

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210365Orig1s000**

**SUMMARY REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	June 22, 2018
<b>From</b>	Teresa Buracchio, MD
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA/BLA # and Supplement#</b>	210365
<b>Applicant</b>	GW Pharma
<b>Date of Submission</b>	October 27, 2018
<b>PDUFA Goal Date</b>	June 27, 2018
<b>Proprietary Name</b>	Epidiolex
<b>Established or Proper Name</b>	Cannabidiol
<b>Dosage Form(s)</b>	100 mg/mL oral solution
<b>Applicant Proposed Indication(s)/Population(s)</b>	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older
<b>Applicant Proposed Dosing Regimen(s)</b>	The recommended 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).
<b>Recommendation on Regulatory Action</b>	Approval
<b>Recommended Indication(s)/Population(s) (if applicable)</b>	Treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older
<b>Recommended Dosing Regimen(s) (if applicable)</b>	The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day). After one week, increase to a maintenance dosage of 5 mg/kg twice daily (10

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	<p>mg/kg/day). Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase to a maximum recommended dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated.</p>
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## 1. Benefit-Risk Assessment

### Benefit-Risk Assessment Framework

#### Benefit-Risk Integrated Assessment

This application provides data to support the efficacy and safety of cannabidiol (GWP43003-P) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older. Cannabidiol (CBD) is a cannabinoid prepared from the *Cannabis sativa* L. plant administered as a 100mg/ml oral solution. It is a new molecular entity and it is structurally unrelated to other drugs approved for the treatment of seizures.

Both LGS and DS are rare, severe, refractory epilepsy syndromes with onset in early childhood. The syndromes are categorized as developmental and epileptic encephalopathies, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The syndromes are characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. Both syndromes are associated with higher rates of mortality than in the general epilepsy population, primarily due to status epilepticus and sudden unexpected death in epilepsy patients (SUDEP).

In addition to drugs approved for the general treatment of seizures, six drugs are approved specifically for the treatment of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam. There are currently no drugs approved specifically for the treatment of seizures in DS.

Clinically meaningful and statistically significant reductions in seizure frequency were demonstrated in three adequate and well-controlled trials in LGS and DS. In Study 1414 in LGS, the median percentage change from baseline in drop seizure (atonic, tonic, or tonic-clonic seizures that could have led to a fall) frequency per 28 days was 37.2 in the 10 mg/kg/day group and 41.9 in the 20 mg/kg group CBD groups compared to 17.2 in the placebo group ( $p=0.002$  and  $p=0.005$ , respectively). In Study 1423 in LGS, the median percentage change from baseline in drop seizure frequency per 28 days 43.9 in the 20 mg/kg/day CBD group and 21.8 in the placebo group ( $p=0.014$ ). In Study 1332B in DS, the median percentage change from baseline in convulsive seizure (tonic, clonic, tonic-clonic, or atonic) frequency per 28 days was 38.9 in the CBD group and 13.3 in the placebo group ( $p=0.012$ ). The results from these three adequate and well-controlled studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS.

The most commonly observed adverse events in the controlled clinical trials conducted with CBD that occurred with a greater incidence in CBD-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations) and infections (e.g., pneumonia). These events were generally mild to moderate in severity. Serious and/or severe adverse events were generally related to transaminase elevations, somnolence and lethargy, and infections.

A signal for drug-induced liver toxicity was identified in the controlled trials and in the Expanded Access Program. Frequencies of adverse events of transaminase elevations were 8% in the CBD 10 mg/kg/day group, 16% in the CBD 20 mg/kg/day group, and 3% in the placebo group. Some events of transaminase elevation were serious or severe; however, there were no Hy's law cases and no events of liver failure or death related to liver injury. All transaminase elevations resolved, with some resolving during continued treatment with CBD.

The applicant proposes the same dosing regimen for both the LGS and DS populations: a titration up to 10 mg/kg/day as a maintenance dose, with further titration up to 20 mg/kg/day, as needed. All three studies assessed a 20 mg/kg/day dose of CBD; however, only Study 1414 in LGS assessed a dose of 10 mg/kg/day. In Study 1414, the 10 mg/kg/day dose of CBD showed an estimated median difference from placebo of 19.2% while the 20 mg/kg/day dose showed a difference of 21.6%. The difference in safety between the two doses showed a more notable difference in dose-response, with the 20 mg/kg/day group showing markedly higher rates of adverse events than the 10 mg/kg/day, particularly transaminase elevations. The dose-response seen with adverse events supports the use of a lower dose as a maintenance dose if efficacy can be supported. Given that the seizure types were similar between the two disease populations and an overall reduction in all seizure types was seen with CBD for both populations, it is reasonable to assume that the 10 mg/kg/day dose that was shown to be efficacious in an LGS population will also be effective in a DS population. Therefore, the proposed maintenance dose of CBD of 10 mg/kg/day with a maximum dose of 20 mg/kg/day is acceptable.

There was an inadequate assessment of the 7-COOH-CBD metabolite in nonclinical studies; however, there are adequate safety data from the clinical development program to support the safety of CBD for approval. Additional nonclinical studies to assess the major metabolite, 7-COOH-CBD, should be conducted as PMR studies.

The risks associated with CBD treatment are acceptable, particularly given the findings of clinical efficacy in LGS and DS, which are serious, debilitating, and life-threatening disorders. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, and further characterization of the risk in the postmarket setting. The risk-benefit profile established by the data in the application support the approval of CBD for the treatment of seizures associated with LGS and DS.

**Benefit-Risk Dimensions**

Dimension	Evidence and Uncertainties	Conclusions and Reasons
<p><b>Analysis of Condition</b></p>	<p><u>Lennox-Gastaut Syndrome</u></p> <ul style="list-style-type: none"> <li>Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy that presents during childhood. LGS is a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity are thought to contribute to 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 the severity of patients' cognitive and</li> </ul>	<p>Lennox-Gastaut syndrome and Dravet syndrome are both severe epilepsy syndromes that are associated with refractory seizures, cognitive impairment, and increased risk of mortality related to seizures.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>behavior impairments varies from minimally affected (rare) to profoundly impaired. Drop attacks are the most disabling of the seizure types (seen in &gt;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. Non-convulsive status epilepticus (continuous seizure activity) is seen in 50-70% of patients. Seizure freedom is essentially never seen in patients with LGS, regardless of antiepileptic drugs (AEDs) or other epilepsy treatments. Children and adolescents with LGS have a higher mortality rate than the general epilepsy population. Common reported proximate causes of death in patients with LGS are SUDEP, status epilepticus, or seizures.</p> <p><u>Dravet Syndrome</u></p> <ul style="list-style-type: none"> <li>• Dravet syndrome (DS) is a severe form of childhood epilepsy that 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 AEDs. Seizure-freedom almost never occurs, but many patients experience fewer seizures in late adolescence and adulthood. 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.</li> </ul>	
<p><b>Current Treatment Options</b></p>	<p><u>Lennox-Gastaut Syndrome</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• There is potential for severe adverse drug reactions with 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,</li> </ul>	<p><u>Lennox-Gastaut Syndrome</u></p> <p>Six drugs are approved by FDA for reduction of seizures in patients with LGS. Despite the availability of approved therapies, most patients continue to have poorly-controlled seizures. Additionally, some drugs are poorly tolerated or have the potential for serious adverse events.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>clobazam, rufinamide), and hematologic abnormalities (felbamate, lamotrigine, topiramate, rufinamide).</p> <p><u>Dravet Syndrome</u></p> <ul style="list-style-type: none"> <li>There are no approved treatments of seizures in patients with DS.</li> </ul>	<p>There remains a need for efficacious therapies for the treatment of seizures in LGS.</p> <p><u>Dravet Syndrome</u></p> <p>There is a high unmet need for effective treatments for Dravet syndrome as there are no approved treatments for this condition.</p>
Benefit	<p><u>Lennox-Gastaut Syndrome</u></p> <ul style="list-style-type: none"> <li>Two randomized, double-blind, placebo-controlled studies were conducted with CBD in LGS. In Study 1414 in LGS, the median percentage change from baseline in drop seizure frequency per 28 days was 37.2 in the 10 mg/kg/day group and 41.9 in the 20 mg/kg group CBD groups compared to 17.2 in the placebo group (p=0.002 and p=0.005, respectively). In Study 1423 in LGS, the median percentage change from baseline in drop seizure frequency per 28 days was 43.9 in the 20 mg/kg/day CBD group and 21.8 in the placebo group (p=0.014).</li> </ul> <p><u>Dravet Syndrome</u></p> <ul style="list-style-type: none"> <li>A single randomized, double-blind, placebo-controlled studies were conducted with CBD in DS. In Study 1332B in DS, the median percentage change from baseline in convulsive seizure frequency per 28 days was 38.9 in the CBD group and 13.3 in the placebo group (p=0.012).</li> </ul>	<p>These well-controlled clinical trials have established that CBD is effective for the treatment of seizures in LGS and DS.</p>
Risk and Risk Management	<ul style="list-style-type: none"> <li>Transaminase elevations were identified as a safety issue of concern. Transaminase elevations were reported as an adverse event in 8% of patients in the CBD 10 mg/kg/day group, 16% of patients in the CBD 20 mg/kg/day group, and 3% of patients in the placebo group. Some events of transaminase elevation were serious or severe; however, there were no Hy's law cases and no events of liver failure or death related to liver injury. All transaminase elevations resolved, with some resolving during continued treatment with CBD. Concomitant use of valproic acid and a higher (20 mg/kg/day) dose of CBD led to an increased risk of transaminase elevations. Concomitant use of clobazam also increased the</li> </ul>	<p>The risks associated with CBD are acceptable. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, encouraging initial use of 10 mg/kg/day dose as an initial maintenance dose, and further characterization of the risk in the post-market setting.</p>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	<p>incidence of transaminase elevations, although to a lesser extent than valproic acid.</p> <ul style="list-style-type: none"> <li>• Somnolence, sedation, and lethargy occurred in a large number of patients (32% and 11% in CBD-treated and placebo subjects, respectively). Somolence, sedation, and lethargy were somewhat dose-related, with rates of 34% of patients taking CBD 20 mg/kg/day, and 27% in patients taking CBD 10 mg/kg/day. The rate was considerably higher in patients on concomitant clobazam (44% in CBD-treated patients taking clobazam compared with 13% in CBD-treated patients not taking clobazam or valproic acid)</li> <li>• Other potential risks identified during the review include:               <ul style="list-style-type: none"> <li>○ GI adverse effects: diarrhea, nausea, decreased appetite, abdominal pain</li> <li>○ Rash</li> <li>○ Infections: pneumonia</li> <li>○ Decreased weight</li> <li>○ Decrease hemoglobin/hematocrit</li> <li>○ Increases in creatinine</li> </ul> </li> </ul> <p>A dose-response was observed for gastrointestinal adverse events and rash, with higher incidences observed at the 20 mg/kg/day dose of CBD.</p>	<p>The following risk mitigation measures are recommended:</p> <ul style="list-style-type: none"> <li>• WARNINGS and PRECAUTIONS should be included in labeling to describe the risks of transaminase elevations; somnolence and sedation; and hypersensitivity reactions. Warnings for suicidal behavior and withdrawal of seizure medications are to be included as class warnings for seizure medications.</li> <li>• Enhanced pharmacovigilance for liver toxicity.</li> <li>• PMR to characterize the effects of CBD on the liver with long-term use.</li> <li>• PMR to characterize the acute changes in creatinine with CBD.</li> <li>• PMRs to characterize drug-drug interactions.</li> <li>• PMRs to assess the effects of 7-COOH-CBD in a battery of nonclinical studies.</li> </ul>

## 2. Background

This application provides data intended to support the effectiveness and safety of cannabidiol (CBD) (investigational product name GWP43003-P) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older. CBD is a cannabinoid prepared from the *Cannabis sativa* L. plant and administered as a 100mg/ml oral solution. It is a new molecular entity and it is structurally unrelated to other drugs approved for the treatment of seizures. The precise mechanism(s) by which Epidiolex exerts its anticonvulsant effect in humans is unknown. In addition to drugs approved for the general treatment of seizures, six drugs are approved specifically for the treatment of seizures in patients with LGS: clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam. There are currently no drugs approved specifically for the treatment of seizures associated with DS.

