ratios to be consistently in favor of CBD-OS (Figure 17).

Figure 17: Negative Binomial Regression Analysis of Drop Seizure Counts during Baseline and Treatment Periods in LGS Studies 1414 and 1423 (ITT)



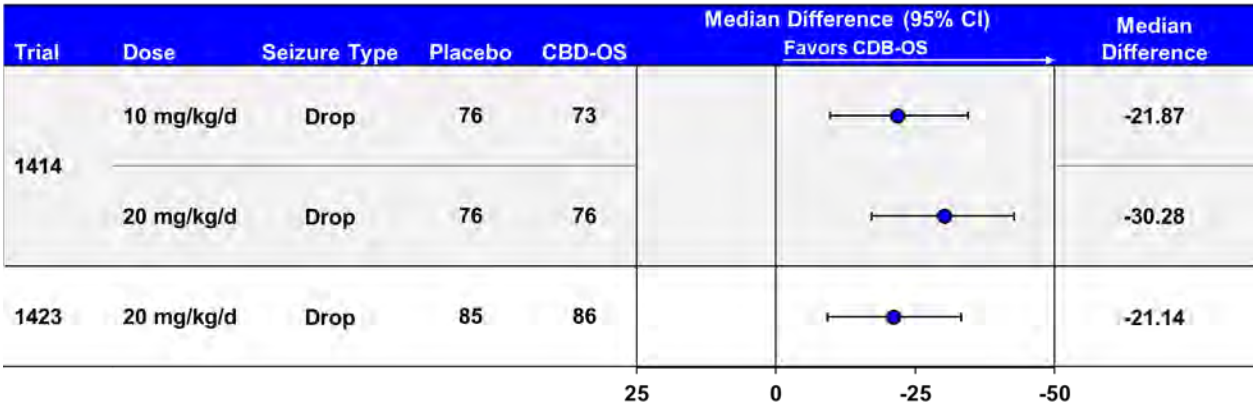
Analyses of time to 10th and 20th drop seizure were performed as an indication of early efficacy that would reduce the potential impact from patient withdrawals. Hazard ratios were in favor of CBD-OS for all seizure types (Figure 18).

Figure 18: Time to 10th and 20th Seizure for Drop Seizures from the Start of the Treatment Period in LGS Studies 1414 and 1423 (ITT)



Analyses of change from baseline in drop seizure frequencies during the titration period were also performed as an indication of early efficacy that reduce the potential impact patient withdrawals. Median differences were in favor of CBD-OS for all seizure types (Figure 19).

Figure 19: Percent Change from Baseline in Drop Seizure Frequency during the Titration Period in LGS Studies 1414 and 1423 (ITT)

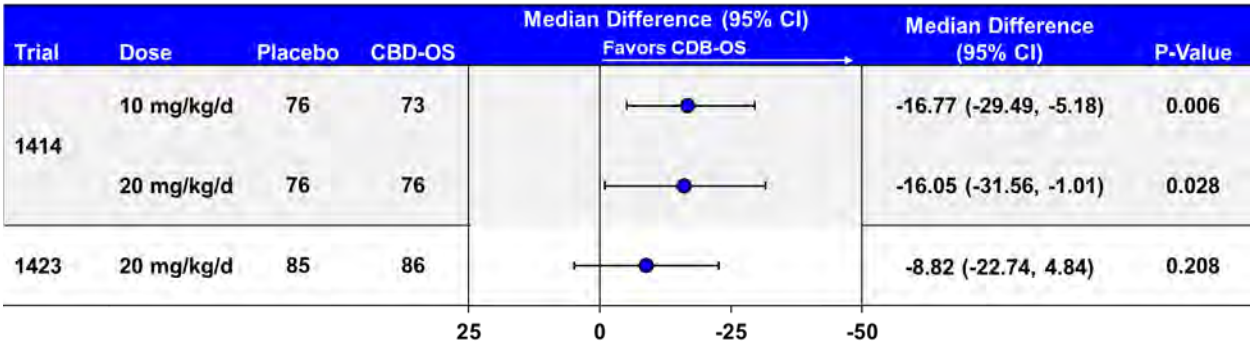


To account for the higher proportion of patients in the 20 mg/kg treatment arms that withdrew during the treatment period when compared with placebo, the primary endpoints for each study were analyzed using a Wilcoxon rank-sum test imputing the following:

- Patients with a reduction (improvement) in percentage change from baseline during the treatment period were imputed with zero percentage change (baseline observation carried forward).
- Patients with an increase in percentage change from baseline during the treatment period remain unchanged.

This penalization imputation was performed for CBD-OS withdrawn patients only. Treatment differences were consistent and in favor of CBD-OS for both studies, with similar point estimates and overlapping CIs (Figure 20).

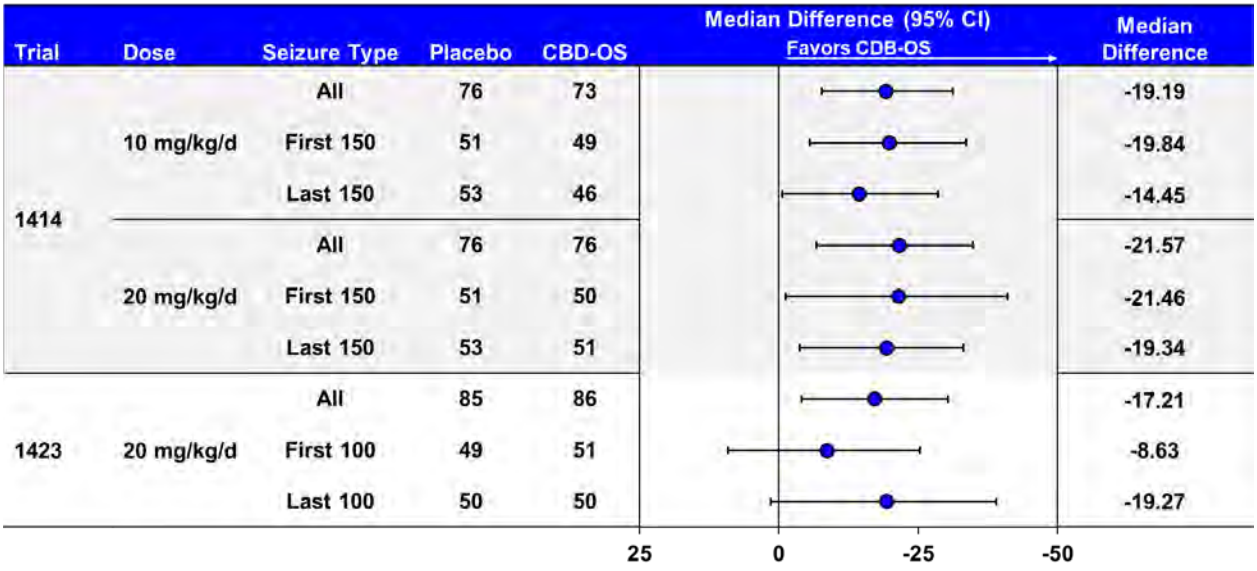
Figure 20: Percent Change from Baseline in Drop Seizure Frequency during the Treatment Period with Imputation for Patients Who Withdrew during the Treatment Period in LGS Studies 1414 and 1423 (ITT)



Following the greater than planned recruitment of the pivotal studies, the primary endpoints for each study were reanalyzed using data from the first and last 150 patients randomized (Study 1414), or the first and last 100 patients randomized (Study 1423). The summary demographics and baseline characteristics were similar between the first patients randomized and the last

patients randomized into each study. Treatment differences were all in favor of CBD-OS irrespective of whether the first or last randomized patients were analyzed (Figure 21).

Figure 21: Percent Change from Baseline in Primary Seizure Frequency during the Treatment Period Overall and by Planned Sample Size in LGS Studies 1414 and 1423



6.3.2. KEY SECONDARY ENDPOINTS

6.3.2.1. PROPORTION OF PATIENTS WHO ACHIEVED ≥50% REDUCTION FROM BASELINE IN DROP SEIZURE FREQUENCY DURING THE TREATMENT PERIOD IN LGS STUDIES 1414 AND 1423

Both studies demonstrated a statistically significant improvement for ≥50% reduction from baseline in drop seizure frequency during the treatment period (Figure 22).

During the treatment period in Study 1414, the proportion of patients with a reduction of ≥50% in their baseline drop seizure frequency (28-day average) was greater in the 20 mg/kg/day and 10 mg/kg/day CBD-OS groups compared with the placebo group (p=0.0006 and p=0.003, respectively).

Similarly, in Study 1423, the proportion of patients with a reduction of ≥50% in their baseline drop seizure frequency was greater in the 20 mg/kg/day CBD-OS group compared with placebo (p=0.0043).

6.3.2.1.1. Proportion of Patients Who Achieved ≥25%, ≥75%, and 100% Reduction from Baseline in Drop Seizure Frequency During the Treatment Period (14 Weeks)

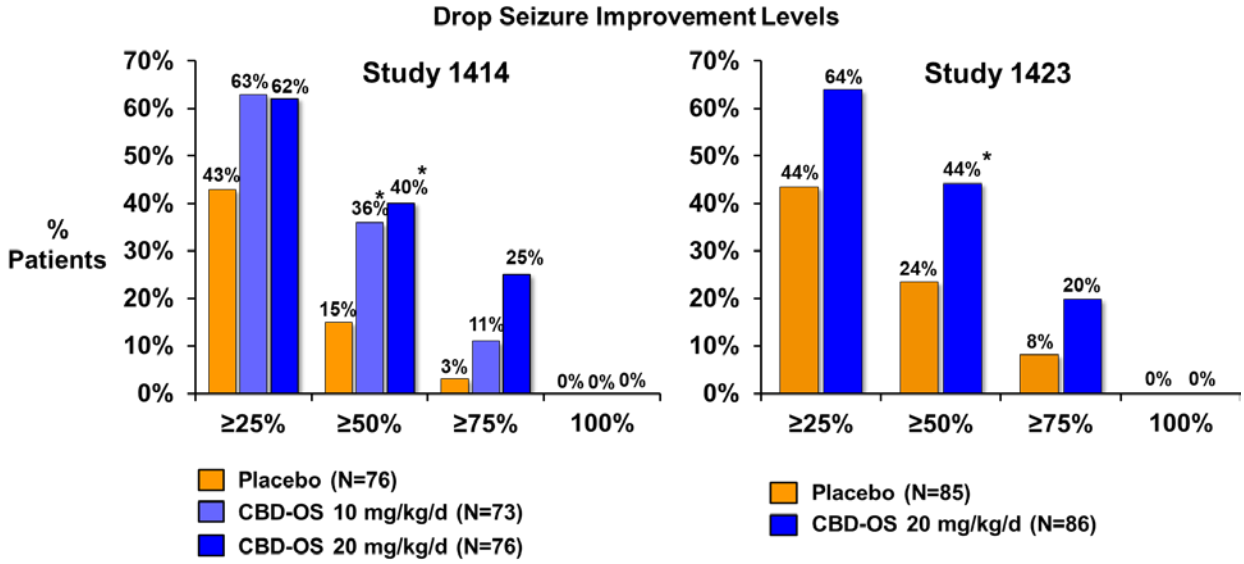
In both LGS studies, the proportion of patients experiencing ≥25% reduction from Baseline in drop seizures during the treatment period was greater in the CBD-OS groups compared with placebo (Figure 22). The treatment difference was higher for the 20 mg/kg/day and 10

mg/kg/day CBD-OS groups vs. placebo in Study 1414 (p=0.0229 and p=0.0149, respectively), and 20 mg/kg/day vs. placebo in Study 1423 (p=0.0081).

Similarly, the proportion of patients experiencing ≥75% reduction from Baseline in drop seizures during the treatment period was greater in the CBD-OS groups compared with placebo (Figure 22). The treatment difference was higher for the 20 mg/kg/day and 10 mg/kg/day CBD-OS groups vs. placebo in Study 1414 (p<0.0001 and p=0.0453, respectively), and 20 mg/kg/day vs. placebo in Study 1423 (p=0.0273).

No patients achieved drop seizure freedom (i.e., 100% reduction from baseline in drop seizure frequency) during the treatment period in either of the LGS studies. Given the very high baseline drop seizure frequency, and the fact that the first 14 days of the treatment period was a period of dose escalation, this finding is to be expected. However, in Study 1414, 9 patients were drop seizure free during the maintenance period (5 in the 20 mg/kg/day CBD-OS group [6.6%]: 3 in the 10 mg/kg/day CBD-OS group [4.1%], and 1 in the placebo group [1.3%]). Similarly, in Study 1423, 5 patients were drop seizure free during the maintenance period (all 5 in the 20 mg/kg/day CBD-OS group [5.9%]).

Figure 22: Proportion of Patients With ≥25%, ≥50, ≥75%, and 100% Reduction in Drop Seizure Frequency during the Treatment Period in LGS Studies 1414 and 1423



* p-value <0.05

6.3.2.2. PERCENT CHANGE FROM BASELINE IN TOTAL SEIZURE FREQUENCY DURING THE TREATMENT PERIOD (14 WEEKS)

Reduction in total seizure frequency provides an estimate of the effect of CBD on a patient's entire seizure burden. As shown in Table 16, CBD-OS at 20 mg/kg/day was superior to placebo in reducing total seizure frequency during the treatment period in both LGS studies (p=0.0091 in Study 1414 and p=0.0005 in Study 1423); CBD-OS at 10 mg/kg/day was also superior to placebo for this endpoint in Study 1414 (p=0.0015).

Table 16: Percent Change from Baseline in Total Seizure Frequency during the Treatment Period in LGS Studies 1414 and 1423 (ITT Analysis Set)

Variable Statistics	Study 1414			Study 1423	
	Placebo (N=76)	CBD-OS 10 mg/kg (N=73)	CBD-OS 20 mg/kg (N=76)	Placebo (N=85)	CBD-OS 20 mg/kg (N=86)
Total Seizure Frequency (Average per 28 Days) during the Baseline Period					
Median	180.63	165.00	174.29	176.69	144.56
Q1; Q3	90.4; 431.3	81.3; 359.0	82.7; 392.4	68.6; 359.5	72.0; 385.7
Percent Change from Baseline in Total Seizure Frequency (Average per 28 Days) during the Treatment Period					
Median	−18.47	−36.44	−38.40	−13.70	−41.24
Q1; Q3	−39.0; 0.5	−64.5; −10.8	−64.6; −0.7	−45.0; 7.3	−62.8; −13.0
Estimated Treatment Difference vs. Placebo					
Median Difference	NA	-19.47	-18.76	NA	-21.23
95% CI	NA	-30.37, -7.47	-31.80, -4.43	NA	-33.26, -9.37
P-value	NA	0.0015	0.0091	NA	0.0005

Note: Total seizures include all seizure types combined.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.

6.3.2.2.1. Percent Change from Baseline in Total Seizure Frequency During the Maintenance Period (12 Weeks)

Consistent with the analysis for the treatment period, statistically significantly greater median reductions in total seizure frequency were also seen during the maintenance period in the 20 mg/kg/day (p=0.0158 in Study 1414 and p=0.0004 in Study 1423) and 10 mg/kg/day (p=0.00026) CBD-OS groups compared with placebo.

Table 17: Percent Change from Baseline in Total Seizure Frequency During the Maintenance Period in LGS Studies 1414 and 1423

Variable Statistics	Study 1414			Study 1423	
	Placebo (N=76)	CBD-OS 10 mg/kg (N=73)	CBD-OS 20 mg/kg (N=76)	Placebo (N=85)	CBD-OS 20 mg/kg (N=86)
Total Seizure Frequency (Average per 28 Days) during the Baseline Period					
Median	180.63	165.00	174.29	176.69	144.56
Q1; Q3	90.4; 431.3	81.3; 359.0	82.7; 392.4	68.6; 359.5	72.0; 385.7
Percent Change from Baseline in Total Seizure Frequency (Average per 28 Days) during the Maintenance Period					
Median	−23.09	−39.99	−41.80	−14.83	−44.68
Q1; Q3	−42.2; −1.3	−70.4; −10.7	−71.4; 1.1	−45.8; 4.9	−67.7; −19.8
Estimated Treatment Difference vs. Placebo					
Median Difference	NA	-19.88	-18.81	NA	-23.27
95% CI	NA	-31.25, -7.14	-32.74, -3.80	NA	-36.29, -10.47
P-value	NA	0.0026	0.0158	NA	0.0004

6.3.2.3. SUBJECT/CAREGIVER GLOBAL IMPRESSION OF CHANGE (S/CGIC) AT LAST VISIT

In each of the LGS studies, the odds of achieving an improvement at last visit were statistically significant in favor of CBD-OS over placebo (Figure 23 and Figure 24). The majority of patients in the 20 mg/kg/day CBD-OS group of each study (57-58%) had an improvement in overall condition at last visit, compared with 34-44% of patients in the placebo group. The OR for achieving an improvement at last visit (20 mg/kg/day CBD-OS vs. placebo) was 1.83 (95% CI: 1.02, 3.30) in Study 1414 and 2.54 (95% CI: 1.45, 4.47) in Study 1423; the difference in each study was statistically significant when analyzed using ordinal logistic regression (p=0.0439 and p=0.0012, respectively). CBD-OS at 10 mg/kg/day was also superior to placebo for this endpoint in Study 1414 (OR: 2.57; 95% CI: 1.41, 4.66; p=0.0020). These results support the improvements in seizure control with CBD-OS as being clinically meaningful.

Figure 23: Subject/Caregiver Global Impression of Change at Last Visit in LGS Study 1414

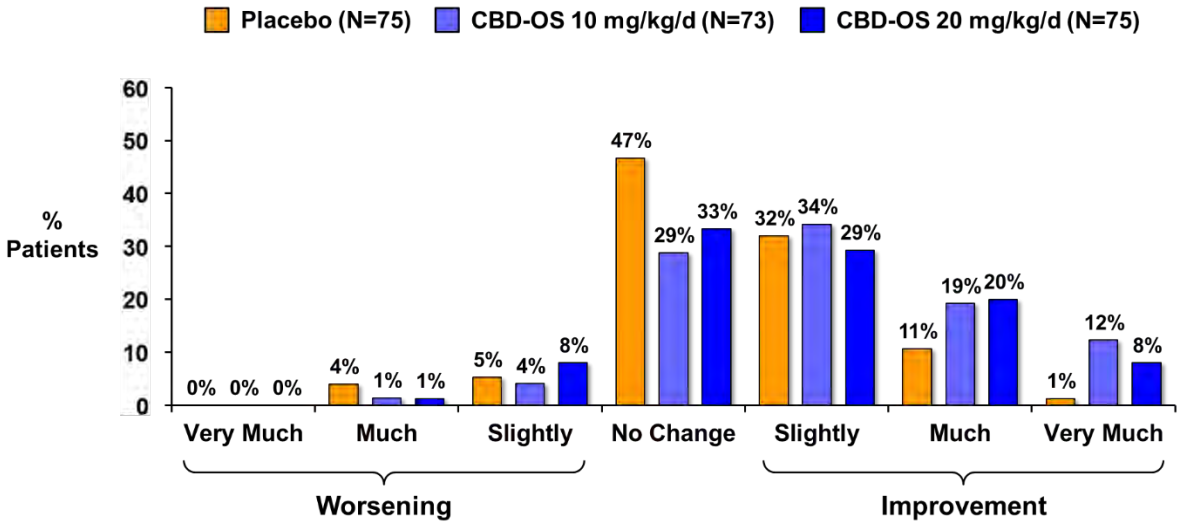
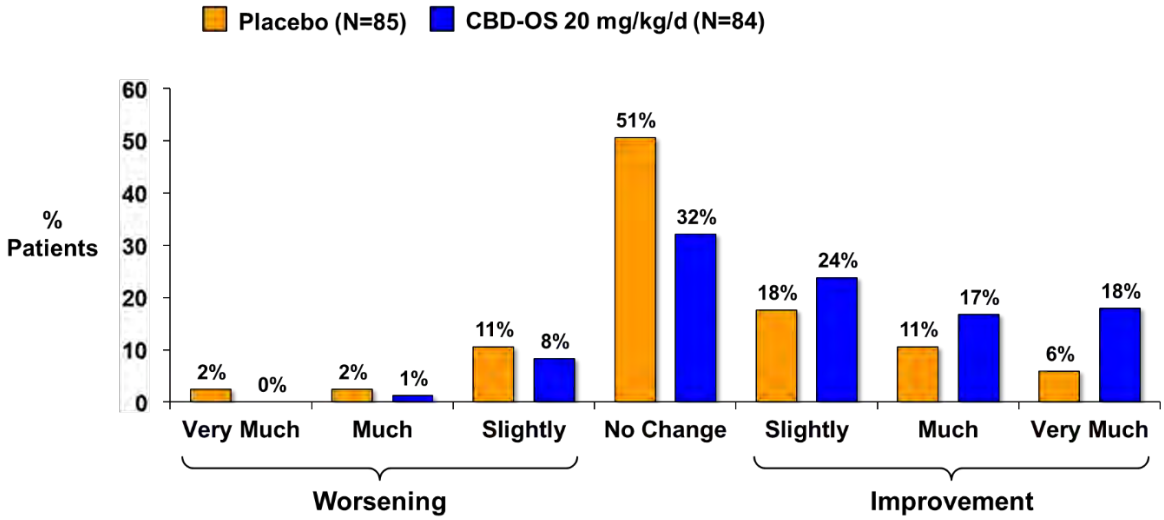


Figure 24: Subject/Caregiver Global Impression of Change at Last Visit in LGS Study 1423



6.3.3. OTHER ANALYSES

6.3.3.1. NUMBER OF DROP SEIZURE FREE DAYS

The number of drop seizure free days was examined as an exploratory analysis (i.e., not alpha protected). The mean number of drop seizure free days (28-day average) was similar between treatment groups during the baseline period in both studies and increased during the treatment and maintenance periods, with greater increases in the CBD-OS groups (Table 18). In Study 1414, there was a difference from placebo in favor of CBD-OS 20 mg/kg/day ($p<0.0001$; treatment difference: 4.64; 95% CI: 2.46, 6.81) and 10 mg/kg/day ($p=0.0030$; treatment difference: 3.34; 95% CI: 1.15, 5.53) during the treatment period. Similarly, the treatment difference was in favor of CBD-OS 20 mg/kg/day during the treatment period in Study 1423 ($p=0.0075$; treatment difference: 2.70; 95% CI: 0.73, 4.67). These results were similar during the maintenance periods of both studies.

