CENTER FOR DRUG EVALUATION AND RESEARCH

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CLINICAL REVIEW(S)

COMBINED CLINICAL AND STATISTICAL REVIEW

Application Type	NDA
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Reviewer Name(s)	Natalie Getzoff, MD and Xiang Ling, PhD
Review Completion Date	6/14/2018
Established/Proper Name	Cannabidiol
(Proposed) Trade Name	Epidiolex
Applicant	GW Pharmaceuticals PLC
Dosage Form(s)	Oral solution
Applicant Proposed Dosing Regimen(s)	(b) (4) to 20 mg/kg/day (divided BID)
Applicant Proposed Indication(s)/Population(s)	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBD	cannabidiol
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLB	clobazam
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DEE	developmental and/or epileptic encephalopathy
DMC	data monitoring committee
DNP	Division of Neurology Products
DS	Dravet syndrome
DSMC	Data Safety Monitoring Committee
ECG	electrocardiogram
eCTD	electronic common technical document
EEG	electroencephalogram
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization

IND	Investigational New Drug Application
INR	international normalized ratio
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
IVRS	Interactive voice response system
LGS	Lennox-Gastaut syndrome
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
nCLB	norclobazam
NDA	new drug application
NME	new molecular entity
OCP	Office of Clinical Pharmacology
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
STP	stiripentol
SUDEP	sudden unexpected death in epilepsy patients
TEAE	treatment emergent adverse event
VPA	valproic acid or valproate

1. Executive Summary

1.1. Product Introduction

The applicant is planning to market cannabidiol (proposed proprietary name Epidiolex) in the United States (US). Cannabidiol (investigational name GWP43003-P) is a cannabinoid prepared from the *Cannabis sativa* L. plant and is a new molecular entity, which is structurally unrelated to currently marketed antiepileptic drugs (AEDs). Although the mechanism of action remains unclear and may depend on multiple factors, it is theorized that cannabidiol modulates adenosine and intracellular calcium, potentially reducing excitability of certain neurons.

Cannabidiol (CBD) is essentially insoluble in water; (b) (4) . Sesame oil was selected (b) (4) . Sucralose (b) (4) and strawberry flavor were added (b) (4) .

The applicant's proposed indication for CBD (Epidiolex) is "adjunctive treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome in patients 2 years of age and older". However, the Division of Neurology Products (DNP) considers adjunctive administration a condition of use, rather than an aspect of the indication. For that reason, adjunctive dosing will be identified in the dosage and administration section, but not the indication statement.

The applicant proposes initiation of dosing for both indications at 5 mg/kg/day and increased weekly by 5 mg/kg to a maintenance dose of 10-20 mg/kg/day. The maximum recommended dose is 20 mg/kg/day. All doses and dose increases are to be divided BID. It is intended only for oral administration and will be marketed as an oral solution (100mg/ml).

1.2. Conclusions on the Substantial Evidence of Effectiveness

The applicant has provided substantial evidence of effectiveness to support approval. The applicant provided data from three adequate and well controlled studies that demonstrated that cannabidiol, as compared to placebo, reduces the frequency of drop seizures in patients with Lennox-Gastaut syndrome and convulsive seizures in patients with Dravet. The applicant showed this effect for both doses (10 and 20 mg/kg/day in Lennox-Gastaut syndrome and 20 mg in Dravet syndrome). The primary endpoint was statistically significant for all three studies. Key secondary endpoints were statistically significant consistently in the Lennox-Gastaut syndrome studies and numerically favored cannabidiol in the Dravet syndrome study. The treatment effect observed in these trials was comparable to what has been accepted in other FDA approved drugs for Lennox-Gastaut syndrome.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Cannabidiol is a cannabinoid prepared from the *Cannabis sativa* L. plant and is structurally unrelated to currently marketed antiepileptic drugs. It is indicated for the treatment of seizures in patients with Dravet syndrome or Lennox-Gastaut syndrome. Cannabidiol is an oral solution given twice daily by mouth.

Dravet syndrome and Lennox-Gastaut syndrome are severe epilepsy syndromes presenting early in childhood and are both associated with multiple seizure types that are frequent and resistant to medications and other treatments and developmental delay due in part to the seizures. While uncommon, patients with either of these epilepsy syndromes have increased risk of prolonged seizures (and status epilepticus) and higher mortality compared to the general pediatric population with epilepsy. Patients with Dravet syndrome or Lennox-Gastaut syndrome are almost always significantly disabled by their seizures and cognitive impairment. There are no approved seizure treatments for patients with Dravet syndrome. The drugs approved for treatment of seizures in patients with Lennox-Gastaut syndrome are only moderately effective and many have significant side effects.

The efficacy of cannabidiol was demonstrated in three randomized clinical trials. Two trials were conducted in patients with Lennox-Gastaut syndrome and one trial was conducted in patients with Dravet syndrome. There is evidence of clinical benefit based on reduction of monthly drop seizure frequency in patients with Lennox-Gastaut syndrome and reduction of monthly convulsive seizure frequency in patients with Dravet syndrome. Other outcome measures were supportive.

Cannabidiol at 10 mg/kg/day and 20 mg/kg/day demonstrated reduction in drop seizures as compared to placebo in the two Lennox-Gastaut syndrome trials and at 20 mg/kg/day in the Dravet syndrome trial. In the Lennox-Gastaut syndrome trials, patients had median baseline seizure frequency ranging from 71 to 87 drop seizures/month. Lennox-Gastaut patients in the cannabidiol groups had 37, 42, and 44% reduction in monthly drop seizure frequency, compared to 17 and 22% in the placebo groups. Additionally, patients in the cannabidiol groups in the Lennox-Gastaut syndrome trials had greater reductions in total seizure frequency and impression of improvement based upon a patient/caregiver assessment. A greater proportion of patients in the cannabidiol groups were considered responders (50% reduction in seizure frequency).

In the Dravet syndrome trial, patients had median baseline monthly convulsive seizure frequencies of 15 and 12 in the cannabidiol and placebo groups, respectively. Dravet patients in the cannabidiol group had a 39% reduction in monthly convulsive seizure frequency, compared to 13%

in the placebo group. Although Dravet patients in the cannabidiol group were twice as likely to be responders than patients in the placebo group, the difference between groups was not statistically significant.

These are all clinically relevant benefits that would justify a low to moderate safety risk. Based on the safety reviews, the risk does appear to be moderate and manageable.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	Lennox-Gastaut Syndrome • Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy which presents during childhood. It is characterized by a triad of electro-clinical findings: multiple refractory seizure types, developmental delay and an interictal EEG pattern of diffuse, slow spike-wave complexes. LGS is a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities. • Onset of LGS typically occurs between ages 3 and 5 years. Some patients (20-60%) have evidence of delayed intellectual development at the time of diagnosis, and severity of patients' cognitive and behavior impairments vary from minimally affected (rare) to profoundly impaired. • Drop attacks are the most disabling of the seizure types (seen in >50% of LGS patients). A drop attack is a seizure that leads to a fall or would have caused a fall, thus frequently leading to injury. Nonconvulsive status epilepticus is seen in 50-70% of patients. Seizure freedom is essentially never seen in patients with LGS, regardless of AED or other epilepsy treatments.	Lennox-Gastaut Syndrome Lennox-Gastaut syndrome is a severe epilepsy syndrome beginning in early childhood that is associated with refractory seizures and cognitive impairment. Patients with LGS are at risk for serious injury caused by drop seizures. Patients almost never achieve seizure freedom, even when multiple treatments are used and almost all patients exhibit lifelong cognitive impairment. Mortality is higher in patients with LGS than the general population or the overall population with epilepsy, and seizures and seizure-related events are frequent causes of death in these patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Children and adolescents with LGS have a higher mortality rate, with an up to 14 times increased risk of death during childhood and adolescence. Common reported proximate causes of death in patients with LGS are SUDEP, status epilepticus, or seizures. <u>Dravet Syndrome</u> • Dravet syndrome (DS) is a severe form of childhood epilepsy which is characterized by early onset of refractory seizures of multiple types, frequent episodes of status epilepticus, and developmental arrest or regression. Patients typically present prior to 2 years of age with a variety of disabling seizure types and developmental delay. The cognitive impairment is considered to be, at least in part, caused by the seizures. Although the diagnosis of DS is made by clinical criteria, most (80%) of patients with DS have mutations in the SCN1A gene, but the individual mutations vary widely. • Seizures in patients with DS are generally refractory to antiepileptic drugs (AEDs). Seizure-freedom almost never occurs, but many patients experience fewer seizures in late adolescence and adulthood. • Sudden unexplained death in epilepsy (SUDEP) and status epilepticus are more common in patients with DS than most other childhood epilepsy syndromes, and DS patients' increased mortality compared to the general population is, in part, due to these seizure-related events.	<u>Dravet Syndrome</u> Dravet syndrome is a severe epilepsy syndrome beginning in infancy that is associated with significant morbidity due to refractory seizures and cognitive impairment. Even with treatment of the seizures, cognitive impairment persists and is lifelong. Mortality is higher in pediatric patients with DS than the general pediatric population or the overall population with epilepsy. Seizures and seizure-related events are frequent causes of death.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	Lennox-Gastaut Syndrome • The primary objective of treatment of seizures in patients with LGS is reduction in frequency of the most incapacitating and injurious seizures (e.g., drop attacks and tonic-clonic seizures). • Six drugs are approved by FDA for reduction of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam. Many other drugs are used to treat seizures in patients with LGS, especially valproic acid (which is generally considered a first-line agent) and levetiracetam. Seizures in LGS are generally resistant to AEDs (even when used as polytherapy) and complete seizure control with resolution of intellectual and psychosocial dysfunction is almost never achieved. • Severe adverse drug reactions are reported for many of the approved and/or frequently used drugs to treat seizures in LGS, such as hepatic failure (felbamate, lamotrigine, and valproic acid), serious skin reactions (lamotrigine, clobazam, rufinamide), and hematologic abnormalities (felbamate, lamotrigine, topiramate, rufinamide). • A recent review of pharmacological therapies used to treat seizures in patients with LGS noted "optimum treatment for LGS remains uncertain and no study to date has shown any one drug to be highly efficacious..." and ..." and "clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects."	Lennox-Gastaut Syndrome Five drugs have been shown in controlled clinical trials to reduce drop attacks and/or tonic-clonic seizures in patients with LGS. Other drugs are used off-label. Yet even when taking multiple AEDs, most patients still have frequent seizures. No AEDs have been shown to alter the cognitive impairment in patients with LGS. Severe adverse drug effects have been reported with all of the approved drugs and must be taken into account when choosing an AED treatment, especially in children and adolescents. The treatment armamentarium in LGS would benefit from therapeutic options that are more efficacious, and are better tolerated. A drug that is better tolerated may improve compliance.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	Dravet Syndrome • There are no approved treatments of seizures in patients with DS in the US, and all drug treatments are off-label with varying degrees of effectiveness. The most commonly used AEDs in the treatment of seizures are clobazam and valproic acid. There are no well-controlled data to support efficacy of either of these drugs in the treatment of seizures in DS patients. Stiripentol is approved in Europe and Japan in conjunction with valproic acid and clobazam for treatment of seizures in patient with DS, based on some small controlled trials. The ketogenic diet may be helpful and is typically used as an adjunct to pharmacologic treatment(s).	Dravet Syndrome There are no approved treatments of seizures in patients with DS in the US, thus a significant unmet medical need exists.
Benefit	Lennox-Gastaut Syndrome • There are two pivotal trials that demonstrate the efficacy of cannabidiol given orally in patients with LGS. Both of the studies demonstrate the efficacy of the 20 mg/kg/day dose and one study demonstrates the efficacy of the 10 mg/kg/day dose. The primary endpoint in both studies is the percentage reduction in drop seizure frequency from baseline to treatment period as compared to placebo. In study 1414, cannabidiol reduced the median seizure frequency by 41.9 in the 20 mg/kg group, 37.2 in the 10 mg/kg/day group, as compared to 17.2 in the placebo group placebo. In Study 1423, CBD reduced the median percentage seizure frequency from baseline to treatment period by 43.9 in the CBD group and 21.8 in the placebo group. The findings of the primary endpoint were statistically significant for all CBD groups tested (p=0.0016 and p=0.0047, respectively, in the 10 and 20 mg/kg/day groups in Study 1414 and p=0.0135 in the 20 mg/kg/day in Study 1423).	Lennox-Gastaut Syndrome Cannabidiol 10 mg/kg/day and 20 mg/kg/day were both found to be effective in reducing drop seizure frequency in patients with Lennox-Gastaut syndrome. The treatment effect was robust statistically and clinically meaningful. Fewer drop seizures in these patients may lead to fewer injuries and days of disability. The benefit of treatment with cannabidiol on seizures in patients with Lennox-Gastaut syndrome is persuasive, justifies the modest and manageable risk (see safety reviews) and justifies approval.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Three key secondary endpoints were statistically significant for all CBD dose groups in Study 1414 and achieved nominal significance in Study 1423 and were consistent with the findings of the primary endpoint. These key secondary endpoints assessed the proportion of patients who were 50% responders, the percentage change in total seizure frequency from baseline to treatment period and the Subject/Caregiver Global Impression of Change. Dravet Syndrome • There is one pivotal trial that demonstrates the efficacy of cannabidiol 20 mg/kg/day given orally in patients with DS. The primary endpoint is the percentage reduction in convulsive seizure frequency from baseline to treatment period as compared to placebo. In patients with DS, CBD reduced the median percentage seizure frequency from baseline to treatment period by 38.9 in the CBD group and 13.3 in the placebo group. This result was statistically significant (p=0.0123). • DS patients in the CBD group were numerically superior to placebo in the key secondary efficacy endpoint. The proportion of 50% responders was greater in the CBD group (42.6%), compared with the placebo group (27.1%) with an OR=2.0 (nominal p=0.0784).	Dravet Syndrome Cannabidiol 20 mg/kg/day was found to be effective in reducing convulsive seizure frequency in patients with Dravet syndrome. The treatment effect was robust statistically and clinically meaningful. Fewer drop seizures in these patients may lead to fewer injuries and days of disability. The benefit of treatment with cannabidiol on seizures in patients with Dravet syndrome is persuasive and justifies approval.
Risk and Risk Management	• See the safety review by Dr. Unger	

1.4. Patient Experience Data

The primary endpoint for all three pivotal trials is based on seizure counts, which were recorded by patients and/or caregivers in a diary and reported to the applicant. Additional patient and/or caregiver reported outcome measures in the trials included measures of quality of life and global impression of change.

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:			
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	See Sections 6.1, 6.2, and 6.3 Study endpoints
		X	Observer reported outcome (ObsRO)	See Sections 6.1, 6.2, and 6.3 Study endpoints

2. Therapeutic Context

2.1. Analysis of Condition

The applicant proposes two indications for this application: adjunctive treatment of seizures in patients ≥ 2 years of age with Dravet syndrome or Lennox-Gastaut syndrome. While these disorders have some clinical similarities, they are sufficiently different that they will be discussed separately in sections 2.1 and 2.2.

Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy which presents during childhood. An epileptic encephalopathy and electroclinical syndrome with a childhood onset, diffuse slow spike-wave complexes, and several types of seizures was first described by Lennox and Davis in 1950[1], and the syndrome was further defined by Gastaut et al in 1966[2]. It is characterized by a triad of electro-clinical findings: multiple refractory seizure types, developmental delay and an

[1] Arzimanoglou A, French J, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009; 8: 82–93

[2] Gastaut H, Roger J, et al. Childhood epileptic encephalopathy with diffuse slow spike-waves (otherwise known as "petit mal variant") or Lennox syndrome. Epilepsia. 1966 Jun;7(2):139-79.

interictal EEG pattern of diffuse, slow spike-wave complexes[3,4]. LGS is considered a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities[5].

The etiology of LGS is often divided into two groups: recognizable (primarily genetic or structural) or unknown. Etiologies can be identified in 60-75% of patients and include a wide variety of causes, such as hypoxic-ischemic insults (most common), tuberous sclerosis complex, brain malformations, and traumatic brain injuries[1,5,6]. Seizures associated with LGS might occur de novo or might follow severe infantile seizure disorders, such as infantile spasms. A variety of genetic anomalies have been reported in patients with the diagnosis of LGS, including variants or mutations in the SCN1A, FOXG1, DNM1, and CHD2 genes.

LGS has been estimated to account for 1-10% of childhood epilepsies; this wide range is likely due to the potential for clinicians to identify many young pediatric patients with multiple seizure types and developmental delay as having LGS. Trevathan et. al. assessed the epidemiology of patients with LGS using data captured in study of pediatric patients with developmental disabilities. The authors found the prevalence of epilepsy to be 6 per 1,000 children, with 4% of those patients classified as LGS[7]. In their evaluation, LGS was defined as onset of multiple seizure types prior to age 11 years and an EEG with slow spike-wave complexes (<2.5 Hz) but developmental delay was not used as a diagnostic criterion. Children and adolescents with LGS have a higher mortality rate than the age-matched cohorts, with an up to 14 times increased risk of death during childhood and adolescence[8]. Common reported proximate causes of death in patients with LGS are SUDEP, status epilepticus, or seizures[8].

Onset of LGS typically occurs before 8 years of age, with peak presentation occurring between ages 3 and 5 years[1,5]. Because all clinical and EEG features may not be present at onset of the disorder, the diagnosis of LGS may be delayed. LGS is an electroclinical syndrome characterized by a triad of findings: multiple seizure types, developmental delay, and an interictal EEG pattern of diffuse, slow spike-wave complexes. Some patients (20-60%)[1] have evidence of delayed intellectual development at the time of diagnosis, especially those who present later. Cognitive impairment becomes more obvious over time, with intellectual dysfunction in 75-95% of

[3] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for Revised Classification of Epilepsies and Epileptic Syndromes. Epilepsia. 30(4):38%399, 1989
[4] Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2013 Feb 28;(2):
[5] Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. Epilepsia, 52(Suppl. 5):3–9, 2011
[6] Asadi-Pooya AA. Lennox-Gastaut syndrome: a comprehensive review. Neurol Sci. 2017 Nov 9.
[7] Trevathan E, Murphy CC, Yeargin-Allsopp M. (1997) Prevalence and descriptive epidemiology of Lennox-Gastaut syndrome among Atlanta children. Epilepsia (1997)38:1283–1288.
[8] Autry AR, Trevathan E, et al. Increased Risk of Death Among Children With Lennox-Gastaut Syndrome and Infantile Spasms. J Child Neuro 25(4) 441-447

patients within 5 years of initial diagnosis[9]. Severity of patients' cognitive and behavior impairments vary from minimally affected (rare) to profoundly impaired.

Tonic seizures are the most characteristic type of seizure in LGS and are characterized by "a sustained increase in muscle contraction lasting a few seconds to minutes"[10]. Tonic seizures may range in severity from a brief flexion of the head and trunk to affecting muscles of the trunk and extremities leading to falls and injuries. Atypical absence seizures are also frequently seen in patients with LGS and present with a brief loss or impairment of consciousness (without the typical EEG pattern of 3 per second spike-wave activity)[5]. Drop attacks occur in more than 50% of patients with LGS and are the most disabling of the seizure types[1]. The most basic definition of a drop attack is a seizure that leads to a fall or would have caused a fall. In patients with LGS, drop attacks are often but not always preceded by a myoclonic jerk but occur too quickly for intervention, thus frequently leading to injury. Other seizure types seen in patients with LGS include non-convulsive status epilepticus in 50-70% of patients[1], myoclonic seizures, focal seizures with or without secondary generalization, generalized tonic-clonic seizures, and hemiclonic seizures.

The hallmark EEG feature in LGS is slow (2.5 Hz) spike-and-wave bursts with abnormal background activity[3,4,10]. Not all waves are preceded by a spike, and the bursts may be remarkably irregular without a clear onset and offset. Distinction between ictal and interictal discharges is often difficult; however, clinically apparent atypical absence seizures almost always have an associated slow spike-wave burst. Bursts of generalized fast polyspikes (10–20 Hz), especially during sleep, also define the EEG profile of the LGS.

Dravet syndrome

Dravet syndrome (DS), previously known as severe myoclonic epilepsy of infancy, is a developmental and/or epileptic encephalopathy (DEE), as defined by the International League Against Epilepsy (ILAE)[11]. Clinically, it is characterized by refractory seizures of multiple types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression[12,13]. The syndrome typically presents prior to 1 year of age as frequent febrile seizures[14], and patients then develop hemi-clonic, bilateral clonic, and/or generalized tonic-

[9] Hancock EC, Cross HJ. (2009) Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev 2013 Feb 28; (2):CD003277.
[10] Blume WT, Luders HO, Mizrahi E, et al. ILAE Commission Report. Glossary of descriptive terminology for ictal semiology: report of the ILAE task force on classification and terminology. Epilepsia 2001; 42: 1212–18.
[11] Scheffer IE, Berkovic S, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr;58(4):512-521
[12] Brunklaus A, Zuberi S. Dravet syndrome—From epileptic encephalopathy to channelopathy. Epilepsia, 55(7):979–984, 2014
[13] Dravet C. Dravet syndrome history. Dev Med Child Neurol. 2011 Apr;53 Suppl 2:1-6.
[14] Wang JW, Shi XY, et al. Prevalence of SCN1A mutations in children with suspected Dravet syndrome and intractable childhood epilepsy. Epilepsy Res. 2012 Dec;102(3):195-200.

clonic seizures before age 2 years[13,15,16]. Other seizure types exhibited by patients with DS include clonic, tonic, atonic, absence, and/or focal seizures. Patients typically present with developmental delay by age 2 years[13,15]. Other neurologic findings include ataxia, pyramidal signs, and interictal myoclonus. Brain imaging is generally normal or non-specific.

As the patient ages, the course of the disease changes. The seizures in patients with DS evolve over time, beginning with a period of seizures of variable frequency related to fever in the first year, seizures increasing in frequency and types from ages 1 to 5 years (a "catastrophic phase"), and stabilization of seizures after age 5 years[16]. Mortality during childhood and adolescence in patients with DS is about 15% (5-20%), primarily due to status epilepticus in the early years and sudden unexpected death in epilepsy patients (SUDEP) in adolescence and adulthood[17,18]. SUDEP rates in the DS population as a whole (9.32/1000 person-years) are notably greater than in the epilepsy population at-large (1.5-5.1/1000 person-years)[18]. Other causes of death are usually indirectly related to the consequences of seizure, especially status epilepticus, and include drowning and traumatic injuries[19]. Seizure-freedom almost never occurs, but most seizures do become less frequent. Some types of seizures (myoclonic and absence) may remit during childhood[17,19].

The syndrome is relatively rare, occurring in less than 1 per 40,000 live births in the United States[20]. Dravet syndrome accounts for less than 2% of epilepsy in children less than 15 years old[21]. A majority (70-80%) of patients with the clinical syndrome have a mutation in the sodium channel (SCN1A)[12,22,23].

Although treatment of seizures in some patients with DEEs may lead to improved cognition, seizures in patient with DS are generally refractory to antiepileptic drugs (AEDs). Some sodium channel blocking AEDs (carbamazepine, oxcarbazepine, lamotrigine, vigabatrin and phenytoin) and GABA re-uptake or GABA enzyme inhibitors (vigabatrin and tiagabine) may exacerbate the

[15] Dravet C, Bureau M, Oguni H, et al. Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (Eds) Epileptic syndromes in infancy, childhood and adolescence. London: John Libbey, 2005:89–113.
[16] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52 Suppl 2:3-9.
[17] Akiyama M, Kobayashi K, et al. A long-term follow-up study of Dravet syndrome up to adulthood. Epilepsia 2010;51(6):1043-1052
[18] Cooper MS, Mcintosh A, et al. Mortality in Dravet syndrome. Epilepsy Res. 2016 Dec;128:43-47.
[19] Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia 2011;52 Suppl 2:44-49.
[20] Hurst DL. Epidemiology of severe myoclonic epilepsy of infancy. Epilepsia 1990;31(4):397-400.
[21] Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. Epilepsy in children in Navarre, Spain: epileptic seizure types and epileptic syndromes. J Child Neurol 2007;22(7):823-828
[22] Claes L, Del-Favero J, et al. De novo mutations in the sodium-channel gene SCN1A cause severe myoclonic epilepsy of infancy. Am J Hum Genet 2001;68(6):1327-1332
[23] Depienne C, Trouillard O, et al. Spectrum of SCN1A gene mutations associated with Dravet syndrome: analysis of 333 patients. J Med Genet 2009;46:183–191

seizures and are generally avoided[24,25].

2.2. Analysis of Current Treatment Options

Lennox-Gastaut Syndrome

Seizures in LGS are usually resistant to AEDs and complete seizure control with resolution of intellectual and psychosocial dysfunction is almost never achieved. The primary objective of treatment of seizures in patients with LGS is reduction in frequency of the most incapacitating and injurious seizures (e.g., drop attacks and tonic-clonic seizures)[26].

Six drugs are approved by the US Food and Drug Administration (FDA) for reduction of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam (see Table 1). Clobazam, felbamate, lamotrigine, rufinamide, and topiramate were studied in patients with LGS in randomized controlled trials. A decrease in the frequency of all seizures was found for patients taking lamotrigine compared with placebo (–32% vs –9%; p=0.02)[27] and felbamate compared with placebo (–19% vs +4%; p=0.002)[28]. In controlled clinical trials, the frequency of drop attacks decreased significantly with adjunctive use of lamotrigine[27], topiramate[29], or clobazam[30]. valproic acid, although not approved for use in patients with LGS, is considered a first line treatment, along with lamotrigine and topiramate. Non-pharmacologic treatments for patients with LGS include corpus callosotomy as palliative treatment for intractable drop attacks[1], vagus nerve stimulation[1,31], and ketogenic diet[31].

In 2013, Hancock and Cross conducted a review of pharmacologic therapies used to treat LGS in terms of control of seizures and adverse effects[9]. They searched various databases (Cochrane Epilepsy Group, MEDLINE, EMBASE) for randomized controlled trials (RCTs) of drug treatment in patients with LGS, identifying 9 RCTs. In their analysis, the authors note that they were unable

[24] Guerrini R, Dravet C, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998;39(5):508-12.
[25] Brunklaus A, Ellis R, et al. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135:2329–2336
[26] Michoulas A, Farrell K (2010) Medical management of Lennox-Gastaut syndrome. CNS Drugs 24(5):363–374
[27] Motte J, Trevathan E, Arvidsson JF, et al. Lamotrigine for generalized seizures associated with Lennox-Gastaut Syndrome. N Engl J Med 1997; 337: 1807–12
[28] The Felbamate Study Group in Lennox-Gastaut Syndrome. Efficacy of felbamate in childhood epileptic encephalopathy (Lennox-Gastaut syndrome). N Engl J Med 1993; 328: 29–33.
[29] Sachdeo RC, Glauser TA, Ritter F, et al. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Neurology 1999; 52: 1882–87.
[30] Ng YT, Conry JA, Drummond R, et al. Randomized, phase III study results of clobazam in Lennox-Gastaut syndrome. Neurology. 2011 Oct 11;77(15):1473-81.
[31] Freeman JM, Vining EP. Seizures decrease rapidly after fasting: preliminary studies with the ketogenic diet. Arch Pediatr Adoles Med 1999; 53: 946–49.

to perform meta-analyses or comparative analyses, "because each trial looked at different populations, different therapies and considered different outcomes." They concluded that "The optimum treatment for LGS remains uncertain and no study to date has shown any one drug to be highly efficacious…" and "clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects."

Dravet Syndrome

There are no approved treatments of seizures in patients with DS in the US, thus a significant unmet medical need exists. All drug treatments are off-label with varying degrees of effectiveness. The most commonly used AEDs in the treatment of seizures are clobazam (CLB) and valproic acid (VPA). Adjunctive treatment with VPA and/or CLB results in a 50% reduction in seizures in about 25% of patients[32,33]. In an open-label study of adjunctive valproic acid and clobazam therapy in patients with DS, 1/24 and 2/16 patients treated with VPA or CLB respectively were seizure free for a 12-week trial period[33]. In a randomized placebo-controlled trial, Chiron et al. found that in the second month of a 2-month double-blind trial period, 5% of placebo treated patients had a 50% or greater reduction in seizures compared to 71% of stiripentol (STP) treated patients and no placebo treated patient was seizure free compared to 43% of those treated with stiripentol[34]. The ketogenic diet may be helpful[35] and is typically used as an adjunct to pharmacologic treatment(s).

[32] Inoue Y, Ohtsuka Y, et al. Stiripentol open study in Japanese patients with Dravet syndrome. Epilepsia 2009;50(11):2362-2368.
[33] Inoue Y, Ohtsuka Y. Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence. Epilepsy Res 2014;108(4):725-731.
[34] Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. STICLO study group. Lancet 2000;356(9242):1638-1642.
[35] Caraballo RH, Cersosimo RO, et al. Ketogenic diet in patients with Dravet syndrome. Epilepsia 2005;46(9):1539-1544.

Table 1: Summary of Treatments of Seizures in Patients with Dravet Syndrome or Lennox-Gastaut Syndrome

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FDA Approved Treatments for Lennox Gastaut Syndrome						
Clobazam	Adjunctive treatment of seizures associated with LGS in patients ≥ 2 years of age	2011	Patients ≤30 kg: 5-20 mg PO daily (divided BID) Patients >30 kg: 20-40 mg/day PO (divided BID)	Statistically significant reduction in mean percent reduction from baseline in weekly drop seizure frequency: Low dose: p<0.05 Med dose: (p<0.01) High dose: (p<0.01)	Somnolence/sedation, withdrawal symptoms, skin reactions (Stevens-Johnson Syndrome [SJS], toxic epidermal necrolysis [TEN])	
Rufinamide	adjunctive treatment of seizures associated with LGS in pediatric patients 1 year of age and older, and in adults	2008	45 mg/kg per day, divided BID, maximum 3200 mg per day	• Median percent change in total seizure frequency per 28 days (p=0.0015) • Median percent change in tonic-atonic seizure frequency per 28 days (p<0.0001) • Improvement in Seizure Severity Rating from Global Evaluation (p=0.0041)	Shortening of the QT interval (unknown clinical risk) Somnolence or fatigue, and coordination abnormalities, dizziness, gait disturbances, and ataxia Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Leukopenia	

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Lamotrigine	adjunctive therapy for generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older:	Initial: 1994 LGS: 1998	> 12 years: 100-500 mg divided BID (depending on concomitant AEDs esp., VPA) ≤12 years: 1-15 mg/kg/day, divided BID depending on concomitant AEDs (esp. VPA)	• Median percentage reduction from baseline in major motor seizures ($p<0.05$) • Drop attacks and tonic-clonic seizures were "significantly reduced" by lamotrigine	Serious skin rashes (including SJS), greater in pediatric than adult patients DRESS Hepatic failure Blood dyscrasias: neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia Aseptic meningitis SUDEP and status epilepticus	
Topiramate	adjunctive therapy for patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome	Initial: 1996 LGS: 2001	Adults: 200-400 mg/day PO divided BID Pediatrics: 5 to 9 mg/kg/day PO divided BID	• Median percent reduction in drop attacks ($p<0.05$) • Parental global rating of seizure severity ($p<0.05$)	Acute Myopia and Secondary Angle Closure Glaucoma; Visual Field Defects; Metabolic Acidosis; Cognitive-related dysfunction; depression or mood problems; Fetal anomalies (cleft lip and/or cleft palate and small for gestational age); hyperammonemia with or without encephalopathy; nephrolithiasis;	
Felbamate	adjunctive therapy in children with seizures associated with Lennox-Gastaut syndrome	Initial: 1993 LGS: ??	45 mg/kg/day PO QID	• Statistically significant reductions in total, atonic, and tonic-clonic seizures	Aplastic anemia; hepatic failure;	

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Clonazepam	useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant)	Initial: 1975 LGS: 1997?	Adults: maintenance dose dependent on response, max 20 mg/day PO (divided TID) Pediatric: infants/children (≤10 years or 30 kg) maintenance dose of 0.1 to 0.2 mg/kg PO divided TID	• N/A	CNS depression, withdrawal symptoms; Worsening of Seizures especially in patients with multiple seizure types;	
Unapproved Treatments for Dravet Syndrome						
Stiripentol (STP)	Not approved in the US; approved in Europe and Canada	N/A	25-50 mg/kg/day PO (divided BID)	Statistically significant reduction in mean seizure frequency compared to baseline: STP: -69 (-50 to -88) PBO: 7 (25 to -11) p<0·0001 And in proportion of 50% responders: STP: 15 (71%) vs PBO: 1 (5%) p<0·0001	Drowsiness and loss of appetite reported, most resolved with adjustment of the concomitant drug.	Small numbers of patients (n=42), unclear if efficacy was due to STP or concomitant clobazam/ norclobazam

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Cannabidiol is a new molecular entity and is not currently marketed in the US.

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 120055 was submitted to FDA on March 31, 2014 for a study of the safety and efficacy of cannabidiol in the treatment of convulsive seizures associated with Dravet syndrome. Two clinical trials evaluating safety and efficacy of cannabidiol in the treatment of drop seizures in patients with Lennox-Gastaut syndrome were started in June 2015 (Study 1414) and April 2015 (Study 1423).

Significant clinical interactions between FDA and the applicant for the Dravet and Lennox-Gastaut syndrome indications include the following:

- Orphan Designation (13-4093) for treatment of Dravet syndrome, granted 14 November 2013
- Orphan Designation (13-4212) for treatment of Lennox-Gastaut syndrome, granted 27 February 2014
- Type B Pre-IND Meeting (February 11, 2014): Meeting held prior to submission of the initial DS protocol to IND-120055, during which clinical pharmacology issues, abuse potential data, and specific trial design concerns (e.g., dosing and titration schedule), were discussed. (b) (4) based on experience in published literature. Clarification of the titration schedule was requested. Guidance on studies needed to determine abuse potential was provided. Final meeting minutes were sent to the applicant on March 14, 2014.
- Fast-Track Designation, granted 2 June 2014
- Type C Guidance Meeting / Written Responses (16 June 2014): Prior to submission of the LGS protocols to IND-120055, during which nonclinical requirements, clinical pharmacology issues, abuse potential data, and specific trial design concerns (e.g., use of concomitant drugs, preferred primary efficacy measure [reduction in drop seizures], dose/titration in LGS vs. DS, testing of multiple doses, assessment during treatment period, etc.), were discussed. Meeting minutes were sent to the applicant.
- Type C Guidance Meeting / Written Responses (24 December 2014): Issues regarding clinical pharmacology and abuse potential data were discussed. Meeting minutes were sent to the applicant, in which the need for a TQT study and requirements of abuse potential studies were presented. Meeting minutes were sent to the applicant.

- Type C Guidance Meeting / Written Responses (22 October 2015): Issues of clinical relevance discussed in these meeting minutes included the following: pooled efficacy analyses for the two expected DS studies and the two expected LGS studies are not acceptable to support an NDA. The applicant was told that "*approval will be based on positive statistically significant findings of efficacy in both of the individual controlled studies for each indication"*. Pooled safety populations as described by the applicant (all pivotal DS patients, all pivotal LGS patients, all pivotal DS and LGS patients) were acceptable. Other pooled analyses were recommended (healthy volunteer studies, patient phase 1 studies, safety from the Expanded Access Program [EAP]). Comments on the proposed structure of the NDA were also provided in the meeting minutes.
- Type B Pre-NDA Meeting (19 July 2016): Important clinical issues discussed in this meeting included the following:
    - The applicant proposed that data from a single, well-controlled study in patients with DS (Study 1332B) plus data from the OLE study (1415), EAP, and Phase 1/2 program will be adequate to support and NDA for DS. DNP noted that this proposal was possible, but that the adequacy of the data would be a review issue.
    - The applicant planned to submit concurrently with Study 1332B for DS, Studies 1414 and 1423 to support an indication for LGS. DNP noted that concurrent submission would be acceptable.
    - DNP encouraged the applicant to explore the relationship between exposure metrics and efficacy and safety endpoints in their planned population pharmacokinetic (pop-PK) study.
- Rare Pediatric Disease Designation for LGS and DS, both granted 20 April 2017
- Rolling Review request, granted 02 May 2017.

3.3. Foreign Regulatory Actions and Marketing History

Cannabidiol (Epidiolex) is not currently marketed outside the US.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

See the review by OSI. The inspection report has not been completed at the time of this review.

4.2. Product Quality

See the review by the Chemistry, Manufacturing and Control reviewers.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

For a full assessment of the nonclinical findings, please see the reviews by Drs. Freed and Fisher.

The applicant reports that in the possible targets for the mechanism of anticonvulsant activity as identified in nonclinical studies are inhibition of adenosine reuptake and modulation of intracellular Ca^{2+} mobilization via GPR55 and/or TRPV1 channels. The applicant reported no adverse effects in CNS, cardiovascular or respiratory function in rats or dogs. No adverse toxicity in repeated dose toxicity studies in juvenile rats were reported. No genotoxicity, carcinogenicity, or impaired fertility were reported by the applicant.

With respect to nonclinical pharmacology, the applicant reported rapid absorption, limited and variable oral bioavailability, and rapid/wide distribution to tissues. Significant penetration into brain tissue of rats and mice (due to lipophilicity) was reported. In vitro testing showed that CBD and its major metabolites were highly protein bound in rat, dog, and human plasma (> 94% for CBD). CBD demonstrated fecal excretion in nonclinical studies.

Dr. Fisher has identified the lack of adequate nonclinical testing of a major human metabolite, as seen below:

> *Following absorption after oral administration, CBD is mostly eliminated by metabolism. The main routes of CBD metabolism appear to be direct glucuronidation and oxidation of CBD to form 7-hydroxy-cannabidiol (7-OH-CBD), which circulates in human plasma at levels of approximately 50% those of parent, making it a major human metabolite. 7-OH-CBD is metabolized by conjugation with glucuronic acid or further oxidation to 7-carboxy-cannabidiol (7-COOH-CBD). This metabolite circulates at levels far exceeding those of parent in humans (> 40 times), representing at least 90% of all drug-related products measured in plasma, and is clearly a major human metabolite. 7-OH-CBD demonstrated anticonvulsant activity in a mouse model and was approximately equipotent compared to CBD. 7-COOH-CBD exhibited no anticonvulsant effects in the mouse. 6-hydroxy-cannabidiol (6-OH-CBD) is formed in in vitro systems utilizing human enzymes, but circulating levels in humans are low (<10% of parent). Compared to humans, the toxicology species do not produce the two major human metabolites to a comparable extent (Table 1), and there is inadequate*

coverage for 7-COOH-CBD in all three. According to the applicant, "while GW accepts that human exposure levels are around 10-fold greater than animal exposure, there has been no safety signals in the clinical trials related to 7-COOH-CBD." However, it is not clear how they could make that determination.

Clinical reviewer's comment: As noted by Dr. Fisher, the applicant has not provided adequate nonclinical testing of the 7-OOH-CBD metabolite. It is likely that a PMR for further information on this metabolite will be necessary.

4.5. Clinical Pharmacology

The key outcomes of the clinical pharmacology discipline review are summarized below. The reader is referred to the review from the Office of Clinical Pharmacology (OCP) for further details.

"Cannabidiol reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 channels and modulation of adenosine-mediated signaling. However, the exact mechanisms by which cannabidiol exerts its anticonvulsant effect in humans is unknown. Cannabidiol does not exert its anticonvulsant effects through interaction with cannabinoid receptors."

CBD exposure exhibits nonlinear increase with dose up to 6000 mg. The median Tmax was 2.5 to 5 hours. Absolute bioavailability has not been determined. High fat meals increased Cmax (~5-fold) and AUC (~4-fold). Cannabidiol is extensively metabolized in the liver and gut, primarily by CYP2C19, CYP3A4 and UGT1A7, UGT1A9, and UGT2B7 enzymes. Two major circulating metabolites were identified: 7-carboxy-cannabidiol (7-COOH-CBD) which was approximately 40-fold higher than CBD and 7-hydroxy-cannabidiol (7-OH-CBD) which was ~38% of CBD, based on AUC of CBD. CBD and 7-OH-CBD were found to be active (equipotent). However, 7-COOH-CBD was found to be inactive in nonclinical animal models of epilepsy. The mean elimination half-life ranged from 56 to 61 hours following twice-daily dosing for 7 days in healthy volunteers. Excretion was predominantly via the fecal route (84%).

Dedicated drug-interaction studies of CYP2C19 and CYP3A inhibitors or inducers were not conducted. OCP is recommending PMRs to evaluate the effects of CYP2C19 and CYP3A inhibitors/inducers on CBD, as well as the effect of cannabidiol on the pharmacokinetics (PK) of a variety of substrates (b) (4), CYP2C19, (b) (4), CYP2C9, CYP2B, UGT1A9, and UGT2B7).

CBD is hepatically metabolized, and the effect of hepatic impairment on CBD was studied in Study GWEP1539. Results of this study demonstrated 2.45- and 5.15-fold increases in AUC for CBD in patients with moderate and severe hepatic-impairment, respectively, and ~50% increase in patients with mild hepatic impairment, as compared to subjects with normal hepatic function. Based on these findings, OCP has the following specific dosing recommendations for

patients with hepatic impairment:

In patients with moderate hepatic impairment a slow dose titration with a 2-fold lower starting dose and 2-fold lower maintenance dose is recommended. The starting dose 1.25 mg/kg of Epidiolex taken twice daily (2.5 mg/kg/day) for 1 week and the dose to be increased weekly by 1.25 mg/kg administered twice daily (2.5 mg/kg/day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 1.25 mg/kg administered twice daily (2.5 mg/kg/day) until attainment of a maintenance dose of 5 or 10 mg/kg/day is recommended to be taken (with food).

In severe hepatic impairment a slow dose titration with a 5-fold lower starting dose and a 5-fold lower maintenance dose is recommended. The starting dose 0.5 mg/kg of Epidiolex taken twice daily (1 mg/kg/day) for 1 week and the dose to be increased weekly by 0.5 mg/kg administered twice daily (1 mg/kg/day) to a therapeutic dose of 2 mg/kg twice daily (2 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 0.5 mg/kg administered twice daily (1 mg/kg/day) until attainment of a maintenance dose of 2 or 4 mg/kg/day is recommended to be taken with food.

OCP evaluated the potential for confounding of study results by an active metabolite of clobazam (norclobazam, nCLB). This issue was raised with the applicant prior to submission of the NDA, because of the known inhibition of CBD on CYP2C19, which metabolizes nCLB. Specifically, PK data collected in Study 1332A demonstrated CBD inhibition of CYP2C19, even at low doses (e.g., 5 mg/kg/day). Clobazam (CLB) is metabolized by CYP3A4 to nCLB, resulting in a 2.5-fold increase in nCLB but no increase in CLB. Additionally, CBD is metabolized by CYP450 isoforms to 7-OH-CBD, which is an active metabolite. Study 1543 was a dedicated DDI study to evaluate effects of CLB on CBD and vice versa. In this study, patients on stable dose of CBD who were given 5 mg of CLB developed increased 7-OH-CBD (47%↑). Because of the complicated interaction between CBD and CLB, as well as the significant use of CLB in patients with LGS or DS, DNP recommended that the applicant explore the relationship between concomitant drugs and efficacy and safety, particularly CLB (pre-NDA meeting July 19, 2016).

Stiripentol (STP) is a concomitant AED that was taken by a subset of patients in Study 1332B. STP also inhibits CYP2C19, and patients receiving concomitant STP were expected to experience CYP2C19 inhibition to such an extent that addition of CBD would not cause additional inhibition of CYP2C19. Therefore, these patients would likely have similar n-CLB levels post-CBD as they had prior. Although the number of patients on STP and CLB were small (37 overall, 23 CBD, and 14 placebo), there was no significant difference between these groups in cumulative reduction in seizure frequency, suggesting that the CBD treatment effect is independent of nCLB. Please also see Section 7.1.3 for further discussion of impact of CLB on CBD efficacy.

Lastly, OCP notes that the exposure-response data are problematic and may not be acceptable

to support efficacy of CBD. Although the applicant conducted exposure-response analyses for safety and efficacy, these analyses are not based on stable intra-patient PK data. A prominent food effect (5-fold increase in Cmax after a high-fat, high calorie meal) was noted in healthy volunteers during Study 1544. During Studies 1332B, 1414, and 1423, patients were allowed unrestricted access to food, and documentation of the patient's fed/fasted state when PK samples were drawn in Phase 3 trials was not collected. These issues raise significant concerns about the stability of the intra-patient PK profiles, and the exposure-response analyses upon which they are based are insufficiently robust and cannot be used to support effectiveness of CBD. This lack of clear exposure-response data does not allow for PK support of efficacy of the 10 mg/kg/day dose in patients with DS (see Section 7.1.4 for further discussion of this issue).

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

See Table 2 below for a summary of the clinical studies reviewed for efficacy.

Table 2: Clinical Studies in Subjects with DS or LGS Contributing Efficacy Data

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
GWEP1332B / NCT02091375	Randomized, double blind, placebo-controlled	CBD oral solution 20 mg/kg/day (divided BID) vs equal volume of placebo. Titration schedule: Initial dose of CBD 2.5 mg/kg/day increasing 2.5 mg/kg QOD over 11 days to 20 mg/kg/day.	Primary: Percentage change from baseline in convulsive seizure frequency during the treatment period	Baseline: 28 days Titration: 2 weeks Maintenance: 12 weeks Follow-up: 4 weeks (or enrollment in OLE)	177 screened 120 randomized CBD 20 mg/kg/day: 61 Placebo: 59 Screen failures: 57	2-18 years with a clinical diagnosis of DS and refractory seizures, ≥ 4 convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks	22 centers in 4 countries: US (13), UK (3), France (4), Poland (2)
GWEP1414 / NCT02224560	Randomized, double blind, 3 arm, placebo-controlled	CBD oral solution 10 or 20 mg/kg/day (divided BID) vs equal volume of placebo. Titration schedule: Initial dose of CBD 2.5 mg/kg/day increasing 2.5 mg/kg QOD over 7 days to 10 mg/kg/day, or 11 days to 20 mg/kg/day	Percentage change from baseline in number of drop seizures (average per 28 days) during the treatment period in patients taking 20 mg/kg/day Key Secondary: Proportion of patients with a ≥ 50% reduction from baseline in convulsive seizure frequency during the treatment period	Baseline: 28 days Titration: 2 weeks Maintenance: 12 weeks Follow-up: 4 weeks (or enrollment in OLE)	293 screened 225 randomized CBD 10 mg/kg/day: 73 CBD 20 mg/kg/day: 76 PBO: 76 Screen failures: 68	LGS patients 2-55 years with refractory seizures and ≥ 2 drop seizures each week during baseline while on ≥ 1 AED at a stable dose for ≥ 4 weeks.	29 centers in 4 countries: US (20), UK (3), France (1), Spain (5)

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
GWEP1423 / NCT02224690	Randomized, double blind, placebo-controlled	CBD oral solution 20 mg/kg/day (divided BID) vs equal volume of placebo. Titration schedule: Initial dose of CBD 2.5 mg/kg/day increasing 2.5-5.0 mg/kg QOD over 11 days to 20 mg/kg/day	Percentage change from baseline in number of drop seizures (average per 28 days) during treatment period. Key secondary (tested hierarchically): • Proportion of patients with a ≥50% reduction from baseline in drop seizure frequency during treatment period • Percentage change from baseline in total seizure frequency during treatment period • • S/CGIC at last visit	Baseline: 28 days Titration: 2 weeks Maintenance: 12 weeks Follow-up: 4 weeks (or enrollment in OLE)	200 screened 171 randomized CBD 20/mg/kg/day: 86 Placebo: 85 Screen failures: 29	LGS patients 2-55 years with refractory seizures and ≥ 2 drop seizures each week during baseline while on ≥ 1 AED at a stable dose for ≥ 4 weeks.	24 centers in 3 countries: US (17), The Netherlands (1), Poland (6)
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							
GWEP1332A / NCT02091375	Randomized, double blind, placebo-controlled	CBD oral solution 5, 10 or 20 mg/kg/day (divided BID) vs equal volume of placebo	Primary: safety profile of single and multiple doses of CBD compared with placebo. Pharmacokinetic assessment of single and multiple doses of CBD	Baseline: 28 days Treatment: 21 days Taper: 10 days Follow-up: 4 weeks (or enrollment in OLE)	41 screened 34 randomized CBD 5 mg/kg/day: 10 CBD 10 mg/kg/day: 8 CBD 20 mg/kg/day: 9 PBO: 7 Screen failures: 7	4-10 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	12 centers in 2 countries: US (8), UK (4)

Sources: Summary of Clinical Efficacy (SCE), pgs. 16-18; also clinical study reports from Studies 1332A, 1332B, 1414, and 1423.

In their SCE, the applicant noted that Study 1415 (a single-arm, open-label extension study which was intended to provide long-term safety data of use of CBD in patients with DS and LGS) and patients enrolled in studies in the Expanded Access Program (EAP, a multitude of small uncontrolled studies of CBD in a variety of refractory epilepsy syndromes) also contributed efficacy data. As these studies are uncontrolled and many included patients with diseases outside the scope of the proposed indication, they were not reviewed for efficacy. See safety review by Dr. Unger for a discussion of the safety data obtained from these studies.

Table 3: Pediatric Enrollment Data

Study#	Trial Type	Trial Design	# of Pediatric Patients Screened / Randomized	# of Centers	Countries (#sites)
1332A	PK, Safety, Tolerability	Randomized, placebo-controlled, population PK	41 / 34	12	US (8), UK (4)
1332B	Efficacy, safety	Randomized, double blind, placebo-controlled	177 / 120	22	US (13), UK (3), France (4), Poland (2)
1414	Efficacy, Safety	Randomized, double blind, placebo-controlled	178 / 158	29	US (20), UK (3), France (1), Spain (5)
1423	Efficacy, Safety	Randomized, double blind, placebo-controlled	158 / 113	24	US (17), The Netherlands (1), Poland (6)

5.2. Review Strategy

An efficacy determination was made by evaluating the results from three double-blind, placebo-controlled trials, one in patients with DS and two in patients with LGS. This reviewer assessed the primary endpoint by examining the source data provided by the applicant.

Statistical analysis of the data was performed and reported by Dr. Xiang Ling and is incorporated in this combined efficacy/statistics review.

Please note that this review focuses solely on clinical efficacy. This application is being reviewed separately for safety by Dr. Ellis Unger.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. GWEP1332B – A double-blind, placebo-controlled, two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.

6.1.1. Study Design

Overview and Objective

GWEP1332B (Study 1332B) is a Phase 3, multicenter, randomized, double-blind, placebo controlled study of cannabidiol (GWP42003-P) in patients with refractory seizures and Dravet syndrome.

The objectives of this study were as follows:

- Primary: *"To assess the efficacy of GWP42003-P as an adjunctive antiepileptic treatment compared with placebo, with respect to the percentage change from baseline during the treatment period of the trial in convulsive seizure frequency."*
- Secondary:
  - *To assess changes from baseline in non-convulsive seizure frequency, duration of seizures, usage of rescue medication, number of inpatient hospitalizations due to epilepsy, episodes of status epilepticus, sleep disruption, daytime sleepiness, quality of life, menstruation cycles (in females), growth and development, and conduct behavioral assessments in patients taking GWP42003-P as an adjunctive treatment, when compared with placebo.*
  - *To determine effects of GWP42003-P on plasma concentrations of concomitant*

AEDs, where available.

- *To assess the safety of GWP42003-P when compared with placebo.*

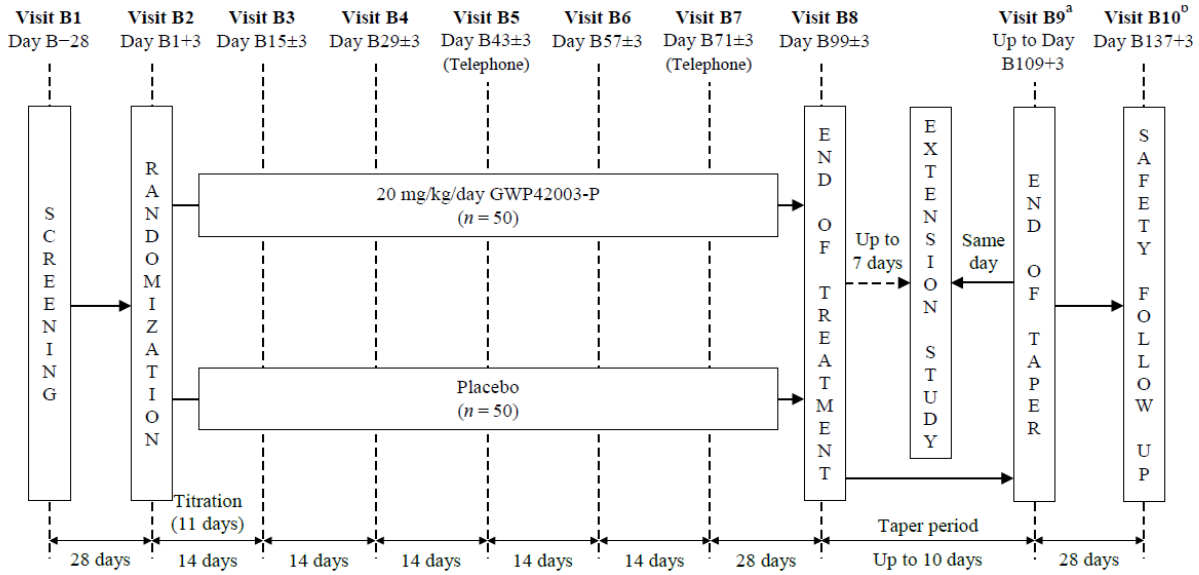
Trial Design

- **Basic Study Design**

  Study 1332B was a Phase 3, multicenter, double-blind, randomized, placebo controlled study of cannabidiol conducted at 22 centers worldwide. Approximately 100 patients were to be randomized into the study. This study was conducted to test the clinical efficacy, safety, and PK of cannabidiol oral solution in patients with seizures due to Dravet syndrome. The total duration of subject participation in the study was approximately 3 months. The study consisted of a Baseline Period, a Treatment Period (titration plus maintenance), and a Taper Period (alternatively, patients enrolled in an open label, long-term extension [LTE] study).

  The general design of Study 1332B was similar to other pivotal trials evaluating efficacy of AED treatments.

Figure 1: Study 1332B, Trial Design and Treatment Schematic



Source: Figure 5.1-2, Study 1332B CSR

- **Trial location**

  Study 1332B was conducted in the US and Europe (United Kingdom [UK], France, and Poland). The patient population and treatment regimen in Europe is expected to be similar to that in the US.

- **Choice of control group**
  The applicant used a concurrent placebo control as the comparator group, as recommended in FDA Guidelines for the Clinical Evaluation of Antiepileptic Drugs (Adults and Children)[36]. As there is no approved treatment for seizures associated with DS in US, comparison to placebo is appropriate.

- **Diagnostic criteria**
  Patients were enrolled if they had a "documented history of DS" – a clinical diagnosis – a variety of treatment-resistant seizures that began in the first year of life (including convulsive seizures) and cognitive decline or developmental delay. Although many patients were tested for genetic anomalies (most importantly SCN1A mutations), presence of such mutations were not required for inclusion in the study, which is consistent with the currently accepted clinical diagnosis of DS.

- **Key inclusion/exclusion criteria**
  Inclusion Criteria:
  1. Willing and able to give informed assent/consent
  2. Age between 2 and 18 years
  3. Have a documented history of DS, not completely controlled by current AEDs.
  4. Must have experienced ≥4 convulsive seizures (i.e., tonic-clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period.
  5. Must be taking one or more AEDs at a dose which has been stable for at least four weeks.
  6. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for four weeks prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study.
  7. Has completed their interactive voice response system (IVRS) telephone diary on at least 25 days of the baseline period.

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

[36] https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071582.pdf

5. 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 or was unwilling to abstain from using these substances during the trial.
6. Patient had a history of symptoms related to a drop in blood pressure due to postural changes.
7. Patient had ingested alcohol in the 24-hour period prior to the first trial visit and/or was unwilling to abstain from drinking alcohol throughout the treatment period.
8. Patient had consumed grapefruit or grapefruit juice 3 days prior to screening and/or was unwilling to abstain from consuming these during the trial.
9. Patient had any known or suspected hypersensitivity to cannabinoids or any of the excipients of the investigational medical product (IMP(s)), e.g., sesame oil.
10. 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.
11. Female patient who was pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial and for 3 months thereafter.
12. Patient had been part of a clinical trial involving an investigational product in the previous 6 months.
13. Patient was taking felbamate for less than 1 year prior to screening.
14. 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.
15. 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). (Patients randomized into the trial who were later found to meet this criterion were withdrawn from the trial.)
16. 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.
17. Patient was unwilling to abstain from donation of blood during the trial.
18. There were plans for the patient to travel outside their country of residence during the trial.
19. Patient was previously randomized into the trial. In particular, patients randomized in Part A of the trial could not enter Part B.
20. Any history of suicidal behavior or any suicidal ideation of type 4 or 5 on the Columbia-Suicide Severity Rating Scale at screening.

Clinical reviewer's comment: The eligibility criteria for Study 1332B were generally

similar to those in other AED treatment trials.

- **Dose selection**
  The 20 mg/kg/day dose of CBD and the titration (dose escalation) regimen used in Study 1332B were based on unblinded safety and PK data from trial GWEP1332A (Study 1332A), which used a completely separate patient population. CBD doses of 5, 10, and 20 mg/kg/day were explored in that study. Other cannabidiol products have been used in patients with refractory seizures at doses of 10-20 mg/kg/day in published literature. As no significant or unanticipated safety issue occurred in Study 1332A and the seizure in DS are generally refractory to AEDs, it was decided to study the highest assessed dose in the pivotal trial.

- **Study treatments**
  Subjects randomized to the CBD treatment group received daily doses of CBD oral solution (100 mg/mL) at 20 mg/kg/day. All doses were divided BID. The study drug (or the equivalent volume of placebo) was started at 2.5 mg/kg/day and increased by 2.5 mg/kg/day every other day to 10 mg/kg/day and then by 5 mg/kg/day every other day to 20 mg/kg/day for a total titration period of 11 days. Patients in the placebo arm received equal volumes of placebo oral solution using an identical titration schedule.

Clinical reviewer's comment: The titration schedule in 1332B was identical to that used in the 20 mg/kg/day arm of Study 1332A. Please see Section 7.1.4 for discussion of the alternative dosing regimen proposed by the applicant in the draft prescribing information.

Please refer to the Office of Pharmaceutical Quality (OPQ) review for discussion of the product formulation used for the active study arm.

- **Assignment to treatment**
  At the start of Visit B1, a unique patient number was assigned to each patient using the IVRS/IWRS, and patients were randomly allocated to 20 mg/kg/day GWP42003-P or equivalent volume of placebo using the IVRS/IWRS.

Clinical reviewer's comment: Patients were randomized after completion of the 28-day baseline period, as they were required to have at least 4 convulsive seizures during this time. Patients who did not have sufficient seizures (or were non-compliant with seizure recording) during the baseline were considered screen failures. This is consistent with other AED trials.

Randomization was stratified by age group (2-5 years, 6-12 years, and 13-18 years)

and was performed globally.

- **Blinding**
  The IMP was provided in 100 mL amber glass bottles labeled "GWP42003-P Oral Solution or Placebo". The identity of the IMP assigned to patients was held by the IVRS/IWRS. The PI at each site, or his/her designee, was responsible for ensuring that information on how to access the IVRS/IWRS was available to the relevant staff in case of an emergency and unblinding was required.

Clinical reviewer's comment: The described methods of blinding appear adequate. The primary endpoint of change in convulsive seizure frequency could potentially be influenced by unblinding, in that an unblinded caregiver could report seizures differently based on assumption of treatment allocation. Even so, seizure counts remain the most clinically relevant outcome measure of efficacy of a seizure treatment, and the outcome measure/endpoint is standard in AED treatment trials.

- **Dose modification, dose discontinuation**
  Patients were to continue on a stable dose after titration. However, in the case of a poorly tolerated dose during the maintenance period, the investigator was permitted to temporarily or permanently reduce the dose for the remainder of the study. If an unacceptable AE occurred at any time during titration, dosing was to be suspended or amended as advised by the investigator, until the event resolved. Such dose modifications were captured in the CRFs.

  See pages 43-44 below for discussion of reasons for drug discontinuation, including stopping criteria.

- **Administrative structure**
  Investigators at 23 study centers worldwide received IRB/IEC approval to participate in this study, and 31 centers enrolled and treated subjects. Safety data were reviewed on an ongoing basis by the applicant's Medical Monitor and by an independent Data Safety Monitoring Committee (DSMC). An independent study consortium evaluated all patients for the DS diagnosis and verified the seizure types of screened patients.

- **Procedures and schedule**
  The following table from the applicant summarizes the schedule of study visits, baseline period, treatment period, taper period, and follow-up period.

Table 4: Study 1332B Schedule of Assessments

Visit Number	1	2	3	4	5 (Tel.)	6	7 (Tel.)	8	9c	Safety Call	10d
Day Number (Visit window)	**–28**	**1 (+3)**	**15 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**71 (±3)**	**99 (±3)**	**100-106/ 109 (+3)**	**116, 123 & 130 (±3)**	**137 (±3)**
Informed consent/assent	X										
Eligibility criteria	X	X									
Randomization		X									
Demographics	X										
Medical history/ diagnostic review form	X										
IVRS and paper diary training	X										
Concomitant medications (including AEDs)	X	X	X	X	X	X	X	X	X	X	X
Physical examination (including height and body weight)	X	X	X	X		X		X	X		
ECG	X	X	X	X		X		X	X		
Vital signs	X	X	X	X		X		X	X		
Postural blood pressure	X	X									
AEs	X	X	X	X	X	X	X	X	X	X	X
Inpatient epilepsy-related hospitalizations		X	X	X	X	X	X	X	X	X	X
Clinical laboratory blood sampling	X	X	X	X		X		X	X		
Clinical laboratory urine sampling (dipstick urinalysis)	X	X	Xf	Xf		Xf		X	X		
Urine THC screen	X	X						X			
Pregnancy test (if appropriate)	X	X						X			
AED blood sampling		X		X		X		X			
Blood sample for *SCN1A* analysis	X										
Sleep Disruption 0–10 NRS		X	X	X		X		X			
ESS		X	X	X		X		X			
Memory aid for CGIC and CGICSD		X									
CGIC			X	X		X		X			
CGICSD								X			
QOLCE		X						X			
C-SSRS	X	X	X	X		X		X	X		
Vineland-II		X	X	X		X		X			
Tanner staging and IGF-1 testing		X						X			

Visit Number	1	2	3	4	5 (Tel.)	6	7 (Tel.)	8	9c	Safety Call	10d
Day Number (Visit window)	**−28**	**1 (+3)**	**15 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**71 (±3)**	**99 (±3)**	**100-106/ 109 (+3)**	**116, 123 & 130 (±3)**	**137 (±3)**
Menstruation question		X						X			
Caregiver Impression of IMP Palatability								X			
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)		X	X	X		X		X	X		
Confirmation of DS diagnosis by ESC		X									
IMP dispensing		X		X		X	X	X			
Collection of IMP				X		X	X	X	X		
IMP compliance review			X	X		X	X	X	X		

Source: Table 5.5.1-2, Study 1332B CSR

- **Concurrent medications**
  Patients had to be on at least one AED at a stable dose during the trial. If plasma concentrations of concomitant AEDs altered following administration of the investigational product, then the dosage of concomitant AEDs were modified, based on clinical need and after discussion with the GW medical advisor. All non-pharmacological therapies for epilepsy (e.g., ketogenic diet, VNS) also had to be stable for four weeks prior to screening and remain so throughout the duration of the study.

  Any medication, other than the IMP, taken during the study was to be recorded on the appropriate Case Report Form (CRF).

  Prohibited therapies during the study period were as follows:
  - *Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.*
  - *Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.*
  - *Any other IMP taken as part of a clinical trial within six months or during the study.*

- **Treatment compliance**
  Patients or caregivers recorded the total volume of IMP administered on each day using the paper diary. Participants were asked to return all IMP (used and unused) to each relevant visit (Visits 4, 6, 8 and 9), and the site checked the returned IMP against both the amount in the paper diary and the projected usage in the IVRS system. Discrepancies were discussed with the patient/caregiver and documented. Investigators were to inform GW of all missing or unaccountable IMP.

- **Rescue medications**
  The use of rescue medication was allowed and was captured on CRFs.

- **Subject completion, discontinuation, or withdrawal**
  Patients who completed the treatment period were invited to participate in an OLE trial under a separate protocol and continue receiving (or start taking) CBD. Patients who did not enter the OLE trial tapered IMP (10% per day over 10 days). However, if the patient decided to enter the OLE trial within 7 days of treatment completion, the taper period could be interrupted. Patients who opted to taper the drug returned for an end of taper period visit (Visit B9, Day B100-106 or Day B109). Patients who did not enter the OLE trial (or who discontinued early) returned for a safety follow-up visit 28 days later (Visit B10, Day B137).