Both LGS and DS are rare, severe, refractory epilepsy syndromes, with onset in early childhood. The syndromes are categorized as developmental and epileptic encephalopathies, in which the epileptic activity is thought to contribute to developmental delay and behavioral abnormalities beyond the pathology of the underlying disease. The syndromes are characterized by multiple seizure types that are generally refractory to many of the drugs typically used for the treatment of seizures. Both syndromes are associated with higher rates of mortality than are seen in the general epilepsy population, primarily because of status epilepticus and sudden unexpected death in epilepsy (SUDEP).

LGS is characterized by a triad of findings: multiple seizure types, developmental delay, and an interictal electroencephalography (EEG) pattern of diffuse, slow spike-wave complexes. Onset of LGS typically occurs before 8 years of age, with peak presentation occurring between 3 and 5 years of age. Etiologies can be identified in approximately 2/3 of patients with LGS, and include a wide variety of causes, such as hypoxic-ischemic insults (most common), tuberous sclerosis complex, brain malformations, and traumatic brain injuries. An initial diagnosis of infantile spasms may also be associated with a later diagnosis of LGS. 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.

DS (previously known as severe myoclonic epilepsy of infancy) is characterized by refractory epilepsy with multiple seizure types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression. Onset of DS is typically before 2 years of age, and occurs with an initial presentation of seizures and developmental delay. Most patients with the clinical syndrome have a gene mutation affecting the sodium channel (SCN1A).

This application provides efficacy and safety data from the following three randomized, double-blind, placebo-controlled trials:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS

- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS

Additional safety data were provided from the following sources:

- Study 1332A – a 3-week, randomized, double-blind, placebo-controlled dose-finding study in patients with DS
- Study 1415 – an open-label extension study in patients with LGS and DS
- Expanded access programs (EAPs) in refractory epilepsy populations

A detailed summary of the regulatory history of CBD is provided in the combined clinical and statistical review by the clinical reviewer, Dr. Natalie Getzoff.

### 3. Product Quality

The technical lead on the Office of Product Quality (OPQ) review was Dr. Wendy Wilson. Dr. Wilson's review lists the entire OPQ team that was involved with the review of this application. Please refer to the OPQ review for details of the product quality assessment.

The drug substance is a (b) (4) yellow, crystalline (b) (4), produced from an extract of *Cannabis sativa* L. plants. OPQ determined that the drug substance is best described as a highly-purified drug substance from a plant source. The drug product is a 100 mg/mL, non-sterile, non-preserved, non-aqueous oral solution of CBD dissolved in sesame oil, (b) (4), and flavoring agent. The drug product is packaged in a 105 mL amber glass bottle. Two 5-mL syringes and a bottle adapter are co-packaged with the drug product. As these components are co-packaged, this drug product is classified as a combination product. The oral syringe and the adapter co-packaged with the drug product are Tier 1 devices and considered low risk.

Stability and release testing were found to be acceptable. The specified impurity limits were found to be acceptable based on the qualification studies. The microbial quality of the API and drug product were found to be adequate. There were no outstanding issues identified in the OPQ review, and all manufacturing facilities for this product were found to be acceptable.

OPQ recommends approval of this NDA.

### 4. Nonclinical Pharmacology/Toxicology

The nonclinical reviewer for this application is Dr. Ed Fisher, with Dr. Lois Freed performing a secondary review.

CBD is metabolized to form 7-hydroxy-cannabidiol (7-OH-CBD), which circulates in human plasma at levels of approximately 50% of the parent, making it a major human metabolite. 7-

OH-CBD is further metabolized to 7-carboxy-cannabidiol (7-COOH-CBD). 7-COOH-CBD circulates at levels far exceeding (approximately 40-fold higher) those of the parent in humans, representing at least 90% of all drug-related material measured in plasma, and is a major human metabolite. Compared to humans, the toxicology species do not produce the two major human metabolites to a comparable extent, and Dr. Fisher has determined that there is inadequate coverage for 7-COOH-CBD in the toxicology studies.

The following additional important findings were noted in the nonclinical reviews:

- In the pivotal oral toxicity studies (26-week in Wistar rat, 39-week in Beagle dog), the primary target organ was the liver in both species. Findings in both species included hepatocellular hypertrophy accompanied by increases in ALT and ALP.
- A carcinogenicity study was conducted using CBD botanical drug substance (BDS), <sup>(b) (4)</sup> it is considered inadequate because of uncertain exposures and potential interactions with impurities. The applicant is conducting a carcinogenicity in mice using purified CBD that will be completed in the postmarketing setting.
- There was no evidence of genotoxicity with CBD in a standard battery of in vitro and in vivo tests.
- A full battery of oral reproductive and developmental studies was conducted using purified CBD in rats and rabbits. Total litter loss at the high dose (250 mg/kg) was observed in the embryofetal development study in rats. In the pre- and postnatal development study in rats, adverse effects were observed on body weight, attainment of developmental landmarks, learning and memory, and reproductive structure and, possibly, function, primarily at the medium and high doses (150 mg/kg and 250 mg/kg).
- A juvenile toxicity study was conducted in rats. Findings included neurobehavioral deficits and delayed sexual maturation in males.

Although the toxicity evaluation of the parent compound can be considered adequate, the assessment of the 7-COOH-CBD metabolite was inadequate. Based on this finding, Dr. Fisher has concluded that the nonclinical studies do not support approval because of the lack of adequate nonclinical safety assessment of the major human metabolite 7-COOH-CBD.

Dr. Freed notes in her secondary review, however, that “because of the seriousness of the indications and the unmet medical need, if the clinical team concludes that the clinical data are sufficient to support approval, the nonclinical studies needed to address the inadequate assessment of the major human metabolite, 7-COOH-CBD, may be conducted as postmarketing requirements.”

Based on the available clinical data, and after discussions with the clinical review team, we believe that there are adequate safety data from the clinical development program to support the safety of CBD for approval. Additional nonclinical studies to assess the major metabolite, 7-COOH-CBD, should be conducted as PMR studies.

## 5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Jagan Parepally (clinical pharmacology reviewer), Dr. Angela Men (clinical pharmacology team leader), Dr. Michael Bewernitz (pharmacometrics reviewer), Dr. Kevin Krudys (pharmacometrics team leader), Dr. Manuela Grimstein, and Dr. Yuching Yang. The primary conclusions of the OCP review are summarized below. Please refer to the OCP review for a more detailed discussion of these findings.

The following summary of the general pharmacokinetic (PK) findings with CBD is extracted from the OCP review.

- Absorption: Cannabidiol exposure exhibits a nonlinear increase with dose up to 6000 mg under fasting conditions. The median cannabidiol  $T_{max}$  ranged from 2.5 to 5 hours. Absolute bioavailability has not been determined.
  - With a high-fat meal, the  $C_{max}$  and AUC of cannabidiol increased by approximately 5-fold and 4-fold respectively.
- Distribution: The estimated volume of distribution in healthy volunteers was 20963 L to 42849 L. High plasma protein binding (i.e., >94 %) was observed for cannabidiol and its metabolites (7-COOH-CBD, 7-OH-CBD and 6-OH-CBD).
- Metabolism: Cannabidiol is extensively metabolized in liver and gut, primarily by CYP2C19, CYP3A4, and UGT1A7, UGT1A9, and UGT2B7 enzymes. The major circulating metabolites include 7-carboxy-cannabidiol (7-COOH-CBD), which was approximately 40-fold higher than the parent, 7-hydroxy-cannabidiol (7-OH-CBD), which was approximately 38% of the parent based on AUC of cannabidiol, and 6-hydroxy-cannabidiol (6-OH-CBD), a minor metabolite (< 10% of CBD). Cannabidiol and 7-OH-CBD were found to be equipotent and active. 7-COOH-CBD was found to be inactive in nonclinical animal models of epilepsy.
- Elimination: The mean elimination half-life of CBD ranged from 56 to 61 hours following twice-daily dosing for 7 days in healthy volunteers. Following a single oral dose of  $^{14}C$ -CBD at 5 mg/kg, radioactivity was excreted predominantly via the fecal route (84%), and smaller proportions of administered radioactivity was recovered in the urine (8%). The total recovery after 168 hours was 94%.

The food effects are large for CBD, with a 4- to 5-fold increase in exposure following a high-fat meal. In the clinical studies, CBD was not administered consistently in the fed or fasted state, and consequently, exposure levels were found to be highly variable. The sponsor is proposing to state in the prescribing information (PI) that CBD (b) (4)

could have been taken with or without food. OCP recommends that the PI recommend that CBD be administered consistently in either the fed or fasting state. As the dose-response between the 10 and 20 mg dose is not steep, intermittent food-related differences should not have a major impact on efficacy. Also, effectiveness was established in studies with the drug administered without any restriction related to the timing of food intake. The drug also has a long half-life, and the natural variability of dosing with respect to food intake should maintain

a relatively constant long-term steady state exposure despite acute superimposed alterations in exposure due to individual doses. Therefore, labeling will not include any specific recommendation to take the drug in a fed or fasted state.

#### Drug-drug interaction

Dedicated drug-interaction trials evaluating concomitant administration of CYP2C19 and CYP3A inhibitors or inducers were not conducted. Co-administration with moderate or strong inhibitors of CYP3A4 or CYP2C19 is predicted to increase CBD plasma concentrations. Co-administration with moderate or strong inducers of CYP3A4 or CYP2C19 is predicted to increase CBD plasma concentrations.