Table 18: Number of Drop Seizure Free Days in Studies 1414 and 1423

Variable Statistics	Study 1414 Placebo (N=76)	Study 1414 CBD-OS 10 mg/kg (N=73)	Study 1414 CBD-OS 20 mg/kg (N=76)	Study 1423 Placebo (N=85)	Study 1423 CBD-OS 20 mg/kg (N=86)
Drop Seizure Free Frequency (Average per 28 Days) during the Baseline Period					
Mean	4.57	5.25	5.29	5.12	6.36
Percent Change from Baseline in Drop Seizure Frequency (Average per 28 Days) during the Treatment Period					
Mean	6.89	10.78	12.11	8.21	12.16
Estimated Treatment Difference vs. Placebo					
Treatment difference	NA	3.34	4.64	NA	2.70
95% CI	NA	1.15, 5.53	2.46, 6.81	NA	0.73, 4.67
p-value	NA	p=0.0030	p<0.0001	NA	p=0.0075

6.4. STUDY 1332B RESULTS (DS)

6.4.1. PRIMARY ENDPOINT: PERCENT CHANGE FROM BASELINE IN CONVULSIVE SEIZURE FREQUENCY DURING THE 14-WEEK TREATMENT PERIOD IN DS STUDY 1332B

As shown in Table 19, CBD-OS at 20 mg/kg/day was superior to placebo in reducing convulsive seizure frequency during the treatment period in Study 1332B (p=0.0123).

Table 19: Percent Change from Baseline in Convulsive Seizure Frequency During the 14-Week Treatment Period in DS Study 1332B (ITT Analysis Set)

Variable Statistics	Placebo (N=59)	CBD-OS 20 mg/kg (N=61)
Convulsive Seizure Frequency (Average per 28 Days) during the Baseline Period		
Median	14.88	12.44
Q1; Q3	7.0; 36.0	6.2; 28.0
Percent Change from Baseline in Convulsive Seizure Frequency (Average per 28 Days) during the Treatment Period		
Median	−13.29	−38.94
Q1; Q3	−52.5; 20.2	−69.5; −4.8
Estimated Treatment Difference vs. Placebo		
Median difference	NA	−22.79
95% CI	NA	−41.06, −5.43
P-value	NA	0.0123

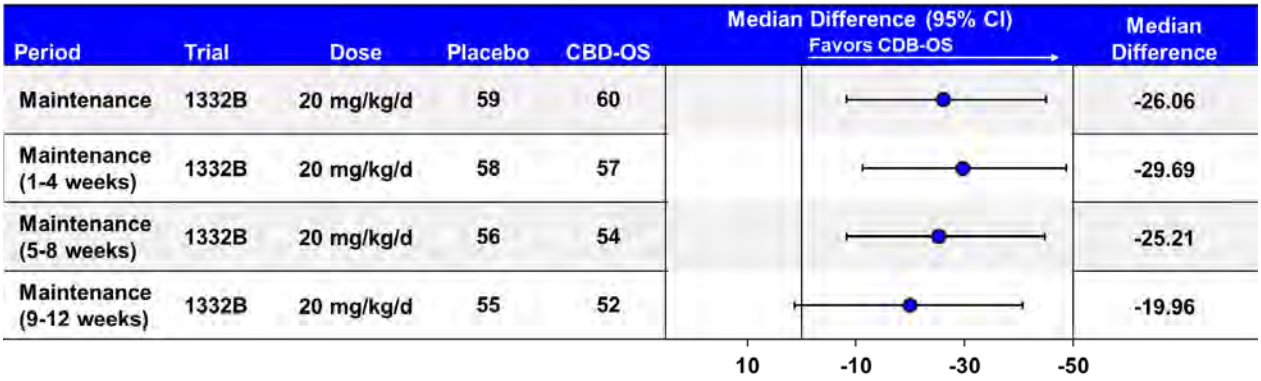
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earliest of Day 99 or the day of last dose up to and including the end of treatment visit.

Note: Estimated median difference and 95% CI calculated using the Hodges-Lehmann approach; p-value calculated from a Wilcoxon rank-sum test.

6.4.1.1. PERCENT CHANGE FROM BASELINE IN CONVULSIVE SEIZURE FREQUENCY DURING THE 12-WEEK MAINTENANCE PERIOD IN STUDY 1332B

Similar to the results in the LGS studies, CBD-OS 20 mg/kg/day was numerically superior to placebo in reducing convulsive seizure frequency during the maintenance period, and each 4-week block thereof, in Study 1332B (Figure 25).

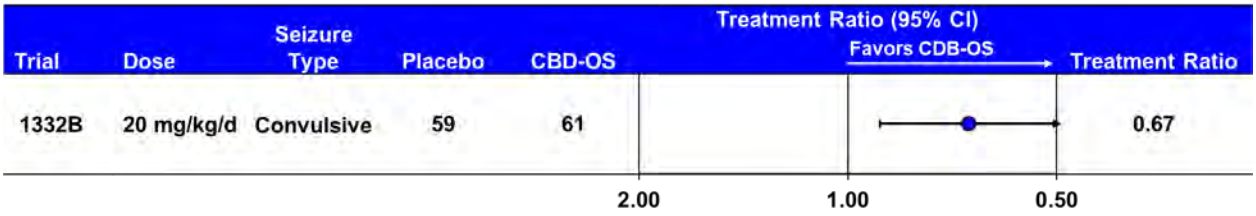
Figure 25: Percent Change from Baseline in Convulsive Seizure Frequency during the 12-Week Maintenance Period in Study 1332B (ITT Analysis Set)



6.4.1.2. SENSITIVITY ANALYSES

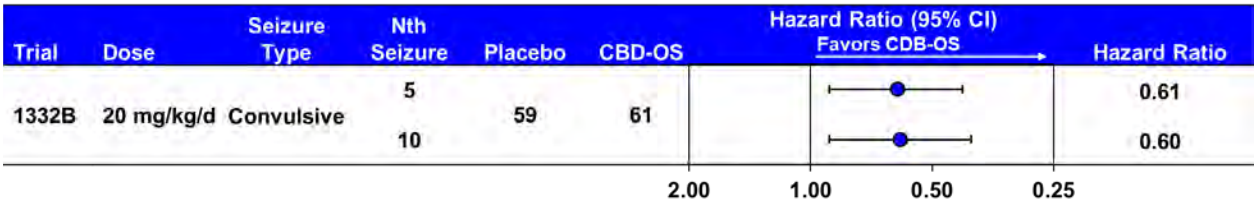
Sensitivity analyses were conducted as described for the LGS studies in Section 6.3.1.2, and the results for Study 1332B were similar to the results for the LGS studies. Negative binomial regression analyses of convulsive and total seizure counts showed the treatment ratios to be consistently in favor of CBD-OS (Figure 26).

Figure 26: Negative Binomial Regression Analysis of Convulsive and Total Seizure Counts during Baseline and Treatment Periods in DS Study 1332B (ITT)



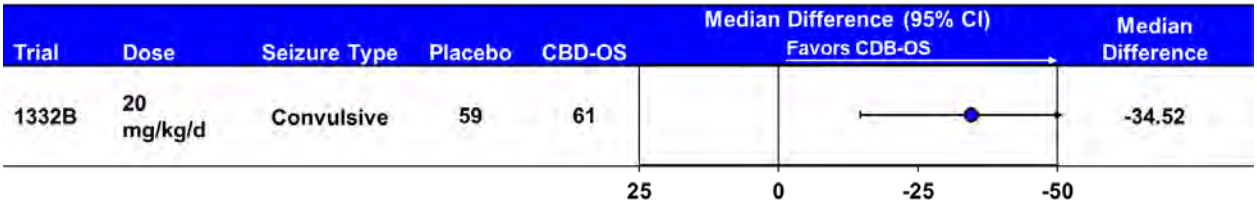
Analyses of time to 5th and 10th convulsive and total seizure showed that hazard ratios were in favor of CBD-OS for all seizure types (Figure 27).

Figure 27: Time to 5th and 10th Seizure for Convulsive and Total Seizures from the Start of the Treatment Period in DS Study 1332B (ITT)



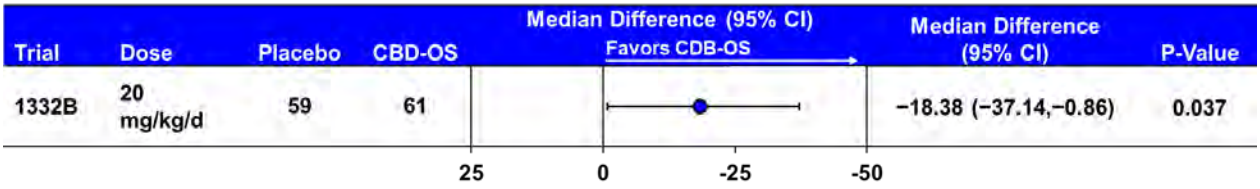
Analyses of change from baseline in convulsive and total seizure frequencies during the titration period showed that median differences were in favor of CBD-OS for all seizure types (Figure 28).

Figure 28: Percent Change from Baseline in Convulsive and Total Seizure Frequency during the Titration Period in DS Study 1332B (ITT)



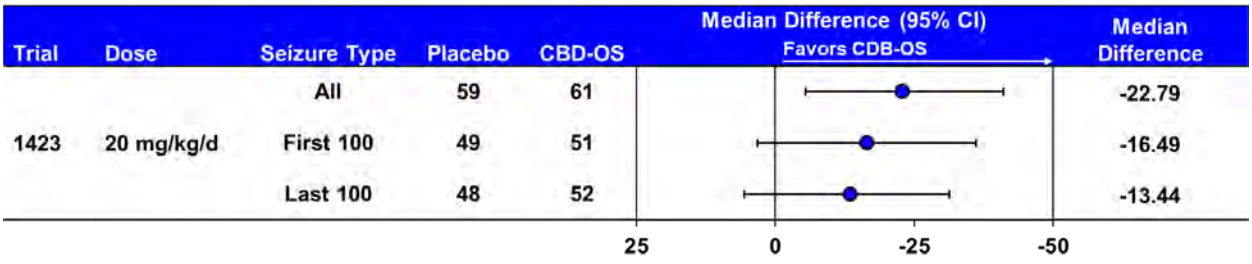
The primary endpoint for Study 1332B was analyzed using a Wilcoxon rank-sum test imputing the conservative scenario of either no change, if a patient improved prior to withdrawal, or the observed worsening if a patient had an increase in seizure frequency from baseline prior to withdrawal; this imputation was performed for CBD-OS withdrawn patients only. Treatment differences were in favor of CBD-OS (Figure 29).

Figure 29: Percent Change from Baseline in Convulsive Seizure Frequency during the Treatment Period with Imputation for Patients Who Withdrew during the Treatment Period in DS Study 1332B (ITT)



Following the greater than planned recruitment of Study 1332B, the primary endpoint was reanalyzed using data from the first and last 100 patients randomized. Comparison of the summary demographics and baseline characteristics revealed no obvious differences between the first patients randomized and the last patients randomized into the study. Treatment differences were all in favor of CBD-OS irrespective of whether the first or last randomized patients were analyzed with a broad overlap in CIs (Figure 30).

Figure 30: Percent Change from Baseline in Convulsive Seizure Frequency during the Treatment Period Overall and by Planned Sample Size in DS Study 1332B



6.4.2. KEY SECONDARY ENDPOINTS

6.4.2.1. PROPORTION OF PATIENTS WHO ACHIEVED ≥50% REDUCTION FROM BASELINE IN CONVULSIVE SEIZURE FREQUENCY DURING THE 14-WEEK TREATMENT PERIOD IN DS STUDY 1332B

During the treatment period, the proportion of patients with a reduction of ≥50% in their baseline convulsive seizure frequency was greater in the CBD-OS group (42.6%) than in the placebo group (27.1%) (Figure 31). The odds of achieving a ≥50% reduction in convulsive seizure frequency was twice as high in the CBD-OS group compared with the placebo group (OR: 2.00; 95% CI: 0.93, 4.30); however, the difference between treatments was not statistically significant (p=0.0784).

6.4.2.1.1. Proportion of Patients Who Achieved ≥25%, ≥75%, and 100% Reduction from Baseline in Convulsive Seizure Frequency During the 14-Week Treatment Period in DS Study 1332B

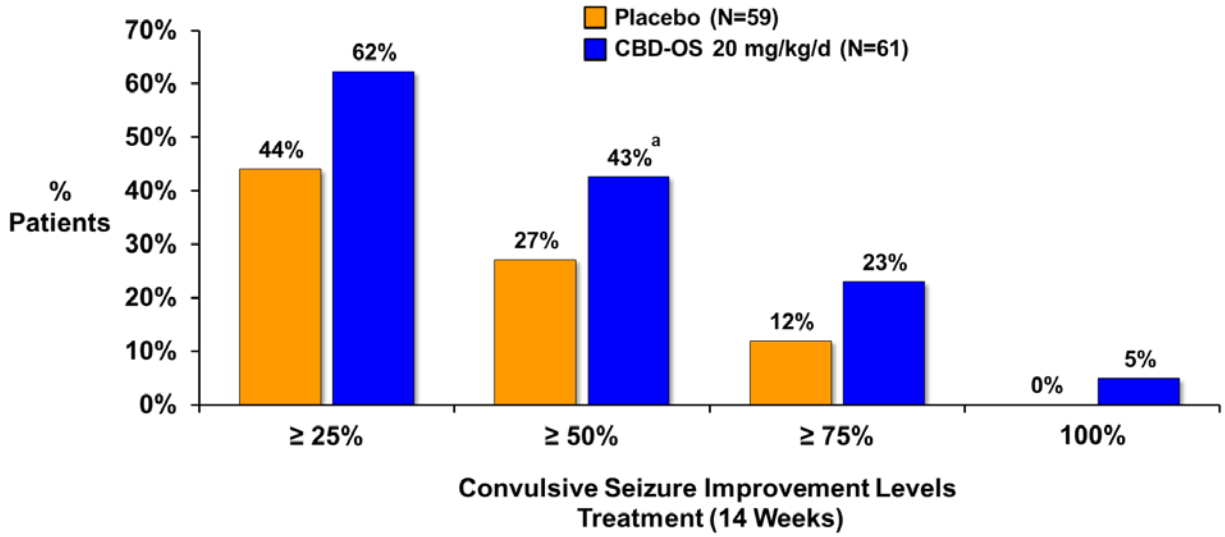
As shown in Figure 31, the proportion of patients with a reduction of ≥25% in their baseline convulsive seizure frequency during the treatment period was greater in the CBD-OS group (62.3%) than in the placebo group (44.1%). The odds of achieving a ≥25% reduction in convulsive seizure frequency were higher for the CBD-OS group compared with the placebo group (p=0.0506).

The proportion of patients with a reduction of ≥75% in their baseline convulsive seizure frequency during the treatment period was greater in the CBD-OS group (23.0%) than in the placebo group (11.9%). The odds of achieving a ≥75% reduction in convulsive seizure frequency were higher for the CBD-OS group compared with the placebo group (p=0.1121).

Three patients in the CBD-OS group (4.9%) experienced convulsive seizure-freedom (i.e., 100% reduction from baseline in seizure frequency) during the treatment period, compared with no patients in the placebo group (p=0.0827).

In addition to the 3 patients who experienced convulsive seizure-freedom during the treatment period (described above), an additional 4 patients in the CBD-OS group (6.7%) experienced convulsive seizure-freedom during the maintenance period, compared with no patients in the placebo group (difference in proportions: 11.7%; 95% CI: 3.5%, 19.8%).

Figure 31: Proportion of Patients with ≥25%, ≥50%, ≥75%, and 100% Reduction in Convulsive Seizure Frequency during the Treatment Period in DS Study 1332B



[a] p-value = 0.0784

6.4.2.2. PERCENT CHANGE FROM BASELINE IN TOTAL SEIZURE FREQUENCY DURING THE 14-WEEK TREATMENT PERIOD IN DS STUDY 1332

The median percent change from baseline in total seizure frequency during the treatment period was −28.57 in the CBD-OS 20 mg/kg/day group compared with −9.00 in the placebo group (Table 20). The estimated median difference was in favor of CBD-OS 20 mg/kg/day over placebo (nominal p-value=0.0335).

Table 20: Percent Change from Baseline in Total Seizure Frequency during the 14-Week Treatment Period in DS Study 1332B (ITT Analysis Set)

Variable Statistics	Placebo (N=59)	CBD-OS 20 mg/kg (N=61)
Total Seizure Frequency (Average per 28 Days) during the Baseline Period		
Median	41.48	24.00
Q1; Q3	12.0; 367.0	10.4; 141.0
Percent Change from Baseline in Total Seizure Frequency (Average per 28 Days) during the Treatment Period		
Median	-9.00	-28.57
Q1; Q3	-51.4; 19.6	-70.4; -4.0
Estimated Treatment Difference vs. Placebo		
Median Difference	-19.20	
95% CI	-39.25, -1.17	
Nominal p-value	0.0335	

Note: Analysis of total seizure frequency in Study 1332B was not protected for Type 1 error.
Note: Total seizures include all seizure types combined.
Note: Baseline period included all data prior to Day 1. Treatment period was defined as Day 1 to the earlier of Day 99 or the day of last dose up to and including the end of treatment visit.

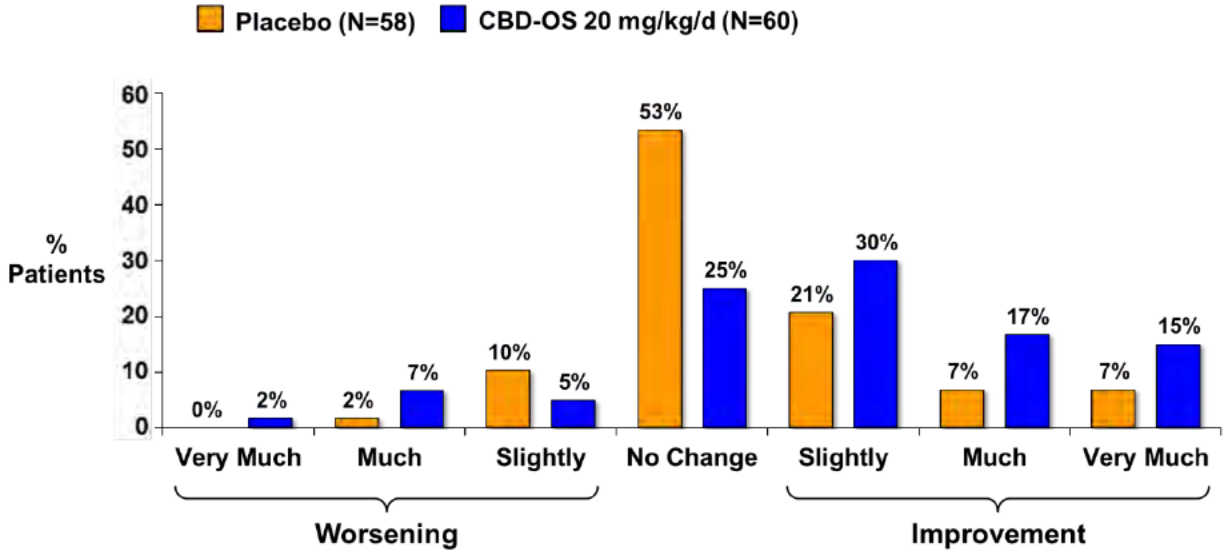
6.4.2.2.1. Percent Change from Baseline in Total Seizure Frequency During the 12-Week Maintenance Period

Results from the maintenance period were consistent with the treatment period. Analyses for the maintenance period, and each 4 weeks thereof, showed that the difference between treatments was in favor of CBD-OS 20 mg/kg/day during weeks 1-4 (estimated median difference: -29.45; 95% CI: -51.15, -8.21), weeks 5-8 (estimated median difference: -19.50; 95% CI: -40.85, -0.89), and weeks 9-12 (estimated median difference: -21.78; 95% CI: -45.64, 1.82) of the maintenance period.

6.4.2.3. CAREGIVER GLOBAL IMPRESSION OF CHANGE (CGIC) AT LAST VISIT

The odds of achieving an improvement on the CGIC at last visit were in favor of CBD-OS 20 mg/kg/day over placebo (Figure 32). The OR for achieving an improvement at last visit (20 mg/kg/day CBD-OS vs. placebo) was 2.29 (95% CI: 1.17, 4.47; nominal p-value=0.0155)

Figure 32: Caregiver Global Impression of Change at Last Visit in DS Study 1332B



6.4.3. OTHER ANALYSES

6.4.3.1. NUMBER OF CONVULSIVE SEIZURE FREE DAYS

The mean number of convulsive seizure free days (28-day average) was similar between treatment groups during the baseline period in Study 1332B and increased during the treatment and maintenance periods, with numerically greater increases in the CBD-OS groups. There was a numerical difference from placebo in favor of CBD-OS 20 mg/kg during the treatment period, (p=0.0571; treatment difference: 0.99; 95% CI: -0.03, 2.00). These results were similar during the maintenance period of the study.

Table 21: Number of Convulsive Seizure Free Days in Study 1332B

Variable Statistics	Placebo (N=59)	CBD-OS 20 mg/kg/day (N=61)
Convulsive Seizure Free Days (Average per 28 Days) during the Baseline Period		
Mean	16.68	17.98
Convulsive Seizure Free Days (Average per 28 Days) during the Treatment Period		
Mean	17.90	20.13
Estimated Treatment Difference vs. Placebo		
Treatment difference	NA	0.99
95% CI	NA	-0.03, 2.00
p-value	NA	p=0.0571

6.5. PERSISTENCE OF EFFICACY

Persistence of efficacy beyond 14 weeks of treatment was assessed in the OLE study (Study 1415) and the EAP. At the time of their respective interim data cuts, 284 patients with LGS or DS in the OLE had a minimum of 37 weeks of CBD-OS treatment, and 77 patients with LGS or DS in the EAP had a minimum of 53 weeks of CBD-OS treatment.

6.5.1. OPEN-LABEL EXTENSION STUDY 1415

At the data cut for the original submission, a total of 630 patients from the pivotal studies (366 with LGS [58%] and 264 with DS [42%]) had entered the OLE study. The mean [SD] number of dosing days was 251 [119] and was similar between the LGS and DS populations, representing a total of 433 patient-years on treatment.

Patients were titrated up to 20 mg/kg/day CBD-OS, and the dose could be reduced or increased to a maximum of 30 mg/kg/day by the Investigator depending on tolerability and efficacy. For all patients with LGS, the mean modal dose was 22.8 mg/kg/day over the treatment period, which ranged per 12-week reporting interval from 21.2-24.3 mg/kg/day over the first 49-60 weeks of treatment. During the last 12 weeks of treatment, the median [mean] modal dose was 22.0 [23.0] mg/kg/day (N=364), indicating no development of tolerance to treatment.