  Patients who met any of the following criteria must be withdrawn from the study:
  - Administrative decision by the investigator, GW, or a regulatory authority.

- Pregnancy.
- Protocol deviation that was considered to potentially compromise the safety of the patient.
- Withdrawal of patient assent or parent(s)/legal representative consent.
- Lost to follow-up.
- Alanine aminotransferase (ALT) > 3 × upper limit of normal (ULN) or aspartate aminotransferase (AST) > 3 × ULN and (total bilirubin [TBL] > 2 × ULN or international normalized ratio [INR] > 1.5).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.

Other potential withdrawal criteria included:

- Patient non-compliance.
- AE which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

All information, including the reason for withdrawal from the study, was to be recorded in the CRF. (1332B Protocol, p. 83)

If a patient withdrew from the study during the treatment period, *"the primary analysis variable will be calculated from all the available data, during the treatment period, prior to the patient withdrawing."* (1332B SAP, pg. 10) Sensitivity analyses to account for missing data arising from unreported days in the IVRS and missing data arising from patients withdrawing during the treatment period were prespecified in the SAP and performed.

Clinical reviewer's comment: The specified criteria for completion, discontinuation, or withdrawal, as well as the statistical methods to address missing data in the case of discontinuation/withdrawal, appear reasonable.

Study Endpoints

Primary Efficacy Endpoint

The primary endpoint for Study 1332B was *"the percentage change from baseline in total convulsive seizure frequency during the treatment period of the study (Day B1 to the end of the evaluable period) in patients taking GWP42003-P compared with placebo").* The primary efficacy endpoint was not assessed at one specific time, but was rather a measure of change in seizure frequency over the entire treatment period, which included the 10-day titration period and the 12-week maintenance period.

Patients or caregivers were to record the number and type of convulsive seizures (tonic, clonic, tonic–clonic, or atonic) and non-convulsive seizures (myoclonic, partial, or absence) each day from screening until completion of dosing (Visit B8/Withdrawal visit or Visit B9, as appropriate) using the Interactive voice response system (IVRS).

Clinical reviewer's comment: The primary endpoint used in Study 1332B (percentage change from baseline in seizure frequency) is the most common efficacy endpoint AED treatment trials, though the outcome variable may differ depending on the underlying type of epilepsy. For example, in a study evaluating a drug intended to treat partial onset seizures (POS), the primary efficacy endpoint would likely be percentage change from baseline in frequency of POS. Patients with DS have multiple seizure types, with seizures ranging in severity from generalized tonic-clonic seizures to atypical absence seizures, so careful definition of the primary outcome variable was important. The applicant separated the seizure types into two broad categories: convulsive and nonconvulsive seizures. Convulsive seizures were defined in the protocol as tonic-clonic, tonic, clonic or atonic seizures. Nonconvulsive seizures included myoclonic, "countable partial", other partial or absence seizures. These definitions were discussed with FDA prior to study commencement. Because convulsive seizures are the most disabling and most likely to lead to patient injury, efficacy of CBD in DS was measured by reduction in convulsive seizure frequency.

Assessment over titration and maintenance periods is standard in epilepsy drug treatment trials rather than the maintenance period only, as patients may withdraw during titration due to lack of efficacy. Capturing these patients is important, because withdrawals due to lack of efficacy may lead to unbalanced results.

Secondary Efficacy Endpoints

Key Secondary Endpoint

Number of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline during the treatment period. Although this was considered a "key" secondary endpoint, there was no pre-specified hierarchical analysis in the US SAP.

Clinical reviewer's comment: The 50% responder rate is a frequently reported outcome measure in clinical epilepsy treatment trials. It is often the preferred primary efficacy outcome by European drug regulatory agencies. Thus, it was considered a key secondary endpoint in Study 1332B and identified in as such in the SAP. As there was no adjustment for multiplicity of the secondary endpoints in the US submission, all secondary endpoints, including the 50% responder rate, are considered exploratory.

Other Secondary Efficacy Endpoints

A number of secondary efficacy endpoints were evaluated in Study 1332B. There was significant redundancy in these endpoints, and only a select number of secondary endpoints will be discussed.

- Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom
- Non-Convulsive Seizures
- Individual Seizure Types and Total Seizures
- Caregiver Global Impression of Change
- Status Epilepticus
- Quality of Life in Childhood Epilepsy
- Use of Rescue Medication

Secondary endpoints of particular clinical interest will be discussed below.

Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom

The number of patients experiencing a >25% worsening, +25 to -25% change, 25 to 50% improvement, 50 to 75% improvement or >75% improvement in convulsive seizure frequency from baseline during the treatment period will be summarized by treatment group. Additionally, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in convulsive seizure frequency from baseline, as well as the proportion of patients who are convulsive seizure free (100% reduction in convulsive seizure frequency from baseline during the treatment period), will be summarized by treatment group and analyzed.

Non-Convulsive Seizures

Non-convulsive seizures were collected, summarized, and analyzed. Patients with no non-convulsive seizures during the baseline period were excluded from the analysis. The percentage change from baseline in total nonconvulsive seizure frequency during the treatment period was calculated for each treatment group for the entire treatment period and compared between groups.

Clinical reviewer's comment: Although this was not prespecified as a key secondary efficacy endpoint, it is a clinically important secondary endpoint.

While generally less severe and less likely to lead to injury than convulsive seizures, nonconvulsive seizures can be significantly disabling (especially POS). It is possible that a drug might reduce the number of convulsive seizures but increase the number or severity of nonconvulsive seizures in patients with multiple seizure types, such as those with DS. Increased severity or frequency of nonconvulsive seizures would be a significant adverse effect of the drug, and has been reported in patients with SCN1A gene mutation who were taking AEDs that impact the sodium channel (e.g.,

carbamazepine, oxcarbazepine, or phenytoin). Primarily for this reason, the frequency of nonconvulsive seizures is an important secondary outcome measure.

Individual Seizure Types and Total Seizures

The percentage change from baseline in total seizure frequency (all seizure types combined) and seizure frequency by individual seizure type was calculated for each treatment group for the entire treatment period. Patients who had no seizures of a particular seizure type during the baseline period were excluded from the analysis of that seizure type.

Caregiver Global Impression of Change (CGI-C)

The overall level of change due to treatment was assessed via the CGI-C at baseline and weeks 2, 4., 8, and 14 (last treatment visit). At the baseline visit, the caregiver was asked to write a brief description of the patient's overall condition as a memory aid for the CGIC questionnaire at subsequent visits. The following question was rated on a 7-point scale: "Since your child started treatment, please assess the status of your child's overall condition (comparing their condition now to their condition before treatment) using the scale below." The 7-point scale is as follows: "Very Much Improved" (1); "Much Improved"; "Slightly Improved"; "No Change"; "Slightly Worse"; "Much Worse"; "Very Much Worse" (7). The CGIC response/score, recorded at each visit, was summarized, on both a categorical and continuous scale, by treatment group and compared to baseline.

Safety Parameters

- Assessment of differences in incidence, type and severity of AEs, Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, ECG, laboratory safety parameters, physical examination parameters, and effects on menstruation cycles (in females) of patients taking CBD compared with placebo.
- Change from baseline in growth and development for patients less than 18 years of age by measurement of height, weight, insulin-like growth factor-1 levels and Tanner Staging (for patients aged 10-17 years, or earlier if clinically indicated).
- Plasma concentrations of concomitant AEDs before and after treatment with CBD, where available.

Clinical reviewer's comment: Please see Dr. Unger's review for discussion of the acceptability of safety endpoints.

Statistical Analysis Plan

The primary analyses used the intention to treat (ITT) analysis set, including all patients randomized to treatment who received at least 1 dose of IMP and had post-baseline efficacy data.

The primary endpoint was analyzed using a Wilcoxon rank-sum test. An estimate of the median difference between CBD and placebo, together with approximate 95% confidence interval (CI), was calculated using the Hodges-Lehmann approach.

The following sensitivity analyses were specified for the primary endpoint:

- Analysis of covariance (ANCOVA) on rank-transformed percentage change from baseline in convulsive seizure frequency during the treatment period, including baseline and age group as covariates and treatment group as a fixed factor.
- ANCOVA model on log-transformed convulsive seizure frequency during the treatment period. If there were any patients with no seizures post-baseline, then 1 was added to the drop seizure frequency for all patients prior to log transformation.
- ANCOVA on percentage change from baseline in convulsive seizure frequency during the treatment period
- Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the maintenance period, and each 4-week period of the maintenance period (Weeks 1–4, 5–8, and 9–12 of the 12-week maintenance period).
- Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period, using the worst case of last observation carried forward (LOCF), next observation carried backward (NOCB), and the mean from the non-missing data for each patient to impute intermittent missing data arising from unreported days during the treatment period only.
- Wilcoxon rank-sum test on percentage change from baseline in convulsive seizure frequency during the treatment period, using multiple imputation (MI) to impute data under the missing not at random (MNAR) assumption for CBD patients who discontinued for certain reasons.

Protocol Amendments

There were 8 submitted protocol amendments. Important modifications to the protocol are summarized in Table 5 below.

Table 5: Study 1332B, Summary of Major Protocol Amendments

Amendment Number	Date	Major Changes
1	20 JUN 2014	• Added a 10-day taper period (10% each day) at the end of the treatment period in both parts of the trial. • Increased the overall treatment period in Part B from 12 to 14 weeks (followed by a 10-day taper period). • Added a 4-week post-drug discontinuation safety follow-up visit to both parts of the trial. • Added criteria for withdrawal and evaluation of laboratory findings that may signal potential DILI.

Amendment Number	Date	Major Changes
		• Clarified that a safety review of Part A data would be required before patients could enroll in the OLE trial. • Increased the number of patients required in Part B from 60 to 80. • Defined the term "convulsive seizures" used in the primary objective. • Added non-parametric testing to the statistical analyses. • Changed the period for analysis of the primary endpoint in Part B from the last 28 days of the treatment period to the maintenance period (Day B15 to the end of evaluable period). • Clarified that an overall mean of the seizure data collected during the maintenance period in Part B (Day B15 to Day B99 or day of withdrawal) would be calculated and presented *pro rata* (as number of seizures in 28 days). • Added C-SSRS to each outpatient visit (except safety telephone calls) in both parts of the study to detect suicidal ideation and behavior. • Added a criterion to exclude patients with a history of suicidal behavior or suicidal ideation of type 4 or 5 on the C-SSRS at screening in both parts of the study • Clarified that that the safety monitoring committee would review the DS diagnosis of screened patients.
3	04 Nov 2014	• Clarified that the baseline period would be a minimum of 28 days. • Clarified that any AE that could compromise patient safety would be grounds for withdrawal. • Clarified that patients with suspected DILI were to be withdrawn. • Clarified that patients who terminated treatment early would commence the 10-day taper period, unless not possible due to an AE. • Clarified when seizures were to be considered AEs and that these AEs would be reviewed by the DSMC.
5	30 Mar 2015	• Changed the primary analysis to an ANCOVA. • Added sensitivity analyses over the full experimental double-blind period using ANCOVA and MMRM. • Added sensitivity analyses (ANCOVA and MMRM) with imputation methods based on the assumption of MNAR, in addition to the primary analysis which would be based on non-missing data for patients who drop out. Clarified that patients with no post-baseline assessments would be excluded from the ITT analysis set. • Added assessment for normality and use of the non-parametric Wilcoxon rank-sum test if data were not normally distributed. • Specified that patients would be stratified by age (2–5, 6–12, and 13– 18 years) across treatment arms. • Amended the exclusion criterion regarding DILI in line with Hy's Law.
7	29 May 2015	• Changed the analyses for the primary and secondary endpoints in Part B to use the full treatment period, which included both the titration and maintenance periods. • Defined "baseline" for statistical analyses. • Changed the seizure frequency used in the sensitivity analyses for the primary endpoint in Part B to average per 28 days.

Amendment Number	Date	Major Changes
		• Added new sensitivity analyses for the primary endpoint in Part B using the maintenance period only and the full treatment period imputing for missing data. • Added details on MI methods for the sensitivity analyses for the primary endpoint in Part B. • Clarified that during follow-up of patients with potential cases of DILI, ALT, AST, TBL, and alkaline phosphatase levels were all to be monitored until levels had normalized or returned to baseline state. • Clarified that seizure counts over 99 for any specific seizure type were also to be collected in the paper diary in Part B.

Data Quality and Integrity: Applicant's Assurance

The applicant reports the following methods for assuring data quality and integrity, which appear adequate:

> *Prior to trial initiation, during the trial, and after trial completion, investigational sites were visited by GW clinical research associates (CRAs) and a visit log was maintained... Direct access to the patient medical and laboratory records was permitted to verify entries on the trial-specific CRFs… A database was set up in Oracle Clinical (Version 4.5) and data entry screens were designed, tested and implemented to capture the CRF, paper diary, and questionnaire data. Double data entry was used to enter data into the database and quality checks were applied… Following data entry, all AE and concomitant medication terms were medically coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.0, and the World Health Organization Drug Dictionary (WHODD), dated June 2014… Quality control (QC) was performed on 100% of the critical variable data within the clinical database. In addition, non-critical variable data were QC checked on a randomly selected sample of patients.*
>
> *GW's clinical quality assurance department provided quality assurance support for this trial. Audits of the quality systems that supported the preparation, conduct and reporting of this trial were conducted periodically in accordance with audit plans. These audits were conducted to assure compliance with the regulations, guidelines, and standard operating procedures in place at the time of the trial. All findings were reported to appropriate personnel for corrective action. Copies of the site audit certificates are appended to this report (Appendix 1.8). The applicant's clinical personnel or designee conducted an on-site evaluation of the clinical site prior to trial initiation.*

6.1.2. Study Results

Compliance with Good Clinical Practices

The applicant stated that Study 1332B was conducted in in compliance with International

Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. The applicant additionally stated that informed consent and assent, if possible, were obtained prior to carrying out any study procedures. The informed consent forms (ICF), protocol, and amendments for this trial were submitted to and approved by the IRB or independent ethics committee (IEC) at each participating trial site.

Financial Disclosure

In the financial disclosure summary, the applicant identified 7 investigators with disclosable financial interests, most of which were related to funding to support data collection in their EAP INDs. The applicant states *"To minimize the potential bias of clinical study results by any of the disclosed arrangements or interests, the Phase 3 safety and efficacy studies were randomized, placebo-controlled, double-blind trials, conducted across multiple study sites, and the Investigators were not given access to study results until after the database lock for each study. GW requirements for confidentiality and financial disclosure were outlined in the protocols and clinical trial agreements, in addition to the financial disclosure requirements specified in 21 CFR part 54."*

Clinical reviewer's comment: Potential concerns about the large amount of remuneration received by a few investigators was discussed with Dr. Cara Alfaro in OSI/DCCE.

For example, although the (b) (6) site demonstrated efficacy in GWEP1332B, it did not demonstrate efficacy in GWEP1414. Additionally, as noted by Dr. Alfaro, some of these sites are being inspected, so FDA is "doing due diligence in evaluating data integrity." Therefore, at the time of this review, it does not appear that these monies influenced study outcomes.

Patient Disposition

A total of 177 patients were screened for Study 1332B, and 120 patients were randomized (Table 6). Fifty-seven patients were excluded from the study prior to randomization and considered screen failures. The single most common reason for screen failure was inadequate number of convulsive seizures at baseline, which was reported in 18 patients (32%), which is common in AED treatment trials.

Table 6: Study 1332B Disposition of Patients

Trial Period	CBD n (%)	Placebo n (%)
Treatment Period		
Randomized	61 (100)	59 (100)
Completed	52 (85.2)	56 (94.9)
Withdrawn	9 (14.8)	3 (5.1)
AE	9 (14.8)	1 (1.7)
Lost to follow-up	0	1 (1.7)
Withdrawal by patient or parent/guardian	0	1 (1.7)
Continued to taper period	29 (47.5)	26 (44.1)
Continued to OLE trial	26 (81.3)	30 (90.9)
OLE Trial (GWEP1415)		
Total in OLE trial	49 (94.2)	56 (100.0)

Source: FDA clinical reviewer

Out of the 120 patients who were randomized into Study 1332B, 61 were randomized to the treatment group and 59 to the placebo group. All patients received the correct treatment according to planned treatment allocation. As seen in Table 6 above, 10% of the 120 randomized patients discontinued participation prior to completion of the treatment period, 9 patients (15%) in the CBD group and 3 (5%) in the placebo group. All 9 discontinued patients in the CBD group withdrew due to adverse event(s). Only 1 patient in the placebo group discontinued due to an AE. One placebo patient withdrew because of lack of efficacy, and the other patient was lost to follow-up.

One of the patients who discontinued in the CBD group (#GWEP1332B-(b) (6)) was withdrawn from the study on Day 43 and coded as "withdrawn by investigator due to non-compliance with study drug". However, this patient experienced 7 serious TEAEs on Day 32, leading to discontinuation of the study drug. Therefore, the cause of discontinuation would be properly coded as due to SAE.

Clinical reviewer's comment: In their disposition analysis, the applicant accounts for patient GWEP1332B-(b) (6) as withdrawn by investigator for non-compliance with the study drug. In the AE analysis, this patient was coded as terminated due to AE. However, for the purposes of this analysis, the patient's reason for withdrawal from the study has been revised to adverse event.

Although the overall numbers and percent of patients who discontinued participation during the treatment period of Study 1332B were small, there was an imbalance between the two groups. Specifically, the completion rate for the placebo group (94.9%) was notably greater than in the treatment group (84.2%), and the reasons for discontinuation differed between groups. All of the patients in the CBD group who withdrew during the treatment period, did

so because of adverse events, while only 1 patient (1.6%) did so in the placebo group. This phenomenon is not uncommon in AED treatment trials.

Protocol Violations/Deviations

Ninety-four patients (78.3%) were reported as having at least one protocol deviation during the study. The incidence of deviations in both groups was very similar, with 48 in the CBD group (78.6%) and 46 in the placebo group (77.9%). Three patients had reported protocol deviations related to eligibility criteria (all with lack of ESC confirmation of diagnosis before randomization); however, diagnosis was subsequently confirmed in all of these patients.

There were 4 instances of protocol deviations that were directly related to safety – all in patients who fulfilled elevated transaminase withdrawal criteria but were not withdrawn from the study. Two patients had elevated ALT or AST > 3 x ULN with a concurrent TEAE of fatigue in 2 patients (1 of whom also had concurrent INR > 1.5) and 1 patient had elevated ALT or AST > 3 x ULN with concurrent eosinophilia. In the remaining case (b) (6) the patient had level of AST > 8 x ULN and ALT > 5 x ULN at end of treatment. The elevated transaminases in these four patients resolved, and these protocol deviations were not expected to impact efficacy.

All of the protocol deviations were considered minor by the applicant with the majority related to visit dates being outside the time windows specified in the protocol. Other protocol deviations were related to entry into the OLE study (17 patients), completion of the informed consent (21 patients), and lack of a urine THC test (17 patients).

Clinical reviewer's comment: The protocol deviations were minor from the perspective of not impacting the study results. Four protocol deviations were related to patients not being withdrawn from the study when they fulfilled a liver stopping criterion and were considered "important".

Table of Demographic Characteristics

The baseline demographics of the patients enrolled and randomized in Study 1332B (ITT dataset) were similar between groups (Table 7). The mean age in the both groups was 9.8 years, and the distribution among the predefined age groups was also similar between treatment groups. There was a sufficient number of patients < 6 years of age in both groups. Most patients in both the CBD and placebo groups were from the US (57.4% and 62.7%, respectively), with the rest of the patients were from France (19.7% and 10.2%), Poland (9.8% and 13.6%), and the UK (13.1% and 13.6%).

Table 7: Study 1332B, Baseline demographics, ITT population

Demographic	CBD 20 mg/kg/day (N=61)	Placebo (N=59)
Age (years)		
n	61	59
Mean (SD)	9.74 (4.73)	9.78 (4.85)
Median	9.1	9.2
Min, Max	2.5, 18.0	2.3, 18.4
Age group [n (%)]		
2–5 years	18 (29.5)	17 (28.8)
6–12 years	23 (37.7)	24 (40.7)
13–18 years	20 (32.8)	18 (30.5)
Sex [n (%)]		
Female	26 (42.6)	32 (54.2)
Male	35 (57.4)	27 (45.8)
Race [n (%)]		
White/Caucasian	44 (72.1)	50 (84.7)
Black/African American	2 (3.3)	2 (3.4)
Asian	1 (1.6)	0
Not Applicable[a]	11 (18.0)	6 (10.2)
Other	3 (4.9)	1 (1.7)
Country [n (%)]		
France	12 (19.7)	6 (10.2)
Poland	6 (9.8)	8 (13.6)
US	35 (57.4)	37 (62.7)
UK	8 (13.1)	8 (13.6)
Height (cm)		
n	60	59
Mean (SD)	132.2 (26.3)	131.1 (24.4)
Median	127.50	127.00
Min, Max	89.3, 188.0	87.6, 189.0
Weight (kg)		
n	61	59
Mean (SD)	33.82 (16.631)	35.11 (18.328)
Median	28.40	29.40
Min, Max	10.8, 88.6	12.0, 88.4
Body Mass Index (kg/m^2)		
n	60	59
Mean (SD)	18.3 (4.5)	19.1 (4.7)
Median	17.4	18.1
Min, Max	13.0, 38.7	13.5, 35.6

[a] *Not applicable as per country-specific data protection law*
Source: Applicant's Tables 8.2.2-1 and 3.1.2B, verified by FDA clinical reviewer

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Baseline characteristics related to the patients' underlying epilepsy were overall similar between the two treatment groups, although some differences are noted, as seen in Table 8 below. The median number of current AEDs was the same for both groups. The proportion of patient who experienced an increase in seizure frequency with previous medications was similar between groups (CBD: 73.8% and placebo: 71.2%). The percentage of patients on a ketogenic diet was similar between groups (9.8% CBD patients vs. 6.8% placebo patients); however, VNS was used by fewer CBD patients (9.8%) than placebo patients (15.3%).

The baseline convulsive seizure frequency (median per 28 days) was very similar between groups (CBD: 12.4, placebo: 14.9), allowing for comparison between groups of the primary efficacy endpoint. The most prominent difference between groups with respect to underlying disease is seen in baseline nonconvulsive seizure frequency: medians of 14.0 and 64.0 in CBD and placebo groups, respectively.

Table 8: Study 1332B, Baseline characteristics, ITT population

Baseline Characteristic	CBD 20 mg/kg/day (N=61)	Placebo (N=59)
Number of current AEDs		
n	61	59
Mean (SD)	3.0 (1.0)	2.9 (0.9)
Median	3	3
Min, Max	1.0, 5.0	1.0, 5.0
Number of prior (failed) AEDs		
n	61	59
Mean (SD)	4.6 (4.3)	4.6 (3.3)
Median	4	4
Min, Max	0.0, 26.0	0.0, 14.0
Concurrent AEDs [n (%)]		
Clobazam	40 (65.6%)	38 (64.4%)
Valproic Acid	36 (59.0%)	32 (54.2%)
Stiripentol	30 (49.2%)	21 (35.6%)
Baseline Convulsive Seizures per 28 Days		
n	61	59
Mean (SD)	67.3 (230.6)	60.6 (129.8)
Median	12.4	14.9
Min, Max	3.9, 1716.7	3.7, 718.0
Baseline Nonconvulsive Seizures per 28 Days		
n	37	41
Mean (SD)	275.3 (564.4)	389.8 (732.9)
Median	14.0	64.0
Min, Max	0.9, 2706.4	1.0, 2767.0

Source: Table 3.2.2B, Study 1332B CSR

As seen in Table 9, the patients' baseline seizure types were reasonably similar between groups. Although the baseline nonconvulsive seizure frequency was notably greater in the placebo group than in the CBD group, similar numbers of patients in both groups reported nonconvulsive seizures: 37 (60.1%) of CBD patients and 41 (69.5%) of placebo patients.

Table 9: Study 1332B, Summary of Seizure Types Reported During Baseline (ITT Population)

Seizure Class/Type	CBD (N=61) n (%)	Placebo (N=59) n (%)
Tonic-clonic	55 (90.2)	52 (88.1)
Absence	20 (32.8)	23 (39.0)
Myoclonic	18 (29.5)	25 (42.4)
Tonic	17 (27.9)	12 (20.3)
Countable partial	15 (24.6)	14 (23.7)
Clonic	14 (23.0)	11 (18.6)
Atonic	5 (8.2)	11 (18.6)
Other partial	3 (4.9)	4 (6.8)
Nonconvulsive seizures	37 (60.1)	41 (69.5)

Source: FDA statistical reviewer

Clinical reviewer's comment: Although there were some differences between the groups with respect to baseline characteristics, the similarity of the baseline characteristics overall suggests that the underlying seizure disorders in the two groups are reasonably similar. The difference between the groups in baseline nonconvulsive seizure frequency is discussed in the review of the secondary endpoints.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Overall, treatment compliance was better in the placebo group than in the CBD group. Ten patients total had at least one day during the treatment period in which both doses were recorded as not being taken, with more patients in the CBD group (7 patients [11.5%]) than the placebo group (3 patients [5.1%]). The maximum number of days in which the IMP was not taken was 21 days, which occurred in a patient in the placebo group. The other 10 patients missed both doses on fewer than 12 days, and all of these missed doses occurred between last treatment dose and withdrawal from the study. Missing one dose/day also occurred more frequently in patients in the CBD group (10 patients [16.4%]) than in the placebo group (5 patients [8.5%]). The median number of days on which both doses of IMP (AM and PM) were taken during the treatment period was 99 days (range: 11–131 days).

Use of rescue medications, however, was more frequent in patients in the placebo group (41 patients [69.5%]) than in the CBD group (36 patients [59.0%]), though the difference between

groups is minor.

Clinical reviewer's comment: Although treatment compliance was slightly worse in the CBD group as compared to the placebo group (which may be a consideration for safety and adverse events), it did not appear to impact efficacy. Rescue medication usage did not predispose towards increased efficacy in the CBD group, as the frequency of use of these drugs was higher in the placebo group.

Efficacy Results – Primary Endpoint

All patients who were randomized, received at least 1 dose of study drug, and had at least one post-baseline efficacy endpoint were included in the ITT analysis dataset, per their allocated treatment group. The primary efficacy analyses were conducted on the ITT analysis set, which comprised a total of 120 patients: 61 patients in the CBD group and 59 patients in the placebo group.

As noted above, the primary efficacy endpoint was the percentage change from baseline in total convulsive seizure frequency per 28 days during the treatment (titration + maintenance) period. There was a statistically significant difference between the groups in the percentage change from baseline in total convulsive seizure frequency during the treatment period, in favor of CBD treatment (p=0.0123). The median percentage change from baseline in total convulsive seizure frequency was −38.9% in the CBD group compared with −13.3% in the placebo group. The estimated median difference was −22.8% (Table 10).

Table 10: Study 1332B, Analysis of the Primary Endpoint

	CBD (N=61)	Placebo (N=59)
Total Convulsive Seizure Frequency (per 28 Days)		
Baseline Period Median	12.4	14.9
Treatment Period Median	5.9	14.1
Median Percentage Change from Baseline (Q1, Q3)	−38.9 (−69.5, −4.8)	−13.3 (−52.5, 20.2)
Estimated Median Difference (CI*)	−22.8 (−41.1, −5.4)	
P-value by Wilcoxon rank-sum test	0.0123	

Source: CSR Table 8.4.1.1-1, confirmed by the FDA statistical reviewer
*based on Hodges-Lehmann estimator

Clinical reviewer's comment: Compared with the placebo group, the CBD group demonstrated a statistically significant decrease in percent change in convulsive seizures from baseline to the treatment period. As noted above, this is the same primary efficacy endpoint used in most AED treatment trials, although the seizure types counted toward the primary endpoint may

differ based on the underlying disease. The findings are both statistically significant (p=0.0123) and clinically meaningful.

As seen in Figure 2 below, sensitivity analyses using ANCOVA on the original data, ranked data, and log-transformed data all yielded similar results to the primary analysis. Consistent results were seen for the maintenance period and each 4-week period of the maintenance period (Table 11).

Table 11: Study 1332B, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint

Analysis Period	Treatment	n	Median	Q1, Q3	Estimated Median Difference[b] (95% CI)	p-value[c]
Maintenance Period	20 mg/kg (N=61)	60	-40.67	-79.9, -10.9	-26.06 (-45.07, -8.24)	0.0052
	Placebo (N=59)	59	-15.95	-54.9, 21.0		
Maintenance Period (Week 1 to 4)[a]	20 mg/kg (N=61)	57	-58.17	-80.0, -19.0	-29.69 (-48.75, -11.23)	0.0020
	Placebo (N=59)	58	-24.70	-53.6, 29.5		
Maintenance Period (Week 5 to 8)[a]	20 mg/kg (N=61)	54	-49.20	-82.3, -15.2	-25.21 (-44.76, -8.33)	0.0055
	Placebo (N=59)	56	-25.00	-56.4, 5.9		
Maintenance Period (Week 9 to 12)[a]	20 mg/kg (N=61)	52	-41.40	-87.9, 7.3	-19.96 (-40.74, 1.25)	0.0756
	Placebo (N=59)	55	-21.74	-64.1, 21.7		

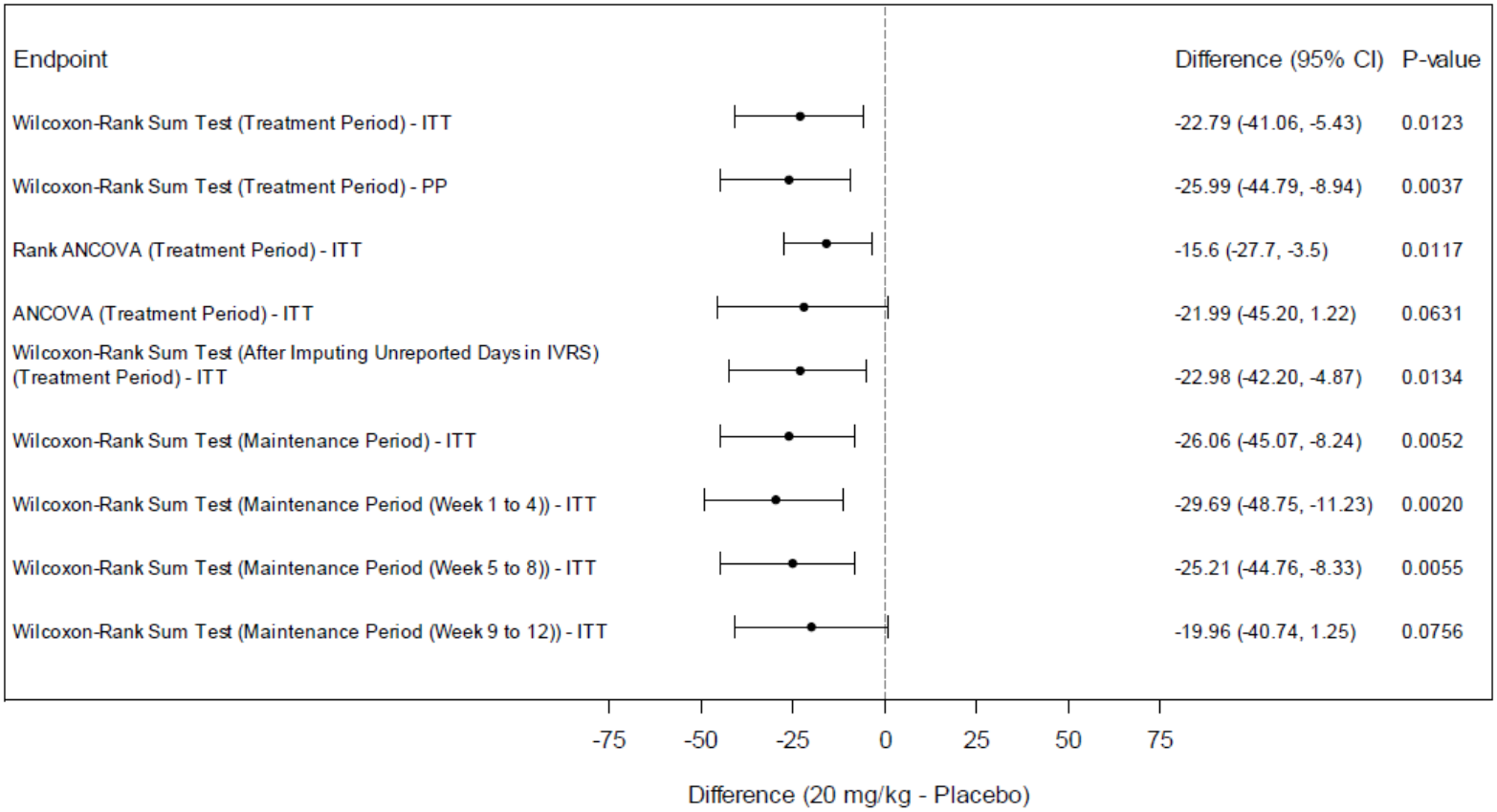
Source: Study 1332B, CSR-Tables, Table 8.1.1B

[a] Patients with at least 7 days of seizure data within the corresponding 4 week period

[b] based on Hodges-Lehmann estimator

[c] by Wilcoxon Rank Sum Test

Figure 2: Study 1332B, Sensitivity Analyses, Primary Efficacy Endpoint



The Hodges-Lehmann median difference and 95% CI and the p-value from the Wilcoxon rank-sum test are presented for the Wilcoxon rank-sum test analyses.
The difference in LS means, 95% CI and p-value for the difference are presented for the ANCOVA analyses.
Note: the log-transformed ANCOVA and multiple imputation to account for MNAR sensitivity analyses are not included.

Source: Figure 8.4.1.1.1-1, Study 1332B CSR

Missing data

Two sensitivity analyses assessing the impact of missing data were conducted by the applicant. One analysis used the worst of last observation, next observation, or the mean value of observed data to impute the intermittent missing values due to unreported days in the IVRS. As there were few intermittent missing data (4% in each group), the result was similar to the primary analysis. This analysis, however, did not address the impact of missing data due to dropouts, which might be of concern as the dropout rates were unbalanced: 9 (15%) in the CBD group vs. 3 (5%) in the placebo group.

The other sensitivity analysis used multiple imputation (MI) to impute all missing data, including missing due to dropout. In this analysis, intermittent missing values before the last visit were first imputed under missing at random assumption (MAR). Then non-intermittent missing data were imputed under the missing not at random (MNAR) assumption that the imputed values for CBD patients who discontinued were different from those of placebo patients. This analysis showed that the result for the primary endpoint remained statistically significant when the values imputed for the dropouts in CBD group were slightly worse (up to one standard error of the observed convulsive seizure frequency in the placebo group) than those of placebo patients.

All dropouts in the CBD group were due to adverse events and most occurred early during the maintenance phase. It seemed that some patients experienced or reported fewer seizures prior to discontinuing the study. For example, 3 patients (all in the CBD group) who withdrew early from the trial had no convulsive seizures reported during the maintenance period. The appearance of seizure reduction in these patients may be artificial. One could argue that they might have behaved similarly as the rest of patients if they had been able to recover from the adverse events. On the contrary, one could also argue that CBD simply failed them because they were no longer able to tolerate CBD treatment even if there was some indication of benefit on seizure frequency from CBD. The two arguments seem equally valid. The latter argument may also shed some light on how useful CBD treatment could be. Therefore, the statistical reviewer conducted a worst-case type of analysis, in which patients who withdrew were assigned the worst result (the largest percentage change from base in convulsive seizure frequency). The resulting estimated median difference between the two groups was −14.1% (Table 12), smaller than the estimated median difference of −22.8% from the primary analysis, but still numerically in favor of the CBD treatment.

Table 12: Study 1332B: Statistical Reviewer's Worst-Case Analysis of the Primary Endpoint

	CBD (N=61)	Placebo (N=59)
Median Percentage Change from Baseline	−35.4	−13.3
Estimated Median Difference (CI*)	−14.1 (−33.3, 8.5)	

*based on Hodges-Lehmann estimator
Source: FDA statistical reviewer

Clinical reviewer's comment: The FDA statistical reviewer performed sensitivity analyses for missing data. One analysis addressed overall missing data and produced statistically significant results very similar to the results of the primary efficacy endpoint analysis.

As noted above, there was an imbalance between treatment groups with respect to dropouts (14.8% and 5.1% in the CBD and placebo groups, respectively), and some of these patients experienced or reported fewer seizures prior to discontinuing the study. The FDA statistician conducted a worst-case analysis to assess this imbalance and if the study results were driven by the patients who discontinued early and experienced/reported few seizures. The estimated median difference in the worst-case analysis, though lower than that in the primary endpoint outcome, still favored the CBD group over placebo, and confirmed the robustness of the primary efficacy results to missing data.

Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, and region in CBD and placebo groups. The sample sizes for each subgroup are small, making it difficult to derive any substantive conclusions of efficacy in a specific subgroup; however, all results trended in favor of CBD, compared to placebo (see Table 13).

As seen in Table 14 below, subgroup analyses were also performed on the primary efficacy endpoint for concomitant drugs of interest, specifically clobazam, valproic acid, and stiripentol. Concomitant use of any of these AEDs with CBD was associated with better results than without these drugs; however, the results favored CBD over placebo for all AED subgroups. Please see Section 4.5 and Section 7.1.3 for further discussion of the potential interaction between clobazam and CBD.

Table 13: Study 1332B, Primary Efficacy Endpoint Analysis by Subgroups

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*	
Sex					
Male	20 mg/kg	35	-37.14	-19.63	(-41.85, 4.89)
	Placebo	27	-9.52		
Female	20 mg/kg	26	-42.97	-24.87	(-53.97, -0.30)
	Placebo	32	-20.60		
Race					
White/Caucasian	20 mg/kg	44	-38.57	-21.52	(-41.46, -0.31)
	Placebo	50	-20.60		
Other	20 mg/kg	17	-39.52	-45.44	(-89.64, 5.61)
	Placebo	9	10.71		

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*	
Age					
2-5 years	20 mg/kg	18	-54.86	-29.58	(-60.63, 8.96)
	Placebo	17	-39.37		
6-12 years	20 mg/kg	23	-28.57	-29.86	(-63.48, 6.02)
	Placebo	24	12.43		
13-18 years	20 mg/kg	20	-49.33	-18.19	(-40.48, 13.82)
	Placebo	18	-24.73		
Region					
USA	20 mg/kg	35	-55.15	-24.67	(-50.50, -3.19)
	Placebo	37	-22.58		
Rest of the World	20 mg/kg	26	-33.79	-19.75	(-48.88, 6.53)
	Placebo	22	-7.43		

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 14: Study 1332B, Primary Efficacy Endpoint Analysis by Concomitant Drugs of Interest

Concomitant Drug Y/N	Treatment	N	Median	Median Difference (95% CI)*
Clobazam				
Yes	20 mg/kg	40	-45.0	-31.8 (-55.9, -10.2)
	Placebo	38	-9.9	
No	20 mg/kg	21	-28.6	-6.3 (-36.5, 23.7)
	Placebo	21	-18.6	
Valproic Acid				
Yes	20 mg/kg	36	-39.6	-26.2 (-51.6, -0.8)
	Placebo	32	-11.8	
No	20 mg/kg	25	-38.3	-20.32 (-47.7, 7.4)
	Placebo	27	-18.6	
Stiripentol				
Yes	20 mg/kg	30	-28.1	-32.7 (-57.1, -9.0)
	Placebo	21	5.4	
No	20 mg/kg	31	-56.8	-20.8 (-45.6, 1.4)
	Placebo	38	-32.0	

Source: Study 1332B, CSR Table 9.15.1B
*based on Hodges-Lehmann estimator

Efficacy Results – Secondary and other relevant endpoints

Most of the secondary endpoints in Study 1332B favored the CBD group.

Key Secondary Endpoint: Proportion of Treatment Responders (50% Reduction in Convulsive Seizure Frequency)

During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the CBD group (42.6%), compared with the placebo group (27.1%). There were twice the odds of achieving a ≥ 50% reduction in convulsive seizure frequency in the CBD group compared with the placebo group; however, the difference between treatments was not statistically significant (p=0.0784; Table 15).

Table 15: Study 1332b, Analyses of the Secondary Endpoint

≥ 50% Reduction in Convulsive Seizure Frequency from Baseline During the Treatment Period	CBD (N=61)	Placebo (N=59)
Yes (%)	26 (42.6)	16 (27.1)
No (%)	35 (57.4)	43 (72.9)
Odds Ratio (95% CI)	2.00 (0.93, 4.30)	
Nominal p-value	0.0784	

Source: Table 8.4.1.2.1-1 of CSR, confirmed by FDA statistical reviewer.

Clinical reviewer's comment: Although the difference between treatment groups for the 50% responder rate was not statistically significant, the results trended in favor of the CBD group. The odds ratio of 2.0 demonstrates that there were twice the odds of a 50% reduction in convulsive seizure frequency in the CBD group compared with the placebo group, which is a clinically meaningful difference. Restricting the assessment of efficacy to 50% responders limits a fuller assessment of efficacy, since a <50% decrease in seizure frequency may provide meaningful improvement for some patients.

Other Secondary Endpoints of Clinical Interest

- **Nonconvulsive Seizures**

  As noted in Section 6.1.1 above, an increase in frequency of nonconvulsive seizures in the setting of reduced convulsive seizure frequency would be considered a significant adverse effect of the drug; therefore, percentage change in nonconvulsive seizure frequency is a secondary endpoint of clinical interest.

  The percentage change from baseline in total nonconvulsive seizure frequency during the treatment period was calculated for both treatment groups. As seen in Table 15, the median percentage change from baseline in nonconvulsive seizure frequency during the treatment period was −40.16 in the CBD group compared with −34.69 in the placebo group. There was essentially no difference between groups, as the estimated median difference was 0.00. There was no difference between groups with respect to nonconvulsive seizure-freedom. Seven of 37 patients (18.9%) in the CBD group experienced non-convulsive seizure-freedom during the treatment period, as compared

to 8/41 patients (19.5%) in the placebo group.

Table 16: Study 1332B, Percentage Change from Baseline in Nonconvulsive Seizure Frequency

	CBD (N=61)	Placebo (N=59)
Total Nonconvulsive Seizure Frequency (per 28 Days)	n=37	n=41
Baseline Period Median (Q1, Q3)	14.00 (6.0, 222.1)	64.00 (9.7, 400.0)
Treatment Period Median (Q1, Q3)	13.55 (0.6, 119.4)	34.29 (1.2, 277.7)
Median Percentage Change During Treatment (Q1, Q3)	−40.16 (−92.1, −3.6)	−34.69 (−97.5, −0.7)
Estimated Median Difference (CI)	0.00 (−21.36, 31.59)	

Source: Applicant's Table 8.4.1.2.5-1, Study 1332B CSR

Reviewer's comment: Analysis of change in nonconvulsive seizure frequency revealed no difference between CBD and placebo.

- **Convulsive Seizure Treatment Responders and Convulsive Seizure Freedom**
  As seen in Table 17, the proportion of patients with a reduction ≥ 25% in baseline convulsive seizure frequency was greater in the CBD group (62.3%) than in the placebo group (44.1%). Similarly, the proportion of patients achieving a reduction of ≥75% in their baseline convulsive seizure frequency favored CBD (23.0%) over placebo (11.9%). Analysis of patients who achieved complete convulsive seizure-freedom was complicated by the very low numbers: 3 patients in the CBD group and 0 patients in the placebo group.

Table 17: Study 1332B, Summary and Analysis of Convulsive Seizure Treatment Responders

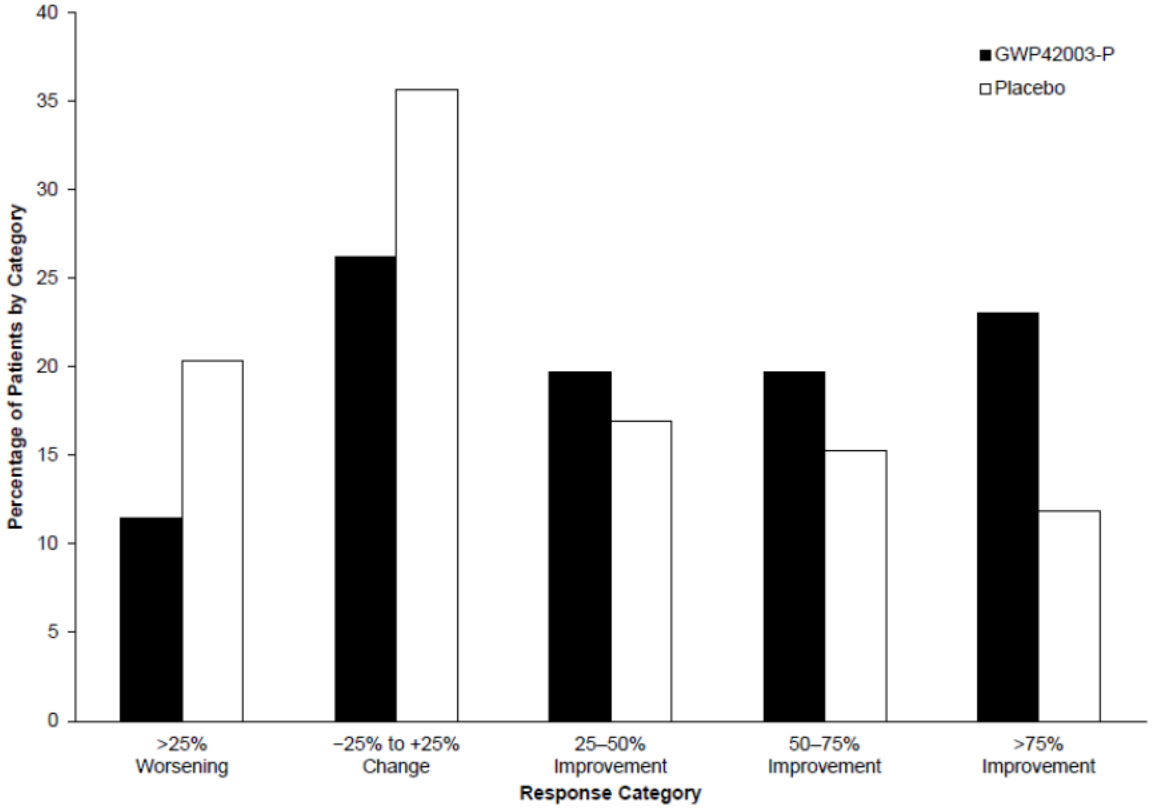
Treatment Responders (Convulsive Seizures)	CBD (N=61)	Placebo (N=59)
≥ 25% Reduction in Convulsive Seizure Frequency from Baseline		
Yes (%)	38 (62.3)	26 (44.1)
No (%)	23 (37.7)	33 (55.9)
Odds Ratio (CI)a	2.10 (1.01, 4.35)	
≥ 50% Reduction in Convulsive Seizure Frequency from Baseline		
Yes (%)	26 (42.6)	16 (27.1)
No (%)	35 (57.4)	43 (72.9)
Odds Ratio (CI)a	2.00 (0.93, 4.30)	
nominal *p*-value	0.0784	

Treatment Responders (Convulsive Seizures)	CBD (N=61)	Placebo (N=59)
≥ 75% Reduction in Convulsive Seizure Frequency from Baseline		
Yes (%)	14 (23.0)	7 (11.9)
No (%)	47 (77.0)	52 (88.1)
Odds Ratio (CI)	2.21 (0.82, 5.95)	
100% Reduction in Convulsive Seizure Frequency from Baseline		
Yes (%)	3 (4.9)	0
No (%)	58 (95.1)	59 (100.0)
Difference in Proportions (CI)	4.9% (–0.5%, 10.3%)	

The 95% CI and the p-value from the CMH test (stratified by age group)
Source: Applicant's Table 8.4.1.2.2-1, Study 1332B CSR

Based on the data above, the number of patients experiencing a > 25% worsening, –25 to +25% change, 25–50% improvement, 50–75% improvement, or > 75% improvement in convulsive seizure frequency from baseline was calculated for each treatment group for the treatment period. Fewer patients in the CBD group than in the placebo group experienced a worsening in total convulsive seizure frequency in all responder groups, as seen in Figure 3 below.

Figure 3: Study 1332B, Continuous Response Analysis for Convulsive Seizures



Source: Figure 8.4.1.2.3-1, Study 1332B CSR

Clinical reviewer's comment: When responder categories are considered, patients in the CBD group generally had a greater improvement or lesser worsening than those in the placebo group. These findings are not independent of the percent change in seizure frequency and are supportive of the primary efficacy endpoint finding.

- **Individual Seizure Types and Total Seizures**

Total Seizures

Analysis of change in total seizure frequency is summarized in Table 18. The CBD group had a greater median percentage change from baseline in total seizure frequency during the treatment period (−28.57) compared with the placebo group (−9.00). The estimated median difference favored the CBD group over placebo (−19.20).

Table 18: Study 1332B, Percentage Change from Baseline in Total Seizure Frequency

Total Seizure Frequency (per 28 Days)	CBD (N=61)	Placebo (N=59)
Baseline Period Median (Q1, Q3)	24.00 (10.4, 141.0)	41.48 (12.0, 367.0)
Treatment Period Median (Q1, Q3)	13.71 (4.8, 137.2)	31.11 (7.7, 282.6)
Median Percentage Change During Treatment (Q1, Q3)	−28.57 (−70.4, −4.0)	−9.00 (−51.4, 19.6)
Estimated Median Difference (CI)	−19.20 (−39.25, −1.17)	

Source: Table 9.4.1.1B, Study 1332B CSR

Seizure subtypes

The sponsor assessed outcomes for the following seizure types: tonic, tonic-clonic, atonic, countable partial seizures, other partial seizures, clonic seizures, myoclonic seizures, and absence seizures. Not all seizure subtype outcomes favored the CBD group. Seizure types in which the results favored CBD over placebo include tonic-clonic, tonic, atonic, countable partial, and other partial seizures. For clonic, myoclonic, and absence seizures, results favored placebo over CBD.

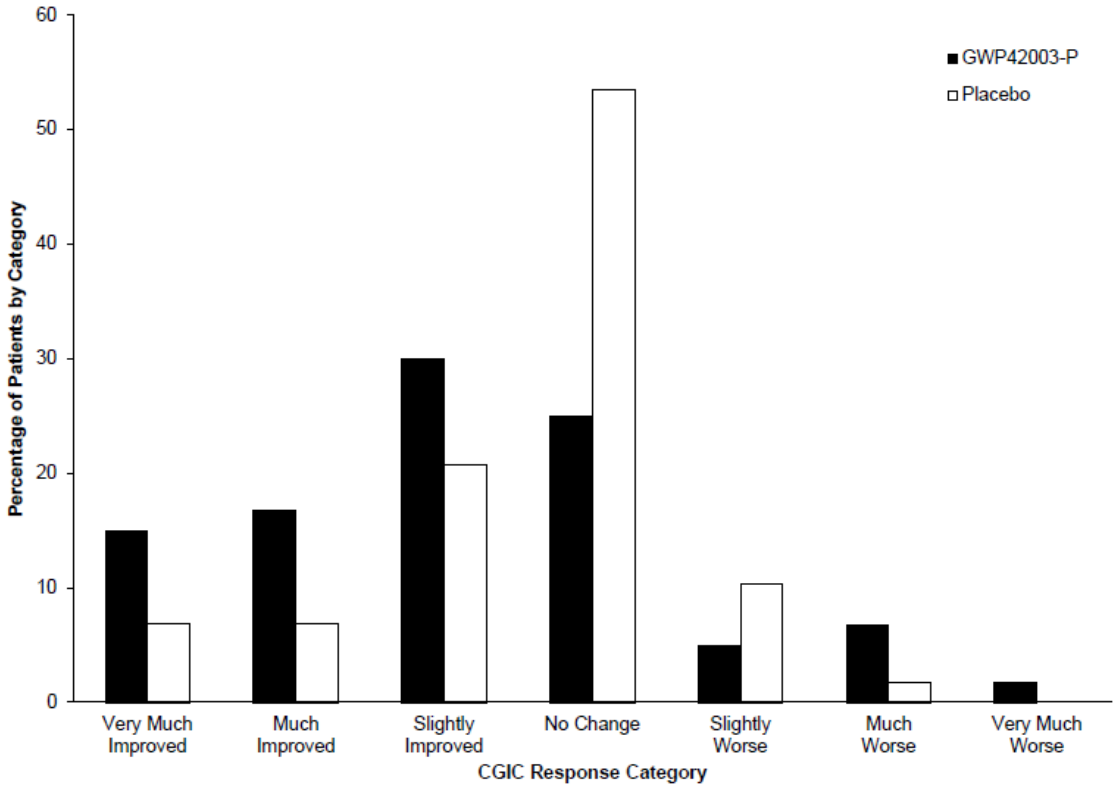
Clinical reviewer's comment: Analysis of change in total seizure frequency favored CBD over placebo. Analysis of the median change in seizure frequency from baseline in most of the seizure subtypes favored CBD over placebo. The ones that favored placebo only did so by small amounts. The numbers of patients/seizures in some subtypes is small, making it difficult to draw conclusions. The reason for lack of efficacy in reducing clonic seizures is unclear but may be related to mischaracterization of seizures by caregivers. Additionally, there is no clinical reason to expect a drug to

reduce tonic-clonic seizures but not clonic seizures. Therefore, the clinical interpretability of the seizure subtypes analyses is uncertain.

Caregiver Reported Outcomes

- **Caregiver Global Impression of Change (CGIC)**
  The caregiver's perception in change from baseline in overall condition was calculated for each treatment group using the CGIC. As seen in Figure 4 below, caregivers reported more CBD patients as very much, much, or slightly improved (63.1%) than placebo (35.1%) at the final visit as compared to overall condition at baseline. More placebo patients were reported as having no change or being slightly worse (63.2%) than CBD patients (28%). Only 1.8% of placebo patients were reported as much worse and none were reported as very much worse, as compared to 7.0% and 1.8% in the CBD group.

Figure 4: Study 1332B, Caregiver Global Impression of Change at Last Visit



Source: Applicant's Figure 8.4.1.2.15-1, Study 1332B, CSR

Clinical reviewer's comment: In general, more patients were reported as having improvement in overall condition in the CBD group than in the placebo group. However, more patients in the CBD group were reported as much or very much worse than in the placebo group (8.8% vs. 1.8%, respectively), though the small number of

patients in these categories makes it challenging to draw any conclusions regarding worsening. The overall analysis does favor CBD patients as having improvement in their overall condition.

Dose/Dose Response

See Section 7.1.4.

Durability of Response and Persistence of Effect

Sensitivity analyses of the primary endpoint were performed on the maintenance period and each 4-week period of the maintenance. Consistent results were seen for each of these time periods in Study 1332B. See also Section 7.1.5.

6.2. GWEP1414 – A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox–Gastaut syndrome in children and adults

6.2.1. Study Design

Overview and Objective

The objectives of this study were as follows:

- Primary: *"To evaluate the efficacy of GWP42003-P as adjunctive treatment in reducing the number of drop seizures (per 28 days) when compared with placebo in patients with Lennox-Gastaut syndrome (LGS)."*

- Secondary:
  - Key Secondary Objectives: *To assess the following in LGS patients taking GWP42003-P as adjunctive treatment, when compared with placebo: number of patients drop seizure-free; responder rate (in terms of reduction in drop seizures); reduction in the number (per 28 days) of non-drop seizures; frequency of subtypes of seizures; safety and tolerability of GWP42003-P through monitoring of the following: adverse events (AEs), suicidal ideation, abuse liability, cannabis withdrawal effects, clinical laboratory tests, vital signs, and menstruation cycles (in females).*
  - *Other Secondary Objectives:*
    - *To assess the following in LGS patients taking GWP42003-P as adjunctive treatment, when compared with placebo: number of episodes of status epilepticus (SE); need for hospitalization due to epilepsy; change in duration of subtypes of seizures; sleep disruption and daytime*

sleepiness; quality of life; adaptive behavior; cognitive function; growth and development.

- *To determine the pharmacokinetics (PKs) of cannabidiol (CBD) and its major metabolites following single and multiple doses of GWP42003-P.*
- *To determine the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), where available.*

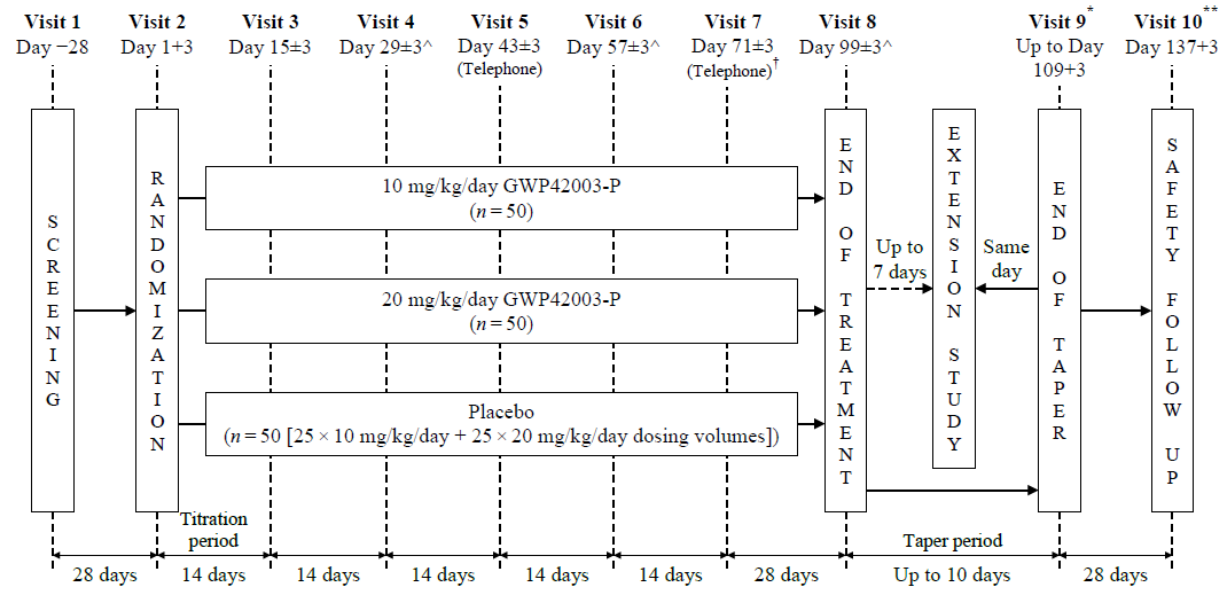
Trial Design

- **Basic Study Design**

  GWEP1414 (Study 1414) was a Phase 3, multicenter, double-blind, randomized, placebo controlled study of cannabidiol conducted at 29 centers worldwide. Approximately 150 patients were to be randomized into the study. This study was conducted to test the clinical efficacy, safety, and PK of cannabidiol oral solution in patients with seizures due to Lennox-Gastaut syndrome. The total duration of subject participation in the study was approximately 3 months. The study consisted of a Baseline Period, a Treatment Period (titration plus maintenance), and a Taper Period (alternatively, patients enrolled in an open label, LTE study).

  The general design of Study 1414 is similar to other pivotal AED treatment trials (Figure 5 below).

Figure 5: Study 1414, Trial Design and Treatment Schematic



*For patients who did not enter the OLE trial at Visit 8 or for those who withdrew early and tapered IMP. Patients who completed treatment but opted not to enter the OLE trial, or who withdrew from the trial early, had weekly (±3 days) safety telephone calls from Visit 9 (or date of final dosing) until Visit 10.
**For patients who did not enter the OLE trial or who withdrew from the study early; could be conducted by telephone.
†For patients in France only: Visit 7 was completed at the clinic and was not conducted by telephone.
^For patients in France only: Visit window was −3 days rather than ±3 days.

Source: Figure 5.1-1, Study 1414 CSR

- **Trial location**
  Study 1414 was conducted in the US and Western Europe (UK, France, and Spain). The patient population and treatment regimen in Europe is expected to be similar to that in the US.

- **Choice of control group**
  The applicant used a concurrent placebo control as the comparator group and administered the study drug (CBD or placebo) as an adjunct to concomitant AEDs. Because the underlying disease is severe and life-threatening and there are six AEDs currently approved for use in the US for the treatment of seizures due to LGS, comparison to placebo is appropriate.

- **Diagnostic criteria**
  Patients were enrolled if they had a "clinical diagnosis of LGS", which included documentation of the patient having met EEG diagnostic criteria and evidence of more than 1 type of generalized seizure, including drop seizures (atonic, tonic or tonic-clonic) for at least 6 months.

- **Key inclusion/exclusion criteria**
  Inclusion Criteria:
  1. Willing and able to give informed assent/consent and able to comply with all study requirements.
  2. Age between 2 and 55 years
  3. *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.*
  4. Had history of slow (< 3.0 Hz) spike-and-wave pattern in an EEG prior to their enrollment into the baseline period.
  5. Must have experienced ≥2 drop seizures (i.e., atonic, tonic, or tonic-clonic, seizures) each week during the first 28 days of the baseline period.
  6. Must be taking at least 1 AED at a stable dose for at least four weeks.
  7. All epilepsy therapies (including ketogenic diet and VNS) must have been stable for four weeks prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study.
  8. Has completed their IVRS telephone diary on at least 25 days of the baseline period.

Exclusion Criteria:

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. Clinically significant unstable medical conditions other than epilepsy.
4. Clinically relevant symptoms or a clinically significant illness in the 4 weeks prior to screening or randomization, other than epilepsy.
5. Clinically significantly abnormal, in the investigator's opinion, laboratory values at screening or randomization.
6. Clinically relevant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which would have, in the investigator's opinion, interfered with the ability to read their ECGs.
7. Alcohol or substance abuse within the last 2 years prior to the trial or daily consumption of 5 or more alcohol-containing beverages.
8. 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.
9. Unwilling to abstain from using recreational or medicinal cannabis, or synthetic cannabinoid based medications (including Sativex) during the trial.
10. History of symptoms indicative of postural hypotension.
11. Ingested alcohol in the 24-hour period prior to the first trial visit and/or was unwilling to abstain from drinking alcohol throughout the treatment period.
12. 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.
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 was taking felbamate for less than 1 year prior to screening.
16. 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.
17. Patient had significantly impaired hepatic function at screening (Visit 1) or randomization (Visit 2): ALT or AST > 5 X ULN; ALT or AST > 3 X ULN **and** total bilirubin > 2 X ULN **or** INR > 1.5; ALT or AST > 3 X ULN with concomitant fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or

eosinophilia (>5%). (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 prevent 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 at screening.
20. Taking more than 4 concurrent AEDs.
21. Had taken corticotropins in the 6 months prior to screening or 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.

Clinical reviewer's comment: The inclusion and exclusion criteria for Study 1414 were generally similar to eligibility criteria in other AED treatment trials for LGS.

- **Dose Selection**

The 10 and 20 mg/kg/day dose of CBD and the titration (dose escalation) regimen used in Study 1414 were based on unblinded safety and PK data from Study 1332A, which assessed a completely different patient population. Other cannabidiol products have been used in patients with refractory seizures at doses of 10-20 mg/kg/day in published literature.

Clinical reviewer's comment: Dosing in Study 1414 was based on PK and safety data collected from Study 1332A. As noted above, CBD doses of 5, 10, and 20 mg/kg/day were explored in that study. In a Type C meeting on 16 June 2014, the Division provided the following recommendations regarding dosing for Study 1414:

- ***Inclusion of multiple doses to assess dose response.***
- ***Consideration of differences in concomitant medications in patients with DS and LGS for the purpose of dose selection. Stiripentol (STP) was more likely to be used concurrently in patients with DS than LGS, and STP inhibits CYP450 and may have an impact on the PK of a variety of AEDs, including CBD.***

Based on these recommendations, the applicant opted to evaluate 10 and 20 mg/kg/day doses in Study 1414. DNP accepted this plan.

- **Study Treatments**

Subjects randomized to the CBD treatment groups received daily doses of CBD oral solution (100 mg/mL) at 10 or 20 mg/kg/day. All doses were divided BID. The drug was started at 2.5 mg/kg/day and increased by 2.5 mg/kg/day over a 7 or 11-day period as

seen in Table 19 below. The patients in the placebo arms received equal volumes of placebo oral solution using an identical titration schedule.

Table 19: Study 1414 Dose Titration Schedule

Day	10 mg/kg/day	20 mg/kg/day
1	2.5 mg/kg	2.5 mg/kg
2	2.5 mg/kg	2.5 mg/kg
3	5.0 mg/kg	5.0 mg/kg
4	5.0 mg/kg	5.0 mg/kg
5	7.5 mg/kg	7.5 mg/kg
6	7.5 mg/kg	7.5 mg/kg
7	10.0 mg/kg	10.0 mg/kg
8	10.0 mg/kg	10.0 mg/kg
9	10.0 mg/kg	15.0 mg/kg
10	10.0 mg/kg	15.0 mg/kg
11	10.0 mg/kg	20.0 mg/kg
12	10.0 mg/kg	20.0 mg/kg
13	10.0 mg/kg	20.0 mg/kg
14	10.0 mg/kg	20.0 mg/kg

- **Assignment to treatment**
  At the start of Visit 1, a unique patient number was assigned to each patient using the IVRS/IWRS, and patients were randomly allocated to 10 mg/kg/day CBD, 20 mg/kg/day CBD or equivalent volume of placebo using the IVRS. The randomization schedules were produced by an independent statistician. Randomization was stratified by age (2-5 years, 6-11 years, 12-17 years, and 18-55 years). Randomization was performed globally.