#### *In vitro Assessments*

*In vitro* studies suggest that CBD inhibits (IC<sub>50</sub> <10 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4. CBD is also a time-dependent inhibitor of CYP3A4, CYP1A2 *in vitro*. CBD is a strong inhibitor of UGT1A9 and UGT2B7 in human liver microsomes.

Cannabidiol induces CYP1A2, CYP2B6, and CYP3A4 *in vitro* at clinically relevant concentrations.

#### *In vivo Assessments*

CBD did not demonstrate significant CYP3A4 inhibition in a dedicated drug-drug interaction study (GWEP17028) with midazolam (a sensitive CYP3A4 substrate).

A dedicated drug-drug interaction study was conducted to evaluate the effect of multiple-dose administration of CBD on steady-state plasma concentrations of CLB and N-desmethyloclobazam (N-CLB), stiripentol (STP), or valproate (VPA) in healthy male and female subjects. There was no significant increase in CLB levels; however, there was a 3-fold increase in N-CLB levels. When CBD was combined with STP, there was a minor increase in STP levels (1.28-fold increase in C<sub>max</sub> and 1.55-fold increase in AUC<sub>tau</sub>). There was no effect of concomitant CBD administration on VPA exposure.

#### Hepatic impairment

The effect of hepatic impairment on the PK of CBD was evaluated in a dedicated study. The geometric mean AUC (0-∞) for total CBD increased 2.45- and 5.15-fold, respectively, in patients with moderate or severe hepatic impairment, and by about 50% in patients with mild hepatic impairment, compared with subjects with normal hepatic function. Based on these findings, OCP recommends a 50% lower starting dose and 50% lower maintenance dose in patients with moderate hepatic impairment, and a slow dose titration with a 80% lower starting dose and a 80% lower maintenance dose in patients with severe hepatic impairment.

#### Renal impairment

A dedicated renal impairment trial was conducted to evaluate the effect of renal impairment on PK of CBD in subjects with mild, moderate, or severe renal impairment. No trends toward

increases in exposure were observed in patients with various degrees of renal impairment; therefore, no dose adjustments are recommended for patients with renal impairment.

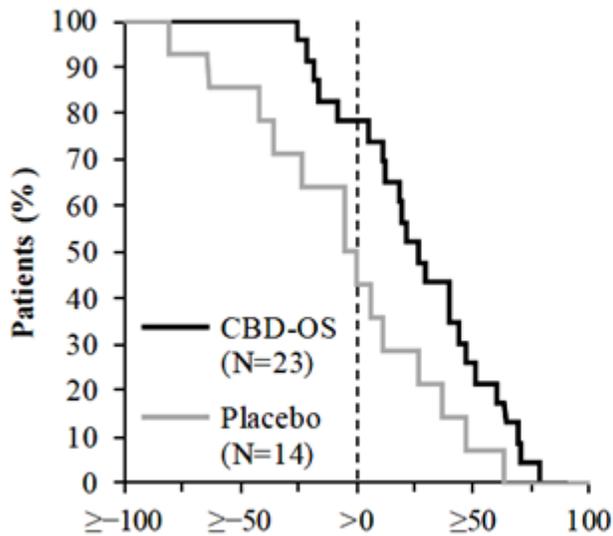
#### Exposure-response

As previously noted, there are large food effects with CBD. Moreover, CBD was not administered consistently in the fed or fasted state in clinical studies; consequently, exposure levels were found to be highly variable. Food diaries were not obtained during the study to help understand the variability in exposures in relation to food. Because of the large food effect seen with CBD and variability in exposures in the Phase 3 trials, the population PK (PPK) models for the DS and LGS populations were not found to be reliable. Exposure-response analyses could not be used to support the efficacy or safety of CBD.

#### Interaction with clobazam and stiripentol

Clobazam (CLB) is metabolized by CYP3A4, and to a lesser extent by CYP2C19 and CYP2B6, to the active metabolite norclobazam (N-CLB), which is thought to have 1/3 to 1/5 the activity of clobazam. N-CLB is metabolized by CYP2C19. CBD is known to inhibit the CYP2C19 enzyme and is therefore predicted to increase CLB and N-CLB levels. No increase in CLB levels was observed in clinical trials, but exposures to N-CLB were found to be up to 300% higher in the CBD arm compared to the placebo arm in the controlled trials. Based on this increase in N-CLB levels, the applicant explored the potential impact of clobazam use and N-CLB levels on the efficacy findings; that is, whether changes in N-CLB levels could explain some or all of the effect of CBD. The applicant conducted a number of subgroup analyses in the pivotal studies for LGS and DS. OCP determined that because of the small numbers of patients in the subgroups and variability in the data, the analyses were not adequately powered to allow reliable evaluation of the effects of CBD independent of clobazam. Additionally, the large number of concomitant medications used by patients made it difficult to analyze the effects of clobazam alone. In an attempt to further explore this issue, the applicant conducted an analysis of concomitant stiripentol (STP) use in Study 1332B. STP was used by a subset of patients in Study 1332B for DS (STP was not used in the LGS studies). STP, like CBD, inhibits the CYP2C19 enzyme. Patients who were taking clobazam and STP at baseline did not show a further increase of N-CLB levels following the initiation of CBD, but did have improved seizure control. The applicant hypothesizes that CLB and N-CLB levels were already maximally increased by STP-induced inhibition of CYP2C19, and patients did not appear to experience further augmentation of the CYP2C19 inhibition with the initiation of CBD. An analysis of the patients taking clobazam and STP showed that CBD was superior to placebo, with 80% of patients showing a reduction in seizures, vs. 50% on placebo. This is shown in Figure 1 below (CBD-OS in Figure 1 is cannabidiol oral solution).

**Figure 1: Cumulative Distribution of Seizure Reduction by Treatment Arm in Study 1332B (Patients taking clobazam and STP)**



Source: *summary-clin-efficacy-dravet-syn.pdf, page 83 of 122*

The OCP review team believes that this observation supports the applicant’s claim that CBD has an effect on seizures that is independent of its ability to increase N-CLB. As STP was not used in the LGS studies, this analysis could not be conducted in the LGS population.

Valproate Interaction

There was no effect of concomitant CBD administration on valproate (VPA) exposures in the clinical trials. Although increased rates of transaminase elevation were observed in the clinical trials with concomitant VPA use, this does not appear to be mediated by a PK interaction. Please refer to the safety section of this memo for further discussion.

Dosing/Titration regimen

*Maintenance dosing*

The OCP review notes that the 20 mg/kg/day dose used in the controlled studies for both LGS and DS demonstrated efficacy, but that the 10 mg/kg/day dose was studied only in the LGS population, where it also demonstrated efficacy. As previously noted, the exposure-response analysis was not found to be sufficiently reliable to support recommendations for dosing. Based on the efficacy seen in the LGS studies, OCP supports labeling for 10 to 20 mg/kg/day as target maintenance dose range in LGS patients. Based on discussions with the clinical team regarding the similarity of the disease populations, concerns regarding the dose-response observed with adverse events, and the desire for flexibility in dosing based on efficacy and tolerability, OCP also supports 10 to 20 mg/kg/day as the target maintenance dose range in DS patients. Please see the efficacy section of this memo for further discussion of the rationale for recommending the same maintenance dosing for LGS and DS.

The applicant has proposed that CBD be labeled for (b) (4) use, as this is how the drug was studied in clinical trials; however, it does not appear that the efficacy of CBD depends on concomitant use of other particular seizure drugs. Therefore, the recommended use of CBD does not need to be explicitly restricted to the (b) (4) setting. The proposed label will include recommendations for dosing adjustments when CBD is used with strong CYP3A4 and CYP2C19 inhibitors/inducers.

*Titration regimen*

The regimen used in the clinical trials was a 2.5 mg/kg/day initiation dose, to be increased by 2.5 mg/kg/day increments every 2 days until a dosage of 10 mg/kg/day was reached. If patients were titrated to the 20 mg/kg/day dosage level, starting from the 10 mg/kg/day dosage level, dosage was increased by 5 mg/kg/day increments every 2 days until the 20 mg/kg/day dosage level was reached.

For labeling, the applicant proposed an alternate titration regimen, with initial dosage of 5 mg/kg/day, with increases of 5 mg/kg/day every week to a maximum dosage of 20 mg/kg/day. The applicant's rationale for this new titration regimen was that it would be simpler and could improve tolerability. The applicant also reported that this regimen has been used in the EAPs and has been well-tolerated.

To support this alternate regimen, the applicant submitted a simulated PK profile for the original titration regimen that was compared with the simulated PK profile for the alternate titration regimen (based on a PPK model developed for DS). Given the previously stated concerns regarding the PPK model from the patient population, the pharmacometrics reviewer utilized the simulated PPK model from the healthy subject dataset to address the acceptability of the new regimen. This model is shown in Figure 2 below. The upper line represents the original titration regimen, and the lower line represents the proposed alternate titration regimen.

**Figure 2: Simulated PK Profile for Original Titration Regimen used in Clinical Trials and Proposed Alternate Regimen up to 20 mg/kg/day**



The model shows that the alternate titration regimen would provide slightly higher exposures until Day 4 following the initiation of the 5 mg/kg/day dose, but the remaining exposures would be generally lower than (within the first 3 weeks) or within the range of the current titration regimen.

Although the applicant did not provide safety data from the EAPs to specifically support the 5 mg/kg/day initiation dosage, the clinical review team has not identified any safety issues uniquely associated with this initiation dosage used in the EAPs. Additionally, safety data for the 5 mg/kg/day dosage in Study 1332A shows a safety profile comparable to placebo (see safety section of this review).

it is reasonable to recommend a slower titration based on the dose-response that was observed with regard to adverse events, particularly transaminase elevations. The titration regimen appears acceptable from a safety perspective and OCP and the clinical review team agree that it is acceptable for labeling. However, the clinical review team also noted that the regimen used in the controlled trials was acceptably tolerated, and there may be some situations (such as a patient with a particularly high seizure burden) where a prescriber may desire a faster titration to the 20 mg/kg/day dosage. Therefore, labeling will also include a statement that dosing may be increased from 10 mg/kg/day to 20 mg/kg/day by increments of 5 mg/kg/day no more frequently than every 2 days for situations where faster titration is warranted.

### QT study

The applicant conducted a thorough QT (TQT) study, GWEP1451, which was reviewed by the Interdisciplinary Review Team for QT Studies (IRT-QT). The IRT-QT team found the study to be inadequate to support the QT risk assessment for the proposed dosing in the current indication. The exposures achieved in the QT study are substantially lower than the therapeutic exposures of the parent and the 7-COOH-CBD metabolite because there are substantial food effects observed with CBD (4- to 5- fold increase in exposure) and the QT study was conducted in the fasted state. The QT-IRT team recommends that the applicant conduct another TQT study with appropriate dosing (e.g., in the fed state) to adequately characterize this risk of QTc prolongation.