The mean modal dose was 21.2 mg/kg/day over the treatment period for all patients with DS, with the mean modal dose per 12-week reporting interval ranging from 19.9-22.7 mg/kg/day over the first 49-60 weeks of treatment. During the last 12 weeks of treatment, the median [mean] modal dose was 20.0 [22.2] mg/kg/day (N=257), indicating no development of tolerance to treatment.

To account for differences in sample size with increasing time, maintenance of efficacy was assessed in patients treated for 37-48 weeks in Study 1415. In patients with LGS (N=209), the median percent reduction from baseline in drop seizure frequency was 52% during Week 1-12, which was maintained through to Week 37-48 (median 60% decrease). Similarly, in patients with DS (N=75), the median percent reduction from baseline in convulsive seizure frequency was 56% during Week 1-12, which was maintained through to Week 37-48 (median 45% decrease). Together these data demonstrate persistence of CBD-OS effect for seizure reduction in both LGS and DS patient populations.

6.5.2. EXPANDED ACCESS PROGRAM

At the data cut for the original submission, a total of 684 patients in the EAP had contributed data to the safety analysis set (including 97 with LGS and 64 with DS) and 623 patients were included in the efficacy analysis set (including 92 with LGS and 58 with DS). In patients with LGS or DS, the mean [SD] number of dosing days was 454 [311], representing an estimated 198 patient-years on treatment.

Following completion of the titration period, the dose of CBD-OS could be escalated up to 50 mg/kg/day, dependent on site. Although dosing varied widely for patients with LGS or DS, the median dose at time of visit per 12-week visit window was stable at 21-25 mg/kg/day over 96 weeks of treatment, indicating no development of tolerance to treatment.

To account for differences in sample size with increasing time, maintenance of efficacy was assessed in patients treated for >52 weeks. The median percent reduction in convulsive seizure frequency from Week 15 onwards was 39% in patients with LGS (N=43) and 36% in patients with DS (N=34), which was maintained to Week 53 onwards (median 45% and 39% reductions in LGS and DS, respectively). Five patients (4%) were free of all motor seizures (Devinsky, 2016).

Together with the OLE study, these data demonstrate persistence of CBD-OS effect for convulsive seizure reduction in both LGS and DS patient populations.

6.6. SUMMARY OF EFFICACY IN LGS AND DS

The totality of the evidence is consistent with attributing the observed reduction in seizure frequency to direct CBD effects.

- Administration of CBD or the active metabolite (7-OH-CBD), in the absence of any other AED, has been shown to reduce seizures in a variety of animal models.
- CBD-OS demonstrated efficacy in 2 well-controlled, multicenter, placebo-controlled studies in LGS, and in a single well-controlled, multicenter, placebo-controlled study in DS.
- Both LGS studies and the DS study met their primary endpoint, providing a statistically significant and clinically meaningful reduction in drop seizures in LGS and convulsive seizures, in DS during the treatment period. Both seizure endpoints are supported by significant reductions in total seizures of CBD-OS vs. placebo in both LGS and DS.
- Prespecified secondary endpoints were also supportive for CBD-OS in the pivotal studies, showing that CBD-OS increased the 50% responder rate, reduced the frequency of total seizures, and improved scores on the S/CGIC at the last visit in the LGS studies.

7. CLINICAL SAFETY

Summary

- The safety and tolerability profile of CBD-OS is predictable and manageable through the proposed label and medication guide.
- CBD-OS has been evaluated for safety in more than 600 LGS and DS patients, including 391 patients treated for one year or more.
- Common AEs in the controlled studies included somnolence, decreased appetite, diarrhea, pyrexia, and fatigue.
- The majority of AEs were mild or moderate in intensity.
- The most common SAEs in the All CBD-OS group were SE, pneumonia, convulsion, and AST increased.
- There was 1 death in the controlled studies, 7 deaths in OLE study, and 12 deaths in the EAP. None of the deaths were considered to be related to CBD-OS by the Investigator or Sponsor. The mortality rate is similar to the reported rates for LGS and DS.
- Elevated transaminases can occur with CBD-OS, but the elevations did not meet Hy's Law criteria or resulted in any cases of severe or permanent hepatic damage.
- Worsening seizures were not observed with use of CBD-OS.

7.1. TREATMENT EXPOSURE

Safety data to support the use of CBD-OS in DS and LGS patients have been collected from 8 completed Phase 1 studies; 3 completed double-blind, placebo-controlled studies in target indications (1 study in DS and 2 studies in LGS); and 1 ongoing Phase 3 OLE study (120-day safety update). The overall demographics and baseline characteristics of the LGS and DS patient populations in the controlled studies were generally representative of the population to which the drug will be marketed. In addition, safety information has been collected from the EAP, although the safety analysis covered in this briefing document will focus on the 3 controlled Phase 3 studies except where otherwise noted. CBD-OS has been evaluated for safety in more than 600 patients in GW sponsored studies, including 391 patients treated for one year or more, which allows for a reasonable benefit-risk assessment of CBD-OS in LGS and DS patients.

Table 22 summarizes the number of patients, mean duration of exposure, and total exposure (patient years) in the placebo-controlled studies, the OLE study, and the EAP. The numbers of patients with ≥6 months, ≥12 months, and ≥2 years of exposure in the OLE and EAP are also presented. Overall, 1419 unique patients with epilepsy were exposed to CBD-OS, including 88 patients with DS and 235 patients with LGS who were enrolled in controlled studies. An additional 209 patients with DS and 157 patients with LGS were exposed to CBD-OS in the ongoing long term OLE study.

Additional safety data from the QT study (Study 1541) are included in Section 7.8.

Table 22: Summary of Drug Exposure for the LGS and DS Populations in the Controlled Studies, Open-label Study, and the Population of Patients with Epilepsy in the EAP

	Comparative Studies in LGS and DS (Pool LGS/DS)		OLE (Study 1415-LGS/DS)[a]	EAP (Pool EAP)
	Placebo	CBD-OS		
Number of patients	227 (LGS: 161; DS: 66)	323 (LGS; 235; DS: 88)	644 (LGS: 366; DS: 278)	684 (LGS: 97; DS: 54)
Mean exposure (days) ± SD	97.2±17.3	88.3±27.7	361.9±162.4	369.5±280.6
No of patients with ≥ 6 months exposure	NA	NA	553 (315 LGS; 218 DS)	439 (58 LGS; 51 DS)
No of patients with ≥ 12 months exposure	NA	NA	391 (271 LGS; 120 DS)	279 (50 LGS; 41 DS)
No of patients with ≥ 24 months exposure	NA	NA	0	121 (27 LGS; 23 DS)
Total Exposure (Patient-years)	60.4 (LGS: 43.8; DS: 16.6)	78.1 (LGS: 60.3; DS: 17.8)	638.15 (LGS: 385.39; DS: 252.76)	690.02 (LGS: 108.38; DS: 92.52)

[a] The unique exposures in the OLE include all patients from Study 1415 who originated from Study 1424 regardless of their treatment in Study 1424. Study 1424 is an ongoing, blinded study that is not included in any pool; therefore, the patients are not otherwise counted. Only patients who completed one of the controlled studies (Study 1414, Study 1423, Study 1332, and Study 1424) were eligible to enter the OLE (Study 1415).

7.2. OVERVIEW OF ADVERSE EVENTS

Overall, CBD-OS showed similar safety profiles in patients with LGS and patients with DS. As shown in Table 23, no notable differences were observed in the AEs, severe AEs, AEs leading to discontinuation, SAEs, or AEs leading to death when comparing the LGS and DS patients. The similarity of the AEs seen in the LGS and DS populations, together with the similarity of the patient demographics (Section 6.2.2), justifies pooling both populations for the overall safety evaluation. Therefore, data from the LGS and DS patients exposed to CBD-OS are pooled in the All CBD-OS group for the controlled studies. Appendix 10.2 provides tables of common AEs separated by disease (LGS and DS).

Table 23: Comparative Summary of AE Overview in Controlled LGS and DS Studies (Pool LGS vs. Pool DS)

	Pool LGS		Pool DS	
Patients with any	Placebo (N=161) n (%)	All CBD-OS (N=235) n (%)	Placebo (N=66) n (%)	All CBD-OS (N=88) n (%)
AEs	114 (70.8)	207 (88.1)	50 (75.8)	77 (87.5)
Mild	66 (41.0)	86 (36.6)	41 (62.1)	37 (42.0)
Moderate	40 (24.8)	90 (38.3)	6 (9.1)	28 (31.8)
Severe	8 (5.0)	31 (13.2)	3 (4.5)	12 (13.6)
AEs leading to discontinuation	2 (1.2)	19 (8.1)	1 (1.5)	11 (12.5)
SAEs	12 (7.5)	46 (19.6)	4 (6.1)	14 (15.9)
Deaths	0	1 (0.4)	0	0

Note: Safety analysis set.

7.2.1. COMMON ADVERSE EVENTS

Of all patients in the controlled studies taking CBD-OS, 284 experienced an AE, and 176 of these (62.0%) occurred during the first 2 weeks of treatment. AEs were most frequently reported in the Nervous system disorders system organ class (SOC), Infections and infestations SOC, and Gastrointestinal disorders SOC (Table 24). The 3 most common AEs were somnolence, decreased appetite, and diarrhea.

When comparing by CBD-OS dose group, the overall incidence of AEs was higher in the 20 mg/kg/day group (90.3%) than in the 10 mg/kg/day group (81.3%). The incidences of the following PTs were higher in the 20 mg/kg/day dose group compared with the 10 mg/kg/day dose group: decreased appetite (22.3% vs. 16.0%), diarrhea (19.7% vs. 9.3%), vomiting (12.2% vs. 6.7%), and fatigue (10.9% vs. 6.7%). Of note, the incidence of diarrhea was similar between the 10 mg/kg/day and placebo groups, and the incidence of vomiting was similar between the 20 mg/kg/day and placebo groups. The incidences of somnolence (25.2% vs. 22.7%) and pyrexia (12.6% vs. 12.0%) were similar between the 20 mg/kg/day and 10 mg/kg/day CBD-OS dose groups; the incidence of pyrexia was also similar in the placebo group. Finally, the incidence of upper respiratory tract infection was lower in the 20 mg/kg/day group compared with the 10 mg/kg/day group (8.4% vs. 14.7%), but similar to the placebo group (9.7%).

Table 24: Summary of Common AEs (≥10% in the All CBD-OS Group) in Controlled LGS and DS Studies (Pool LGS/DS)

SOC PT	Placebo in Controlled Studies (N=227) n (%)	All CBD-OS in Controlled Studies[a] (N=323) n (%)	CBD-OS	
			10 mg/kg/day (N=75) n (%)	20 mg/kg/day (N=238) n (%)
Patients with at least 1 AE	164 (72.2%)	284 (87.9)	61 (81.3)	215 (90.3)
Gastrointestinal disorders	**57 (25.1)**	**107 (33.1)**	**16 (21.3)**	**90 (37.8)**
Diarrhoea	20 (8.8)	54 (16.7)	7 (9.3)	47 (19.7)
Vomiting	26 (11.5)	35 (10.8)	5 (6.7)	29 (12.2)
General disorders and administration site conditions	**34 (15.0)**	**78 (24.1)**	**16 (21.3)**	**59 (24.8)**
Pyrexia	24 (10.6)	42 (13.0)	9 (12.0)	30 (12.6)
Fatigue	8 (3.5)	31 (9.6)	5 (6.7)	26 (10.9)
Infections and infestations	**71 (31.3)**	**134 (41.5)**	**32 (42.7)**	**98 (41.2)**
Upper respiratory tract infection	22 (9.7)	32 (9.9)	11 (14.7)	20 (8.4)
Metabolism and nutrition disorders	**14 (6.2)**	**79 (24.5)**	**15 (20.0)**	**63 (26.5)**
Decreased appetite	11 (4.8)	65 (20.1)	12 (16.0)	53 (22.3)
Nervous system disorders	**67 (29.5)**	**153 (47.4)**	**31 (41.3)**	**116 (48.7)**
Somnolence	19 (8.4)	79 (24.5)	17 (22.7)	60 (25.2)

[a] All CBD-OS includes patients in the 5 mg/kg/day treatment group
Note: Common AEs were defined as having an incidence of ≥ 10% (after rounding up) in the All CBD-OS group.
Note: Safety analysis set.

7.2.2. ADVERSE EVENTS BY SEVERITY

In the controlled studies, most AEs were mild to moderate in intensity (Table 23). The incidence of severe AEs was 13.3% in the All CBD-OS group (N=323) and 4.8% in the placebo group (N=227) (Table 25). The most common severe AEs in the All CBD-OS group included somnolence (1.9%), pneumonia (1.5%), and convulsion (1.5%); convulsion was most common in the placebo group (1.8%).

Table 25: Severe Common AEs in the Controlled LGS and DS Studies (Pool LGS/DS)

SOC PT	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)
Patients with at least 1 severe AE	**11 (4.8)**	**43 (13.3)**
Gastrointestinal disorders	**1 (0.4)**	**5 (1.5)**
Diarrhoea	0	1 (0.3)
Vomiting	0	1 (0.3)
Constipation	0	1 (0.3)
General disorders and administration site conditions	**0**	**3 (0.9)**
Pyrexia	0	1 (0.3)
Fatigue	0	0
Infections and infestations	**2 (0.9)**	**9 (2.8)**
Upper respiratory tract infection	0	0
Nasopharyngitis	0	0
Pneumonia	0	5 (1.5)
Ear infection	0	0
Bronchitis	0	0
Sinusitis	0	0
Investigations	**2 (0.9)**	**8 (2.5)**
ALT increased	0	4 (1.2)
AST increased	0	3 (0.9)
Weight decreased	0	1 (0.3)
GGT increased	0	2 (0.6)
Liver function test abnormal	1 (0.4)	1 (0.3)
Transaminases increased	0	0
Metabolism and nutrition disorders	**0**	**4 (1.2)**
Decreased appetite	0	3 (0.9)
Increased appetite	0	0
Nervous system disorders	**5 (2.2)**	**17 (5.3)**
Somnolence	0	6 (1.9)
Convulsion	4 (1.8)	5 (1.5)
Lethargy	0	4 (1.2)
Sedation	0	2 (0.6)
Status epilepticus	2 (0.9)	4 (1.2)
Headache	0	0
Drooling	0	0
Psychiatric disorders	**0**	**3 (0.9)**
Irritability	0	0
Insomnia	0	0
Aggression	0	1 (0.3)
Respiratory, thoracic and mediastinal disorders	**2 (0.9)**	**6 (1.9)**
Cough	0	0
Nasal congestion	0	0

SOC PT	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)
Patients with at least 1 severe AE	**11 (4.8)**	**43 (13.3)**
Skin and subcutaneous tissue disorders	**0**	**2 (0.6)**
Rash	**0**	1 (0.3)

Note: Common AEs are defined as those with an incidence of ≥3% (after rounding up) in the All CBD-OS group.
Note: For patients who have multiple AEs in the same SOC or PT category, the worst intensity is counted.
Note: Events with missing intensity are imputed to 'Severe'.
Note: Investigator assigned causality.
Note: Safety analysis set.

7.2.3. ADVERSE EVENTS LEADING TO DOSE REDUCTION

In the controlled studies, Investigators were allowed to reduce the dose of study medication from the target dose if patients experienced AEs and were encouraged to titrate patients back up to the target dose where possible.

The incidence of permanent dose reductions was higher in the All CBD-OS group (6.2%) than in the placebo group (0.9%). When comparing by CBD-OS dose group, the incidences of dose reductions and stopping treatment were higher in the 20 mg/kg/day group than in the 10 mg/kg/day group.

Common AEs that led to dose reductions in the All CBD-OS group included: somnolence (2.5%), decreased appetite (1.2%), diarrhea (0.9%), fatigue (0.9%), and vomiting (0.3%) (Table 26).

Table 26: Level of Action Taken for Common AEs that Reached an Incidence of ≥10% in the All CBD-OS Group in the Controlled LGS and DS Studies (Pool LGS/DS)

	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)	CBD-OS 10 mg/kg/day (N=75) n (%)	CBD-OS 20 mg/kg/day (N=238) n (%)
Patients with at least 1 AE	**164 (72.2)**	**284 (87.9)**	**61 (81.3)**	**215 (90.3)**
Dose reduced temporarily	2 (0.9)	11 (3.4)	1 (1.3)	10 (4.2)
Dose reduced	2 (0.9)	20 (6.2)	2 (2.7)	18 (7.6)
Dose interrupted	1 (0.4)	2 (0.6)	1 (1.3)	1 (0.4)
Diarrhea	**20 (8.8)**	**54 (16.7)**	**7 (9.3)**	**47 (19.7)**
Dose reduced temporarily	0	1 (0.3)	0	1 (0.4)
Dose reduced	0	3 (0.9)	0	3 (1.3)
Dose interrupted	0	0	0	0
Vomiting	**26 (11.5)**	**35 (10.8)**	**5 (6.7)**	**29 (12.2)**
Dose reduced temporarily	0	2 (0.6)	0	2 (0.8)
Dose reduced	0	1 (0.3)	0	1 (0.4)
Dose interrupted	0	0	0	0
Pyrexia	**24 (10.6)**	**42 (13.0)**	**9 (12.0)**	**30 (12.6)**
Dose reduced temporarily	0	1 (0.3)	0	1 (0.4)
Dose reduced	0	0	0	0
Dose interrupted	0	1 (0.3)	0	1 (0.4)
Fatigue	**8 (3.5)**	**31 (9.6)**	**5 (6.7)**	**26 (10.9)**
Dose reduced temporarily	0	4 (1.2)	1 (1.3)	3 (1.3)
Dose reduced	0	3 (0.9)	0	3 (1.3)
Dose interrupted	0	0	0	0
Upper respiratory tract infection	**22 (9.7)**	**32 (9.9)**	**11 (14.7)**	**20 (8.4)**
Dose reduced temporarily	0	0	0	0
Dose reduced	0	0	0	0
Dose interrupted	0	0	0	0
Decreased appetite	**11 (4.8)**	**65 (20.1)**	**12 (16.0)**	**55 (22.3)**
Dose reduced temporarily	0	2 (0.6)	0	2 (0.8)
Dose reduced	0	4 (1.2)	0	4 (1.7)
Dose interrupted	0	0	0	0
Somnolence[a]	**19 (8.4)**	**79 (24.5)**	**17 (22.7)**	**60 (25.2)**
Dose reduced temporarily	0	3 (0.9)	0	3 (1.3)
Dose reduced	1 (0.4)	8 (2.5)	2 (2.7)	6 (2.5)
Dose interrupted	0	1 (0.3)	0	1 (0.4)

[a] Somnolence does not include sedation
Note: Common AEs that reached an incidence of ≥ 10% (after rounding up) in the All CBD-OS group were based on the overall incidence.
Note: For patients who have multiple AEs in the same SOC or PT category, the worst action taken was counted. Events with missing action taken were excluded.
Note: Safety analysis set.

7.2.4. ADVERSE EVENTS LEADING TO DISCONTINUATION

AEs leading to withdrawal from studies are shown in Table 27. Increased ALT, increased AST, and somnolence were the most common reasons for withdrawal. AEs that led to withdrawal from the study were more common in patients taking CBD-OS than in the placebo group. There also appears to be a relationship between dose and withdrawal due to an AE; when comparing results between CBD-OS dose groups, nearly all of the AEs leading to discontinuation were reported in

the CBD-OS 20 mg/kg/day group (28/30 [93.3%]) compared with the 10 mg/kg/day group (2/30 [6.7%]).

Table 27: AEs Leading to Discontinuation Reported in > 1 Patient in the All CBD-OS Group in Controlled LGS and DS Studies (Pool LGS/DS)

SOC PT	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)	CBD-OS 10 mg/kg/day (N=75) n (%)	CBD-OS 20 mg/kg/day (N=238) n (%)
Patients with at least 1 AE leading to discontinuation	**3 (1.3)**	**30 (9.3)**	**2 (2.7)**	**28 (11.8)**
General disorders and administration site conditions	**0**	**5 (1.5)**	**1 (1.3)**	**4 (1.7)**
Fatigue	0	2 (0.6)	0	2 (0.8)
Pyrexia	0	2 (0.6)	1 (1.3)	1 (0.4)
Investigations	**1 (0.4)**	**15 (4.6)**	**1 (1.3)**	**14 (5.9)**
AST increased	0	8 (2.5)	1 (1.3)	7 (2.9)
ALT increased	0	7 (2.2)	1 (1.3)	6 (2.5)
GGT increased	0	4 (1.2)	0	4 (1.7)
Transaminases increased	0	3 (0.9)	0	3 (1.3)
Liver function test abnormal	1 (0.4)	2 (0.6)	0	2 (0.8)
Metabolism and nutrition disorders	**0**	**5 (1.5)**	**0**	**5 (2.1)**
Decreased appetite	0	4 (1.2)	0	4 (1.7)
Nervous system disorders	**2 (0.9)**	**9 (2.8)**	**0**	**9 (3.8)**
Somnolence	0	5 (1.5)	0	5 (2.1)
Convulsion	1 (0.4)	4 (1.2)	0	4 (1.7)
Hypotonia	0	2 (0.6)	0	2 (0.8)
Lethargy	0	2 (0.6)	0	2 (0.8)
Psychiatric disorders	**1 (0.4)**	**3 (0.9)**	**0**	**3 (1.3)**
Aggression	0	2 (0.6)	0	2 (0.8)

Note: Safety analysis set.

7.2.5. SERIOUS ADVERSE EVENTS

In the pooled patient population from the randomized controlled studies, 60 (18.6%) patients had at least 1 event that was considered serious compared with 16 (7.0%) of those on placebo. Of the 60 CBD-OS patients who experienced an SAE, the majority had an SAE that resulted in hospitalization (57%). Table 28 shows the SAEs that occurred in at least 2 patients in the pooled population. The most commonly reported AEs which met serious AE criteria were SE, elevations of liver-related enzymes (ALT increased, AST increased, gamma glutamyltransferase (GGT) increased, liver function test abnormal), pneumonia, convulsion, and somnolence.

When comparing the incidence of events reported by more than 1 patient in the All CBD-OS group by CBD-OS dose, pyrexia, transaminases increased, pneumonia, and SE were all lower in the 20 mg/kg/day group compared with the 10 mg/kg/day group. In contrast, elevations of liver-related tests (AST increased, ALT increased, GGT increased, liver function test abnormal), convulsion, acute respiratory failure, viral infection, constipation, lethargy, and somnolence were all higher in the 20 mg/kg/day group compared with the 10 mg/kg/day group.