Clinical reviewer's comment: Patients were randomized after completion of the 28-day baseline period, as they were required to have at least 2 drop seizures per week during this time. Patients who did not have sufficient seizures (or were non-compliant with seizure recording) during the baseline were considered screen failures. This method of randomization is consistent with other AED trials.

- **Blinding**
  The IMP was provided in 100 mL amber glass bottles labeled "GWP42003-P Oral Solution or Placebo". The identity of the IMP assigned to patients was held by the IVRS/IWRS. The PI at each site, or his/her designee, was responsible for ensuring that information on how to access the IVRS/IWRS was available to the relevant staff in case of an emergency and unblinding was required.

- **Dose modification, dose discontinuation**
  Patients were to continue on a stable dose after titration. However, in the case of a poorly tolerated dose during the maintenance period, the investigator was permitted to temporarily or permanently reduce the dose for the remainder of the study. If an unacceptable AE occurred at any time during titration, dosing was to be suspended or amended as advised by the investigator, until the event resolved. Such dose modifications were captured in the CRFs.

  See pages 77-78 below for discussion of reasons for drug discontinuation, including stopping criteria.

- **Administrative structure**
  Investigators at 37 study centers worldwide received IRB/IEC approval to participate in this study, 30 sites screened patients, and 29 centers enrolled and treated patients. Safety data were reviewed on an ongoing basis by the applicant's Medical Monitor and by an independent DSMC. An independent Epilepsy Study Consortium verified the seizure types of screened patients.

- **Procedures and schedule**
  The following table from the applicant summarizes the schedule of study visits, baseline period, treatment period, taper period, and follow-up period.

Table 20: Schedule of Assessments, Studies 1414 and 1423

Visit Number	1	2	3	4	5 (Tel.)	6	7‡ (Tel.)	8♣	9*	Safety Calls	10** (Tel.)
Day Number (Visit window)	**−28**	**1 (+3)**	**15 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**71 (±3)**	**99 (±3)**	**100-106 or 109 (+3)**	**116, 123 & 130 (±3)**	**137 (+3)**
Informed consent/assent	X										
Eligibility Criteria	X	X									
Randomization		X									
Demographics	X										
Medical history	X										
Vital signs	X	X♦	X	X		X		X	X		
Postural BP	X	X									
Physical examination (including height and body weight)	X	X	X	X		X		X	X		
ECG	X	X♦	X	X		X		X	X♦		
Clinical laboratory blood sampling	X	X	X	X		X		X	X♦		
Clinical laboratory urine sampling (dipstick urinalysis)	X	X	X§	X§		X§		X	X♦		
Urine THC screen	X	X						X			
Pregnancy test (if appropriate)†	X	X						X			
PK blood sampling^		X						X◊			
AED blood sampling^^		X		X		X		X			
AEs	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Inpatient epilepsy- related hospitalizations		X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X		X		X	X		
Sleep Disruption 0-10 NRS		X	X	X		X		X			
ESS		X	X	X		X		X			
Vineland-II		X	X	X		X		X			
S/CGIC¶		X▲	X	X		X		X			
S/CGICSD¶		X▲						X			
QOLCE/QOLIE-31-P		X						X			
Cognitive Assessment Battery††		X						X			

Visit Number	1	2	3	4	5 (Tel.)	6	7‡ (Tel.)	8♣	9*	Safety Calls	10** (Tel.)
Patient/Caregiver Impression of IMP Palatability								X			
CWS/PCWS†††		X							X	X^∞	X
Tanner Staging and IGF-1 levels♥		X						X			
Menstruation question (females)		X						X			
Patient diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)		X	X	X		X		X	X		
IVRS and diary training	X	X									
IMP dispensing		X		X		X	X▼	X			
Collection of IMP				X		X	X▼	X	X		
IMP compliance review			X	X		X	X▼	X	X		
Study Medication Use and Behavior Survey#								X			

♣ *Performed for all patients who completed or withdrew from the trial. Patients who completed treatment but did not enter the OLE trial on Day 99 commenced a 10-day IMP taper period, which could be interrupted at any time within 7 days if the patient subsequently opted to participate in the OLE trial. Patients who withdrew early were to commence the 10-day IMP tapering period, if possible.*

* *Only required for those patients who delayed entry into or did not participate in the OLE trial, or for those who withdrew from the trial early and tapered IMP. Visit 9 was to be within 7 days of Visit 8 for patients who delayed entry to the OLE trial. For patients who completed treatment but did not participate in the OLE trial, Visit 9 was to be 10 (+3) days after Visit 8. For patients who withdrew early and tapered IMP, this visit was to occur 10 (+3) days after the Withdrawal visit. Patients who opted not to enter the OLE trial, or who withdrew early, had weekly (±3 days) safety telephone calls from Visit 9 or date of final dosing, until Visit 10.*

** *For patients who did not enter the OLE study or who withdrew from the trial early; could be conducted by telephone.*

♠ *Vital signs and ECG were required to be re-assessed 2 to 3 hours postdose.*

♦ *Only required for patients who opted not to enter the OLE study or who withdrew from the trial early (including withdrawal during the taper period).*

§ *Urine sample taken if possible.*

† *Conducted using serum samples (Visits 1, 2 and 8/the Withdrawal visit) and a urine dipstick (Visit 2).*

†† *Only completed at participating sites; Visit 8/the Withdrawal visit assessment were ideally completed before any other trial procedures but could be conducted on a separate day, if necessary, within 3 days of the visit.*

††† *CWS used for 18 years old and above; PCWS used for children aged 4-17 years old.*

♥ *Tanner Staging assessed in all adolescent patients (i.e., 10 to less than 18 years of age at the time of signing the ICF, or earlier if clinically indicated by onset of menarche or other signs of precocious puberty). IGF-1 level testing conducted in all patients less than 18 years of age.*

^ *For 2-17 year-olds, if ≥ 20 kg: blood samples were collected predose and at 2–3 hours and 4–6 hours postdose; there must have been a minimum period of at least 2 hours between each of the 3 blood sampling time-points. For 18–55 year-olds: blood samples were collected predose and at 0.5 hours (+15 min), 1 hour (+15 min), 2 hours (+30 min), 4 hours (+30 min) and 6 hours (+30 min) postdose.*

^^ *For all patients, provided the risk/benefit outcome is favorable in the investigator's opinion. Blood samples were taken prior to administration of IMP. Patients recorded the dosing time of their concomitant AEDs in the diary.*

◊ *Blood samples were taken at the same time intervals as at Visit 2.*
▲ *Completion of memory aid; to be referred back to at subsequent assessments.*
¶ *Caregivers compared the memory aid from Visit 2.*
∞ *Performed on Day 123 (±3) only.*
Performed at final dosing visit (Visit 8/the Withdrawal visit or Visit 9, as applicable) for patients 12 years of age and older.
‡ *For patients in France only: Visit 7 was completed at the clinic and was not conducted by telephone.*
▼ *For patients in France only: IMP was dispensed at Visit 7 since the maximum duration of prescriptions of IMP in France was 28 days.*

Source: Study 1414, CSR, Table 5.5.1-1

- **Concurrent medications**
  Patients had to be on at least one AED at a stable dose during the trial. If plasma concentrations of concomitant AEDs altered following administration of the investigational product, then the dosage of concomitant AEDs were modified, based on clinical need and after discussion with the GW medical advisor. All non-pharmacological therapies for epilepsy (e.g., ketogenic diet, VNS) also had to be stable for four weeks prior to screening and remain so throughout the duration of the study.

  Any medication, other than the IMP, taken during the study was to be recorded on the appropriate Case Report Form (CRF).

  Prohibited therapies prior to or during the study period were as follows:
  - *Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.*
  - *Recreational or medicinal cannabis or synthetic cannabinoid based medications (including Sativex) within three months prior to or during the study.*
  - *Any other IMP taken as part of a clinical trial within six months or during the study.*
  - *Long-term systemic steroids (excluding inhaled medication for asthma treatment) or any other daily medication known to exacerbate epilepsy. An exception will be made for prophylactic medication, for example, for idiopathic nephrotic syndrome or asthma.*
  - *Felbamate that has been taken for less than 1 year prior to screening.*

- **Treatment compliance**
  Patients or caregivers recorded the total volume of IMP administered on each day using the paper diary. Participants were asked to return all IMP (used and unused) at each relevant visit, and the site checked the returned IMP against both the amount in the paper diary and the projected usage in the IVRS system. Discrepancies were discussed with the patient/caregiver and documented. Investigators were to inform GW of all missing or unaccountable IMP.

- **Rescue medications**
  The use of rescue medication was allowed and was captured on CRFs.

- **Subject completion, discontinuation, or withdrawal**
  Patients who completed the treatment period were invited to participate in an OLE trial under a separate protocol and continue receiving (or start taking) CBD. Patients who did not enter the OLE trial tapered IMP (10% per day over 10 days). However, if the patient decided to enter the OLE trial within 7 days of treatment completion, the taper period could be interrupted. Patients who opted to taper the drug returned for an end of taper period visit (Visit 9, Day 100-106 or Day 109). Patients who did not enter the OLE trial

(or who discontinued early) returned for a safety follow-up visit 28 days later (Visit 10, Day 137).

Patients who met any of the following criteria must be withdrawn from the study:

- Administrative decision by the investigator, GW, or a regulatory authority.
- Pregnancy.
- Protocol deviation that was considered to potentially compromise the safety of the patient.
- Withdrawal of parent(s)/legal representative consent or patient assent.
- Lost to follow-up.
- ALT > 3X ULN or AST > 3X ULN **and** total bilirubin > 2X ULN or INR > 1.5).
- ALT or AST > 3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)a.
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for more than 2 weeks.

Other potential withdrawal criteria included:

- Patient non-compliance.
- AE which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

All information, including the reason for withdrawal from the study, was to be recorded in the CRF.

If a patient withdrew from the study during the treatment period, "*the primary analysis variable will be calculated from all the available data, during the treatment period, prior to the patient withdrawing.*" (Study 1414, SAP, pg. 12) Sensitivity analyses to account for missing data arising from unreported days in the IVRS, and missing data arising from patients withdrawing during the treatment period were prespecified in the SAP and performed.

Clinical reviewer's comment: The specified criteria for completion, discontinuation, or withdrawal, as well as the statistical methods to address missing data in the case of discontinuation/withdrawal, appear reasonable.

Study Endpoints

The primary endpoint for Study 1414 was "*percentage change from baseline in drop seizure frequency (average per 28 days) during the treatment period, based on the ITT analysis set*". (Study 1414, CSR, pg. 85). The primary efficacy endpoint was not assessed at one specific time, but was rather a measure of change in seizure frequency over the entire treatment period,

which included the 10-day titration period and the 12-week maintenance period.

A drop seizure in Study 1414 is defined as *"an attack or spell (atonic, tonic or tonic-clonic) 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."* Non-drop seizures were defined as *"all other countable seizures, except drop attacks, and is atypical absence, focal with or without loss of consciousness and any seizure that would not result in a fall."*

Patients or caregivers were to record the number and type of drop seizures (atonic, tonic or tonic-clonic) and non-drop seizures (myoclonic, partial, or absence) each day from screening until completion of dosing (Visit 8/Withdrawal visit or Visit 9, as appropriate) using the IVRS.

Clinical reviewer's comment: The primary endpoint used in Study 1414 (percentage change from baseline in seizure frequency) is the most common efficacy endpoint AED treatment trials, though, as noted in the discussion of the primary endpoint for Study 1332B above, the outcome variable may differ depending on the underlying type of epilepsy. Patients with LGS have multiple seizure types, with seizures ranging in severity from generalized tonic-clonic seizures to atypical absence seizures, so careful definition of the primary outcome variable was important.

The applicant separated the seizure types into two broad categories: drop seizures (or drop attacks) and non-drop seizures. Drop seizures were prespecified as events (atonic, tonic, or tonic-clonic) that led or could have led to a fall, injury, slumping in a chair or hitting the patient's head on a surface. Non-drop seizures included atypical absence seizures, focal seizures with or without loss of consciousness, and any seizure that did not or would not result in a fall. Drop seizures often result in trauma to the patient's head or face, and many patients wear helmets with face guards to reduce injury. As drop seizures are the most disabling in the LGS population, reduction in their frequency was chosen as the primary efficacy endpoint.

Assessment over titration and maintenance periods is standard in epilepsy drug treatment trials rather than the maintenance period only, as patients may withdraw during titration due to lack of efficacy. Capturing these patients is important, because withdrawals due to lack of efficacy may lead to unbalanced results.

Secondary Efficacy Endpoints

Key Secondary Endpoints

- *Treatment Responder Rate*
  Number of patients considered treatment responders, defined as those with a ≥50% reduction in drop seizures from baseline during the treatment period.

Clinical reviewer's comment: The 50% responder rate is a frequently reported outcome measure in clinical epilepsy treatment trials. It is generally preferred by European drug regulatory agencies. It is related closely to change in seizure frequency.

- *Total Seizures*
  The percentage change from baseline in total seizure frequency (all seizure types combined) was calculated for each treatment group for the entire treatment period and analyses were performed on the ITT analysis dataset.

- *Subject/Caregiver Global Impression of Change (SGI-C and CGI-C)*
  The overall level of change due to treatment was assessed via the S/CGI-C at baseline and weeks 2, 4, and 8. At the baseline visit, the caregiver was asked to write a brief description of the patient's overall condition as a memory aid for the S/CGIC questionnaire at subsequent visits. The following question was rated on a 7-point scale: "Since [you/your child] started treatment, please assess the status of [your/your child's] overall condition (comparing [your/their] condition now to [your/their] condition before treatment) using the scale below." The 7-point scale is as follows: "Very Much Improved" (1); "Much Improved"; "Slightly Improved"; "No Change"; "Slightly Worse"; "Much Worse"; "Very Much Worse" (7). The S/CGIC response/score, recorded at each visit, was summarized, on both a categorical and continuous scale, by treatment group and compared to baseline.

Other Secondary Efficacy Endpoints

A large number of secondary efficacy endpoints were evaluated in Study 1414. There was significant overlap in these outcome measures, and only a select number of secondary endpoints will be discussed.

- Drop Seizure Treatment Responders and Drop Seizure Freedom
- Non-Drop Seizures
- Individual Seizure Types and Convulsive and Non-Convulsive Seizures
- Status Epilepticus
- Quality of Life in Childhood Epilepsy
- Quality of Life in Epilepsy, Version 2 (19 Years and Above)

Only the secondary endpoints of particular clinical interest are described in this review (see also Section 6.2.2).

Drop Seizure Treatment Responders and Drop Seizure Freedom
The number of patients experiencing a >25% worsening, +25 to -25% change, 25 to 50%

improvement, 50 to 75% improvement or >75% improvement in drop seizure frequency from baseline during the treatment period will be summarized by treatment group. Additionally, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in drop seizure frequency from baseline, as well as the proportion of patients who are drop seizure free (100% reduction in drop seizure frequency from baseline during the treatment period), will be summarized by treatment group and analyzed.

Non-Drop Seizures
Non-drop seizures were collected, summarized, and analyzed. Patients with no non-drop seizures during the baseline period were excluded from the analysis. The percentage change from baseline in total non-drop seizure frequency during the treatment period was calculated for each treatment group for the entire treatment period and compared between groups.

Clinical reviewer's comment: Although this was not prespecified as a key secondary efficacy endpoint, it is a clinically important secondary endpoint.

While generally less severe and less likely to lead to injury than drop seizures, non-drop seizures can be significantly disabling (particularly focal seizures). It is possible that a drug might reduce the number of drop seizures but increase the number or severity of non-drop seizures in patients with multiple seizure types, such as those with LGS. Increased severity or frequency of non-drop seizures would be a significant adverse effect of the drug. Primarily for this reason, the frequency of non-drop seizures is an important secondary outcome measure.

Individual Seizure Types
The percentage change from baseline in seizure frequency by individual seizure type was calculated for each treatment group for the entire treatment period. Patients who had no seizures of a particular seizure type during the baseline period were excluded from the analysis of that seizure type.

Pharmacokinetic Parameters

- Concentration/time curves of CBD and its major metabolites: 7-hydroxy-cannabidiol (7-OH-CBD), 6-hydroxy-cannabidiol (6-OH-CBD), and 7-carboxy-cannabidiol (7-COOH-CBD) to define the following:
    - Peak plasma concentration (C_{max});
    - Time to peak plasma concentration (t_{max});
    - Area under the plasma concentration-time curve from time zero to infinity ($AUC_{(0-\infty)}$) or to the last measurable concentration ($AUC_{(0-tz)}$);

- Terminal half-life ($t_{1/2}$)

Safety Parameters

- Assessment of differences in incidence, type and severity of AEs, Columbia-Suicide Severity Rating Scale (C-SSRS), vital signs, ECG, laboratory safety parameters, physical examination parameters, and effects on menstruation cycles (in females) of patients taking CBD compared with placebo.
- Change from baseline in growth and development for patients less than 18 years of age by measurement of height, weight, insulin-like growth factor-1 levels and Tanner Staging (for patients aged 10-17 years, or earlier if clinically indicated), Cannabis Withdrawal Scale (CWS) or Pediatric Cannabinoid Withdrawal Scale (PCWS, for patients 4-17 years) score, as appropriate.
- Plasma concentrations of concomitant AEDs before and after treatment with CBD, where available.

Statistical Analysis Plan

The primary analyses used the intention to treat (ITT) analysis set, consisting of all randomized patients who received at least one dose of IMP and have post-baseline efficacy data.

All statistical tests were 2-sided and used the 5% significance level. The Type I error was controlled by use of a hierarchical gate-keeping procedure, in the sequence given below.

Table 21: Study 1414, Hierarchical Testing for Endpoints

Test	Endpoint	Treatment Comparison
1	Primary endpoint	20 mg/kg/day CBD vs. Placebo
2	Primary endpoint	10 mg/kg/day CBD vs. Placebo
3	1st key secondary endpoint	20 mg/kg/day CBD vs. Placebo
4	2nd key secondary endpoint	20 mg/kg/day CBD vs. Placebo
5	3rd key secondary endpoint	20 mg/kg/day CBD vs. Placebo
6	1st key secondary endpoint	10 mg/kg/day CBD vs. Placebo
7	2nd key secondary endpoint	10 mg/kg/day CBD vs. Placebo
8	3rd key secondary endpoint	10 mg/kg/day CBD vs. Placebo

The primary endpoint of percentage change from baseline in seizure frequencies was analyzed using a Wilcoxon rank-sum tests. Estimates of the median differences between CBD and placebo and the approximate 95% confidence intervals (CI) were calculated using the Hodges-Lehmann approach. The sensitivity analyses specified for the primary endpoint were the same as for Study 1332b.

The proportion of responders was analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by age group. Analyses of total seizures were performed as per the primary endpoint. For the analysis of S/CGIC score, the CGIC was used unless in the situation that only a SGIC was completed then the SGIC were to be used. The 7-point scale scores at the end of treatment visit and last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. However, the analysis of S/CGIC score at the end of treatment visit is essentially a completer analysis. This analysis is considered valid only under the assumption of missing completely at random, which is unlikely to be true. Therefore, this reviewer considered the analysis of S/CGIC score at the last visit as the main analysis and the analysis of the end of treatment visit a sensitivity analysis.

Protocol Amendments

There were 6 submitted protocol amendments. Important modifications to the protocol are summarized in Table 22 below.

Table 22: Study 1414, Summary of Major Protocol Amendments

Amendment Number	Date	Major Changes
1	29 SEP 2014	• Clarification of the definition of drop seizure. • Additional collection of a full record of epilepsy-specific genetic testing and prior antiepileptic drugs taken as part of the patient's medical history. • Clarification that the baseline period must be a minimum of 28 days in order to capture sufficient baseline data. • Clarification that the safety follow-up period must be a minimum of 28 days after end of treatment in order to capture sufficient safety data. • Clarification of subtypes of seizures and definition of "countable partial seizures" in order to aid identification of seizure types.
2	27 OCT 2014	• Revised patient stopping criteria for transaminitis (DILI). Patients must be withdrawn if they fulfil any of the following: – ALT or AST >3 × ULN and (TBL >2 × ULN or INR >1.5). – ALT or AST >3 × ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%). – ALT or AST >8 × ULN. – ALT or AST >5 × ULN for more than two weeks
4	17 FEB 2015	• Clarification of the definition of drop seizures. • Update eligibility criteria for EEG • To clarify the criteria for withdrawal. • Introduction of age stratification • Revised Intention To Treat (ITT) analysis set criteria per FDA request • Modification of the statistical analysis of primary endpoints and additional statistical analysis of secondary endpoints • Changes to statistical methods dealing with missing data • To incorporate additional assessments; pharmacokinetics (PK), Cognitive Assessment Battery, Growth and Development measurements, insulin-like

Amendment Number	Date	Major Changes
		growth factor-1 (IGF-1) levels, menstruation, and Tanner Staging per FDA request.
6	11 Jun 15	• *The number of patients per treatment group has been increased from 40 to 50 (a total increase from 120 to 150 patients). The new assumption is that patients in the placebo group will experience a mean reduction in drop seizure frequency of 18% (previously 10%). This assumption is based upon an expanded review of published clinical trial data, in which placebo response rates above 10% have been shown to be commonplace. In a pivotal trial of clobazam for the treatment of LGS, patients treated with placebo demonstrated a 12.1% reduction in drop attacks (95% confidence intervals: −3.6%, 27.8%) with 31.6% achieving a ≥50% improvement. In a similar study of rufinamide, 16.7% of placebo-treated patients achieved a 50% reduction in tonic–atonic seizures associated with LGS. In addition, a high response rate in the placebo-treated arm is now expected due to the high levels of patient interest in the Epidiolex program and expectations surrounding treatment.* • During follow-up of patients with potential cases of DILI, ALT, AST, total bilirubin, and alkaline phosphatase levels should all be monitored until levels have normalized (in the investigator's opinion) or returned to baseline state. • Analyses for the primary and secondary endpoints will use the "full treatment period", which includes both the titration and maintenance phases. • The randomization now stratified by four age groups (2–5 years, 6–11 years, 12–17 years and 18–55 years).

Clinical reviewer's comment: Sample size increase from 120 to 150 patients (40 to 50 patients per group) was proposed in protocol amendment 6 (11 JUN 2015). The applicant's justification for this sample size increase was a greater than previously expected rate of reduction of seizure frequency in the placebo group (was originally 10%, increased to 18% based on placebo rates in RDBPC trials of clobazam (12.1% reduction in placebo group) and rufinamide (16.7% reduction in placebo arm). Additionally, the applicant posited a greater response rate due to high levels of patient interest. This justification for the increase in sample is acceptable from the clinical perspective. However, the final study population was 50% greater than 150 patients (293 screened, 225 enrolled) without any prespecified change in the protocol or SAP.

Data Quality and Integrity: Applicant's Assurance

The applicant reports the following methods for assuring data quality and integrity, which appear adequate:

> *Prior to trial initiation, during the trial, and after trial completion, investigational sites were visited by GW clinical research associates (CRAs) and a visit log was maintained... Direct access to the patient medical and laboratory records was permitted to verify entries on the trial-specific CRFs… A database was set up in Oracle Clinical (Version 4.5) and data entry screens were designed, tested and implemented to capture the CRF,*

paper diary, and questionnaire data. Double data entry was used to enter data into the database and quality checks were applied… Following data entry, all AE and concomitant medication terms were medically coded using the Medical Dictionary for Regulatory Activities (MedDRA), Version 17.1, and the World Health Organization Drug Dictionary (WHODD), dated June 2014… Quality control (QC) was performed on 100% of the critical variable data within the clinical database. In addition, non-critical variable data were QC checked on a randomly selected sample of patients.

GW's Clinical Quality Assurance department provided quality assurance support for this trial. Audits of the quality systems that support the preparation, conduct and reporting of this trial were conducted periodically in accordance with audit plans. These audits were conducted to assure compliance with the regulations, guidelines and standard operating procedures in place at the time of the trial. All findings were reported to appropriate personnel for corrective action. Copies of the site audit certificates are appended to this report (Appendix 1.8) for the 9 audits conducted (6 in USA, 2 in Spain, and 1 in UK). The applicant's clinical personnel or designee conducted an on-site evaluation of the clinical site prior to trial initiation.

6.2.2. Study Results

Compliance with Good Clinical Practices

The applicant stated that Study 1414 was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and local requirements, and in consideration of applicable regulatory guidance.

Financial Disclosure

Please see Financial Disclosure discussion in summary of Study 1332B (page 51).

Patient Disposition

A total of 293 patients were screened for Study 1414, and 225 patients were randomized. Sixty-eight patients were considered screen failures. The first patient was enrolled on 08 June 2015 and the date of the last trial observation was 19 May 2016.

Out of the 225 patients who were randomized into Study 1332B, 76 were randomized to the CBD 20/kg/day group, 73 to the CBD 10/kg/day group, and 76 to the placebo group. Six patients randomized to receive CBD 10 mg/kg/day and 3 patients randomized to receive placebo 10 mg/kg/day were given dosing schedules for 20 mg/kg/day patients and received > 10mg/kg/day dosing volumes before the mistake was corrected. These patients are analyzed according to the treatment group to which they were randomized. Of the 225 randomized patients, 5.8% (n=13) overall discontinued participation prior to completion of the treatment period, 9 patients

(11.8%) in the CBD 20 mg/kg/day group, 2 (2.7%) in the CBD 10 mg/kg/day group, and 2 (2.6%) in the placebo group. The most common reason for early discontinuation was adverse event. Nine patients (4.0%) overall, 7 patients (9.2%) in the 20 mg/kg group, 1 patient each in the 10 mg/kg (1.4%) and placebo (1.3%) groups exited the study early due to AEs. (Table 23)

Table 23: Study 1414, Disposition of Patients

Disposition	CBD 20 mg/kg/day n (%)	CBD 10 mg/kg/day n (%)	Placebo n (%)
Randomized	76 (100)	73 (100)	76 (100)
Completed treatment period	67 (88.2)	71 (97.3)	74 (97.4)
Withdrawn	9 (11.8)	2 (2.7)	2 (2.6)
Adverse Event	6 (7.9)	1 (1.4)	1 (1.3)
Withdrawal by patient or parent/guardian	2 (2.6)	0	1 (1.3)
Withdrawn by the investigator	1 (1.3)	1 (1.4)	0

Source: FDA clinical reviewer

Two of the patients who discontinued in the 20 mg/kg/day CBD group were not coded as discontinuation due to adverse events, but both terminated participation as a direct result of AEs:

- (b) (6) was coded as "Protocol deviation compromise the safety of the patient" because she would not attend the withdrawal visit, but the stated reason for discontinuation was *"serious TEAEs of upper respiratory tract infection, pleural effusion, device malfunction, and constipation".*
- (b) (6) was coded as "Met withdrawal criteria", because he developed elevated transaminases and eosinophilia and met the stopping criteria.

Therefore, the cause of discontinuation for these two patients would be more appropriately coded as due to adverse events.

Clinical reviewer's comment: As noted above, in their disposition analysis, the applicant accounts for 1 patient as withdrawn due to protocol violation and 1 patient as met withdrawal criteria. In the AE analysis, these patients were coded as terminated due to AE. For the purposes of this analysis, these patients' reason for withdrawal from the study have been revised to "adverse event".

Although the overall numbers and percentage of patients who discontinued participation during the treatment period of Study 1414 were relatively small, there was an imbalance between the two groups. Specifically, the completion rate for the placebo group (97.4%) and 10 mg/kg/day group (97.3%) were notably greater than in the 20 mg/kg/day group (88.2%), and the reasons for discontinuation differed between groups. Although AEs were the most common reason for study discontinuation overall, it was most notable in the 20 mg/kg group (6/9 patients) as compared to 1/2 in each of the 10 mg/kg and placebo groups.

Protocol Violations/Deviations

Of the 225 patients randomized in Study 1414, 215 patients (95.6%) were reported as having at least one protocol deviation during the study. The incidence of deviations in both groups was very similar, with 72 (94.7%) in the 20 mg/kg CBD group, 69 (94.5%) in the 10 mg/kg group, and 74 (97.3%) in the placebo group.

A total of 12 patients had protocol deviations that could potentially impact efficacy with greater incidence in the drug treatment arms [8 patients (11%) in the 10 mg/kg group, 3 (3.9%) in the 20 mg/kg group and 1 (1.3%) in the placebo arm.

- Six CBD patients were randomized to receive 10 mg/kg/day CBD but were accidentally given the dosing schedules intended for the 20 mg/kg/day patients and received > 10 mg/kg/day dosing volumes before the mistake was corrected. The mistake was corrected by day 42 in all 6 of these patients (range day 15-42), so the longest period in which the higher dose was taken was 33 days. All of these patients completed the trial. Three placebo patients were also randomized to receive 10 mg/kg/day but were given dosing schedules for 20 mg/kg/day patients.
- One patient in the CBD 20 mg/kg/day group had no current AEDs recorded; additionally, topiramate was stopped during the screening period due to an SAE.
- Three patients (1 in each dose group) were taking > 4 current AEDs.
- One patient in the CBD 10 mg/kg/day group had clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization. Furthermore, on re-review, the patient's EEG did not confirm slow spike-and-wave pattern prior to their enrollment in the baseline period.
- One patient in the CBD 20 mg/kg/day group was randomized into the trial while hospitalized for an SAE that occurred following the screening visit.

Clinical reviewer's comment: Six patients in the 10 mg group received instructions for the 20 mg group and thus received 20 mg/kg for up to 33 days (range 6-33 days). The applicant performed a post hoc analysis of the primary efficacy endpoint with these 6 patients in the 20 mg group. The difference between groups with respect to median percentage change in drop seizure frequency remained statistically significant (p=0.0070), suggesting that the incorrect dosing protocol violations did not impact the primary efficacy endpoint.

Table of Demographic Characteristics

The baseline demographics of the patients enrolled and randomized in Study 1414 (ITT dataset) were similar between groups, as seen in Table 24. The mean age and distribution amongst the

predefined age groups in all three treatment groups were similar. A sufficient percentage of patients in the 2-5 years group were enrolled in all three treatment groups (~11%). Overall, more males than females were enrolled, but all three groups had similar sex distributions. Most patients in the 20 mg/kg, 10 mg/kg, and placebo groups were from the US. Distributions of patients from the non-US countries were similar between groups.

Table 24: Study 1414, Baseline Demographics (ITT population)

		20 mg/kg (N=76)		10 mg/kg (N=73)		Placebo (N=76)	
Age (Years)	Mean (SD)	16.0 (10.8)		15.4 (9.5)		15.3 (9.3)	
	Median	13.4		12.7		12.7	
	Min, Max	2.6, 48.0		2.6, 38.2		2.6, 43.4	
Age group n (%)	2-5 years	9	(11.80%)	8	(11.00%)	9	(11.80%)
	6-11 years	25	(32.90%)	24	(32.90%)	24	(31.60%)
	12-17 years	20	(26.30%)	19	(26.00%)	20	(26.30%)
	18-55 years	22	(28.90%)	22	(30.10%)	23	(30.30%)
Sex n (%)	Female	31	(40.80%)	33	(45.20%)	32	(42.10%)
	Male	45	(59.20%)	40	(54.80%)	44	(57.90%)
Race n (%)	White/Caucasian	67	(88.20%)	62	(84.90%)	69	(90.80%)
	Black/African American	4	(5.30%)	4	(5.50%)	3	(3.90%)
	Asian	1	(1.30%)	1	(1.40%)	2	(2.60%)
	Not Applicable[a]	0		1	(1.40%)	0	
	Other	4	(5.30%)	5	(6.80%)	2	(2.60%)
Country n (%)	France	0		1	(1.40%)	0	
	Spain	11	(14.50%)	9	(12.30%)	12	(15.80%)
	USA	59	(77.60%)	60	(82.20%)	62	(81.60%)
	United Kingdom	6	(7.90%)	3	(4.10%)	2	(2.60%)

Source: Table 3.1.2 Study 1414 CSR-tables.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The patients' current seizure types, based on their medical history, are summarized in Table 24. The distribution of current seizure types reported at screening was similar across the treatment groups, with tonic and atonic being most common. Number of current and prior AEDs were also similar between groups, as were specific concurrent AEDs.

Table 25: Study 1414, Summary of Baseline characteristics, ITT population

Characteristic	CBD 20 mg/kg (N=76)	CBD 10 mg/kg (N=73)	Placebo (N=76)
Drop Seizures per 28 Days			
Median	85.5	86.9	80.3
Min, Max	13.0, 1092.0	14.0, 7494.0	8.7, 1278.3
Baseline Seizure Subtype			
Tonic Seizures	59 (77.6%)	56 (76.7%)	57 (75.0%)
Clonic Seizures	3 (3.9%)	8 (11.0%)	5 (6.6%)
Tonic-Clonic Seizures	41 (53.9%)	37 (50.7%)	34 (44.7%)
Atonic Seizures	50 (65.8%)	40 (54.8%)	41 (53.9%)
Myoclonic Seizures	33 (43.4%)	22 (30.1%)	30 (39.5%)
Countable Partial Seizures	17 (22.4%)	18 (24.7%)	19 (25.0%)
Other Partial Seizures	5 (6.6%)	6 (8.2%)	4 (5.3%)
Absence Seizures	40 (52.6%)	28 (38.4%)	37 (48.7%)
Number of Concurrent AEDs Patient (Continuous)			
Median	3.00	3.00	3.00
Min, Max	0.0, 5.0	1.0, 5.0	1.0, 5.0
Number of Concurrent AEDs Patient (Categorical)			
0	1 (1.3%)	0	0
1	4 (5.3%)	4 (5.5%)	5 (6.6%)
2	20 (26.3%)	20 (27.4%)	20 (26.3%)
3	33 (43.4%)	27 (37.0%)	29 (38.2%)
4	17 (22.4%)	21 (28.8%)	21 (27.6%)
5	1 (1.3%)	1 (1.4%)	1 (1.3%)
Number of Prior AEDs (failed)			
Median	6.00	6.00	6.00
Min, Max	1.0, 18.0	0.0, 21.0	1.0, 22.0
Concurrent AEDs			
Clobazam	36 (47.4%)	37 (50.7%)	37 (48.7%)
Valproic Acid	28 (36.8%)	27 (37.0%)	30 (39.5%)
Lamotrigine	20 (26.3%)	22 (30.1%)	25 (32.9%)
Levetiracetam	24 (31.6%)	22 (30.1%)	23 (30.3%)
Rufinamide	26 (34.2%)	19 (26.0%)	20 (26.3%)

Source: Table 3.2.2, Study 1414, csr-tables

EEG history was very similar between the treatment groups. All patients were reported to have previously had an abnormal EEG, except for 1 patient in the 10 mg/kg/day group. Other information provided by the investigator confirmed that the patient did have a history of abnormal EEG. Most patients never had a normal EEG (75.6%, 85.1%, and 77.6% of the 20 mg/kg, 10 mg/kg, and placebo groups, respectively). Similar proportions of patients were on a ketogenic diet or using VNS.

Clinical reviewer's comment: Baseline characteristics of the three treatment groups were reasonably similar.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Twenty-four patients (10.7%) had 1 or more days during the treatment period on which at least 1 dose of IMP was recorded as not being taken, more in the 20 mg/kg group (17.1%) than in the 10 mg/kg group (9.0%) or the placebo group (5.3%). In most of these patients (20/24, 83.3%), the number of days in which at least 1 dose was missed was less than 5 days. Eight patients missed both doses in at least 1 day, more commonly in the 20 mg/kg group (6.1%) than in the 10 mg/kg group (3.0%) or placebo group (1.3%).

Use of rescue medications did not differ significantly between the groups: 56.1% in the 20 mg/kg group, 49.3% in the 10 mg/kg group, and 53.9% in the placebo group.

Clinical reviewer's comment: Treatment compliance was slightly worse in the 20 mg/kg group than in the 10 mg/kg or placebo groups, but the differences between groups were small and, thus, unlikely to impact the efficacy analysis. Rescue medication usage did not predispose towards increased efficacy in the CBD groups, as the frequency of use of these drugs was similar between groups.

Efficacy Results - Primary Endpoint

All patients who were randomized, received at least 1 dose of study drug, and had at least one post-baseline efficacy endpoint were included in the ITT analysis dataset, according to their allocated treatment group. The primary efficacy analyses were conducted on the ITT analysis set, which comprised a total of 225 patients: 76 patients in the 20 mg CBD group, 73 patients in the 10 mg CBD group, and 76 patients in the placebo group.

As noted above, the primary efficacy endpoint was the percentage change from baseline in total drop seizure frequency per 28 days during the treatment (titration + maintenance) period. There were statistically significant differences between each CBD group (20 mg/kg/day and 10 mg/kg/day) and the placebo group in the percentage change from baseline in drop seizure frequency during the treatment period, in favor of CBD treatments (p =0.0047 and p =0.0016, respectively; Table 26). The estimated median difference was −21.6% and -19.2%, respectively.

Table 26: Study 1414: Analysis of the Primary Endpoint

	20 mg/kg/day (N=76)	10 mg/kg/day (N=73)	Placebo (N=76)
Drop Seizure Frequency (per 28 Days)			
Baseline Period Median	85.5	86.9	80.3
Treatment Period Median	44.9	50.0	72.7
Median Percentage Change During Treatment (Q1, Q3)	−41.9 (−72.4, −1.3)	−37.2 (−63.8, −5.6)	−17.2 (−37.1, 0.9)
Comparison over placebo			
Estimated Median Difference (CI*)	−21.6 (−34.8, −6.7)	−19.2 (−31.2, −7.7)	
P-value by Wilcoxon rank-sum test	0.0047	0.0016	

Source: Study 1414 CSR, Table 8.4.1.1-1, confirmed by FDA statistical reviewer
*based on Hodges-Lehmann estimator

Sensitivity analyses using ANCOVA on original data, ranked data, and log-transformed data all yielded similar results to the primary analysis (Figure 6 and Figure 7 below). Consistent results were seen for the maintenance period and each 4-week period of the maintenance (Table 27).

Clinical reviewer's comment: Compared with the placebo group, both CBD groups demonstrated a statistically significant decrease in percent change in drop seizures from baseline to the treatment period. As noted above in the discussion of the primary efficacy outcome, this is the same primary efficacy endpoint used in most AED treatment trials, although the seizure types counted toward the primary endpoint may differ based on the underlying disease. The findings are both statistically significant (p=0.0123) and clinically meaningful. As noted by the FDA statistician, the sensitivity analyses on original data, ranked data, and log-transformed data all yielded similar results to the primary analysis and similar results were seen for the maintenance period and each 4-week period of the maintenance period. These are all supportive of the primary efficacy results.

Table 27: Study 1414, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint

Analysis Period	Treatment	n	Median	Q1 Q3	Estimated Median Difference[b] (95% CI)	p- value[c]
Maintenance Period	10 mg/kg (N=73)	73	-39.99	-67.4, -2.2	-19.54 (-32.22, -6.50)	0.0033
	20 mg/kg (N=76)	76	-47.15	-78.8, 1.7	-21.23 (-36.40, -6.24)	0.0067
	Placebo (N=76)	76	-18.73	-40.6, -1.2		
Maintenance Period (Week 1 to 4)[a]	10 mg/kg (N=73)	73	-41.74	-61.1, -10.0	-20.40 (-31.78, -8.29)	0.0017
	20 mg/kg (N=76)	75	-39.73	-85.6, -0.5	-25.19 (-40.94, -8.97)	0.0015
	Placebo (N=76)	75	-19.97	-37.1, 0.0		
Maintenance Period (Week 5 to 8)[a]	10 mg/kg (N=73)	72	-44.13	-71.9, -0.4	-17.10 (-31.72, -1.79)	0.0255
	20 mg/kg (N=76)	68	-53.54	-89.9, -5.4	-29.11 (-43.59, -12.93)	0.0008
	Placebo (N=76)	75	-22.16	-45.6, -1.9		
Maintenance Period (Week 9 to 12)[a]	10 mg/kg (N=73)	71	-49.01	-79.6, -6.3	-21.95 (-35.60, -6.61)	0.0068
	20 mg/kg (N=76)	67	-36.44	-76.6, 10.1	-14.80 (-32.05, 2.11)	0.0848
	Placebo (N=76)	74	-22.80	-46.0, 0.0		

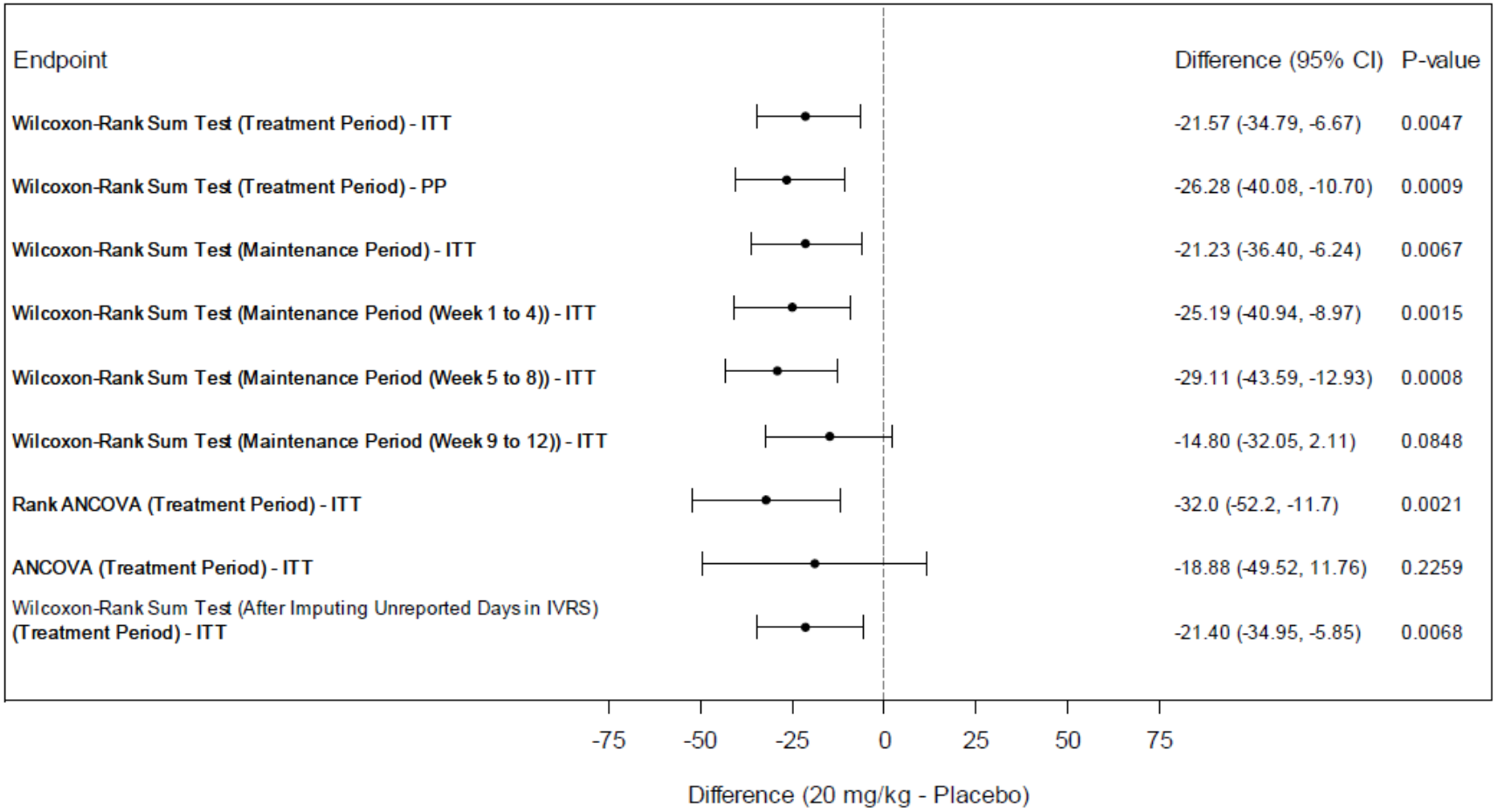
Source: Study 1414, Unblinded Final Tables, Table 8.1.1

[a] Patients with at least 7 days of seizure data within the corresponding 4 week period

[b] based on Hodges-Lehmann estimator

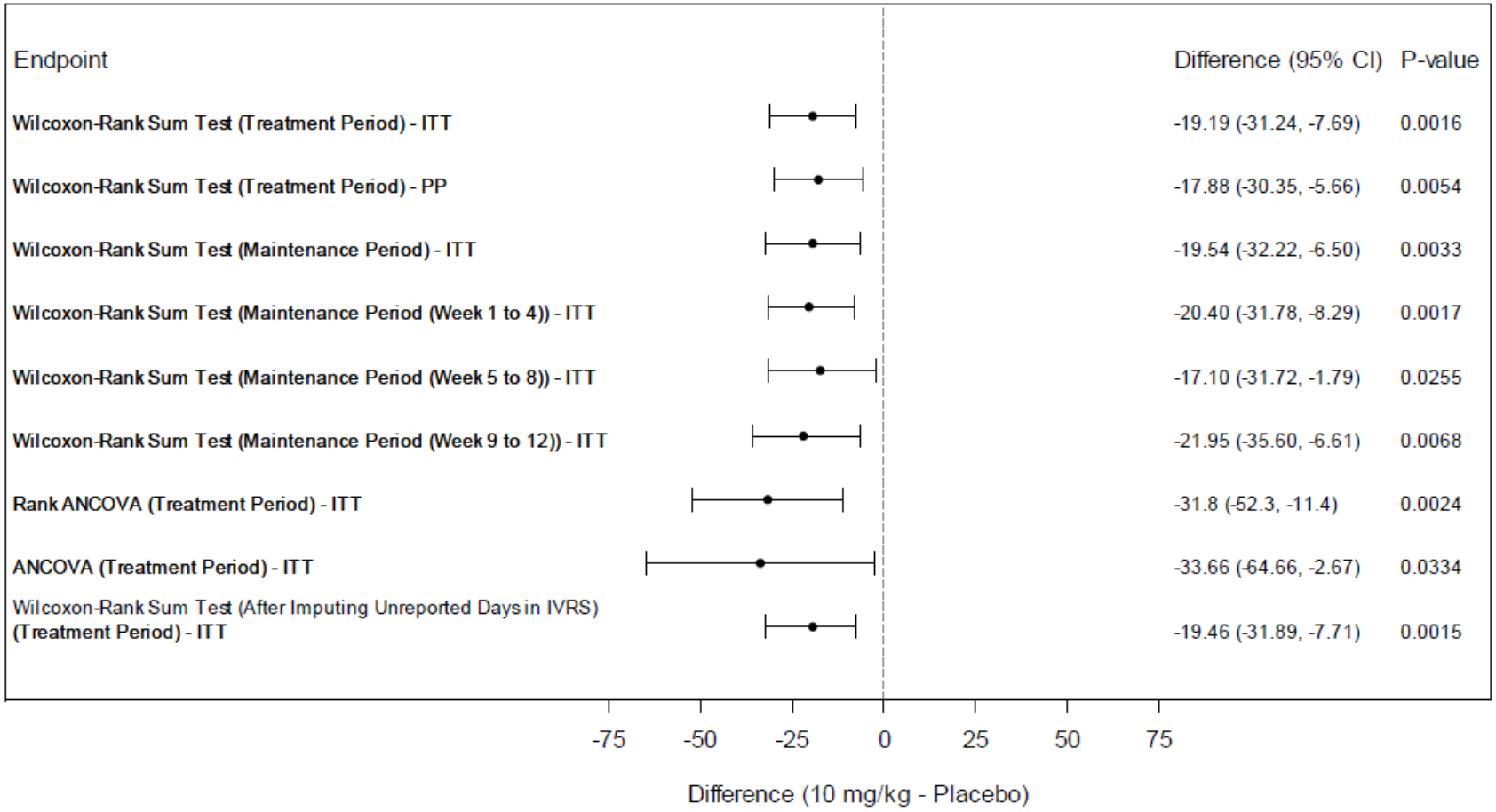
[c] by Wilcoxon Rank Sum Test

Figure 6: Study 1414, Sensitivity Analyses, Primary Efficacy Endpoint (20 mg/kg vs. placebo)



Source: Figure 8.4.1.1.1-1, Study 1414 CSR

Figure 7: Study 1414, Sensitivity Analyses, Primary Efficacy Endpoint (10 mg/kg vs. placebo)



Source: Figure 8.4.1.1.1-2, Study 1414 CSR

Missing data

Two sensitivity analyses assessing the impact of missing data were conducted by the applicant. One analysis used the worst of last observation, next observation, or the mean value of observed data to impute the intermittent missing values due to unreported days in the IVRS. As there were few intermittent missing data (2%), the result was similar to the primary analysis. However, this analysis did not address the impact of missing data due to dropouts, which might be of concern as the dropout rates were unbalanced: 9 (12%) in the 20 mg/kg/day CBD group vs. 2 (3%) in each of the 10 mg/kg/day CBD group and placebo group.

The sensitivity analysis using multiple imputation (MI) examined the impact of missing data due to dropouts on the efficacy results. In this analysis, intermittent missing values before the last visit were first imputed under missing at random assumption (MAR). Then non-intermittent missing data were imputed under the missing not at random (MNAR) assumption that the imputed values for the missing data of CBD patients (discontinued for certain reasons) were different from those of placebo patients. This analysis showed that the result for the primary endpoint remained statistically significant when values imputed for the dropouts in the CBD group were moderately worse (up to 4 times the standard error of the observed drop seizure frequency in the placebo group) than those of placebo patients.

The data indicated that some patients experienced or reported fewer seizures prior to withdrawing from the study. The appearance of seizure reduction in these patients may be artificial. One could argue that they might have behaved similarly as the rest of patients if they had been able to recover from the adverse events. On the contrary, one could also argue that CBD simply failed them because they were no longer able to tolerate CBD treatment even if there was some indication of benefit on seizure frequency from CBD. The two arguments seem equally valid. The latter argument may also shed some light on how useful CBD treatment could be. Therefore, the statistical reviewer conducted a worst-case type of analysis, in which patients who withdrew were assigned the worst result (the largest percentage change from base in convulsive seizure frequency). The resulting estimated median difference between the CBD 20 mg/kg/day and placebo groups was −15.6% (Table 28), smaller than the estimated median difference of −21.6% from the primary analysis, but still numerically in favor of the CBD treatment. The result for the CBD 10 mg/kg/day group was similar to the primary analysis as there were few dropouts in this group.

Table 28: Study 1414, Reviewer's Worst-Case Analysis of the Primary Endpoint

Variable	20 mg/kg/day (N=76)	10 mg/kg/day (N=73)	Placebo (N=76)
Drop Seizure Frequency (per 28 Days)			
Median Percentage Change from Baseline	−39.2	−36.2	−17.2
Estimated Median Difference (95% CI)*	15.6 (−31.7, 1.2)	−17.4 (−30.3, −5.4)	

Source: FDA Statistical Reviewer; *based on Hodges-Lehmann estimator

~~*based on Hodges-Lehmann estimator~~

Over-enrollment

The planned total sample size for this study was 150 patients. However, the study randomized 225 patients, which was a 50% increase in the number of patients. This reviewer conducted an analysis of the primary endpoint on the first 150 randomized patients. The results showed similar treatment effects as the primary analysis on the ITT set (Table 29).

Table 29: Study 1414, Analysis of the Primary Endpoint on the First 150 Randomized Patients

Variable	20 mg/kg/day (N=50)	10 mg/kg/day (N=49)	Placebo (N=51)
Drop Seizure Frequency (per 28 Days)			
Baseline Period Median	82.0	86.9	76.3
Treatment Period Median	44.0	40.9	55.4
Median Percentage Change During Treatment	−44.7	−45.1	−23.0
Comparison over placebo			
Estimated Median Difference (95% Confidence Interval)* P-value	−21.5 (−41.1, −1.2) 0.0349	−19.8 (−33.5, −5.4) 0.0101	

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Clinical reviewer's comment: From the clinical perspective, the FDA statistician's sensitivity analyses and worst-case analyses to explore the impact of missing data support the primary efficacy results.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, region, clobazam use, valproic acid use, lamotrigine use, rufinamide use, baseline drop seizure frequency groups, number of current AEDs and number of prior AEDs for both the 20 mg/kg and 10 mg/kg groups. The results favored both 20 and 10 mg/kg groups over placebo in all subgroups and are summarized in Table 30 and Table 31 below.

Table 30: Study 1414, Subgroup Analysis of the Primary Endpoint (Demographics)

Subgroup Item	Treatment	N	Median	Median Difference (95%CI)*
Male	10 mg/kg	40	-36.08	-16.86 (-31.34, -0.32)
	20 mg/kg	45	-39.62	-22.09 (-39.78, -3.89)
	Placebo	44	-17.17	
Female	10 mg/kg	33	-49.33	-22.04 (-41.29, -5.75)
	20 mg/kg	31	-43.65	-19.75 (-42.63, 6.35)
	Placebo	32	-17.85	
White/ Caucasian	10 mg/kg	62	-36.69	-16.81 (-28.46, -5.18)
	20 mg/kg	67	-39.62	-15.74 (-29.81, -1.30)
	Placebo	69	-19.13	
Other	10 mg/kg	11	-49.65	-43.02 (-109.51, 19.09)
	20 mg/kg	9	-85.08	-67.37 (-123.15, 1.68)
	Placebo	7	1.30	
2-5 years	10 mg/kg	8	-39.69	-22.68 (-56.60, 19.18)
	20 mg/kg	9	-29.55	-10.58 (-62.35, 35.11)
	Placebo	9	-13.37	
6-11 years	10 mg/kg	24	-49.41	-28.92 (-49.07, -2.19)
	20 mg/kg	25	-25.74	-15.16 (-41.19, 10.06)
	Placebo	24	-17.17	
12-17 years	10 mg/kg	19	-46.74	-26.44 (-44.30, -7.62)
	20 mg/kg	20	-50.18	-27.05 (-51.09, 3.47)
	Placebo	20	-26.94	
18-55 years	10 mg/kg	22	-18.16	-2.31 (-22.90, 17.98)
	20 mg/kg	22	-44.65	-29.35 (-50.30, -0.99)
	Placebo	23	-8.90	

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 31: Study 1414, Subgroup Analysis of the Primary Endpoint (Concomitant AEDs)

Subgroup/Item	Treatment	N	Median	Median Difference (95% CI)*	
Clobazam Use					
Yes	10 mg/kg	37	-43.43	-17.55	(-36.84, -1.27)
	20 mg/kg	36	-56.85	-33.97	(-51.78, -15.57)
	Placebo	37	-26.54		
No	10 mg/kg	36	-35.19	-20.29	(-35.28, -5.18)
	20 mg/kg	40	-23.18	-4.63	(-25.68, 12.85)
	Placebo	39	-9.63		
Valproic Acid Use					

Subgroup/Item	Treatment	N	Median	Median Difference	(95% CI)*
Yes	10 mg/kg	27	-34.44	-18.35	(-34.96, 1.77)
	20 mg/kg	28	-39.87	-14.57	(-39.49, 9.96)
	Placebo	30	-15.31		
No	10 mg/kg	46	-40.30	-19.88	(-36.18, -4.57)
	20 mg/kg	48	-41.86	-25.02	(-41.49, -6.36)
	Placebo	46	-18.11		
Lamotrigine Use					
Yes	10 mg/kg	22	-40.30	-13.32	(-34.96, 10.31)
	20 mg/kg	20	-44.65	-22.01	(-49.84, 8.18)
	Placebo	25	-30.30		
No	10 mg/kg	51	-36.44	-22.59	(-36.88, -8.12)
	20 mg/kg	56	-39.42	-22.83	(-38.70, -5.65)
	Placebo	51	-13.33		
Levetiracetam Use					
Yes	10 mg/kg	22	-46.82	-16.55	(-41.59, 11.97)
	20 mg/kg	24	-37.27	-9.85	(-35.31, 17.13)
	Placebo	23	-28.23		
No	10 mg/kg	51	-36.44	-22.14	(-33.99, -8.55)
	20 mg/kg	52	-44.65	-25.52	(-42.44, -8.33)
	Placebo	53	-9.63		
Rufinamide Use					
Yes	10 mg/kg	19	-34.44	-15.95	(-41.46, 7.79)
	20 mg/kg	26	-25.55	-17.70	(-40.52, 3.55)
	Placebo	20	-17.17		
No	10 mg/kg	54	-45.91	-19.75	(-33.99, -7.18)
	20 mg/kg	50	-46.21	-24.68	(-41.81, -4.62)
	Placebo	56	-19.76		

Source: Table 9.20.1, Study 1414 CSR
*based on Hodges-Lehmann estimator

Clinical reviewer's comment: The results of the subgroup analyses of the primary efficacy endpoint favored the CBD groups in all cases and did not raise any clinical concerns.

Efficacy Results - Secondary and other relevant endpoints

Key Secondary Endpoints

- Proportion of 50% responders
  During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency was greater in the 20 mg/kg/day and 10

mg/kg/day CBD groups (39.5% and 35.6% respectively), compared with the placebo group (14.5%). The odds ratios (ORs) were statistically significant for both the 20 mg/kg/day group (OR =3.9; p=0.0006) and the 10 mg/kg/day group (OR =3.3; p=0.0030).

- Change in total seizure frequency
  A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in both the 20 mg/kg/day and 10 mg/kg/day CBD groups, compared with the placebo group. The difference between each CBD group and placebo was statistically significant (p =0.0091 and p =0.0015, respectively).

- Subject/Caregiver Global Impression of Change (S/CGIC)
  For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. The treatment differences were in favor of both the 20 mg/kg/day and 10 mg/kg/day CBD groups (OR =1.8 and OR =2.6, respectively) and were both statistically significant (p=0.0439 and p=0.0020, respectively).

Table 32: Study 1414, Analyses of the Key Secondary Endpoints

Variable	20 mg/kg/day (N=76)	10 mg/kg/day (N=73)	Placebo (N=76)
≥ 50% Reduction in Drop Seizure Frequency			
n (%)	30 (39.5)	26 (35.6)	11 (14.5)
Odds Ratio (95% CI)	3.9 (1.8, 8.5)	3.3 (1.5, 7.3)	
P-value by CMH test	0.0006	0.0030	
Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period			
Median Percentage Change During Treatment	−38.4	−36.4	−18.5
Estimated Median Difference (95% CI)*	−18.8 (−31.8, −4.4)	−19.5 (−30.4, −7.5)	
P-value by Wilcoxon rank-sum test	0.0091	0.0015	
Subject/Caregiver Global Impression of Change Score at the Last Visit			
Mean	3.0	3.2	3.6
Odds Ratio (95% CI)	1.8 (1.0, 3.3)	2.6 (1.4, 4.7)	
P-value by Logistic Regression	0.0439	0.0020	

Source: Table 8.4.1.2.1.1-1, Table 8.4.1.2.1.2-1 and Table 9.3.1.2 of Study 1414 CSR
*based on Hodges-Lehmann estimator

Clinical reviewer's comment: The results of the key secondary analyses are statistically significant and generally supportive of the primary efficacy endpoint. The ≥ 50% reduction in drop seizure frequency analysis (50% responder analysis) is not independent of the primary efficacy outcome and, while helpful in defining a subset of patients who might be considered responders, does not provide information separate from the primary efficacy endpoint.

The comparative reduction in the percentage change in total seizure frequency is somewhat

related to the primary efficacy but does include the full range of seizures assessed in Study 1414 and suggests a broad efficacy in seizures in patients with LGS.

The S/CGIC analyses generally support that the change in the primary efficacy endpoint is clinically meaningful for both doses of CBD.

Other Secondary Endpoints of Clinical Interest

- **Non-Drop Seizures**
  Non-drop seizures were reported during baseline in 84.2% of 20 mg/kg/day patients, 75.3% of 10 mg/kg/day patients, and 92.1% of placebo patients in the ITT analysis set. A greater median reduction from baseline in non-drop seizure frequency during the treatment period was seen in both the 20 mg/kg/day and the 10 mg/kg/day groups, compared with the placebo group (Table 33).

Table 33: Study 1414, Percentage Change in Non-Drop Seizure Frequency

Variable	CBD 20 mg/kg/day (N=76)	CBD 10 mg/kg/day (N=73)	Placebo (N=76)
Total Non-Drop Seizure Frequency (per 28 Days)	n=64	n=55	n=70
Baseline Period Median (Q1, Q3)	93.65 (22.2, 278.4)	95.74 (14.0, 280.0)	77.98 (22.0, 216.0)
Treatment Period Median (Q1, Q3)	24.24 (4.9, 113.5)	16.33 (5.7, 121.1)	54.87 (9.7, 201.4)
Median Percentage Change During Treatment (Q1, Q3)	−54.55 (−86.0, −10.1)	−61.11 (−85.0, −23.2)	−34.31 (−56.0, 13.0)
Estimated Median Difference (CI) compared to placebo	−22.36 (−40.10, −2.22)	−28.31 (−43.75, −10.54)	

Source: Table 8.4.1.2.2.3-1, Study 1414, CSR

Clinical reviewer's comment: Although not pre-specified in the SAP as a hierarchical secondary endpoint for the purposes of statistical analysis, change in non-drop seizures is an important endpoint from the clinical perspective. A general concern with epilepsy disorders in which there are frequent multiple seizure types, is that a treatment may improve one type of seizures and worsen another. Non-drop seizures, while not as disabling as drop attacks, still cause significant morbidity for patients with LGS. The analysis of median change in non-drop seizure frequency favors both CBD groups over placebo, suggesting that CBD may have a broad antiepileptic effect in patients with LGS.

- **Drop Seizure Treatment Responders and Drop Seizure Freedom**

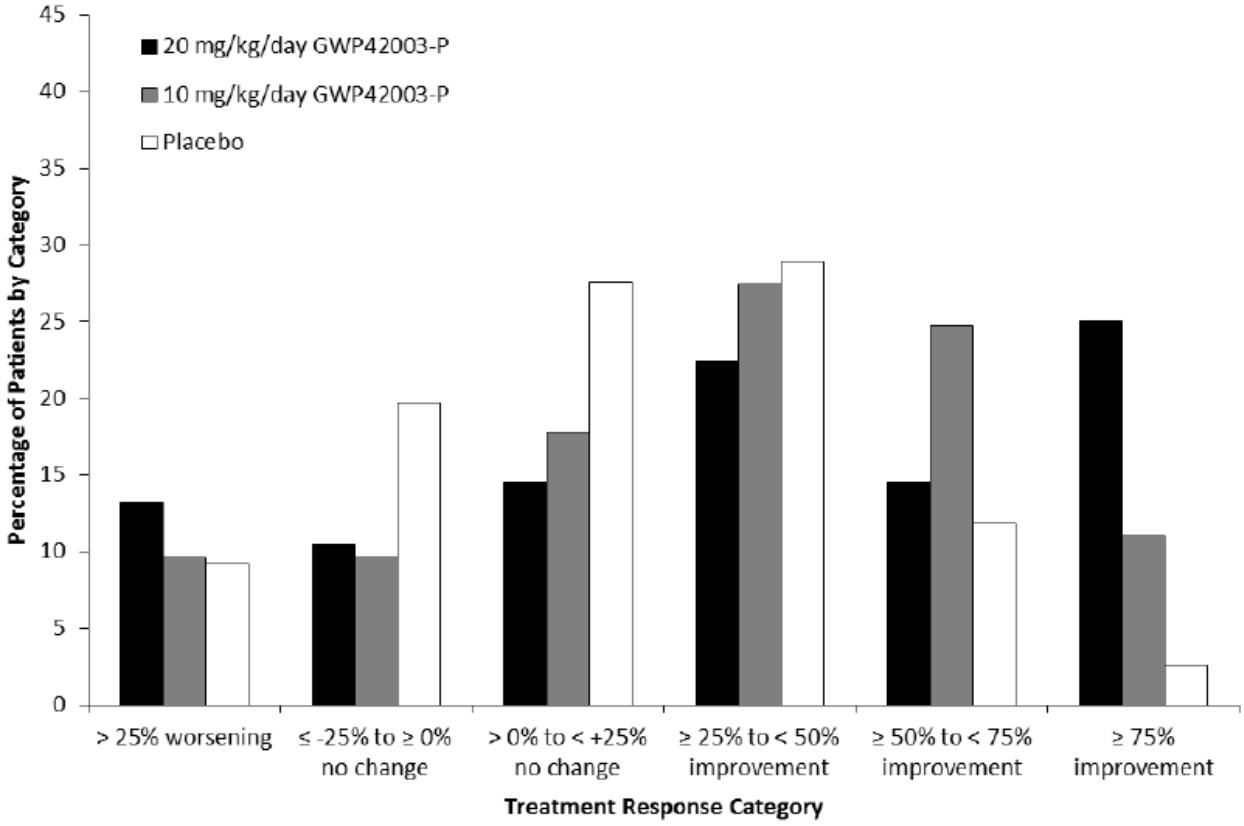
A higher proportion of patients in both the 20 mg/kg and 10 mg/kg CBD groups had a ≥ 25% reduction in drop seizure frequency from baseline during the treatment period compared with patients in the placebo group (61.8% and 63.0% vs. 43.4%, respectively). Twenty-five percent (25%) of patients in the CBD 20 mg/kg group achieved a ≥75% reduction in drop seizure frequency during the treatment period compared with 11.0% in the CBD 10 mg/kg group and 2.6% in the placebo group. Conversely, a greater proportion of patients in the CBD 20 mg/kg group (13.2%) had a >25% worsening in drop seizure frequency than in the placebo and 10 mg/kg groups (9.2% and 9.6%, respectively). See Table 34 and Figure 8 below for specifics.