The OCP review team recommends approval of the NDA. The OCP team proposes a variety of PMRs to further evaluate drug-drug interactions, as outlined in Section 13 of this review. A TQT study with appropriate dosing will also be required as a PMR.

## **6. Clinical Microbiology**

N/A

## **7. Clinical/Statistical- Efficacy**

Dr. Natalie Getzoff was the clinical reviewer for this application. Dr. Xiang Ling was the biometrics reviewer and Dr. Kun Jin was the biometrics team leader for this application.

The applicant conducted three randomized, double-blind, placebo-controlled trials in LGS (2 studies) and DS (1 study), which served as the basis for this application:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS
- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS

All three studies had a similar study design, with a 28-day baseline period followed by a 14-week treatment period that included a 7- or 11-day titration period.

The results of these studies will be described below. A detailed analysis of the studies can be found in the combined clinical and statistical review by Dr. Getzoff and Dr. Ling.

### **Study 1414 in LGS**

Study 1414 was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with LGS. There were 225 patients randomized in a 1:1:1 ratio to either CBD 10

mg/kg/day (divided twice daily), CBD 20 mg/kg/day (divided twice daily), or placebo. CBD (or the equivalent volume of placebo) was started at a dosage of 2.5 mg/kg/day, and increased by 2.5 mg/kg/day increments every other day, over a 7-day period, to a dosage of 10 mg/kg/day. Patients were then further titrated by 5 mg/kg/day increments every other day to a dosage of 20 mg/kg/day (or matching placebo), for a total of 11 days of titration. Randomization was stratified by age group (2-5 years, 6-11 years, 12-17 years, and 18-55 years). Patients were required to meet the following enrollment criteria: have a clinical diagnosis of LGS (including documentation of having met EEG diagnostic criteria) not completely controlled by AEDs, experience  $\geq 2$  drop seizures per week during a 28-day baseline period, be taking one or more AEDs at a stable dose, and be between 2 and 55 years of age. Concomitant AEDs and doses were to remain constant during the treatment period. The study was conducted in the United States (US), United Kingdom (UK), France, and Spain.

The primary endpoint for Study 1414 was the percentage change from baseline in drop seizure frequency (average per 28 days) during the 14-week treatment period. A drop seizure 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.”* Non-drop seizures were defined as *“all other countable seizures, except drop attacks, and [included] atypical absence, focal [seizures] with or without loss of consciousness, and any seizure that would not result in a fall.”* Patients or caregivers recorded the number and type of drop seizures (atonic, tonic, or tonic-clonic) and non-drop seizures (myoclonic, partial, or absence) each day using an interactive voice response system (IVRS) telephone diary during the 28-day baseline period and during the entire treatment period until completion of dosing.

Secondary “key” endpoints controlled for multiplicity were:

- Number of patients considered treatment responders, defined as those with a  $\geq 50\%$  reduction in drop seizure frequency from baseline during the treatment period
- Percentage change from baseline in number of total seizures (average per 28 days)
- Subject/Caregiver Global Impression of Change (S/CGIC) [in the patient’s overall condition]: the S/CGIC was rated using a 7-point scale (1 = very much improved; 7 = very much worse) and compared the patient’s status at the last visit with baseline.

Exploratory endpoint

The sponsor assessed “drop seizure free days” as an exploratory endpoint.

The primary analyses used the intention-to-treat (ITT) analysis set, which included all patients randomized to treatment who received at least 1 dose of the investigational treatment and who had any 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, as presented in the sequence listed in Table 1 below.

**Table 1: 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	1 <sup>st</sup> key secondary endpoint	20 mg/kg/day CBD vs. Placebo
4	2 <sup>nd</sup> key secondary endpoint	20 mg/kg/day CBD vs. Placebo
5	3 <sup>rd</sup> key secondary endpoint	20 mg/kg/day CBD vs. Placebo
6	1 <sup>st</sup> key secondary endpoint	10 mg/kg/day CBD vs. Placebo
7	2 <sup>nd</sup> key secondary endpoint	10 mg/kg/day CBD vs. Placebo
8	3 <sup>rd</sup> key secondary endpoint	10 mg/kg/day CBD vs. Placebo

The primary endpoint of percent change from baseline in seizure frequency was analyzed using a Wilcoxon rank-sum test. Seizure frequency was calculated as a 28-day frequency. Estimates of the median differences between CBD and placebo and the approximate 95% confidence intervals (CI) were calculated using the Hodges-Lehmann approach.

The proportion of responders was analyzed using a Cochran-Mantel-Haenszel (CMH) test stratified by age group. Analyses of total seizures were performed with the same analysis method used for the primary endpoint. For the analysis of S/CGIC scores, the CGIC was used, except in the situation where only a SGIC was completed, in which case the SGIC was to be used. The 7-point scale scores at the end of treatment visit and last visit (if different from the end of treatment) were analyzed using ordinal logistic regression. However, Dr. Ling notes that 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, Dr. Ling 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.

## Results

### Primary Endpoint

The primary efficacy analysis population comprised a total of 225 patients: 76 patients in the 20 mg/kg/day CBD group, 73 patients in the 10 mg/kg/day CBD group, and 76 patients in the placebo group. The overall discontinuation rate in the study was low (5.8%); however, discontinuations were greater in the 20 mg/kg/day CBD groups (11.8% in the 20 mg/kg/day group compared to 2.7% in the 10 mg/kg/day group and 2.6% in the placebo group). The majority of discontinuations in the CBD group were due to adverse events. Demographic variables were well balanced across the three treatment groups. The study population was predominantly White/Caucasian (88%). Other racial groups consisted of Black/African-American, Asian, and other. There is no indication of differences in the phenotype of LGS by race/ethnicity to suggest a differential response to treatment. Therefore, the findings of these studies should be applicable to the general LGS population.

The treatment groups were reasonably well matched for baseline drop seizure counts. Patients took a median of 3 concomitant AEDs in all treatment groups. Approximately 50% of patients took concomitant clobazam, and approximately 40% of patients took concomitant valproic acid. Other frequently used AEDs included lamotrigine, levetiracetam, and rufinamide.

There were statistically significant differences between each CBD group (20 mg/kg/day and 10 mg/kg/day) compared to the placebo group in the percent change from baseline in drop seizure frequency in favor of CBD ( $p=0.005$  and  $p=0.002$ , respectively). **Table 2**, from the clinical study report (CSR), and confirmed by the FDA statistical reviewer, presents the results of the analysis of the primary endpoint.

**Table 2: Primary Endpoint Analysis Results from Study 1414 (LGS)**

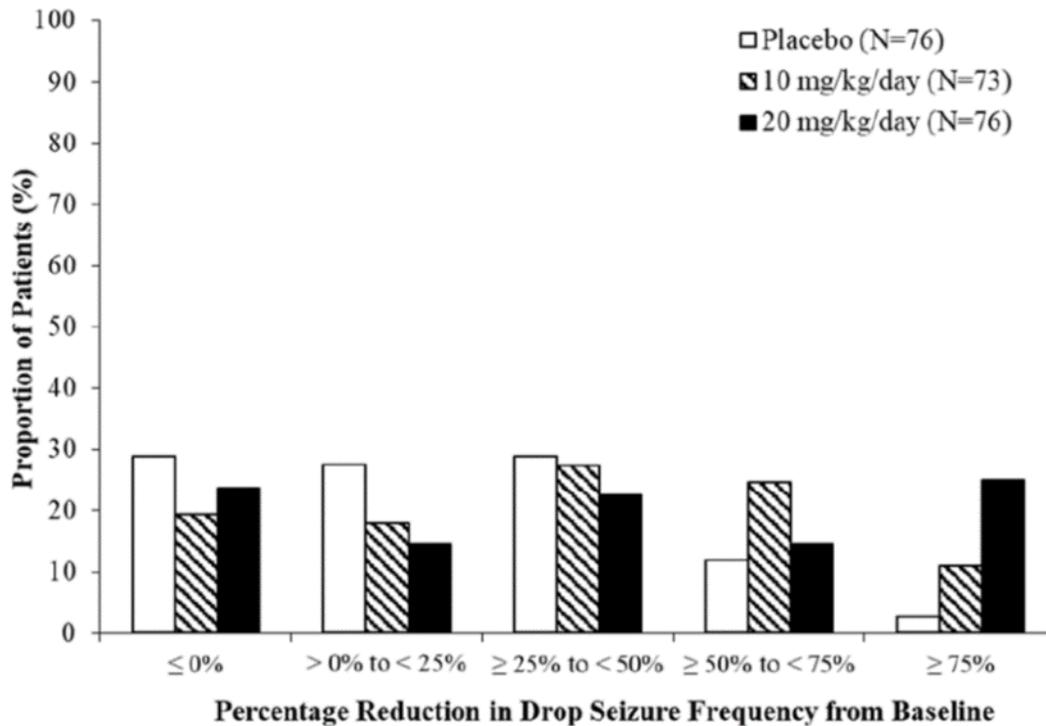
Drop Seizure Frequency (per 28 Days)	20 mg/kg/day (N=76)	10 mg/kg/day (N=73)	Placebo (N=76)
Baseline Period Median	85.5	86.9	80.3
Treatment Period Median	44.9	50.0	72.7
Median Percentage Change During Treatment, Interquartile range (Q1, Q3)	-41.9 (-72.4, -1.3)	-37.2 (-63.8, -5.6)	-17.2 (-37.1, 0.9)
<b>Comparison over Placebo</b>			
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: CSR Table 8.4.1.1-1, confirmed by FDA statistical reviewer

\*based on Hodges-Lehmann estimator

Overall, the study results show a statistically significant seizure reduction in both the 10 mg/kg/day and 20 mg/kg/day CBD groups, compared to placebo. The distribution of responders, shown in Figure 3, suggests that the efficacy findings may be largely driven by a subset of patients who show a large (>50%) reduction in seizures.

**Figure 3: Study 1414, Proportion of Patients by Category of Seizure Response**



Source: Applicant submission, May 3, 2018.

Sensitivity analyses using ANCOVA on ranked data and log-transformed data yielded results similar to the primary analysis. Consistent results were seen for the maintenance period and each 4-week period of the maintenance period (Table 3).

**Table 3: Study 1414, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint**

Analysis Period	Treatment	n	Median	Q1 Q3	Estimated Median Difference <sup>b</sup> (95% CI)	p-value <sup>c</sup>
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) <sup>a</sup>	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) <sup>a</sup>	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) <sup>a</sup>	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

<sup>a</sup> Patients with at least 7 days of seizure data within the corresponding 4 week period

<sup>b</sup> based on Hodges-Lehmann estimator

<sup>c</sup> by Wilcoxon Rank Sum Test

There were few missing data (2%); therefore, results of sensitivity analyses for missing data were generally similar to the primary analysis. Dr. Liang performed an additional sensitivity analysis using multiple imputation to account for missing data because of dropouts, because of an imbalance in discontinuation rates between the 20 mg/kg/day CBD group and placebo. Although the resulting estimated difference between the two groups was smaller (-15.6% vs. -21.6%), the difference still favored treatment with CBD.