Table 28: Serious AEs Reported in ≥1 Patient in the All CBD-OS Group in Controlled DS and LGS Studies (Pool LGS/DS)

SOC PT	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)	CBD-OS 10 mg/kg/day (N=75) n (%)	CBD-OS 20 mg/kg/day (N=238) n (%)
Patients with at least 1 serious AE	**16 (7.0)**	**60 (18.6)**	**15 (20.0)**	**44 (18.5)**
Gastrointestinal disorders	**1 (0.4)**	**7 (2.2)**	**1 (1.3)**	**6 (2.5)**
Constipation	0	2 (0.6)	0	2 (0.8)
General disorders and administration site conditions	**1 (0.4)**	**6 (1.9)**	**2 (2.7)**	**4 (1.7)**
Pyrexia	1 (0.4)	3 (0.9)	2 (2.7)	1 (0.4)
Infections and infestations	**4 (1.8)**	**20 (6.2)**	**4 (5.3)**	**16 (6.7)**
Pneumonia	0	9 (2.8)	3 (4.0)	6 (2.5)
Viral infection	1 (0.4)	2 (0.6)	0	2 (0.8)
Investigations	**2 (0.9)**	**13 (4.0)**	**2 (2.7)**	**11 (4.6)**
AST increased	0	7 (2.2)	1 (1.3)	6 (2.5)
ALT increased	0	5 (1.5)	0	5 (2.1)
GGT increased	0	4 (1.2)	0	4 (1.7)
Liver function tests abnormal	0	2 (0.6)	0	2 (0.8)
Transaminases increased	0	2 (0.6)	1 (1.3)	1 (0.4)
Nervous system disorders	**10 (4.4)**	**28 (8.7)**	**8 (10.7)**	**19 (8.0)**
Status epilepticus	7 (3.1)	16 (5.0)	7 (9.3)	8 (3.4)
Convulsion	2 (0.9)	7 (2.2)	1 (1.3)	6 (2.5)
Somnolence	0	5 (1.5)	0	5 (2.1)
Lethargy	0	3 (0.9)	0	3 (1.3)
Respiratory, thoracic and mediastinal disorders	**3 (1.3)**	**9 (2.8)**	**1 (1.3)**	**8 (3.4)**
Acute respiratory failure	0	3 (0.9)	0	3 (1.3)
Hypoxia	1 (0.4)	3 (0.9)	1 (1.3)	2 (0.8)
Sleep apnea syndrome	0	2 (0.6)	1 (1.3)	1 (0.4)

Note: Safety analysis set.

7.2.6. DEATHS

Across all LGS and DS controlled studies (N=323), 1 patient with LGS experienced a fatal AE. The death was considered by the Investigator to be due to acute respiratory distress syndrome and was not considered treatment-related. The patient experienced convulsive SE, acute respiratory distress syndrome, aspiration pneumonia, acute respiratory failure with hypoxia and hypercapnia, left renal calculus, deep vein thrombosis, and pneumothorax (left and right) and subsequently died. The patient was receiving concomitant LEV, lacosamide, zonisamide, and clobazam and had several ongoing medical conditions at screening.

In the ongoing long-term safety studies, a total of 7 patients had fatal AEs in the OLE study (as of 01 May 2017 data cutoff) and 12 patients had fatal AEs in the EAP (as of 08 December 2016 data cutoff). These deaths are described in more detail in Appendix 10.4. None of the deaths were considered by the Investigator to be related to CBD-OS.

Both LGS and DS are associated with high epilepsy-related mortality. Considering the controlled studies and OLE studies together, where there was approximately 700 patient-years of exposure in patients with DS or LGS, approximately 7 deaths would be expected from SUDEP, and more than 7 from other causes (Berg, Nickels et al. 2013, Donner 2014, Cooper, McIntosh et al. 2016). In the controlled studies and OLE, there were 2 deaths due SUDEP and 6 from other causes, which is consistent with the high mortality rate seen in this patient population.

Additional details for all deaths across the CBD-OS studies can be found in Appendix 10.4.

7.3. ADVERSE EVENTS OF SPECIAL INTEREST

7.3.1. TRANSAMINASE ELEVATIONS

The monitoring of liver tests in the clinical studies was sufficiently frequent and thorough to characterize the CBD-OS risk for producing drug-induced liver injury (DILI). In the LGS and DS placebo-controlled studies there was a systematic acquisition of liver test data at baseline and beginning at the time of steady-state for the assigned CBD-OS dose (2 weeks), then after 4 weeks, 8 weeks, and 14 weeks of treatment. In the OLE, liver test monitoring was conducted at 2 weeks following initiation of dosing, then at 4 weeks and 12 weeks, and subsequently at 12-week intervals.

The pivotal study results showed that CBD-OS was associated with dose-related ALT/AST elevations in a subset of patients (Table 29). Evaluation of the liver test results and AE reports from the 540 unique patients who were administered chronic CBD-OS in the controlled studies and the OLE did not identify any patient as meeting published consensus criteria for severe DILI. None of these patients were identified as meeting the DILI laboratory criteria for Hy's Law (ALT >3×ULN and bilirubin >2×ULN) (Figure 33). Additionally, there have been no Hy's law cases reported in the EAP.

Among the 540 CBD-OS patients from the controlled studies and the OLE, 61 (11.3%) had ALT >3 and <5×ULN, and 38 (7.0 %) met the clinical chemistry criteria for potential DILI of ALT ≥5×ULN. These ALT elevations were generally accompanied by normal alkaline phosphatase (ALP) and bilirubin values. For the 38 patients with ALT ≥5×ULN, the CBD-OS doses at the time of peak ALT elevation were: 5 (n=1); 10 (n=2); 18 (n=1); 20 (n=30); 23 (n=1); and 25 (n=3) mg/kg/day.

A total of 32 of the 38 (84.2%) CBD-OS patients with ALT ≥5×ULN were taking concomitant VPA. Eighteen of the patients with ALT ≥5×ULN were discontinued from treatment, including 16 who had ALT >8×ULN, one of the prospective withdrawal criteria included in each study protocol. Despite the withdrawal criteria present, 18 of the 38 patients (47.4%) with ALT ≥5×ULN recovered without stopping CBD-OS. Of these 18 patients:

- 13 patients recovered without any dose reduction of CBD-OS.
- 5 patients recovered after dose reduction or during taper of CBD-OS.

- VPA was the most common concomitant medication where dose reduction occurred after observation of ALT ≥5×ULN. A total of 6/18 patients had their VPA dose reduced or stopped after such an ALT elevation.

Typically the transaminase elevations were transient and reversed with discontinuation or dose adjustment of CBD-OS or concomitant VPA, or both, and often with continued treatment with these drugs. Individual patient estimated recovery times to ALT ≤3×ULN were typically within 2 weeks.

Among the 540 exposures, there were 9 CBD-OS patients who met consensus DILI criteria (ALP ≥2×ULN). However, the frequency of ALP ≥2×ULN was similar in the CBD-OS and placebo groups, and no patient was discontinued because of this finding.

A total of 37 of the 38 patients with ALT ≥5×ULN had an R value (ratio of ALT×ULN to ALP×ULN) of ≥5, indicating a hepatocellular pattern of DILI. One patient had an R value of 2, indicating a cholestatic pattern of DILI. A hepatology expert conducted an unblinded review of individual narratives describing the clinical and laboratory data for these patients and assessed that CBD-OS probably caused or contributed to the ALT elevations in 36 of the 38 cases (94.7%), and that this was possible for the remaining 2 cases (5.3%).

In the absence of valproate, the risk window was generally confined to the first 30 days of treatment. In the CBD-OS 20 mg/kg/day group, TE elevations in all 3 patients with ALT >5×ULN (3/3, 100%), and in 5 of the 6 patients (83.3%) with ALT >3×ULN, were observed within the first 30 days of treatment.

The risk window was wider for patients taking concomitant valproate. After 30 and 60 days of treatment with CBD-OS, 8 of 14 (57.1%) and 12 of 14 (85.7%) elevations of ALT >5×ULN had been observed, respectively. At the same respective times, 21 of 31 (67.7%) and 27 of 31 (87.1%) elevations of ALT >3×ULN had been observed, respectively.

The single observations of ALT elevation to >3 and >5×ULN in the CBD-OS 10 mg/kg/day group and placebo group occurred during the first 30 days of treatment. Both patients were taking concomitant VPA.

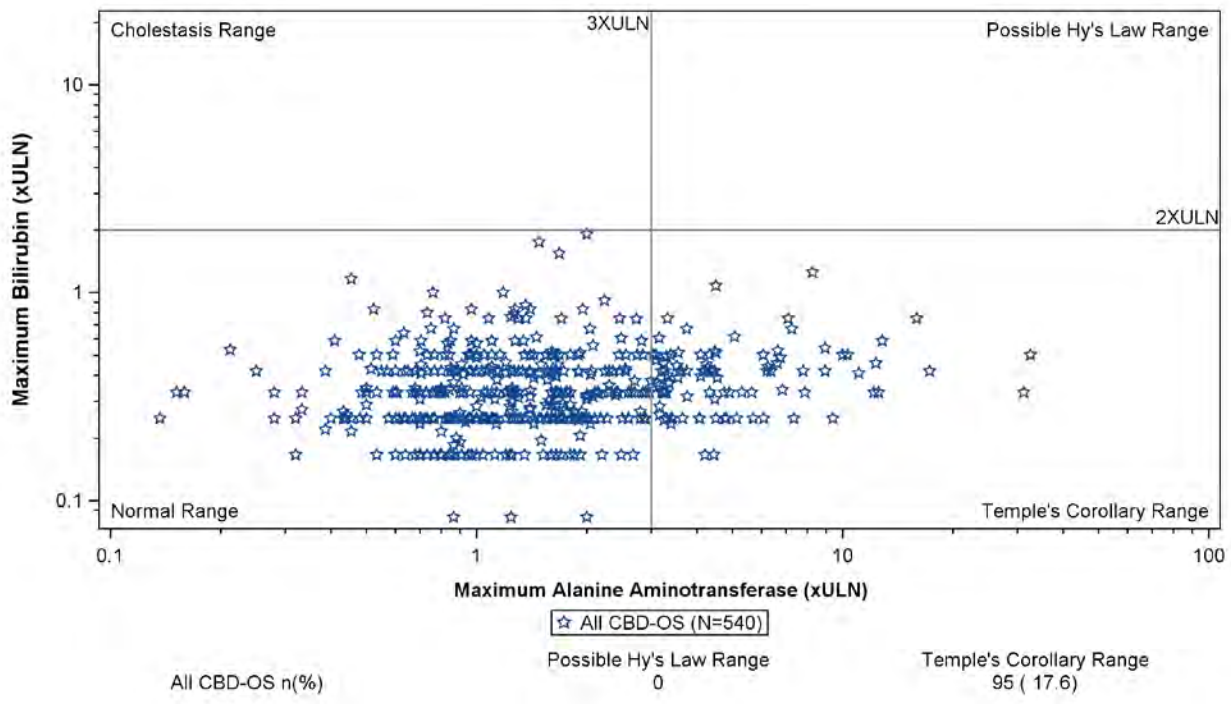
Table 29: Frequency of Liver Test Elevations in Pivotal Studies

Liver Test	Multiple of ULN	Placebo (N=220) *n / N* (%)	CBD-OS 10 mg/kg/day (N=67) *n / N* (%)	CBD-OS 20 mg/kg/day (N=229) *n / N* (%)
ALT	> ULN	32 / 175 (18.3)	19 / 56 (33.9)	84 / 177 (47.5)
	> 2 ×	8 / 214 (3.7)	4 / 67 (6.0)	53 / 224 (23.7)
	> 3 ×	2 / 219 (0.9)	1 / 67 (1.5)	37 / 227 (16.3)
	> 5 ×	2 / 220 (0.9)	1 / 67 (1.5)	17 / 229 (7.4)
	> 8 ×	1 / 220 (0.5)	1 / 67 (1.5)	6 / 229 (2.6)
	> 10 ×	1 / 220 (0.5)	0 / 67	3 / 229 (1.3)
	> 20 ×	1 / 220 (0.5)	0 / 67	1 / 229 (0.4)
AST	> ULN	20 / 206 (9.7)	15 / 62 (24.2)	70 / 202 (34.7)
	> 2 ×	5 / 220 (2.3)	4 / 67 (6.0)	35 / 227 (15.4)
	> 3 ×	1 / 220 (0.5)	2 / 67 (3.0)	18 / 228 (7.9)
	> 5 ×	1 / 220 (0.5)	1 / 67 (1.5)	5 / 229 (2.2)
	> 8 ×	1 / 220 (0.5)	0 / 67	3 / 229 (1.3)
	> 10 ×	1 / 220 (0.5)	0 / 67	1 / 229 (0.4)
	> 20 ×	0 / 220	0 / 67	0 / 229
ALT or AST	> ULN	35 / 170 (20.6)	24 / 54 (44.4)	82 / 167 (49.1)
	> 2 ×	9 / 214 (4.2)	5 / 67 (7.5)	61 / 224 (27.2)
	> 3 ×	2 / 219 (0.9)	2 / 67 (3.0)	41 / 226 (18.1)
	> 5 ×	2 / 220 (0.9)	1 / 67 (1.5)	19 / 229 (8.3)
	> 8 ×	1 / 220 (0.5)	1 / 67 (1.5)	8 / 229 (3.5)
	> 10 ×	1 / 220 (0.5)	0 / 67	3 / 229 (1.3)
	> 20 ×	1 / 220 (0.5)	0 / 67	1 / 229 (0.4)

Note: Due to its short duration, the 3-week pilot placebo-controlled study in DS (Study 1332 Part A) was not included in this analysis.

Note: N corresponds to the total number of patients in the treatment group. *n / N* : *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at baseline.

Figure 33: eDISH Plot of Maximum ALT and Bilirubin Values for Individual Patients During Treatment in Controlled Studies and OLE



Increasing exposure to CBD and its 7-OH-CBD metabolite (as measured by AUC) was significantly correlated with an increased frequency of ALT elevations >2×ULN.

Separate factor analyses showed that elevated baseline ALT value, and particularly concomitant VPA, increased the risk for elevations of ALT including elevation to ≥5×ULN.

Pooled data from the pivotal 14-week controlled studies clearly showed the importance of concomitant VPA as a risk factor for potential DILI (Table 30).

- Patients who were not taking concomitant VPA exhibited ALT ≥5×ULN frequencies of 0/44 (0%) in the CBD-OS 10 mg/kg/day group, 3/123 (2.4%) in the CBD-OS 20 mg/kg/day group, and 1/123 (0.8%) in the placebo group. Only patients taking concomitant VPA exhibited ALT >8×ULN.
- Patients taking concomitant VPA exhibited frequencies of ALT ≥5×ULN of 1/23 (4.3%) in the CBD-OS 10 mg/kg/day group, 14/106 (13.2%) in the CBD-OS 20 mg/kg/day group, and 1/97 (1.0%) in the placebo group. In contrast to the groups of patients not taking concomitant VPA, ALT >8×ULN was observed in 4.3%, 5.7%, and 1.0% of patients taking CBD-OS 10 mg/kg/day or 20 mg/kg/day, or placebo, respectively.

Table 30: Frequency of ALT Elevations for Patients Taking or Not Taking Concomitant VPA in Pivotal Studies

Multiple of ULN for ALT	Concomitant VPA	Placebo (N=220) n / N (%)	CBD-OS 10 mg/kg/day (N=67) n / N (%)	CBD-OS 20 mg/kg/day (N=229) n / N (%)
>ULN	Yes	13/82 (15.9)	12/20 (60.0)	62/87 (71.3)
	No	19/93 (20.4)	7/36 (19.4)	22/90 (24.4)
>2×	Yes	4/95 (4.2)	2/23 (8.7)	44/104 (42.3)
	No	4/119 (3.4)	2/44 (4.5)	9/120 (7.5)
>3×	Yes	1/97 (1.0)	1/23 (4.3)	31/106 (29.2)
	No	1/122 (0.8)	0/44	6/121 (5.0)
>5×	Yes	1/97 (1.0)	1/23 (4.3)	14/106 (13.2)
	No	1/123 (0.8)	0/44	3/123 (2.4)
>8×	Yes	1/97 (1.0)	1/23 (4.3)	6/106 (5.7)
	No	0/123	0/44	0/123
>10×	Yes	1/97 (1.0)	0/23	3/106 (2.8)
	No	0/123	0/44	0/123
>20×	Yes	1/97 (1.0)	0/23	1/106 (0.9)
	No	0/123	0/44	0/123

Note: Due to its short duration, the 3-week pilot placebo-controlled study in DS (Study 1332 Part A) was not included in this analysis.
Note: N corresponds to the total number of patients in the treatment group. *n / N* : *n* = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. *N* = number of patients who did not have an elevation above the criterion at baseline.

The mechanisms underlying the liver effects of CBD-OS are currently being investigated, including through in-silico modelling (DILIsym). The clear dose and exposure correlation with incidence of serum ALT elevations support a direct effect on the liver. Given the titration schedule and the long half life of CBD-OS and its metabolites, the characteristic onset within the first 30 days is consistent with achievement of steady-state liver exposure. The rapid reversal of the ALT elevations with or without continued treatment with CBD-OS, together with the general absence of clinical hypersensitivity signs, make involvement of an innate or adaptive immune response unlikely.

7.3.2. SOMNOLENCE/SEDATION

Somnolence and sedation are common occurrences with many AEDs and other drugs and were frequently observed as an AE with CBD-OS. Somnolence was the single most common AE PT across all groups in the controlled studies and was consistently more frequent in patients treated with CBD-OS. The incidence of somnolence or sedation was 29.4% in the All CBD-OS group vs. 9.3% in the placebo group, and the majority were first reported during the first 2 weeks of treatment (Table 31).

In the controlled studies, somnolence was the third most common AE leading to discontinuation of CBD-OS; however, of the 79 patients in the All CBD-OS group with somnolence, 5 (6.3%) had serious events, and 5 (6.3%) had events that led to discontinuation. The majority of these AESIs were first reported most frequently during the first 2 weeks of treatment, and most cases of somnolence/sedation were of mild to moderate intensity.

Table 31: Incidence of AESI Somnolence and Sedation in Controlled Studies

SOC PT	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)
Patients with at least 1 AESI somnolence sedation	**21 (9.3)**	**95 (29.4)**
Nervous system disorders	**21 (9.3)**	**95 (29.4)**
Somnolence	19 (8.4)	79 (24.5)
Sedation	2 (0.9)	18 (5.6)

Note: Safety analysis set.
[a]Two patients in the 20 mg/kg/day CBD-OS group had AEs of both somnolence and sedation and were therefore counted only once towards the total.

7.3.3. ADVERSE EVENT REPORTS OF WORSENING SEIZURES

The incidence of AEs meeting the search criteria for AESI worsening seizures or change in the pattern or severity of seizures was 14.2% in the All CBD-OS group (N=323) compared with 12.3% in the placebo group (N=227) (Table 32). Given the severity of the epilepsy in these patient populations, fluctuations in seizure frequency were expected. For All CBD-OS patients, the incidence was similar in the 20 mg/kg/day and 10 mg/kg/day dose groups (14.3% and 14.7%, respectively). SAEs and AEs leading to discontinuation occurred less frequently but were both higher in the All CBD-OS group compared with the placebo group. Overall, based on analysis of the safety data, the frequency of AE reports of worsening seizures was not increased with use of CBD-OS.

Table 32: Overall Worsening Seizures in All CBD-OS vs. Placebo

Worsening Seizures	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)
Any AE	28 (12.3)	46 (14.2)
AEs leading to discontinuation	1 (0.4)	5 (1.5)
SAEs	10 (4.4)	23 (7.1)

7.3.4. STATUS EPILEPTICUS

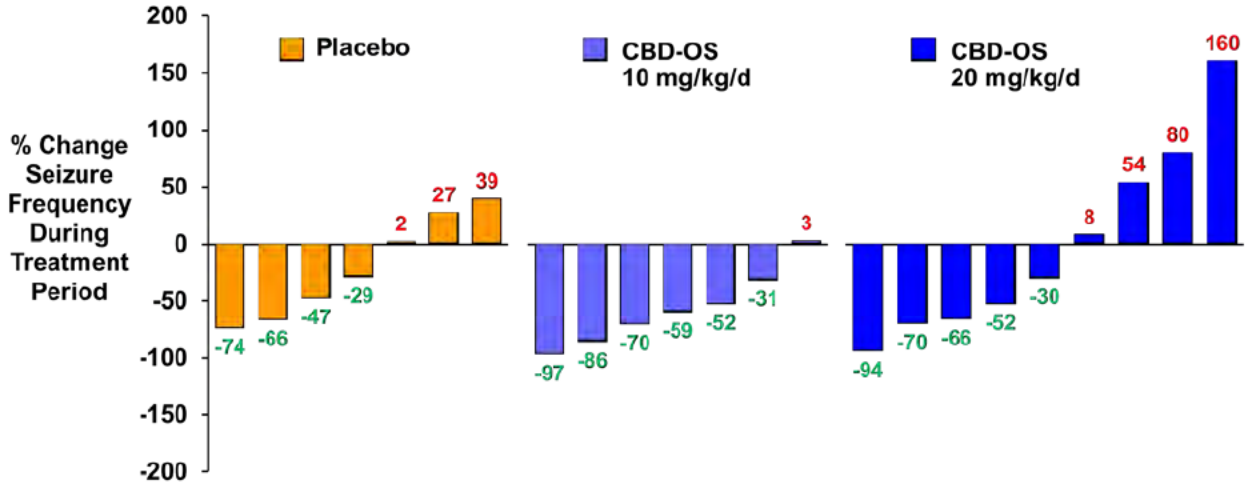
In the controlled studies, the incidence of AESI SE was 5.3% in the All CBD-OS group vs. 3.1% in the placebo group. The similar incidence of SE AEs between the groups suggests that these events are most likely spontaneous fluctuations in disease severity rather than a response to CBD-OS treatment. Further support is provided by the fact that AESIs of SE were more common in the 10 mg/kg/day dose group compared with the 20 mg/kg/day dose group (Table 33), suggesting that SE is related to the underlying epilepsy in the LGS and DS patient populations.