Table 34: Study 1414, Summary and Analysis of Drop Seizure Treatment Responders

	20 mg/kg (N=76)	10 mg/kg (N=73)	Placebo (N=76)
>25% (Worsening)	10 (13.2%)	7 (9.6%)	7 (9.2%)
≥0% to ≤25% (Worsening)	8 (10.5%)	7 (9.6%)	15 (19.7%)
>25% to <0% (Improvement)	11 (14.5%)	13 (17.8%)	21 (27.6%)
>50% to ≤25% (Improvement)	17 (22.4%)	20 (27.4%)	22 (28.9%)
>75% to ≤50% (Improvement)	11 (14.5%)	18 (24.7%)	9 (11.8%)
≤75% (Improvement)	19 (25.0%)	8 (11.0%)	2 (2.6%)
≥25% Reduction			
Yes	47 (61.8%)	46 (63.0%)	33 (43.4%)
No	29 (38.2%)	27 (37.0%)	43 (56.6%)
Difference in Proportions (95% CI) [Active-Placebo]	0.184 (0.028, 0.340)	0.196 (0.039, 0.353)	
Odds Ratio (95% CI) [Active/Placebo]	2.11 (1.10, 4.04)	2.22 (1.15, 4.28)	
≥50% Reduction			
Yes	30 (39.5%)	26 (35.6%)	11 (14.5%)
No	46 (60.5%)	47 (64.4%)	65 (85.5%)
Difference in Proportions (95% CI) [Active-Placebo]	0.250 (0.115, 0.385)	0.211 (0.076, 0.347)	
Odds Ratio (95% CI) [Active/Placebo]	3.85 (1.75, 8.47)	3.27 (1.47, 7.26)	
p-value	0.0006	0.0030	
≥75% Reduction			
Yes	8 (11.0%)	19 (25.0%)	2 (2.6%)
No	65 (89.0%)	57 (75.0%)	74 (97.4%)
Difference in Proportions (95% CI) [Active/Placebo]	0.083 (0.003, 0.163)	0.224 (0.120, 0.327)	
Odds Ratio (95% CI) [Active/Placebo]	4.55 (0.93, 22.22)	12.33 (2.76, 55.13)	

Source: Applicant's Table 9.1.1, Study 1414, Unblinded final tables

Figure 8: Study 1414, Continuous Response Analysis for Drop Seizures (Treatment Period)



Clinical reviewer's comment: Overall, the responder analysis favored CBD (both dose groups) over placebo. However, this is complicated by the increased proportion of patients in the 20 mg/kg group that demonstrated >25% worsening of drop seizures when compared to patients in the 10 mg/kg and placebo groups. Because of the small numbers of patients in all of these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses, but the overall analysis is supportive of CBD over placebo.

- **Seizure Subtypes**
  The sponsor assessed outcomes for the following seizure types: tonic, tonic-clonic, atonic, countable partial seizures, other partial seizures, clonic seizures, myoclonic seizures, and absence seizures. All seizure subtype outcomes favored the CBD groups over placebo.

Clinical reviewer's comment: Analysis of the median percentage change in seizure frequency of all seizure subtypes all favored the CBD treatment groups over placebo

and are supportive of the primary efficacy endpoint.

Dose/Dose Response

See Section 7.1.4.

Durability of Response and Persistence of Effect

Sensitivity analyses of the primary endpoint were performed on the maintenance period and each 4-week period of the maintenance. Consistent results were seen for both doses of CBD for each of these time periods in Study 1414. See also Section 7.1.5.

6.3. GWEP1423 – A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox–Gastaut syndrome in children and adults.

6.3.1. Study Design

Overview and Objective

The objectives of this study were as follows:

- Primary: *"To evaluate the efficacy of GWP42003-P as adjunctive treatment in reducing the number of drop seizures when compared with placebo in patients with LGS."*
- Secondary:
  - Key Secondary Objectives: *"To assess the following in LGS patients taking GWP42003-P as adjunctive treatment, when compared with placebo: number of patients drop seizure-free; responder rate (in terms of reduction in drop seizures); reduction in the number of non-drop seizures; frequency of subtypes of seizures; and safety and tolerability of GWP42003-P through monitoring of adverse events (AEs), suicidal ideation, abuse liability, cannabis withdrawal effects, clinical laboratory tests, vital signs, and menstruation cycles …"*
  - Other Secondary Objectives:
    - *To assess the following in LGS patients taking GWP42003-P as adjunctive treatment, when compared with placebo: number of patients with episodes of status epilepticus (SE); need for hospitalization due to epilepsy; change in duration of subtypes of seizures; sleep disruption and daytime sleepiness; quality of life; adaptive behavior; cognitive function; and growth and development.*
    - *To determine the pharmacokinetics (PKs) of cannabidiol (CBD) and its major metabolites following single and multiple doses of GWP42003-P.*

- *To determine the effects of GWP42003-P on plasma concentrations of concomitant antiepileptic drugs (AEDs), where available.*]

Trial Design

- **Basic Study Design**
  GWEP1423 (Study 1423) was a Phase 3, multicenter, double-blind, randomized, placebo controlled study of cannabidiol conducted at 24 centers worldwide. A total of 100 patients were to be randomized into the study. This study was conducted to test the clinical efficacy, safety, and PK of cannabidiol oral solution in patients with seizures due to Lennox-Gastaut syndrome. The total duration of subject participation in the study was approximately 3 months. The study consisted of a Baseline Period, a Treatment Period (titration plus maintenance), and a Taper Period (alternatively, patients enrolled in an open label, LTE study).

  The general design of Study 1423 is similar to other AED treatment trials and is almost identical to Study 1414 as described in Section 6.2 above. The primary difference between Studies 1414 and 1423 was the inclusion of only a single CBD dosing group (20 mg/kg/day vs placebo) in Study 1423 vs. two CBD dosing groups (10 and 20 mg/kg/day vs placebo) in Study 1414. Other differences include trial location (US, Netherlands and Poland) and number of sites (24).

Study Endpoints

Primary Efficacy Endpoint
The primary endpoint for Study 1423 was *"percentage change from baseline in drop seizure frequency (average per 28 days) during the treatment period, based on the ITT analysis set"*. (Study 1423, CSR, pg. 84). The primary efficacy endpoint was a measure of change in seizure frequency over the entire treatment period, which included the 10-day titration period and the 12-week maintenance period.

A drop seizure in Study 1423 is defined identically to that in Study 1414: *"an attack or spell (atonic, tonic or tonic-clonic) 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."* (Study 1423 CSR, pg. 38)

Clinical reviewer's comment: The applicant used the identical primary efficacy endpoint for Study 1423 as in Study 1414. Please see discussion of the clinical relevance and applicability of this endpoint on page 79 above.

Secondary Efficacy Endpoints

Key Secondary Endpoints

- Treatment Responder Rate
- Total Seizures
- Subject/Caregiver Global Impression of Change (SGI-C and CGI-C)

Other Clinically Relevant Secondary Efficacy Endpoints

- Drop Seizure Treatment Responders and Drop Seizure Freedom
- Non-Drop Seizures
- Individual Seizure Types and Convulsive and Non-Convulsive Seizures
- Status Epilepticus
- Quality of Life in Childhood Epilepsy
- Quality of Life in Epilepsy, Version 2 (19 Years and Above)

Only the secondary endpoints of particular clinical interest are described in this review (see also Section 6.3.2).

Clinical reviewer's comment: The efficacy outcome measures (endpoints) in Study 1423 are identical to those in Study 1414. See below for differences between Studies 1423 and 1414 in the planned statistical analyses of efficacy.

Statistical Analysis Plan

The primary analyses used the intention to treat (ITT) analysis set, consisting of all randomized patients who received at least one dose of IMP and have post-baseline efficacy data.

All statistical tests were 2-sided and used the 5% significance level. The secondary endpoints were tested hierarchically for European regulatory submissions only, in the order listed on page 82.

The primary endpoint of percentage change from baseline in seizure frequencies were analyzed using a Wilcoxon rank-sum tests. An estimate of the median difference between CBD and placebo and the approximate 95% confidence interval (CI) were calculated using the Hodges-Lehmann approach. The sensitivity analyses specified for the primary endpoint were the same as for Study 1332B.

Protocol Amendments

There were 4 submitted protocol amendments. Important modifications to the protocol are summarized in Table 35 below.

Table 35: Study 1423, Summary of Major Protocol Amendments

Amendment Number	Date	Major Changes
1	13 OCT 2014	• Clarification of the definition of drop seizure. • Additional collection of a full record of epilepsy-specific genetic testing and prior antiepileptic drugs taken as part of the patient's medical history. • Clarification that the baseline period must be a minimum of 28 days in order to capture sufficient baseline data. • Clarification that the safety follow-up period must be a minimum of 28 days after end of treatment in order to capture sufficient safety data. • Clarification of subtypes of seizures and definition of "countable partial seizures" in order to aid identification of seizure types. • Inclusion of the Pediatric Cannabinoid Withdrawal Scale (PCWS) for children 4–17 years of age.
2	05 FEB 2015	• Clarification of the definition of drop seizures. • To clarify the criteria for withdrawal. • To incorporate additional assessments; pharmacokinetics (PK), Cognitive • Assessment Battery, Growth and Development measurements, insulin-like growth factor-1 (IGF-1) levels, menstruation, and Tanner Staging.
3	03 JUN 2015	• *Changing the primary analysis to an analysis of covariance (ANCOVA).* • *Addition of sensitivity analyses over the full experimental double-blind period using ANCOVA and mixed effect model repeated measures (MMRM).* • *Sensitivity analyses (ANCOVA and MMRM) with imputation methods based on the assumption of missing not at random will be conducted, in addition to the primary analysis which will be based on non-missing data for patients who drop out.* • *Clarification that patients with no post-baseline assessments will be excluded from the intent to treat analysis set.* • *Inclusions of assessment for normality and addition of the non-parametric Wilcoxon Rank Sum Test for use if data is not normally distributed.* • *Analyses for the primary endpoint, and the secondary endpoints (unless specified otherwise), will use the "full treatment period", which includes both the titration and maintenance phases.* • Age group stratification changed from two groups (2-17 and 18-55), to four groups (2-5 years, 6-11 years, 12-17 years, and 18-55 years). • *The number of patients per treatment group has been increased from 40 to 50 (a total increase from 80 to 100 patients). The new assumption is that patients in the placebo group will experience a mean reduction in drop seizure frequency of 18% (previously 10%). This assumption is based upon an expanded review of published clinical trial data, in which placebo response rates above 10% have been shown to be commonplace. In a pivotal trial of clobazam for the treatment of LGS, patients treated with placebo demonstrated a 12.1% reduction in drop attacks (95% confidence intervals: −3.6%, 27.8%) with 31.6% achieving a ≥50% improvement. In a similar study of rufinamide, 16.7% of placebo-treated patients achieved a 50% reduction in tonic–atonic seizures associated with LGS. In addition, a high response rate in the placebo-treated arm is now expected due to the high levels of patient interest in the Epidiolex program and expectations surrounding treatment.* • Average number of seizures per 28 days (rather than per week) will be assessed

Amendment Number	Date	Major Changes
		(more standard in clinical trials for epilepsy). • During follow-up of patients with potential cases of DILI, ALT, AST, total bilirubin, and alkaline phosphatase levels should all be monitored until levels have normalized (in the investigator's opinion) or returned to baseline state. • Analyses for the primary and secondary endpoints will use the "full treatment period", which includes both the titration and maintenance phases. • The randomization now stratified by four age groups (2–5 years, 6–11 years, 12–17 years and 18–55 years).

Clinical reviewer's comment: Sample size increase from 80 to 100 patients (40 to 50 patients per group) was proposed in protocol amendment 3 (03 JUN 2015). The applicant's justification for this sample size increase was a greater than previously expected rate of reduction of seizure frequency in the placebo group (was originally 10%, increased to 18% based on placebo rates in RDBPC trials of clobazam (12.1% reduction in placebo group) and rufinamide (16.7% reduction in placebo arm). Additionally, the applicant posited a greater response rate due to high levels of patient interest. This justification for the increase in sample is acceptable from the clinical perspective. However, the final study population was 171 patients, which was 71% greater than was prespecified without any change to the SAP.

When queried about the reason for the over-enrollment of participants in Study 1423, the applicant noted that the over-enrollment was not in response to any interim analyses. It was primarily due to many patients having been pre-identified by investigators prior to completion of the site initiation, a prolonged site initiation process (need for Schedule 1 DEA license), and the required 28-day time lag between screening and randomization. One-third of the 24 sites opened for screening during the final 5 weeks of study enrollment, and 37 patients were screened in the final week of open enrollment. It was decided that all patients who had been screened and were randomizable, could continue participation even though the study had been over enrolled. As the over-enrollment was not due to any interim analysis, analysis of the entire ITT dataset was accepted for the primary endpoint, although a post hoc analysis on the first 100 patients enrolled into Study 1423 was performed (see page 112).

Data Quality and Integrity: Applicant's Assurance

See applicant's assurance of data quality on page 84.

6.3.2. Study Results

Compliance with Good Clinical Practices

The applicant stated that Study 1423 was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki and local requirements, and in consideration of applicable regulatory guidance.

Financial Disclosure

Please see the Financial Disclosure discussion in summary of Study 1332B on page 51 above.

Patient Disposition

A total of 200 patients were screened, and 171 patients were randomized. Twenty-nine patients were screen failures. Twenty-four sites (17 in the US, 1 in the Netherlands and 6 in Poland) screened and randomized patients into the trial. Most of the patients randomized into Study 1423 were from the US (n=128), the rest were from the Netherlands (n=5) and Poland (n=38). The first patient was enrolled in the study on 28 Apr 2015, and the date of the last trial observation was 18 March 2016.

As seen in Table 36 below, 14 patients (16.3%) in the CBD group and 1 (1.2%) in the placebo group discontinued participation prior to completion of the treatment period. Eleven of the 14 patients in the CBD group who discontinued withdrew due to adverse event(s). One placebo patient "met withdrawal criteria", because they refused to continue taking the product. The reason for discontinuation in the other two CBD patients was "other", one in whom the IMP was administered via G-tube (protocol violation) and the other patient stopped taking the drug. The one placebo patient discontinued due to an AE.

Three of the 11 CBD patients who exited the study because of adverse events were coded as "met withdrawal criteria" by the applicant. However, these three patients had liver-related TEAEs causing their study exit. Therefore, the disposition table below differs from the applicant's.

Table 36: Study 1423, Summary of Patient Disposition

		20 mg/kg (N=86)	Placebo (N=85)
Treatment Phase	Completed	72 (83.7%)	84 (98.8%)
	Withdrawn	14 (16.3%)	1 (1.2%)
Primary Reason for Withdrawal (Treatment Phase)	Adverse Event	11 (12.8%)	1 (1.2%)
	Met Withdrawal Criteria	1 (1.2%)	0
	Other	2 (2.3%)	0

		20 mg/kg (N=86)	Placebo (N=85)
Continued to the Taper Phase	No	71 (82.6%)	76 (89.4%)
	Yes	15 (17.4%)	9 (10.6%)
Continued to Open Label Extension?	No	9 (12.7%)	1 (1.3%)
	Yes	62 (87.3%)	75 (98.7%)

^ *Percentages are based on the number of patients who did not continue to the taper phase.*
Source: FDA clinical reviewer

All of the patients who completed the treatment period entered the OLE study.

Clinical reviewer's comment: In their disposition analysis, the applicant accounts for 4 patients as discontinued due to meeting withdrawal criteria; however, 3 of these 4 patients met liver withdrawal criteria and would be more appropriately considered as discontinuing due to AEs. In the FDA disposition analysis, these patients' reasons for withdrawal from the study have been changed to "adverse event".

As with Studies 1332B and 1414, there was an imbalance between the two groups with respect to discontinuations. Specifically, the completion rate for the placebo group (98.8%) was notably greater than in the treatment group (83.7%), and the reasons for discontinuation differed between groups. Most of the patients (11/14) who discontinued participation from the CBD group (12.8%), did so because of adverse events, while only 1 patient (1.2%) did so in the placebo group.

Protocol Violations/Deviations

Out of the 171 randomized patients, 157 (91.8%) had at least one protocol deviation. The distribution between treatment groups was similar, with 93.0% in the CBD group and 90.1% in the placebo group. Most of the reported deviations were due to missed visits, visits outside of the time window, or missed lab tests.

There were 16 protocol violations that were deemed "important but minor" by the applicant and were not expected to impact the efficacy analysis:

- Three patients (2 in the CBD group and 1 in the placebo group) used G-tubes during the trial, and 1 (a CBD patient) was withdrawn from the study due to this violation. Initially, administration via G-tube was prohibited due lack of information on drug product compatibility with G-tubes. After a study was performed that demonstrated compatibility with "careful use" of G-tubes, the other 2 patients were able to continue in the study.
- A placebo patient under dosed slightly during the first 4 weeks of treatment due to use of an incorrect body weight value for dose calculations, which was subsequently corrected.

- One placebo and 1 CBD patient missed multiple doses due to vomiting.
- Two patients at the same site (1 randomized to CBD and the other randomized to placebo) accidentally received each other's IMP at the randomization visit and continued in the received rather than randomized treatment group for the rest of the study.
- One placebo patient had a positive THC at the randomization visit (sample was obtained after randomization so participation was allowed). Screening and end of treatment THC results were negative.
- One patient did not have THC measured at screening or randomization.
- Transaminase elevations identified after unblinding of the data:
  - 6 patients in the CBD group had elevations in ALT or AST to levels > 3 × ULN with concurrent TEAE of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%), but were not withdrawn from the trial.
  - One CBD patient had ALT >3xULN at screening with coincidental vomiting but was not withdrawn from the study.

Clinical reviewer's comment: While important, these protocol violations would likely not impact the efficacy analysis. Upon review of the list of protocol deviations, no other violations that would impact efficacy were identified.

Table of Demographic Characteristics

The baseline demographics of the patients enrolled and randomized in Study 1423 (ITT dataset) were similar between groups and are summarized in Table 37. The mean age and distribution amongst the predefined age groups in all three treatment groups were similar. A sufficient percentage of patients in the 2-5 years group were enrolled in both treatment groups (12.8% and 14.1%). Similar proportions of males and females were enrolled, and both groups had similar sex distributions. Most patients in the CBD and placebo groups were from the US (72.1% and 77.6%, respectively). Distributions of patients from the non-US countries were similar between groups.

Table 37: Study 1423, Baseline Demographics (ITT Analysis Set)

	Statistic	CBD 20 mg/kg (N=86)	Placebo (N=85)
Age (Years)	Mean	15.5	15.3
	Median	14.2	13.2
	Min, Max	2.7, 39.0	2.8, 45.1

	Statistic	CBD 20 mg/kg (N=86)	Placebo (N=85)
Age group	2-5 years	11 (12.8%)	12 (14.1%)
	6-11 years	26 (30.2%)	27 (31.8%)
	12-17 years	19 (22.1%)	18 (21.2%)
	18-55 years	30 (34.9%)	28 (32.9%)
Sex	Female	41 (47.7%)	42 (49.4%)
	Male	45 (52.3%)	43 (50.6%)
Race	White/Caucasian	75 (87.2%)	79 (92.9%)
	Black/African American	2 (2.3%)	3 (3.5%)
	Asian	3 (3.5%)	3 (3.5%)
	Other	6 (7.0%)	0
Country	Netherlands	3 (3.5%)	2 (2.4%)
	Poland	21 (24.4%)	17 (20.0%)
	USA	62 (72.1%)	66 (77.6%)
Region	Rest of the world	24 (27.9%)	19 (22.4%)
	USA	62 (72.1%)	66 (77.6%)

Source: Table 3.1.2, Study 1423, CSR

Clinical reviewer's comment: Baseline demographics were adequately similar between treatment groups.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

The patients' current seizure types, based on their medical history; i.e., collected retrospectively during screening, are summarized below in Table 38. The distribution of current seizure types reported at screening was similar across the treatment groups, with tonic, tonic-clonic, and atonic being most common. Baseline drop seizure frequency was also very similar in both groups (71.4% and 74.7% in CBD and placebo groups, respectively).

Table 38: Study 1423, Summary of Baseline Characteristics (ITT Analysis Set)

Statistic	CBD 20 mg/kg (N=86)	Placebo (N=85)
Drop Seizure Frequency Per 28 Days		
Median	71.4	74.7
Min, Max	10.3, 855.9	11.2, 3174.6
Baseline Seizure Type n (%)		
Tonic Seizures	71 (82.6%)	65 (76.5%)
Clonic Seizures	7 (8.1%)	12 (14.1%)
Tonic-Clonic Seizures	49 (57.0%)	53 (62.4%)
Atonic Seizures	47 (54.7%)	59 (69.4%)
Myoclonic Seizures	38 (44.2%)	41 (48.2%)

Statistic	CBD 20 mg/kg (N=86)	Placebo (N=85)
Countable Partial Seizures	20 (23.3%)	19 (22.4%)
Other Partial Seizures	4 (4.7%)	2 (2.4%)
Absence Seizures	42 (48.8%)	40 (47.1%)
Number of Current AEDs (Continuous)		
Median	3.00	3.00
Min, Max	1.0, 5.0	1.0, 4.0
Number of Current AEDs (Categorical) n (%)		
1	5 (5.8%)	5 (5.9%)
2	26 (30.2%)	21 (24.7%)
3	31 (36.0%)	34 (40.0%)
4	22 (25.6%)	25 (29.4%)
5	2 (2.3%)	0
Specific Baseline AEDs n (%)		
Clobazam	42 (48.8%)	42 (49.4%)
Valproic Acid	36 (41.9%)	33 (38.8%)
Lamotrigine	33 (38.4%)	31 (36.5%)
Levetiracetam	23 (26.7%)	35 (41.2%)
Rufinamide	25 (29.1%)	21 (24.7%)
Number of Former AEDs (Continuous)		
Median	6.00	6.00
Min, Max	1.0, 18.0	0.0, 28.0

Source: Applicant's Table 3.2.2. Study 1423, CSR

EEG history was very similar between the treatment groups. All patients were reported to have previously had an abnormal EEG. Most patients never had a normal EEG (83.7% and 83.5%, of the CBD and placebo groups, respectively). Fewer patients in the CBD group (4.7%) were on a ketogenic diet during the study than in the placebo group (11.8%), but proportions of patients in both groups were using VNS.

Clinical reviewer's comment: The baseline disease-related characteristics were similar between groups.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Twenty-one patients (12.3%) had 1 or more days during the treatment period on which at least 1 dose of IMP was recorded as not being taken, more in the CBD group (15.1%) than in the placebo group (9.4%). In most of these patients (17/21, 81%), the number of days in which at least 1 dose was missed was less than 5 days. Eight patients missed both doses in at least 1 day, more commonly in the CBD group (6, 7%) than in placebo group (2, 2.4%). Four patients in the

CBD group did not take the study drug for >10 days and one patient in the placebo group took no study drug for 5 days, most of which occurred just prior to withdrawal from the study.

Use of rescue medications during the study did not differ significantly between groups with 61.6% in the CBD group and 58.8% in the placebo group.

Clinical reviewer's comment: Although treatment compliance was slightly worse in the CBD group as compared to the placebo group, the difference was small enough that it is not expected to impact efficacy. Most of the multi-day missed doses were in patients prior to them exiting the study. Rescue medication usage did not predispose towards increased efficacy in the CBD group, as the frequency of use of these drugs was similar between groups.

Efficacy Results - Primary Endpoint

There was statistically significant difference between the groups in the percentage change from baseline in drop seizure frequency during the treatment period, in favor of CBD treatment (p =0.0135). The median percentage change from baseline in drop seizure frequency during the treatment period was −43.9% in the CBD group compared with −21.8% in the placebo group. The estimated median difference was −17.2% (Table 39).

Table 39: Study 1423, Analysis of the Primary Endpoint

	CBD 20 mg/kg/day (N=86)	Placebo (N=85)
Drop Seizure Frequency (per 28 Days)		
Baseline Period Median	71.4	74.7
Treatment Period Median	31.4	56.3
Median Percentage Change from Baseline (Q1, Q3)	−43.9 (−69.6, −1.9)	−21.8 (−45.7, 1.7)
Estimated Median Difference (CI)*	−17.2 (−30.3, −4.1)	
P-value by Wilcoxon rank-sum test	0.0135	

Source: Study 1423 CSR Table 8.4.1.1-1, confirmed by FDA statistical reviewer.
*based on Hodges-Lehmann estimator

Figure 9 below shows that sensitivity analyses using ANCOVA on ranked data and log-transformed data yielded similar results to the primary analysis. Consistent results were seen for the maintenance period and each 4-week period of the maintenance (Table 40).

Table 40: Study 1423, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint

Analysis Period	Treatment	n	Median	Q1, Q3	Estimated Median Difference[b] (95% CI)	p-value[c]
Maintenance Period	20 mg/kg (N=86)	85	-48.77	-74.6, 2.2	-19.45 (-33.05, -4.68)	0.0096
	Placebo (N=85)	85	-20.45	-48.5, -0.2		
Maintenance Period (Week 1 to 4)[a]	20 mg/kg (N=86)	82	-51.30	-81.5, -21.4	-23.63 (-37.19, -11.03)	0.0005
	Placebo (N=85)	85	-23.33	-51.9, 0.0		
Maintenance Period (Week 5 to 8)[a]	20 mg/kg (N=86)	73	-45.36	-70.8, -17.4	-16.77 (-30.87, -2.56)	0.0205
	Placebo (N=85)	84	-23.46	-53.8, 0.0		
Maintenance Period (Week 9 to 12)[a]	20 mg/kg (N=86)	72	-52.56	-77.9, -13.1	-23.58 (-38.42, -6.76)	0.0062
	Placebo (N=85)	84	-26.99	-46.9, 5.1		

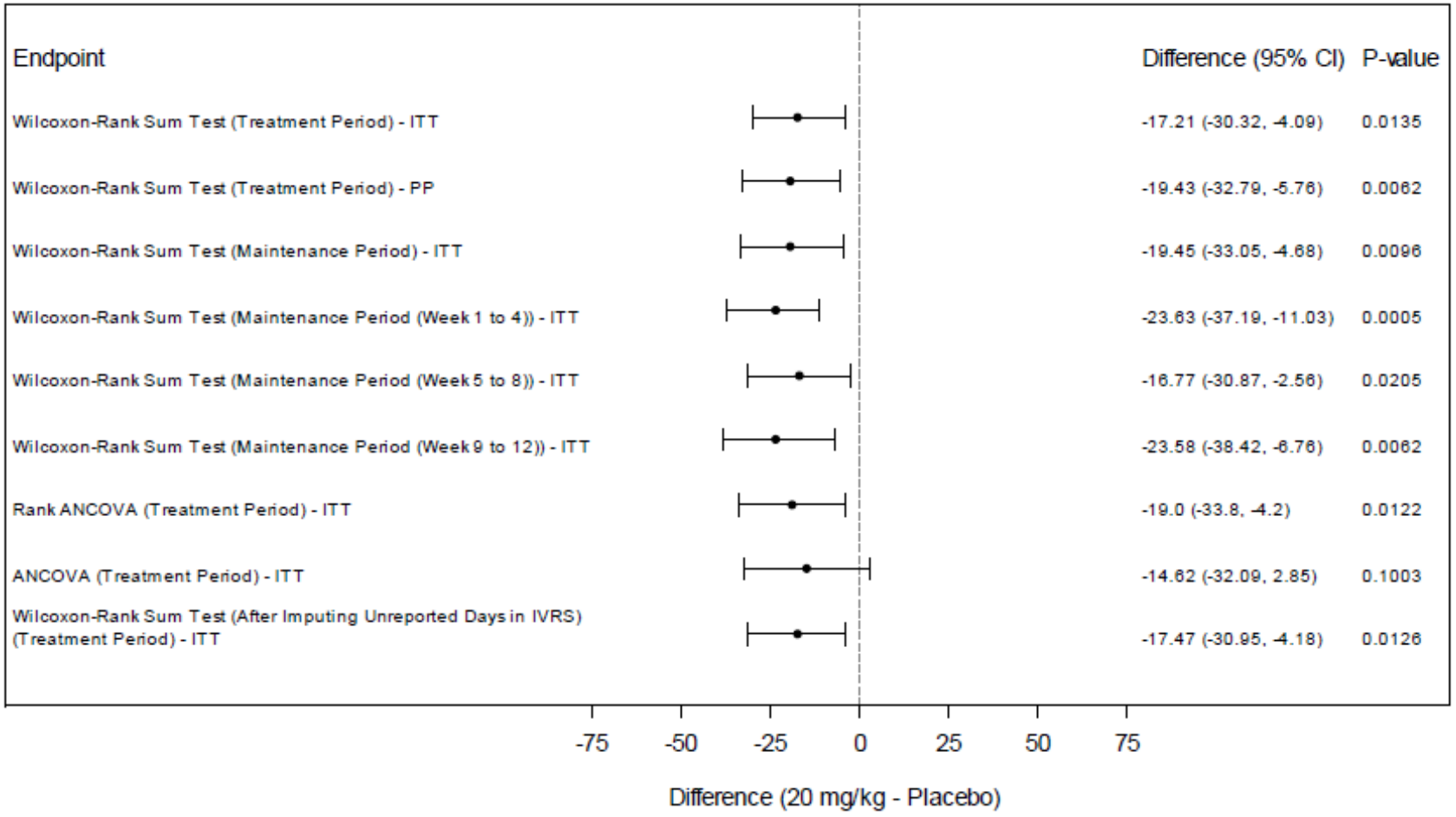
Source: Study 1423, Unblinded Final Tables, Table 8.1.1

[a] Patients with at least 7 days of seizure data within the corresponding 4 week period

[b] based on Hodges-Lehmann estimator

[c] by Wilcoxon Rank Sum Test

Figure 9: Study 1423, Sensitivity Analyses, Primary Efficacy



Source: Figure 8.4.1.1.1-1, Study 1423 CSR

Missing data

Two sensitivity analyses assessing the impact of missing data were conducted by the applicant. One analysis used the worst of last observation, next observation, or the mean value of observed data to impute the intermittent missing values due to unreported days in the IVRS. As there were few intermittent missing data (2%), the result was similar to the primary analysis. However, this analysis did not address the impact of missing data due to dropouts, which might be of concern as the dropout rates were unbalanced: 14 (16%) in the CBD group vs. 1 (1%) in the placebo group.

The sensitivity analysis using multiple imputation (MI) examined the impact of missing data due to dropouts on the efficacy results. In this analysis, intermittent missing values before the last visit were first imputed under missing at random assumption (MAR). Then non-intermittent missing data were imputed under the missing not at random (MNAR) assumption that the imputed values for CBD patients who discontinued were different from those of placebo patients. This analysis showed that the result for the primary endpoint remained statistically significant when values imputed for the dropouts in the CBD group were slightly worse (up to one standard error of the observed drop seizure frequency in the placebo group) than those of placebo patients.

The data indicated that some patients experienced or reported fewer seizures prior to withdrawing from the study. The appearance of seizure reduction in these patients may be artificial. One could argue that they might have behaved similarly as the rest of patients did, had they been able to recover from the adverse events. On the contrary, one could also argue that CBD simply failed them because they were no longer able to tolerate CBD treatment even if there was some indication of benefit on seizure frequency from CBD. The two arguments seem equally valid. The latter argument may also shed some light on how useful CBD treatment could be. Therefore, the statistical reviewer conducted a worst-case type of analysis, in which patients who withdrew were assigned the worst result (the largest percentage change from base in convulsive seizure frequency). The resulting estimated median difference between the two groups was −5.5% (Table 41), much smaller than the estimated median difference of −17.2% from the primary analysis, but still numerically in favor of the CBD treatment.

Table 41: Study 1423, Reviewer's Worst-Case Analyses of the Primary Endpoint

	CBD (N=86)	Placebo (N=85)
Assuming that patients who withdrew did not improve from baseline		
Median Percentage Change from Baseline	−32.0	−21.8
Estimated Median Difference (CI)*	−5.5 (−21.0, 12.1)	

Source: FDA statistical reviewer.
*based on Hodges-Lehmann estimator

Given the above sensitivity analyses, the result of the primary endpoint seemed less robust to the missing data caused by unbalanced dropouts between the treatment groups, compared to Study 1332B and Study 1414.

Over-enrollment

The planned total sample size for this study was 100 patients. However, the study randomized 171 patients, which was a 71% increase in the number of patients. This reviewer (FDA statistician) conducted an analysis of the primary endpoint on the first 100 randomized patients. The placebo group had higher drop seizure frequency at baseline in this subset. The results showed a smaller median treatment difference of -8.6%, which was not statistically significant (Table 42). In response to the Agency's inquiry, the applicant explained that the over-enrollment was due to the logistics of the trial, and was not based on blinded or unblinded interim analysis of the data. Therefore, this reviewer considered it appropriate to include all randomized patients in the primary analysis.

Table 42: Study 1423, Analysis of the Primary Endpoint on the First 100 Randomized Patients

	CBD (N=51)	Placebo (N=49)
Drop Seizure Frequency (per 28 Days)		
Baseline Period Median	56.0	80.0
Treatment Period Median	28.0	55.1
Median Percentage Change from Baseline	−39.6	−24.8
Estimated Median Difference in Percentage Change from Baseline(CI)* -	−8.6 (−25.3, 9.1)	
P-value by Wilcoxon rank-sum test	0.3484	
P-value by Ranked ANCOVA test	0.3420	

Source: FDA statistical reviewer.
*based on Hodges-Lehmann estimator

Clinical reviewer's comment: Compared with the placebo group, the CBD group demonstrated a statistically significant decrease in percent change in drop seizures from baseline to the treatment period in the primary efficacy analysis. As noted above, this is the same primary efficacy endpoint used in most AED treatment trials, although the seizure types counted toward the primary endpoint differ based on the underlying disease. This efficacy analysis is both statistically significant (p=0.0135) and clinically meaningful.

As noted above, there was an imbalance between treatment groups with respect to dropouts (16.3% and 1.2% in the CBD and placebo groups, respectively), and some of these patients experienced or reported fewer seizures prior to discontinuing the study. The FDA statistician conducted a worst-case analysis to assess this imbalance and if the study results were driven by the patients who discontinued early and experienced/reported few seizures. The estimated median difference between groups was much lower in the worst-case analysis than in the

primary efficacy analysis (–5.5 vs –17.2, respectively), suggesting that the primary efficacy results, though statistically significant, were less robust to missing data.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, region, clobazam use, valproic acid use, lamotrigine use, rufinamide use, baseline drop seizure frequency groups, number of current AEDs and number of prior AEDs for the CBD and placebo groups. Although not all differences were statistically significant, the results favored CBD over placebo in all subgroups and are summarized in Table 43 and Table 44 below.

Table 43: Study 1423, Subgroup Analysis of the Primary Endpoint (Demographics)

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*	
Sex					
Male	20 mg/kg	45	-46.43	-10.29	(-30.52, 9.26)
	Placebo	43	-21.66		
Female	20 mg/kg	41	-42.00	-21.57	(-39.51, -5.24)
	Placebo	42	-21.93		
Race					
White/Caucasian	20 mg/kg	75	-42.00	-17.92	(-32.25, -3.81)
	Placebo	79	-21.66		
Other	20 mg/kg	11	-49.91	-3.36	(-47.41, 45.20)
	Placebo	6	-45.75		
Age					
2-5 years	20 mg/kg	11	-50.68	-8.55	(-49.19, 42.37)
	Placebo	12	-28.29		
6-11 years	20 mg/kg	26	-40.73	-22.16	(-50.49, 2.02)
	Placebo	27	-14.04		
12-17 years	20 mg/kg	19	-45.81	-27.28	(-59.50, 5.15)
	Placebo	18	-26.54		
18-55 years	20 mg/kg	30	-39.89	-13.32	(-32.04, 13.74)
	Placebo	28	-22.35		
Region					
USA	20 mg/kg	62	-40.80	-18.91	(-33.71, -4.22)
	Placebo	66	-21.81		
Rest of the World	20 mg/kg	24	-48.52	-10.76	(-42.85, 25.80)
	Placebo	19	-9.49		

Source: FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 44: Study 1423, Subgroup Analysis of the Primary Endpoint (Concomitant AEDs)

Subgroup/Item	Treatment	N	Median	Median Difference (95% CI)*	
Clobazam Use					
Yes	20 mg/kg	42	-59.60	-28.17	(-46.12, -10.05)
	Placebo	42	-22.91		
No	20 mg/kg	44	-28.61	-6.04	(-25.25, 15.46)
	Placebo	43	-21.66		
Valproic Acid Use					
Yes	20 mg/kg	36	-53.88	-28.51	(-44.24, -5.76)
	Placebo	33	-21.80		
No	20 mg/kg	50	-36.98	-12.15	(-28.89, 6.37)
	Placebo	52	-21.74		
Lamotrigine Use					
Yes	20 mg/kg	33	-29.79	-9.32	(-32.94, 15.99)
	Placebo	31	-11.68		
No	20 mg/kg	53	-50.68	-22.16	(-37.80, -6.18)
	Placebo	54	-27.12		
Levetiracetam Use					
Yes	20 mg/kg	23	-42.00	-16.39	(-37.93, 7.42)
	Placebo	35	-32.32		
No	20 mg/kg	63	-45.81	-21.36	(-37.24, -3.23)
	Placebo	50	-19.80		
Rufinamide Use					
Yes	20 mg/kg	25	-29.79	-19.42	(-44.64, 6.69)
	Placebo	21	-15.42		
No	20 mg/kg	61	-46.43	-17.03	(-32.25, -0.72)
	Placebo	64	-21.93		

Source: Table 9.20.1, Study 1423 CSR
*based on Hodges-Lehmann estimator

Efficacy Results - Secondary and other relevant endpoints

Key Secondary Endpoints

Table 45 below presents results of the key secondary endpoints for descriptive purpose only.

- Proportion of 50% responders
  During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency was greater in the CBD group (44.2%), compared with the placebo group (23.5%). The odds ratio (OR) was 2.6 and reached nominal significance.

- Change in total seizure frequency
  A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in the CBD group compared with the placebo group with an estimated median difference of -21.1.

- Subject/Caregiver Global Impression of Change (S/CGIC)
  For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit were analyzed using ordinal logistic regression. The mean S/CGIC score at last visit was 3.0 (corresponding to "slightly improved") in the CBD group compared with 3.7 (most closely associated with "no change") in the placebo group. There were approximately 2.5-times the odds of patients recording a lower score (improvement) in overall condition in the CBD group compared with the placebo group at last visit.

Table 45: Study 1423, Analyses of the Key Secondary Endpoints

Variable	CBD (N=86)	Placebo (N=85)
≥ 50% Reduction in Drop Seizure Frequency		
n (%)	38 (44.2)	20 (23.5)
Odds Ratio (CI)	2.6 (1.3, 5.0)	
Nominal p-value by CMH test	0.0043	
Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period		
Median Percentage Change During Treatment	−41.2	−13.7
Estimated Median Difference (CI*)	−21.1 (−33.3, −9.4)	
Subject/Caregiver Global Impression of Change Score at the Last Visit		
Mean	3.0	3.7
Odds Ratio (CI)	2.5 (1.5, 4.5)	

Source: Table 8.4.1.2.1.1-1, Table 8.4.1.2.1.2-1 and Table 9.3.1.2 of Study 1423 CSR.
*based on Hodges-Lehmann estimator

Clinical reviewer's comment: The results of the key secondary analyses are generally supportive of the primary efficacy endpoint. The ≥ 50% reduction in drop seizure frequency analysis (50% responder analysis), while nominally significant, is not independent of the primary efficacy outcome. While it may be helpful in defining a subset of patients who might be considered responders, it does not provide information separate from the primary efficacy endpoint. The comparative reduction in the percentage change in total seizure frequency is somewhat related to the primary efficacy but does include the full range of seizures assessed in Study 1423 and suggests a broad efficacy in seizures in patients with LGS. The S/CGIC analyses generally support that the change in the primary efficacy endpoint is clinically meaningful.

Other Secondary Endpoints of Clinical Interest
These endpoints are presented for descriptive purposes only.

- **Non-Drop Seizures**
  Non-drop seizures were reported during baseline in 89.5% of CBD patients and 93.0% of placebo patients in the ITT analysis set. A greater median reduction from baseline in non-drop seizure frequency during the treatment period was seen in both the 20 mg/kg/day and the 10 mg/kg/day groups, compared with the placebo group, as seen in Table 46.

Table 46: Study 1423, Percentage Change in Non-Drop Seizure Frequency

Variable	CBD (N=86)	Placebo (N=85)
Total Non-Drop Seizure Frequency (per 28 Days)	n=77	n=79
Baseline Period Median (Q1, Q3)	94.00 (19.8, 311.0)	85.00 (20.5, 220.0)
Treatment Period Median (Q1, Q3)	39.38 (4.7, 136.2)	57.71 (11.3, 186.4)
Median Percentage Change During Treatment (Q1, Q3)	−49.43 (−81.6, −25.3)	−22.90 (−67.8, 31.7)
Estimated Median Difference (CI)	−26.06 (−46.09, −8.34)	

Source: Table 8.4.1.2.2.3-1, Study 1423, CSR

Clinical reviewer's comment: Although not pre-specified in the SAP as a hierarchical secondary endpoint for the purposes of statistical analysis, change in non-drop seizures is an important endpoint from the clinical perspective. A general concern with epilepsy disorders in which there are frequent multiple seizure types, is that a treatment may improve one type of seizures and worsen another. Non-drop seizures, while not as disabling as drop attacks, still cause significant morbidity for patients with LGS. The analysis of median change in non-drop seizure frequency favors the CBD group over placebo, providing some reassurance that there is no increase in non-drop seizures with CBD.

- **Drop Seizure Treatment Responders and Drop Seizure Freedom**
  A similar proportion of patients in both groups had any reduction in drop seizure frequency from baseline during the treatment period (74.4% vs. 74.1%). A higher proportion of placebo patients had improvements in the range of > 0 to < 25% (30.6% vs. 10.5%), while a higher proportion of patients in the CBD group had improvements in the ≥ 50 to < 75% and ≥ 75% categories, as seen in Figure 10. No patients in either group achieved seizure freedom. See Table 47 for specifics.

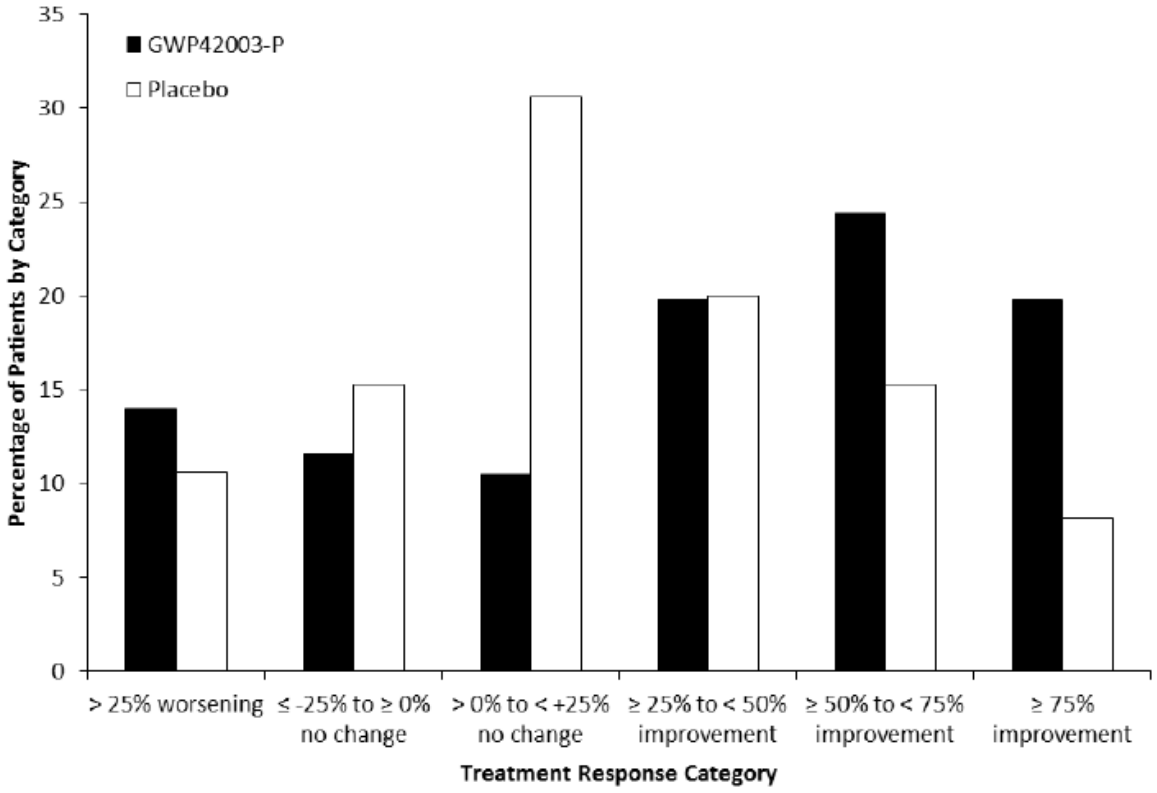
Table 47: Study 1423, Summary and Analysis of Drop Seizure Treatment Responders

Variable	CBD (N=86)	Placebo (N=85)
>25% (Worsening)	12 (14.0%)	9 (10.6%)
>=0% to <=25% (Worsening)	10 (11.6%)	13 (15.3%)
>-25% to <0% (Improvement)	9 (10.5%)	26 (30.6%)
>-50% to <=-25% (Improvement)	17 (19.8%)	17 (20.0%)
>-75% to <=-50% (Improvement)	21 (24.4%)	13 (15.3%)
<=-75% (Improvement)	17 (19.8%)	7 (8.2%)
≥25% Reduction		
Yes	55 (64.0%)	37 (43.5%)
No	31 (36.0%)	48 (56.5%)
Difference in Proportions [Active-Placebo] (95% CI)	0.204 (0.058, 0.351)	
Odds Ratio [Active/Placebo] (95% CI)	2.30 (1.24, 4.26)	
≥50% Reduction		
Yes	38 (44.2%)	20 (23.5%)
No	48 (55.8%)	65 (76.5%)
Difference in Proportions [Active-Placebo] (95% CI)	0.207 (0.068, 0.345)	
Odds Ratio [Active/Placebo] (95% CI)	2.57 (1.33, 4.97)	
Nominal *p*-value	0.0043	
≥75% Reduction		
Yes	17 (19.8%)	7 (8.2%)
No	69 (80.2%)	78 (91.8%)
Difference in Proportions [Active-Placebo] (95% CI)	0.115 (0.013, 0.218)	
Odds Ratio [Active/Placebo] (95% CI)	2.75 (1.07, 7.01)	

Source: Table 9.1.1, Study 1423 CSR

Clinical reviewer's comment: Overall, the responder analysis favored CBD over placebo. However, this is complicated by the increased proportion of patients in the CBD group that demonstrated >25% worsening of drop seizures when compared to patients in the placebo group. Because of the small numbers of patients in these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses, but the overall analysis is supportive of CBD over placebo.

Figure 10: Study 1423, Continuous Response Analysis for Drop Seizures (Treatment Period)



Source: Figure 8.4.1.2.2.1-1, Table 9.1.1, Study 1423 CSR

- **Individual Seizure Types**
  The sponsor assessed outcomes for the following seizure types: tonic, tonic-clonic, atonic, countable partial seizures, other partial seizures, clonic seizures, myoclonic seizures, and absence seizures. All seizure subtype outcomes favored the CBD groups over placebo.

Clinical reviewer's comment: Analysis of the median percentage change in seizure frequency of all seizure subtypes all favored the CBD treatment groups over placebo and are supportive of the primary efficacy endpoint.

Dose/Dose Response

See Section 7.1.4.

Durability of Response and Persistence of Effect

Sensitivity analyses of the primary endpoint were performed on the maintenance period and each 4-week period of the maintenance. Consistent results were seen for each of these time periods in Study 1423. See also Section 7.1.5.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This application contains data from three pivotal trials to support two indications – treatment of seizures in Dravet syndrome or Lennox-Gastaut syndrome. While both proposed indications are for treatment of seizures, the intended use populations are not the same, and thus do not allow for pooling of all three trials to demonstrate efficacy. Studies 1414 and 1423, however, were very similar in design (differing primarily in the testing of two cannabidiol doses in Study 1414 and one dose (20 mg/kg) of cannabidiol in Study 1423 and were conducted in the same population (patients with LGS). Although the primary efficacy dataset cannot be combined for these two pivotal trials, they are assessed together to examine efficacy further in the LGS population. A single trial (Study 1332B) is used to examine efficacy in the Dravet patient population.

7.1.1. Primary Endpoints

Given the differences between the LGS and DS populations and the primary efficacy endpoints used in Studies 1332B, 1414, and 1423, direct comparison of the primary efficacy results cannot be made between the three trials.

Lennox-Gastaut Syndrome

Reduction in drop seizures was the efficacy outcome measure used in both Studies 1414 and 1423 and the primary efficacy endpoint in both trials was defined as *"percentage change from baseline in drop seizure frequency (average per 28 days) during the treatment period, based on the ITT analysis set".* The primary efficacy endpoint was not assessed at one specific time, but was rather a measure of change in seizure frequency over the entire treatment period, which included the 10-day titration period and the 12-week maintenance period. A drop seizure in both trials was defined as *"an attack or spell (atonic, tonic or tonic-clonic) 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."* As noted elsewhere in this review, this is the preferred primary efficacy endpoint for AED treatment trials in general and for LGS, in particular.

Both trials used the same diagnostic criteria for LGS and the identical eligibility criteria. The study populations in Studies 1414 and 1423 were almost identical based on baseline demographics and disease-related characteristics (see Tables 23, 24, 35, and 36).

The effectiveness of CBD for the treatment of drop seizures associated with LGS was established in patients ages 2 years and older, as seen in Table 48 below. Study 1414 (N=225) compared two doses of CBD (20 mg/kg/day and 10 mg/kg/day) with placebo. Study 1423 compared CBD (20 mg/kg/day) with placebo. Studies 1414 and 1423 both randomized more patients than the respective planned sample sizes. Study 1423 had a larger over-enrollment (increase of 71%) than Study 1414 (increase of 50%). In addition to over-enrollment, both trials had imbalances in drop-out rates. A much greater proportion of the 20 mg/kg/day groups in both trials (11.8% and 16.3%, respectively) withdrew during the treatment period than the placebo groups (2.6% and 1.2%, respectively) or the 10 mg/kg/day group (2.7%, Study 1414 only).

In Study 1414, there were statistically significant differences between each CBD group and the placebo group in the percentage change from baseline in drop seizure frequency during the treatment period, favoring CBD (p=0.0047 and p=0.0016, respectively). The estimated median difference was −21.6% and -19.2%, respectively. The analysis results were consistent across subgroups. A sensitivity analysis examining the impact of missing data due to dropouts showed that the result for the primary endpoint remained statistically significant, as did an analysis of the impact of patients who had fewer seizures prior to withdrawing from the study. These sensitivity analyses suggest that the primary efficacy results of Study 1414 were robust to missing data.

In Study 1423, there was statistically significant difference between the groups in the percentage change from baseline in drop seizure frequency during the treatment period, in favor of CBD treatment (p=0.0135), and the estimated median difference was −17.2%. The analysis results were consistent across subgroups. A sensitivity analysis examining the impact of missing data due to dropouts showed that the result for the primary endpoint remained statistically significant. However, an analysis of the impact of patients who had fewer seizures prior to withdrawing from the study resulted in an estimated median difference (-8.8%) that was smaller compared to the primary analysis, and was not statistically significant (0.2080). These sensitivity analyses suggest that the results of Study 1423, while statistically favoring CBD over placebo, were less robust to missing data. Additionally, an analysis of the primary efficacy endpoint in the first 100 patients enrolled demonstrated a smaller median treatment difference of -8.6%, which was also not statistically significant, again suggesting the primary efficacy data were less robust to missing data. However, the primary efficacy endpoint was significantly positive and is supported by the robust results in Study 1414.

Table 48: Summary Comparison of Primary Efficacy Analyses for Studies 1414 and 1423

	Study 1414			Study 1423	
	20 mg/kg/day (N=76)	10 mg/kg/day (N=73)	Placebo (N=76)	20 mg/kg/day (N=73)	Placebo (N=76)
Primary Efficacy Analysis					
Baseline Period Median	85.5	86.9	80.3	71.4	74.7
Treatment Period Median	44.9	50.0	72.7	31.4	56.3
Median Percentage Change During Treatment (Q1, Q3)	−41.9 (−72.4, −1.3)	−37.2 (−63.8, −5.6)	−17.2 (−37.1, 0.9)	−43.9 (−69.6, −1.9)	−21.8 (−45.7, 1.7)
Estimated Median Difference (CI)	−21.6 (−34.8, −6.7)	−19.2 (−31.2, −7.7)		−17.2 (−30.3, −4.1)	
P-value by Wilcoxon rank-sum test	0.0047	0.0016		0.0135	
Sensitivity analysis of the Primary Endpoint in patients with fewer seizures prior to withdrawal					
Assuming that patients who withdrew did not improve from baseline					
Median Percentage Change from Baseline	−39.2	−36.2	−17.2	−32.0	−21.8
Estimated Median Difference (95% CI)	−16.0 (−31.6, −1.0)	−16.8 (−29.5, −5.2)		−8.8 (−22.7, 4.8)	
P-value by Wilcoxon rank-sum test	0.0279	0.0056		0.2080	
Assuming that patients who withdrew did not improve more than the average of the placebo					
Estimated Median Difference (95% CI)	--	--	--	−12.0 (−24.6, 0.43)	
P-value by Wilcoxon rank-sum test	--	--	--	0.0709	
Analysis of the Primary Endpoint on the Number of Randomized Patients in the SAP (First Consecutive Randomized)					
N	50	49	51	51	49
Baseline Period Median	82.0	86.9	76.3	56.0	80.0
Treatment Period Median	44.0	40.9	55.4	28.0	55.1
Median Percentage Change During Treatment	−44.7	−45.1	−23.0	−39.6	−24.8
Estimated Median Difference (CI)	−21.5 (−41.1, −1.2)	−19.8 (−33.5, −5.4)		−8.6 (−25.3, 9.1)	
P-value by Wilcoxon rank-sum test	0.0349	0.0101		0.3484	
P-value by Ranked ANCOVA test				0.3420	

Source: FDA statistical reviewer

Dravet Syndrome

Reduction in convulsive seizures was the efficacy outcome measure used in Study 1332B, and the primary efficacy endpoint was defined as "percentage change from baseline in convulsive seizure frequency (average per 28 days) during the treatment period, based on the ITT analysis set". The primary efficacy endpoint was not assessed at one specific time, but was rather a measure of change in seizure frequency over the entire treatment period, which included the 10-day titration period and the 12-week maintenance period. Convulsive seizure included tonic-clonic, tonic, clonic or atonic seizures. As noted elsewhere in this review, percentage change

from baseline in seizure frequency (average per 28 days) during the treatment period is the preferred primary efficacy endpoint for AED treatment trials.

The effectiveness of CBD for the treatment of convulsive seizures associated with Dravet syndrome was established in pediatric patients ages 2-18 years, as seen in Table 49 below. Study 1223B (N=120) compared CBD (20 mg/kg/day) with placebo. As in Studies 1414 and 1423, Study 1332B randomized more patients (N=120) than the planned sample size (N=100). Study 1332B also had an imbalance in drop-out rates, with a much greater proportion of the CBD group than the placebo group withdrawing during the treatment period (14.8% and 5.1%, respectively).

In Study 1332B, there was a statistically significant difference between CBD and placebo in the percentage change from baseline in drop seizure frequency during the treatment period, favoring CBD (p=0.0123). The estimated median difference was −22.8%. The results were consistent across subgroups. A sensitivity analysis examining the impact of missing data due to dropouts showed that the result for the primary endpoint remained statistically significant, as did an analysis of the impact of patients who had fewer seizures prior to withdrawing from the study. These sensitivity analyses suggest that the primary efficacy results of Study 1332B were robust to missing data as seen in Table 46 below.

Table 49: Summary Comparison of Primary Efficacy Analyses for Study 1332B

	CBD (N=61)	Placebo (N=59)
Primary Efficacy Analysis		
Baseline Period Median	12.4	14.9
Treatment Period Median	5.9	14.1
Median Percentage Change from Baseline (Q1, Q3)	−38.9 (−69.5, −4.8)	−13.3 (−52.5, 20.2)
Estimated Median Difference (CI)	−22.8 (−41.1, −5.4)	
P-value by Wilcoxon rank-sum test	0.0123	
Sensitivity Analysis of the Primary Endpoint for Patients with Fewer Seizures Prior to Discontinuation		
Median Percentage Change from Baseline	−35.4	−13.3
Estimated Median Difference (CI)	−14.1 (−33.3, 8.5)	

Source: FDA statistical reviewer

7.1.2. Secondary and Other Endpoints

Given the differences between the LGS and DS populations, comparison of comparable secondary endpoints cannot be made between the three trials in these two populations.

Lennox-Gastaut Syndrome

Studies 1414 and 1423 prespecified a hierarchical examination of the same three key secondary endpoints, although these endpoints were examined for both CBD dose groups in Study 1414. These hierarchical analyses are intended for European regulatory submissions. All of the prespecified key secondary analyses favored CBD over placebo with statistically significant results (Table 50) and are supportive of the efficacy of CBD in the treatment of drop seizures in patient with LGS.

Key Secondary Endpoints

- Proportion of 50% responders
  During the treatment period in study 1414, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency was greater in the 20 mg/kg/day and 10 mg/kg/day CBD groups, compared with the placebo group. The odds ratios (ORs) were statistically significant for both the 20 mg/kg/day group (OR =3.9; p=0.0006) and the 10 mg/kg/day group (OR =3.3; p=0.0030). In study 1423, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency was also greater in the CBD group, compared with the placebo group. The odds ratios (OR) was 2.6 and achieved nominal significance (p=0.0043).

- Change in total seizure frequency
  A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in both the 20 mg/kg/day and 10 mg/kg/day CBD groups, compared with the placebo group during Study 1414. The difference between each CBD group and placebo was statistically significant (p=0.0091 and p=0.0015, respectively). Similar findings were seen in Study 1423, based on descriptive statistics.

- Subject/Caregiver Global Impression of Change (S/CGIC)
  For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. In study 1414, the treatment differences were in favor of CBD 20 mg/kg/day and 10 mg/kg/day (OR =1.8 and OR =2.6, respectively) and were both statistically significant (p=0.0439 and p=0.0020, respectively). The S/CGIC analysis in Study 1423 was similar with ~2.5-times the odds of patients recording a lower score (improvement) in overall condition in the CBD group compared with the placebo group at last visit.

Table 50: Summary of Key Secondary Endpoint Analyses in Studies 1414 and 1423

Variable	Study 1414			Study 1423	
	CBD 20 mg/kg/day (N=76)	CBD 10 mg/kg/day (N=73)	Placebo (N=76)	CBD 20 mg/kg/day (N=86)	Placebo (N=85)
≥ 50% Reduction in Drop Seizure Frequency					
n (%)	30 (39.5)	26 (35.6)	11 (14.5)	38 (44.2)	20 (23.5)
Odds Ratio (95% CI)	3.9 (1.8, 8.5)	3.3 (1.5, 7.3)		2.6 (1.3, 5.0)	
P-value by CMH test	0.0006	0.0030		0.0043*	
Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period					
Median Percentage Change During Treatment	−38.4	−36.4	−18.5	−41.2	−13.7
Estimated Median Difference (95% CI)	−18.8 (−31.8, −4.4)	−19.5 (−30.4, −7.5)		−21.1 (−33.3, −9.4)	
P-value by Wilcoxon rank-sum test	0.0091	0.0015		0.0005*	
Subject/Caregiver Global Impression of Change Score at the Last Visit					
Mean	3.0	3.2	3.6	3.0	3.7
Odds Ratio (95% CI)	1.8 (1.0, 3.3)	2.6 (1.4, 4.7)		2.5 (1.5, 4.5)	
P-value by Logistic Regression	0.0439	0.0020		0.0012*	

* Nominal p-values, as adjustment for multiplicity for these endpoints was not prespecified in the US version of the SAP for Study 1423

Source: Tables 8.4.1.2.1.1-1, 8.4.1.2.1.2-1 and 9.3.1.2 of Study 1414 CSR and Tables 8.4.1.2.1.1-1, 8.4.1.2.1.2-1 and 9.3.1.2 of Study 1423 CSR

Other Secondary Endpoints of Clinical Relevance

- **Continuous Response Analysis of Drop Seizures**

  (b) (4)

  This type of analysis, while deemed dependent on and not assessing a different domain from the primary efficacy endpoint, is frequently included in the clinical trials summaries of the prescribing information of AEDs. The continuous response analyses are summarized in Section 6.2.2 (Table 34 and Figure 8) and Section 6.3.2 (Table 47 and Figure 10) for Studies 1414 and 1423, respectively. The results of these analyses in both trials overall favored CBD (both doses) over placebo. However, the analysis is complicated by the increased proportion of patients in the 20 mg/kg group that demonstrated >25% worsening of drop seizures when compared to patients in the 10 mg/kg and placebo groups. Because of the small numbers of patients in all of these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses, but the overall analysis is supportive of the proposed indication.

- **Change in Percentage of Non-Drop Seizures**
  Although not pre-specified in the SAP for either Study 1414 or 1423 as a hierarchical secondary endpoint for the purposes of statistical analysis, change in non-drop seizures is an important clinical endpoint. In epilepsy disorders in which there are frequent multiple seizure types, treatment may improve one type of seizures and worsen another. Non-drop seizures, while not as disabling as drop attacks, still cause significant morbidity for patients with LGS. As seen in Table 51 below, the analysis of median change in non-drop seizure frequency showed no major difference between trials, favors both CBD groups over placebo, and the potential safety concern of increased non-drop seizures was not identified.

Table 51: Percentage Change in Non-Drop Seizure Frequency, Studies 1414 and 1423

Variable	CBD 20 mg/kg/day (N=76)	CBD 10 mg/kg/day (N=73)	Placebo (N=76)	CBD 10 mg/kg/day (N=73)	Placebo (N=76)
Total Non-Drop Seizure Frequency (per 28 Days)	n=64	n=55	n=70	n=77	n=79
Baseline Period Median	93.65	95.74	77.98	94.00	85.00
Treatment Period Median	24.24	16.33	54.87	39.38	57.71
Median Percentage Change During Treatment	−54.55	−61.11	−34.31	−49.43	−22.90
Estimated Median Difference (CI) compared to placebo	−22.36 (−40.10, −2.22)	−28.31 (−43.75, −10.54)		−26.06 (−46.09, −8.34)	

Source: Table 8.4.1.2.2.3-1 in Study 1414 CSR and Table 8.4.1.2.2.3-1 in Study 1423 CSR

Dravet Syndrome

Key Secondary Endpoint: Proportion of 50% responders

During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline convulsive seizure frequency was greater in the CBD group (42.6%), compared with the placebo group (27.1%). Although there were twice the odds of achieving a ≥ 50% reduction in convulsive seizure frequency in the CBD group compared with the placebo group, the difference between treatments did not reach nominal significance (p=0.0784; see Table 15). As noted in Section 6.1.2, the 50% responder endpoint limits the definition of efficacy to only patients who achieve a 50% reduction in seizure frequency. A less than 50% reduction in seizure frequency may be clinically meaningful and is better captured by the primary efficacy endpoint.

Other Clinically Relevant Secondary Endpoints

- **Continuous Response Analysis of Convulsive Seizures**
  (b) (4) . This type of analysis, while deemed dependent on and not assessing a different domain from the primary efficacy endpoint, is frequently included in the clinical trials summaries of the prescribing information of AEDs. The continuous response analyses are summarized in Section 6.1.2 (Table 17 and Figure 2). The results of this analysis overall favor CBD over placebo and are consistent with the proposed indication for treatment of seizures in patients with DS.