There were 6 protocol amendments during the study. Dr. Getzoff notes that Amendment 6 increased the planned sample size from 120 patients to 150 patients, based on a review of published clinical trial literature that showed a greater placebo response rate than was previously used in the initial sample size calculation. Although this justification was found to be acceptable by the clinical reviewer, Dr. Getzoff notes that the final enrollment of the study was 225 subjects, without further justification for the increase above 150. Dr. Ling 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.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, region, clobazam use, valproic acid use, lamotrigine use, and rufinamide use for both the 20 mg/kg and 10 mg/kg groups, as shown below (Table 4, Table 5). The results of the subgroup analyses generally favored CBD for both doses in all groups.

**Table 4: 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 5: Study 1414, Subgroup Analysis of the Primary Endpoint (Concomitant AEDs)**

Subgroup/Item	Treatment	N	Median	Median Difference (95% CI)*	
<b>Clobazam Use</b>					
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		
<b>Valproic Acid Use</b>					
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		
<b>Lamotrigine Use</b>					
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		
<b>Levetiracetam Use</b>					
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		
<b>Rufinamide Use</b>					
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

### Secondary Endpoints

The analysis of the secondary endpoint of  $\geq 50\%$  reduction in convulsive seizures from baseline demonstrated a greater reduction 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;  $p=0.001$ ) and the 10 mg/kg/day group (OR =3.3;  $p = 0.003$ ).

A greater median reduction in total seizure frequency (28-day average) during the treatment period was observed in both the 20 mg/kg/day and 10 mg/kg/day CBD groups (-38.4% and -36.4%, respectively), compared with the placebo group (-18.5%). The difference between each CBD group and placebo was statistically significant ( $p=0.009$  and  $p=0.002$ , respectively).

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 than the end of treatment) were analyzed using ordinal logistic regression. The mean S/CGIC score at last visit was 3.0 in the 20 mg/kg/day CBD group and 3.2 in the 10 mg/kg/day CBD group (corresponding to “slightly improved”), compared with 3.6 (most closely associated with “no change”) in the placebo group. The treatment differences were in favor of 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 ( $p=0.044$  and  $p=0.002$ , respectively).

The results of the secondary endpoints of  $\geq 50\%$  reduction in convulsive seizures and total seizure frequency were generally consistent with effects on seizure reduction seen on the primary endpoint. The reduction in total seizure frequency suggests that the efficacy of CBD is not limited to drop attacks. The changes on the S/CGIC provide additional support for the clinical meaningfulness of the effects on seizure reduction.

### Exploratory Endpoint

There were 3 patients in the CBD 10 mg/kg/day group, 5 patients in the CBD 20 mg/kg/day group, and 1 patient in the placebo group who completed the study and reported no drop seizures during the maintenance period. Although this was an exploratory endpoint, there appears to be a clinically meaningful difference between the treatment and placebo groups.

### **Study 1423 in LGS**

Study 1423 was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with LGS. The study design and study population was identical to Study 1414 with the exception that Study 1423 included only a 20 mg/kg/day CBD dose arm. Please refer to the description of Study 1414 above for details of the study design and population. There were 171 patients randomized in a 1:1 ratio to CBD 20 mg/kg/day (divided twice daily) or placebo. The study was conducted in the US, Poland, and the Netherlands.

As with Study 1414, the primary endpoint for Study 1423 was the percent change from baseline in drop seizure frequency (average per 28 days) during the treatment period. Please refer to the definition of drop seizures described under Study 1414 above.

The statistical analysis of the primary endpoint was identical to that described for Study 1414. The study contained the same secondary endpoints as Study 1414. It was inconsistently stated in the in the statistical analysis plan (SAP) whether there was pre-specified hierarchal testing of secondary endpoints in the United States (US) SAP; however, the applicant provided a clarification that the secondary endpoints were pre-specified for hierarchical testing and that a sentence in the SAP stating that secondary endpoints were only pre-specified for hierarchical testing in the EU was an error. However, this is difficult to verify. All statistical tests were 2-sided and used the 5% significance level.

The sponsor also assessed “drop seizure free days” as an additional secondary endpoint that was not tested hierarchically.

## Results

### Primary Endpoint

The primary efficacy analysis population comprised a total of 171 patients: 86 patients in the 20 mg/kg/day CBD group and 85 patients in the placebo group. Discontinuations were 16.3% in the CBD group vs. 1.2% in the placebo group. The majority of discontinuations in the CBD group were due to adverse events. Demographic variables were well balanced across the three treatment groups. As with Study 1414, the study population was predominantly White/Caucasian (approximately 90%). Other racial groups consisted of Black/African-American, Asian and other.

Baseline seizure count and concomitant AED use were similar to those observed in Study 1414. The treatment groups were reasonably well matched for baseline drop seizure counts. Patients took a median of 3 concomitant AEDs in all treatment groups. Approximately 50% of patients took concomitant clobazam, and approximately 40% of patients used concomitant valproic acid. Other frequently used AEDs include lamotrigine, levetiracetam, and rufinamide.

There was a statistically significant difference between the groups in the percent change from baseline in drop seizure frequency during the treatment period, in favor of CBD treatment ( $p=0.014$ ). **Table 6**, from the CSR, and confirmed by the FDA statistical reviewer, presents the results of the analysis of the primary endpoint:

**Table 6: Primary Endpoint Analysis Results from Study 1423(LGS)**

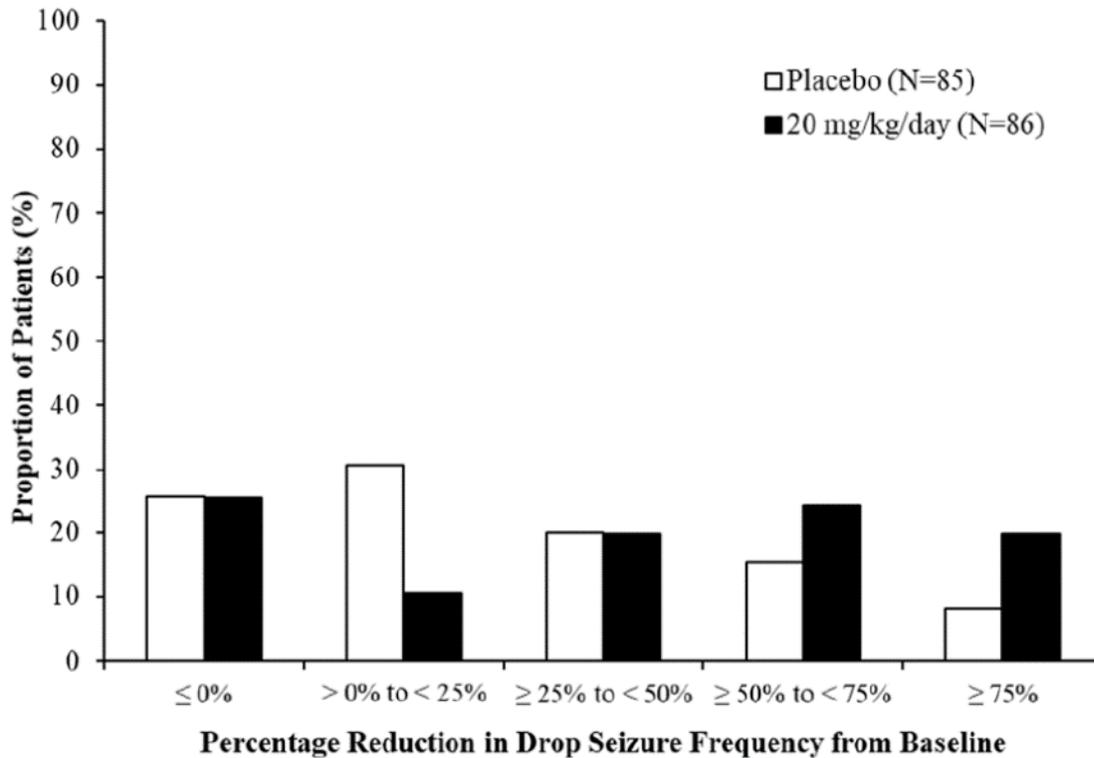
Drop Seizure Frequency (per 28 Days)	CBD 20 mg/kg/day (N=86)	Placebo (N=85)
Baseline Period Median	71.4	74.7
Treatment Period Median	31.4	56.3
Median Percentage Change from Baseline (Q1, Q3)	-43.9 (-69.6, -1.9)	-21.8 (-45.7, 1.7)
Estimated Median Difference (CI)*	-17.2 (-30.3, -4.1)	
p-value by Wilcoxon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

Source: CSR Table 8.4.1.1-1, confirmed by FDA statistical reviewer

\*based on Hodges-Lehmann estimator

The study results were generally consistent with those of Study 1414, showing a statistically significant seizure reduction in the 20 mg/kg/day CBD groups compared to placebo. As with Study 1414, the distribution of responders, shown in Figure 4, suggests that the efficacy findings may be largely driven by a subset of patients who show a large (>50%) reduction in seizure frequency.

**Figure 4: Study 1423, Proportion of Patients by Category of Seizure Response**



Source: Applicant submission, May 3, 2018.

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 period (Table 7).

**Table 7: Study 1423, Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint**

Analysis Period	Treatment	n	Median	Q1, Q3	Estimated Median Difference <sup>b</sup> (95% CI)	p-value <sup>c</sup>
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) <sup>a</sup>	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) <sup>a</sup>	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) <sup>a</sup>	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

<sup>a</sup> Patients with at least 7 days of seizure data within the corresponding 4 week period

<sup>b</sup> based on Hodges-Lehmann estimator

<sup>c</sup> by Wilcoxon Rank Sum Test

There were few missing data (2%); therefore, results of sensitivity analyses for missing data were generally similar to the primary analysis. Dr. Liang performed an additional sensitivity analysis using multiple imputation to account for missing data because of dropouts due to the imbalance in discontinuation rates between the 20 mg/kg/day CBD group and placebo. Although the resulting estimated difference between the two groups was smaller (-5.5% vs. -17.2%), the difference still favored treatment with CBD.

There were 3 protocol amendments during the study. Amendment 3 increased the planned sample size from 80 patients to 100 patients, based on a review of published clinical trial literature that showed a greater placebo response rate than was previously used in the initial sample size calculation. However, the final enrollment for the study was 171 subjects. To explore the impact of the over-enrollment, Dr. Liang conducted an analysis on the first 100 patients enrolled into Study 1423. The placebo group had a 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. A query was sent to the applicant to understand the reason for the over-enrollment. The following description from the clinical/statistical provides the rationale for the over-enrollment:

*“...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 based on any interim analysis, Dr. Liang felt that analysis of the entire ITT dataset was appropriate for the primary endpoint.