Table 33: Incidence of AESI Status Epilepticus in Controlled Studies

	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)	CBD-OS		
			5 mg/kg/day (N=10) n (%)	10 mg/kg/day (N=75) n (%)	20 mg/kg/day (N=238) n (%)
Patients with any AESI status epilepticus	**7 (3.1)**	**17 (5.3)**	**1 (10.0)**	**7 (9.3)**	**9 (3.8)**
Mild	4 (1.8)	5 (1.5)	0	1 (1.3)	4 (1.7)
Moderate	1 (0.4)	8 (2.5)	0	4 (5.3)	4 (1.7)
Severe	2 (0.9)	4 (1.2)	1 (10.0)	2 (2.7)	1 (0.4)
Serious	7 (3.1)	16 (5.0)	1 (10.0)	7 (9.3)	8 (3.4)
Led to dose reduction	0	0	0	0	0
Led to discontinuation	0	1 (0.3)	0	0	1 (0.4)

Importantly, most patients that experienced a SE event reported a clinically meaningful decrease in seizure frequency (e.g., 6 of 7 patients receiving 10 mg/kg/day) (Figure 34).

Figure 34: Change in Total Seizure Frequency During the Treatment Period in Controlled Studies



With the exception of 1 event in the All CBD-OS group, all events of SE in both the All CBD-OS group and placebo group were serious. However, only 1 of the 17 patients in the All CBD-OS group with at least 1 event of SE had an event that led to discontinuation.

While SE is a concern with abrupt AED withdrawal, this was not observed with CBD-OS. This is likely due to the very long half-life, which essentially tapers the drug over days and avoids an abrupt reduction in blood levels. However, as with all AEDs, abrupt discontinuation should be avoided when possible; when discontinuing CBD-OS, the dose should be decreased gradually.

Patient vignettes for SE events are provided in Appendix 10.3.

7.3.5. RASH

Within the controlled studies, there was a higher incidence of AESI rash in CBD-OS patients than in placebo patients (9.0% vs. 3.1%; Table 34). Most events occurred during the first

6 weeks on treatment, were self-limiting, and did not show a clear relation to dose. Most of the patients in the All CBD-OS and placebo groups with this AESI had events that were not considered treatment-related, and nearly all events were of mild to moderate intensity (only 1 was considered serious); only 2 led to discontinuation. All but 1 event resolved on treatment with CBD-OS. None of the events showed systemic involvement or involvement of mucous membranes. The etiology of the rashes in patients with epilepsy was confounded by the association with concomitant AEDs, which have known incidences of rash (Blaszczyk, Lason et al. 2015).

Table 34: Incidence of AESI Rash, Generalized Maculopapular Rash in Controlled Studies

SOC PT	Placebo (N=227) n (%)	All CBD-OS (N=323) n (%)
Patients with at least 1 AESI rash, generalized maculopapular rash	**7 (3.1)**	**29 (9.0)**
General disorders and administration site conditions	**2 (0.9)**	**0**
Injection site rash	1 (0.4)	0
Venipuncture site rash	1 (0.4)	0
Infections and infestations	**0**	**3 (0.9)**
Viral rash	0	3 (0.9)
Skin and subcutaneous tissue disorders	**5 (2.2)**	**26 (8.0)**
Rash	3 (1.3)	14 (4.3)
Rash maculo-papular	0	5 (1.5)
Rash erythematous	0	3 (0.9)
Rash generalized	1 (0.4)	2 (0.6)
Rash macular	0	2 (0.6)
Rash papular	1 (0.4)	1 (0.3)

7.3.6. PNEUMONIA

Pneumonia is a relatively common SAE in childhood epilepsy and is one of the more common causes of death (Berg, Nickels et al. 2013). In some cases, pneumonia is likely due to aspiration, and may be more common in LGS, where nasogastric feeding is also more common. In other cases, it may follow on from an upper respiratory infection and develop into pneumonia because of the general debility of the child with drug-resistant epilepsy.

Compared to placebo, patients on CBD-OS in the controlled studies experienced a greater frequency of pneumonia. Overall, there were 18 pneumonia cases (PTs: pneumonia, pneumonia aspiration, pneumonia adenoviral, pneumonia mycoplasma, and pneumonia respiratory syncytial virus) on CBD-OS (5.6%) compared with 2 on placebo (0.9%). Pneumonia was the second most common AE across the controlled studies. Of the 18 pneumonia cases in the All CBD-OS group, 13 were considered serious, but only 1 led to discontinuation. Excluding the 1 patient that discontinued due to an AE of aspiration pneumonia, all other cases resolved; 2 of these patients had events that resolved following temporary reduction of CBD-OS, the remaining patients all resolved with no action taken regarding CBD-OS. The only fatality in the controlled studies was attributed to pneumonia, in a patient with a complicated history, including previous episodes of pneumonia.

The causal association between CBD-OS and the occurrence of pneumonia remains uncertain; however, pneumonia was observed at all doses. Possible risk factors include concomitant use of gastronomy tubes (G-tubes) (7/18 All CBD-OS cases) and the presence of a past history of aspiration (7/18 All CBD-OS cases). In particular, pneumonia did not demonstrate an association with somnolence and sedation, which occurred in 5 of the 18 cases in the controlled studies, and which is similar to the rate of somnolence and sedation seen in the overall study population.

7.3.7. DIARRHEA

The incidence of AESI diarrhea in All CBD-OS population (N=323) was 16.7% compared with 8.8% in the placebo group (N=227). This common dose-related event was generally first reported during the initial 6 weeks of therapy but seems to be well tolerated based on the low number of events leading to discontinuation.

7.3.8. FALLS AND INJURIES

The incidence of AESI falls and injuries in the controlled studies was similar for patients in the All CBD-OS and placebo groups (8.4% vs. 9.7%). For CBD-OS patients, the events did not show a clear relation to dose; the incidence of falls and injuries was similar in the CBD-OS 20 mg/kg/day (8.0%; N=238) and 10 mg/kg/day (9.3%; N=75) dose groups. The 3 most common AESI PTs were fall (2.8% in the All CBD-OS group vs. 3.5% in the placebo group),contusion (1.9% vs. 1.3%), and laceration (1.5% vs. 1.8%).

Only 1 patient in the All CBD-OS group had an SAE that met the criteria for AESI falls and injuries, and no events led to discontinuation for patients in either the All CBD-OS group or the placebo group. Overall for both the All CBD-OS and placebo groups, there was no clear trend for the first onset of AESI falls and injuries. Given these results, the potential for falls and injuries is not considered to be increased with use of CBD-OS.

7.4. ADVERSE EVENTS BY DOSE

Table 35 summarizes AEs reported in the Phase 3 pivotal studies according to CBD-OS dose. When comparing by dose group, the overall incidence of AEs was higher in the 20 mg/kg/day group (90.3%) than in the 10 mg/kg/day group (81.3%). The following common PTs that reached an incidence of ≥ 10% in the All CBD-OS group were higher in the 20 mg/kg/day dose group compared with the 10 mg/kg/day dose group: decreased appetite, diarrhea, vomiting, and fatigue.

The incidences of dose reductions and temporary dose reductions were higher in the 20 mg/kg/day group than in the 10 mg/kg/day group (dose reduction: 7.6% vs. 2.7%; temporary dose reduction: 4.2% vs. 1.3%).

Incidences of AEs leading to discontinuation also appear to be dose-dependent and were higher in the 20 mg/kg/day group than in the 10 mg/kg/day group (11.8% vs. 2.7%). This imbalance appears to be due to liver function test abnormalities, described in Section 7.3.1.

The incidence of severe AEs was higher in the 20 mg/kg/day group (14.3%; N=238) compared with the 10 mg/kg/day group (9.3%; N=75). However, the incidence of SAEs was not dose-dependent and was similar between the 2 dose groups.

Table 35: Overall Summary of AEs in the Controlled Studies by Dose

Patients Reporting Any:	Placebo (N=227) n %	All CBD-OS (N=323) n (%)	
		10 mg/kg/day (N=75) n (%)	20 mg/kg/day (N=238) n (%)
AE	164 (72.2)	61 (81.3)	215 (90.3)
Severe AE	11 (4.8)	7 (9.3)	34 (14.3)
AEs Leading to Discontinuation	3 (1.3)	2 (2.7)	28 (11.8)
SAE	16 (7.0)	15 (20.0)	44 (18.5)
Deaths	0	0	1 (0.4)

7.5. CLINICAL LABORATORY EVALUATIONS

Except for transaminase elevations, mean changes in hematology and clinical chemistry laboratory values over time and potentially clinically significant laboratory abnormalities over time were similar for all treatment groups in the controlled studies. There was a small but persistent decrease in hemoglobin levels over time in patients on CBD-OS; however, there was no corresponding decrease in hematocrit, mean corpuscular hemoglobin or volume, and no difference from placebo in the incidence of anemia AEs.

7.5.1. CREATININE CLEARANCE

A decrease of 12.2 percentage points in mean percentage change from baseline to end of treatment in creatinine clearance in the CBD-OS groups compared with placebo was seen in Study 1332B but not in Studies 1414 or 1423. This decrease in creatinine clearance in Study 1332B was due to a corresponding increase in creatinine (Jaffe; 13.8%) without a corresponding increase in BUN levels. No changes in creatinine or BUN were noted in the active arms of the LGS studies 1414 and 1423 vs. placebo.

7.6. OPEN LABEL EXTENSION STUDY

The overall incidence of AEs in CBD-OS-treated patients was similar in the controlled studies and the OLE (87.9% vs. 95.0%, respectively). Differences in the incidence of AEs between these studies would be expected, as the overall exposure to CBD-OS in the OLE was higher than in the controlled studies. Table 36 provides an overview of AEs reported in the OLE study.

The overall incidence of SAEs was higher in the OLE study than in the controlled studies (32.6% vs. 18.6%, respectively). The most common SAEs in CBD-OS patients in the OLE were SE, convulsion, and pneumonia. These were also common SAEs in the All CBD-OS group of the controlled studies.

The overall incidence of AEs leading to discontinuation of CBD-OS was similar in the controlled studies and in the OLE (9.3% vs. 9.2%, respectively). The most common AE leading to discontinuation in the OLE was ALT increased (1.9%).

In the OLE study, 7 patients had fatal AEs. Five deaths occurred in the LGS cohort and 2 in the DS cohort. The 5 LGS deaths were due to: intestinal obstruction, gastrointestinal necrosis, peritonitis and septic shock; pneumonia aspiration and respiratory failure; convulsion; Rett's

disorder, respiratory failure, and cardiac arrest; and hypoxic-ischemic encephalopathy. The 2 DS deaths were due to SUDEP. None of the deaths were considered by the Investigators to be related to CBD-OS.

Table 36: Summary of AEs in the Open Label Extension Study vs. Controlled Studies

Patients with any	OLE: All CBD-OS (N=644) n (%)	Controlled Studies: All CBD-OS (N=323) n (%)
AEs	612 (95.0)	284 (87.9)
Severe AEs	126 (19.6)	43 (13.3)
AEs leading to discontinuation	59 (9.2)	30 (9.3)
SAEs	210 (32.6)	60 (18.6)
Deaths	7 (1.1)	1 (0.3)

7.6.1. COMMON ADVERSE EVENTS IN THE OPEN LABEL EXTENSION

Common AEs that reached an incidence of ≥10% in the All CBD-OS group were generally similar to the controlled studies. These AEs included diarrhea, somnolence, pyrexia, decreased appetite, convulsion, vomiting, upper respiratory tract infection, and nasopharyngitis (Table 37).

Table 37: Incidence of Common AEs (≥10% of Patients in the All CBD-OS Group) in the Open-label Extension Study

SOC PT	All CBD-OS (N=644) n (%)
Patients with at least 1 AE	**612 (95.0)**
Gastrointestinal disorders	**352 (54.7)**
Diarrhoea	220 (34.2)
Vomiting	128 (19.9)
General disorders and administration site conditions	**261 (40.5)**
Pyrexia	183 (28.4)
Infections and infestations	**403 (62.6)**
Upper respiratory tract infection	117 (18.2)
Nasopharyngitis	103 (16.0)
Metabolism and nutrition disorders	**208 (32.3)**
Decreased appetite	152 (23.6)
Nervous system disorders	**400 (62.1)**
Somnolence	167 (25.9)
Convulsion	148 (23.0)
Status epilepticus	66 (10.2)
Respiratory, thoracic and mediastinal disorders	**182 (28.3)**
Cough	68 (10.6)

7.6.2. ADVERSE EVENTS OF SPECIAL INTEREST IN THE OLE

Transaminase Elevations

Transaminase elevations in the OLE are discussed in Section 7.3.1.

Somnolence/Sedation

The incidence of AESI somnolence/sedation in the OLE study (30.7%) was similar to that seen in the controlled studies (29.4%), with no evidence of new patterns of AEs.

Pneumonia

The incidence of pneumonia cases in the OLE was 10.1% and was similar to the incidence of pneumonia cases in the EAP (9.2%). By comparison, the incidence of pneumonia cases in the All CBD-OS group of the controlled studies was 5.6%.

Status Epilepticus

The incidence of SE was 10.2% in the OLE study, which was higher than that in the All CBD-OS group of from the controlled studies (5.3%).

7.7. EXPANDED ACCESS PROGRAM

GW did not monitor the EAP, and the AEs reported are based upon spontaneous safety reporting unless AE reports were solicited from physicians.

The incidence of AEs in the EAP is summarized in Table 38. The incidence of AEs leading to discontinuation in the All CBD-OS group (5.0%) was lower compared with the All CBD-OS group of the controlled studies (9.3%), and most of the AEs leading to discontinuation occurred in no more than 1 patient.

The overall incidence of SAEs (32.6%) was higher than that in the All CBD-OS group of the controlled studies (18.6%), but the most common SAEs were similar.

In the EAP, 12 patients (1.8%) had a fatal AE. The deaths were due to SE; SUDEP; hyponatremia and SUDEP; disease progression; asphyxia; seizure cluster, aspiration, and respiratory failure; hypoxia; septic shock and respiratory failure; respiratory arrest; early infantile epileptic encephalopathy; convulsion and pulmonary edema; and neuronal ceroid lipofuscinosis. Note that of the 12 patients with fatal AEs in the EAP, none were in Pool EAP-LGS (N=97; mean treatment duration 408.1 days) or Pool EAP-DS (N=64; mean treatment duration 528.0 days). None of the deaths were considered by the Investigators to be related to CBD-OS.

Table 38: Overall Summary of AEs in the EAP

Patients with any	**All CBD-OS (N=684) n (%)**
AEs	577 (84.4)
Severe AEs	182 (26.6)
AEs leading to discontinuation	34 (5.0)
SAEs	223 (32.6)
Deaths	12 (1.8)

7.7.1. COMMON ADVERSE EVENTS IN THE EXPANDED ACCESS PROGRAM

Overall, the most common AEs for patients in the EAP were generally consistent with those observed in the combined primary safety data from the controlled studies. The 3 most common AEs in the EAP All CBD-OS population were diarrhea (27.0%), somnolence (21.9%), and convulsion (15.9%), compared to somnolence (24.5%), decreased appetite (20.1%), and diarrhea (16.7%) in the controlled studies. A comparison of common AEs in the EAP by dose group showed that the overall incidence of AEs tended to increase with increasing dose. AEs of diarrhea, somnolence, convulsion, SE, and ataxia had the greatest difference in incidence between the >40 mg/kg/day dose group (N=75) and the >20 but ≤30 mg/kg/day dose group (N=379).

7.7.2. ADVERSE EVENTS OF SPECIAL INTEREST IN THE EXPANDED ACCESS PROGRAM

Transaminase Elevations

The frequency of reported ALT elevations was lower in the EAP than in the CBD-OS controlled studies; however, the effect of concomitant VPA on the frequency of ALT elevations was the same as observed in the CBD-OS controlled studies. DILI, as defined by ALT ≥5×ULN, was reported by individual Investigators for a total of 30 patients taking CBD-OS doses of: 6 (n=2), 10-15 (n=5), 20 (n=5), 23-26 (n=14), and 40-50 (n=4) mg/kg/day. Among these 30 patients, 22

(73.3%) were taking concomitant VPA and 29 (96.7%) continued CBD-OS treatment through the ALT elevation.

Of the 30 patients in Pool EAP who had ALT ≥5×ULN during treatment with CBD-OS, 24 patients (80%) recovered from this ALT elevation without, or prior to, stopping CBD-OS. Among these 24 patients mentioned above:

- 17 patients recovered without any dose reduction of CBD-OS.
- 7 patients recovered after dose reduction or during taper of CBD-OS.

No cases meeting Hy's law laboratory criteria have been observed.

Interpretation of the EAP results must be tempered by the uncontrolled design of the program and the variability among Investigators with respect to the acquisition and reporting of liver test safety data.

Status Epilepticus

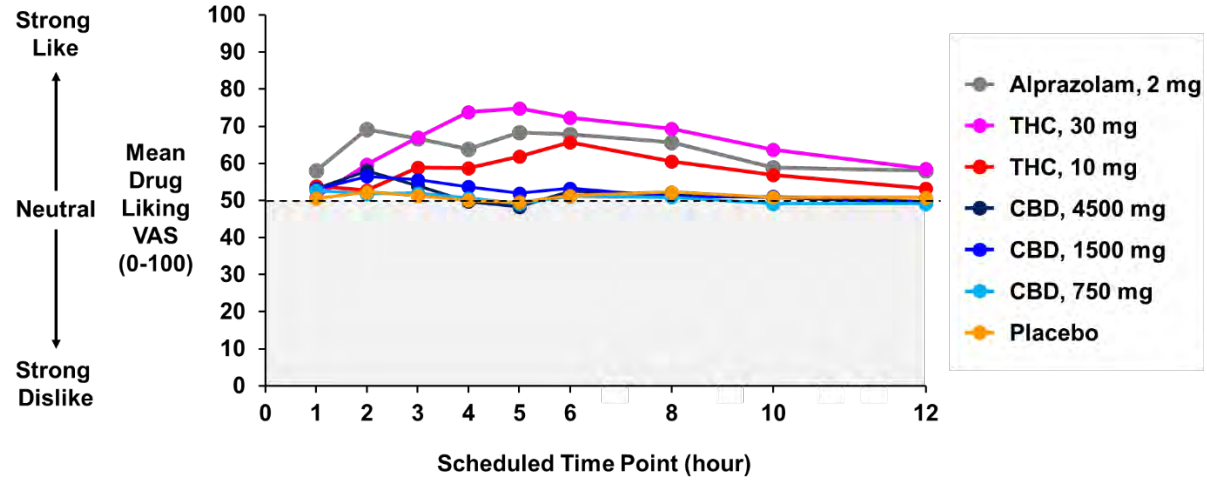
When comparing events of SE in the EAP by CBD-OS dose group, the overall incidence was highest in the >40 mg/kg/day CBD-OS group (14.7% [N=75]), with incidence of SE increasing with increasing dose. This increased rate of SE could reflect the need for high doses among a patient population prone to SE. Few events led to discontinuation, reflecting the nature of the underlying diseases in this population.

7.8. ABUSE LIABILITY/DEPENDENCE

A Phase 1 Human Abuse Liability study (1431) was conducted in a population of recreational polydrug users. The primary objective of this study was to evaluate the abuse potential of single doses of CBD-OS compared with alprazolam (ALZ) at a dose of 2 mg, dronabinol (DRO) at doses of 10 mg and 30 mg, and placebo in 35 healthy recreational polydrug users. Single doses of CBD-OS were administered at the proposed therapeutic dose of 750 mg, and at high therapeutic and supratherapeutic doses of 1500 mg and 4500 mg. The study showed CBD-OS to have significantly less abuse potential than either THC given as 2 doses of dronabinol (Schedule III of the Controlled Substances Act) or a single dose of ALZ (Schedule IV).

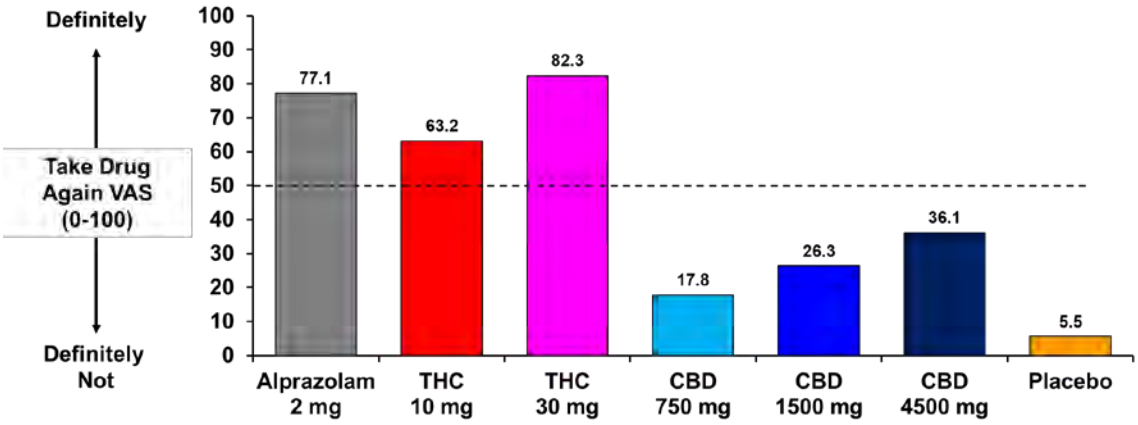
For the primary endpoint of drug liking maximum effect (E_{max}), no CBD-OS dose was more than 15 points (clinically meaningful threshold) greater than placebo, while the active comparators were each more than 15 points greater than placebo. All doses of CBD-OS produced a drug liking visual analogue scale (VAS) E_{max} that was statistically significantly lower compared with the single dose of ALZ and compared with both doses of DRO ($p \leq 0.0033$ in each case). Descriptive statistics for drug liking VAS scores at each time point are illustrated Figure 35 below. When compared with ALZ and DRO, CBD-OS was significantly less likely to be associated with drug liking, or with the desire to take the drug again (Figure 36).

Figure 35: Mean Drug Liking Visual Analogue Scale Scores vs. Time, by Treatment (Completer Population)



Drug liking VAS item: "At this moment, my liking for this drug is", where responses range from 0 (strong disliking) to 50 (neither like nor dislike) to 100 (strong liking).

Figure 36: Mean Drug Take Drug Again Visual Analogue Scale Scores by Treatment (Completer Population)



The human data from clinical studies show that, following the abrupt cessation of CBD-OS in patients in the clinical trial setting, no signals of physical dependence were detected according to the Cannabis Withdrawal Scale or Pediatric Cannabinoid Withdrawal Scale. In addition, a targeted Phase 1 study (1542) designed to assess dependence effects following abrupt cessation of CBD-OS in healthy subjects showed no psychological or physical dependence on CBD-OS.