- **Change in Percentage of Nonconvulsive Seizures**
  An increase in frequency of nonconvulsive seizures in the setting of reduced convulsive seizure frequency would be considered a significant adverse effect of the drug; therefore, percentage change in nonconvulsive seizure frequency is a secondary endpoint of clinical interest, though it was not pre-specified in the SAP for Study 1332B as a hierarchical secondary endpoint for the purposes of statistical analysis. There was essentially no difference between CBD and placebo, as the estimated median difference was 0.00 (−21.36, 31.59) (Table 16). Therefore, the potential safety concern of increased non-convulsive seizures was not identified.

7.1.3. Subpopulations

In general, pooled subgroup analyses provided little useful information beyond the individual subgroup analyses, as only the 20 mg and placebo groups from Studies 1414 and 1423 were poolable.

Lennox-Gastaut Syndrome (Studies 1414 and 1423)

The applicant performed analyses of the primary efficacy endpoint on all relevant subgroups (age groups, sex, region, concomitant AED use, and number of prior/current AEDs) for Studies 1414 and 1423 separately. Race was not assessed as a subgroup as the majority of all patients in the LGS studies were White/Caucasian. All of the subgroup analyses favored CBD (both doses) over placebo (as seen in Table 30, Table 31, Table 43, and Table 44). There was no notable difference between subgroups/treatment arms for all analyses except for that of clobazam use in patients taking 20 mg/kg/day, in which the treatment effect was notably smaller for patients not currently taking CLB compared with those taking CLB. Specifically, in the 20 mg/kg/day groups in Studies 1414 and 1423 respectively, the estimated median difference in seizure frequency between treatment and placebo were -33.97 and -28.17 in patients taking concomitant CLB and -4.63 and -6.04 in patients not on concomitant CLB (interaction p-values: 0.0067 and 0.0123, see Tables 29 and 41).

Dravet Syndrome (Study 1332B)

Study 1332B was not included in any pooled subgroup analyses as the patient population was

sufficiently different from that in Studies 1414 and 1423 due to differences in the underlying diseases and seizures included in the primary efficacy endpoint analyses. Please see Section 6.1.2 for discussion of subgroup analyses performed in Study 1332B.

Exploration of Effect of Clobazam on Efficacy

As noted in Section 4.5 above, DNP recommended that the applicant explore the effect of concomitant AEDs on the efficacy of CBD. The effect of CLB on the efficacy of CBD was of especial interest, because of the known inhibition of CBD on CYP2C19, which metabolizes nCLB, CLB's active metabolite. The applicant performed a number of analyses, attempting to examine for such an effect. Certain factors impacted the ability to draw conclusions from the CLB analyses described below. For example, PK data for CLB and nCLB were not collected; therefore, the investigators could not control for increases in CLB or nCLB during the treatment period. Additionally, assessing the effect of a single drug was difficult, as many patients were on multiple concomitant AEDs, so separating out the impact of one concomitant drug among many is difficult.

The applicant plotted the proportion of patients against the percent change from baseline in drop or convulsive seizure frequency for patients who were taking CLB or not taking CLB concurrently, comparing CBD to placebo. In patients on concomitant CLB, reduction in seizure frequency was greater in patients taking CBD than in patients taking placebo. In patients who were not on concomitant CLB, results were mixed. In Study 1332B, there was no difference in seizure reduction between patients not on concomitant CLB and taking CBD or placebo. In Studies 1414 and 1423, patients taking placebo without concomitant CLB had a greater reduction in seizure frequency than patients taking CBD (Figure 7). Patients on CBD 10 mg/kg/day without CLB had a greater reduction in seizure frequency than patients on placebo, when the seizures improved (change in seizure frequency >0%). There was no difference between CBD and placebo, if the patient's seizures worsened (i.e., change in seizure frequency <0%) (Figure 8). There were no clear trends in these analyses, making it difficult to determine if presence or absence of concomitant CLB had any impact on the efficacy of CBD.

Figure 11: Study 1414, Cumulative Distribution Functions for Drop Seizures: 20 mg/kg/day CBD vs. Placebo by CLB Use (Treatment Period, ITT Analysis Set)

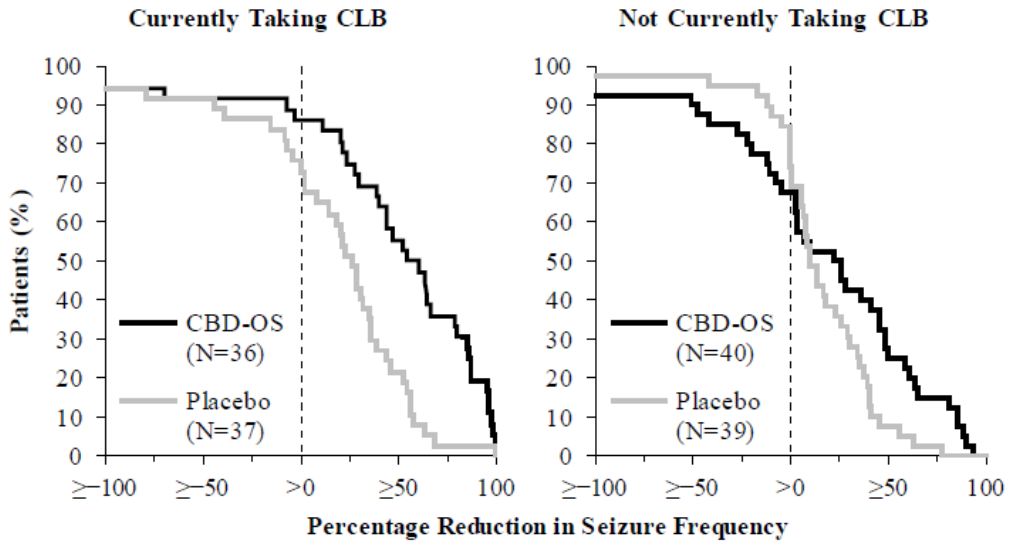
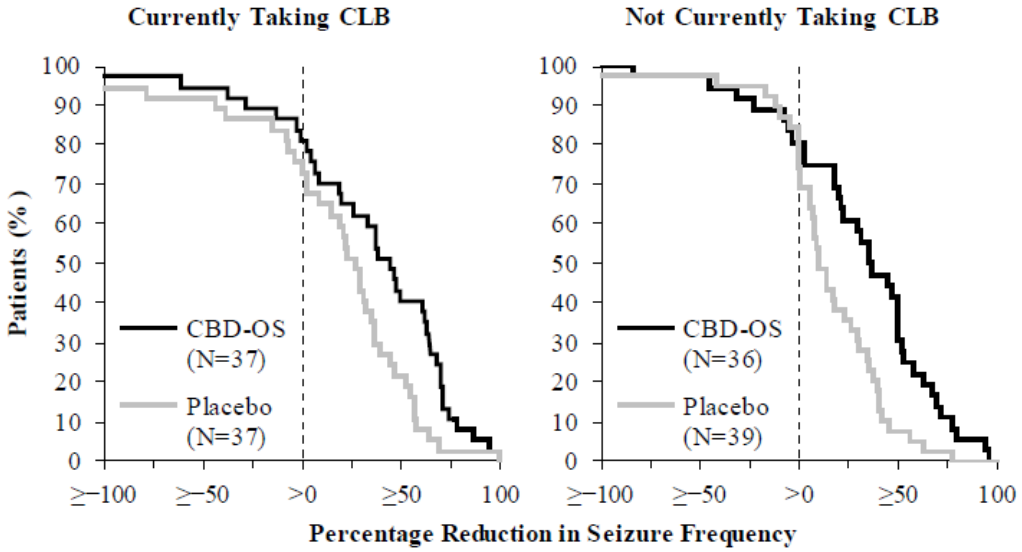


Figure 12: Study 1414, Cumulative Distribution Functions for Drop Seizures: 10 mg/kg/day CBD vs. Placebo by CLB Use (Treatment Period, ITT Analysis Set)



The applicant also performed logistic regression analyses of drop and convulsive seizure responders during the treatment periods for all three trials. These analyses were also complicated by small numbers of patients in some of the subgroups (particularly in patients with ≥75% reduction in seizure frequency), making it difficult to determine if there was any effect of CLB on the efficacy endpoint.

Lastly, patients receiving concomitant STP were expected to experience CYP2C19 inhibition to such an extent that addition of CBD would not cause additional inhibition of CYP2C19, thus the n-CLB levels were not expected to change post-CBD. Although the number of patients on STP and CLB were small (23 CBD, and 14 placebo), there was no significant difference between these groups in reduction in seizure frequency, suggesting that the CBD treatment effect is independent of nCLB.

Because of the difficulty in interpreting the cumulative distribution function and logistic regression analyses, we have relied on the STP analysis to conclude that the treatment effect of cannabidiol is not dependent on nor-clobazam or clobazam.

7.1.4. Dose and Dose-Response

Proposed Lower Maintenance Dosing in Dravet Syndrome

The applicant's proposed "therapeutic" dose for both indications in the prescribing information is 10 mg/kg/day (5 mg/kg BID) with the option to increase the dose to 20 mg/kg/day (10 mg/kg BID) if the lower dose is deemed ineffective and tolerability allows for higher dosing. CBD was assessed at only 20 mg/kg/day in the Dravet population, therefore, there are no efficacy data to support the 10 mg/kg/day maintenance dose in this population. There is a phase 3 pivotal trial underway in Dravet patients (Study 1424) which includes a 10 mg/kg/day arm, but results from this study are not available at the time of this review.

Utilization of exposure-response data to support the lower dose in DS patients is problematic. As is noted in the review by OCP, the applicant conducted exposure-response analyses for safety and efficacy, but these analyses are not based on PK data that adequately characterizes the CBD time profile during the pivotal trials. Specifically, the prominent food effect (5-fold increase in Cmax after a high-fat, high calorie meal), unrestricted access to food during the trials, and a complete lack of documented fed/fasted state when PK samples were drawn in Phase 3 trials, raises significant concerns about the stability of the intra-patient PK profiles. If the patient PK profiles are not stable, then the exposure-response analyses upon which they are based are insufficiently robust and cannot be used to support effectiveness of CBD. Thus, there are neither efficacy data nor reliable exposure-response data to support any claims of the 10 mg/kg/day dose as therapeutic in the DS population.

Nevertheless, it is likely that 10 mg/kg/day dose will be efficacious in patients with DS for several reasons relating to the underlying disease, efficacy outcome measures, and/or potential mechanism of action of CBD. First, the underlying diseases are similar. Onset occurs during early childhood in both LGS and DS with presence of multiple seizure types, seizures refractory to many AEDs, and cognitive impairment caused, at least in part, by the seizures. The seizure types included in the primary efficacy endpoints for the LGS and DS studies were also similar. Studies 1414 and 1423 (LGS) defined drop seizures as atonic, tonic, or tonic-clonic seizures that led or might have led to a fall. Study 1332B included tonic-clonic, tonic, clonic, atonic seizures in their definition of convulsive seizures.

The mechanism of action of CBD is not specific to either DS or LGS. Instead, CBD appears to have a broad anticonvulsant activity. This hypothesis is supported by the greater reduction of total seizure frequency, rather than just drop or convulsive seizures, in the CBD groups as compared to placebo in all three pivotal trials. Furthermore, the 10 mg/kg/day dose in Study 1414 demonstrated similar efficacy to the 20 mg/kg/day dose in patients with LGS. Lastly, the 10 mg/kg/day dose was better tolerated than the 20 mg/kg/day dose with a lower incidence of adverse events overall. Additionally, there is an apparent dose response with some serious and non-serious adverse events, but this effect was not seen for all AEs. Therefore, the proposed target dose of 10 mg/kg/day for both disorders with the option to increase to 20 mg/kg/day based on efficacy and tolerability is clinically acceptable.

Proposed (Alternate) Titration Regimen Change

The applicant has proposed a titration regimen in the prescribing information that differs from the regimen used in the three pivotal trials. This titration regimen will be referred to as the "alternate" regimen for this discussion.

During Studies 1332B and 1423, the starting dose for patients in the CBD group was 2.5 mg/kg/day (divided BID) and was increased by 2.5 mg/kg/day every 2 days to 10 mg/kg/day, then the dose was further increased by 5 mg/kg/day every other day to the target dose of 20 mg/kg/day over an 11-day titration period. In Study 1414, patients in both CBD groups started at 2.5 mg/kg/day (divided BID), and the dose was increased by 2.5 mg/kg/day every 2 days to a dose of 10 mg/kg/day over 7 days. Patients who were randomized to 10 mg/kg/day remained at that dose and received further titration with placebo. Patients who were randomized to 20 mg/kg/day increased the dose by 5 mg/kg/day every 2 days to 20 mg/kg/day for a total titration period of 11 days (see Table 19). All doses and dose titration increments were divided BID.

In the alternate dosing regimen, CBD is proposed to be initiated at 5 mg/kg/day and increased after 1 week by 5 mg/kg/day to 10 mg/kg/day. Further weekly increases of 5 mg/kg/day would occur as needed, based on therapeutic need and tolerability, to a total of 20 mg/kg/day. All doses and dose increases described above are divided BID.

To support the alternate dose regimen, the applicant performed a simulation using a population PK model derived from Study 1332A PK data. They state their simulation "*showed no real difference in the concentration-time profiles between the original titration scheme and the alternative one, for the 5 and 10 mg/kg/day treatment arms, whilst concentrations were lower (geometric mean ratio $C_{trough\ 24h}$ CBD = 0.759 on average) in the 20 mg/kg/day treatment group.*" The OCP review team performed their own simulation, based on healthy volunteer PK data, due to concerns about food effect and unreliable PK models for DS and LGS patients. As seen in Figure 13 below, the OCP simulation demonstrates that the proposed regimen will result in higher PK exposures as compared to the original dosing for the first 2 days of dosing then result in lower exposures on days 4-8 for the 10 mg/kg/day dose. Comparable exposures will be attained on day 9, as per OCP's simulation. In patients in whom CBD is increased from 10 to 20 mg/kg/day, the alternate dosing regimen will lead to lower exposures for the first 10-14

days, achieving comparable exposures after that point.

Figure 13: Simulated PK Profile for Titration Regimen used in Clinical Trials and Proposed Alternate Regimen up to 20 mg/kg/day

Source: OCP analysis

An information request (IR) was sent to the applicant requesting clinical support for the revised dosing regimen. In response to the IR. the applicant simply noted that they consider the proposed dosing regimen *"to be safe, simpler and more efficient than the dosing regimen used in the clinical trials"* and that it was used in patients in the EAP. The sponsor provided no specific analyses to demonstrate safety of the alternate titration regimen in the EAP.

The proposed titration regimen will cause increased exposures, as compared to those in the pivotal trials, for the first few (2-3) days, which might potentially lead to increased incidence and/or severity of early adverse effects. However, the safety profile of the 5 mg/kg/day dose in study 1332A was similar to that of placebo (see Dr. Unger's review), suggesting that the higher starting dose should not materially impact safety. Based on exposures modeled by OCP, the revised regimen will prolong the time to reach the target maintenance dose (10 mg/kg/day) by only 1-2 days; however, the time to reach the maximum efficacious dose (20 mg/kg/day) will be increased by 10-14 days with the alternate titration regimen.

Although the applicant provided no clinical data to support their contention that the alternate

titration regimen is safer or more easily tolerated than the titration regimen used in the clinical trials, it is possible that the slower titration, particularly from 10 to 20 mg/kg/day may reduce some adverse effects of CBD. The slower titration may be beneficial, as the incidences of AEs and SAEs were greater in the 20 mg/kg/day group than in the 10 mg/kg/day group and the placebo group (see Dr. Unger's safety review). However, the longer titration will lead to a 10-14 day delay in reaching the maximum exposure, which may be of importance in these populations with particularly refractory seizures.

Assessing the potential tradeoff between earlier efficacy and the potential for increased early adverse drug effects (ADRs) vs. longer time to achieve an efficacious dose and possibly fewer ADRs is a common clinical decision point in the treatment of seizures. From the clinical perspective, the alternate titration regimen is acceptable, as the higher starting dose is not expected to lead to increase adverse effects based on safety information from Study 1332A, and slower titration may mitigate some ADRs seen with the 20 mg/kg/day dose. However, more rapid titration to the maximum efficacious dose may be warranted under certain circumstances; therefore, the package insert should also describe the original titration regimen.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

In chronic seizure disorders, such as DS and LGS, persistence of treatment effect is of interest. In each pivotal trial, 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). Sensitivity analyses of the primary endpoint favored CBD at 20 mg/kg/day and 10 mg/kg/day over placebo in reducing drop seizure frequency during the maintenance period and each 4-week block in the LGS trials. In the DS trial, sensitivity analyses of the primary efficacy endpoint during the maintenance period and each 4-week block favored CBD over placebo. There are no controlled efficacy data in reduction of seizures in patients with LGS or DS on CBD beyond 14 weeks.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

There are few issues that may arise in the postmarketing setting when the drug becomes more widely available that were not captured in the development program. The development plan only included patients up to age 55, and the oldest patient enrolled in any of the pivotal trials was 48 years of age. Therefore, there are no data available to inform on the efficacy or safety of the product in patients over the age of 48. The need for specific efficacy or safety data in the older population is low due to the low likelihood of patients with DS or LGS achieving ages > 60 years.

7.2.2. Other Relevant Benefits

See discussion of original and proposed dosing regimens in Section 7.1.4 above.

7.3. Integrated Assessment of Effectiveness

Lennox Gastaut syndrome

The applicant provided results from two randomized, double-blind, placebo-controlled pivotal trials to support the cannabidiol in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age and older. Both of these studies used a primary efficacy outcome measure (reduction in frequency of drop seizures) and primary efficacy endpoint (percentage change from baseline in drop seizure frequency [average per 28 days] during the treatment period) that are considered to be a standard measure of efficacy in antiepileptic drug trials.

Study 1414 provides robust statistical and clinical evidence for the efficacy of cannabidiol in the treatment of drop seizures. Both doses of cannabidiol (10 and 20 mg/kg/day) showed statistical superiority over placebo in the reduction of drop seizure frequency over the treatment period, and the results were clinically meaningful (−41.9%, −37.2%, and −17.2% in the 20 mg/kg, 10 mg/kg, and placebo groups, respectively) and statistically robust (p=0.0047 and p=0.0016, respectively). Sensitivity analyses including those to assess the impact of missing data were also statistically significant. Additionally, similar results were seen for each 4-week period during the maintenance period, suggesting no effect drop-off during the trial. Lastly, CBD was statistically superior over placebo in the key secondary endpoints, providing more support for the efficacy of CBD in treating seizures in patients with LGS.

Study 1423 also provided statistical and clinical evidence of CBD's efficacy in treating drop seizures in patients with LGS. CBD at 20 mg/kg/day showed statistical superiority over placebo (p=0.0135) with clinically meaningfully reductions in median seizure frequency (−43.9% in the CBD group vs. −21.8% in the placebo group. However, the primary efficacy results of Study 1423 were not robust to missing data/imbalanced dropouts. Sensitivity analyses were performed to assess if the study results were driven by the patients who discontinued early and experienced/ reported few seizures. These analyses changed the primary endpoint outcome (p=0.2080 and p=0.0709), suggesting that the primary efficacy results, though statistically significant, were less robust to missing data. Study 1423 was over-enrolled by 71%, and analysis of the primary efficacy endpoint on the first 100 patients randomized (the prespecified sample size in the SAP) did not demonstrate a statistically significant difference between CBD and placebo in the primary efficacy endpoint, although the results were numerically better in the CBD group (p=0.34). Even so, CBD showed statistical superiority over placebo for the sensitivity analyses of the primary efficacy endpoint in each 4-week period of the maintenance period and for all three key secondary endpoints, providing support for the primary efficacy endpoint results.

Overall, there are statistically and clinically positive data from two well-designed and conducted, pivotal trials supporting the efficacy of CBD in the treatment of seizures associated with LGS.

Dravet syndrome

The applicant provided results from a single randomized, double-blind, placebo-controlled pivotal trial to support cannabidiol in the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. This study used a primary efficacy outcome measure (reduction in frequency of convulsive seizures) and primary efficacy endpoint (percentage change from baseline in convulsive seizure frequency [average per 28 days] during the treatment period), which are considered to be standard measures of efficacy in antiepileptic drug trials.

Study 1332B provides robust statistical and clinical evidence for the efficacy of cannabidiol in the treatment of convulsive seizures in patients with DS. Cannabidiol (20 mg/kg/day) showed statistical superiority over placebo in the reduction of convulsive seizure frequency over the treatment period, and the results were clinically meaningful (median percent reductions in the CBD and placebo groups were −38.9% and −13.3%, respectively. These results were statistically robust (p=0.0123). Subgroup analyses all favored CBD over placebo. Sensitivity analyses, including those to assess the impact of missing data, were also statistically significant. Additionally, similar results were seen for each 4-week period during the maintenance period, suggesting no effect drop-off during the trial. Although the results of this analysis did not achieve nominal significance, CBD was numerically superior (p=0.0784) to placebo in the key secondary endpoint, providing more support for the efficacy of CBD in treating seizures in patients with LGS. This evidence, taken with the two statistically and clinically positive trials of CBD for the treatment of drop seizures in LGS, support the proposed indication.

8. Review of Safety

Please see safety review by Dr. Ellis Unger.

9. Advisory Committee Meeting and Other External Consultations

A Peripheral and Central Nervous System Drugs Advisory Committee meeting occurred on April 19, 2018 during which efficacy and safety data of cannabidiol for the treatment of seizures associated with LGS and DS in patients 2 years of age and older were presented to the Committee. The Committee voted unanimously that the benefit-risk profile of cannabidiol is favorable for this population.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The label has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

The need for a REMS has not been determined at the time of this review.

12. Postmarketing Requirements and Commitments

The necessity of post-marketing requirements or commitments has not been determined at the time of this review.

13. Appendices

13.1. References

See footnotes throughout the review.

13.2. Financial Disclosure

See Section 6.1.2 for discussion of financial disclosures.

Covered Clinical Study (Name and/or Number): 1332B, 1414, 1423

Was a list of clinical investigators provided:	Yes ☒ ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 1332B: 114, 1414: 195, 1423: 166		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 7		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 7 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1332: 2, 1414: 14, 1423: 3		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

XIANG LING
06/13/2018

NATALIE B GETZOFF
06/13/2018

KUN JIN
06/14/2018
I concur with the statistical review.

HSIEN MING J HUNG
06/14/2018

TERESA J BURACCHIO
06/22/2018

CLINICAL REVIEW (SAFETY)

Application Type	New Drug Application (NDA)
Application Number(s)	210365
Priority or Standard	Priority
Submit Date(s)	October 27, 2017
Received Date(s)	October 27, 2017
PDUFA Goal Date	June 27, 2018
Division/Office	Division of Neurology Products/Office of Drug Evaluation-I
Reviewer Name(s)	Ellis Unger, M.D.
Review Completion Date	May 22, 2018
Established/Proper Name	cannabidiol
(Proposed) Trade Name	EPIDIOLEX
Applicant	Greenwich Research Ltd, Cambridge, Cambridgeshire, UK
Dosage Form(s)	strawberry flavored clear, colorless to yellow solution supplied in a (b) (4) mL amber glass bottle with child-resistant closure (NDC 70127-100-01). Each mL contains 100 mg of cannabidiol.
Applicant Proposed Dosing Regimen(s)	Starting dose of EPIDIOLEX is 2.5 mg/kg taken twice daily (5 mg/kg/day) for 1 week. After one week's treatment, each dose should be increased weekly by 2.5 mg/kg administered twice daily (5 mg/kg/day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) to 10 mg/kg twice daily (20 mg/kg/day).
Applicant Proposed Indication(s)/Population(s)	EPIDIOLEX (cannabidiol) is indicated for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older.
Recommendation on Regulatory Action	Approve from a safety perspective, if the NDA is deemed to provide substantial evidence of effectiveness.
Recommended Indication(s)/Population(s)	As above.

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8. Review of Safety

8.1. Safety Review Approach

The applicant conducted concurrent development programs for two indications: adjunctive treatment of seizures associated with Dravet syndrome (DS) and adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS). FDA recommended submission of a single NDA for both indications (pre-NDA meeting; August 18, 2016).

The individual studies are well described and tabulated in the review of efficacy. The primary safety data were generated from the controlled safety database, which includes the following sources of data:

- DS
  - Study 1332B, a 14-week, double-blind, placebo-controlled, multicenter phase 3 study
  - Study 1332A, a 3-week, double-blind, placebo-controlled, dose-finding study
- LGS
  - Studies 1414 and 1423, both 14-week double-blind, placebo-controlled, multicenter phase 3 studies

Uncontrolled Data:

- Subjects completing the above studies had the option of continuing in an open-label extension study (Study 1415), which remains ongoing. Subjects who had been randomized to cannabidiol in the controlled trials continued on drug; subjects who had been randomized to placebo in the controlled trials were switched to cannabidiol.
- An expanded access program (EAP) and compassionate access scheme (CAS) are ongoing at 38 sites in the US and Australia, respectively, for patients with drug-resistant epilepsy. The applicant exerted no control over these programs; site physicians were responsible for specific treatment plans and actions.

The uncontrolled safety data from Study 1415 and these programs served an important but secondary role in my assessment of safety.

Of note, Study 1424 is an ongoing 14-week, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of cannabidiol in DS. The study remains blinded, and only limited safety data were submitted from this study, i.e., CIOMS forms for deaths, discontinuations, pregnancies, and serious adverse events.

120-Day Safety Update:
A 120-day safety update was submitted February 21, 2018, and included an additional 179 days of safety data from the open-label extension study (1415). There were 1369 additional adverse events reported, and my analyses of the uncontrolled studies include these data.

Pooling Data across Indications:
Because patients with DS and LGS are similar in many respects, and because the study designs and cannabidiol doses were comparable in the two indications, the applicant proposed to pool safety analyses across both indications. The Division agreed with this approach (written responses to a Type C/Guidance meeting, October 22, 2015), although additional separate analyses were requested. The analyses in Section 8 are based largely on pooled data from both indications.

Analyses of Adverse Event Data:

Translation of verbatim terms to preferred terms: The ADAE.xpt datafile was examined for accuracy of translation from verbatim to preferred term through manual review of all unique pairs of verbatim and preferred terms. There were 13,426 adverse events in the ADAE.xpt datafile (including subjects enrolled in all trials, the EAP and CAS, and including the 120-day safety update). After converting spelling from British to US (substituting "AE" → "E" and "OE" → "E") and removing identical pairs of verbatim and preferred terms, there remained 4,757 unique pairs. (For example, if there were 3 verbatim terms of "Cephalgia," all translated to the preferred term "Headache," the two duplicate pairs were removed.) These 4,757 pairs of verbatim and preferred terms, representing some 35% of the original 13,426 adverse events, were sorted by their verbatim term and manually reviewed for completeness and accuracy.

Following review, a modified datafile was produced as the basis for the safety analyses. Where *changes* in the preferred term were indicated, there was direct substitution of the correct term for the incorrect term. For example, the applicant had translated the verbatim term "LOW GRADE TEMPERATURE" to the preferred term "body temperature decreased." The preferred term was changed to "pyrexia" by replacing the preferred term in the column "AEDECOD."

USUBJID	AETERM	AEDECOD	ASTDT	ASTDY	AEENDTC	AENDT	TRT01A	AESER
1332B-Q-1121-...	LOW GRADE TEMPERATURE	~~Body temperature decreased~~	04/12/2015	•	2015-04-13	04/13/2015	CBD-OS 20 mg/kg/day	N
1332B-Q-1121-...	LOW GRADE TEMPERATURE	Pyrexia ↑ deleted	04/12/2015	•	2015-04-13	04/13/2015	CBD-OS 20 mg/kg/day	N

Where *additions* were made, the original record from the adverse event data file was duplicated (e.g., time of onset, intensity, severity, relatedness), and the new preferred term(s) was used. For example, the applicant translated the verbatim term "CHIPPED FRONT TOOTH FROM FALL" to the preferred term "tooth fracture," but the fall itself had not generated a preferred term. In such cases, the record for the tooth fracture was duplicated, and the newly inserted preferred term (fall) was added on a new line (below). See Table 17 in Appendix.

USUBJID	AETERM	AEDECOD	ASTDT	TRT01A	AESER	AESEV
VEP1423-V-108	CHIPPED FRONT TOOTH FROM FALL	Tooth fracture	09/15/2015	CBD-OS 20 mg/kg/day	N	MILD
VEP1423-V-108	CHIPPED FRONT TOOTH FROM FALL	Fall ← added	09/15/2015	CBD-OS 20 mg/kg/day	N	MILD

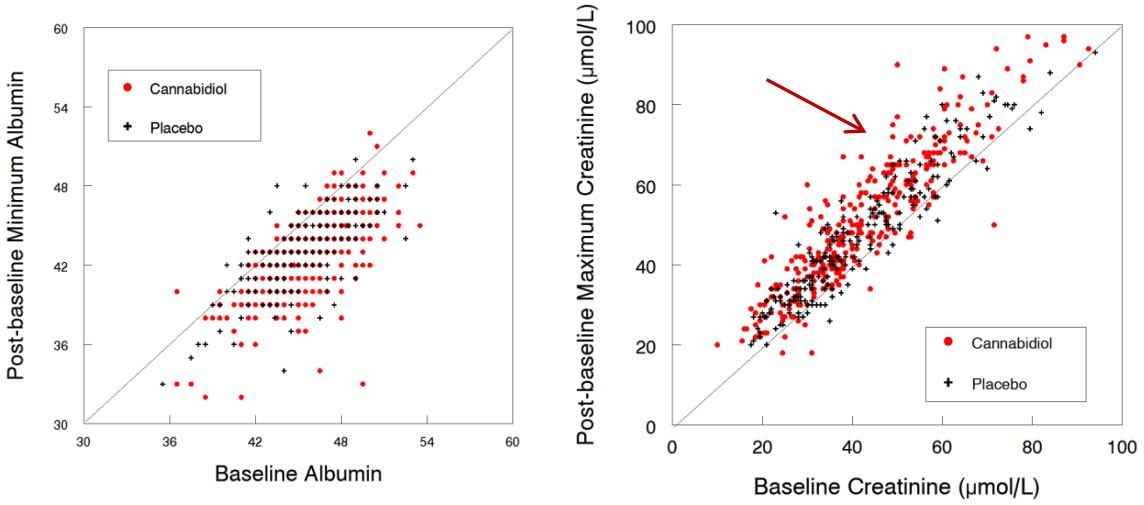
Grouping of related preferred terms: Applicants typically tabulate preferred terms individually, markedly reducing the apparent magnitude of safety signals. I assessed some ~200 groupings of related preferred terms in my safety analyses. For example, the preferred terms 'alanine

aminotransferase increased,' 'aspartate aminotransferase increased,' 'gamma-glutamyltransferase increased,' 'hepatic enzyme increased,' 'hepatotoxicity,' 'liver function test abnormal,' and 'transaminases increased' were combined into a single hepatotoxicity grouping. 'Somnolence,' 'sedation,' and 'lethargy' were combined in a grouping. 'Candida infection,' 'fungal infection,' 'oral candidiasis,' and 'tinea cruris' were combined in a fungal infection grouping. Frequencies of adverse events were based on this grouping scheme.

Analyses of Laboratory Data:

Because mean changes in laboratory values are not sensitive to outliers, in addition to assessing mean values over time, critical laboratory parameters were visually inspected in scatter plots. Where *lower* than normal values were of interest (e.g., sodium, potassium, glucose, calcium, albumin), each subject's baseline value was plotted against their post-baseline nadir (Figure 1, left). In this figure, markers below and to the right of the diagonal indicate various degrees of hypoalbuminemia, and the numbers of red (cannabidiol) and black (placebo) markers are similarly distributed. Where *higher* than normal values were of interest (e.g., creatinine, ALT, glucose), each subject's baseline value was plotted against their highest post-baseline value (Figure 1, right). The preponderance of red markers towards the top-left of the creatinine plot (red arrow, right) suggest a trend towards increases in creatinine, post-baseline, in cannabidiol-treated subjects.

Figure 1: Assessing Outliers with Scatterplots of Post-baseline Minimum Values vs. Baseline (Albumin, Left) and Post-baseline Maximum Values vs. Baseline (Creatinine, Right)



This review was based predominantly on my original analyses of the data submitted by the applicant. Important differences between findings of this reviewer and the applicant are highlighted.

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The principal safety data were generated in two trials in DS (1332, Parts A and B) and two trials in LGS (1414 and 1423). (Studies 1332 Parts A and B were independent, and enrolled entirely different subjects.) The data from these 4 double-blind, placebo-controlled studies constitute the controlled safety database and provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs, as well as the basis for the table of adverse drug reactions for Section 6 of labeling. Study 1424 is an ongoing phase 3 study in subjects with DS. Treatment allocation remains blinded, and the submitted safety data are necessarily limited.

Subjects who completed studies for both indications had the option of continuing (or switching to) open-label cannabidiol treatment in an ongoing, multi-center, open-label extension trial to investigate the safety of cannabidiol in subjects with inadequately controlled DS or LGS, Study 1415. Study 1415 includes a 2-week dose titration period, a maintenance period, a 10-day taper period, and a 4-week follow-up period. Patients could be treated for up to 3 years, depending on the country. The cannabidiol dose was titrated from 1.25 to 20 mg/kg/day and continued at a constant dose during the maintenance period. Investigators could decrease the dose for intolerance, or increase the dose to as high as 30 mg/kg/day if needed for better seizure control (after discussion with the medical monitor). Investigators were to consider reducing the dose of concomitant antiepileptic drugs after 6 months if freedom from seizures was achieved. A total of 644 subjects entered the trial, as of the last cut-off date.

As noted above, an EAP and CAS are ongoing for patients with drug-resistant epilepsy, and there was substantial patient exposure in these studies.

As defined, the safety population included all subjects who received $\geq$ 1 dose of cannabidiol or placebo, and subjects were categorized by actual drug (or placebo) received.

The NDA includes 1808 subjects who were exposed to cannabidiol oral solution in the applicant's development program; 1419 of these subjects were treated for epilepsy. Exposure-by-use is summarized in Table 1. Approximately 18% of subject exposures (323) were in the placebo-controlled trials for DS (Study 1332, Parts A and B) and LGS (Studies 1414 and 1423). There were 366 new exposures in the extension study 1424 (subjects originally randomized to placebo in the controlled studies), and these subjects account for some 20% of overall exposure.

Approximately half of the subjects with epilepsy were exposed in the uncontrolled EAP or CAS for drug-resistant epilepsy (n = 684), including 64 patients with DS and 97 patients with LGS. (The vast majority of patients in the EAP and CAS had other types of treatment-resistant seizures.) Three hundred twenty-two (322) subjects were exposed to cannabidiol in Phase 1 clinical pharmacology trials. These were heathy volunteers or patients with specific issues.

Table 1: Overall Cannabidiol Exposure in the Clinical Development Program

All subjects exposed to cannabidiol	1808		
Subjects with epilepsy	1419		
Controlled trials	323		
DS (Study 1332, Parts A and B)		88	
LGS (Studies 1414 and 1423)		235	
Extension trial* (Study 1415)	644		366 unique
DS		278	209 unique
LGS		366	157 unique
Expanded access for refractory epilepsy	684		
DS		64	
LGS		97	
other seizure disorders		523	
Other epilepsy	46		not in ISS
Subjects without epilepsy	389		
Phase 1 clinical pharmacology (healthy subjects and special patient populations)	346		
Other conditions (schizophrenia, diabetes, fatter liver disease)	43		not in ISS

*Includes unique patients who had received placebo in controlled studies
Adapted from Table 5-1 of applicant's 120-Day Updated ISS

Duration of exposure is summarized in Table 2 for the important studies in the development program. In total, in the dedicated trials for DS and LGS, 218 and 315 subjects, respectively, were treated for > 6 months; 120 and 271 subjects, respectively, were treated for > 12 months. Considering patients with all types of seizure disorders, 972 patients have been treated for ≥ 6 months, and 670 patients have been treated for ≥ 12 months.

The applicant communicated its plans for analysis of the safety database in one or more pre-NDA submissions, and the Division responded that the adequacy of the database would be a review issue.

Table 2: Cannabidiol Exposure and Time-on-Treatment

			Controlled				Open-label Extension (1415)		Expanded Access
			Dravet		Lennox-Gastaut		Dravet	Lennox-Gastaut	
			Cannabidiol	Placebo	Cannabidiol	Placebo	Cannabidiol	Cannabidiol	Cannabidiol
Dravet	1332 Part A	n (%)	27 (31%)	7 (11%)			24 (9%)		
	1332 Part B	n (%)	61 (69%)	59 (89%)			105 (38%)		
	1424	n (%)					149 (54%)		
	Access								64 (9%)
Lennox-Gastaut	1414	n (%)			149 (63%)	76 (47%)		210 (57%)	
	1423	n (%)			86 (37%)	85 (53%)		156 (43%)	
	Access								97 (14%)
Other seizure									523 (76%)
Total	Total		88 (100%)	66 (100%)	235 (100%)	161 (100%)	278 (100%)	366 (100%)	684 (100%)
Time on Treatment	Patient-years	Total	18	17	60	44	253	385	690
	Days on treatment	Mean	74	92	94	99	332	385	369
		Median	99	100	99	99	349	427	275
		Min; Max	7; 131	17; 122	10; 114	17; 111	8; 691	3; 608	1; 1025
	Days on treatment, number (%)	1–14 d	2 (2%)	0 (0%)	1 (0%)	0 (0%)	1 (0%)	2 (1%)	7 (1%)
		15–28 d	8 (9%)	3 (5%)	6 (3%)	2 (1%)	5 (2%)	4 (1%)	14 (2%)
		29–42 d	24 (27%)	7 (11%)	10 (4%)	0 (0%)	8 (3%)	7 (2%)	19 (3%)
		43–84 d	2 (2%)	0 (0%)	8 (3%)	1 (1%)	12 (4%)	14 (4%)	57 (8%)
		85–182 d	52 (59%)	56 (85%)	210 (89%)	158 (98%)	34 (12%)	24 (7%)	146 (21%)
		183–364 d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	98 (35%)	44 (12%)	160 (23%)
		365–729 d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	120 (43%)	271 (74%)	158 (23%)
		≥ 730 d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	121 (18%)

Adapted from applicant's Table 5.1.7-1 in the ISS, Tables 5.5.5-1 and 5.1.2-1 in the ISS 120-Day Safety Update

Cannabidiol was granted orphan-drug designation for the treatment of both DS (November 14, 2013) and LGS (February 27, 2014). Thus, although the drug is intended for long-term treatment of both disorders, exposure recommendations in the International Conference on Harmonization E1 Guideline do not apply, and given the prevalence of these diseases, the exposure is deemed adequate to support a reasonable assessment of safety.

8.2.1. Relevant Characteristics of the Safety Population

There were 550 subjects in the controlled DS plus LGS safety population (323 received cannabidiol; 227 placebo), enrolled from 58 sites in the US, UK, France, Spain, Poland, and The Netherlands. Demographic and important baseline characteristics are summarized in Table 3. There were notable differences between the indications in baseline age (median 8.4 and 13

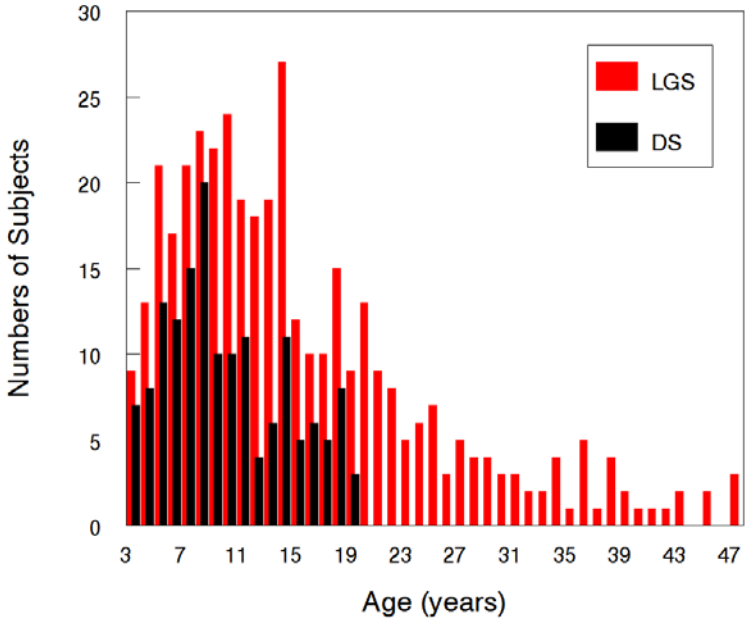
Table 3: Demographic and Baseline Characteristics in the Controlled DS/LGS Population

			Cannabidiol				Placebo
			5	10	20	All	
		n	10	75	238	323	227
Dravet	GWEP1332 Part A	n (%)	10 (100%)	8 (11%)	9 (4%)	27 (8%)	7 (3%)
	GWEP1332 Part B	n (%)	0 (0%)	0 (0%)	61 (26%)	61 (19%)	59 (26%)
Lennox-Gastaut	GWEP1414	n (%)	0 (0%)	67 (89%)	82 (34%)	149 (46%)	76 (33%)
	GWEP1423	n (%)	0 (0%)	0 (0%)	86 (36%)	86 (27%)	85 (37%)
	Patient-years	Total	0.8	18.8	58.4	78.1	60.4
	Age	Mean ± SD	7.2 ± 1.9	14.0 ± 8.6	14.1 ± 9.2	13.9 ± 9.0	13.6 ± 8.8
		Median	6.7	11.9	11.8	11.5	11.4
		Min; Max	5; 11	3; 38	3; 48	3; 48	2; 45
	Age categories, n (%)	2–5	2 (20%)	10 (13%)	39 (16%)	51 (16%)	38 (17%)
		6–11	8 (80%)	28 (37%)	81 (34%)	117 (36%)	79 (35%)
		12–17	0 (0%)	18 (24%)	62 (26%)	80 (25%)	57 (25%)
		18–45	0 (0%)	19 (25%)	53 (22%)	72 (22%)	53 (23%)
		46–55	0 (0%)	0 (0%)	3 (1%)	3 (1%)	0 (0%)
		≥ 56	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	Sex, n (%)	Male	5 (50%)	39 (52%)	132 (55%)	176 (54%)	119 (52%)
		Female	5 (50%)	36 (48%)	106 (45%)	147 (46%)	108 (48%)
	Race, n (%)	White	9 (90%)	60 (80%)	200 (84%)	269 (83%)	201 (89%)
		Black	0 (0%)	7 (9%)	8 (3%)	15 (5%)	8 (4%)
		Asian	0 (0%)	1 (1%)	6 (3%)	7 (2%)	5 (2%)
		Other	1 (10%)	7 (9%)	24 (10%)	32 (10%)	13 (6%)
	Location, n (%)	US	8 (80%)	62 (83%)	170 (71%)	240 (74%)	171 (75%)
		Spain	0 (0%)	9 (12%)	11 (5%)	20 (6%)	12 (5%)
		France	0 (0%)	1 (1%)	12 (5%)	13 (4%)	6 (3%)
		UK	2 (20%)	3 (4%)	15 (6%)	20 (6%)	11 (5%)
		Netherlands	0 (0%)	0 (0%)	3 (1%)	3 (1%)	2 (1%)
		Poland	0 (0%)	0 (0%)	27 (11%)	27 (8%)	25 (11%)
	BMI (kg/m^2)	Mean ± SD	28 ± 9	41 ± 26	40 ± 21	40 ± 22	41 ± 22
		Median	17.0	18.2	17.7	17.7	18.5
		Min; Max	14; 26	11; 50	10; 94	10; 94	10; 51
	Number of current AEDs, n (%)	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
		1	2 (20%)	3 (4%)	15 (6%)	20 (6%)	11 (5%)
		2	2 (20%)	19 (25%)	48 (20%)	69 (21%)	54 (24%)
		3	4 (40%)	29 (39%)	94 (39%)	127 (39%)	83 (37%)
		≥ 4	2 (20%)	24 (32%)	81 (34%)	107 (33%)	79 (35%)
	Valproate/ Clobazem use, n (%)	Valproate	2 (20%)	18 (24%)	59 (25%)	79 (24%)	52 (23%)
		Clobazem	1 (10%)	31 (41%)	70 (29%)	102 (32%)	76 (33%)
		Both	5 (50%)	10 (13%)	55 (23%)	70 (22%)	47 (21%)
		Neither	2 (20%)	16 (21%)	54 (23%)	72 (22%)	52 (23%)

From Table DSLGS 2.3.1 in the applicant's ISS, with derived data from ADSL.xpt

years in DS and LGS, respectively, see Figure 2 for distribution), and corresponding differences in body mass (mean body mass 27 and 38 kg in DS and LGS, respectively), but other characteristics were similar.

Figure 2: Age Distribution for the DS and LGS Populations in the Controlled Safety Database



Subjects were evenly distributed by sex. Eighty percent to 90% of subjects were white; 5% were black, and 2% were Asian. Three-quarters of subjects were enrolled at US sites. In both indications, approximately 95% of subjects were taking 2 or more antiepileptic drugs (AEDs). In addition to the other AEDs they were taking, approximately 24% of subjects were taking valproate without clobazam, 33% were taking clobazam without valproate, 22% were taking both drugs, and 22% were taking neither drug.

8.2.2. Adequacy of the Safety Database

Based on the characteristics in Table 3, the development program is deemed to provide generally adequate representation across the DS and LGS populations; however, the studies enrolled only 23 black subjects and only 12 Asian subjects. DS is a genetic disease and LGS has various genetically identifiable etiologies in some cases; nevertheless, the courses of these diseases are not known to differ importantly in these minority populations, and there are no known factors that would predispose these populations to cannabidiol-induced toxicity. Given the above, and in light of the rarity of these diseases, the patient exposure seems adequately diverse, representative of, and generalizable to, the to-be-marked US patient population.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

A data fitness assessment was performed by (b) (4), and no anomalies were identified.

Routine clinical safety evaluations were scheduled (and generally occurred) at the following timepoints:

Study 1332 Part A (21-day treatment period): On-treatment visits were scheduled on Days 8 and 15, with end-of-treatment visits on Days 22 and 32.

Study 1332 Part B (98-day treatment period): On-treatment visits were scheduled on Days 15, 29, and 57, with additional safety telephone calls on Days 43 and 71. In addition, an end-of-treatment visit was scheduled at Day 99, 6 weeks after the last clinic visit (4 weeks after the last phone call).

Study 1414 (98-day treatment period): On-treatment visits were scheduled on Days 15, 29, and 57, with additional telephone calls on Days 43 and 71. Patients were to return for an end-of-treatment visit on Day 99, 42 days after the last visit and 28 days after the last phone call.

Study 1423 (98-day treatment period): On-treatment visits were scheduled on Days 15, 29 and 57, with additional safety telephone calls on Days 43 and 71. Patients were to return for an end-of-treatment visit on Day 99.

For the 58 individual study sites, the median number of adverse events reported per subject was 3.3. Two sites, site 1115 in Spain and site 1123 in Poland, reported no adverse events (both enrolled 4 subjects).

8.3.2. Categorization of Adverse Events

The applicant used standard procedures to collect and analyze adverse event data. Adverse events were recorded at all subject visits, and subjects were to be monitored for adverse events through 28 days after the last dose of test drug. Investigators were asked to render a decision with respect to causality and to opine on intensity (mild, moderate, severe). The standard definition of serious adverse event was used in the development program. Treatment-emergent adverse events were defined as "those absent prior to treatment, but started during the treatment period or at start of the treatment period or whose severity worsened during the treatment period relative to the pre-treatment state."

Events that resulted from trial procedures were to be recorded as adverse events. Expected seizure types were not to be recorded as adverse events; however, changes in the pattern or severity of seizures were to be considered adverse events. Clinically significant abnormalities in clinical laboratory tests were to be documented as adverse events. Surgical/investigational

procedures were not considered adverse events, whereas the medical reason for the procedure was to be recorded as the adverse event. Elective hospitalizations for preexisting conditions and elective procedures were not considered adverse events.

Multiple occurrences of adverse events were counted once, per specific Medical Dictionary for Regulatory Activities (MedDRA) preferred term. In Study 1415, the open-label extension trial, adverse events that were continuing from the original trial were carried over as medical history, and not classified as adverse events unless they were deemed to be worsened.

MedDRA was used for coding of adverse events for all clinical studies; however, not all trials were coded using the same MedDRA version. For analyses in the applicant's Integrated Summary of Safety (ISS), all adverse events were recoded to MedDRA Version 17.1 using DsNavigator software and reviewed for medical correctness by the applicant.

The applicant designated the following adverse events of special interest (AESI), and these received specific attention:

- Abnormal liver treatment-emergent adverse events
- Somnolence, fatigue, lethargy, sedation
- Rash, generalized maculopapular rash
- Falls and injuries
- Drug reaction with eosinophilia and systemic symptoms (DRESS)
- Seizure worsening, or change in the pattern or severity of seizures
- Status epilepticus
- Abuse liability
- Suicide, suicidal ideation
- Agitation, psychosis
- Significant cardiovascular disease
- Abnormal menstruation
- Diarrhea
- Decreased appetite
- Aggression, irritability

Assessment: As noted above, the ADAE.xpt datafile was reviewed for accuracy of translation from verbatim to preferred term through manual review.

There were 234 terms (1.7% of the original number) for which translation was deemed to be incomplete, or occasionally, inaccurate (Appendix, Table 17).

For example, despite the fact that "falls and injuries" was one of the applicant's adverse events of special interest, Table 4 and Figure 3 show how some falls were omitted through incomplete translation from the verbatim term to the preferred term. Note in Table 4 that the yellow highlighted verbatim terms indicated the presence of a fall; however, there was no translation to a preferred term of "fall."

Table 4: Incomplete Translation of Verbatim Terms to Preferred Terms for "Falls" (Note: Subject identifiers are redacted)

#	Study/Site	Verbatim term	Applicant's preferred term(s)	Reviewer's preferred term
1	GWEP1332B-Q-10	lip laceration due to fall	Fall	Fall
2	GWEP1332B-Q-10	ecchymosis bilateral elbows status post fall (not seizure related)	Fall	Fall
3	GWEP1332B-Q-11	falling	Fall	Fall
4	GWEP1414-S-1078	right occipital bump from fall	Fall	Fall
5	GWEP1414-S-1080	superficial scalp wound ((result of a fall during seizure activity)	Fall	Fall
6	GWEP1414-S-1094	head (forehead) laceration (patient had a seizure, fell and cut forehead)	Convulsion. Laceration	Fall
7	GWEP1414-S-1109	fall from seizure,bruise and swelling on right forehead and right eye	Fall	Fall
8	GWEP1414-S-1191	fall(sip drop seizure)	Atonic seizures	Fall
9	GWEP1414-S-1196	bump on head from fall	Head injury	Fall
10	GWEP1414-S-1200	scratch of back 2 degree to fall	Fall	Fall
11	GWEP1423-V-1079	fall,tripped	Fall	Fall
12	GWEP1423-V-108	lip laceration & brueses on extremities from fall during seizure	Injury	Fall
13	GWEP1423-V-108	bump/bruise on forehand from fall	Contusion	Fall
14	GWEP1423-V-1087	bruises secondary to fall due to increased seizure	Fall	Fall
15	GWEP1423-V-1180	fall	Fall	Fall
16	GWEP1423-V-1187	stitches from fall	Fall	Fall
17	GWEP1423-V-1188	head laceration due to fall	Laceration	Fall

One might surmise that when a primary adverse event led to a secondary event, only the initial event was counted as an adverse event. For example, for a seizure leading to a fall, the seizure would be counted as an adverse event, whereas the fall would not. The paired verbatim and preferred terms in Table 4, however, are not consistent with this concept. Note, for example, that "bump on head from fall" was translated to "head injury," but was not counted as a fall, even though the fall was the primary event.

Figure 3: Applicant's Table of Falls and Injuries from Integrated Summary of Safety: Falls = 12

Table 8.8.7.1.3-1 Incidence of AESI Falls and Injuries in Controlled DS and LGS Trials (Pool DS/LGS)

SOC PT	CBD-OS 5 mg/kg/day (N=10) n (%)	CBD-OS 10 mg/kg/day (N=75) n (%)	CBD-OS 20 mg/kg/day (N=238) n (%)	All CBD-OS (N=323) n (%)	Placebo (N=227) n (%)
Patients with at least 1 AESI falls and injuries	**1 (10.0)**	**7 (9.3)**	**19 (8.0)**	**27 (8.4)**	**22 (9.7)**
Injury, poisoning and procedural complications	**1 (10.0)**	**7 (9.3)**	**19 (8.0)**	**27 (8.4)**	**22 (9.7)**
Contusion	0	2 (2.7)	4 (1.7)	6 (1.9)	3 (1.3)
Fall	0	0	6 (2.5)	6 (1.9)	6 (2.6)

The applicant's table summarizing the adverse event of special interest "Falls and Injuries" shows a total of 12 falls (Figure 3); however, 5 falls had not been counted. (The correct numbers were 9 in the cannabidiol group and 8 in the placebo group.)

Also note that 3 of the first 4 verbatim terms in Table 4 that had been coded to the preferred term "FALL" were not completely coded:

- "lip laceration due to fall" was not coded as a laceration
- "ecchymosis bilateral elbows status post fall (not seizure related)" was not coded as an ecchymosis
- "right occipital bump from fall" was not coded as an injury or head injury

"Rash, generalized maculopapular rash" was another of the applicant's adverse events of special interest, and here there was also some degree of incomplete coding. Note the translation of these verbatim terms (left) to preferred terms (right):

rash after starting new medication solodyn	→	drug eruption
rash contact dermatitis	→	dermatitis contact
red dots on cheeks and belly	→	hypersensitivity

None of these preferred terms denote "rash;" therefore, these adverse events were not included in the applicant's tabulation of rashes.

Pooling of Related Preferred Terms:

In some cases, the applicant grouped related terms, providing a sensible accounting of adverse event frequencies. For example, the applicant grouped the following terms for pneumonia: 'pneumonia,' 'pneumonia respiratory syncytial virus,' 'pneumonia mycoplasmal,' 'pneumonia adenoviral,' 'aspiration pneumonia.'

In other cases, however, grouping of closely related terms was not undertaken, or the results of pooled analyses were not used in the proposed labeling. The applicant tabulated all subjects with rashes from the controlled safety database, finding 29 subjects (9.0%) in the cannabidiol group and 7 (3.1%) in the placebo group (Figure 4, top). These results agree with my analysis. However, their proposed table for the adverse reaction section (Section 6) of the prescribing information displays rash rates of only (b)(4)% and (b)(4)% in the cannabidiol and placebo groups, respectively (Figure 4, bottom). Presumably, the applicant counted only the preferred term "rash," and omitted the other related preferred terms recorded in the database (e.g., "viral rash," "rash erythematous," "rash macular," "rash maculo-papular," "rash generalised," "venipuncture site rash," "rash papular," "injection site rash").

Figure 4: Applicant's Analyses of Rash – Disparate Results in the Applicant's Integrated Summary of Safety (Top) and Proposed Prescribing Information (Bottom)

Table 8.8.3.1.3-1 Incidence of AESI Rash, Generalized Maculopapular Rash in Controlled DS and LGS Trials (Pool DS/LGS)

SOC PT	CBD-OS 5 mg/kg/day (N=10) n (%)	CBD-OS 10 mg/kg/day (N=75) n (%)	CBD-OS 20 mg/kg/day (N=238) n (%)	All CBD-OS (N=323) n (%)	Placebo (N=227) n (%)
Patients with at least 1 AESI rash, generalized maculopapular rash	1 (10.0)	5 (6.7)	23 (9.7)	29 (9.0)	7 (3.1)

Table (b) (4) Adverse Reactions in Patients Treated with (b) (4) in Controlled Trials

Adverse Reaction	Placebo (N=227) %	(b) (4) 10 mg/kg/day (N=75) %	(b) (4) 20 mg/kg/day (N=238) %	(b) (4)
(b) (4)				
Rash				(b) (4)

With respect to liver laboratory abnormalities, the data proposed for inclusion in the adverse reaction table for Section 6 of the prescribing information are copied in Figure 5.

By considering the various preferred terms for transaminase elevation separately, the apparent frequency was reduced. Combining the various laboratory abnormalities in the table, and adding "hepatic enzyme increased," the overall percentages are 14% and 3% in the cannabidiol and placebo groups, respectively. Clearly, when related terms are not grouped together, safety signals can be greatly diluted or obscured.

(b) (4)

In summary, therefore, the translation (coding) of verbatim terms to preferred terms has important inaccuracies, in some cases affecting the adverse event tables in the clinical study reports and ISS. In addition, grouping of related adverse event terms was inconsistent, and in some cases, lack of grouping was responsible for underestimating the magnitude of safety signals.

8.3.3. Routine Clinical Tests

In addition to queries for adverse events at the above timepoints, assessments of vital signs and laboratory monitoring were performed. Laboratory monitoring included assessments of sodium, potassium, calcium, glucose, transaminases, bilirubin, alkaline phosphatase, albumin, total protein, prothrombin time, international normalized ratio (INR), prolactin, insulin-like growth factor, creatinine, blood urea nitrogen, triglycerides, HDL-cholesterol, complete blood count with differential white blood cell count and platelet count, and urinalysis (dipstick). Missing data were sparse. There was no indication that laboratory data were obtained in the fasting state. Given the pharmacokinetics of cannabidiol, there would have been no reason to collect laboratory values at peak or trough. The applicant evaluated laboratory values based on the Common Terminology Criteria for Adverse Events grading scheme (version 4.03).

8.4. Safety Results

8.4.1. Deaths

Twenty-one (21) deaths have been reported in the development program. In the controlled trials, 1 death was reported in a subject in the cannabidiol 20 mg/kg group and none in the placebo group. Seven (7) deaths have been reported in patients taking cannabidiol in the open-label extension trial (7/644 = 1.1%), and 13 deaths have been reported in the EAP (13/684 = 1.9%). The mean time-on-treatment was 1.0 years for patients in both the open-label extension trial and the EAP; therefore, the reported death rates are 1.1% and 1.9% per year, respectively.

Patients who died in the EAP program had refractory seizures; none were reported to have had DS or LGS. Causes of death were given as: respiratory failure due to aspiration, probable SUDEP, severe progressive mitochondrial disorder, asphyxia, hypoxemia, respiratory failure/septic shock from human pneumovirus, respiratory arrest, status epilepticus with a working diagnosis of febrile infection-related epilepsy syndrome (FIRES), death due to progressive condition, Batten disease, Ohtahara syndrome with acquired epileptic encephalopathy, pulmonary edema due to prolonged seizure, and possible SUDEP (also hyponatremia).

Patients in all of these studies were quite ill, with complex, chronic multisystem diseases and complicated courses. It is not possible to attribute the deaths to cannabidiol; conversely, it is not possible to be confident that the drug was not in some way contributory. As noted by the applicant, the proximate causes of death were typical for these patient populations; there was

no suggestion that an off-target drug effect was responsible.

The death rates are similar to rates that have been reported in the literature for DS and LGS. Cooper *et al* report an annual DS-specific mortality rate of 1.58% in a cohort of 100 consecutively recruited patients with a median follow-up of 17 years (*Epilepsy Res* 2016;128:43). A population-based cohort study of 688 ten-year-olds with epilepsy in metropolitan Atlanta showed that all-cause mortality was 14 times greater in LGS than in the general population (Autry *et al*; *J Child Neurol* 2010;25:441).

In conclusion, therefore, it would not seem appropriate to attribute these deaths to the investigational drug. Causality is certainly possible, but the cases do not have features that suggest a specific off-target drug effect.

8.4.2. Serious Adverse Events

Controlled Trials:

Serious adverse events (and groupings of related serious adverse events) from the controlled trials in DS and LGS are tabulated by treatment group in Table 5. Serious adverse events that were reported in at least 2 more cannabidiol-treated subjects than placebo subjects are shown; the relative risk (RR) and absolute risk difference (Δ Risk %) are shown at right.

Table 5: Serious Treatment-emergent Adverse Events in the Controlled Safety Database (DS and LGS)

	Cannabidiol				Placebo	RR	Δ Risk (%)
Cannabidiol dose (mg/kg/d)	**5**	**10**	**20**	**All**			
N =	**10**	**75**	**238**	**323**	**227**		
Transaminases ↑, hepatic failure	(0%)	2 (3%)	10 (4%)	12 (4%)	(0%)	-	3
Somnolence, lethargy	(0%)	(0%)	7 (3%)	7 (2%)	(0%)	-	2
Lethargy	(0%)	(0%)	3 (1%)	3 (1%)	(0%)	-	0
Infection, all	(0%)	5 (7%)	17 (7%)	22 (7%)	5 (2%)	3.1	5
Pneumonia	(0%)	4 (5%)	9 (4%)	13 (4%)	1 (0%)	9.1	4
Infection, viral	(0%)	1 (1%)	6 (3%)	7 (2%)	1 (0%)	4.9	2
Infection, bacterial	(0%)	1 (1%)	1 (0%)	2 (1%)	(0%)	-	1
Sepsis	(0%)	1 (1%)	1 (0%)	2 (1%)	(0%)	-	1
Sleep apnea	(0%)	1 (1%)	1 (0%)	2 (1%)	(0%)	-	1
Fatigue, asthenia	(0%)	(0%)	2 (1%)	2 (1%)	(0%)	-	1
Bleeding	(0%)	(0%)	2 (1%)	2 (1%)	(0%)	-	1
Constipation	(0%)	(0%)	2 (1%)	2 (1%)	(0%)	-	1
Fever	(0%)	2 (3%)	1 (0%)	3 (1%)	1 (0%)	2.1	0
Seizure	1 (10%)	8 (11%)	14 (6%)	23 (7%)	10 (4%)	1.6	3
Respiratory failure	(0%)	1 (1%)	4 (2%)	5 (2%)	3 (1%)	1.2	0

Transaminase elevations are clearly drug-related and are discussed in 8.4.6 and 8.5.1. Although two serious adverse events of "hepatic failure" were reported, neither subject had hyperbilirubinemia or an elevated INR. Somnolence, lethargy, and infections also appear to show signals and will be discussed in 8.5.2. A notable difference in seizures is evident; however, changes in either the pattern or severity of seizures were to be considered adverse events, making interpretation difficult. Thus, with literal interpretation of the study protocol, *improvements* in the pattern of seizures could be reported as an adverse event.

Uncontrolled Trials:

The uncontrolled experience includes the open-label extension study (1415) and the EAP/CAS. For both, the mean duration of exposure per subject is 1.0 years, as noted above. Table 6 shows the serious adverse events (and groupings of closely related serious adverse events) where the reported frequency was $\geq$ 1% in either study.

Again, infections and transaminase elevations are notable. The somnolence signal observed in the controlled database is not found in the uncontrolled database. Lower-frequency serious adverse events seem consistent with expected frequencies in the patient populations, but of course, there are no control groups.

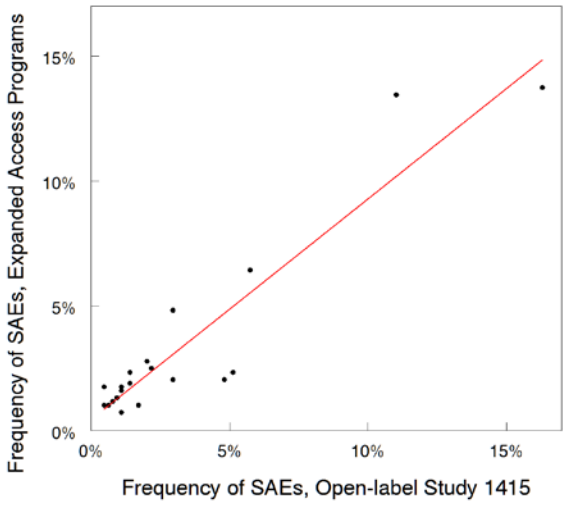
Suicidal ideation/behavior deserves special mention, because all AEDs carry a warning for this adverse reaction. Serious adverse events for suicidal ideation/behavior were not reported in the controlled trial, but reported in 2 patients in the EAP. Subject (b) (6), an 11-year-old male, reported suicidal thoughts (moderate severity) and suicidal behavior (severe severity) on study days 453 and 564, respectively. Patient (b) (6), a 21-year-old male, had suicidal ideation (severe) reported on day 321.