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, region, and concomitant AED use (Table 8, Table 9). The results generally favored CBD over placebo in the subgroups.

**Table 8: Study 1423, Subgroup Analysis of the Primary Endpoint (Demographics)**

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*
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	
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	
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	
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 9: Study 1423, Subgroup Analysis of the Primary Endpoint (Concomitant AEDs)**

Subgroup/Item	Treatment	N	Median	Median Difference (95% CI)*
<b>Clobazam Use</b>				
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	
<b>Valproic Acid Use</b>				
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	
<b>Lamotrigine Use</b>				
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	
<b>Levetiracetam Use</b>				
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	
<b>Rufinamide Use</b>				
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

Secondary endpoints

Hierarchical testing of the secondary endpoints was not specified in the EU SAP, but not in the US SAP. A descriptive summary of selected secondary endpoints is provided.

- 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 nominal p value was 0.004.
- A greater median reduction in total seizure frequency (28-day average) during the treatment period was seen in the CBD group (44.2%), compared with the placebo group (23.5%). The nominal p-value was 0.001.
- 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. The treatment difference was in favor of the CBD group (OR=2.5) and nominally statistically significant ( $p=0.001$ ).

- 3 of 86 (3%) patients in the EPIDIOLEX 20 mg/kg/day group reported no drop seizures during the maintenance period, compared to 0 patients in the placebo group.

The secondary endpoints results were generally consistent with the results of the primary endpoint.

### **Study 1332B in DS**

Study 1332B was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS. The study consisted of a baseline period, a treatment period (titration plus maintenance), and a taper period (alternatively, patients could be enrolled in an open-label, long-term extension study). There were 120 patients randomized in a 1:1 ratio to either CBD 20 mg/kg/day (divided twice daily) or placebo. 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 increments every other day to 10 mg/kg/day, and then increased by 5 mg/kg/day increments every other day to 20 mg/kg/day. Randomization was stratified by age group (2-5 years, 6-12 years, and 13-18 years). Subjects were required to meet the following enrollment criteria: have a documented history of DS not completely controlled by current AEDs, experience  $\geq 4$  convulsive seizures during a 28-day baseline period, be taking one or more AEDs at a stable dose, and be between 2 and 18 years of age. Concomitant AEDs and doses were to remain constant during the treatment period. The study was conducted in the US, UK, France, and Poland.

The primary endpoint was the percent change from the baseline in total convulsive seizure frequency during the entire treatment period of the study. Convulsive seizures were defined as tonic, clonic, tonic-clonic, or atonic. Patients or caregivers recorded the number and type of convulsive seizures and non-convulsive seizures (myoclonic, partial, or absence) each day using an IVRS telephone diary during a 28-day baseline period and during the entire treatment period (titration and maintenance periods) until completion of dosing.

The number of patients considered treatment responders, defined as those with a  $\geq 50\%$  reduction in convulsive seizures from baseline during the treatment period, was designated as a “key” secondary endpoint; however, there was no pre-specified hierarchical analysis in the US SAP. Other secondary endpoints included: convulsive seizure treatment responders and convulsive seizure freedom, status epilepticus, non-convulsive seizures, individual seizure types and total seizures, use of rescue medication, the Quality of Life in Childhood Epilepsy scale, and Caregiver Global Impression of Change (CGIC).

The primary analyses used the intention to treat (ITT) analysis set, which included all patients randomized to treatment who received at least 1 dose of the investigational treatment and had any post-baseline efficacy data. All statistical tests were 2-sided and used the 5% significance level.

The primary endpoint of percentage change from baseline in seizure frequencies was analyzed using a Wilcoxon rank-sum test. Seizure frequency was calculated as a 28-day frequency. Estimates of the median differences between CBD and placebo and the approximate 95% confidence intervals (CI) were calculated using the Hodges-Lehmann approach.

## Results

### Primary Endpoint

The primary efficacy analysis population comprised a total of 120 patients: 61 patients in the CBD group and 59 patients in the placebo group.

Discontinuations were 14.8% in the CBD group vs. 5.1% in the placebo group. All of the discontinuations in the CBD group were due to adverse events. Demographic variables were well balanced across the three treatment groups. The study population was predominantly White/Caucasian (approximately 78%). Other racial groups consisted of Black/African-American, Asian and other. There were 14% of patients who were classified as “not applicable” due to country-specific data protection laws. As with LGS, there is no indication of a variation in the phenotype of DS by race/ethnicity to suggest a differential response to treatment. Therefore, the findings from the study should apply to the broad DS population.

The treatment groups were reasonably well matched for baseline drop seizure counts. Patients took a median of 3 concomitant AEDs in both treatment groups. Approximately 65% of patients took concomitant clobazam, approximately 55% of patients used valproic acid, and approximately 43% of patients were taking concomitant stiripentol.

There was a statistically significant difference between the groups in the percent change from baseline in total convulsive seizure frequency, in favor of CBD treatment ( $p=0.012$ ).

**Table 10**, adapted from the CSR, and confirmed by the FDA statistical reviewer, presents the results of the analysis of the primary endpoint:

**Table 10: Primary Endpoint Analysis Results from Study 1332B (DS)**

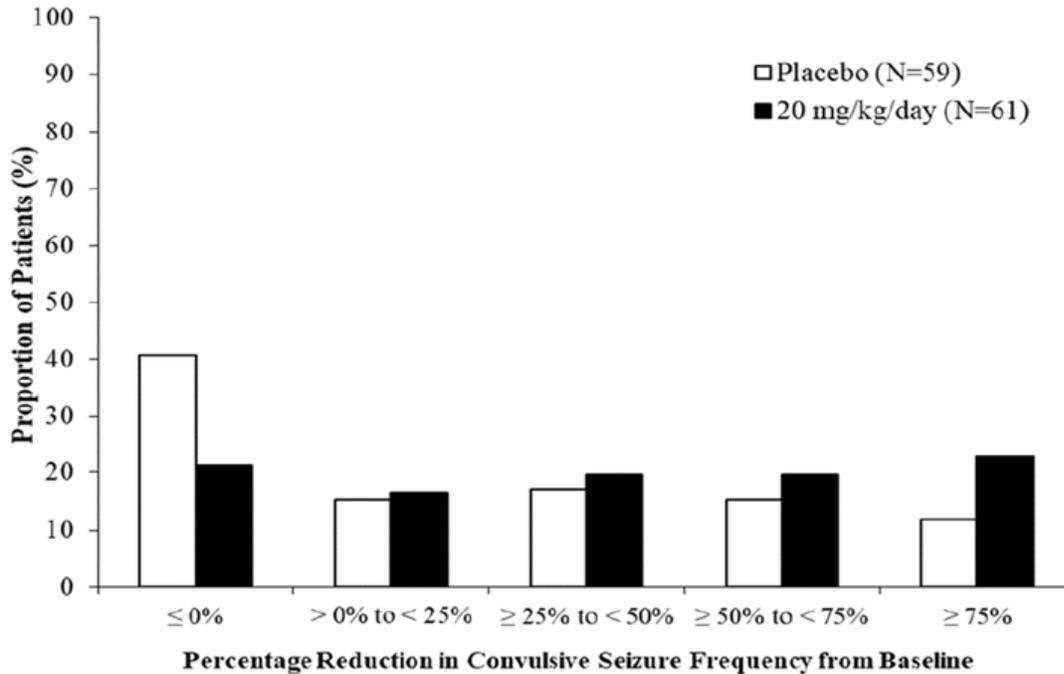
Total Convulsive Seizure Frequency (per 28 Days)	CBD (N=61)	Placebo (N=59)
Baseline Period Median	12.4	14.9
Treatment Period Median	5.9	14.1
Median Percentage Change from Baseline (Q1, Q3)	-38.9 (-69.5, -4.8)	-13.3 (-52.5, 20.2)
Estimated Median Difference (CI)*	-22.8 (-41.1, -5.4)	
p-value by Wilcoxon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

Source: CSR Table 8.4.1.1-1, confirmed by statistical reviewer

\*based on Hodges-Lehmann estimator

The study results show a statistically significant reduction in seizures, with treatment effects comparable to those seen in the LGS studies. The distribution of responders, shown in Figure 5, shows a consistent response across the responder categories; however, as with the LGS studies, it does appear that the numerically greater difference is in patients with a large reduction in seizures (>75%).

**Figure 5: Study 1332B, Proportion of Patients by Category of Seizure Response**



Source: Applicant submission, May 3, 2018.

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 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 <sup>b</sup> (95% CI)	p-value <sup>c</sup>
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) <sup>a</sup>	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) <sup>a</sup>	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) <sup>a</sup>	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		

<sup>a</sup> Patients with at least 7 days of seizure data within the corresponding 4 week period

<sup>b</sup> based on Hodges-Lehmann estimator

<sup>c</sup> by Wilcoxon Rank Sum Test

There was little missing data (4%); therefore, sensitivity analyses for missing data were generally similar to the primary analysis. Dr. Liang performed an additional sensitivity analysis using multiple imputation to account for missing data due to dropouts due to the imbalance in discontinuation rates between the 20 mg/kg/day CBD group and placebo. Although the resulting estimated difference between the two groups was smaller (-14.1% vs. -22.8%), the difference still favored treatment with CBD.

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 (Table 12).

Subgroup analyses were also performed on the primary efficacy endpoint for concomitant drugs of interest, specifically clobazam, valproic acid, and stiripentol (Table 13). 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.

**Table 12: Study 1332B, Primary Efficacy Endpoint Analysis by Subgroups**

Subgroup Item	Treatment	N	Median	Median Difference (95% CI)*	
<b>Sex</b>					
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		
<b>Race</b>					
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		
<b>Age</b>					
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		
<b>Region</b>					
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 13: Study 1332B, Primary Efficacy Endpoint Analysis by Concomitant Drugs of Interest**

Concomitant Drug Y/N	Treatment	N	Median	Median Difference (95% CI)*
<b>Clobazam</b>				
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	
<b>Valproic Acid</b>				
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	
<b>Stiripentol</b>				
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

Secondary endpoints

Hierarchical testing of the secondary endpoints was specified in the EU SAP, but not in the US SAP. A descriptive summary of selected secondary endpoints is provided.

- There were 26 (42.6%) patients on CBD versus 16 (27.1%) patients on placebo who showed a ≥50% reduction from baseline in convulsive seizures. The nominal *p*-value was 0.078.
- The median percentage change from baseline in total seizure frequency during the treatment period was -28.57 in the CBD group compared with -9.00 in the placebo group. The estimated median difference was -19.20 (-39.25, -1.17), favoring CBD over placebo.
- There were 4 patients treated with CBD 20 mg/kg/day who reported no convulsive seizures during the maintenance period, compared to 0 patients in the placebo group.

The secondary endpoints results were generally consistent with the results of the primary endpoint.