7.9. OVERDOSE

The highest single dose of CBD-OS administered during clinical development was 6000 mg (over 8 times the daily dose of 20 mg/kg/day [divided into 2 doses] for a 70 kg adult), which produced diarrhea in 4 of 6 healthy volunteers. There was no evidence of clinically important changes in vital signs or laboratory parameters. The types of adverse events experienced by

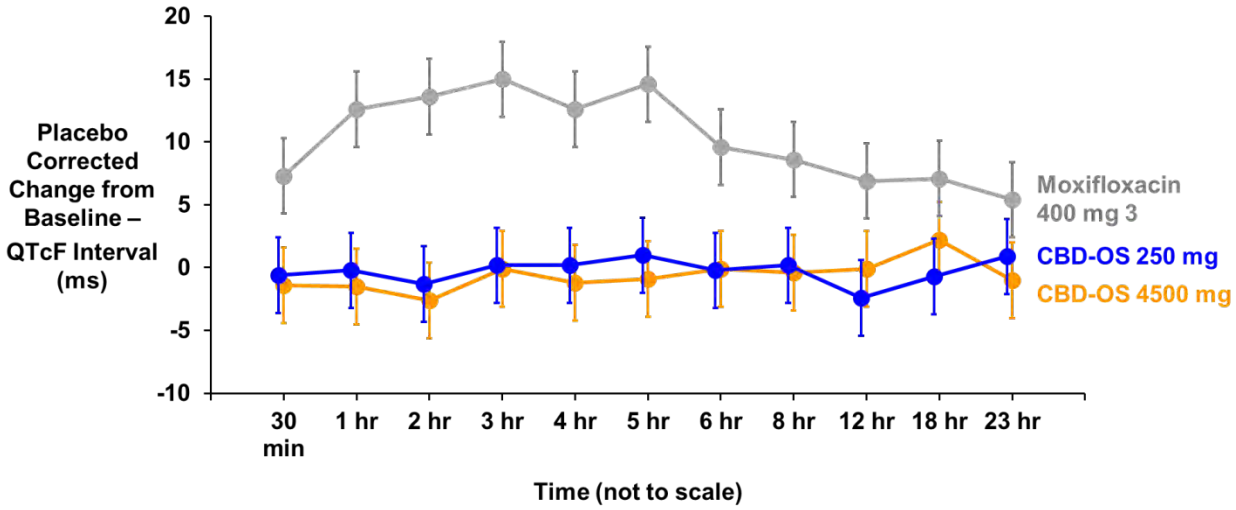
healthy volunteers exposed to supratherapeutic doses during the trials were not considered clinically different from those of patients administered recommended doses of CBD-OS.

7.10. QT STUDY IN HEALTHY VOLUNTEERS (STUDY 1541)

A thorough QT study in healthy subjects (Study 1541) demonstrated that at both therapeutic and supratherapeutic doses (750 mg and 4500 mg, respectively), CBD-OS did not prolong the QT interval and was not associated with other abnormalities of cardiac conduction.

In the study, 50 subjects were administered placebo and 400 mg moxifloxacin, 49 (98%) received 750 mg CBD-OS, and 48 (96%) received 4500 mg CBD-OS; the 49 subjects who received CBD-OS were included in the PK analysis set. The primary (QT interval corrected for heart rate [QTc]) endpoint, secondary endpoints, and PK analysis demonstrated no significant effects of CBD-OS on cardiac repolarization. The upper bounds of the 90% CI for the placebo-corrected changes from baseline in QTc with Fridericia correction (QTcF) interval were below the 10 ms threshold at all time points for both the therapeutic and supratherapeutic doses of CBD-OS (Figure 37). CBD-OS also had no significant effects on heart rate, RR, PR or QRS interval duration or ECG morphology. Therefore, the results of the thorough QT study demonstrated that CBD-OS did not significantly affect ECG parameters.

Figure 37: Mean (±90% CI) Placebo-corrected Change from Baseline in QTcF



7.11. RISK MANAGEMENT

The potential risks of CBD-OS will be addressed in the proposed labeling and Medication Guide. Enhanced pharmacovigilance will monitor the safety profile of CBD-OS in the post-marketing setting, with a particular focus on the risks observed in the clinical trial program (e.g., transaminase elevations).

7.12. SAFETY CONCLUSIONS

Patients with treatment resistant LGS and DS have high underlying morbidity and mortality associated with persistent seizures and are often taking 3 or more AEDs. The majority of patients treated with CBD-OS in the controlled studies had previously used 4 or more AEDs, and most

were taking 3 or more concomitant AEDs during the treatment phases. Because of this, it is difficult to attribute an AE to a single AED.

Based on findings from the CBD-OS clinical program, the safety and tolerability profile of CBD-OS is predictable and manageable. No notable differences were observed in the AEs, SAEs, AEs leading to discontinuation, or AESIs when comparing the LGS and DS patient populations. The 3 most common AEs were somnolence, decreased appetite, and diarrhea. These identified risks are manageable through the label and medication guide.

AESIs were based on CBD-OS-related risks as well as common AED AEs, and included transaminase elevations, somnolence/sedation, worsening seizures, SE, rash, pneumonia, diarrhea, and falls and injuries. To date, none of the transaminase elevations have met Hy's law or been associated with severe liver injury or permanent hepatic damage. The suggested monitoring should minimize risk from this concern.

Incidences of worsening seizures and SE did not increase with use of CBD-OS. Somnolence is a common occurrence with other AEDs and was a frequent AE with CBD-OS.

The limitations of small sample size of the orphan diseases are mitigated by an extensive long-term OLE study and safety data from the EAP, which both lend a degree of reassurance to the safety profile established in the controlled studies, especially because the EAP was likely similar to regular clinical practice. The majority of AEs observed from CBD-OS were successfully managed by dose reduction or resolved spontaneously.

8. BENEFIT RISK ANALYSIS

Both LGS and DS are severe drug-resistant encephalopathic epilepsies with onset in early childhood and are characterized by a severe seizure disorder, developmental delays and increased risk of death. Despite 6 approved therapies for LGS and no FDA-approved options for DS, more than 80% of patients with either of these syndromes continue to experience drug-resistant seizures. CBD-OS is a first-in-class, new chemical entity that has been shown to reduce seizure frequency in patients with drug-resistant LGS and DS, while exhibiting a predictable and manageable safety profile.

CBD-OS has demonstrated efficacy in 2 randomized, placebo-controlled, multicenter studies in patients with LGS, and in a single randomized, placebo-controlled, multicenter study in children and adolescents with DS. The patient population in each of the 3 clinical studies was drug-resistant, had failed multiple previous AEDs, and had experienced a high seizure frequency despite ongoing treatment with multiple AEDs. All 3 pivotal studies met their primary endpoint, reducing seizure frequency during the 14-week treatment period compared to placebo. In addition, a series of pre-planned sensitivity analyses and the positive outcomes of secondary efficacy endpoints confirm the robustness and relevance of the effect on seizure frequency reduction. This efficacy was seen with 10 mg/kg/day and 20 mg/kg/day CBD-OS, as well as when titrated up to 30 mg/kg/day in the long-term OLE study. The EAP also showed similar seizure frequency reductions across multiple encephalopathic epilepsies and used doses up to 50 mg/kg/day.

The safety of CBD-OS has been studied in 1419 unique patients with epilepsy, with 391 patients with more than 1 year of continuous exposure. Given the orphan nature of the conditions, the size of the safety database (totaling at least 1406.2 patient-years of exposure and including both placebo-controlled and long-term open-label data) allows for a reasonable characterization of the safety profile. While CBD-OS has been generally well-tolerated, several potentially important safety signals have emerged, including elevation of transaminases, increased risk for pneumonia, somnolence and sedation, and rash. The consistency of the data allows relative reassurance that the common adverse reactions have been identified in the controlled study safety data, and the safety profile will be closely monitored post-marketing based on ongoing pharmacovigilance data collection.

Overall, the benefit-to-risk assessments conclude that there is a positive benefit-to-risk balance for CBD-OS, which offers a new chemical entity and first-in-class medication option for the adjunctive treatment of seizures in patients with LGS or DS. The consistent ~20% reduction in primary seizure frequency with CBD-OS vs. placebo across the 3 pivotal trials, with a substantial proportion of patients reaching 50% and 75% reductions, translates into a meaningful seizure-related reduction in morbidity and potentially mortality. The idenitified risks carry much less morbidity and mortality, either quantitatively or qualitatively.

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10. APPENDICES

10.1. INCLUSION AND EXCLUSION CRITERIA

Study 1414 and Study 1423

Table 39: Inclusion Criteria for Studies 1414 and 1423

1.	Patient or parent(s)/legal representative were willing and able to give informed assent/consent for participation in the trial.
2.	Patient and their caregiver were willing and able (in the investigator's opinion) to comply with all trial requirements.
3.	Patient was male or female aged 2-55 years (inclusive).
4.	Patient must have a clinical diagnosis of LGS. This includes written documentation of having met EEG diagnostic criteria during the patient's history and evidence of more than 1 type of generalized seizure, including drop seizures (atonic, tonic or tonic-clonic) for at least 6 months. Care was to be taken not to include benign myoclonic epilepsy of infancy, atypical benign partial epilepsy (pseudo-Lennox syndrome), or continuous spike-waves of slow sleep.
5.	Patients who had a history of slow (< 3.0 Hz) spike-and-wave pattern in an EEG prior to their enrollment into the baseline period.
6.	Patients must have had at least 2 drop seizures each week during the first 28 days of the baseline period.
7.	Patients were refractory; that is having documented failures on more than 1 AED.
8.	Patient was taking 1 or more AEDs at a dose which had been stable for at least 4 weeks prior to screening.
9.	All medications or interventions for epilepsy (including ketogenic diet and VNS) were stable for 4 weeks prior to screening and patient was willing to maintain a stable regimen throughout the trial. The ketogenic diet and VNS treatments were not counted as an AED.
10.	Patient or parent(s)/legal representative was willing to allow his or her primary care practitioner and consultant to be notified of participation in the trial.
11.	Patient had completed their IVRS telephone diary on at least 25 days of the baseline period.

Table 40: Exclusion Criteria for Studies 1414 and 1423

1.	Etiology of patient's seizures was a progressive neurologic disease. Patients with tuberous sclerosis were not excluded from trial participation, unless there was a progressive tumor.
2.	Patient had an anoxic episode requiring resuscitation within 6 months of screening.
3.	Patient had clinically significant unstable medical conditions other than epilepsy.
4.	Patient had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to screening or randomization, other than epilepsy.
5.	Patient had clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization.
6.	Patient had clinically relevant abnormalities in the ECG measured at screening or randomization.
7.	Patient had any concurrent cardiovascular conditions, which, in the investigators opinion, interfered with the ability to assess their ECGs.
8.	Patient had a history or presence of alcohol or substance abuse within the last 2 years prior to the trial or daily consumption of 5 or more alcohol-containing beverages.
9.	Patient was currently using or had in the past used recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex®) within the 3 months prior to trial entry.
10.	Patient was unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex) during the trial.
11.	Patient had a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes.

12.	Patient had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.
13.	Female patient was of child bearing potential or male patient's partner was of child bearing potential; unless willing to ensure that they or their partner used a highly effective method of contraception for the duration of the trial and for 3 months thereafter. Highly effective methods of contraception were defined as those, alone or in combination, that resulted in low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods include hormonal contraceptives, intrauterine devices/ hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.
14.	Female patient was pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial and for 3 months thereafter.
15.	Patient had been part of a clinical trial involving another IMP in the previous 6 months.
16.	Any other significant disease or disorder which, in the opinion of the investigator, may either have put the patient at risk because of participation in the trial, may have influenced the result of the trial, or affected the patient's ability to participate in the trial.
17.	Patient had significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2), defined as **any** of the following: Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 5 × upper limit of normal (ULN); ALT or AST > 3 × ULN **and** total bilirubin (TBL) > 2 × ULN **or** international normalized ratio (INR) > 1.5); ALT or AST > 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, or eosinophilia (>5%). *This criterion could only be confirmed once the laboratory results were available; patients randomized into the trial who were later found to meet this criterion were withdrawn from the trial.*
18.	Following a physical examination, the patient had any abnormalities that, in the opinion of the investigator, would have prevented the patient from safe participation in the trial.
19.	Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale (C-SSRS) at screening.
20.	Patient was unwilling to abstain from donation of blood during the trial.
21.	There were plans for the patient to travel outside their country of residence during the trial.
22.	Patient had previously randomized into the trial.
23.	Patient was taking more than 4 concurrent AEDs.
24.	Patient had taken corticotropins in the 6 months prior to screening.
25.	Patient was currently taking long-term systemic steroids (excluding inhaled medication for asthma treatment) or any other daily medication known to exacerbate epilepsy. An exception was made for prophylactic medication, for example, for idiopathic nephrotic syndrome or asthma.
26.	Patient was taking felbamate, and they had been taking it for less than 1 year prior to screening.

Study 1332

Table 41: Inclusion Criteria for Study 1332 Part A

1.	Patient or parent(s)/legal representative were willing and able to give informed assent/consent for participation in the trial.
2.	Patient and their caregiver were willing and able (in the investigator's opinion) to comply with all trial requirements.
3.	Patient was male or female aged between 4 and 10 years (inclusive).
4.	Patient had a documented history of DS which was not completely controlled by current AEDs.
5.	Patient experienced fewer than 4 convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the 28-day baseline period.
6.	Patient was taking 1 or more AEDs at a dose which had been stable for at least 4 weeks.
7.	All medications or interventions for epilepsy (including ketogenic diet and VNS) were stable for 4 weeks prior to screening and patient and caregiver were willing to maintain a stable regimen throughout the trial. The ketogenic diet and VNS treatments were not counted as an AED.
8.	Patient or parent(s)/legal representative were willing to allow his or her primary care practitioner and consultant to be notified of participation in the trial.

VNS: vagus nerve stimulation.

Table 42: Inclusion Criteria for Study 1332 Part B

1.	Patient or parent(s)/legal representative were willing and able to give informed assent/consent for participation in the trial.
2.	Patient and their caregiver were willing and able (in the investigator's opinion) to comply with all trial requirements.
3.	Patient was male or female aged between 2 and 18 years (inclusive).
4.	Patient had a documented history of DS which was not completely controlled by current AEDs.
5.	Patient experienced 4 or more convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period.
6.	Patient was taking 1 or more AEDs at a dose which had been stable for at least 4 weeks.
7.	All medications or interventions for epilepsy (including ketogenic diet and VNS) were stable for 4 weeks prior to screening and patient and caregiver were willing to maintain a stable regimen throughout the trial. The ketogenic diet and VNS treatments were not counted as an AED.
8.	Patient or parent(s)/legal representative were willing to allow his or her primary care practitioner and consultant to be notified of participation in the trial.
9.	Patient had completed their IVRS telephone diary on at least 25 days of the baseline period; patients who were non-compliant were deemed ineligible to continue.

VNS: vagus nerve stimulation.

Table 43: Exclusion Criteria for Study 1332 Parts A and B

1.	Patient had clinically significant unstable medical conditions other than epilepsy.
2.	Patient had clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to screening or randomization, other than epilepsy.
3.	Patient had clinically significantly abnormal, in the investigator's opinion, laboratory values at screening or randomization.
4.	Patient had clinically relevant abnormalities in the ECG measured at screening or randomization.
5.	Patient had any concurrent cardiovascular conditions, which would have, in the investigator's opinion, interfered with the ability to read their ECGs.

6.	Patient had a history or presence of alcohol or substance abuse within the last 2 years prior to the trial or daily consumption of 5 or more alcohol-containing beverages.
7.	Patient was currently using or had in the past used recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex®) within the 3 months prior to trial entry.
8.	Patient was unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid-based medications (including Sativex) during the trial.
9.	Patient had a history of symptoms (e.g., dizziness, light-headedness, blurred vision, palpitations, weakness, syncope) related to a drop in blood pressure due to postural changes.
10.	Patient had ingested alcohol in the 24-hour period prior to the first trial visit or was unwilling to abstain from drinking alcohol throughout the treatment period.
11.	Patient had consumed grapefruit or grapefruit juice 3 days prior to screening or was unwilling to abstain from consuming these during the trial.
12.	Patient had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the IMP(s), e.g., sesame oil.
13.	Female patient was of child bearing potential or male patient's partner was of child bearing potential; unless willing to ensure that they or their partner used highly effective contraception for the duration of the trial and for 3 months thereafter. Highly effective methods of contraception were defined as those, alone or in combination, that resulted in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Such methods included hormonal contraceptives, intrauterine devices/hormone-releasing systems, bilateral tubal occlusion, vasectomized partner or sexual abstinence.
14.	Female patient who was pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial and for 3 months thereafter.
15.	Patient had been part of a clinical trial involving an investigational product in the previous 6 months.
16.	Patient was taking felbamate and they had been taking it for less than 1 year prior to screening.
17.	Any other significant disease or disorder which, in the opinion of the investigator, may have either put the patient at-risk because of participation in the trial, influenced the result of the trial, or affected the patient's ability to participate in the trial.
18.	Patient had significantly impaired hepatic function at screening (Visit A1 or B1) or randomization (Visit A2 or B2) (ALT > 5 × ULN **and** TBL > 2 × ULN) OR the ALT or AST > 3 × ULN **and** (TBL > 2 × ULN **or** INR > 1.5). *This criterion could only be confirmed once the laboratory results were available; patients randomized into the trial who were later found to meet this criterion were withdrawn from the trial.*
19.	Following a physical examination, the patient had any abnormalities that, in the opinion of the investigator, would prevent the patient from safe participation in the trial.
20.	Patient was unwilling to abstain from donation of blood during the trial.
21.	There were plans for the patient to travel outside their country of residence during the trial.
22.	Patient was previously randomized into the trial. In particular, patients randomized in Part A of the trial could not enter Part B.
23.	Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale at screening.

ALT: alanine aminotransferase; AST: aspartate aminotransferase; INR: international normalized ratio; TBL: total bilirubin; ULN: upper limit of normal.

10.2. COMMON ADVERSE EVENTS BY DISEASE

Table 44: Comparative Summary of Common AEs that Reached an Incidence of ≥ 10% in the All CBD-OS Group in Controlled LGS and DS Studies

SOC PT	Pool LGS		Pool DS	
	Placebo (N=161) n (%)	All CBD-OS (N=235) n (%)	Placebo (N=66) n (%)	All CBD-OS (N=88) n (%)
Patients with at least 1 AE	**114 (70.8)**	**207 (88.1)**	**50 (75.8)**	**77 (87.5)**
Gastrointestinal disorders	**44 (27.3)**	**72 (30.6)**	**13 (19.7)**	**35 (39.8)**
Diarrhoea	13 (8.1)	35 (14.9)	7 (10.6)	19 (21.6)
Vomiting	23 (14.3)	23 (9.8)	3 (4.5)	12 (13.6)
General disorders and administration site conditions	**24 (14.9)**	**50 (21.3)**	**10 (15.2)**	**28 (31.8)**
Pyrexia	19 (11.8)	27 (11.5)	5 (7.6)	15 (17.0)
Fatigue	4 (2.5)	18 (7.7)	4 (6.1)	13 (14.8)
Infections and infestations	**50 (31.1)**	**96 (40.9)**	**21 (31.8)**	**38 (43.2)**
Upper respiratory tract infection	17 (10.6)	24 (10.2)	5 (7.6)	8 (9.1)
Metabolism and nutrition disorders	**11 (6.8)**	**53 (22.6)**	**3 (4.5)**	**26 (29.5)**
Decreased appetite	8 (5.0)	43 (18.3)	3 (4.5)	22 (25.0)
Nervous system disorders	**45 (28.0)**	**109 (46.4)**	**22 (33.3)**	**44 (50.0)**
Somnolence	12 (7.5)	52 (22.1)	7 (10.6)	27 (30.7)

Note: Common AEs were defined as having an incidence of ≥ 10% (after rounding up) in the All CBD-OS group.
Note: Safety analysis set.

10.3. STATUS EPILEPTICUS PATIENT VIGNETTES

Study 1332A

Treatment Group: CBD-OS 5 mg/kg

A female patient (age range 6-11) with a history of DS, generalized tonic-clonic seizures (1/8 weeks), absence seizures (140-700/week), myoclonic seizures (140-700/ week), *SCN1A* missense mutation, atypical febrile convulsion and ketogenic diet began treatment with CBD-OS 5 mg/kg/day. She was receiving clobazam (5 mg/day) concomitantly. The patient received her final dose of CBD-OS on day 30 and on day 31 she experienced SE as a prolonged absence followed by a generalized tonic-clonic seizure; she was treated with rectal paraldehyde with no benefit. She was treated with 2 doses of rectal diazepam on the way to the hospital. In hospital, she was given phenobarbitone and recovered the same day. No action was taken with CBD-OS. The Investigator considered the event of SE to be related to study medication, as she did not respond to paraldehyde like she usually does.

Study 1332B

Treatment Group: CBD-OS 20 mg/kg

A male patient (age range 6-11) with a history of DS, convulsive and non-convulsive SE (2/year), generalized tonic-clonic seizures (6/week), tonic seizures (14/week), atonic seizures (2/week), *SCN1A* mutation and unspecified mental retardation began treatment with CBD-OS 20 mg/kg/day. He was receiving clobazam (15 mg/day), rufinamide (800 mg/day), zonisamide (150 mg/day), clonazepam (0.25 mg PRN), macrogol and salbutamol concomitantly. On day 59

the patient experienced SE with a concomitant fever and recovered later that day. On day 86 the patient experienced another event of SE. SE continued on day 87 and he was treated with benzodiazepines, barbiturates and admitted to hospital. On day 89 the patient recovered from the event of SE. No action was taken with CBD-OS due to the events of SE. The Investigator considered all events of SE to be unrelated to study medication and noted that the patient had events of SE 1-2 times per year prior to receiving treatment with CBD-OS.