Table 6: Serious Treatment-emergent Adverse Events from Uncontrolled Trials

	Long-term Extension n=644	Expanded Access Program n=684
Seizure	105 (16.3%)	94 (13.7%)
Infection, all	71 (11%)	92 (13.5%)
Pneumonia	37 (5.7%)	44 (6.4%)
Infection, viral	19 (3%)	33 (4.8%)
Influenza	11 (1.7%)	7 (1%)
Upper respiratory tract infection	9 (1.4%)	13 (1.9%)
Infection, bacterial	7 (1.1%)	11 (1.6%)
Urinary tract infection	5 (0.8%)	8 (1.2%)
Sepsis	3 (0.5%)	7 (1%)
Hepatic		
Transaminases increased, hepatitis, hepatic failure	33 (5.1%)	16 (2.3%)
Transaminases increased	31 (4.8%)	14 (2%)
Fever, rigors	19 (3%)	14 (2%)
Respiratory failure, cyanosis, hypoxemia, desaturation	14 (2.2%)	17 (2.5%)
Dyspnea, shortness of breath, respiratory distress	3 (0.5%)	12 (1.8%)
Nausea, vomiting	9 (1.4%)	16 (2.3%)
Dehydration	7 (1.1%)	12 (1.8%)
Diarrhea	7 (1.1%)	5 (0.7%)
Fracture	6 (0.9%)	9 (1.3%)
Weight loss	4 (0.6%)	7 (1%)

Figure 6 shows the correlation between the open-label extension study (1415) and the EAP/CAS with respect to the frequencies of serious adverse events. (The points on the scatterplot represent the frequencies of serious adverse events shown in Table 6.) Despite differences between the populations (DS and LGS in the extension study, versus mostly other types of treatment-resistant seizures in the EAP/CAS) and the monitoring paradigms (more intense monitoring in the extension study), there is remarkable concordance between these independent sources of data with respect to frequencies of serious adverse events (R=0.94).

Figure 6: Serious Treatment-emergent Adverse Events – Concordance in Frequencies between the Long-term Extension Study and the Expanded Access Program



8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

According to the applicant (Table 7), 30 subjects in the cannabidiol groups (9.3%) reported adverse events leading to discontinuation, compared to 3 subjects (1.3%) in the placebo group. Half of the discontinuations were related to elevations in transaminases; a quarter of the discontinuations were associated with somnolence/lethargy. This pattern follows the trends in serious adverse events, shown above.

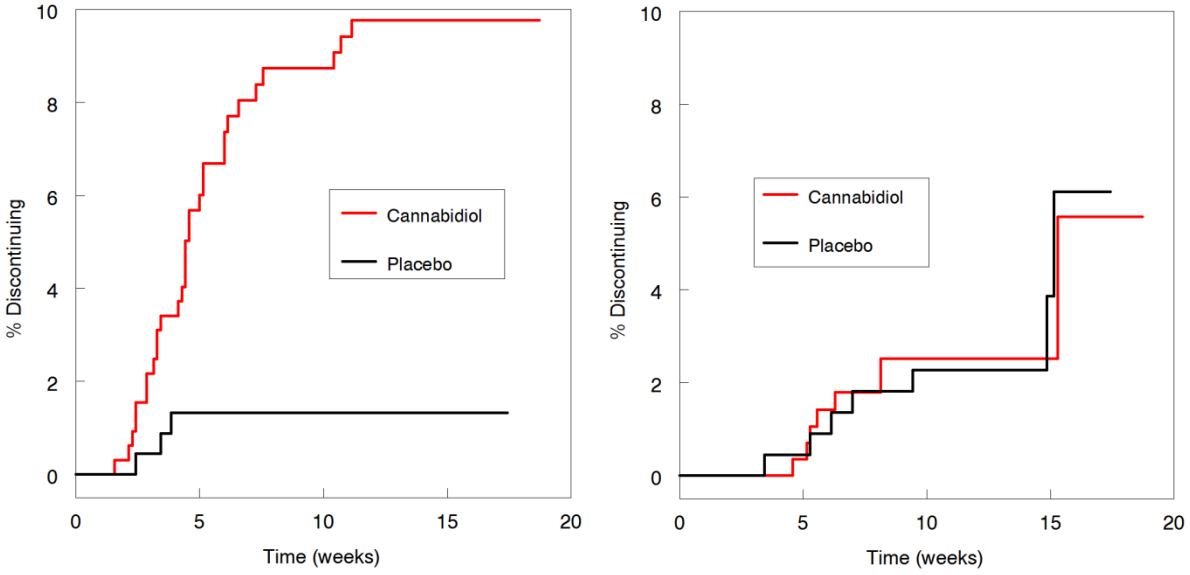
Figure 7 shows this reviewer's time-to-event analyses for discontinuations for adverse events (left) and other causes (right) in the placebo-controlled studies for DS and LGS. Discontinuations for adverse events accrue at a much higher rate in cannabidiol-treated subjects than placebo subjects, and the rate of discontinuation is similar through the first 12 weeks of the studies (left). Discontinuations for causes other than adverse events are similar between treatment groups (Figure 7, right).

Table 7: Applicant's ISS Table 8.7.1.3-1 – Adverse Events Leading to Discontinuation Reported in > 1 Subject in Controlled DS and LGS Trials

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

Given the reluctance of some investigators to attribute trial discontinuation to adverse events, this reviewer tabulated all adverse events that occurred within 14 days of a trial discontinuation as a way of assessing adverse events that were potentially related to trial discontinuation (Table 8). This analysis provides less specificity than the applicant's analysis, but greater sensitivity.

Figure 7: Time-to-discontinuation 2° Adverse Events (left) and Time-to-discontinuation for Causes Other Than Adverse Events (right) in the Placebo-controlled DS and LGS Trials



The signal for transaminase elevation matches the applicant's, except that there were two subjects with preferred terms of "acute liver failure" or "liver failure" for whom transaminase elevations were not reported as adverse events. (When the liver consult investigated these cases, they were not thought to represent liver failure.) Combining these terms, there were 18 (6%) and 1 (0%) subjects in the cannabidiol and placebo groups, respectively, for whom hepatic adverse events were reported within 14 days of trial discontinuation. Compared to the analyses of the applicant, my analysis found similar signals for somnolence/lethargy, decreased appetite, and fever (pyrexia), although with greater numbers of events than the applicant reported. Infection (all) and abdominal pain/ distension were detected by my analysis, whereas they were not detected by the applicant through the usual means (tabulation of investigators' assessments of causes of discontinuation).

Table 8: Treatment-emergent Adverse Events Reported within 14 Days of Discontinuation from Controlled Studies (DS and LGS)

	Cannabidiol				Placebo	RR
Cannabidiol dose (mg/kg/d)	5	10	20	All		
N =	10	75	238	323	227	
Transaminase elevations	0 (0%)	2 (3%)	14 (6%)	16 (5%)	1 (0%)	11.2
Infection, all	1 (10%)	0 (0%)	13 (5%)	13 (4%)	3 (1%)	3.0
Somnolence, lethargy	0 (0%)	1 (1%)	7 (3%)	8 (2%)	0 (0%)	-
Seizure	0 (0%)	0 (0%)	7 (3%)	7 (2%)	1 (0%)	4.9
Abdominal pain, distension	0 (0%)	0 (0%)	6 (3%)	6 (2%)	0 (0%)	-
Decreased appetite	0 (0%)	0 (0%)	6 (3%)	6 (2%)	0 (0%)	-
Fever	0 (0%)	1 (1%)	3 (1%)	4 (1%)	0 (0%)	-
Hypoxia, respiratory failure	0 (0%)	0 (0%)	4 (2%)	4 (1%)	0 (0%)	-
Infection, viral	0 (0%)	0 (0%)	3 (1%)	3 (1%)	0 (0%)	-
Rash	0 (0%)	1 (1%)	2 (1%)	3 (1%)	0 (0%)	-
Fatigue, asthenia, malaise	0 (0%)	0 (0%)	3 (1%)	3 (1%)	0 (0%)	-
Irritability, agitation	0 (0%)	0 (0%)	3 (1%)	3 (1%)	0 (0%)	-
Cough	0 (0%)	0 (0%)	3 (1%)	3 (1%)	0 (0%)	-
Nausea, vomiting	0 (0%)	0 (0%)	4 (2%)	4 (1%)	2 (1%)	1.4
Infection, bacterial	0 (0%)	0 (0%)	3 (1%)	3 (1%)	1 (0%)	2.1
Hepatic failure	0 (0%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)	-

8.4.4. Significant Adverse Events

Severe treatment-emergent adverse events (and groupings of closely related severe adverse events) are shown in Table 9 from the DS and LGS controlled trials. The "All Cannabidiol" column has been replaced by a 10 + 20 mg/kg/d column, because these are the to-be-marketed doses. The table shows the RR with its 95% CI, and the absolute risk difference (Δ Risk, right). Signals are evident for infections, particularly pneumonia, somnolence/lethargy, and hepatic toxicity, with weaker signals for decreased appetite and rash. Some of the severe adverse events show an apparent dose-response, notably transaminase elevations and somnolence; however, the numbers of events are small, and the sample sizes for the 5 and 10 mg/kg/d doses are particularly small.

Table 9: Severe Treatment-emergent Adverse Events in the Controlled Safety Database (DS and LGS)

	Cannabidiol (mg/kg/day)				Placebo	RR	95% CI	Δ Risk (%)
	5	10	20	10 + 20				
N =	10	75	238	313	227			
Infection, all	0 (0%)	3 (4%)	8 (3%)	11 (4%)	3 (1%)	2.7	(0.8, 9.4)	3
Pneumonia	0 (0%)	2 (3%)	4 (2%)	6 (2%)	1 (0%)	4.4	(0.5, 35.9)	2
Infection, viral	0 (0%)	0 (0%)	2 (1%)	2 (1%)	1 (0%)	1.5	(0.1, 15.9)	1
Sepsis	0 (0%)	1 (1%)	1 (0%)	2 (1%)	0 (0%)	-	-	1
Tracheobronchitis, lower respiratory tract infection	0 (0%)	0 (0%)	1 (0%)	1 (0%)	1 (0%)	0.7	(0, 11.5)	0
Seizure	1 (10%)	2 (3%)	6 (3%)	9 (3%)	5 (2%)	1.3	(0.4, 3.8)	1
Somnolence, lethergy, sedation, disorientation, confusion	1 (10%)	1 (1%)	9 (4%)	9 (3%)	0 (0%)	-	-	3
Transaminases increased, hepatitis, hepatic failure	0 (0%)	0 (0%)	7 (3%)	7 (2%)	1 (0%)	5.1	(0.6, 41)	2
Transaminases increased	0 (0%)	0 (0%)	6 (3%)	6 (2%)	1 (0%)	4.4	(0.5, 35.9)	2
Respiratory failure, hypoxemia, desaturation, hypercapnia, ARDS	0 (0%)	0 (0%)	4 (2%)	4 (1%)	2 (1%)	1.5	(0.3, 7.9)	0
Decreased appetite	0 (0%)	0 (0%)	3 (1%)	3 (1%)	0 (0%)	-	-	1
Rash, diffuse maculopapular rash	0 (0%)	1 (1%)	1 (0%)	2 (1%)	0 (0%)	-	-	1

8.4.5. Treatment Emergent Adverse Events of All Severities

Table 10 shows all treatment-emergent adverse events (and groupings of closely related adverse events) from the controlled DS and LGS trials. Adverse events that occurred at a frequency ≥ 2% in cannabidiol-treated subjects with Δ risk of ≥ 2% are included. These adverse events can be divided into several broad categories, and some of the interrelations among adverse events within categories suggest that the adverse events are cannabidiol-related:

- Hepatic adverse events - elevated transaminases (as detected as adverse events – transaminase elevations detected in the laboratory data are discussed in Section 8.4.6., below). Frequencies are 14% and 3% in cannabidiol-treated and placebo subjects, respectively, and there is a clear dose-response in the controlled trials, i.e., 8% and 16% in the 10 mg/kg and 20 mg/kg groups, respectively (Table 10). (The frequency is 10% in the 5 mg/kg group, but the estimate is difficult to interpret with only 10 subjects in that group.) As previously noted, a review of the two adverse events of "hepatic failure" showed that the subjects had neither hyperbilirubinemia nor elevated INR.
- Central nervous system events. These include irritability, agitation, somnolence, sedation, lethargy, disorientation, fatigue, malaise, asthenia, ataxia, tremor, aggression, anger, drooling, hypersalivation, insomnia and other sleep disturbances, falls, dizziness, balance disorders, and gait disturbances. There is an apparent dose-response for somnolence and drooling, but the reverse was true (higher frequency at lower dose) for some of the other CNS adverse events, making interpretation difficult.

- Decreased appetite (21% vs. 5%) and weight decreased (4% vs. 1%) in the cannabidiol and placebo groups, respectively, with a dose-response for both (greater frequencies in the 20 mg/kg group than the 10 mg/kg group).
- Gastrointestinal events (non-hepatic), including diarrhea, abdominal pain/distension/ discomfort, gastroenteritis, and dry mouth. Diarrhea is notable because of the risk difference (9%) and the apparent dose-response.
- Infections (risk difference 11%, RR = 1.3), with imbalances in pneumonia and upper respiratory infections, as well as viral and fungal infections. The RR of 1.3 seems borderline in significance, especially considering the multiplicity (numerous adverse events tested for differences) and the lack of a plausible mechanism of action to account for the finding.
- Rash, reported in 11% vs. 3% of subjects in the cannabidiol and placebo groups, respectively, with an apparent dose-response.
- Respiratory failure and hypoxemia.

Not shown in Table 10, an 8 year-old female experienced what was called (by the investigator) an allergic reaction/hypersensitivity, moderate in severity. She nevertheless stayed on cannabidiol and the adverse event resolved. (The subject was receiving 13 concomitant medications at the time of adverse event onset.)

The important findings above are discussed in Section 8.5.

Reviewer's Comment(s): There are a number of disparities between my results and those of the applicant, mostly a result of the applicant's lack of grouping. For example, I combined the following preferred terms, whereas the applicant tabulated them separately: alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyl transferase increased, liver function test abnormal, and transaminases increased. I grouped 'viral gastroenteritis' and 'gastroenteritis,' whereas the applicant did not. Unlike the applicant, I grouped irritability and agitation. The largest difference was for rash, where I found 10% vs. 3% in the cannabidiol and placebo groups, respectively, and the applicant found (b) (4)% vs. (b) (4)%. As noted above (Figure 4), the applicant did not combine rash terms when producing their able.

Uncontrolled Adverse Event Data:
Treatment-emergent adverse events from the long-term open-label extension trial in DS and LGS (Study 1415) are shown in Table 11. The left side of Table 11 shows adverse events by dose (≤20 mg/kg/d; >20 mg/kg/d); the right side according to whether subjects received cannabidiol throughout both the controlled trial and the open-label extension trial, or were randomizaed to placebo during the controlled trial and switched to cannabidiol in the open-label extension.

I posited that there would be differences in frequencies of adverse events between subjects entering Study 1415 who had been taking cannabidiol prior to entry and those who were cannabidiol-naïve (Table 11, right). In fact, there do not appear to be meaningful differences in the frequencies of adverse events.

Treatment-emergent adverse events from the uncontrolled EAP and CAS are shown in Table 12.

Table 10: All Treatment-emergent Adverse Events in the Controlled Safety Database (DS and LGS)

	Cannabidiol (mg/kg/day)				Placebo	RR	95% CI	Δ Risk (%)
	5	10	20	10 + 20				
N:	10	75	238	313	227			
Hepatic								
Transaminases elevated	1 (10%)	6 (8%)	37 (15.5%)	43 (13.7%)	6 (2.6%)	5.2	(2.3, 12)	11.2
Other gastrointestinal								
Decreased appetite	(0%)	12 (16%)	53 (22.3%)	65 (20.8%)	11 (4.8%)	4.3	(2.3, 7.9)	16.1
Weight decreased	(0%)	2 (2.7%)	11 (4.6%)	13 (4.2%)	3 (1.3%)	3.1	(0.9, 10.9)	2.9
Abdominal pain, discomfort	(0%)	2 (2.7%)	7 (2.9%)	9 (2.9%)	2 (0.9%)	3.3	(0.7, 15)	2.0
Gastroenteritis	1 (10%)	(0%)	10 (4.2%)	10 (3.2%)	3 (1.3%)	2.4	(0.7, 8.7)	1.9
Diarrhea	(0%)	7 (9.3%)	47 (19.7%)	54 (17.3%)	20 (8.8%)	2.0	(1.2, 3.2)	8.8
Central nervous system								
Irritability, agitation	(0%)	7 (9.3%)	12 (5%)	19 (6.1%)	4 (1.8%)	3.4	(1.2, 10)	4.4
Somnolence, sedation, lethargy	4 (40%)	20 (26.7%)	81 (34%)	101 (32.3%)	26 (11.5%)	2.8	(1.9, 4.2)	21.3
Somnolence	2 (20%)	17 (22.7%)	60 (25.2%)	77 (24.6%)	19 (8.4%)	2.9	(1.8, 4.7)	16.6
Sedation	2 (20%)	2 (2.7%)	14 (5.9%)	16 (5.1%)	2 (0.9%)	5.8	(1.3, 25)	4.3
Lethargy	0 (0%)	3 (4%)	18 (7.6%)	21 (6.7%)	5 (2.2%)	3.0	(1.2, 8)	4.6
Fatigue, malaise, asthenia	(0%)	8 (10.7%)	28 (11.8%)	36 (11.5%)	9 (4%)	2.9	(1.4, 5.9)	7.7
Fatigue	(0%)	5 (6.7%)	26 (10.9%)	31 (9.9%)	8 (3.5%)	2.8	(1.3, 6)	6.5
Ataxia, coordination abnormal	2 (20%)	1 (1.3%)	5 (2.1%)	6 (1.9%)	(0%)	-	-	1.9
Tremor	(0%)	1 (1.3%)	4 (1.7%)	5 (1.6%)	(0%)	-	-	1.6
Aggression, anger	(0%)	2 (2.7%)	11 (4.6%)	13 (4.2%)	1 (0.4%)	9.4	(1.2, 71.6)	3.7
Drooling, salivary hypersecretion	(0%)	1 (1.3%)	10 (4.2%)	11 (3.5%)	1 (0.4%)	8.0	(1, 61.4)	3.1
Insomnia, sleep disorder, poor quality sleep	1 (10%)	8 (10.7%)	12 (5%)	20 (6.4%)	10 (4.4%)	1.5	(0.7, 3)	2.2
Insomnia	(0%)	4 (5.3%)	9 (3.8%)	13 (4.2%)	5 (2.2%)	1.9	(0.7, 5.2)	2.1
Gait disturbance	(0%)	2 (2.7%)	4 (1.7%)	6 (1.9%)	1 (0.4%)	4.4	(0.5, 35.9)	1.5
Infectious								
Infection, all	4 (40%)	31 (41.3%)	96 (40.3%)	127 (40.6%)	70 (30.8%)	1.3	(1, 1.7)	11.2
Infection, viral	2 (20%)	5 (6.7%)	25 (10.5%)	30 (9.6%)	13 (5.7%)	1.7	(0.9, 3.1)	4.1
Pneumonia	(0%)	6 (8%)	12 (5%)	18 (5.8%)	2 (0.9%)	6.5	(1.5, 27.9)	4.9
Infection, fungal	(0%)	1 (1.3%)	6 (2.5%)	7 (2.2%)	(0%)	-	-	2.2
Other								
Rash	1 (10%)	5 (6.7%)	30 (12.6%)	35 (11.2%)	7 (3.1%)	3.6	(1.6, 8)	8.2
Hypoxia, respiratory failure	(0%)	2 (2.7%)	8 (3.4%)	10 (3.2%)	3 (1.3%)	2.4	(0.7, 8.7)	1.9

Table 11: Treatment-emergent Adverse Events from the Open-label Extension Study (1415)

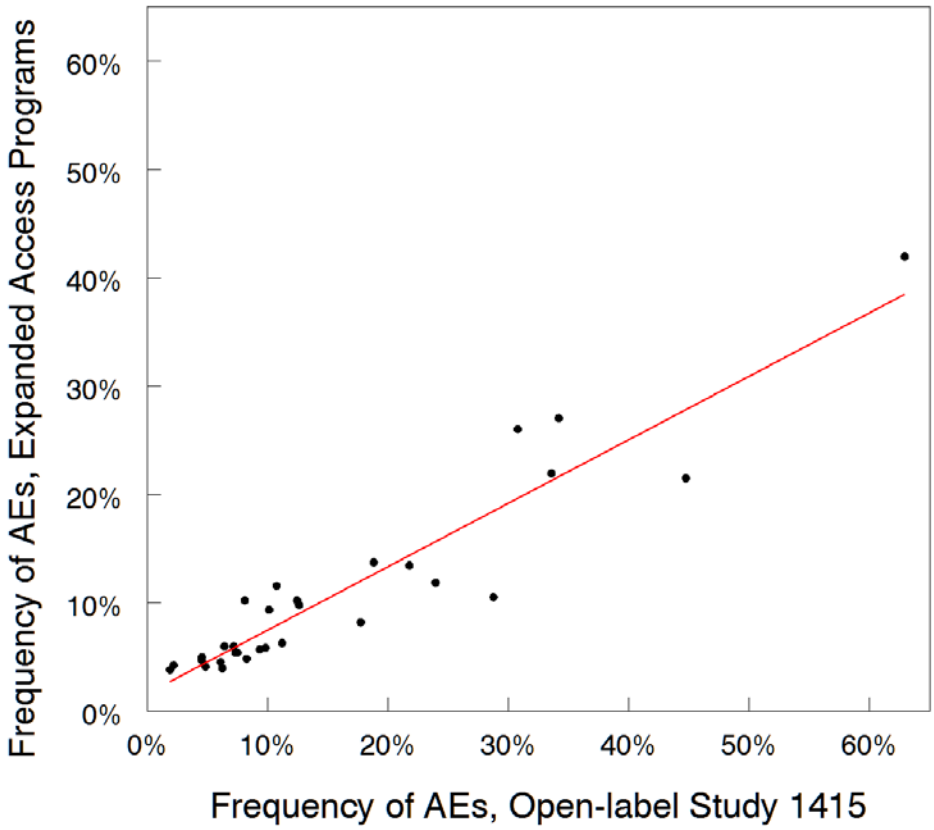
	Cannabidiol <= 20	Cannabidiol > 20	Cannabidiol Throughout	Naïve - Cannabidiol
	352	**292**	**278**	**366**
Infection, all	198 (56%)	207 (71%)	180 (65%)	225 (61%)
Upper respiratory tract infections	143 (41%)	145 (50%)	120 (43%)	168 (46%)
Infection, viral	64 (18%)	57 (20%)	57 (21%)	64 (17%)
Pneumonia	26 (7%)	39 (13%)	28 (10%)	37 (10%)
Infection, bacterial	18 (5%)	28 (10%)	18 (6%)	28 (8%)
Urinary tract infection	21 (6%)	27 (9%)	22 (8%)	26 (7%)
Gastroenteritis, C-difficile colitis	23 (7%)	24 (8%)	19 (7%)	28 (8%)
Hepatic				
Transaminase elevations	70 (20%)	44 (15%)	41 (15%)	73 (20%)
Other gastrointestinal				
Diarrhea	104 (30%)	116 (40%)	87 (31%)	133 (36%)
Nausea, vomiting	71 (20%)	69 (24%)	59 (21%)	81 (22%)
Decreased appetite	92 (26%)	62 (21%)	54 (19%)	100 (27%)
Constipation	25 (7%)	28 (10%)	18 (6%)	35 (10%)
Abdominal pain, distension, discomfort	21 (6%)	18 (6%)	19 (7%)	20 (5%)
Central nervous system				
Somnolence, sedation	101 (29%)	97 (33%)	80 (29%)	118 (32%)
Seizure	107 (30%)	109 (37%)	104 (37%)	112 (31%)
Irritability, aggression, agitation, anger, homicidal ideation	42 (12%)	39 (13%)	38 (14%)	43 (12%)
Insomnia, sleep disorder, poor quality sleep, hypersomnia, parasomnia	34 (10%)	38 (13%)	31 (11%)	41 (11%)
Insomnia	18 (5%)	22 (8%)	20 (7%)	20 (5%)
Ataxia	8 (2%)	6 (2%)	4 (1%)	10 (3%)
Abnormal behavior, personality change, mood disturbances (non-depressive)	34 (10%)	29 (10%)	22 (8%)	41 (11%)
Headache, migraine	17 (5%)	12 (4%)	12 (4%)	17 (5%)
Agitation, psychomotor hyperactivity, restlessness	12 (3%)	19 (7%)	15 (5%)	16 (4%)
Fall, dizziness, gait disturbance, balance disorder	38 (11%)	31 (11%)	37 (13%)	32 (9%)
Fall, dizziness, balance disorder	30 (9%)	22 (8%)	29 (10%)	23 (6%)
Fall	16 (5%)	13 (4%)	18 (6%)	11 (3%)
Dizziness	6 (2%)	6 (2%)	7 (3%)	5 (1%)
General				
Pyrexia	85 (24%)	100 (34%)	78 (28%)	107 (29%)
Fatigue, asthenia, muscular weakness	42 (12%)	38 (13%)	27 (10%)	53 (14%)
Rash	18 (5%)	23 (8%)	17 (6%)	24 (7%)
Weight decreased, malnutrition, failure to thrive	30 (9%)	30 (10%)	27 (10%)	33 (9%)

Table 12: Treatment-emergent Adverse Events from the EAP and CAS

	Cannabidiol Dose (mg/kg/day)					Overall
	0-10	>10-20	>20-30	>30-40	>40	
n =	48	123	379	59	75	684
Infection, all	10 (21%)	38 (31%)	164 (43%)	29 (49%)	46 (61%)	287 (42%)
Upper respiratory tract infections	6 (13%)	22 (18%)	84 (22%)	14 (24%)	21 (28%)	147 (21%)
Infection, viral	(0%)	10 (8%)	55 (15%)	9 (15%)	20 (27%)	94 (14%)
Pneumonia	2 (4%)	4 (3%)	37 (10%)	5 (8%)	16 (21%)	64 (9%)
Infection, bacterial	(0%)	4 (3%)	24 (6%)	3 (5%)	10 (13%)	41 (6%)
Urinary tract infection	1 (2%)	5 (4%)	22 (6%)	5 (8%)	4 (5%)	37 (5%)
Gastroenteritis, C-difficile colitis	(0%)	2 (2%)	24 (6%)	4 (7%)	7 (9%)	37 (5%)
Hepatic						
Transaminase elevations	2 (4%)	11 (9%)	32 (8%)	7 (12%)	4 (5%)	56 (8%)
Other gastrointestinal						
Diarrhea	8 (17%)	29 (24%)	97 (26%)	24 (41%)	27 (36%)	185 (27%)
Nausea, vomiting	2 (4%)	11 (9%)	57 (15%)	7 (12%)	15 (20%)	92 (13%)
Decreased appetite	2 (4%)	11 (9%)	47 (12%)	12 (20%)	9 (12%)	81 (12%)
Constipation	1 (2%)	9 (7%)	16 (4%)	(0%)	7 (9%)	33 (5%)
Abdominal pain, distension, discomfort	1 (2%)	3 (2%)	16 (4%)	5 (8%)	6 (8%)	31 (5%)
Central nervous system						
Somnolence, sedation	11 (23%)	26 (21%)	97 (26%)	14 (24%)	30 (40%)	178 (26%)
Seizure	4 (8%)	20 (16%)	92 (24%)	11 (19%)	23 (31%)	150 (22%)
Irritability, aggression, agitation, anger, homicidal ideation	2 (4%)	9 (7%)	40 (11%)	5 (8%)	11 (15%)	67 (10%)
Insomnia, sleep disorder, poor quality sleep, hypersomnia, parasomnia	(0%)	7 (6%)	25 (7%)	6 (10%)	5 (7%)	43 (6%)
Insomnia	(0%)	5 (4%)	13 (3%)	5 (8%)	4 (5%)	27 (4%)
Ataxia	(0%)	3 (2%)	15 (4%)	2 (3%)	9 (12%)	29 (4%)
Abnormal behavior, personality change, mood disturbances (non-depressive)	2 (4%)	4 (3%)	26 (7%)	5 (8%)	3 (4%)	40 (6%)
Headache, migraine	2 (4%)	8 (7%)	17 (4%)	3 (5%)	2 (3%)	32 (5%)
Agitation, psychomotor hyperactivity, restlessness	1 (2%)	3 (2%)	14 (4%)	5 (8%)	5 (7%)	28 (4%)
Fall, dizziness, gait disturbance, balance disorder	3 (6%)	11 (9%)	47 (12%)	8 (14%)	10 (13%)	79 (12%)
Fall, dizziness, balance disorder	3 (6%)	8 (7%)	43 (11%)	6 (10%)	10 (13%)	70 (10%)
Fall	1 (2%)	4 (3%)	20 (5%)	4 (7%)	5 (7%)	34 (5%)
Dizziness	2 (4%)	2 (2%)	17 (4%)	1 (2%)	4 (5%)	26 (4%)
General						
Pyrexia	2 (4%)	11 (9%)	44 (12%)	6 (10%)	9 (12%)	72 (11%)
Fatigue, asthenia, muscular weakness	2 (4%)	11 (9%)	38 (10%)	10 (17%)	9 (12%)	70 (10%)
Rash	2 (4%)	4 (3%)	30 (8%)	2 (3%)	3 (4%)	41 (6%)
Weight decreased, malnutrition, failure to thrive	2 (4%)	6 (5%)	25 (7%)	1 (2%)	5 (7%)	39 (6%)

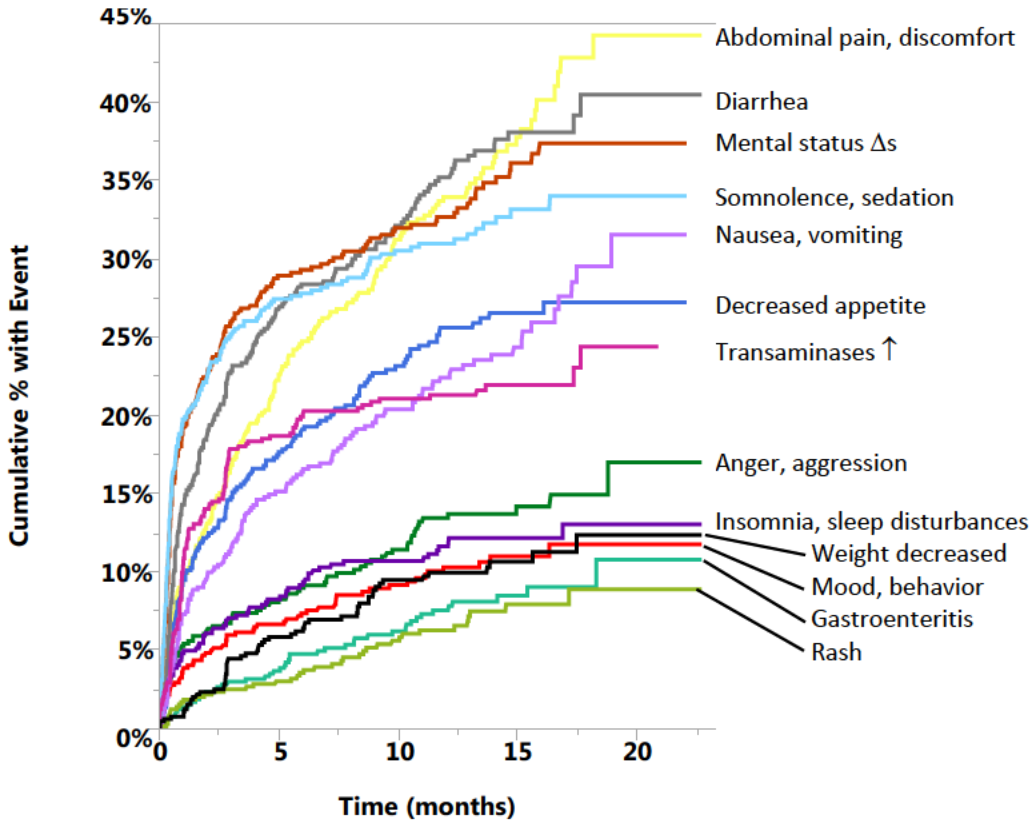
Figure 8 shows the correlation between the open-label extension study (1415) and the EAP/CAS with respect to the frequencies of *all* adverse events (serious and non-serious). As noted previously, the mean duration of exposure is 1.0 year/subject in both the open-label extension study and the EAP/CAS. Despite differences between the patient populations and the monitoring paradigms, there is striking concordance with respect to the frequencies of adverse events, though they are higher (by 50% on a relative basis) in the open-label extension study than in the EAP/CAS. The strong correlation (R = 0.94) conveys nothing with respect to the certainty of causality of the adverse events, but suggests that the rates from both sources are *reliable* – whether caused by the drug or a background event. (Figure 8 is analogous to the scatterplot shown for the serious adverse events, Figure 6.)

Figure 8: Treatment-emergent Adverse Events – Concordance in Frequencies between the Long-term Extension Study and the Expanded Access Program



For uncontrolled studies, time-to-event (Kaplan-Meier) plots can provide some insight into causality of adverse events, as background events tend to accrue at a fairly consistent rate throughout the period of observation, whereas the cumulative frequency of drug-related adverse events tends to increase rapidly after treatment initiation, and accumulate more slowly as the study proceeds. The cumulative frequencies of adverse events are shown for the open-label extension study and the EAP/CAS in Figure 9 and Figure 10, respectively.

Figure 9: Time-to-Major Adverse Events in the Open-label Extension Study (1415)



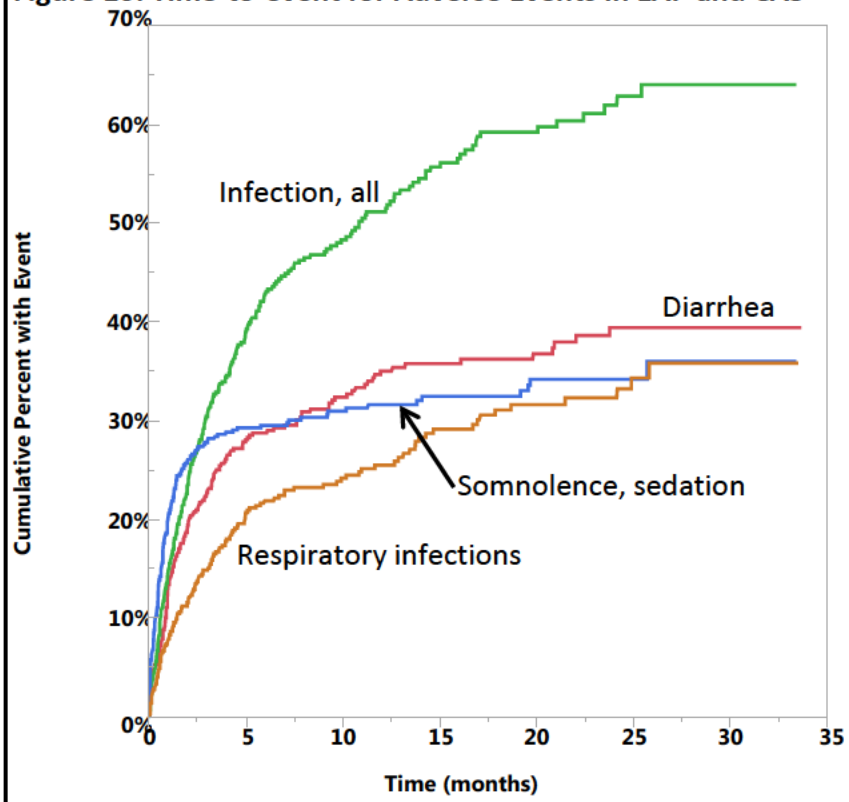
In Figure 9, note the brisk "upstroke" and inflection point of the curves for mental status changes, diarrhea, somnolence, and transaminase elevations. Anger/aggression, insomnia/sleep disturbances, and mood/behavior also appear to increase more rapidly at initiation of treatment, suggesting causality.

In the EAP/CAS (Figure 10), the cumulative frequency plots of somnolence/sedation and diarrhea have a morphology that suggests drug-relatedness. Conversely, infections (all) and respiratory infections tend to increase throughout the treatment period, suggesting they are not drug-related. Note: infections are not shown in Figure 9.

<u>Important Adverse Events from Other Controlled Trials:</u>

In Study 1542, a study conducted to assess potential withdrawal symptoms following abrupt discontinuation of cannabidiol, 8 of 30 health volunteers experienced a rash (27%), and most of these subjects were withdrawn from the study. Rashes were initially reported from study day 2 through day 11; 5 were judged to be moderate in severity; 2 were severe.

Figure 10: Time-to-event for Adverse Events in EAP and CAS



In Study 1431, an abuse liability study, a 41 year-old healthy male volunteer had an adverse event of hypersensitivity (verbatim term: "allergic reaction") approximately 3 hours following administration of cannabidiol 4500 mg. Symptoms included swelling of the cheeks, generalized redness, and pruritus, all of which were moderate in severity and considered to be treatment-related. The subject received intravenous saline and diphenhydramine (50 mg), as well as oral diphenhydramine (50 mg). Symptoms lasted for approximately 1 day and resolved. There was no relevant medical history or physical findings.

8.4.6. Laboratory Findings

Hematology:

- Anemia

A small but persistent decrease in hemoglobin was observed in cannabidiol-treated subjects over time (mean decrease from baseline to end of treatment was −0.40 g/dL in cannabidiol-treated subjects and −0.03 g/dL in the placebo group). A corresponding decrease in hematocrit was also observed: mean changes were -1.3% in cannabidiol-treated subjects and -0.4% in the placebo group. There were no associated longitudinal changes in mean corpuscular hemoglobin (MCH) or mean corpuscular volume (MCV).

An FDA analysis was conducted to determine the numbers of subjects who developed laboratory-defined anemia at any time during the course of the study, i.e., subjects who had a normal hemoglobin concentration at baseline, with a reported value < LLN at a subsequent time point (for age and sex, per Robertson J, Shilkofski N, eds. The Harriet Lane Handbook. 17th ed. Philadelphia, Pa.: Mosby; 2005:337). Twenty-four percent (24%) of cannabidiol-treated subjects developed a new laboratory-defined anemia during the course of the study, versus 11% of subjects who received placebo. Anemia was reported only twice as an adverse event (one in cannabidiol; one in placebo), however, and severity was mild.

In summary, there were small decreases in hemoglobin and hematocrit in the cannabidiol group, with normal red blood cell indices. There are no signals for anemia in the animal toxicology studies, and no known mechanism of action that would account for the finding. Thus, it is not known if anemia is drug-related, but the significance seems small in any case.

- Other Hematological

There were no other notable changes in hematological parameters (total leukocytes, lymphocytes, neutrophils, eosinophils, or platelet count) in cannabidiol-treated subjects compared to placebo subjects.

Chemistry:

In the controlled trial database, there were no notable changes in sodium, potassium, random glucose, total protein, albumin, prolactin, or high-density lipoproteins.

Renal Parameters:

The applicant calculated creatinine clearance using the Schwartz formula for subjects under the age of 18, and using the Cockcroft-Gault equation for older subjects. The applicant's renal laboratory data are shown in Table 13, at baseline and as change from baseline ($\pm$ 1 standard deviation [SD]). The changes in creatinine and creatinine clearance in the cannabidiol groups relative to the placebo group are not trivial (highlighted in yellow), particularly as calculated by the Cockcroft-Gault equation in older subjects. There are no apparent changes in mean BUN from baseline and no differences in BUN between groups.

The applicant drew attention to these differences in creatinine clearance, but noted that only 2 cannabidiol-treated subjects had creatinine clearance values < LLN at end-of-treatment (2 subjects assigned to placebo also had creatinine clearance values < LLN at end-of-treatment).

In seeking to determine whether such changes in creatinine were drug-related and whether they were reversible, I assessed the laboratory data from Study 1542, a double-blind randomized withdrawal study conducted in healthy adult subjects, to evaluate potential adverse effects of cannabidiol withdrawal. Thirty (30) subjects received cannabidiol, 750 mg twice daily for 4 weeks, followed by a randomized withdrawal where 15 subjects were to be continued on cannabidiol for 2 weeks, and 15 subjects were to be switched abruptly to placebo.

Table 13: Renal Parameters, Change from Baseline – Controlled Safety Database

		Cannabidiol n=323	Placebo n=227
Creatinine Jaffe (mean ± SD) µmol/L	Baseline	42.4 ± 15.8 (n=323)	44.1 ± 19.1 (n=227)
	Δ from baseline to end-of-treatment	3.5 ± 8.5 (n=293)	1.5 ± 8.4 (n=210)
BUN (mean ± SD) µmol/L	Baseline	4.6 ± 1.6 (n=323)	4.7 ± 1.6 (n=227)
	Δ from baseline to end-of-treatment	0.1 ± 1.5 (n=293)	0.0 ± 1.1 (n=210)
Creatinine clearance Schwartz (mean ± SD) mL/min/1.73 m^2	Baseline	139.0 ± 38.8 (n=248)	139.9 ± 40.4 (n=174)
	Δ from baseline to end-of-treatment	−10.0 ± 26.7 (n=223)	−4.3 ± 26.9 (n=163)
Creatinine clearance Cockroft-Gault (mean ± SD) mL/min/1.73 m^2	Baseline	156.6 ± 52.9 (n=75)	143.6 ± 47.2 (n=53)
	Δ from baseline to end-of-treatment	−14.1 ± 20.7 (n=70)	−1.2 ± 19.7 (n=47)

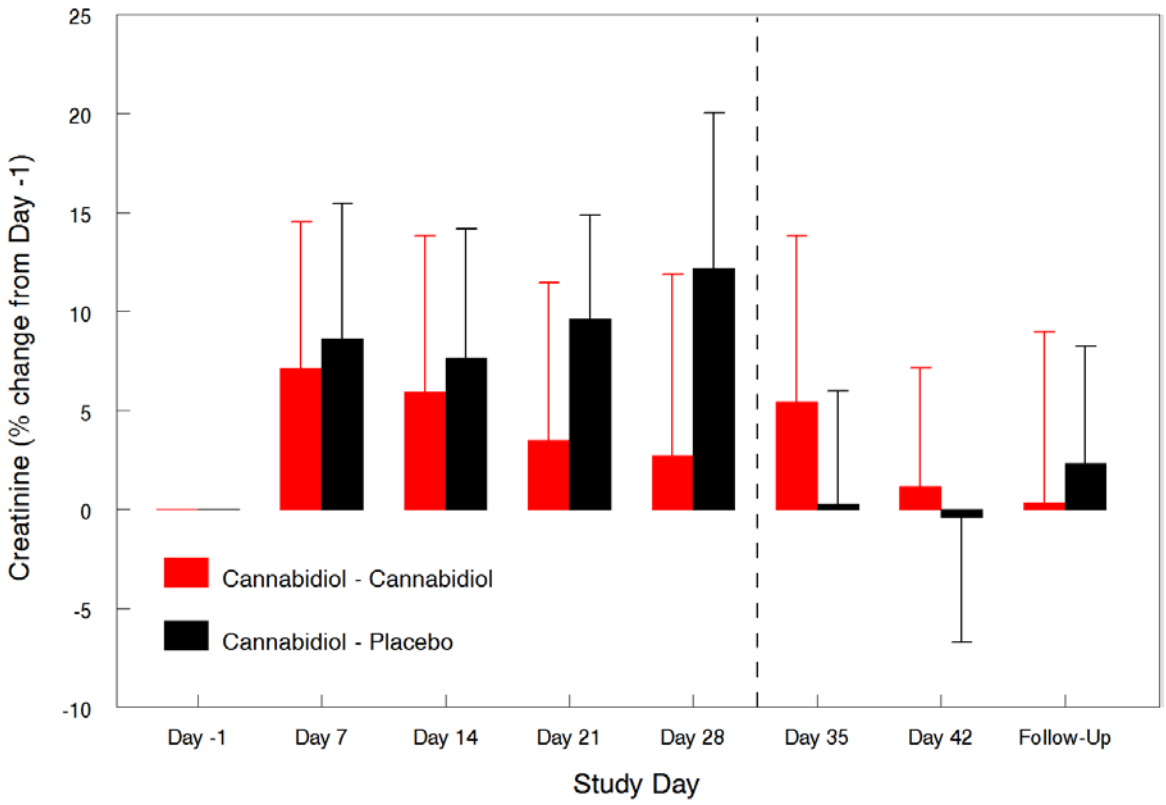
Source: Applicant's ISS, Table 9.1.2.1.3.2-1

The randomized withdrawal design provided an opportunity to assess changes in creatinine with cannabidiol treatment, as well as the potential reversibility of such changes after discontinuation. Unfortunately, a number of subjects were withdrawn from the study because of adverse events. All subjects did, however, have a follow-up assessment at ~8 weeks (mean, Day 59). Creatinine is expressed in Figure 11 as mean (± 1 SD) percent change from the baseline (Day -1) assessment. Mean creatinine increased by approximately 7% to 8% in both treatment groups at Day 7 (with both groups were receiving cannabidiol at that time). Between Days 7 and 28, mean creatinine tended to increase in the group that would be switched to placebo, and decrease in the group that would remain on cannabidiol. With withdrawal of cannabidiol after Day 28 in the cannabidiol-placebo group (black bars), creatinine decreased to its baseline value at Day 35. Despite continued cannabidiol administration in the cannabidiol-cannabidiol group (red bars), creatinine decreased to its baseline value by Day 42 (note, however, that there are substantial missing data [see n's at bottom of figure]). Recognizing that this was a small study and that there is considerable variability in serum creatinine, the data show a rapid increase in serum creatinine with initiation of treatment, with a return to baseline values after discontinuation. All 30 subjects contributed data at the follow-up visit. (Note: The decrease in serum creatinine despite continued treatment [red bars] is counter to the much larger and longer experience in the controlled trials, shown in Table 13.)

We obtained consultation from the Division of Cardiovascular and Renal Products to review all

of the renal parameters and to gain a better understanding of these changes; the overall findings are discussed in Section 8.5.6.

Figure 11: Study 1542 – Changes in Creatinine with Cannabidiol Treatment, and Reversibility of Changes after Randomized Withdrawal: Percent Change from Baseline (Mean +/- SD)



Cannabidiol	n=	15	15	15	13	11	10	9	15
Placebo	n=	15	15	15	15	13	13	12	15

Transaminases, Bilirubin, and Alkaline Phosphatase Elevations

Transaminase elevations were obviously increased in cannabidiol treated subjects in the controlled trials and were one of the applicant's adverse events of special interest. Prior to NDA submission, FDA asked the applicant to address the hepatic safety by including evaluation of the data by an external expert in liver disease. The data were also extensively reviewed by consultants from the Division of Gastroenterology and Inborn Errors Products and the Office of Surveillance and Epidemiology.

Some of the transaminase elevations were serious adverse events (12 (4%) vs. 0; Table 5) or severe adverse events (7 (2%) vs 1 (0%); Table 9); however, there were no events of liver failure or deaths related to liver injury, i.e., no cases with concomitant bilirubin increases.

Table 14 shows my analyses of ALT elevations by subgroup in the controlled trial database.

Table 14: ALT Elevations in the Controlled Trial Database by Subgroup

		% of subjects	↑ ALT > 3X ULN		RR	↑ ALT > 5X ULN		RR
			CBD	Placebo		CBD	Placebo	
All		100%	13%	1%	15.1	7%	1%	7.4
Disease	Dravet	28%	14%	2%	9.0	6%	2%	3.8
	Lennox-Gastaut	72%	13%	1%	21.2	7%	1%	11.0
Age group	2-5 years	16%	14%	3%	5.2	4%	3%	1.5
	6-11 years	36%	15%	0%	-	9%	0%	-
	12-17 years	25%	11%	2%	6.4	8%	2%	4.3
	>= 18 years	23%	13%	1%	15.1	6%	1%	7.4
Sex	Male	54%	16%	0%	-	7%	0%	-
	Female	46%	10%	2%	5.1	5%	2%	2.9
Race	White	85%	14%	1%	13.8	7%	1%	6.7
	Black	4%	7%	0%	-	0%	0%	-
	Asian	2%	0%	0%	-	0%	0%	-
	Other	8%	16%	0%	-	9%	0%	-
Dose	5 mg	3%	10%	1%	11.4	10%	1%	11.4
	10 mg	23%	1%	1%	1.5	1%	1%	1.5
	20 mg	74%	17%	1%	19.6	8%	1%	9.1
Weight quartile*	1	25%	14%	2%	7.3	6%	2%	3.0
	2	25%	10%	0%	-	5%	0%	-
	3	25%	13%	0%	-	7%	0%	-
	4	25%	17%	2%	11.0	8%	2%	5.5
Location	USA	75%	12%	1%	20.7	7%	1%	12.1
	Poland	9%	26%	0%	-	7%	0%	-
	Spain	6%	5%	0%	-	0%	0%	-
	UK	6%	15%	9%	1.7	5%	9%	0.6
	France	3%	23%	0%	-	8%	0%	-
	Netherlands	1%	0%	0%	-	0%	0%	-
Other AEDs	Valproate (only)	24%	20%	0%	-	6%	0%	-
	Clobazem (only)	32%	5%	1%	3.7	2%	1%	1.5
	On Both	21%	29%	2%	13.4	19%	2%	8.7
	On Neither	23%	3%	0%	-	1%	0%	-

* weight quartiles: <23.23; 23.23 to <34.45; 34.45 to <53.15; >=53.15 kg

Alanine aminotransferase elevations > 3 times the ULN were reported in 13% vs. 1% of subjects in the cannabidiol and placebo groups, respectively. For elevations > 5 times the ULN, the corresponding frequencies were 7% and 1%. Elevations of ALT were independent of the underlying condition (DS vs. LGS), age, sex, and body mass. Data in non-whites were too sparse to suggest differences by race. Only 10 subjects received the 5 mg/kg/d dose; therefore, the frequency of ALT elevations at this dose is difficult to interpret. For the 10 and 20 mg/kg/d doses, however, there is an apparent dose-response; *nearly all subjects with ALT elevations had received 20 mg/kg/d*. Subjects typically received numerous AEDs during the controlled studies. In addition to multiple other AEDs, it is notable that 45% of subjects received valproate, a known hepatotoxin (includes 24% of subjects on valproate, plus 21% on both valproate and clobazam), and 53% received clobazam (includes 32% of subjects on clobazam, plus 21% on valproate and clobazam). Approximately one-fourth of subjects received both drugs (21%) and one-fourth received neither (23%). For subjects taking cannabidiol, concomitant use of valproate increased the likelihood of ALT elevations by a factor of ~7 (20% for subjects taking valproate without clobazam, versus 3% for subjects taking neither valproate nor clobazam). Concomitant clobazam use also appeared to increase cannabidiol-induced hepatotoxicity, but to a smaller extent than valproate.

Figure 12 shows time-to-first ALT elevation >3X ULN from the controlled trial database (DS and LGS). The top plot shows all cannabidiol subjects (solid line) vs. all placebo subjects (broken line). For the bottom plot, solid lines = cannabidiol; broken lines placebo. Orange = valproate & clobazam; purple = valproate; blue = clobazam; black = neither.

Figure 12: Controlled Trials - Time-to-Initial ALT Elevation to >3X ULN

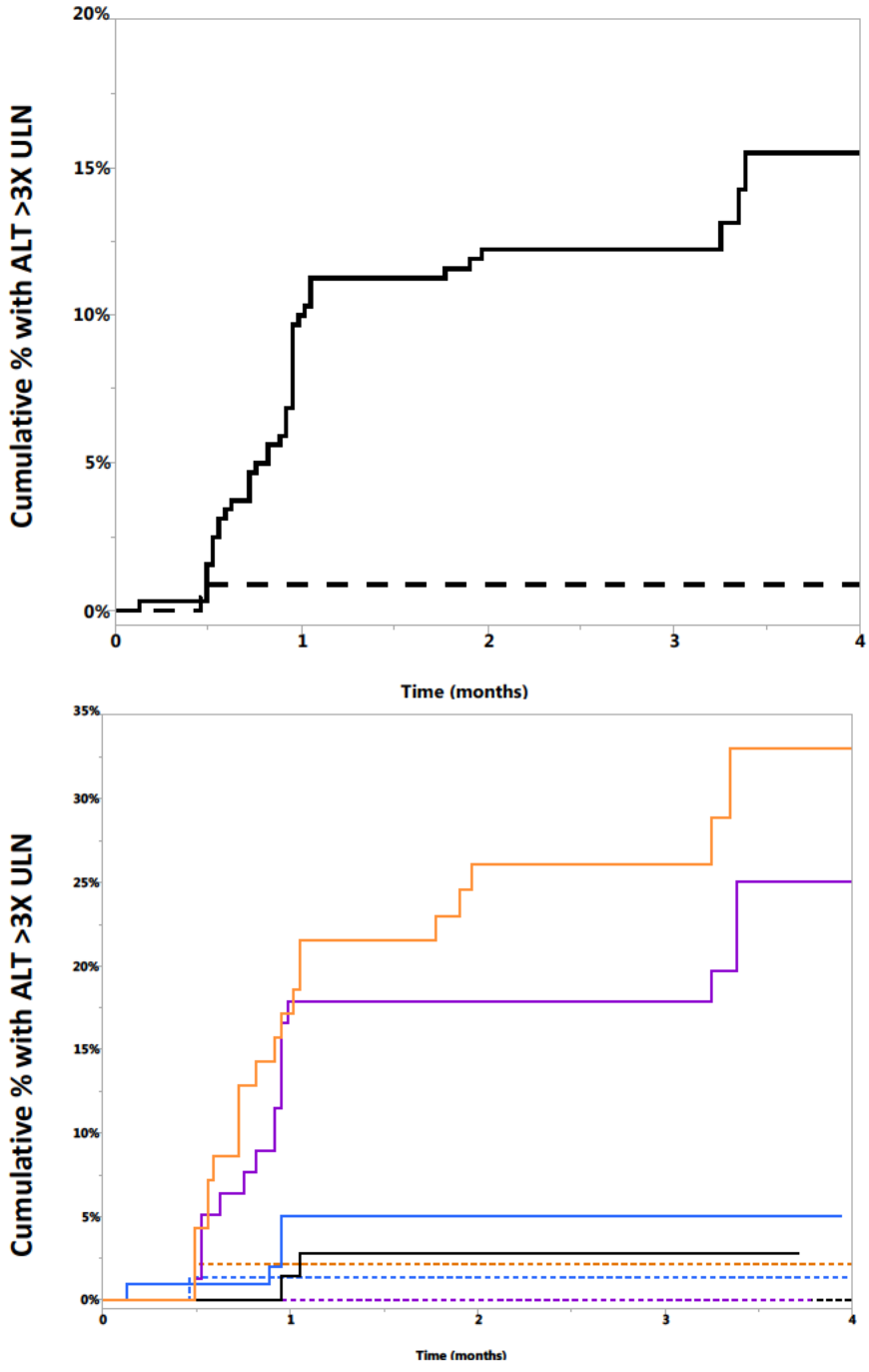
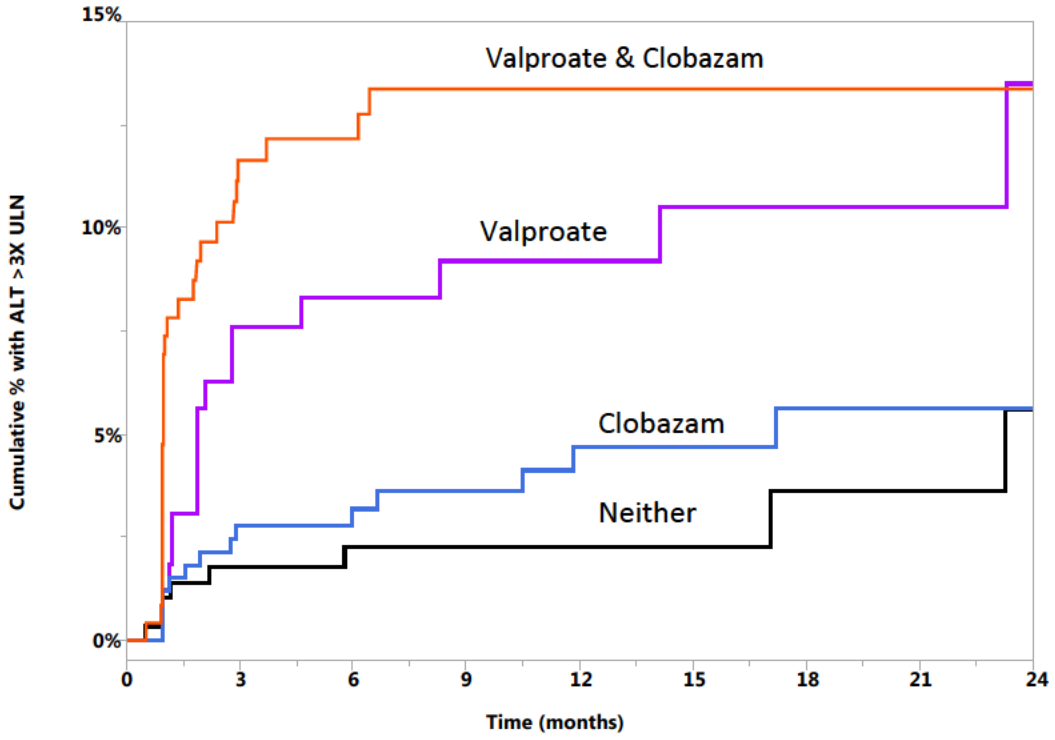


Figure 13 shows a similar analysis for the uncontrolled patient data, combining the EAP/CAS with subjects in the open-label extension study who were cannabidiol-naïve when they entered

Figure 13: EAP/CAS and Open-label Extension (Subjects Originally on Placebo) – Time-to-Initial ALT Elevation to >3X ULN



the study (i.e., subjects who had been randomized to placebo in the controlled trials). The plot breaks down subjects by valproate and clobazam use (as per Figure 12). Most transaminase elevations were observed within 2 to 3 months of initiation of cannabidiol treatment; however, additional elevations were observed through 18 months. Transaminase elevations generally resolved with discontinuation of cannabidiol or after decreasing the dose of cannabidiol or valproate; however, some events resolved during continued treatment with cannabidiol at the same dose.

Elevations of ALT were greater than those of aspartate aminotransferase (AST), suggesting that the liver was the source of the transaminase elevations. Although small increases in total bilirubin were reported in a few cases, the bilirubin levels generally remained within normal limits and no cases met Hy's law criteria (ALT ≥ 3X ULN and bilirubin > 2X ULN).

For more details, refer to the consultation memo from the Division of Gastroenterology and Inborn Errors Products and the Office of Surveillance and Epidemiology.

With respect to bilirubin, there were 4 subjects in the submission with a post-baseline value > 1.5X the ULN; these ranged only to as high as 1.9 X ULN. No patients had a post-baseline value > 2X the ULN, and by definition, there were no Hy's Law cases. There were no important increases in alkaline phosphatase in the controlled trial database.

8.4.7. Vital Signs

This reviewer analyzed the applicant's vital signs data including weight, body mass index (BMI), heart rate, blood pressure (systolic and diastolic; sitting, standing, and supine) and temperature. There were no notable differences in heart rate, blood pressure, or temperature.

The applicant found that weight decreases of ≥ 7% from baseline were reported in more subjects in the 20 mg/kg/day cannabidiol group than in the placebo group (26 patients [10.9%] vs. 9 patients [4.0%], respectively). Conversely, weight increases of ≥ 7% from baseline were reported in fewer subjects in the 20 mg/kg/day and 10 mg/kg/day cannabidiol groups than in the placebo group (33 subjects [13.9%] vs. 14 subjects [18.7%] vs. 54 subjects [23.8%], respectively).

Table 15: Changes in Vital Signs (≥5%) in the Controlled Trial Database

	Cannabidiol (mg/kg/day)				Placebo	RR
	5	10	20	10 + 20		
N:	10	75	238	313	227	
Weight decreased	(0%)	7 (9.3%)	44 (18.5%)	51 (16.3%)	19 (8.4%)	1.9
BMI decreased	1 (10%)	13 (17.3%)	64 (26.9%)	77 (24.6%)	39 (17.2%)	1.4
Weight increased	0 (0%)	22 (29.3%)	59 (24.8%)	81 (25.9%)	84 (37%)	0.7
Standing diastolic BP decreased	1 (10%)	4 (5.3%)	4 (1.7%)	8 (2.6%)	0 (0%)	-

I compared the nadir post-baseline weight and the nadir post-baseline BMI of each subject to their baseline values, and noted when decreases were greater than 5, 10, and 15%. My findings were consistent with those of the applicant (Table 15). Note that the frequency of weight decreases (≥ 5%) was similar in the cannabidiol 10 mg/kg/d group and the placebo group. In contrast, in the 20 mg/kg/d cannabidiol group, the frequency of weight decreases was approximately 10% higher than in the placebo group (18.5% vs. 8.4%, respectively). Findings for ≥ 5% decreases in BMI followed the same pattern: there was no difference between the cannabidiol 10 mg/kg/d group and the placebo group, whereas the frequency of BMI decreases was approximately 10% higher in the cannabidiol 20 mg/kg/d group than in the placebo group (26.9% vs. 17.2%, respectively). For weight increases, I compared the post-baseline maximum for each subject to their baseline, and noted weight increases greater than 5, 10, and 15%. Note that my findings are similar to those of the applicant: increased weight was more frequent in the placebo group than in the cannabidiol groups.

8.4.8. Electrocardiograms (ECGs)

There were no significant mean effects on the mean QTcB (corrected QT; Bazett's formula), PR,

or QRS intervals. I assessed outliers by examining scatterplots of baseline vs. post-baseline maximum values, and baseline vs. post-baseline nadir values (Appendix, Figure 14). No important outliers were found.

8.4.9. **QT**

The applicant performed a thorough QT (TQT) study (Study 1541) between 2015 and 2016, at a time before the food effect of cannabidiol had been characterized. The TQT utilized a typical study design, and compared single oral doses of 750 mg cannabidiol (therapeutic range), 4500 mg cannabidiol (supratherapeutic range), moxifloxacin, and placebo. The 1° endpoint was the time-matched QT interval using Fridericia's Correction Formula (QTcF) as recommended by the ICH E14 Guideline. The upper 1-sided 95% confidence interval did not exceed 10 ms at either dose for any timepoint, and there were no findings of concern in an analysis of outliers. The moxifloxacin group met the assay sensitivity criteria outlined in the protocol.

(b) (4) administration with a high-fat, high-calorie meal increased C_{max} of the parent and metabolites by 5-fold and 2- to 3-fold, respectively, relative to the fasting state. Because the 4500-mg supratherapeutic dose given in the fasted state would not cover the therapeutic exposures of the parent or the 7-carboxy-cannabidiol metabolite when the highest proposed dose of the drug is administered with food, the QT Interdisciplinary Review Team is recommending the conduct of an additional TQT study, with cannabidiol dosing in the fed state.

8.4.1. **Immunogenicity**

Not applicable. Cannabidiol is a small molecule.

8.5. **Analysis of Submission-Specific Safety Issues**

8.5.1. Liver

A detailed assessment of hepatotoxicity was performed by consultants from the Division of Gastroenterology and Inborn Errors Products, Office of Drug Evaluation-III, Office of New Drugs and the Office of Pharmacovigilance and Epidemiology, Office of Surveillance and Epidemiology.

The non-clinical studies showed increases in alkaline phosphatase and/or ALT with liver injury characterized by centrilobular hypertrophy. There was a tendency towards reversal of findings at the terminal kill.

The clinical studies included enrolment exclusions for increases in transaminases, bilirubin, and INR at screening, typically ALT or AST > 3 X ULN, bilirubin > 2 X ULN, and INR > 1.5. For the controlled studies, transaminases, bilirubin, and INR were generally assessed at baseline, with monitoring at 2, 4, 8, and 12 weeks. Additional monitoring was conducted in the open-label extension study at 24, 36, and 48 weeks. The studies included various criteria for withdrawing

subjects from the trials, generally ALT or AST > 3 X ULN with eosinophilia and symptoms, bilirubin > 2 X ULN, or INR > 1.5. Sustained ALT or AST elevations > 5 X ULN and elevations > 8 X ULN were also used as withdrawal criteria, depending on the specific study.

In the controlled safety database, transaminase elevations were reported as serious adverse events in 4% vs. 0% of subjects in the cannabidiol and placebo groups, respectively (Table 5), and as severe adverse events in 2% vs. 0% of subjects, respectively (Table 9). Transaminase elevations led to discontinuation of approximately 5% of trial participants (Table 7). For adverse events of any severity, elevated transaminases were reported in 14% and 3% in cannabidiol-treated and placebo subjects, respectively, and there was a clear dose-response in the controlled trials. The frequency of adverse events for transaminase elevations of any severity in the open-label extension study was 18%, and 8% in the EAP/CAS.