**Efficacy Discussion:**

The applicant submitted data from three randomized, double-blind, placebo-controlled trials conducted in patients with LGS (2 studies) and DS (1 study). The studies compared the change in seizure frequency (primary endpoints assessed drop seizures for LGS and convulsive seizures for DS; total seizure counts were also assessed), as assessed by seizure diaries, between the 14-week treatment period and a 28-day baseline period. The studies all utilized a similar design that is typical for trials that assess drugs to treat seizures. The

primary endpoint for the LGS studies was the change in “drop seizures”, and the primary endpoint for the DS study was the change in “convulsive seizures”. Both endpoints were agreed upon with the Agency prior to the initiation of the studies. The studies were generally well-conducted, with little missing data, and no concerns with study integrity were identified. It is noted that both LGS studies were over-enrolled; however, Dr. Getzoff and Dr. Ling reviewed the reasons for over-enrollment, performed sensitivity analyses to assess the impact of the over-enrollment, and concluded that the over-enrollment did not impact the overall interpretation of the study results. Overall, the three studies showed an approximate 20% decrease in seizure frequency in CBD-treated patients, compared to placebo-treated patients. The secondary endpoints in the studies also generally favored CBD. The study results were both clinically meaningful and statistically significant, and support the effectiveness of CBD for both the LGS and DS patient populations. There was a demonstrated effect of CBD alone and when added to clobazam, but the effect was consistently greater in the latter group, perhaps because of increased levels of clobazam’s active metabolite.

The applicant is seeking an indication for the treatment of seizures associated with LGS and DS. The primary endpoint for the LGS studies was change in “drop seizures”, which was defined as atonic, tonic or tonic-clonic seizures that led or could have led to fall or injury. The primary endpoint for the DS study was the change in “convulsive seizures”, which were defined as atonic, tonic, clonic, or tonic-clonic seizures. This endpoint is similar to “drop seizures”, but includes clonic seizures, and does not require that the seizures led or could have led to a fall or injury. Although the seizure definitions were not identical, it is reasonable to assume that the studies were measuring seizure types of similar character and severity. Additionally, both studies demonstrated positive effects on total seizure counts, which included other seizure types (e.g., absence, focal seizures) that did not meet the definition of drop or convulsive seizures. Given that the seizure types were similar between the two disease populations and an overall reduction in all seizure types was seen with CBD for both populations, we believe the study findings support an indication for the treatment of seizures associated with both LGS and DS.

The applicant is also proposing the same dosing regimen for both the LGS and DS populations: a titration up to 10 mg/kg/day as a maintenance dosage, with further titration up to 20 mg/kg/day, as needed. All three studies assessed a 20 mg/kg/day dosage of CBD; however, only Study 1414 in LGS assessed a dosage of 10 mg/kg/day. In Study 1414, the 10 mg/kg/day dosage of CBD showed an estimated median difference from placebo of 19.2%, while the 20 mg/kg/day dosage showed a difference of 21.6%. The difference in safety between the two dosages showed a more notable difference in dose-response, with the 20 mg/kg/day group showing markedly higher rates of adverse events than the 10 mg/kg/day, particularly transaminase elevations (see safety section of this review). The dose-response seen with adverse events supports initial use of lower effective dosages with higher dosages being reserved for patients with inadequate seizure control at the initial dose. As noted above, given that the seizure types were similar between the two disease populations, and as an overall reduction in all seizure types was seen with CBD for both populations, it is reasonable to assume that the 10 mg/kg/day dosage that was shown to be effective in LGS

will also be effective in DS. Although there was a marginal difference in efficacy between the 10 mg/kg/day dosage and the 20 mg/kg/day dosage in Study 1414, there are some patients who may show additional benefit from higher doses. The ability to titrate CBD to 20 mg/kg/day based on clinical response and tolerability allows prescribers to use a higher dose if that is warranted for their patient. Therefore, the applicant's proposal for dosing is reasonable. Please refer to the Clinical Pharmacology section of this review for a discussion of the potential impact of concomitant clobazam use on the efficacy findings for CBD.

### **Efficacy conclusions**

The applicant has provided positive results from three randomized, double-blind, placebo-controlled trials conducted in patients with LGS and DS. The design of the studies and primary endpoints are consistent with other studies that have been used to support drug approvals for epilepsy indications, including LGS. The studies are adequate and well-controlled. The statistically significant and clinically meaningful results from these three adequate and well-controlled studies in two similar diseases with comparable study endpoints provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS. In both diseases, there were more patients on active treatment with substantial effects on seizure frequency (50-75% reduction). Despite the uncertainty of the effect of food on blood levels, the overall difference between 10 and 20 mg is a necessary indicator that dose-response is not steep and should not be greatly affected by intermittent food-related differences.

## **8. Safety**

Dr. Ellis Unger performed the safety review.

The primary safety analysis was conducted using the controlled safety database, derived from the following sources:

- Study 1414 and Study 1423 – two 14-week, multicenter, randomized, double-blind, placebo-controlled trials in patients with LGS
- Study 1332B – a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with DS
- Study 1332A – a 3-week, randomized, double-blind, placebo-controlled dose-finding study in patients with DS

Additional uncontrolled safety data were analyzed on the uncontrolled safety database, derived from the following sources:

- Study 1415- an ongoing open-label extension study in LGS and DS patients expanded access programs and compassionate access schemes at 38 sites in the US and Australia for patients with drug-resistant epilepsy.

The 120-day safety update submitted on February 21, 2018, included additional adverse events from these studies and these events were included in the uncontrolled safety database. These data provided a secondary role in the safety analysis.

Additionally, Study 1424 is an ongoing 14-week, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of CBD 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.

Safety data were pooled for patients with LGS and DS because the diseases are similar, and study designs and CBD doses were comparable for the studies.

Exposures and Adequacy of the Safety Database

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

Table 14, copied from Dr. Unger’s review, describes the exposures with CBD and the sources that comprise the safety data to support this application. These exposures include data from the 120-day safety update.

**Table 14: Overall Cannabidiol Exposure in the Clinical Development Program**

<b>All subjects exposed to cannabidiol</b>	<b>1808</b>	
<b>Subjects with epilepsy</b>	<b>1419</b>	
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
<b>Subjects without epilepsy</b>	<b>389</b>	
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

Of these 1808 individual exposures, there are 291 patients with DS and LGS and 158 patients with drug-resistant epilepsy in EAP who have been exposed to CBD for over 1 year. As noted in the efficacy section of this memo, the baseline demographics in the controlled safety population were generally well-balanced across the treatment groups. Approximately 80% of subjects in the controlled safety database were from the US. As previously noted, the safety population was predominantly white/Caucasian (approximately 85%); however, there is no indication that the phenotype of LGS or DS varies with race/ethnicity to suggest a differential response to treatment or susceptibility to drug toxicity. Therefore, the safety findings should be generalizable to the indicated US patient population. Dr. Unger has determined that the patient exposures are adequate to support an assessment of safety in the application.

The methods for assessing and collecting safety data appear to be adequate. Dr. Unger performed an independent analysis of the safety data. He reviewed the translation of verbatim terms to preferred terms for completeness and accuracy. Dr. Unger identified some inaccuracies and changes or additions were made, as indicated. Grouping of related adverse event terms was performed by the applicant and was found to be inconsistent, and underestimated the magnitude of safety signals in some cases. Dr. Unger performed his own analysis with grouping of related preferred terms, as appropriate. In addition to assessing change in mean values over time, critical laboratory parameters were visually inspected in scatter plots.

#### Deaths

There were 21 deaths reported in the development program. One death was reported in the controlled trials in a patient taking CBD 20 mg/kg/day. There were seven deaths reported in the open-label extension trial and 13 deaths in the EAP. Dr. Unger reviewed the causes of death. For the majority of cases, the causes of death appeared to be related to the underlying disease. These patients were generally very ill, with multiple comorbidities and complex disease courses. Dr. Unger notes that: "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...the proximate causes of death were typical for these patient populations; there was no suggestion that an off-target drug effect was responsible."

#### Serious and Significant Adverse Events

Table 15 below, from the safety review, shows the serious adverse events (SAEs) that were reported in at least two more patients treated with CBD than in patients on placebo. Transaminase elevations are notable and will be described further below. There were two reports of "hepatic failure"; however, neither patient had elevations of bilirubin or INR consistent with generally accepted criteria for liver failure. They are more accurately considered as transaminase elevations. Infections and seizures are common in this population and do not appear to be markedly different from placebo. Respiratory failure does not appear to be markedly different from placebo.

**Table 15: Serious Adverse Events in the controlled LGS/DS population**

Cannabidiol dose (mg/kg/d)	Cannabidiol				Placebo	RR	$\Delta$ Risk (%)
	5	10	20	All			
	N = 10	75	238	323	227		
Transaminases $\uparrow$ , 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

Dr. Unger reviewed SAEs in the uncontrolled safety population. Transaminase elevations and infections were also observed most frequently in this population. No new signals were identified.

Dr. Unger also reviewed severe adverse events. Severe adverse events were generally similar to the serious adverse events in character. There were 2 severe cases of rash and 3 severe cases of decreased appetite in the CBD group that were not seen in the serious adverse events.

#### Discontinuations Due to Adverse Events

In the controlled safety database, discontinuations due to adverse events were reported in 2.7% of patients taking CBD 10 mg/kg/day, 11.8% of patients taking CBD 20 mg/kg/day, and 1.3% in patients on placebo. As with the SAEs, adverse events leading to discontinuation are most notable for transaminase elevations and somnolence.

#### Treatment-Emergent Adverse Events (TEAEs) of All Severities

Table 16, copied from Dr. Unger's review, shows all TEAEs in the controlled safety database that occurred in  $\geq 2\%$  of CBD-treated patients and more frequently than in the placebo group. The most commonly observed adverse events in controlled clinical trials that occurred with a greater incidence in CBD-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations) and infections (e.g., pneumonia). These events were generally mild to moderate in severity. There was some trend towards higher rates at the 20 mg dose, but this was not consistent and differences were generally small.

**Table 16: All TEAEs in the Controlled Safety Database**

	Cannabidiol (mg/kg/day)				Placebo	RR	95% CI	Δ Risk (%)
	5	10	20	10 + 20				
N:	10	75	238	313	227			
<b>Hepatic</b>								
Transaminases elevated	1 (10%)	6 (8%)	37 (15.5%)	43 (13.7%)	6 (2.6%)	5.2	(2.3, 12)	11.2
<b>Other gastrointestinal</b>								
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
<b>Central nervous system</b>								
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
<b>Infectious</b>								
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
<b>Other</b>								
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

Dr. Unger also explored TEAEs in the uncontrolled patient population and did not identify any new safety signals.

Laboratory Findings

There were notable changes in hemoglobin/hematocrit, creatinine clearance, and liver function tests that are described further below. There were no notable changes in other hematology or chemistry laboratory values.