Treatment Group: Placebo
A male patient (age range 2-5) with a history of DS, generalized tonic-clonic seizures (twice), absence seizures (15/week), tonic seizures (1/month), complex partial seizures (1/month) and febrile seizures began treatment with placebo. He was receiving LEV (1200 mg/day), topiramate (120 mg/day) and diazepam (10 mg PRN) concomitantly. On day 72 the patient experienced convulsive SE with respiratory failure and was hospitalized. He was treated with benzodiazepines, intubation and midazolam and recovered from all events on day 73. No action was taken with placebo. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: CBD-OS 20 mg/kg
A male patient (age range 6-11) with a history of DS, secondarily generalized tonic-clonic seizures (7/week), myoclonic seizures (>500/week), complex partial seizures (100/week), severe oropharyngeal dysphagia, recurrent aspiration and truncal hypotonia began treatment with CBD-OS 20 mg/kg/day. He was receiving rufinamide (360 mg/day), clonazepam (0.75 mg/day), VPA (750 mg/day), STP (1000 mg/day), levocarnitine, ranitidine, levosalbutamol and hydrocortisone concomitantly. The patient had 2 episodes of SE on days -30 and -28 prior to commencing treatment with CBD-OS. The patient recovered from the events on the same day. On day 36 the patient experienced SE with a concomitant gastrointestinal (GI) infection and was treated with diazepam. The patient recovered on the same day. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: Placebo
A female patient (age range 12-17) with a history of DS, non-convulsive SE (10/month), secondarily generalized tonic-clonic seizures (10/month), myoclonic seizures (4/week) and tonic seizures (24/month) began treatment with placebo. She was receiving STP (1000 mg/day), clobazam (10 mg/day), verapamil hydrochloride (80 mg/day), clonazepam (1 mg PRN), midazolam (3.5 mg PRN), levocarnitine and macrogol concomitantly. The patient experienced non-convulsive SE on day -26 prior to commencing treatment with placebo. She recovered from the event on day -16. On day 18 the patient experienced recurrent non-convulsive SE and was treated with clonazepam and midazolam and began to recover. She experienced a second episode of SE on day 28 and was treated with clonazepam and midazolam and recovered on the same day. No action was taken with placebo. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: Placebo
A male patient (age range 6-11) with a history of DS, non-convulsive SE (2/month), generalized tonic-clonic seizures (5/week), hemiclonic seizures (1/week), absence seizures (1/week), *SCN1A* mutation and ketogenic diet began treatment with placebo. He was receiving VPA (360 mg/day), zonisamide (120 mg/day), midazolam (20 mg PRN) and carnitine concomitantly. On day -14 prior to commencing treatment with placebo the patient experienced non-convulsive SE and recovered the following day. On day 1 the patient experienced non-convulsive SE recurrent for 4 days with short recovery in between; he received 5 doses of rescue medication. Recurrent non-convulsive SE continued on day 37 and he was treated with midazolam. The patient showed no signs of non-convulsive SE on an EEG on day 38. The event of recurrent non-convulsive SE was ongoing at the time of reporting. No action was taken with placebo. The Investigator considered the events of SE to be unrelated to study medication and noted that prior to the study the patient had events of non-convulsive SE "on an approximately monthly basis".

Treatment Group: CBD-OS 20 mg/kg
A male patient (age range 12-17) with a history of DS, generalized tonic-clonic seizures (1/month) and myoclonic seizures (15/day) began treatment with CBS-OS 20 mg/kg/day. The patient was receiving VPA (500 mg/day), STP (1500 mg/day), topiramate (130 mg/day), clobazam (10 mg/day) and melatonin concomitantly. On day 77 the patient experienced SE and was treated with 5 mg clonazepam. He recovered on the same day; no action was taken with CBD-OS. The Investigator considered the event to be non-serious and unrelated to study medication.

Treatment Group: CBD-OS 20 mg/kg
A male patient (age range 12-17) with a history of DS, generalized tonic-clonic seizures (4/week), absence seizures (1/week), myoclonic seizures and *SCN1A* mutation began treatment with CBD-OS 20 mg/kg/day. He was receiving LEV (2250 mg/day), VPA (1375 mg/day) and clobazam (5 mg/day) concomitantly. On day 4 he experienced SE. He received 0.5 mg of lorazepam and recovered the same day. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

<u>Study 1414</u>

Treatment Group: CBD-OS 20 mg/kg
A male patient (age range 2-5) with a history of LGS, non-convulsive SE, generalized tonic-clonic seizures (3/week), absence seizures (70/week), myoclonic seizures (70/week) and is receiving a ketogenic diet began treatment with CBD-OS 20 mg/kg/day. He was receiving LEV (750 mg/day), VPA (375 mg/day), human immunoglobulin, macrogol and levocarnitine concomitantly. On day 29 the patient was hospitalized due to non-convulsive SE, the seizures were typically absence and myoclonic events with frequent tonic seizures, head drops and atonic seizures. He was treated with IV corticosteroids and rufinamide. Treatment with CBS-OS was stopped without taper on day 29 due to the event of SE. The patient recovered on day 32. The Investigator considered the event of SE to be related to study medication.

Treatment Group: CBD-OS 20 mg/kg
A female patient (age range 6-11) with a history of LGS, SE, generalized tonic-clonic seizures (15/month), atonic seizures (500/week), myoclonic seizures (9/week) and brain damage began treatment with CBD-OS 20 mg/kg/day. The patient was receiving VPA (550 mg/day), diazepam (5 mg PRN), dopamine and omeprazole concomitantly. The patient experienced 4 events of non-convulsive SE on days -7, -3, -2 and - 1 prior to commencing treatment with CBD-OS and was non-reactive. She recovered from each event. On day 2 the patient was hospitalized with non-convulsive SE. The patient was treated with IV midazolam and VPA and recovered on day 6. On days 66, 69 and 72 the patient had events of non-convulsive SE which were treated with diazepam. She recovered from all events 1 hour after taking diazepam. No action was taken with CBD-OS as a result of the events of SE. The Investigator considered the events of SE to be unrelated to study medication.

Treatment Group: Placebo
A female patient (age range 12-17) with a history of LGS, tonic seizures (70/week), absence seizures (90/week), atonic seizures (1/month) and a stroke began treatment with placebo. She was receiving lacosamide (400 mg/day), PB (125 mg/day), carbamazepine (1600 mg/day) and diazepam (5 mg PRN) concomitantly. On day 3 the patient experienced convulsive SE and recovered spontaneously without using medication. The patient experienced 5 further events of convulsive SE on days 13, 20, 27, 56 and 75 that were treated with diazepam and resolved on the day of onset. No action was taken with placebo as a result of the events of SE. The Investigator considered the events of SE to be unrelated to study medication.

Treatment Group: CBD-OS 10 mg/kg
A female patient (age >18) with a history of LGS began treatment with CBD-OS 10 mg/kg/day. She was receiving perampanel (500 mg/day), LTG (50 mg/day), VPA (500 mg/day) and ranitidine concomitantly. The patient experienced convulsive SE on day 7 and recovered on the same day. The Investigator noted that the event is similar to events that the patient experienced prior to commencing treatment with CBD-OS. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: CBD-OS 20 mg/kg
A male patient (age range 2-5) with a history of LGS, tonic seizures (10/week), myoclonic spasms, spastic quadriplegic cerebral palsy and hypoxic-ischemic encephalopathy began treatment with CBD-OS 20 mg/kg/day. He was receiving LTG (300 mg/day), zonisamide (200 mg/day), clobazam (4 mg/day), diazepam (10 mg PRN), salbutamol, amantadine hydrochloride, glycopyrrolate, macrogol, trazodone hydrochloride and omeprazole concomitantly. On day 33, the patient experienced convulsive SE and was taken to the emergency room due to a prolonged cluster of seizures with tongue quiver and head jerking on and off. He was treated with zonisamide and increased dosage of LTG. The patient recovered the next day. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication and noted that the patient may have had Norovirus in the week prior to the event.

Treatment Group: CBD-OS 10 mg/kg
A female patient (age >18) with a history of LGS, SE (2/month, coinciding with her menstrual cycle), secondarily generalized tonic-clonic seizures (4/week), myoclonic seizures (28/week), tonic seizures (10/week) and brain lobectomy began treatment with CBD-OS 10 mg/kg/day. She was receiving LEV (3300 mg/day), clobazam (20 mg/day), LTG (525 mg/day) and oxcarbazepine (450 mg) concomitantly. The patient experienced 2 events of SE on days -24 and -17 prior to commencing treatment with CBD-OS; she was treated with diazepam and recovered from both events. Treatment with CBD-OS was temporarily discontinued on day 7 due to a rash and a viral syndrome. On day 17 CBD-OS was restarted at a dose of 2.5 mg/kg and on the same day in the evening the patient experienced SE reported as generalized tonic-clonic seizures lasting 50 minutes. The duration and type of seizures was not unusual for the patient. The patient was treated with midazolam and 10mg diazepam and the SE resolved that day. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: CBD-OS 10 mg/kg
A male patient (age >18) with a history of LGS, generalized tonic-clonic seizures (2/week) complex partial seizures (3/week), tonic seizures (2/week) and hyponatremia began treatment with CBD-OS 10 mg/kg/day. He was receiving eslicarbazepine acetate (1200 mg/day), VPA (1500 mg/day), clonazepam (2 mg/day) and diazepam (10 mg PRN) concomitantly. The patient experienced one episode of SE approximately 1 month prior to commencing treatment with CBD-OS. On day 11 the patient experienced convulsive SE classified as generalized tonic-clonic seizures and was treated with diazepam (10 mg). The SE resolved in 30 minutes. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: CBD-OS 10 mg/kg
A female patient (age range 12-17) with a history of LGS, generalized tonic-clonic seizures (2/week), complex partial seizures (105/week) and tonic seizures (105/week) began treatment with CBD-OS 10 mg/kg/day. The patient was receiving LEV (1000 mg/day), LTG (375 mg/day), lacosamide (200 mg/day) and clobazam (50 mg/day) concomitantly. The patient experienced an episode of SE on day -14 prior to commencing treatment with CBD-OS and recovered on the same day. The patient experienced non-convulsive SE on day 8. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: CBD-OS 10 mg/kg
A male patient (age range 6-11) with a history of LGS, SE (3-4/week), generalized tonic-clonic seizures (2/week), atonic seizures (2/week), myoclonic seizures (2/month) and a vagal nerve stimulator implantation began treatment with CBD-OS 10 mg/kg/day. The patient was receiving rufinamide (1040 mg/day), LTG (150 mg/day), clonazepam (3 mg/day), topiramate (250 mg/day), diazepam (17.5 mg PRN), macrogol, methylphenidate, clonidine, hydroxyzine, gabapentin, cyproheptadine and ondansetron concomitantly. The patient experienced non-convulsive SE on day -23 prior to commencing treatment with CBD-OS. He experienced non-convulsive SE on day 7. On days 18, 24, 31, 75 and 95 the patient experienced an episode of convulsive SE. The patient was treated with diazepam and recovered within 2 hours of each

event. No action was taken with CBD-OS. The Investigator considered the events of SE to be unrelated to study medication.

Treatment CBD-OS 10mg/kg

A female patient (age >18) with a history of LGS, generalized tonic-clonic seizures (2/month), tonic seizures (28/week), absence seizures (1/month), Aicardi syndrome and a vagal nerve stimulator implantation began treatment with CBD-OS 10 mg/kg/day. She was receiving vigabatrin (7000 mg/day), PB (56 mg/day), clobazam (90 mg/day), LEV (5100 mg/day), diazepam (15 mg PRN), clonazepam (0.25 mg PRN), macrogol, triamcinolone acetonide, bisacodyl, cetirizine, clotrimazole, diphenhydramine, ursodeoxycholic acid and salbutamol concomitantly. The patient has one episode of SE on day -14 prior to commencing treatment with CBD-OS. On day 25 the patient experienced SE, she was treated with oxygen and diazepam and recovered on the same day. On day 36 the patient experienced a second event of SE classified as tonic-clonic seizures and was treated with midazolam and diazepam. The patient recovered on the same day. No action was taken with CBD-OS. The Investigator considered the events of SE to be unrelated to study medication.

Treatment Group: CBD-OS 10 mg/kg

A male patient (age range 12-17) with a history of LGS, generalized tonic-clonic (28/week), tonic seizures (7/week), complex partial seizures (3/week), intractable epilepsy, corpus callosotomy and cerebral palsy began treatment with CBD-OS 10 mg/kg/day. He was receiving rufinamide (1200 mg/day), clonazepam (0.75mg/day), clorazepate dipotassium (15 mg/day), felbamate (1600 mg/day), lorazepam (PRN), clonidine, ondansetron, salbutamol, esomeprazole sodium and promethazine concomitantly. On day 39 the patient experienced convulsive SE, he was hospitalized and treated with lorazepam, midazolam and PB. The patient recovered on the same day. No action was taken with CBD-OS. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: Placebo

A female patient (age >18) with a history of LGS, convulsive SE (1/week), generalized tonic-clonic seizures (8/week), tonic seizures (28/week), absence seizures (10/week) and myoclonic seizures (10/week) began treatment with placebo. She was receiving topiramate (500 mg/day), LEV (50 ml/day), rufinamide (3200 mg/day) and diazepam (5 mg PRN) concomitantly. On day 73 the patient experienced convulsive SE. She was treated with rescue medication but did not recover. At the time of reporting the event of SE was ongoing. No action was taken with placebo. The Investigator considered the event of SE to be unrelated to study medication.

Treatment Group: CBD-OS 20 mg/kg

A female patient (age range 6-11) with a history of LGS, tonic seizures, (50/week), atonic seizures (3/week), myoclonic seizures (3/month), scoliosis and syringomyelia began treatment with CBD-OS 20 mg/kg/day. She was receiving carbamazepine (600 mg/day), LTG (200 mg/day), clonazepam (12 mg/day), rufinamide (1000 mg/day), diazepam (10 mg/day), cyproheptadine hydrochloride and ondansetron concomitantly. On day 36 the patient experienced convulsive SE and was treated with diazepam. The patient's seizure stopped, and

she recovered from the event on the same day. No action was taken with CBD-OS. The Investigator considered the event of convulsive SE to be unrelated to study medication.

Treatment Group: Placebo
A female patient (age range 6-11 years) with a history of LGS, generalized tonic-clonic seizures (1/month), atonic seizures (350/week), absence seizures (70/week) began treatment with placebo. She was receiving VPA (500 mg/day), rufinamide (1000 mg/day), zonisamide (150 mg/day), levocarnitine and cyproheptadine concomitantly. She experienced non-convulsive status epilepticus on day 24 and recovered on the same day. No action was taken with placebo. The Investigator considered the event of non-convulsive SE to be unrelated to study medication.

Study 1423

Treatment Group: CBD-OS 20 mg/kg
A male patient (age range 6-11) with a history of LGS, intermittent non-convulsive status epilepticus, tonic seizures (21/week), absence seizures (99/week), myoclonic seizures (99/week), hypoxic-ischaemic encephalopathy, spastic quadriplegia, cerebral palsy and vagal nerve stimulator began treatment with CBD-OS 20 mg/kg/day. He was receiving LTG (200 mg/day), LEV (500mg/day), clobazam (30 mg/day), midazolam (3 mg PRN), metoclopramide, pantoprazole, macrogol, triamcinolone and salbutamol, cetirizine and dexamethasone concomitantly. On day 92, the patient experienced non-convulsive SE; no action was taken with CBD-OS. The patient had not recovered from the event at the time of reporting. The Investigator considered the event of non-convulsive SE to be unrelated to study medication.

Treatment Group: Placebo
A male patient (age > 18) with a history of LGS, convulsive status epilepticus (2/month), generalized tonic-clonic seizures (3/week), complex partial seizures (4/week), tonic seizures (2/week), corpus callosotomy and a vagal nerve stimulator began treatment with placebo. The patient was receiving clonazepam (3 mg/day), felbamate (2400 mg/day), LEV (4000 mg/day), diazepam (10 mg PRN), clonidine, ranitidine and risperidone concomitantly via a G tube (rectal for PRN diazepam). On the day prior to commencing placebo the patient experienced convulsive SE; he was treated with diazepam and recovered on the same day. On day 21 the patient experienced a moderate event of SE; he was treated with diazepam and recovered on the same day. On day 37 the patient experienced a severe event of SE and was treated with sedatives, antibiotics and benzodiazepines. He recovered on day 39. No action was taken with placebo. The Investigator considered the events of SE to be unrelated to study medication.

10.4. TABULATION OF DEATHS

Table 45: Tabulation of Deaths

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
1423	M	17	20mg/kg/d	Acute Respiratory Distress Syndrome SE Acute Respiratory Failure Aspiration pneumonia Pneumothorax DVT Nephrolithiasis	D16	D38	No	Clobazam Lorazepam LEV Lacosamide Zonisamide	Status Epilepticus leading to aspiration pneumonia in a patient with compromised lung function. Subsequent deterioration
1415 (OLE)	F	12	20mg/kg/d	SUDEP	D225	D225	No	VPA LTG	Found dead in bed in the morning. Had been on CBD-OS during 1332B and reduced seizure frequency by 29% (from 10 to 7)
1415 (OLE)	F	5	18mg/kg/d	SUDEP	D94 (But had been on CBD-OS in parent study)	D94	No	VPA Clobazam STP	Found dead in bed in the morning. Had been on CBD-OS during 1332B and reduced seizure frequency from 6.4 to 3.4 (46%)
1415 (OLE)	M	10	20mg/kg/d	Respiratory failure Aspiration pneumonia	D30 (Had been on placebo in parent study)	D47	No	LEV Clonazepam PB Diazepam - rescue	Developed fever and vomiting post G-tube. Respiratory failure due to aspiration pneumonia. COPD and reflux.

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
1415 (OLE)	F	8	20mg/kg/d	Seizure disorder Cerebral edema Pulmonary edema	D94 (Had been on placebo in parent study)	D99	No	Zonisamide Clobazam Topiramate Rufinamide	Major co-morbidities. Developed high fever + seizures. Diagnosed with RSV in ER and sent home with fentanyl. Found dead in bed the next morning.
1415 (OLE)	F	13	20mg/kg/d	Bowel Obstruction and necrotic bowel Severe septic shock Fecal peritonitis	D144 (But had been on CBD-OS in parent study)	D145	No	Lacosamide Clobazam Perampanel	Multiple co-morbidities including chronic lung disease, G-tube, cerebral palsy, global developmental delay. Had been a >50% responder on 20mg dose in Study 1423. Admitted to hospital for emergency surgery, which found necrotic bowel and fecal peritonitis. She died the following day.

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
1415 (OLE)	F	5	25mg/kg/d	Seizure disorder due to hypoxic ischemic encephalopathy	D75 (But had been on CBD-OS in the parent study)	D75	No	Lacosamide Diazepam - rescue	Multiple co-morbidities - Cerebral palsy with a spastic quadriparesis and severe global developmental delay. Microcephaly, airways disease. She had multiple AEs in Study 1423 including acute hypoxemic respiratory failure following an adenovirus infection. She was a responder (>50 % seizure reduction) on 20mg/kg/day. She was found dead in bed without immediate prior AEs. She was said to have recovered from gastric flu and a separate viral bronchiolitis more than a week prior to death.
1415 (OLE)	F	8	30mg/kg/d	Rett's disorder	D311	D405	No	Carbamazepine, LEV, PB and Clobazam	h/o developmental delay, chromosome abnormality, reactive airway disease, obstructive sleep apnea, recurrent aspiration pneumonia, and Rett's syndrome.
				Cardiac arrest; respiratory failure	D405 (Had been on placebo in parent study)				

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
EAP	F	8	10 - 25 mg/kg/d	Status epilepticus (Working Diagnosis of FIRES)	D-1 to D28	D28	No	PB, LEV topiramate lacosamide and VPA all at supra-therapeutic doses. Ketogenic diet, Isoflurane and Ketamine infusion	Working diagnosis of FIRES. SE started before CBD-OS dosing commenced. SE worsened progressively as Ketamine & Isoflurane was withdrawn leading to cerebral edema and multi organ failure.
EAP	F	3	6mg/kg/d	Probable SUDEP	D55	D55	No	VPA, rufinamide, clobazam, and LEV	h/o Aicardi syndrome, global developmental delay, and intractable epilepsy. Sleepy and tired on day of death. Found not breathing and resuscitation attempted. Parents declined an autopsy.

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
EAP	M	30	20mg/kg/d	Possible SUDEP	D58	D58	No	LTG, oxcarbazepine, retigabine, lorazepam,	h/o temporal lobe tumor resection, intractable epilepsy with generalised tonic clonic seizure, intense aura, GERD, hypertension, and sleep seizures documented via video/EEG monitoring. Had ongoing hyponatremia. Experienced a seizure in the evening, administered lorazepam and went to bed. Found deceased in his bed with tongue lacerations and "foam around his mouth".
EAP	F	14	10mg/kg/d	Severe progressive mitochondrial disorder	D183	D183	No	clobazam, clonazepam, lacosamide, LTG, LEV	h/o significant developmental delays, epileptic encephalopathy (possible Landau Kleffner variant), corpus callosotomy. h/o prolonged hospitalisations in the setting of increased seizure frequency, myoclonic activity and status epilepticus. Admitted to hospital due to respiratory issues, fever and leucocytosis. 10 days later found unresponsive. Autopsy revealed severe mitochondrial disorder.

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
EAP	M	10	15mg/kg/d	Asphyxia	D18	D18	No	felbamate clobazam, rufinamide, LEV, lacosamide,	h/o highly refractory epilepsy, Trisomy 21, hypothyroidism, growth hormone deficiency, sleep apnoea (on BiPAP) and respiratory distress secondary to viral upper respiratory tract infection prior to start of CBD. Was found face down in his pillow, cyanosed and in asystole.
EAP	M	14	29 mg/kg/d	Seizure clusters	D160-D167	D167	No	On clobazam, diazepam, lacosamide.	h/o generalized severe intractable epilepsy, developmental delay, corpus collosotomy, VNS, precocious puberty, ADHD, gynecomastia, gastrostomy, tracheostomy. Previous h/o desaturation requiring hospitalization (D44). Experienced seizure clusters and was hospitalized. Intubation was refused. Developed respiratory failure due to aspiration. Parents refused antibiotics or further invasive measures. Was under a palliative care team in hospital at time of death.
				Aspiration leading to Respiratory failure	D166-D167				

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
EAP	M	11	25 mg/kg/d	Hypoxemia	D169-D171	D171	No	zonisamide, felbamate, clobazam and LEV.	h/o cerebral palsy, global developmental delay, aspiration, intractable epilepsy, asthma, pericarditis requiring pericardial drain, gastrostomy and vocal cord paralysis. Previous hospital admission for Status asthmaticus (D149-D150). Admitted to PICU day before death and then decision was made to withdraw support. Hypoxemia due to chronic respiratory disease was reported as the cause of death.
EAP	M	2	25 mg/kg/d	Respiratory failure from human pneumovirus.	D228	D233	No	ketogenic diet, vigabatrin and clobazam.	h/o intractable epilepsy and profound global developmental delay

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
				Septic shock	D228				likely due to a KCNQ2 mutation, with seizure onset from second day of life. H/O asthma exacerbation on D202. Hospitalized for septic shock which led to DIC and required inotrope support. Developed ARDS following which respiratory support was withdrawn.
EAP	F	5	12.5mg/kg/d	Respiratory Arrest	D369	D369	No	ketogenic diet, LEV, perampanel, phenytoin and zonisamide.	h/o epileptic encephalopathy, SCN8A mutation, status epilepticus, chronic respiratory insufficiency, gastrojejunostomy, chronic kidney disease, global development delay .H/O multiple admissions for respiratory failure secondary to viral infections, aspiration. Developed bradycardia and died. The primary cause of death was reported as respiratory arrest leading to cardiac arrest.