Based on the laboratory data from the controlled studies, AST elevations > 3 X ULN were reported in 13% vs. 1% of subjects in the cannabidiol and placebo groups, respectively, and > 5 X ULN in 7% and 1% of subjects (Table 14). For the 10 and 20 mg/kg/d doses, there was a clear dose-response; importantly, *nearly all subjects with ALT elevations had received 20 mg/kg/d.* As noted in Section 8.4.6., the probability of ALT elevations was not related to underlying condition (DS vs. LGS), age, sex, or body mass. Data in non-whites were too sparse to suggest differences by race. For subjects taking cannabidiol, concomitant use of valproate increased the likelihood of ALT elevations by a factor of ~7 (20% for subjects taking valproate without clobazam, versus 3% for subjects taking neither valproate nor clobazam). Concomitant clobazam use also appeared to increase cannabidiol-induced hepatotoxicity, but to a smaller extent. No subject had a bilirubin increase by as much as 2X ULN, and there were no important increases in alkaline phosphatase in the controlled trial database.

Plots of time-to-first ALT elevation >3X ULN show that transaminase elevations were generally reported within 2 to 3 months of initiating cannabidiol; however, additional elevations were observed through 18 months.

The liver consultants noted that transaminase elevations generally resolved with discontinuation of cannabidiol or after decreasing the dose of cannabidiol or valproate; however, some events resolved despite continued treatment with cannabidiol at the same dose.

The transaminase elevations, primarily increases in ALT, are consistent with drug-induced hepatocellular injury. Severe hepatic injury, with coincident increases in bilirubin and INR, were not reported, i.e., there were no Hy's Law cases and no cases of overt hepatic failure. Given that the cannabidiol exposure in patients with all types of seizure disorders (the controlled safety data, open-label extension study, and EAP/CAS) includes 972 patients treated for $\geq$ 6 months and 670 patients treated for $\geq$ 12 months, the 'rule of three' estimates the incidence of Hy's Law cases at no more than 1/324 (0.3%) in patients treated for 6 months and 1/223 (0.4%) in patients treated for 12 months.

My conclusions and recommendations are: 1) given the modest numbers of subjects exposed to cannabidiol in the development program and the as yet unknown risk of severe liver injury, cannabidiol's use should be confined to patients with severe epilepsy due to DS and LGS, although restricted distribution is not necessary; 2) given the dose-related nature of the transaminase elevations, the dose of cannabidiol should generally be limited to 10 mg/kg/d; 3) the labeling should indicate that the risk is significantly higher with concomitant valproate, and (b) (4) with concomitant clobazam; 4) specific recommendations should be provided for monitoring transaminases in labeling; 5) labeling should include a strategy for dose modification and discontinuation for patients with liver biochemical abnormalities; 6) an enhanced pharmacovigilance program should be considered; 7) as recommended by the consultants, the review team should consider a non-invasive study in cannabidiol users to determine whether long-term exposure (> 1-2 years) causes chronic liver disease/fibrosis.

8.5.2. Central Nervous System

Somnolence and lethargy are the most frequent of the CNS toxicities, reported as serious adverse events in the controlled safety database in 2% vs. 0% of subjects in the cannabidiol and placebo groups, respectively. Dropouts were attributed to somnolence/lethargy at similar frequencies, and somnolence/sedation/lethargy was reported as a severe adverse event at similar frequencies. For somnolence/sedation/lethargy of any severity, frequencies in the cannabidiol and placebo groups were 32% vs. 11% respectively, for an attributable risk difference of 21%. There was an apparent dose-response for this adverse drug reaction, but the risk was appreciable even at the lower 10 mg/kg/d dose.

Irritability, agitation, sedation, disorientation, fatigue, malaise, asthenia, ataxia, tremor, aggression, anger, drooling, hypersalivation, insomnia and other sleep disturbances, falls, dizziness, balance disorders, and gait disturbances were also reported at higher frequencies in the cannabidiol group than in the placebo group, and generally at notable frequencies in the open-label extension study and the EAP/CAS experience. For these adverse events, the frequencies were similar at the 10 and 20 mg/kg/d doses in the controlled trials. Given that the drug crosses the blood-brain barrier, and in light of the relatedness of some of the events and the abrupt upslopes of the cumulative frequencies of these events in time-to-event analyses, these are reasonably likely to be drug-related and should be included as adverse reactions in Section 6 of labeling.

8.5.3. Weight Loss/Decreased Appetite

Weight loss and decreased appetite do not stand out as drug-related side effects when considering only the serious and severe adverse events, although decreased appetite was cited as the reason for study discontinuation in some 2% of subjects. Similarly, weight loss was reported as a serious adverse event at a frequency of only 1% in the open-label extension trial and the EAP/CAS. Signals for weight loss/decreased appetite are evident only when *all* adverse events and actual subject weights are considered. In the controlled trials, 21% vs. 5% of subjects in the cannabidiol and placebo groups, respectively, reported decreased appetite as an adverse event. Corresponding frequencies for decreased weight were 4% and 1%. In the open-

label extension study, 24% of subjects reported decreased appetite, and 9% reported weight loss. Frequencies of decreased appetite and weight loss were 12% and 6%, respectively, in the EAP/CAS. Importantly, the frequencies of measured weight loss (≥ 5%) in the controlled trials were 16% and 8% in the cannabidiol and placebo groups, respectively. Corresponding frequencies of decreases in calculated BMI (≥ 5%) were 25% and 17%. There were also fewer subjects with weight *gain* (≥ 5%) in cannabidiol-treated subjects than placebo subjects: 26% vs. 37%, respectively. Considering the relative risks of these events, the concordance of adverse events with changes in measured body mass/BMI, and the ages of these subjects (mostly pediatric), weight loss and decreased appetite are important adverse events that warrant listing as adverse reactions in Section 6 of labeling. It will be important to draw attention to the fact that weight loss is mostly observed at the higher dose of cannabidiol.

8.5.4. Other Gastrointestinal

Diarrhea is common in this age group, but there was a signal in the controlled trial database, with adverse events of diarrhea in 17% vs. 9% of subjects in the cannabidiol and placebo groups, respectively. There was also an apparent dose-response in the controlled trials (9% and 20% in the 10 and 20 mg/kg/d groups, respectively) and a reasonable dose-response in the EAP/CAS. Time-to-event curves also exhibited a rapid increase in the cumulative frequency of diarrhea, suggesting causality. Other gastrointestinal adverse events with small differences between the cannabidiol and placebo groups include abdominal pain/distension/discomfort and gastroenteritis (both 3% vs. 1%, respectively), as well as dry mouth (2% vs. 1%, respectively). These adverse gastrointestinal reactions warrant mention in Section 6 of labeling as adverse reactions.

8.5.5. Infections

Cannabidiol has no known effects that would predispose patients to infections, and no apparent adverse effects on white blood cells were discernable in the controlled trials. Infections are extremely common in this age group, particularly in patients with DS and LGS. It is noteworthy, however, that there were signals for infection in the controlled trials. For infections of all types as a serious adverse event, the frequencies were 7% vs. 2% in cannabidiol- and placebo-treated subjects, respectively (13 subjects vs. 1 subject). This difference was driven by pneumonia (4% vs. 0%) and viral infections (2% vs. 0%). Serious adverse events of infection were reported at 11% and 13% in the long-term extension study and the EAP/CAS, respectively, but these numbers are difficult to interpret in the absence of a randomized control group. In the controlled trials, the frequencies of infections of all types and all severities were 41% and 31% in the cannabidiol and placebo groups, respectively (risk difference 10%, RR = 1.3). Much of the difference was driven by pneumonia (6% vs. 1%), and there were no trends with respect to type of pathogen, i.e., viral, bacterial, or fungal. The accounting of all adverse events of infection in the EAP/CAS shows an overall 42% frequency of infections as adverse events. Although difficult to interpret in the absence of a randomized control group, there is a monotonic increase in the frequency of infections with dose: the frequency increases by approximately 10% for each 10 mg/kg/d increase in dose (Table 12).

Kaplan-Meier curves for time-to-first infection tended to show gradual changes in slopes of cumulative frequencies, without inflection points, suggesting that the underlying rate of infections was not influenced by initiation of treatment with cannabidiol. The green line in Figure 10 is representative.

Given the modest relative risk (1.3), the absence of a known mechanism of action that would predispose to infections, and the morphology of the cumulative frequencies of infections in the Kaplan-Meier curves, this reviewer is not convinced that infections are cannabidiol-related.

8.5.6. Renal

Changes in creatinine are discussed extensively above. It is clear that cannabidiol causes a rapid increase in serum creatinine on the order of 8%, which persists for at least 28 days. The change in creatinine occurred in the absence of changes in BUN or blood pressure, and in the absence of renal/genitourinary adverse events. Urinary protein was not quantified. An acute increase in creatinine of the same magnitude was also observed in a study of 30 healthy adult volunteers (conducted to assess withdrawal effects of cannabidiol). The non-clinical studies are difficult to interpret; one study showed evidence of nephropathy, but there were impurities in the test drug that might have caused the findings.

In the study of 30 volunteers, the mean serum creatinine value decreased to baseline after subjects had been off cannabidiol for 2 or more weeks, providing good evidence of reversibility (Figure 11). The renal consultants thought it important to confirm the mechanism of cannabidiol's effect on creatinine and to better establish the magnitude of elevation in serum creatinine. The consultants had some concerns with respect to accuracy of the calculated creatinine clearance data (I had similar concerns, leading me to analyze the serum creatinine values rather than the calculated creatinine clearances). The consultants are suggesting a post-marketing study in healthy volunteers that includes measurement of GFR (b) (4), to help resolve the issue of whether cannabidiol inhibits the tubular secretion of creatinine or has a true effect on GFR. This will need to be considered by the review team.

8.5.7. Rash

There were no important differences in the frequency of rash as a *serious adverse event* in any of the studies. Rash was not cited as a reason for discontinuation in any subjects in the controlled DS/LGS trials, although 2 cannabidiol-treated subjects had rash reported as a severe adverse event (1%), vs. none in the placebo group. With respect to adverse events of any severity, however, rash was reported in 11% vs. 3% of subjects in the cannabidiol and placebo groups, respectively, with an apparent dose-response. Rash was reported at a frequency of 6% in both the open-label extension study and the EAP/CAS. As noted above, 8 of 30 health volunteers in a randomized withdrawal study experienced a rash (27%), and most of these subjects were withdrawn from the study. Rashes were initially reported from study day 2 through day 11; 5 were judged moderate in severity and 2 were severe. Given the lack of confounding factors in this study of healthy volunteers, there is little question that rash is

cannabidiol-related.

8.5.8. Anemia

There were small decreases in hemoglobin and hematocrit in the cannabidiol group, with normal red blood cell indices. There are no signals for anemia in the animal toxicology studies, and no known mechanism of action that would account for the finding. Thus, it is not known if anemia is drug-related, and the significance seems small. Nevertheless, it would be important for prescribers to be aware of the potential for mild anemia so that they can manage patients expectantly and appropriately.

8.5.9. Suicidal Behavior and Ideation

Based on results of the C-SSRS, no treatment-emergent suicidal ideation or behavior was found in subjects who received cannabidiol during the trials.

Of note, however, serious adverse events for suicidal ideation/behavior were reported in 2 patients in the EAP. Subject (b) (6) an 11-year-old male, reported suicidal thoughts (moderate severity) and suicidal behavior (severe severity) on study days 453 and 564, respectively. Patient (b) (6), a 21-year-old male, had suicidal ideation (severe) reported on day 321. There were no non-serious adverse events for suicidal ideation/ behavior.

It is difficult to interpret the meaning of 2 reports of suicidal ideation/behavior in this patient population in an uncontrolled experience. The applicant is seeking a warning for suicidal behavior and ideation, which at present is a class warning for AEDs, and I support use of this warning in labeling. Although cannabidiol's mechanism of action differs from that of other AEDs, it would be difficult to support making cannabidiol the only AED that lacks such a warning, especially in light of the above.

8.5.10. Hypersensitivity

One subject experienced an adverse event of allergic reaction/hypersensitivity, but nevertheless stayed on cannabidiol with resolution of symptoms, strongly suggesting that the diagnosis was dubious. On the other hand, a patient in the abuse liability study had an adverse event of hypersensitivity that seems fairly convincing, based on the symptoms reported and treatment administered. On this basis, hypersensitivity should appear in labeling.

8.6. **Safety Analyses by Demographic Subgroups, Baseline Disease, Dose**

Table 16 shows important safety signals by disease (DS vs. LGS), demographics, baseline weight, dose, and use/non-use of valproate and clobazam. Note that the table combines adverse events of all severities (decreased appetite, diarrhea, somnolence/lethargy), and *measured* weight decrease $\geq$ 5% (measured weight loss differs from weight loss as an adverse event. This table is identical in format to Table 14, which showed ALT elevations by subgroup.

Table 16: Safety Signals by Baseline Disease, Demographics, and Other Characteristics

		% of	↓Appetite		RR	Diarrhea		RR	Somnolence, sedation, lethergy		RR	Weight loss		RR
		subjects	CBD	Placebo		CBD	Placebo		CBD	Placebo		CBD	Placebo	
All		100%	20%	5%	4.2	17%	9%	1.9	33%	11%	2.8	14%	8%	1.7
Disease	Dravet	28%	25%	5%	5.5	22%	11%	2.0	38%	15%	2.5	14%	6%	2.3
	Lennox-Gastaut	72%	18%	5%	3.7	15%	8%	1.8	31%	10%	3.1	14%	9%	1.5
Age group	2-5 years	16%	16%	5%	3.0	12%	8%	1.5	35%	8%	4.5	10%	16%	0.6
	6-11 years	36%	22%	5%	4.4	13%	9%	1.4	29%	9%	3.3	16%	5%	3.2
	12-17 years	25%	20%	2%	11.4	28%	11%	2.6	34%	21%	1.6	14%	5%	2.6
	>= 18 years	23%	20%	5%	4.2	17%	9%	1.9	32%	11%	2.8	14%	8%	1.7
Sex	Male	54%	23%	4%	5.5	22%	10%	2.2	32%	9%	3.4	16%	8%	2.2
	Female	46%	16%	6%	2.9	10%	7%	1.4	33%	14%	2.4	11%	9%	1.2
Race	White	85%	20%	4%	4.6	17%	9%	1.8	32%	11%	2.8	13%	8%	1.6
	Black	4%	20%	0%	-	27%	0%	-	33%	0%	-	20%	0%	-
	Asian	2%	14%	20%	0.7	0%	0%	-	29%	20%	1.4	0%	20%	0.0
	Other	8%	19%	8%	2.4	16%	8%	2.0	34%	15%	2.2	25%	15%	1.6
Dose	5 mg	3%	0%	5%	0.0	0%	9%	0.0	40%	11%	3.5	0%	8%	0.0
	10 mg	23%	16%	5%	3.3	9%	9%	1.1	27%	11%	2.3	8%	8%	1.0
	20 mg	74%	22%	5%	4.6	20%	9%	2.2	34%	11%	3.0	16%	8%	2.0
Weight quartile *	1	25%	14%	6%	2.4	14%	8%	1.8	34%	10%	3.5	8%	12%	0.7
	2	25%	19%	7%	2.9	12%	13%	0.9	29%	10%	2.9	16%	12%	1.3
	3	25%	28%	2%	13.9	15%	6%	2.4	34%	10%	3.3	19%	6%	3.2
	4	25%	18%	5%	4.0	28%	8%	3.7	33%	15%	2.2	13%	5%	2.8
Location	USA	75%	17%	6%	2.9	15%	9%	1.8	36%	13%	2.8	13%	6%	1.9
	Poland	9%	7%	0%	-	19%	4%	4.6	7%	0%	-	15%	20%	0.7
	Spain	6%	30%	0%	-	15%	0%	-	30%	17%	1.8	15%	8%	1.8
	UK	6%	55%	0%	-	30%	27%	1.1	35%	9%	-	10%	9%	1.1
	France	3%	31%	17%	1.8	23%	0%	-	23%	17%	1.4	38%	17%	2.3
	Netherlands	1%	67%	0%	-	0%	50%	0.0	0%	0%	-	33%	0%	
Other AEDs	Valproate (only)	45%	28%	8%	3.6	25%	12%	2.2	19%	10%	2.0	19%	15%	1.2
	Clobazem (only)	54%	10%	4%	2.5	7%	11%	0.7	44%	16%	2.8	7%	8%	0.9
	On Both	21%	31%	6%	4.9	24%	9%	2.9	51%	15%	3.5	24%	11%	2.3
	On Neither	23%	15%	2%	7.9	14%	4%	3.6	13%	4%	3.3	8%	0%	-

* weight quartiles: <23.23; 23.23 to <34.45; 34.45 to <53.15; >=53.15 kg

One must be careful in interpreting these differences because of the small numbers of events overall, and, in particular, even smaller numbers of adverse events within subsets of the population. Moreover, numerous comparisons are made in the table, providing ample opportunity to observe differences due to chance.

Having considered these comparisons, the differences that seem meaningful and worthy of mention in labeling are: 1) diarrhea and weight loss are observed only at the higher dose; 2) somnolence, sedation, and lethargy seem meaningfully more frequent with concomitant clobazam and valproate use, particularly the former. Somnolence, sedation, and lethargy are dose-related, but nevertheless occur fairly frequently, even at the lower dose.

From Table 14, it is clear that ALT elevations occur almost exclusively at the higher dose, and are importantly exacerbated by concomitant valproate use (and, to a lesser extent, by concomitant clobazam use), as discussed above.

Note that none of the adverse reactions tend to increase in frequency with decreasing weight, undoubtedly because dosing was weight-based.

8.1. Specific Safety Studies/Clinical Trials

The Columbia-Suicide Severity Rating Scale (C-SSRS) was included in all of the controlled studies in target indications and most of the Phase 1 trials.

The applicant concluded that results of the C-SSRS identified no treatment-emergent suicidal ideation or behavior in subjects who received cannabidiol during the trials, and I agree (data not shown).

Two patients in the EAP with serious adverse events for suicidal ideation/behavior were discussed in sections 8.4.2. and 8.5.9.

8.2. Additional Safety Explorations

8.2.1. Human Carcinogenicity or Tumor Development

Not assessed.

8.2.2. Human Reproduction and Pregnancy

No studies were conducted with cannabidiol in pregnant women to assess risks. One pregnancy was reported in an abuse liability study. A subject presented with a positive pregnancy test at a follow-up visit, and subsequently had an uncomplicated delivery of a full-term healthy baby.

8.2.3. Pediatrics and Assessment of Effects on Growth

The applicant assessed effects on growth and development through measurements of height, weight, serum insulin-like growth factor-1 (IGF-1) (for subjects < 18 years old), BMI, and a cognitive assessment battery. For adolescent subjects, the onset and progression of pubertal changes was assessed with Tanner Staging. In both DS and LGS indications, more cannabidiol-treated subjects than placebo subjects had weight decreases ≥ 7% and fewer cannabidiol-treated subjects than placebo subjects had weight increases of ≥ 7% (as noted above), but differences in other parameters were not consequential.

8.2.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

To evaluate withdrawal effects of cannabidiol, the applicant conducted Study 1542, a double-blind, placebo-controlled, randomized withdrawal study in healthy male and female volunteers. All (30) subjects were to take a therapeutic dose (750 mg/day twice daily) of cannabidiol for 1 month, followed by abrupt discontinuation and replacement by placebo in half the subjects.

There was no evidence of a withdrawal syndrome with abrupt discontinuation of cannabidiol, based on the profile of adverse events, overall time-to-onset of adverse events, and assessments on the Cannabis Withdrawal Scale (CWS) and Penn Physician Withdrawal Checklist-20 (PWC-20). The incidence of adverse events was comparable between groups following randomized withdrawal, without evidence of a withdrawal syndrome. Scores on the CWS and PWC-20 were low throughout the trial, and no increases were observed after abrupt discontinuation of cannabidiol.

The applicant conducted a human abuse potential study, which was evaluated by the Controlled Substance Staff. They concluded that cannabidiol does not appear to have abuse potential based on either non-clinical or clinical data, and their overall assessment was that cannabidiol has negligible abuse potential.

8.3. Safety in the Postmarket Setting

8.3.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.3.2. Expectations on Safety in the Postmarket Setting

I expect the patterns in adverse reactions in the postmarketing data will be similar to the patterns observed in the pre-marketing data. There will, no doubt, be suicides reported on the drug, given the nature of the patient population, and these will be difficult to interpret. By no means do the premarketing data rule out the possibility of severe liver injury in the post-marketing setting. The risk of severe hepatic injury is unknown, but estimated to be < 0.3% in

patients treated for 6 months, and < 0.4% in patients treated for 12 months. It seems likely that the risk would be much lower at the lower dose.

8.3.3. Additional Safety Issues from Other Disciplines

None.

8.4. Integrated Assessment of Safety

Cannabidiol's principal toxicity is hepatic; the drug causes transaminase elevations in a significant fraction of patients, as summarized in Section 8.5.1. Although there were no Hy's Law cases and no patients in the development program who developed acute liver failure, the program was modest in size. The chief concern, therefore, is that the drug could, in fact, cause severe acute and/or chronic liver injury in the marketed setting, when patient exposure markedly increases, and the magnitude of this risk is unknown. Based on the data in the development program and using the rule of three, I estimate the risk of severe liver injury to be no greater than 0.3 to 0.4%. These estimates are based on patients with *all types of seizure disorders*, 972 of whom received cannabidiol for ≥ 6 months, and 670 of whom were treated for ≥ 12 months.

The estimate from the Division of Gastroenterology and Inborn Errors Products and Office of Surveillance of Epidemiology differs, because their calculations are based on exposure of 540 subjects. Their exposure estimate was taken directly from the applicant's Liver Safety Report, which was written prior to the cut-off date for the 120-day safety update; moreover, their estimate includes only patients with DS or LGS. (I believe the risk of hepatic toxicity would be comparable for patients with all seizure types, assuming that concomitant medications are similar.) In any case, they believe that the data exclude an incidence of Hy's law cases > 1 in 174 patients (0.6%) and likely exclude an incidence of acute liver failure due to DILI > 1 in 1740 patients (0.06%), assuming 'real world' patients are treated and monitored in a fashion similar to that in the development program.

These estimates all assume that if severe liver toxicity were to occur, it would occur in patients with antecedent ALT elevations. If that were not true, it would decrease the effectiveness of monitoring in mitigating the risk of severe hepatic toxicity.

Focusing on ALT elevations, the *attributable risk* (i.e., difference in frequency between cannabidiol and placebo) is 12% with respect to ALT elevations > 3X ULN, and 6% for elevations > 5X ULN. These risks, however, apply only to patients who are similar to those in the development program, and who are screened, dosed, monitored, and have the drug discontinued per the various study protocols. Labeling should recommend patient management that is similar to the management used in the development program, because such management is not overly burdensome, and because we hope that by intervening appropriately in patients with transaminase elevations, the risk of severe hepatic toxicity will be mitigated to the extent possible.

The attributable risk for somnolence/lethargy is 18% overall, of which 3% is severe. This side effect tends to be dose-related, but occurs fairly frequently even at the lower dose. Fatigue and lethargy seem closely related, and the attributable risk of fatigue is 7%.

For other central nervous system adverse reactions, i.e., irritability, agitation, sedation, disorientation, malaise, asthenia, ataxia, tremor, aggression, anger, drooling, hypersalivation, insomnia and other sleep disturbances, falls, dizziness, balance disorders, and gait disturbances, the attributable risk ranges from approximately 1% to 4%.

In the controlled trials, the attributable risks were 16% and 3% for decreased appetite and decreased weight, respectively. For diarrhea, the attributable risk was 9%.

The attributable risk of rash is approximately 8%.

It is clear that many patients will develop cannabidiol-induced adverse reactions; however, those actually observed in the development program would be expected to be detectable by patients and/or caregivers, self-limited, and reversible. There is no evidence from within the development program that the drug causes actual *harm*, i.e., irreversible and consequential damage, although it remains possible that there will be rare severe hepatotoxicity once the drug is marketed. In general, patients and caregivers will be able to make individual decisions with respect to the drug's value to *them* – based on the change in seizure frequency and the perceived adverse reactions.

9. Advisory Committee Meeting and Other External Consultations

A meeting of the Peripheral and Central Nervous System Drugs Advisory Committee was convened on April 19, 2018, and chaired by G. Caleb Alexander, MD. The Committee considered the efficacy and safety of cannabidiol for the treatment of seizures associated with LGS and DS in patients 2 years of age and older, and voted unanimously that the benefit-risk profile of cannabidiol is favorable for the proposed indication. They agreed that efficacy was well demonstrated and that the safety concerns could be managed with labeling, education, and monitoring.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

The applicant is proposing the following warnings and precautions for labeling:

5.1 Transaminase Elevations: Perform liver tests before EPIDIOLEX use and periodically during treatment as clinically indicated
5.2 Somnolence and Sedation: Monitor for somnolence or sedation, and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX
5.3 Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts
5.4 Withdrawal of Antiepileptic Drugs: EPIDIOLEX should be gradually withdrawn to minimize the risk of increased seizure frequency

I agree with the applicant's proposed list of warnings and precautions, including the warning/precaution for suicidal behavior and ideation, given that this is a class warning for AEDs, and given that there were two patients in the EAP in whom suicidal ideation/behavior was reported.

The table in Section 6 will need considerable revision in order to bring it into alignment with the findings in this review (Table 10). Various related adverse event terms will need to be grouped (e.g., rashes, transaminase elevations). In addition to the adverse reactions in the table, prescribers will need to be apprised of the potential for increases in serum creatinine, as well as small decreases in hemoglobin/hematocrit. The applicant proposed more detail than needed in describing the open-label studies, and much of this can be removed.

11. Risk Evaluation and Mitigation Strategies (REMS)

None recommended.

12. Postmarketing Requirements and Commitments

The following postmarketing requirements should be considered:

The renal consultants are suggesting a post-marketing study in healthy volunteers that includes measurement of GFR (b) (4), to help resolve the issue of whether cannabidiol inhibits the tubular secretion of creatinine or has a true effect on GFR.

The QT Interdisciplinary Review Team is recommending the conduct of an additional thorough QT study, with cannabidiol dosing in the fed state.

The applicant should perform a non-invasive study in cannabidiol users to determine whether long-term exposure (> 1-2 years) causes chronic liver disease/fibrosis.

The review team should work with the liver consultants to consider a postmarketing strategy to capture severe liver events.

13. Appendices

Figure 14: Outlier Analyses for PR, QRS, and QT Intervals

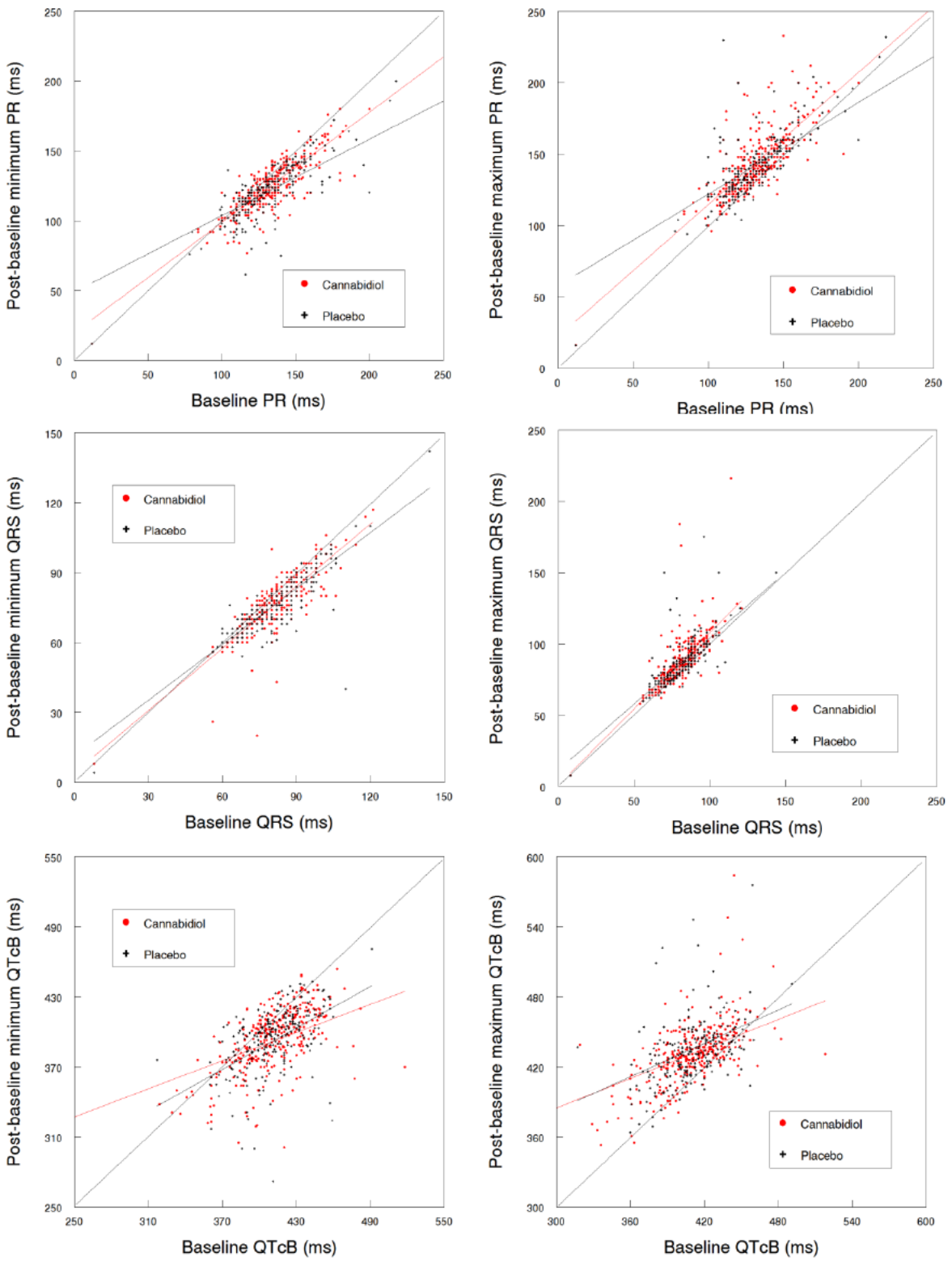


Table 17: Additions and Changes in Translation of Verbatim Terms to Preferred Terms

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	bdominal pain due to stone in ommon bile duct	Bile duct stone	add	abdominal pain
	brasion on nose	Skin erosion	change to	skin abrasion
	bscess post appendectomy	Postoperative abscess	add	appendectomy
	cute hypoxemic respiratory failure	Acute respiratory failure	add	hypoxia
	dmitted to hospital with abdo pain + omiting caused by constipation	Constipation	add	abdominal pain
	ltered mental status	Mental disorder	change to	mental status changes
	behavioral changes with inappropriate aughter and crying	Abnormal behaviour	add	inappropriate affect
	ilirubin in urine	Bilirubin urine	change to	bilirubinuria
	lack eye secondary to fall from a eizure	Convulsion	add	fall
	oil on stomach	Gastric ulcer	change to	furuncle
	ruise on bridge of nose from fall due o seizure	Fall	add	contusion
	ruised left shoulder secondary to fall	Fall	add	contusion
	ruises secondary to fall due to ncreased seizure	Convulsion	add	contusion
	ruises secondary to fall following left hemiparesis	Fall	add	contusion
	ruises sore left foot	Limb injury	change to	contusion
	ump on forehead from fall	Head injury	add	fall
	ump on head from fall	Head injury	add	fall
	ump/bruise on forehand from fall	Contusion	add	fall
	.diff(clostridium difficile bacteremia	Clostridium difficile infection	change to	bacteraemia
	hipped front tooth due to fall	Tooth fracture	add	fall
	hipped front tooth from fall	Tooth fracture	add	fall
	hipped tooth secondary to drop eizure	Atonic seizures	add	tooth fracture
	losed head injury caused by fall due to eizure	Convulsion	add	fall
	onfused	Disorientation	add	disorientation
	onfusion	Disorientation	add	confusional state
	onstipated stool fresh blood as passed motion	Constipation	add	haematochezia
	ramp on back of head 2 degree to fall	Head discomfort	add	fall
	reatine kinase increased due to muscle injury	Muscle injury	add	blood creatine phosphokinase increased
	ut foot	Limb injury	add	laceration
	death secondary to respiratory ailure/septic shock from human pneumovirus	Respiratory failure	add	sepsis
	declining food/fluid	Decreased appetite	add	fluid intake reduced
	decrease in attention	Attention deficit/hyperactivity disorder	change to	disturbance in attention
	decreased responsiveness	Altered state of consciousness	add	depressed level of consciousness

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	defiance	Abnormal behaviour	add	defiant behaviour
	defiant behavior	Abnormal behaviour	add	defiant behaviour
	defiant mood change	Mood altered	add	defiant behaviour
	dehydration secondary to small bowel obstruction	Small intestinal obstruction	add	dehydration
	diminished verbal output	Illiteracy	add	speech disorder
	eating less or nothing	Hypophagia	add	decreased appetite
	ecchymosis bilateral elbows status post fall (not seizure related)	Fall	add	ecchymosis
	elevated alt amino transferase asparate	Liver function test abnormal	add	alanine aminotransferase increased
	elevated alt,ast,ggt	Liver function test abnormal	add	alanine aminotransferase increased
	elevated ast amino transferase protein total	Liver function test abnormal	add	aspartate aminotransferase increased
	elevated lfts: alt 75 (ref: 0-24) ast 61 (ref: 0-40)	Liver function test abnormal	add	alanine aminotransferase increased
	elevated liver enzymes (alt & ast)	Liver function test abnormal	add	alanine aminotransferase increased
	episode of acute airay obstruction (o2 sat dropped to 50%)	Obstructive airways disorder	add	oxygen saturation decreased
	episode of acute airway obstruction (o2 sat dropped to 50%) er visit	Obstructive airways disorder	add	oxygen saturation decreased
	excessive sleepiness	Somnolence	add	hypersomnia
	excoriation to perianal area	Anal injury	add	excoriation
	face and chest scrapes (sz fall)	Convulsion	add	fall
	facial abrasions	Face injury	add	skin abrasion
	facial and arms injuries related to falls during seizures	Convulsion	add	fall
	fall 2nd to seizure	Convulsion	add	fall
	fall dermabrasion elbow above and knee	Fall	add	injury
	fall down wound on the sublip	Fall	add	injury
	fall due to myoclonic seizures	Myoclonic epilepsy	add	fall
	fall due to seizure	Convulsion	add	fall
	fall due to seizures	Convulsion	add	fall
	fall due to slip	Accident	add	fall
	fall during seizure	Convulsion	add	fall
	fall form second story window with closed head injury and right arm fracture	Fall	add	fracture
	fall from seizure	Fall	add	fall
	fall from seizure,bruise and swelling on right forehead and right eye	Fall	add	convulsion
	fall on the head during seizure	Fall	add	convulsion
	fall right hand (ligament damage)	Fall	add	injury
	fall secondary to seizure; right eyelid scraped;	Fall	add	convulsion
	fall with damage on the shoulder	Fall	add	injury
	fall with tooth fissure	Fall	add	injury

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	fall with trauma and injury	Fall	add	injury
	fall(sip drop seizure)	Atonic seizures	add	fall
	fall, trauma on left eye	Fall	add	injury
	fall/chin laceration	Fall	add	injury
	falls secondary to cerebral palsy	Cerebral palsy	add	fall
	falls secondary to scoliosis	Scoliosis	add	fall
	fall-swollen r middle finger	Balance disorder	add	injury
	fatigue due to high level of liver test	Liver function test abnormal	add	fatigue
	feeling of weakness chest	Chest discomfort	add	muscular weakness
	feeling unhappy	Mood altered	add	depressed mood
	fever due to ear infection	Ear infection	add	pyrexia
	fever due to pneumonia	Pneumonia	add	pyrexia
	fever/viral illness	Pyrexia	add	viral infection
	flu and fever	Influenza like illness	add	pyrexia
	flue/fever	Influenza	add	pyrexia
	forehead bruise 2 degree to fall (unk reason for fall)	Fall	add	head injury
	fractured l humerus (sz fall)	Convulsion	add	fall
	front tooth fracture and lower lip laceration (sz fall)	Convulsion	add	fall
	gastro-intestinal occasionally abdominal pain/once diarrhea	Abdominal pain	add	diarrhoea
	ggt 115 u/l	Gamma-glutamyltransferase	change to	gamma-glutamyltransferase increased
	head (forehead) laceration (patient had a seizure, fell and cut forehead)	Convulsion	add	injury
	head injury 2 degree fall from seizure	Convulsion	add	fall
	head injury/head eye laceration	Head injury	add	laceration
	head laceration (sz fall)	Convulsion	add	fall
	head laceration 2nd to fall/seizure	Convulsion	add	fall
	head laceration due to fall	Laceration	add	fall
	head laceration due to fall from seizure	Convulsion	add	fall
	head laceration from fall	Fall	add	laceration
	head laceration secondary from fall from seizure	Convulsion	add	fall
	head laceration secondary to fall from seizure	Convulsion	add	fall
	head's wound after epileptic seizure	Wound	add	convulsion
	hematoma on forehead front drop seizure	Atonic seizures	add	haematoma
	high level of valproic acid	Toxicity to various agents	change to	anticonvulsant drug level increased
	hip pain	Arthralgia	add	arthralgia
	hit head during seizure required 6 stitches over eye blow	Convulsion	add	head injury

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	hit head durning seizure and received staples	Convulsion	add	head injury
	hospital admission for headaches and lethargy following urti	Upper respiratory tract infection	add	headache
	hyperalert before bed (slight difficulty falling asleep)	Hypervigilance	add	psychomotor hyperactivity
	hypoxic resp failure	Respiratory failure	add	hypoxia
	increase in behavior defiance	Abnormal behaviour	add	defiant behaviour
	increased aggressive/self injury	Aggression	add	intentional self-injury
	increased body temperature 99.8 degree f	Body temperature increased	add	pyrexia
	increased clotting during menstrual cycle	Coagulation time prolonged	change to	menstrual disorder
	increased defiance	Oppositional defiant disorder	add	defiant behaviour
	increased oppositional behaviors	Abnormal behaviour	add	defiant behaviour
	increased sleepiness, g1	Convulsion	add	somnolence
	increasing cluster seizures	Seizure cluster	add	convulsion
	intermittent temperature increased 37.5	Body temperature increased	add	pyrexia
	laceration above eye	Eye penetration	change to	laceration
	laceration beside right eye	Eye injury	change to	laceration
	laceration on head d/t drop seizure	Laceration	add	convulsion
	laceration on head secondary to fall	Fall	add	laceration
	laceration to right eyebrow due to fall while playing	Fall	add	laceration
	laughing	Elevated mood	add	inappropriate affect
	laughing episodes	Conversion disorder	add	inappropriate affect
	laughing uncontrollably	Conversion disorder	add	inappropriate affect
	left knee abrasion	Joint injury	change to	skin abrasion
	lethargy and seizure increase due to urinary infection	Urinary tract infection	add	convulsion
	linear skin abrasions on back 2nd to fall with seizure	Convulsion	add	fall
	lip injury secondary to fall from a seizure	Convulsion	add	fall
	lip injury secondary to fall from seizure	Convulsion	add	fall
	lip laceration	Lip injury	add	laceration
	lip laceration & brueses on extremities from fall during seizure	Injury	add	convulsion
	lip laceration due to fall	Fall	add	laceration
	low grade fever 100.4f, after flu vaccine given	Vaccination complication	add	pyrexia
	low grade temp	Body temperature decreased	add	pyrexia
	low grade temperature	Body temperature decreased	change to	pyrexia
	mild head trauma from fall	Fall	add	head injury
	noisy breathing	Respiratory distress	delete	
	nose injury secondary to fall from seizure	Convulsion	add	face injury

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	obstinate behavior	Oppositional defiant disorder	add	defiant behaviour
	oppositional	Negativism	add	defiant behaviour
	oppositional behaviors	Oppositional defiant disorder	add	defiant behaviour
	pain after seizure	Pain	add	convulsion
	passing excessively urine	Urine output increased	add	pollakiuria
	platelet count 89 10 exp9/l	Platelet count	change to	platelet count decreased
	pneoumonia, fever cough	Pneumonia	add	cough
	prolonged laughing episode	Euphoric mood	add	inappropriate affect
	rash after starting new medication solodyn	Drug eruption	add	rash
	rash contact dermatitis	Dermatitis contact	add	rash
	red dots on cheeks and belly	Hypersensitivity	add	rash
	right clavicle open reduction and internal fixation	Internal fixation of fracture	add	clavicle fracture
	right occipital bump from fall	Fall	add	injury
	rt.arm bruises	Contusion	add	ecchymosis
	scalp lesion lossing hair	Skin injury	add	alopecia
	scrape bridge of nose	Scratch	change to	skin abrasion
	scrape inside right arm	Scratch	change to	skin abrasion
	scrape left shoulder	Scratch	change to	skin abrasion
	scrape right forehead	Scratch	change to	skin abrasion
	scraped knee	Scratch	change to	skin abrasion
	scratch of back 2 degree to fall	Fall	add	skin abrasion
	scratch on right hip	Scratch	change to	skin abrasion
	scratch right arm	Scratch	change to	skin abrasion
	scratch right hand (scrape)	Scratch	change to	skin abrasion
	scratches on dorsum of the hands	Scratch	change to	skin abrasion
	scratches on legs	Scratch	change to	skin abrasion
	seizure and fall with cut over left eye	Convulsion	add	laceration
	seizure causng bruise & cheek laceration	Convulsion	add	ecchymosis
	sepsis due to pneumonia	Pneumonia	add	sepsis
	severe sepsis due to right middle lobe pneumonia	Sepsis	add	pneumonia
	sickness	Malaise	delete	
	sinus problems	Sinusitis	change to	sinus disorder
	sirs with sepsis secondary to rsv bronchiolitis	Respiratory syncytial virus bronchiolitis	add	sepsis
	soreness in both legs 2nd to fall/seizure	Convulsion	add	fall
	split bottom lip 2 fall from a seizure	Convulsion	add	fall

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	sprained thumb secondary seizure fall	Convulsion	add	fall
	superficial scalp wound ((result of a fall during seizure activity)	Fall	add	skin laceration
	surgical repair of lip laceration due to fall	Fall	add	lip injury
	teeth fractures (sz fall)	Convulsion	add	fall
	tracheitis due to pseudomonas	Pseudomonas infection	add	tracheitis
	unspecified urticarial rash	Urticaria	add	rash
	unstable standing	Dysstasia	add	balance disorder
	upper respiratory tract infection, viral induced wheeze	Upper respiratory tract infection	add	viral upper respiratory tract infection
	viral bronchitis	Bronchitis	add	viral infection
	viral cold	Nasopharyngitis	add	viral infection
	vision loss	Blindness	change to	visual disturbance
	visual disturbance	Visual impairment	change to	visual disturbance
	walking pneumonia	Atypical pneumonia	change to	pneumonia
	wheezing-associated respiratory infection	Respiratory tract infection	add	wheezing
	worsening chest congestion and cough leading to acute respiratory distress	Acute respiratory distress syndrome	add	cough
	ety Update:			
	abdo pain/vomiting caused by constipation	Constipation	add	abdominal pain
	abdo pain/vomiting caused by constipation	Constipation	add	vomiting
	acute hypoxic respiratory failure	Respiratory failure	add	oxygen saturation decreased
	bilateral ear pain with bleeding after possible q tip trauma to ear drum	Tympanic membrane perforation	add	haemorrhage
	bruised hip from fall due to ataxia	Ataxia	add	contusion
	bruised hip from fall due to ataxia	Ataxia	add	fall
	bruised lip from fall due to ataxia	Ataxia	add	injury
	bruised upper torso from fall due to ataxia	Ataxia	add	contusion
	bruised upper torso from fall due to ataxia	Ataxia	add	fall
	bruised upper torso from fall due to ataxia	Ataxia	add	injury
	chipped tooth from fall due to ataxia	Ataxia	add	fall
	chipped tooth from fall due to ataxia	Ataxia	add	injury
	contusion/edema left eye	Eye contusion	add	eye oedema
	contusion/edema right eye	Eye oedema	add	eye contusion
	cut lip as result of fall during seizure	Convulsion	add	fall
	cut lip as result of fall during seizure	Convulsion	add	laceration
	decreased eating	Hypophagia	add	decreased appetite
	dehydration secondary to influenza	Influenza	add	dehydration
	drop seizure,hit eye when fallen,bruised right eye	Atonic seizures	add	fall
	drop seizure,hit eye when fallen,bruised right eye	Atonic seizures	add	contusion

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	drug toxicity symptoms-decreased balance and tired	Toxicity to various agents	add	fatigue
	drug toxicity symptoms-decreased balance and tired	Toxicity to various agents	add	balance disorder
	drug toxicity symptoms-intermittent vomiting, decreased balance, nystagmus, tired	Toxicity to various agents	add	fatigue
	drug toxicity symptoms-intermittent vomiting, decreased balance, nystagmus, tired	Toxicity to various agents	add	nystagmus
	drug toxicity symptoms-intermittent vomiting, decreased balance, nystagmus, tired	Toxicity to various agents	add	balance disorder
	drug toxicity symptoms-intermittent vomiting, decreased balance, nystagmus, tired	Toxicity to various agents	add	vomiting
	episodes of decreased responsiveness	Slow response to stimuli	add	depressed level of consciousness
	all secondary to seizure	Convulsion	add	fall
	all-cut tongue from a seizure	Convulsion	add	fall
	all-cut tongue from a seizure	Convulsion	add	laceration
	all-cut tongue from a seizure	Convulsion	add	injury
	ell down during a seizure	Convulsion	add	fall
	ell down stairs due to atonic seizure	Atonic seizures	add	fall
	ractures related to a fall during a seizure	Convulsion	add	fall
	ractures related to a fall during a seizure	Convulsion	add	fracture
	g-tube infection	Stoma site reaction	add	device related infection
	g-tube site infection	Stoma site reaction	add	device related infection
	ead injury secondary to fall (not seizure related)	Fall	add	head injury
	ead injury with occipital fracture	Skull fracture	add	head injury
	ead laceration from fall secondary to seizure	Convulsion	add	fall
	ead laceration from fall secondary to seizure	Convulsion	add	laceration
	yperthermia	Hyperthermia	add	pyrexia
	ncreased respiratory effort	Respiratory depth increased	add	dyspnoea
	rritability from increased seizure activity	Convulsion	add	irritability
	aceration lip	Lip injury	add	laceration
	aceration on tongue	Tongue injury	add	laceration
	aceration upper gum	Mouth injury	add	laceration
	eft parietal scalp hematoma due to fall rom seizure	Convulsion	add	haematoma
	eft parietal scalp hematoma due to fall rom seizure	Convulsion	add	fall
	eft parietal scalp hematoma due to fall rom seizure	Convulsion	add	head injury
	ower lip cut	Lip injury	add	laceration
	atient is not eating and drinking well.	Hypophagia	add	decreased appetite
	neumonia/ with pleural effusion	Pneumonia	add	pleural effusion
	ash in the neck, may not be caused by he medication but by new type of diapers.	Dermatitis diaper	add	rash
	espiratory distress due to pneumonia	Pneumonia	add	respiratory distress

Subject	Verbatim term	GW Preferred term	action	Added FDA Preferred Terms
(b) (6)	sleep pattern reversal	Sleep phase rhythm disturbance	add	sleep disorder
	sleeping poorly	Poor quality sleep	add	sleep disorder
	staphylococcus epidermidis bacteremia	Staphylococcal infection	add	bacteraemia
	subject fell down due to a drop seizure	Atonic seizures	add	fall
	uncontrollable behavior	Abnormal behaviour	add	oppositional defiant disorder
	uti: p. aeruginosa	Urinary tract infection	add	urinary tract infection pseudomonal
	worsening behavior problems	Abnormal behaviour	add	oppositional defiant disorder
	worsening disruptive behavior	Abnormal behaviour	add	oppositional defiant disorder

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/s/

ELLIS F UNGER
06/11/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS

Medical Officer Consult Review for Potential Drug Induced Liver Injury

NDA	210365
Sponsor	GW Research Ltd.
Drug	(b) (4) (cannabidiol) 100 mg/ml oral solution
Proposed Indication	Treatment of seizures associated with Lennox-Gastaut Syndrome and Dravet Syndrome
Consulting Division	Division of Neurology Products Stephanie Parncutt, MHA, Senior Regulatory Project Teresa Buracchio, MD, Team Leader Billy Dunn, MD, Division Director
Consult Due Date	3/28/2018
Date review Completed	4/29/2018
Clinical Reviewer	Lara Dimick-Santos, MD
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1 Introduction

NDA 210365 was submitted on October 27, 2017, for cannabidiol (CBD) for the treatment of seizures associated with Lennox-Gastaut Syndrome and Dravet Syndrome. During clinical development, a signal for drug-induced liver injury (DILI) was identified.

The Division of Neurology Products (DNP) requests assistance in the description of the liver findings in product labeling and recommendations regarding any further investigations that should be conducted in the post-approval setting.

CBD, the active ingredient of Cannabidiol Oral Solution (CBD-OS), is comprised of highly purified CBD; a naturally occurring component of Cannabis sativa L. (marijuana). In pivotal 14-week placebo-controlled trials, adjunctive CBD-OS was tested for the treatment of convulsive seizures associated with Dravet Syndrome (DS) in children (1 controlled trial), and drop seizures associated with Lennox-Gastaut Syndrome (LGS) in children and adults (2 controlled trials). In addition, other smaller clinical trials in other populations and an expanded access program that enrolled patients with uncontrolled seizures were conducted.

The review below summarizes the clinical trial data as related to the findings of CBD-induced aminotransferase elevations and concerns surrounding a potential signal for liver injury associated with this product.

2 Clinical Pharmacology

CBD rapidly appears in plasma with little or no lag time following oral administration of CBD-OS. Generally, there is slow attainment of maximum measured plasma concentration (Cmax), within 4-6 hours after a single dose, but at steady state, time to maximum plasma concentration (tmax) is around 3 hours. Food (a high-fat meal) significantly increases exposure to CBD (4- to 5-fold). CBD appears to reach steady state within 4 days of twice-daily dose administration. When CBD-OS is administered twice daily, the accumulation of CBD following multiple dosing for 7 days was approximately 3-fold based on the area under the concentration-time curve (AUC).

CBD has 2 major metabolites, 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD). A third metabolite, 6-hydroxy-cannabidiol (6-OH-CBD) is found at relatively low levels. CBD is primarily eliminated from systemic circulation through hepatic phase 1 metabolism by CYP2C19 and CYP3A4. The major route of excretion is the feces. Between 30–35% of the CBD dose is eliminated by the fecal route and a further 10–15% is excreted in the urine over 72 hours.

CBD and major metabolites follow a multi-phasic decline and model-based predictions suggest a long terminal elimination phase. Model predictions of the CBD terminal (elimination) half-life (t½) (following discontinuation of CBD-OS dosing) show a tendency for t½ to increase with duration of dosing. In healthy subjects, terminal t½ was 85 hours, in DS patients, t½ was 139 hours, and in LGS patients, t½ was 196 hours. The long elimination phase may indicate a depot effect from deep compartments, or may suggest there is time dependency (auto-inhibition) mediated by time-dependent inhibition (TDI) of CYP3A4.

Evaluation of the potential for CBD-OS to increase exposure to concomitant anti-epileptic drugs (AEDs), commonly administered to patients with DS or LGS, has led the sponsor to conclude that CBD-OS administration does not lead to any pharmacokinetically relevant increases in the systemic circulatory exposure for valproate, stiripentol, or clobazam. It should be noted that this conclusion by itself does not rule out potential drug-drug interactions that may occur due to intra-hepatic effects related to metabolism, apical secretion or mitochondrial functions.

3 Preclinical Findings

There were signals of liver injury with elevated aminotransferases in all nonclinical studies; however, there were no associated deaths. The liver was identified as a site of histopathological change (characterized by centrilobular hypertrophy) in rodents and dogs given CBD orally (as gavage) as CBD-OS, purified CBD, or CBD botanical drug substance (BDS), and this was associated with adaptive thyroid hypertrophy. Hepatic microsomal enzymes that are induced to metabolize the test material also increased clearance of thyroid hormones, resulting in thyroid stimulation and follicular cell hypertrophy. These findings were not adverse (i.e., there was an absence of inflammation and/or necrosis). At the end of the recovery period, there was a tendency towards reversal of treatment-related findings noted at the terminal kill, with reductions in incidence and severity levels of all such changes. Based on the data presented, the sponsor has concluded that there is an adequate margin of safety for CBD at a daily dose of 20 mg/kg/day in both juvenile and adult preclinical animal populations using multiple different models of seizures using mice and rats.

Reviewer Comments:
Based on a preliminary assessment by DNP, there appears to be efficacy in preventing seizures associated with these two debilitating and rare seizure disorders that typically present in pediatric age groups. Much of this review will draw primarily from clinical analyses presented in the Liver Safety Report (LSR) that was submitted by the sponsor and prepared in consultation for GW Research Ltd. by Dr. Paul Watkins, MD, who is a hepatologist with recognized expertise in the assessment of DILI.

4 Summary of Clinical Trials

Table 1: Overall Summary of Unique CBD-OS Exposures in the Clinical Development Program Included in the Liver Safety Report

Population Source	Number of unique CBD-OS exposures
Placebo-Controlled Trials in the Target Indications	
GWEP 1332 Part A (3 weeks)	27
Pool DS/LGS (Pivotal DS and LGS) (14 weeks) GWEP1332 Part B (DS), GWEP1414 (LGS), GWEP1423 (LGS)	296
Open-label Trial in the Target Indications	
GWEP1415 (includes patients who received placebo in previous controlled trials listed above).	217
Total Unique Exposures in Target Indications (Pool LT-DS/LGS)	**540**
Phase 1 Clinical Pharmacology Trials	
Pool H-SD (Healthy-Single Dose)	110
Pool H-MD (Healthy-Multiple Dose)	125
Pool PP1-SD (Special Patient Populations-Single Dose)	87
Total Unique Exposures in Clinical Pharmacology Trials	**322**
EAP (Expanded Access Program)	
Pool EAP patients with drug-resistant epilepsy enrolled in the EAP or other compassionate use programs (months to years)	**684**
Trials in Other Epilepsy Patient Populations	
GWEP1428 (DDI trial in patients with epilepsy)	**16**
GWEP1428 OLE	**4**
Trials in Other Exploratory Indications	
GWAP1241 (schizophrenia or related psychotic disorder) (6 weeks)	**43**
Total Unique Exposures to CBD-OS	**1609**
Total Unique Exposures to Multiple Doses of CBD-OS	**1412**

From Table 7.1 – sponsor LSR

Four placebo-controlled trials of CBD-OS have been completed in patients with DS or LGS and 1 placebo-controlled trial is ongoing in patients with DS (See Table 1). In addition, an open-label extension (OLE) trial is ongoing, which allowed patients who participated in the controlled trials to continue or begin treatment with CBD-OS. The NDA cutoff date for safety data from the OLE trial was November 3, 2016.

The LSR provides an evaluation of the liver safety data that have been acquired from the 540 patients with DS or LGS who were treated in the controlled trials in conjunction with findings in an OLE trial (See Table 1). The number of DS and LGS patients exposed to CBD-OS included: 478 (88.5%) exposed for over 12 weeks; 443 (82.0%) exposed for over 26 weeks; and 203 (37.6%) exposed for over 1 year at the time of the NDA data cutoff (November 3, 2016). In addition, liver safety data were acquired from CBD-OS trials conducted in subjects (treated under an Expanded Access Program) with epilepsy (n=20), schizophrenia or related psychotic disorder (n=43). In addition, healthy subjects were chronically administered twice-daily doses of CBD-OS (n=125). The LSR also summarizes the “real world” experience that was reported to the sponsor for

684 patients with DS, LGS, and a variety of severe epilepsy conditions who received chronic administration of CBD-OS in the Expanded Access Program (EAP) for compassionate use led by individual investigators.

A. Completed Placebo-controlled Trials

Pilot Trial - GWEP1332 Part A

A 3-week blinded pilot trial where patients with DS were randomized to adjunctive treatment with 5 mg/kg/day (n=10), 10 mg/kg/day (n=8), 20 mg/kg/day (n=9) CBD-OS or placebo (n=7). After 3 weeks on blinded study medication (BSM), patients were tapered by decreasing the BSM daily dose by 10% each day for 10 days. Following conclusion of the trial and result analysis, participating patients were offered the opportunity to enroll into an OLE trial (GWEP1415).

Pivotal Dravet Syndrome and Lennox-Gastaut Syndrome Trials

GWEP1332 Part B

A 14-week blinded trial where patients with DS were randomized to adjunctive treatment with 20 mg/kg/day CBD-OS (n=61) or placebo (n=59). Concomitant AEDs and doses were to remain constant during the treatment period. After 14 weeks on BSM, patients were eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415.

GWEP1414

A 14-week blinded trial where patients with LGS were randomized to adjunctive treatment with 10 mg/kg/day CBD-OS (n=67), 20 mg/kg/day CBD-OS (n=82) or placebo (n=76). Concomitant AEDs and doses were to remain constant during the treatment period. After 14 weeks on BSM, patients were eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415.

GWEP1423

A 14-week blinded trial where patients with LGS were randomized to adjunctive treatment with 20 mg/kg/day CBD-OS (n=86) or placebo (n=85). Concomitant AEDs and doses were to remain constant during the treatment period. After 14 weeks on BSM, patients were eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415.

Ongoing DS Placebo-controlled Trial - GWEP1424

An ongoing 14-week blinded trial where patients with DS are planned for randomization to adjunctive treatment with 10 mg/kg/day CBD-OS (n=62), 20 mg/kg/day CBD-OS (n=62) or placebo (n=62). Concomitant AEDs and doses are to remain constant during the treatment period. After 14 weeks on BSM, patients are eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415. Due to the blinded nature of ongoing trial GWEP1424, data for patients from this trial and any GWEP1424 patient who subsequently participated in trial GWEP1415 will not be presented in this LSR. GWEP1424 will not be mentioned in subsequent sections of the LSR.

B. Ongoing Open-label Extension Trial - GWEP1415

This is an extended duration trial that enrolled patients who had been transitioned from trials GWEP1332 Part B, GWEP1414, GWEP1423, and GWEP1332 Part A. Patients were to be titrated beginning with 2.5 mg/kg/day CBD-OS on Day 1 up to a dose of 20 mg/kg/day beginning on Day 11. Subsequently the CBD-OS dose could be lowered or titrated to up to 30 mg/kg/day based on investigator assessment. Likewise, AEDs and doses could be changed in OLE trial GWEP1415 based on investigator assessment. Trial GWEP1415 remains open. The data cutoff date for the current NDA was November 3, 2016. The GWEP1415 data for 136 patients from the blinded, ongoing trial GWEP1424 have not been integrated into the GWEP1415 data analyses. Thus, data from 494 patients who were originally evaluated in GWEP1332 Part B, GWEP1414, GWEP1423, and GWEP1332 Part A and received CBD-OS in GWEP1415 were available for analysis.

C. CBD-OS Dose Escalation, Maintenance, and Taper Regimens

Dosing was started at a low 2.5 mg/kg/day and tapered upward over an 11-14 days period to the target dose of 10 or 20 mg/kg/day. Subsequently, dosing was tapered slowly over 10 days when completing or discontinuing drug. If an unacceptable AE developed at any time during the titration period, dosing was to be suspended or amended, at the investigator's discretion, until the event resolved or the AE became well tolerated. If that dose became poorly tolerated, the investigator could temporarily or permanently reduce the dosage for the remainder of the maintenance period.

D. Inclusion/Exclusion Criteria Related to Liver

Based on the results of liver biochemical tests, a patient was not to receive treatment in a trial if one or more of the following exclusion criteria shown in Table 2 below were met. It should be noted that, in recognition of the range of background laboratory abnormalities inherent in the DS and LGS populations with uncontrolled seizures, the liver test-related exclusion criteria were quite liberal.

Table 2: Liver Test-Related Exclusion Criteria for Placebo-Controlled Trials and the OLE Trial in Patients with DS and LGS

Trial Number	Exclusion Criteria
GWEP1332	ALT > 5 ×ULN and bilirubin > 2×ULN ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5.
GWEP1414 GWEP1415 GWEP1423	ALT or AST > 5 × ULN. ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5). ALT or AST > 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Source: Sponsor's Table 8.6-1 LSR: Protocols for GWEP1332, GWEP1414, GWEP1423, GWEP1415

E. Monitoring during Clinical Trials

The monitoring of liver tests in clinical trials appeared to be sufficiently frequent and thorough to characterize the CBD-OS risk for producing acute DILI. In the DS and LGS placebo-controlled trials, 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. For patients who subsequently entered the long-term OLE trial, liver tests were again acquired at 2 weeks following initiation of dosing, then at 4 weeks and 12 weeks and subsequently at 12 week intervals (See Table 3).

Table 3: Timing of Planned Liver Test Acquisition in Placebo- Controlled DS and LGS Trials and Open-label Extension Trial

	Planned Dosing Day[a] for Liver Test Acquisition[b]										
Trial Number	8	15	22	29	57	85	99	109[c]	169	253	337
Pilot											
GWEP1332 Part A	X		X								
Pivotal											
GWEP1332 Part B		X		X	X		X	X			
GWEP1414		X		X	X		X	X			
	Planned Dosing Day[a] for Liver Test Acquisition[b]										
Trial Number	8	15	22	29	57	85	99	109[c]	169	253	337
GWEP1423		X		X	X		X	X			
Open-label Extension											
GWEP1415		X		X		X			X	X	X

Source: Protocols for GWEP1332, GWEP1414, GWEP1423, GWEP1415.

[a] Windows used for summary statistical analyses of controlled trials. Day 8 (2-11); Day 15 (12-18); Day 22 (19-25); Day 29 (26-36); Day 57 (37-81); Day 99 (82-103).

[b] CBD-OS doses of 10 mg/kg/day and 20 mg/kg/day reached on Dosing Days 7 and 11, respectively.

[c] Follow-up off BSM

F. Withdrawal Criteria

The protocol-specified withdrawal criteria in each trial, including the EAP, included the following:

- ALT or AST > 3 × ULN with (or the appearance of) fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%.
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for or more than 2 weeks.
- ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5.

Following completion of the pilot trial GWEP1332 Part A, the following directions were agreed with the FDA and added to CBD-OS protocols:

- If a patient met one of the above criteria, the investigator was to arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, bilirubin and alkaline phosphatase (ALP), detailed history, and physical examination. Patients were to be followed in this way until all abnormalities had normalized (in the investigator's opinion) or returned to the baseline state. If the patient could not return to the investigational site, repeat assessments could be performed at a local laboratory (and the results were then to be sent to the sponsor by the investigator).
- Elevations in ALT or AST > 3 × ULN or bilirubin > 2 × ULN alone, i.e., when not concomitant, were not grounds for withdrawal but were to be followed up, as above, within 72 hours of notice of abnormal results. As will be described below, treatment with CBD was either paused or discontinued in some study subjects because of treatment-related elevations of liver test results that met the criteria described above.

G. Pooling Strategy

The 14-week placebo-controlled trials in patients with DS (GWEP1332 Part B) or LGS (GWEP1414 and GWEP1423) were pooled for the liver safety analyses (Pool DS/LGS, N=296). Due to its short duration, the 3-week pilot placebo-controlled trial in DS (GWEP1332 Part A) was analyzed separately.

Pool LT-DS/LGS (N=540) included all DS and LGS patients exposed to CBD-OS in the preceding 3 trials listed above (Pool DS/LGS, in GWEP1332 Part A, and/or during participation in the OLE trial GWEP1415). Thus, a patient (taking CBD-OS) with a liver test elevation or AE observed in a placebo-controlled trial would also have that event represented in analyses for Pool LT-DS/LGS.

H. Demographics

In Pool DS/LGS, the mean age of patients in the 3 treatment groups ranged from 13.8–14.7 years. The 6–11 years and 12–17 years age brackets accounted for nearly 60% of patients in the pool. Age, sex, race, body weight, BMI and region distribution were similar across CBD-OS 10 mg/kg/day, CBD-OS 20 mg/kg/day, and placebo groups.

Patient demographics for Pool LT-DS/LGS show that overall, the mean age of patients was 13.8 years (range: 2.3–48.0 years of age) with the greatest proportion of patients within the 6–11 years age bracket. There were similar proportions of males and females.

Liver Test Results at Baseline

Over 20% of the CBD-OS and placebo patients had an ALT value > ULN and 11 patients across groups had a baseline ALT value > 2 × ULN. The frequency of elevated (> ULN) baseline ALP values ranged from 16.4% to 17.9% across the 3 treatment groups. A lower but consistent frequency of elevation (> ULN) in AST was also observed at the baseline assessment across the treatment groups and ranged from 6.4% to 11.8%. All enrolled patients had normal total bilirubin levels at baseline.

INR, a marker for liver synthetic function, was elevated to > ULN at baseline in 4.5% of the patients randomized to 10 mg/kg/day, 3.2% of the patients randomized to CBD-OS 20 mg/kg/day, and 5.0% of patients randomized to placebo. The GGT results were quite variable. Across the 3 treatment groups, the frequency of a baseline GGT value > 3 × ULN ranged from 7.4% to 10.5% and across groups.