Study	Sex	Age (yrs)	Dose	Preferred Terms of Fatal AE	Day of onset of Fatal AE after starting CBD-OS	Day of death	Related	Concomitant AEDs	Notes
EAP	F	18	12.5mg/kg/d	Ohtahara syndrome with acquired epileptic encephalopathy	From birth	D547	No	phenytoin, zonisamide lacosamide and clobazam.	Cause of death reported as Ohtahara syndrome with acquired epileptic encephalopathy.
EAP	F	15	30 mg/kg/d	Convulsion (Prolonged seizure) leading to pulmonary edema	D276	D276	No	Clonazepam	h/o intractable generalized epilepsy, Angelman syndrome, developmental encephalopathy with global delays, was non-ambulatory and non-verbal. Had increased Tonic Clonic seizures in the week before death. Was found unresponsive in bed. Death certificate states cause of death as complications from prolonged seizure.
EAP	M	6	22.5mg/kg/d	Neuronal ceroid lipofuscinosis (Batten disease) Died due to progressive condition	From birth	D125	No	LEV, zonisamide and clobazam	h/o Batten's disease and recurrent pneumonia.

10.5. ALT ELEVATIONS LEADING TO DISCONTINUATION

Table 46: Patients with ALT Values ≥5×ULN in Placebo-controlled Studies of Patients with DS or LGS Resulting in Discontinuation

Study	Age (yr) Sex	VPA	CBD-OS Dose (mg/kg/day)	Day of Peak	Multiple of ULN at Peak			
					ALT	AST	ALP	Bilirubin
1423	10 F	Yes	20	31	32.6	15.4	0.6	0.5
1332B	4 F	Yes	Placebo	15	20.4	17.9	1.1	0.3
1332A	10 F	Yes	20	19	20.1[L]	8.3*[L]	0.5*	0.3*
1414	14 F	Yes	20	17	12.2	2.9	1.0*	0.3*
1423	9 M	Yes	20	102	10.0	2.6	0.6*	0.5
1423	28 M	Yes	20	31[L]	9.7[L]	7.4[L]	0.7[L]	0.4
1423	5 M	Yes	20	29	9.4	4.1	0.5*	0.2*
1414	12 M	Yes	10	29	8.3	5.6	1.2*	1.3*
1423	3 M	Yes	20	28	6.6	3.3	0.8*	0.5

*Maximum on-treatment value during study but different day than peak ALT.
L: Local laboratory result.
VPA: Patient was on concomitant VPA
Shade = Value ≤1 × ULN

10.6. ALT ELEVATIONS IN PATIENTS WHO CONTINUED TREATMENT

Table 47: Patients with ALT Values ≥5×ULN in Placebo-controlled Studies of Patients with DS or LGS who Continued Treatment

Study	Age (yr) Sex	VPA	CBD-OS Dose (mg/kg/day)	Day of Peak	Multiple of ULN at Peak (×ULN)				Entered OLE
					ALT	AST	ALP	Bilirubin	
1423	14 M	Yes	20	54	15.9	5.0	0.5	0.8	Yes
1423	8 M	No	20	29	7.9	1.7	1.1	0.3	Yes
1414	9 M	Yes	20	32	7.8	3.2	0.7	0.4	No
1423	21 M	Yes	20	77	7.4	5.5	0.8*	0.2	No
1414	10 M	Yes	20	29	7.3	4.9	0.6	0.6	Yes♦
1332A	10 F	Yes	20	22	7.1	6.1	0.9*	0.6	Yes♦
1332B	13 F	Yes	20	36	7.1L	4.9*	0.5*	0.3	Yes
1423	8 M	Yes	20	15	6.1	3.6	0.6	0.2	Yes♦
1414	24 F	Yes	20	30	6.1	2.3	1.3	0.5*	No
1423	14 F	No	20	27	5.7	1.9	0.4*	0.2	Yes
1332A	6 M	Yes	5	22	5.2	3.1	0.6*	0.3	Yes♦
1423	17 F	No	Placebo	60	5.3	2.4	0.8*	0.4	Yes
1332B	15 M	Yes	20	99	5.1	8.9	0.5*	0.5	Yes♦

VPA: Patient was on concomitant VPA
*Maximum on-treatment value during study but different day than peak ALT.
L: Local laboratory result.
♦ Also had elevation in OLE Study 1415
Shade = Value ≤1 × ULN

10.7. TRANSAMINASE ELEVATION VIGNETTES – EXAMPLES OF KEY CHARACTERISTICS

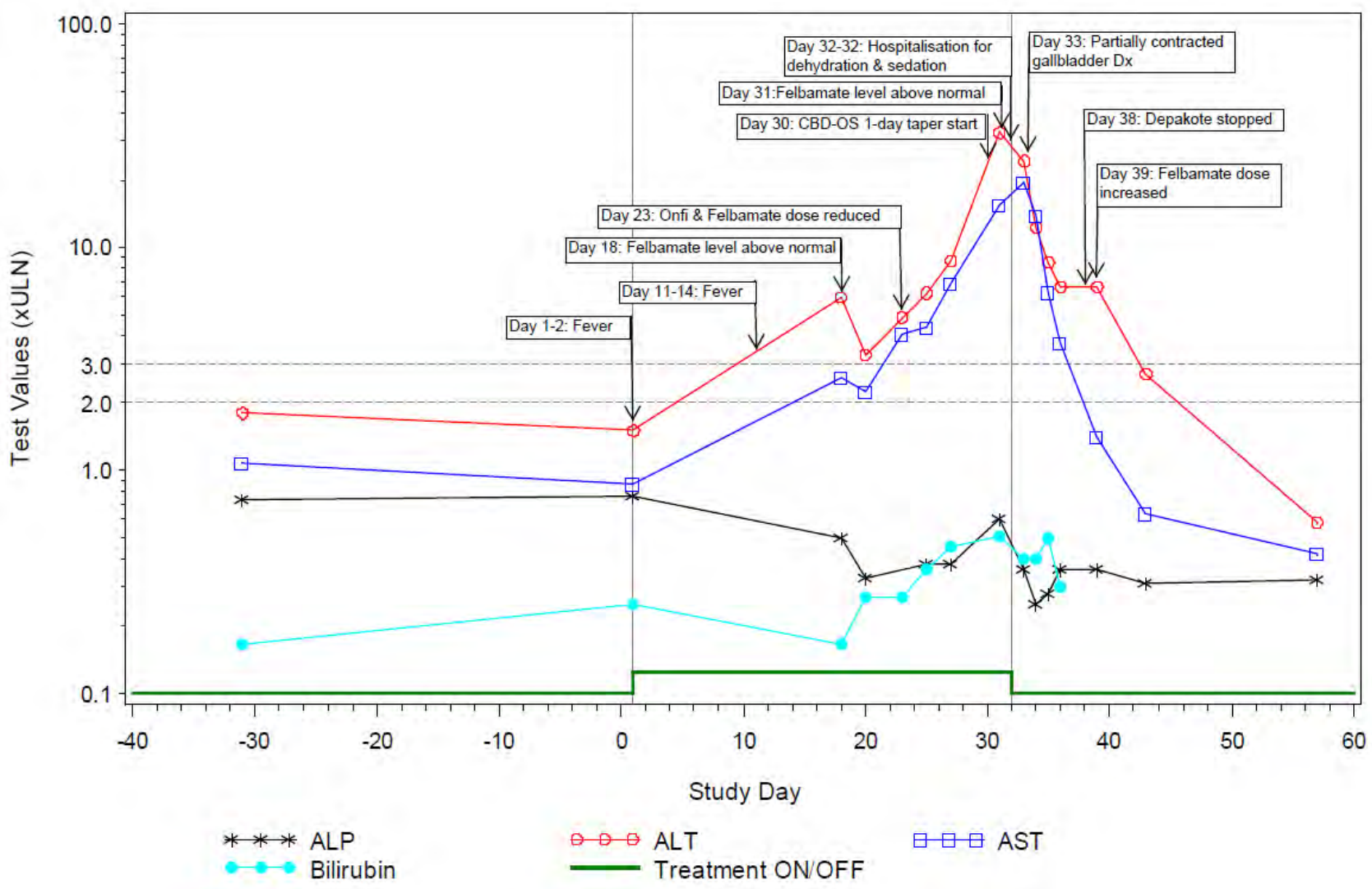
Largest transaminase elevation observed in placebo-controlled studies:

Study 1423; CBD-OS 20 mg/kg/day

SAE PT: Transaminases increased

A female patient (age range 9-11) with a history of LGS, developmental delay, elevated ammonia, tonsillectomy and adenoidectomy commenced treatment with CBD-OS, dose-titrated to 20 mg/kg/day over an 11-day period. She was receiving VPA 61.3 mg/kg/day, felbamate 73.6 mg/kg/day, LEV 81.7 mg/kg/day, clobazam 0.7 mg/kg/day and diazepam (0.4 mg/kg/PRN) concomitantly. Between day 18 and day 27, the patient experienced transaminitis with ALT ranging between 3.3×ULN and 8.7×ULN, and CBD-OS was reduced to 15 mg/kg/day due to this transaminitis (Figure 38). On day 31, a day after CBD-OS was further reduced to 5 mg/kg/day, she experienced peak elevations of ALT: 32.6×ULN and AST: 19.4×ULN and was hospitalized with concurrent sedation and dehydration. The girl stopped treatment with CBD-OS on day 32 and transaminase levels began to decrease. On day 38, VPA was discontinued and the patient recovered from the event of elevated transaminases four days later on day 43, 12 days from the peak ALT elevation. The Investigator considered the event of transaminitis to be related to CBD-OS.

Figure 38: Time Course of Liver Tests – Largest Transaminase Elevation Observed in Placebo-Controlled Studies



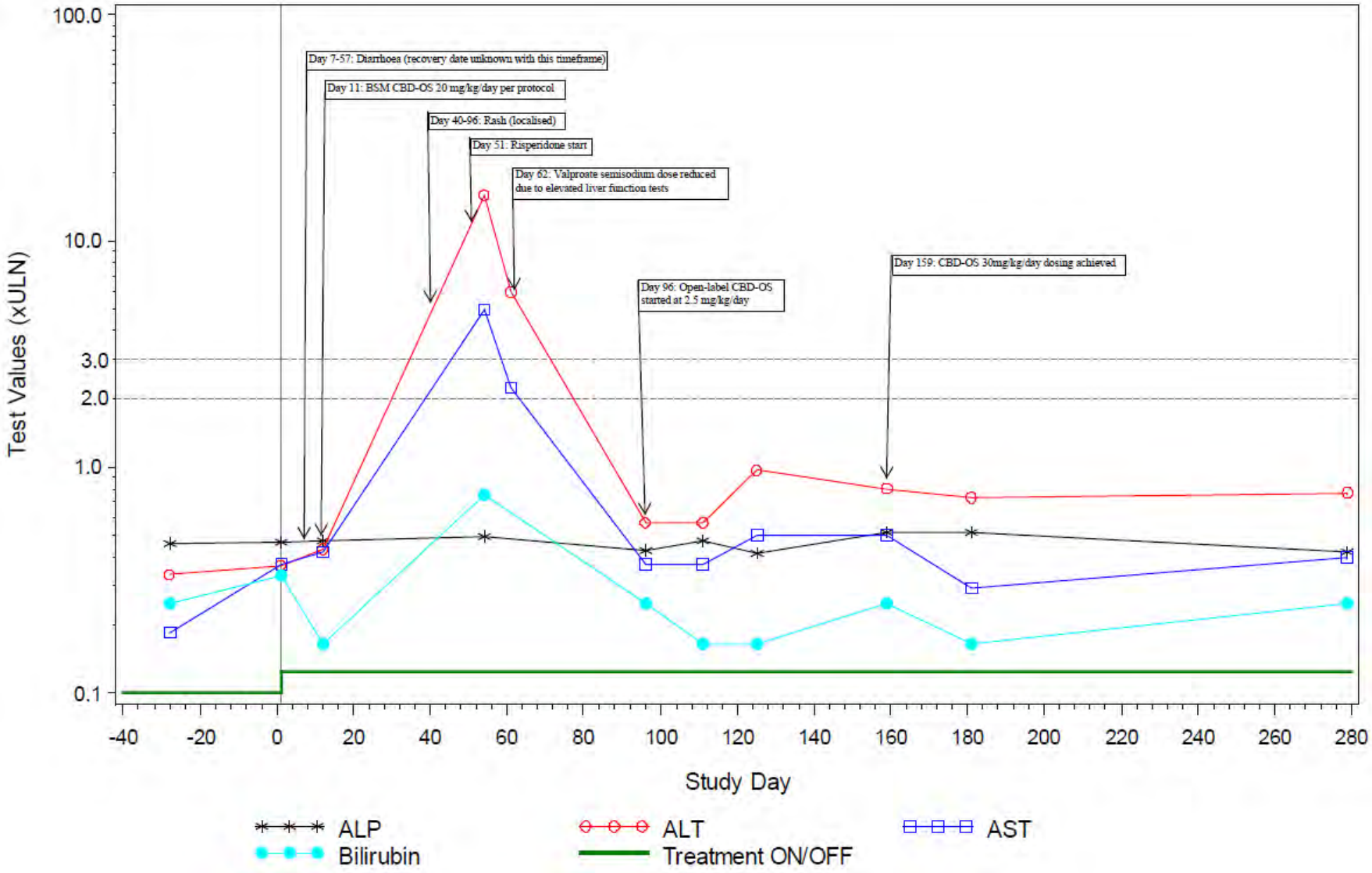
Large Transaminase Elevation – VPA was Reduced, Transaminase elevation resolved while Patient Continued CBD-OS with no change of CBD-OS Dose:

Study 1423; CBD-OS 20 mg/kg/day

PT: Alanine aminotransferase increased, Aspartate aminotransferase increased

A male patient (age range 13-15) with a history of LGS, mental retardation, autism, VNS and corpus callosotomy commenced treatment with CBD-OS, dose-titrated to 20 mg/kg/day over an 11 day period. He was receiving VPA 12.0 mg/kg/day, rufinamide 6.4 mg/kg/day, clobazam 0.3 mg/kg/day and LEV (unclear dose) concomitantly. The patient had a localized rash below the belly button between day 40 and day 96 (non-serious event). On day 54, the patient experienced elevated ALT: 15.9×ULN and AST: 5.0×ULN (Figure 39). No action was taken with CBD-OS. On day 62, 8 days after the ALT and AST elevation, VPA was reduced to 7.98 mg/kg/day due to the elevated liver function tests. On day 96, 42 days after experiencing elevated ALT and AST, the patient recovered from the events. The subject met Study 1423 withdrawal criteria (ALT >8×ULN), however the Investigator continued the subject in the study. The patient subsequently entered the OLE and had at least a cumulative 279 ongoing days of exposure to CBD-OS at the data cut-off without any subsequent transaminase elevations documented. The Investigator considered the events of elevated ALT and elevated AST to be related to CBD-OS.

Figure 39: Time Course of Liver Tests – Large Transaminase Elevation, VPA Reduced, Resolved with Continued CBD-OS



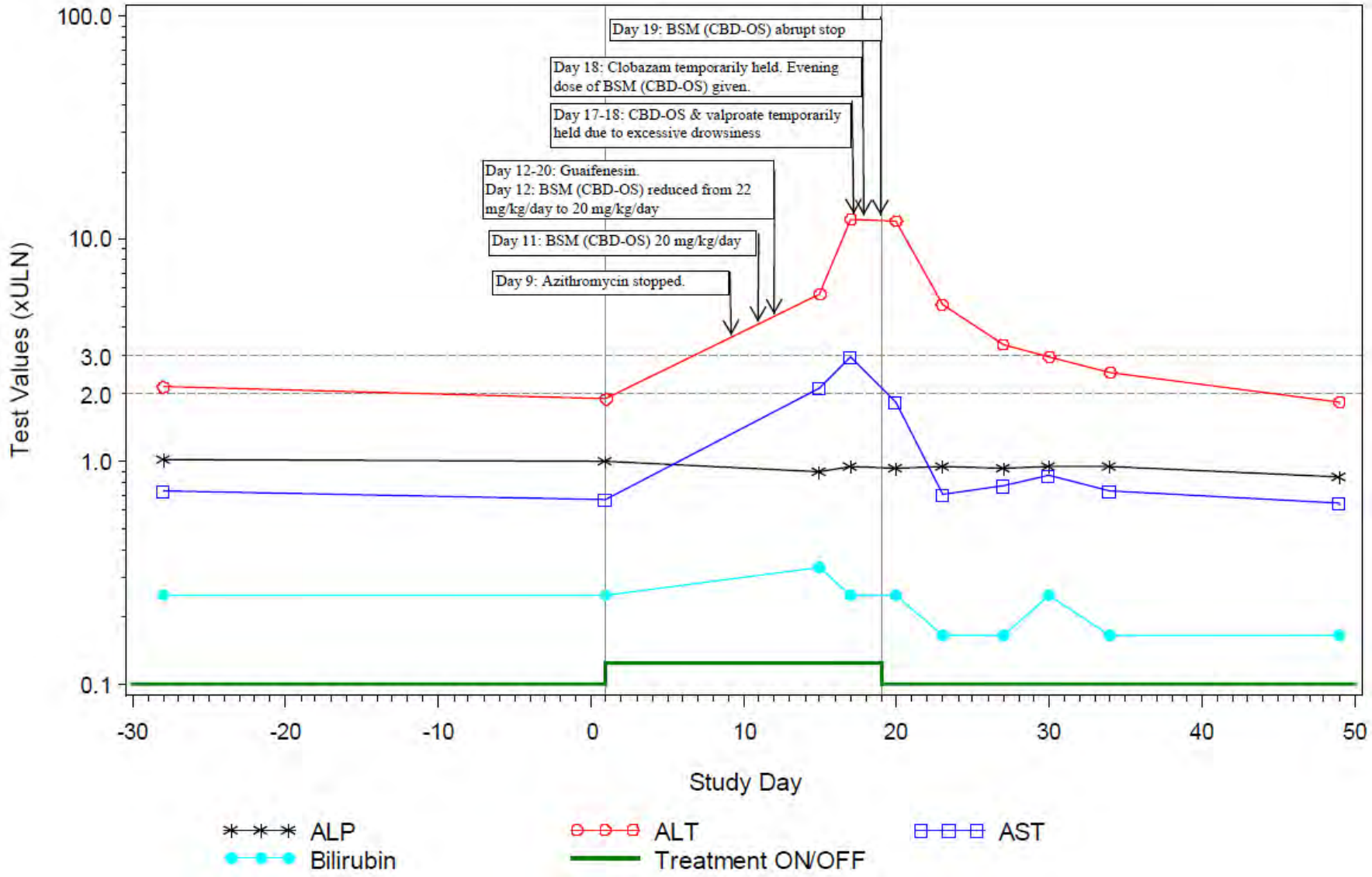
Large transaminase elevation – shows a rapid reversal after CBD-OS stopped:

Study 1414; CBD-OS 22 mg/kg/day

SAE PT: Alanine aminotransferase increased, Aspartate aminotransferase increase

A female patient (age range 13-15) with a history of gastroesophageal reflux, microcephaly, nephrocalcinosis, developmental delay, cerebellar ataxia, cerebral palsy, atypical Rett syndrome, congenital quadriplegia, dystonia, erythema (bottom lip), hip dysplasia, status epilepticus, strabismus, strabismus repair, and also non-verbal, commenced treatment with CBD-OS, dose-titrated to 20 mg/kg/day (actually achieved 22 mg/kg/day). She was receiving VPA 11.1 mg/kg/day, clobazam 0.9 mg/kg/day, zonisamide 4.4 mg/kg/day and clonazepam (22.2 μg/kg/PRN) concomitantly. The patient had been treated with azithromycin for bronchitis from day 5 to day 9. On day 15, the patient developed elevated ALT: 5.7×ULN and AST: 2.1×ULN (Figure 40). The investigator noted that there had been no recent changes to her concomitant antiepileptic drugs. Two days after the elevation, with peak ALT: 12.2×ULN, CBD-OS was temporarily discontinued and VPA temporarily held due to the events. On day 18, treatment with clobazam was also temporarily held and CBD-OS was restarted. On day 19, the girl abruptly discontinued treatment with CBD-OS due to the elevated liver enzymes, with no dose tapering period, and she withdrew from the study on the following day (day 20) with ALT: 12 ×ULN. On day 30, 13 days after experiencing the peak ALT value, the patient's ALT value recovered to <3 ×ULN. The Investigator considered the events of elevated ALT and AST to be related to CBD-OS.

Figure 40: Time Course of Liver Tests – Large Transaminase Elevation and Rapid Reversal After CBD-OS Stopped



Large transaminases elevation – with a later onset (Day 102):

Study 1423; CBD-OS 20 mg/kg

SAE PT: Alanine aminotransferase increased, Aspartate aminotransferase increased

A male patient (age range 8-10) with a history of LGS, developmental delay, vagal nerve stimulator implant, VNS generator replacement, parainfluenza virus pneumonia, influenza A, acute otitis media, leukocytosis, pneumonia, breakthrough seizure, asthma, reactive airway disease, aspiration of liquid, fall, and ADHD, commenced treatment with CBD-OS, dose-titrated to 20 mg/kg/day over an 11 day period. He was receiving VPA 7.55 mg/kg/day, lisdexamfetamine 0.6 mg/kg/day, clobazam 1.2 mg/kg/day, felbamate 84.6 mg/kg/day and diazepam (0.3 mg/kg/PRN) concomitantly. The doses of CBD-OS remain unchanged throughout the blinded study. On day 102, when the patient completed CBD-OS and commenced treatment with open-label study medication CBD-OS 2.5 mg/kg/day, he experienced elevated ALT: 10.0×ULN and AST: 2.6×ULN (Figure 41). On day 104, the boy abruptly discontinued open-label CBD-OS with no dose tapering period. On day 119, 17 days after experiencing the peak elevated ALT and AST, the boy recovered from the events. The Investigator considered the events of elevated ALT and AST to be related to CBD-OS.

Figure 41: Time Course of Liver Tests – Large Transaminase Elevation With Later Onset