I. Disposition

Overall, 3.0%, 14.4%, and 3.6% of the patients in the CBD-OS 10 mg/kg/day, CBD-OS 20 mg/kg/day, and placebo groups, respectively, discontinued prematurely from their study. In the same respective groups, a total of 1.5%, 8.7%, and 1.4% were discontinued due to an AE.

A higher rate of discontinuation in the higher 20 mg/kg/day dose is notable.

J. Exposure

Table 4: Exposure in Pool LT-DS/LGS

Parameter	Statistics	All CBD-OS (N=540)
Safety Analysis Data Set	**n (%)**	**540 (100.0)**
GWEP1332A	n (%)	31 (5.7)
GWEP1332B	n (%)	117 (21.7)
GWEP1414	n (%)	222 (41.1)
GWEP1423	n (%)	170 (31.5)
Total number days:		
On Treatment[a] n (%)	N (missing)	540 (0)
	Mean ± SD	304.4 ± 136.0
	Median	327.5
	Q1 ; Q3	234.0 ; 396.0
	Min ; Max	7.0 ; 555.0
On Treatment[a] n (%)	1–14 days	3 (0.6)
	15–28 days	15 (2.8)
	29–42 days	23 (4.3)
	43–84 days	21 (3.9)
	85–182 days	35 (6.5)
	183–364 days	240 (44.4)
	365–729 days	203 (37.6)
	≥ 730 days	0

Source: Sponsor Table 10.4.2-1 LSR

a - Total number of days on treatment includes the titration and taper periods, up to last dose date. Compliance with dosing is based on completion of a daily paper diary. If the diary was not fully completed then this may result in inaccurate compliance.

Table 5: Common (≥ 10% in All CBD-OS group) Concomitant AEDs in Pivotal Trials (Pool DS/LGS)

Type of AED	CBD-OS 10 mg/kg/day (N=67) N (%)	CBD-OS 20 mg/kg/day (N=229) N (%)	All CBD-OS (N=296) N (%)	Placebo (N=220) N (%)
Clobazam	35 (52.2)	119 (52.0)	154 (52.0)	118 (53.6)
Valproic Acid	23 (34.3)	105 (45.9)	128 (43.2)	97 (44.1)
Levetiracetam	19 (28.4)	67 (29.3)	86 (29.1)	74 (33.6)
Lamotrigine	19 (28.4)	57 (24.9)	76 (25.7)	58 (26.4)
Rufinamide	18 (26.9)	55 (24.0)	43 (19.5)	43 (19.5)
Topiramate	13 (19.4)	38 (16.6)	51 (17.2)	39 (17.7)
Clonazepam	10 (14.9)	29 (12.7)	39 (13.2)	30 (13.6)
Zonisamide	8 (11.9)	31 (13.5)	39 (13.2)	26 (11.8)
Lacosamide	9 (13.4)	22 (9.6)	31 (10.5)	22 (10.0)
Stiripentol	0	30 (13.1)	21 (9.5)	21 (9.5)

Note: Safety analysis set.
Note: Patients from study GWEP1332 Part A are excluded.
Percentages based on column header N. Dictionary Coding: WHO Drug version June 2014 Source: LSR Table DSLGS.3.1.2.

5 Analyses and Results

A. Controlled Trial Results

Controlled trial results showed that CBD-OS was associated with dose-related ALT elevations in a subset of patients who manifested less pronounced AST elevations. Evaluation of the liver test results and adverse event (AE) reports from the 540 patients with DS or LGS who were administered chronic CBD-OS did not identify any patient as meeting published consensus criteria for severe drug-induced liver injury (DILI) (i.e., ALT > 3 x ULN and TB > 2x ULN). None of the clinical trial patients were identified as meeting the DILI laboratory criteria for Hy's Law (ALT ≥ 3 × ULN and bilirubin > 2 × ULN).

Among the 540 CBD-OS patients, there were 50 (9.3%) who had a treatment-emergent (TE) ALT > 3 and < 5 × ULN and 37 (6.9 %) who met the DILI biochemical criterion of TE ALT ≥ 5 × ULN. These ALT elevations were generally accompanied by normal ALP (a marker of bile duct injury) and bilirubin values. For the 37 patients with TE 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=2) mg/kg/day. A total of 32 of the 37 (86.5%) CBD-OS patients with TE ALT ≥ 5 ULN were taking concomitant valproate., which is also associated with hepatotoxicity. Eighteen of the patients with TE ALT ≥ 5 × ULN were discontinued from treatment, including 16 who had a TE ALT > 8 × ULN, one of the prespecified withdrawal criteria included in each trial protocol.

Table 6 shows that for the CBD-OS 20 mg/kg/day group, TE ALT > 3 × ULN (16.3%) was about twice as common as AST > 3 × ULN (7.9%). This difference suggests that the origin of the ALT elevation is the liver and not other organ sources. Amino transferase levels (either ALT or AST, AT) > 3 × ULN were observed at only a slightly higher rate (18.1%) than ALT alone (16.3%). For this reason, subsequent analyses in text will focus on ALT; however, analysis results will also be provided for AST and AT in supporting tables.

Table 6: Frequency of TE Liver Test Elevations (Observed Peak Levels) Any Time Post-baseline in Pool DS/LGS

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

AT = ALT or AST. 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.
Source: LSR Table DSLGS.5.1.4.

The frequency of ALT elevations was dose-related. The frequencies of ALT > 3 × ULN and > 5 × ULN in the placebo group (both 0.9%) were only slightly lower than those in the CBD 10 mg/kg/day group (1.5% for each). The CBD-OS 20 mg/kg/day group exhibited higher frequencies, as 16.3% of these patients had TE ALT values > 3 × ULN and 7.4% had TE ALT values > 5 × ULN.

There was a similar frequency of TE ALP > 1.5 × ULN and ALP > 2 × ULN across all 3 treatment groups (Table 7).

Table 7: Frequency of Treatment-Emergent Liver Test Elevations (Observed Peak) Any Time Post-Baseline in Pool DS/LGS

Liver Test	Multiple of ULN	CBD-OS 10 mg/kg/day (N=67) *n / N* (%)	CBD-OS 20 mg/kg/day (N=229) *n / N* (%)	Placebo (N=220) *n / N* (%)
ALP	> ULN	5 / 56 (8.9)	13 / 188 (6.9)	17 / 181 (9.4)
	> 1.5 × ULN	1 / 64 (1.6)	8 / 222 (3.6)	5 / 212 (2.4)
	> 2 × ULN	1 / 65 (1.5)	3 / 227 (1.3)	5 / 219 (2.3)
	> 3 × ULN	0 / 67	0 / 229	3 / 220 (1.4)

Source: Sponsor Table 11.4-2 LSR - Table LSR DSLGS.5.1.2, Table LSR DSLGS.5.1.21.

Table 8: Frequency of Treatment-Emergent Liver Test Elevations (Observed Peak) Any Time Post-Baseline During Exposure to CBD-OS (Pool LT-DS/LGS)

Liver Test	Multiple of ULN	All CBD-OS (N=540) *n / N* (%)
ALT (U/L)	> 1×	223 / 426 (52.3)
	> 2×	134 / 534 (25.1)
	> 3×	84 / 538 (15.6)
	> 5×	33 / 540 (6.1)
	> 8×	15 / 540 (2.8)
	> 10×	10 / 540 (1.9)
	> 20 ×	2 / 540 (0.4)
AST (U/L)	> 1×	191 / 488 (39.1)
	> 2×	93 / 537 (17.3)
	> 3×	42 / 539 (7.8)
	> 5×	16 / 540 (3.0)
	> 8×	7 / 540 (1.3)
	> 10×	2 / 540 (0.4)
	> 20 ×	0 / 540

Source: sponsor Table LSR Table 11.5-1 LSR - LTDSLGS.5.2.4.

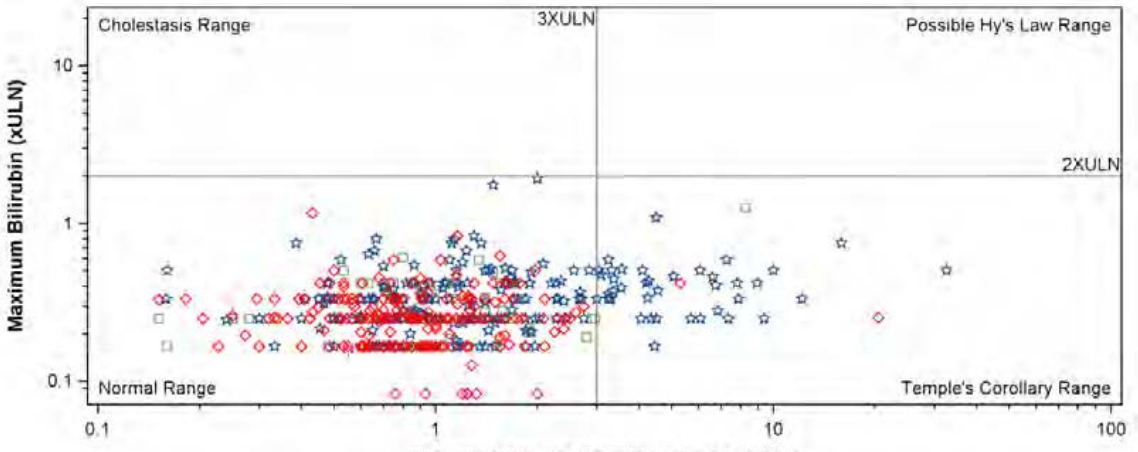
B. eDISH Plots

Figure 1 below

In the eDISH plot, no CBD-OS or placebo patient was charted in the upper right quadrant, thus demonstrating the absence of any potential TE Hy's Law case, defined as one with peak ALT levels > 3 × ULN in conjunction with peak bilirubin levels >2 × ULN. Likewise, the absence of points in the upper left quadrant showed the absence of cases with potential TE severe cholestasis.

As illustrated in the lower left quadrant, approximately 91% of the CBD-OS and placebo patients combined did not exhibit a TE ALT value > 3 × ULN during treatment. Points in the lower right quadrant represent the 0.9% of placebo patients, the 1.5% of CBD-OS 10 mg/kg/day patients, and the 17.0% of CBD-OS 20 mg/kg/day patients who had a TE maximum ALT value > 3 × ULN.

Figure 1: eDISH Plot of Maximum Treatment-Emergent ALT and Bilirubin Values for Individual Patients During Treatment in Pool DS/LGS (Pivotal DS and LGS)

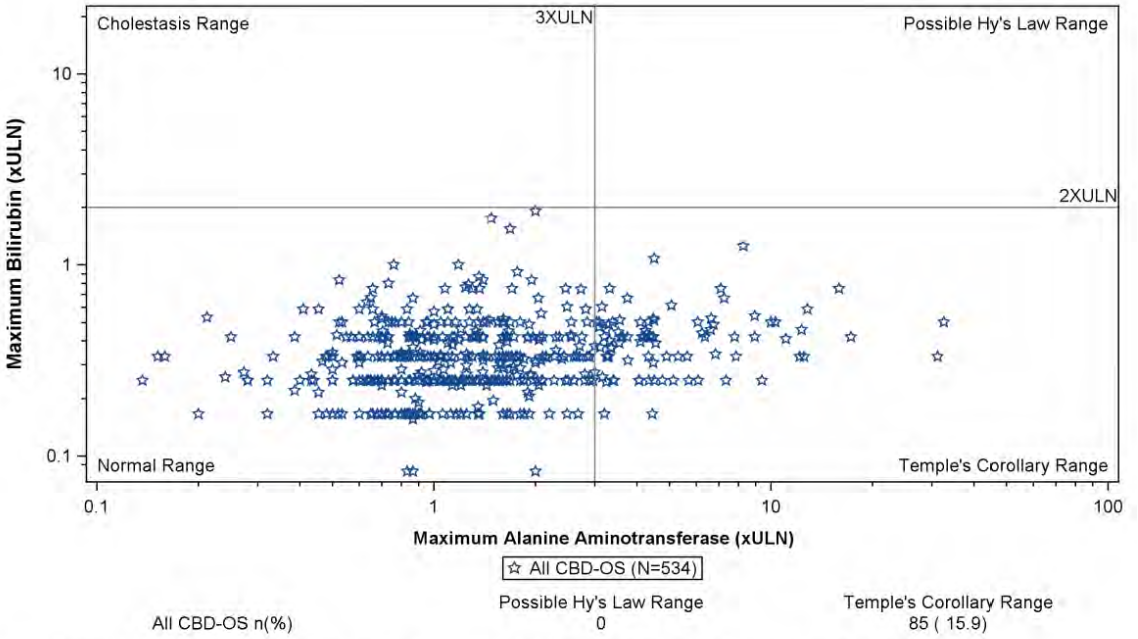


	Possible Hy's Law Range	Temple's Corollary Range
CBD-OS 10 mg/kg/day n(%)	0	1 (1.5)
CBD-OS 20 mg/kg/day n(%)	0	38 (17.0)
Placebo n(%)	0	2 (0.9)

Normal patients are on the lower left quadrant, while possible Hy's Law cases appear on the right upper quadrant.
Data from the studies 1332 Part B, 1414 and 1423 are included.

A similar picture is seen with the LT safety data where no Hy's law cases were observed; however, ALT elevations were frequent.

Figure 2: eDISH Plot of Maximum Treatment-Emergent ALT and Bilirubin Values for Individual Patients During CBD-OS Treatment in Pool LT-DS/LGS



	Possible Hy's Law Range	Temple's Corollary Range
All CBD-OS n(%)	0	85 (15.9)

Normal patients are on the lower left quadrant, while possible Hy's Law cases appear on the right upper quadrant.

Source: sponsor Figure 11.3-3 LSR:

A total of 36 of the 37 patients with TE ALT ≥ 5 × ULN had an R value[1] of ≥ 5, indicating a hepatocellular pattern of DILI. One patient had an R value of 2, suggesting a cholestatic pattern of DILI.

Reviewer Comments:
On review of the 30 narratives in the LSR appendix where transaminases were elevated, several cases are noted where the total bilirubin (TB) also increased from baseline in conjunction with the transaminase elevations (cases S195, V182, P033). None of the changes in TB resulted in the TB being above the ULN, but several of the patients with changes from baseline in TB were also noted to have symptoms consistent with DILI (cases V182, Q072, P033). It is noted that in the expanded access program (EAP), most patients did not have TB values measured. It would be prudent to include in the prescriber labeling, instructions to discontinue drug for development of symptoms (e.g., abdominal pain, anorexia, nausea or vomiting, fatigue) and for significant increases in TB from baseline, even if the TB does not rise above ULN.

Note that secondary to the relatively limited treatment periods of the controlled clinical trials (<14 weeks), little data are available to rule out whether continuous CBD exposure with or without mild elevations of aminotransferase levels over a longer term period is associated with a potential to cause chronic liver injury, or the slow development of liver fibrosis. While some patients have been treated for up to 2 years in open-label or uncontrolled studies, no screening for development of chronic liver injury has apparently been performed (e.g., histopathology or elastography).

It is also not clear from the available data if patients would adapt if they were kept on the drug after developing acute aminotransferase elevations, as study subjects, based on protocol stop rules, were supposed to be discontinued from treatment when ALT or AST were > 8 x ULN.

By-and-large we agree with the causality assessments provided in the LSR.

C. Time to Onset of TE Liver Test Elevations

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 (Pool controlled studies), 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. In the 20mg/kg/day group, after 30 and 60 days of treatment with CBD-OS, 8 of 14

[1] The R-value is defined as serum ALT/upper limit of normal (ULN) divided by serum ALP/ULN. By common convention, R≥5 is labeled as hepatocellular DILI, R<2 is labeled as cholestatic DILI, and 2<R<5 is labeled as "mixed" DILI.

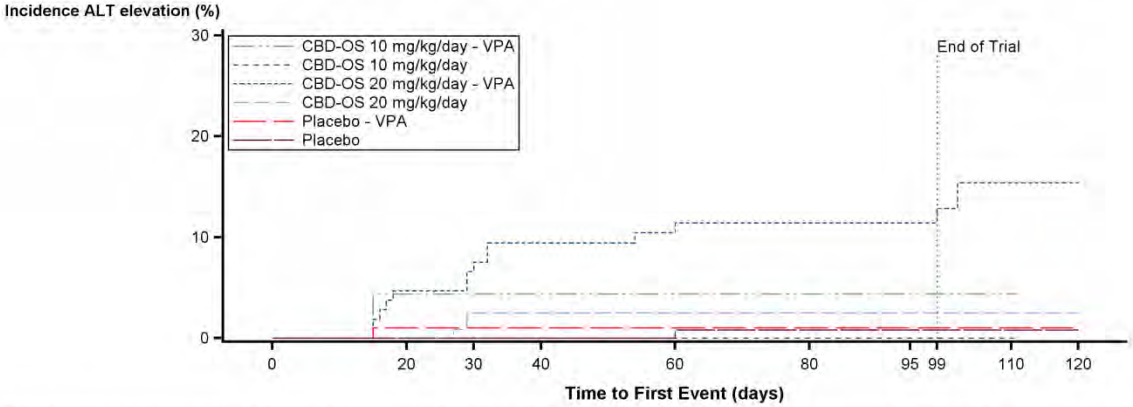
(57.1%) and 12 of 14 (85.7%) elevations of ALT > 5 × ULN had been observed, respectively. At the same respective times, 21 of 31 (67.7%) and 27 of 31 (87.1%) elevations of ALT > 3 × ULN had been observed. The single observations of ALT elevation to > 3 and > 5 × ULN in the CBD-OS 10 mg/kg/day group and placebo group occurred during the first 30 days of treatment. Both patients were taking concomitant valproate.

In the Pool LT-DS/LGS, the pattern of the Kaplan-Meier plots shows that the majority of ALT elevations occurred during the first 60 days of treatment with CBD-OS in patients regardless of their use of concomitant valproate.

For CBD-OS patients not taking concomitant valproate, all 5 of the elevations of TE ALT > 5 × ULN (100%) were observed in less than 100 days (~3 months) of treatment. For the same group, 12 of the 13 elevations of TE ALT > 3 × ULN (92%) were observed in less than 100 days (~3 months) of treatment.

For CBD-OS patients taking concomitant valproate, 24 of the 28 elevations (85.7%) of TE ALT > 5 × ULN were observed in less than the first 100 days (~3 months) of treatment, and the remaining 4 elevations were observed prior to the first 200 days (~6 months) of treatment. For the same group, 49 of the 71 elevations (69.0%) of TE ALT > 3 × ULN were observed in less than the first 100 days (~3 months) of treatment, and 61 of the 71 elevations (86%) were observed during the first 200 days (~6 months) of treatment.

Figure 3: Kaplan-Meier Plot of Incidence of ALT Elevations to > 5 × ULN for Patients Taking or Not Taking Concomitant Valproate in Pool DS/LGS (Pivotal DS and LGS)



Patients without events/censoring before or at the corresponding timepoint (Patients with events on or before the corresponding timepoint)

CBD-OS 10 mg/kg/day - VPA	23(0)	22(1)	22(1)	22(1)	22(1)	22(1)	22(1)	1(1)	0(1)
CBD-OS 10 mg/kg/day	44(0)	44(0)	44(0)	44(0)	44(0)	44(0)	44(0)	1(0)	0(0)
CBD-OS 20 mg/kg/day - VPA	106(0)	101(5)	97(8)	93(10)	87(12)	81(12)	77(12)	14(14)	0(14)
CBD-OS 20 mg/kg/day	123(0)	122(0)	116(3)	116(3)	113(3)	111(3)	107(3)	7(3)	0(3)
Placebo - VPA	97(0)	96(1)	96(1)	96(1)	95(1)	95(1)	94(1)	5(1)	0(1)
Placebo	123(0)	123(0)	123(0)	123(0)	120(1)	120(1)	116(1)	8(1)	0(1)

Valproate=VPA
Subjects from study GWEP1332 Part A are excluded.
Censoring is done at last known date or Day 120, whichever comes first.

Source: LSR Figure DSLGS.7.1.11.

D. DILI Defined as TE ALT ≥ 5 × ULN

Controlled Trials (Pool DS/LGS and GWEP1332 Part A):

TE ALT ≥ 5 × ULN was observed in a total of 23 patients who (at the time of their peak ALT elevation) were taking CBD-OS [5 mg/kg/day (n=1); 10 mg/kg/day (n=1); 20 mg/kg/day (n=19] or placebo (n=2) in the controlled trials. It should be noted that 18 of the 21 CBD-OS patients and 1 of the 2 placebo patients were taking valproate concomitantly.

The time to onset of the ALT elevation was similar across patients. Seventeen of the 21 patients (80.9%) taking CBD-OS had peak ALT values ≥ 5 × ULN first observed ≤ 36 days after the initiation of treatment. Four patients (all taking concomitant valproate) had peak ALT observed at Day 54, Day 77, Day 99, and Day 102. The 2 placebo elevations occurred on Day 15 and Day 60.

The remaining CBD-OS patients continued to receive CBD-OS for the duration of the trials, including 2 patients with TE ALT values = 15.9 × ULN and 10.0 × ULN. Thirteen of the 21 CBD-OS patients with TE ALT ≥ 5 × ULN continued to take CBD-OS after the elevation; 9 entered the OLE trial after the conclusion of their controlled trial.

Although rising above baseline levels in a few cases, the bilirubin value remained in the normal range for 20 of the 21 CBD-OS patients and was 1.3 × ULN in 1 patient. The ALP value remained within the normal range for 17 of the 21 CBD-OS patients, and was 1.1, 1.2, 1.3, and 2.9 × ULN in the remaining four patients.

In the LSR, Dr. Watkins conducted un-blinded reviews of individual narratives for each of the 37 CBD-OS patients with TE ALT ≥ 5 × ULN. He assessed that CBD-OS probably caused or contributed to the elevations in 35 of the 37 patients (94.6%) and that this was possible for the remaining 2 (5.4%). Dr. Watkins noted that he would also have assessed one of the placebo elevations as probable and the other as possible had the patients been taking CBD-OS. The probable assessment represents a 50-100% likelihood of causation and possibly represents a 25-49% likelihood. By-and-large, we agree with the conclusions of this causality analysis.

E. Recovery Times

Estimated recovery times were calculated for the period from an ALT elevation ≥ 5 × ULN to a value of 2.9 × ULN. Notably, the endpoints of ALT reversal do not represent full resolution of the abnormalities to a normal range. When defined in the manner, the estimated recovery times were commonly less than 2 weeks for patients who had treatment with CBD-OS abruptly discontinued, tapered then discontinued, or CBD-OS continued at the same or lower daily dose.

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

The occurrence of DILI (defined as TE ALT ≥ 5 × ULN) was also observed in multiple-dose phase 1 studies in healthy subjects and phase 2 studies in adult epilepsy patients administered CBD-OS for several weeks. The frequency and pattern of ALT elevations in these trials was similar to those observed in the DS and LGS trials. There was also a relevant 6-week phase 2 pilot trial of adjunctive CBD-OS for schizophrenia or related psychotic disorder in which initiation and continuation of CBD-OS 500 mg twice daily (~11.9 mg/kg/day in 43 adults 19-64 years of age) did not result in any observations of TE ALT ≥ 5 × ULN. This may be secondary to the lower dose and duration.

Recovery of treatment-emergent ALT ≥ 5 × ULN without stopping CBD-OS: Pooled Controlled Studies:

37/540 patients (6.9%) in Pool LT-DS/LGS[2] had treatment-emergent (TE) ALT ≥ 5 × ULN. Of the 37 patients in Pool LT-DS/LGS who had TE ALT ≥ 5 × ULN during treatment with CBD-OS, 17 patients (45.9%) recovered from this ALT elevation without, or prior to, stopping CBD-OS. Of these 17 patients:

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

F. Expanded Access Program:

30/647 patients (4.6%) in Pool Expanded Access Program (EAP) had TE ALT ≥ 5 × ULN. Of the 30 patients in Pool EAP who had TE ALT ≥ 5 × ULN during treatment with CBD-OS, 24 patients (80%) recovered from this ALT elevation without, or prior to, stopping CBD-OS. Of the 24 patients:

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

It is notable that protocol CBD stop rules were inconsistently adhered to by practitioners managing these patients. Several patients had reduction in dose of other concomitant medications, especially valproate.

Thirteen patients with ALT > 8 × ULN recovered without stopping CBD-OS, including patients with peak ALT elevations up to 40.3 × ULN (b) (4) and 21.1 × ULN (b) (4).

[2] Pool LT-DS/LGS included all DS and LGS patients exposed to CBD-OS in trials GWEP1332A and B, GWEP1414 and GWEP1423, and/or during participation in the OLE trial GWEP1415. Thus, a patient (taking CBD-OS) with a liver test elevation or AE observed in a placebo-controlled trial would also have that event represented in analyses for Pool LT-DS/LGS.

One patient (b) (6) in study GWEP1428 (phase 2 drug-drug interaction trial with clobazam) experienced a peak ALT elevation to 5.1 × ULN on Day 32 of CBD-OS dosing. This 36-year-old male patient with epilepsy was on 20 mg/kg/day at the time of the peak ALT elevation, as well as concomitant valproate. The day after the peak ALT elevation, the patient completed the double-blind phase of study GWEP1428, enrolled in the GWEP1428 OLE and commenced open-label CBD-OS, titrating up to 20 mg/kg/day over an 11-day period. Nine days after the peak ALT elevation, the patient's ALT returned to < 3 × ULN. On that same day, the patient withdrew from the GWEP1428 OLE.

Reviewer Comments:
While CBD clinical trial protocols stipulate that CBD should be discontinued if ALT levels rise above 8 x ULN, the above-mentioned patients were continued on CBD and apparently showed improvement of ALT levels (as defined above). However, these data are sparse and more data should be obtained to clarify if reversal of injury acceleration or full adaptation would occur in most or all patients with continued treatment. These data could be obtained in an open-label trial with very close monitoring of patients who developed ALT elevations on treatment, with drug discontinuation rules for patients who developed significant elevations in bilirubin or clinical symptoms of DILI.

In an uncontrolled investigator-initiated study of 14 patients with Parkinson's disease, 2 patients (aged 69 and 70) developed evidence of cholestasis (ALP > 2 × ULN) and one also had elevated transaminases. An additional 2 patients (both aged 68) had elevations of ALP (< 2 × ULN) without elevated transaminases. The patients were exposed to doses of CBD-OS in the range of 20 to 25 mg/kg/day for 25 to 30 days. All elevations resolved.

G. Re-challenge experience:

Eleven patients with uncontrolled epilepsy were re-challenged with CBD-OS after experiencing a liver enzyme elevation (TE ALT or AST > 3 × ULN) which resulted in CBD-OS discontinuation for more than 2 days. Of these:

- 4 patients experienced a recurrence of ALT or ALT > 3 × ULN – in 3 patients, the recurrence was observed within 29 days of restarting CBD-OS. In the 4 patients with a recurrence of transaminase elevations after CBD-OS re-challenge, the nature and characteristics of the recurrence was not significantly different from the initial elevations in terms of magnitude, time to onset, or the continued absence of functional impairment. None of the 4 patients with elevated transaminases after re-challenge were Hy's law cases.
- 7 did not experience a recurrence of ALT or ALT > 3 × ULN

H. Recovery from elevated ALT while still taking CBD

As noted in Section F, 37/540 patients (6.9%) in Pool LT-DS/LGS had TE ALT ≥ 5 × ULN. Examination of these 37 patients shows that 17 patients (45.9%)

recovered from this ALT elevation without, or prior to, stopping CBD-OS. Of these 17 patients:

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

Valproate was the most common concomitant medication where dose reduction occurred after observation of ALT ≥ 5 × ULN. A total of 6 patients had their valproate dose reduced after such an ALT elevation.

There were 4 patients who recovered from ALT > 8 × ULN without stopping CBD-OS. Of note, patient (b) (6) had ALT 15.9 × ULN on day 54; however, the patient recovered from the ALT elevation while continuing in study GWEP1423, and later enrolled into the OLE.

I. Intrinsic/Extrinsic Factors

- The frequency of ALT elevations when expressed as multiples of baseline values were similar for males and females (> 3 x baseline males (24.8%) and females (20.0%) in the CBD-OS 20 mg/kg/day group).
- Age did not appear to be a significant contributing risk factor; however, few children in the 2-5 year age range were included.
- Comparison of the CBD-OS 20 mg/kg/day groups showed that when ALT was > ULN at baseline, there was a higher frequency of TE ALT > 3 × ULN (30.0%) compared to when ALT was within the normal range at baseline (12.4%). Similarly, patients with an ALT > ULN at baseline were twice as likely to exhibit a TE ALT > 5 × ULN.
- Although the sample size for the CBD-OS 10 mg/kg/day group with baseline ALT > ULN (n=11) was relatively small, it was notable than none of the patients in the group exhibited even an ALT > 2 × ULN during treatment.
- The number of patients in the LGS CBD-OS 20 mg/kg/day group (n=168) was approximately 2.8 times larger than the corresponding DS group (n=61).
    - The frequencies of TE ALT > 3 × ULN (17.5%) and 5 × ULN (8.9%) in the LGS CBD-OS 20 mg/kg/day group were higher than the frequencies of 13.1% and 3.3%, respectively, observed in the corresponding DS group. None of the DS patients had a TE ALT > 8 × ULN compared with 3.6% for the LGS patients.
    - The Pool LT-DSLGS results suggest that, although there is an imbalance in the number of patients in the 2 groups, patients with DS and patients with LGS appeared to have a similar risk for TE ALT elevations > 3 × ULN and > 5 × ULN when administered CBD-OS 20 mg/kg/day.

MO Comment:
The liver injury associated with CBD appears to be relatively mild and reversible on drug discontinuation. It is dose-related, with a much higher incidence on the 20 mg/kg/day dose. Liver injury is noted most frequently in the first 30-90 days of treatment and is rare after 200 days of treatment. Therefore, it is recommended that patients be monitored frequently for 3 months and then at regular intervals for 1 year of treatment and then at 6-12 month intervals thereafter.

J. Concomitant AEDs

Both valproate and felbamate have previously been associated with elevations of liver test results.

Valproate

Table 10 shows a clear association between treatment with valproate plus CBD-OS and an increased frequency of ALT elevations. The use of valproate was common in the populations studied. Across groups, ~44% (n=225) of patients were being treated with concomitant valproate at the time of randomization and during the trial.

Comparison of the CBD-OS 20 mg/kg/day groups showed that patients with concomitant valproate treatment had a higher frequency of TE ALT > 3 × ULN (29.2%) than patients not taking valproate (5.0%). Similarly, patients taking concomitant valproate exhibited a higher frequency of TE ALT > 5 × ULN (13.2%) and > 8 × ULN (5.7%) compared to patients not taking valproate, at 2.4% and 0%, respectively.

Patients taking concomitant valproate exhibited TE ALT > 5 × ULN in 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, in the groups of patients not taking concomitant valproate, TE of ALT > 5 x ULN was observer in 0%. 2.4% and 0.8% of patients taking CBD-OS 10 mg/kg/day, 20 mg/kg/day, or placebo. ALT > 8 × ULN was observed in 4.3%, 5.7%, and 1.0% of patients not taking concomitant valproate and taking CBD-OS 10 mg/kg/day, 20 mg/kg/day, or placebo (Table 10).

Reviewer Comments: The combined effects of liver injury signaling with concomitant CBD and valproate treatment pose an important challenge with regard to the sequencing of treatment adjustments in patients treated with these agents who manifest TE high levels of ALT. It is well recognized that valproate alone is an idiosyncratic hepatotoxic agent that can cause severe liver injury. Given that CBD either contributed to the resulting liver injuries or was the primary cause of DILI in the study subjects who were receiving both agents, it will be important to establish a decision tree for the triggering and agent-specific

sequencing of dose modification, drug discontinuation and patient observation when monitoring indicates acute injury.

Table 9: Frequency of ALT Elevations for Patients Taking or Not Taking Concomitant Valproate in Pool DS/LGS (Pivotal DS and LGS)

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

Source: Sponsor Table 13.2.2.1-1 LSR - LSR Table DSLGS.5.1.7.

Felbamate

The small numbers of patients taking felbamate limit interpretation of the results. Across groups, only ~10% (n=50) of patients were being treated with concomitant felbamate. In the CBD-OS 20 mg/kg/day group, patients taking concomitant felbamate exhibited a higher frequency (22.2%) of ALT values >3 × ULN than patients not taking felbamate (15.8%). However, the apparent higher frequency in the felbamate group appears to be driven by the presence of concomitant valproate in patients exhibiting ALT elevations.

MO Comment:
The small number of patients on felbamate and not on valproate makes conclusions impossible. All patients on concomitant felbamate should be monitored closely and for longer periods when starting CBD.

Clobazam

Clobazam had been observed to be associated with a low frequency of AT elevations (3.1% and 2.8% for doses of 0.25 and 1.0 mg/kg/day in 1 LGS trial. However, there was an interest in exploring a potential transaminase elevation interaction between clobazam and CBD-OS because CBD-OS increases exposure to the major metabolite of clobazam (N-desmethylclobazam).

The overall results support that apparent increased frequencies in ALT elevations in CBD-OS patients taking clobazam may be explained by the fact that valproate

tended to be a concomitant AED in CBD-OS patients who exhibited ALT elevations to > 5 × ULN while taking clobazam.

MO Comment:
CBD inhibits CYP2C19 and has the potential to increase plasma concentrations of drugs that are metabolized by CYP2C19, which includes phenytoin and clobazam. While no increases in valproic acid, stiripentol or clobazam levels were seen in a dedicated drug-drug interaction study (GWEP1543), there was an active metabolite of clobazam, n-desmethylclobazam (aka., nor-clobazam), that did show a 3-fold increase. N-clobazam is thought to have 1/5 the activity of clobazam, so the clinical significance of this increase is not clear.

6 Exploration of Potential Mechanisms for Observed Elevations of ALT

CBD and its major plasma metabolite, 7-COOH-CBD, were incubated for 1 hour and 24 hours with HepG2 cells and analyzed for effects on mitochondrial function via the mitochondria stress test measured in the Seahorse XF Analyzer. Three independent experimental runs were completed.

These in vitro data suggest that 7-COOH-CBD could cause serum ALT elevations via direct action on hepatic mitochondria at concentrations achieved in vivo. Furthermore, the commonly used antiepileptic drug (AED), valproate, and its metabolite 4-ene-valproic acid, have been implicated as ETC inhibitors. Therefore, a potential interaction effect between CBD and valproate at the level of the mitochondria could underlie observations in the clinical data. This hypothesis is currently being investigated further via additional data collection and simulations in collaboration with (b) (4).

7 SUMMARY

In summary, CBD-OS administration to the target DS and LGS population in controlled clinical trials and an open label extension trial (n=540), and the large EAP program (n=684) was causally associated with elevations in serum ALT, consistent with hepatocellular DILI, but cases of severe hepatocellular injury marked by coincidentally substantial rises of serum bilirubin or changes of other indicators of worsening liver cell function did not occur. There were no reports of severe DILI and no reports of Hy's Law cases among the 540 DS and LGS patients receiving CBD-OS treatment. Among these patients, 522 were exposed to CBD-OS for longer than 28 days. There was a higher frequency for aminotransferase elevations in the higher 20 mg/kg/day dose compared with 10 mg/kg/day dosing.

Because the intended population for treatment with adjunctive CBD-OS (patients with DS or LGS) is the same as the population evaluated in the phase 3 trials,

the frequency of TE ALT ≥ 5 × ULN post-marketing is expected to be similar to the frequencies observed in the CBD-OS controlled trials. Based on the rule of 3, the absence of serious liver injury in the 522 patients were studied in these trials excludes an incidence of Hy's law cases greater that 1 in 174 treated patients and likely excludes an incidence of acute liver failure due to CBD-induced DILI greater than 1 in 1740 treated patients treated in a similar fashion, with respect to dosing, duration of treatment, and use of concomitant medications.

However, trial protocol and guideline recommendations provided liver test-based withdrawal criteria including trial withdrawal for patients with ALT values > 8 × ULN and may have prevented cases of more serious liver injury in some instances in which the agent was promptly stopped. It is notable that several patients continued on drug despite significant elevations in transaminases and did not develop evidence of severe liver injury with hyperbilirubinemia. Some patients developed mild increases in bilirubin above baseline though not above ULN.

Concomitant valproate is identified as the most common risk factor for elevations in transaminases. Some patients resolved transaminase elevations while on CBD, in some of these patients, the valproate dose may have been decreased. From these data, it appears that in addition to the hepatotoxic profile of CBD alone marked by elevations of aminotransferases, there can be an additive toxic effect in some instances when CBD is combined with valproic acid.

Most cases of aminotransferase (ALT) elevations occurred in the first 30 days and almost all in the first 90 days of treatment, though a few did occur after 100 days, but before 200 days. All cases of transaminase elevations for which data were available recovered, most within 2 weeks.
Unknowns now include the unknown risk for chronic liver injury even in patients who do not exhibit transaminase elevations or who recover from transaminase elevations in patients treated with CBD for long periods of time. Whether longer exposures could result in chronic liver injury, such as the development of liver fibrosis over time, has not been studied.

8 Recommendations

- Due to the rarity of these syndromic epilepsies, currently the numbers of study subjects who have been treated with CBD to manage DS and LGS are modest, with protocols that did not interrogate liver injury effects of long-term use. At this time, until there is more exposure experience with use of CBD, if the product is approved based on consideration of benefits and risks, its use should be confined to patients with DS and LGS (or equivalent serious and uncontrolled epilepsy), who are at considerable risk due to their severe epilepsy and for whom gaining effective treatments continues to pose a large challenge.

- Although there remains uncertainty regarding the impact of CBD dosing on clinically significant hepatotoxic risk, because of dose-related differences in the frequency of ALT elevations between the 20 mg/kg/day and 10 mg/kg/day doses, the lowest effective dose should be used.
- With product label warnings and other educational tools, the sponsor should recommend a strategy for liver test screening prior to CBD treatment and then specify intervals for liver monitoring and product discontinuation instructions that conform to those utilized in the pivotal studies. Until more information is available, for patients on long-term treatment with no treatment-emergent liver test abnormalities after 6 months, serum testing should be performed at 3 month intervals and then after one year, at 6 month intervals. Careful and more frequent monitoring should be performed in patients showing new onset abnormalities of serum aminotransferases that do not meet the threshold for product discontinuation. It would be prudent to include in the prescriber labeling instructions to discontinue drug for development of symptoms (e.g., abdominal pain, anorexia, nausea or vomiting, fatigue) and for significate increases in TB from baseline, even if TB remains below ULN.
- The sponsor should provide instructions to healthcare providers and patients/families regarding management strategies to address episodes of acute biochemical or clinical liver injury during treatment. These should include recommendations about when to modify the dosing of CBD or interrupt use of the product. Alterations in the use of concomitant agents, such as valproic acid, that have a hepatotoxic profile should also be taken into consideration.
- To gain important information on the hepatotoxic risk profile of CBD, the sponsor should institute an enhanced pharmacovigilance program. Physicians with expertise in the management of DS and LGS should be encouraged to report all cases of serious liver injury to the sponsor with sufficient information to assess causality. The sponsor should actively follow up on these cases and provide FDA with 15-day expedited reports on all serious liver injury cases and then follow up by eliciting clinical and diagnostic information that will facilitate a comprehensive evaluation of causality and severity. In the Periodic Benefit-Risk Evaluation Reports to FDA, the sponsor should analyze the incidence and range of severity of liver toxicity, describe all individual cases of severe injury or liver failure, and provide estimates of the numbers of CBD-treated patients in the US market and globally if indicated.
- The sponsor should perform a non-invasive study in CBD users to determine whether long-term exposure (> 1-2 years) to the agent has a potential to cause chronic liver disease of fibrosis.

9 Appendix – Example Cases

Cases #1:
A 12 year old female with Lennox-Gastaut syndrome in trial GEWP1414 and rolled over to the open-label extension trial. Baseline labs normal. In her background treatment, she was taking concomitant clobazam, valproic acid, ethosuximide, Keppra and Multivitamins.

She was started on placebo then after 3 months started on CBD and tapered-up to 26mg/kg day. At day 20 to 30 she became symptomatic and developed altered mental status and was hospitalized with significant elevations in transaminases AST 14.8× ULN and ALT 9.9× ULN AND as you can see from Figure 4 there was a slight increase in TB. Valproate acid levels were also high and it was stopped. The patient recovered. CDB dose was adjusted down and then titrated back to 26mg/kg day and she continued in the CBD study without recurrent liver injury. This case is adjudicated by the sponsor as likely related to CBD, and demonstrates the multiple approaches that were taken in the trial in response to CBD-associated DILI.

Figure 4: Case #1 – Liver Biochemistries Over Time

Case #2
A 28 year old with Lennox-Gastaut syndrome and mental retardation, on Topamax, valproic acid, Clobazam, and Dilantin and Diazepam. Baseline liver chemistries were normal except for a mildly elevated GGT.

He was started on CBD in trial GWEP1423 and the dose was titrated to 20mg/kg/day. Within 2 weeks he experienced lethargy and then elevations in

transaminases with an ALT of 9.0× ULN. The Clobazam dose was decreased at day 29 and 30. However, at day 31 the Subject discontinued drug abruptly. His liver injury and symptoms resolved. This case is adjudicated by the sponsor to be likely related to CBD.

Figure 5: Case #2 - Liver Biochemistries Over Time

Case #3

7 year old male patient with LGS in trial GWEP1423 and rolled over to open-label extension. He was on concomitant valproic acid and lamotrigine, clobazam. Baseline liver biochemistries were normal.

He was started on placebo, after 3 months CBD was stared and titrated to 20 mg/kg day, however within 15 days developed symptoms and work-up revealed mild elevations of transaminases (ALT 30 AST43 U/L), bilirubin increased to 1.5 x ULN then CBD was tapered. Pt recovered completely. This case was adjudicated by the sponsor as probably related to CBD.

Figure 6: Case #3 - Liver Biochemistries Over Time

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/s/

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Date: April 25, 2018
From: Kimberly Smith, Medical Officer, Division of Cardiovascular and Renal Products
Through: Aliza Thompson, Team Leader
Norman Stockbridge, Director
Division of Cardiovascular and Renal Products
To: Stephanie Parncutt, Regulatory Project Manager, Division of Neurology Products
Subject: Renal safety of cannabidiol (NDA 210365)

Background

Cannabidiol is a phytocannabinoid extracted from the cannabis plant that is believed to have anticonvulsant effects through an unknown mechanism. On October 27, 2017, the Division of Neurology Products (DNP) received the last components of a rolling submission for cannabidiol oral solution for the treatment of seizures associated with Lennox-Gaustaut syndrome (LGS) and Dravet syndrome (DS). Both are rare, severe forms of epilepsy that manifest in early childhood and are often treatment resistant.

In support of the proposed indication, the applicant has completed three double-blind, placebo-controlled phase 3 trials: one in DS (GWEP1332B) and two in LGS (GWEP1414 and GWEP1423). Subjects in these trials could continue treatment in an ongoing open-label extension trial (GWEP1415). The applicant also has an ongoing phase 3, double-blind, placebo-controlled trial in patients with DS (GWEP1424) that remains blinded.

During the safety review, the team noted decreases in creatinine clearance in the cannabidiol group relative to placebo. The sponsor believes the increases may be caused by OCT inhibition by cannabidiol and that the findings should not be described in labeling. DNP has requested input from the Division of Cardiovascular and Renal Products regarding the potential mechanism of the observed changes and the clinical relevance.

Materials Reviewed

1. Integrated Summary of Safety
2. Clinical Information Amendment dated March 13, 2018
3. Protocols for GWEP1332, GWEP1414, and GWEP1423
4. Draft labeling
5. Email from Dr. Ellis Unger dated February 26, 2018 containing analyses of GWEP1542

Overview of Trials

GWEP1332B, 1414, and 1423 were all double-blind, randomized, placebo-controlled trials. In study GWEP1332B, pediatric patients with DS were randomized to cannabidiol 20 mg/kg/day (n=61) or placebo (n=59) for 14 weeks. In study GWEP1414, patients 2 to 55 years of age with LGS were randomized to cannabidiol 10 mg/kg/day (n=67), cannabidiol 20 mg/kg/day (n=82), or placebo (n=85) for 14 weeks. In study GWEP1423, patients 2 to 55 years of age with LGS were randomized to cannabidiol 20 mg/kg/day (n=86) or placebo (n=85) for 14 weeks. Patients in these trials could transition to an open-label extension and receive cannabidiol 20 to 30 mg/kg/day.

For all three studies, there were no specific renal exclusion criteria, but patients were excluded for clinically significant abnormal laboratory values, in the investigator's opinion, at screening or randomization. Renal function and a dipstick urinalysis were assessed at screening and on Days 1, 15, 29, 57, and 99. In addition, subjects that did not enter the open label extension study were to have an additional visit following taper of study medication during which renal function was assessed. Urine albumin/protein was not quantitated, and serum cystatin C was not measured. Serum creatinine was measured at a central laboratory.

Renal Findings

Baseline Characteristics

The mean age of study subjects was 13.9 years (range 2.5 to 48 years.) The mean baseline creatinine clearance was over 135 mL/min/1.73m^2.

Exposure

Across the phase 3 DS and LGS studies, 323 patients received at least one dose of cannabidiol (88 DS and 235 LGS). The mean duration of treatment was 74 days and 94 days for DS and LGS subjects, respectively.

Change in Renal Parameters

Across the three phase 3 trials, mean creatinine clearance in adults randomized to cannabidiol fell 14.1 (20.7) mL/min from baseline to end of treatment compared with 1.2 (19.7) mL/min in placebo subjects (Table 1). In pediatric patients, mean creatinine clearance fell an average of 10.0 (26.7) and 4.3 (26.9) mL/min/1.73m^2 in cannabidiol and placebo subjects, respectively. There was no change in mean BUN.

Table 1: Change from baseline in creatinine clearance and BUN across phase 3 studies

		Cannabidiol (n=323)	**Placebo (n=227)**
Creatinine clearance – Cockroft-Gault[1] (mean ± SD)	Baseline	156.6 ± 52.9 (n=75)	143.6 ± 47.2 (n=53)
	Change from baseline to end of treatment	−14.1 ± 20.7 (n=70)	−1.2 ± 19.7 (n=47)
Creatinine clearance – Schwartz[2] (mean ± SD)	Baseline	139.0 ± 38.8 (n=248)	139.9 ± 40.4 (n=174)
	Change from baseline to end of treatment	−10.0 ± 26.7 (n=223)	−4.3 ± 26.9 (n=163)
BUN (mean µmol/L ± SD)	Baseline	4.6 ± 1.6 (n=323)	4.7 ± 1.6 (n=227)
	Change from baseline to end of treatment	0.1 ± 1.5 (n=293)	0.0 ± 1.1 (n=210)

Source: Applicant, ISS, Table 9.1.2.1.3.2-1

[1]For subjects 18 years of age and older.

[2]For subjects less than 18 years of age.

In both adult and pediatric patients receiving cannabidiol 20 mg/kg, a mean decrease in creatinine clearance was apparent at Day 15 and then remained stable (Table 2). In the 10 mg/kg group, no clear pattern emerges. The pattern in the 20 mg/kg group is evident in Figure 1 for adult patients with LGS enrolled in GWEP1414 and GWEP1423 and in Figure 2 for pediatric patients with DS enrolled in GWEP1332B but is not evident in Figure 3 for pediatric patients with LGS enrolled in GWEP1414 and GWEP1423.

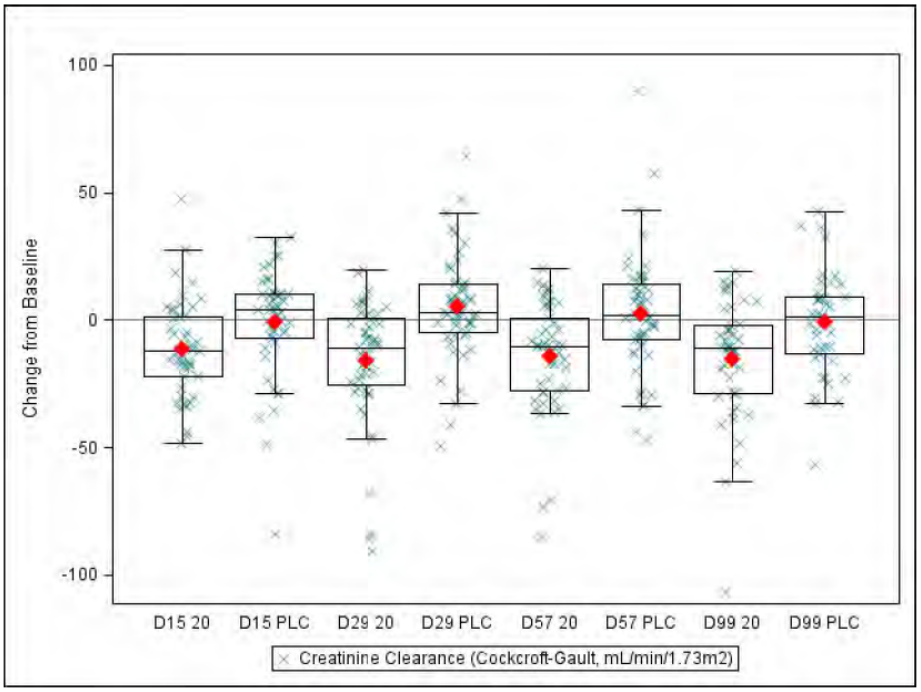
Reviewer's comment: Several subjects in both groups have large changes in creatinine clearance from baseline in the Figures 1, 2, and 3 (e.g., 50-100 mL/min/1.73m^2) and the standard deviations in Table 2 are large (e.g., 35-60 mL/min/1.73m^2). In the associated tables in the applicant's March 13, 2018 clinical information amendment, the upper limits of creatinine clearance ranges are often over 250 mL/min/1.73 m^2 with some over 450 mL/min/1.73 m^2. These are implausible. The applicant should confirm the validity of the values and corresponding analyses.

Table 2: Change from baseline in creatinine clearance over time

		Cannabidiol 10 mg/kg n=73	Cannabidiol 20 mg/kg n=223	Placebo n=220
Creatinine clearance – Cockroft-Gault[2] (mean ± SD)	Baseline	162.6 (54.9) (n=22)	154.1 (52.4) (n=53)	143.6 (47.2) (n=53)
	Day 15	154.5 (59.5) (n=21)	142.9 (38.4) (n=46)	141.9 (44.0) (n=48)
	End of Treatment	145.4 (50.5) (n=22)	139.7 (47.4) (n=48)	142.0 (45.5) (n=47)
Creatinine clearance – Schwartz[1] (mean ± SD)	Baseline	128.6 (34.8) (n=51)	142.1 (40.1) (n=170)	140.8 (40.4) (n=167)
	Day 15	135.1 (47.0) (n=51)	128.1 (35.1) (n=157)	135.2 (38.6) (n=162)
	End of Treatment	124.6 (35.1) (n=47)	129.6 (36.1) (n=150)	135.8 (37.0) (n=156)

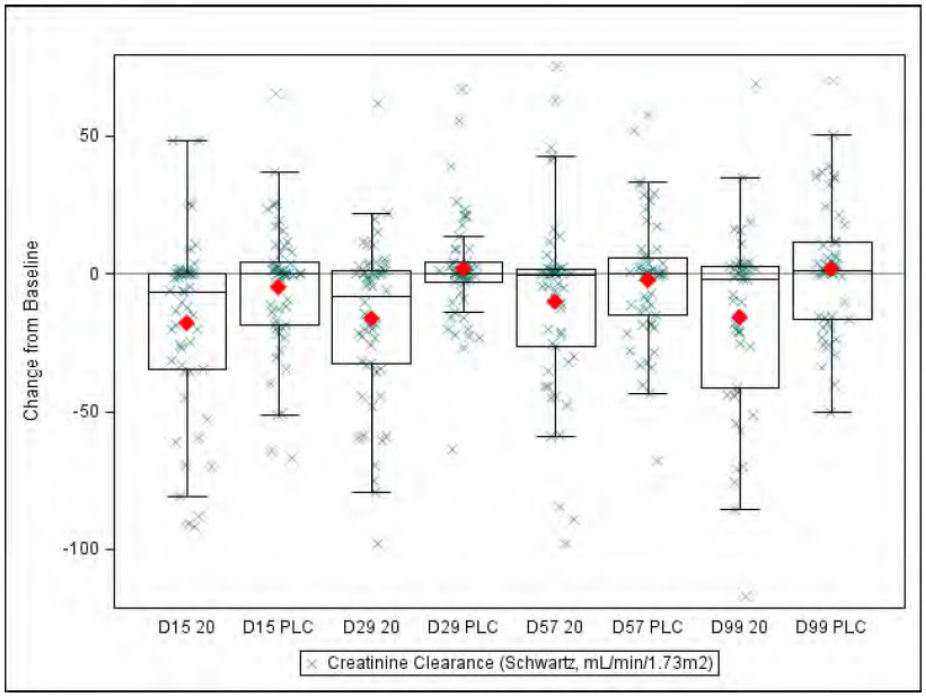
Source: Applicant, Clinical Information Amendment dated March 13, 2018, Table 10.2.1.4
[1]For subjects 18 years of age and older.
[2]For subjects less than 18 years of age.

Figure 1: Change in creatinine clearance from baseline in studies GWEP1414 and GWEP1423 – adult patients



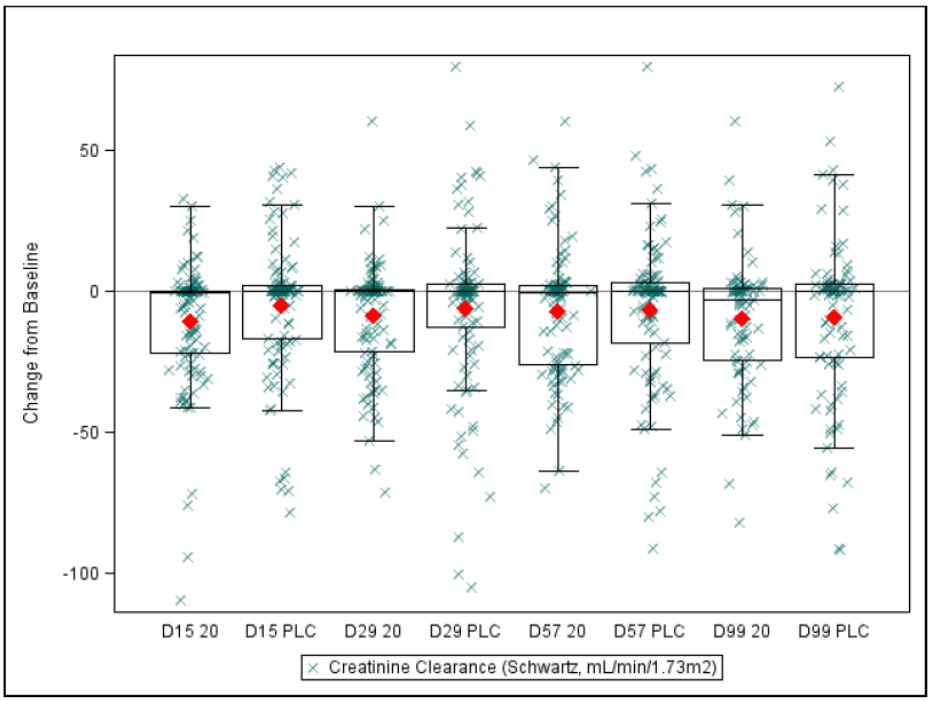
Source: Applicant, Clinical Information Amendment dated March 13, 2018, "ISS-creatinine-bun-analysis2.pdf" page 111.

Figure 2: Change in creatinine clearance from baseline in study GWEP1332B - pediatric patients



Source: Applicant, Clinical Information Amendment dated March 13, 2018, "ISS-creatinine-bun-analysis2.pdf" page 81.

Figure 3: Change in creatinine clearance from baseline in studies GWEP1414 and GWEP1423 – pediatric patients



Source: Applicant, Clinical Information Amendment dated March 13, 2018, "ISS-creatinine-bun-analysis2.pdf" page 96.

To evaluate whether the decrease in creatinine clearance reverses following discontinuation of treatment, the primary review team analyzed data from study GWEP1542, a phase 1 study intended to assess

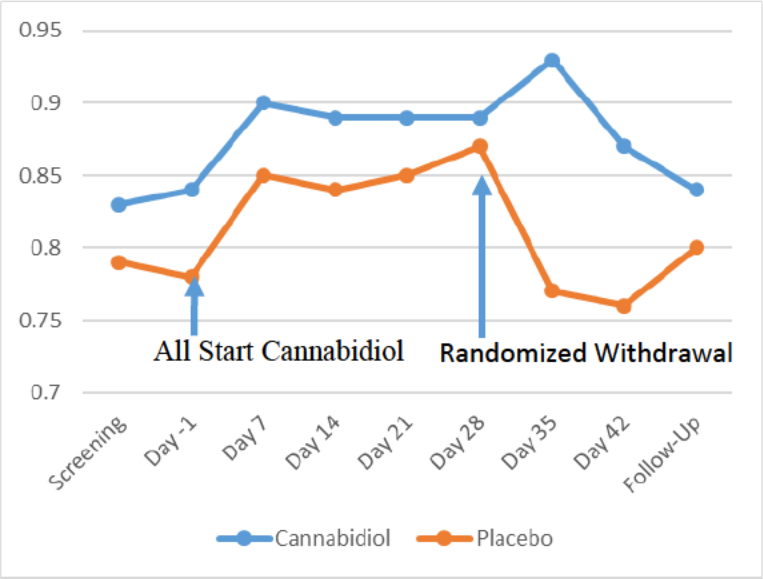
withdrawal symptoms in which 30 healthy volunteers were treated with cannabidiol 750 mg twice daily for 28 days and then were randomized to continue cannabidiol or switch to placebo for 14 days. As shown in Table 3 and Figure 4, serum creatinine increased within one week of starting cannabidiol and returned to baseline within one week after discontinuing therapy. The change in creatinine was generally small (≤0.1 mg/dL).

Table 3: Change in mean creatinine (mg/dL) over time in study GWEP1542

	Cannabidiol in Withdrawal Period			Placebo in Withdrawal Period		
Study Day	**n**	**Creatinine**	**SD**	**n**	**Creatinine**	**SD**
Screening	15	0.83	0.15	15	0.79	0.17
Day -1	15	0.84	0.17	15	0.78	0.13
Cannabidiol started in both groups						
Day 7	15	0.90	0.18	15	0.85	0.18
Day 14	15	0.89	0.19	15	0.84	0.17
Day 21	13	0.89	0.17	15	0.85	0.14
Day 28	11	0.89	0.17	13	0.87	0.15
Randomized Withdrawal						
Day 35	10	0.93	0.18	13	0.77	0.13
Day 42	9	0.87	0.16	12	0.76	0.16
Follow-Up	15	0.84	0.15	15	0.80	0.14

Source: Analyses by primary review team emailed February 26, 2018.

Figure 4: Change in creatinine (mg/dL) over time in study GWEP1542



Source: Derived from analyses by primary review team emailed February 26, 2018.

Change in Blood Pressure

There was no obvious difference in systolic blood pressure between the treatment arms (Table 4).

Table 4: Change from baseline in systolic blood pressure across phase 3 studies

		Cannabidiol (n=323)	Placebo (n=227)
Systolic blood pressure (mean mmHg ± SD)	Baseline	106.9 ± 13.7 (n=320)	107.3 ± 12.7 (n=224)
	Change from baseline to end of treatment	-0.9 ± 13.7 (n=307)	-0.3 ± 12.7 (n=217)

Source: Applicant, Integrated Summary of Safety, Table 10.1.1.3-1.

Renal Adverse Events

Events in the renal and urinary disorders SOC were uncommon but were reported more frequently in subjects on cannabidiol (Table 5). None appear to be related to acute kidney injury. We note that there appears to be an imbalance in urinary retention events that may be worth investigating further.

Table 5: Renal/urinary adverse events across phase 3 studies

Preferred Term	All CBD-OS group N = 323 n (%)	Placebo N = 227 n (%)
Urinary retention	5 (1.5%)	0
Chromaturia	1 (0.3%)	0
Hematuria	1 (0.3%)	0
Nephrolithiass	1 (0.3%)	1 (0.4%)
Pollakuria	1 (0.3%)	0
Proteinuria	1 (0.3%)	0
Urethral Discharge	1 (0.3%)	0

Source: Applicant, Clinical Information Amendment dated March 13, 2018, Table 1.

In the open label extension (GWEP1415), there were seven reports of "renal failure acute" or "acute pre-renal failure." The applicant provided narratives for each case and all have alternative explanations including infection, septic shock, gastroenteritis, vomiting, and administration of intravenous contrast.

Non-clinical Data

According to the applicant, only one pre-clinical mouse study (GWTX1688, a CD-1 mouse pre-carcinogenicity study) showed renal toxicity with elevated creatinine and phosphate and kidney nephropathy in all test-item treated groups; however, the applicant notes that a change in the extraction procedure for the active pharmaceutical ingredient used in that study may have led to impurities that exceeded specifications. Specifically, the impurities were suspected to be (b) (4) which have been linked to nephrotoxicity. The applicant notes that renal toxicity was not observed in other studies in mice or in other species.

Other Data

The applicant notes that the Jaffe assay was used to measure creatinine in all subjects and the enzymatic assay was used in a small number of subjects, but there is no reason to believe cannabidiol would interfere with either assay. Creatinine increased regardless of the method.

The applicant notes that creatinine elimination is primarily driven by the organic cation transporters (OCT1 and OCT2) which share some structural homology with the endonucleotide transporters (ENTs) and that cannabidiol is a moderately potent inhibitor of ENT1. Although cannabidiol did not inhibit OCT1 or OCT2 at concentrations up to 10 μM, the applicant hypothesizes that small increases in serum creatinine could result from marginal OCT inhibition by cannabidiol.

Reviewer's comment: The clinical pharmacology reviewer for this application confirms that cannabidiol does not have inhibitory effect on transporters including OCT, MATE, and OAT transporters up to 10 uM concentrations in vitro. He notes that the total C_{max} with a high fat meal is approximately 4 uM, and with protein binding, only 6% of cannabidiol is free.

Consult Question
Please comment on the clinical relevance of the observed changes in creatinine/creatinine clearance and the potential mechanism for these changes.

DCRP Response:
Based on data from three phase 3 studies in patients with DS and LGS and a phase 1 randomized withdrawal study in healthy volunteers, it appears that serum creatinine may increase within one to two weeks of starting cannabidiol then stabilize and that it returns to baseline after discontinuation of treatment, although the pattern is not obvious with the 10 mg/kg dose or in pediatric patients in the LGS studies. We note, however, that there appear to be irregularities in the renal function data and the applicant should confirm that the data and analyses are valid. Specifically, the applicant's analyses show large changes in creatinine clearance between visits, large standard deviations, and implausibly high creatinine clearance values.

Generally speaking, an acute decrease in renal function followed by stabilization suggests either a hemodynamic effect or interference with the tubular secretion of creatinine. The reported adverse events do not suggest renal toxicity. With drugs that have hemodynamic effects on renal function, there can be a corresponding reduction in systolic blood pressure and/or albuminuria/proteinuria. There was no obvious difference in mean systolic blood pressure between the treatment groups. Urine protein was not quantitated. It is possible that cannabidiol has a hemodynamic effect on renal function through changes in intraglomerular pressure. As we understand, the renal transporter data do not suggest that cannabidiol inhibits the tubular secretion of creatinine. Cystatin C data can be helpful to identify drugs that inhibit creatinine secretion because cystatin C levels are not affected; however, cystatin C was not assessed.

In general, we believe it is important to include information in labeling about effects on creatinine that are hemodynamic or related to inhibition of the tubular secretion of creatinine. This can inform treating physicians of the level of change in creatinine that might be expected from the drug alone and the level above which additional investigation of the cause may be warranted. For example, the label for the drug Genvoya states:

> *Cobicistat, a component of GENVOYA, produces elevations of serum creatinine due to inhibition of tubular secretion of creatinine without affecting glomerular filtration. The elevation is typically seen within 2 weeks of starting therapy and is reversible after discontinuation. Patients who experience a confirmed increase in serum creatinine of greater than 0.4 mg per dL from baseline should be closely monitored for renal safety.*

To describe the finding accurately in labeling, it will be important to confirm the mechanism and to more definitively establish the degree of elevation in serum creatinine expected. We note that subjects that did not enter an open-label extension study were to have an additional visit with assessment of renal function following taper of study medication. Depending on the number of subjects with off-treatment assessments of renal function, these data may provide additional insight into the magnitude of the change and confirm reversibility. We note that the pattern was evident in GWEP1542 in healthy volunteers, so it may also be informative to conduct an additional study in healthy volunteers that includes measured GFR (b) (4) *to help to resolve the issue of whether cannabidiol inhibits the tubular secretion of creatinine or has a true effect on GFR. This could occur in the post-marketing setting. We reiterate, however, that the first step is for the applicant to address concerns regarding validity of the renal function data.*

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

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04/25/2018

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