*Decreases in hemoglobin and hematocrit*

There was a small decrease in hemoglobin and hematocrit, with normal red blood cell indices, that was seen in patients taking CBD, but not those on placebo. The change is small; however, Dr. Unger recommends that it be described in labeling so that prescribers can be aware of the potential for anemia and manage patients appropriately.

*Creatinine Clearance*

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. Decreases in creatinine clearance were identified in Table 17 below. There were no notable changes in BUN.

**Table 17: Renal parameters in the controlled safety dataset**

		<b>Cannabidiol n=323</b>	<b>Placebo n=227</b>
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 Baseline	4.6 ± 1.6 (n=323)	4.7 ± 1.6 (n=227)
(mean ± SD) µmol/L	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 <sup>2</sup>	139.0 ± 38.8 (n=248)	139.9 ± 40.4 (n=174)
(mean ± SD) mL/min/1.73 m <sup>2</sup>	Δ from baseline to end-of-treatment	-10.0 ± 26.7 (n=223)	-4.3 ± 26.9 (n=163)
	Creatinine clearance Cockcroft-Gault (mean ± SD) mL/min/1.73 m <sup>2</sup>	156.6 ± 52.9 (n=75)	143.6 ± 47.2 (n=53)
(mean ± SD) mL/min/1.73 m <sup>2</sup>	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

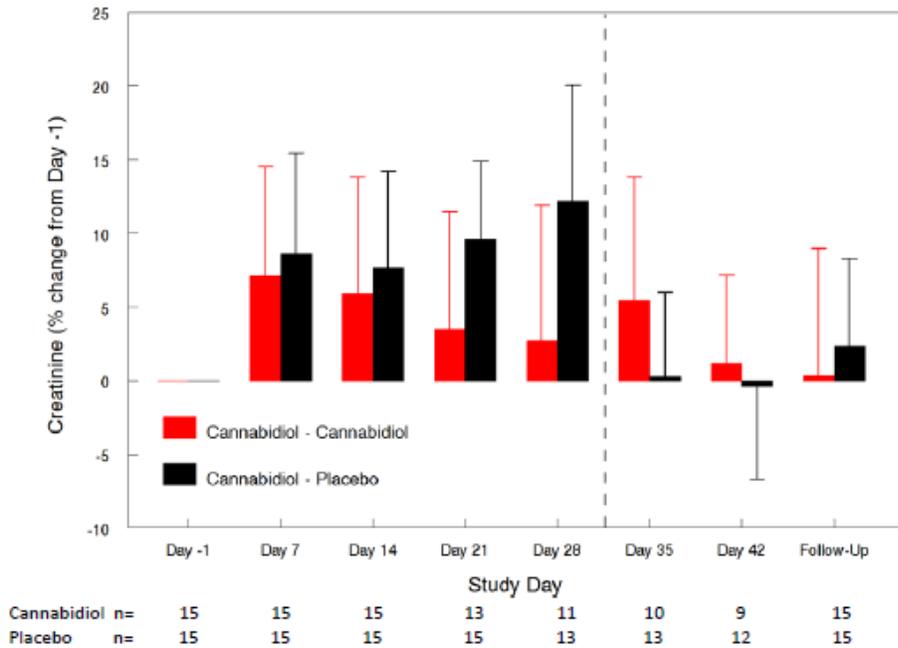
In the ISS, the applicant identified the changes, but noted that the majority of patients remained within normal range for creatinine clearance, so they felt that the finding was not clinically significant and should not be described in labeling.

To further investigate the signal, Dr. Unger performed an analysis of data from Study 1542, a double-blind randomized withdrawal study conducted in healthy adult subjects, to evaluate potential adverse effects of CBD withdrawal. Thirty (30) subjects received CBD 750 mg twice daily for 4 weeks, followed by a randomized withdrawal where 15 subjects were continued on CBD for 2 weeks, and 15 subjects were switched abruptly to placebo. As can be seen in

Figure 6, creatinine levels increase by approximately 8% within one week of starting CBD, and rapidly decrease following withdrawal of CBD after day 28. Those who continued to receive CBD also showed reduction in creatinine over time. This demonstrates that the effects on creatinine appear to be reversible.

The current laboratory findings appear to represent an acute change that is reversible and do not indicate a nephrotoxic process. Additionally, Dr. Unger reviewed renal adverse events and did not identify any events that suggest a direct toxicity to the kidneys.

**Figure 6: Study 1542- Changes in Creatinine with treatment and withdrawal of cannabidiol**



A consultation was requested from the Division of Cardiovascular and Renal Products to evaluate these findings. The consultants noted some concerns with the creatinine clearance values; however, the applicant confirmed the validity of the findings. Nonetheless, there does appear to be a real trend of increase in creatinine levels and findings of reversibility noted in the analysis above. The consultants felt that this could represent a hemodynamic effect or possibly an effect of CBD on tubular secretion. Although the clinical significance of these findings is unclear, the consultants recommended that this effect be described in the PI so that prescribers can be aware of these effects and manage patients appropriately. They also suggested conducting a PMR study in healthy adults that includes measurements of GFR (b) (4) to help elucidate the underlying mechanism of this change. Dr. Unger and I agree with the recommendation for a PMR study and inclusion of the description of change in creatinine levels in labeling.

### *Transaminase elevations*

A signal for transaminase elevations was identified during the development program. During a pre-submission meeting, the Agency requested that the applicant have an external expert in liver disease evaluate the liver data for the NDA submission. A liver safety evaluation was conducted by Dr. Paul Watkins and an extensive Liver Safety Report was included in the submission. Dr. Lara Dimick of the Division of Gastroenterology and Inborn Errors Products (DGIEP) and Dr. Mark Avigan of the Office of Surveillance and Epidemiology (OSE) provided a consultation on the liver safety findings during the review. Additionally, an information request was sent to the applicant during the NDA review to request additional information on the management of transaminase elevations during the studies and the applicant submitted a response on February 23, 2018, that was reviewed by the liver consultants.

According to Dr. Unger's review, transaminase elevations were reported as adverse events in 2.6% of patients on placebo, 8% of patients taking CBD 10 mg/kg/day and 15.5% of patients taking CBD 20 mg/kg/day. Some of the elevations were serious [assessed as medically significant or led to hospitalization](4% in CBD-treated patients vs 0% on placebo), and some were severe (2% in CBD-treated patients vs 0% on placebo)]; however, there were no cases of liver failure, and no deaths due to liver injury. As previously noted in the section on SAEs, there were two cases that were reported as hepatic failure; however, the cases did not have elevations of bilirubin or INR consistent with standard definitions of liver failure.

Review of the laboratory data showed that elevations of ALT were greater than elevations of AST, suggesting that the liver was the source of the transaminase elevations. The majority of ALT elevations were less than 5 times the upper limit of normal (ULN); however, ALT elevations up to 10 times ULN were observed. Although there were small increases from baseline values in bilirubin levels reported in a few cases, the bilirubin levels generally remained within normal limits. No cases met Hy's law criteria ( $ALT \geq 3X$  ULN and bilirubin  $> 2X$  ULN). Given the modest overall exposure, it remains possible that there will be patients who could develop such elevations in a post-approval setting.

Table 18 shows Dr. Unger's analysis of ALT elevations by subgroup. The incidence of transaminase elevations was highest in patients taking concomitant VPA and in patients taking the 20 mg/kg/day dosage of CBD. Concomitant use of clobazam was also associated with a higher incidence of transaminase elevations, although to a lesser extent than that seen with VPA. In CBD-treated patients, the incidence of ALT elevations greater than 3 times the ULN was 20% in patients taking concomitant valproic acid (without clobazam), 5% in patients taking concomitant clobazam (without valproic acid), 29% in patients taking both drugs, and 3% in patients taking neither drug.

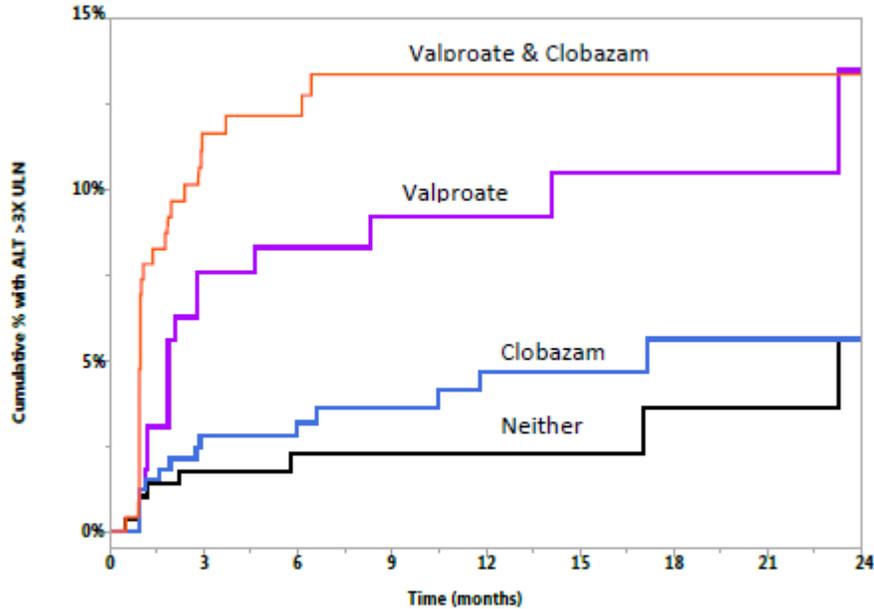
**Table 188: ALT Elevation in the Controlled Trial Database by Subgroup**

		% of subjects	↑ ALT > 3X ULN			↑ ALT > 5X ULN		
			CBD	Placebo	RR	CBD	Placebo	RR
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
Other AEDs	Valproate (Yes)	45%	24%	1%	23.9	12%	1%	12.0
	Valproate (No)	55%	4%	1%	5.1	2%	1%	2.2
	Clobazem (Yes)	54%	15%	2%	8.9	9%	2%	5.4
	Clobazem (No)	46%	12%	0%	-	4%	0%	-
	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

In the controlled studies, transaminase elevations were typically seen in the first 2 months of treatment. The open-label extension study and the EAP experience provide information on the occurrence of transaminase elevations with longer durations of treatment. Dr. Unger performed a Kaplan-Meier analysis of the data in Figure 7 that shows that elevations were seen up to 18 months after initiation of therapy, particularly in patients taking VPA.

**Figure 7: Time-to-initial ALT Elevation >3X ULN in Uncontrolled studies**



The DGIEP/OSE consultation and liver safety report submitted by the applicant were concordant with the findings described in Dr. Unger’s review. There was agreement in all reviews that the transaminase elevations appeared to be causally related to CBD, and that higher doses of CBD, concomitant VPA, and possibly concomitant use of clobazam, appear to be risk factors for transaminase elevations. Baseline liver function tests > ULN was also identified as a risk factor for transaminase elevations. The liver consult provided additional assessment of recovery times, management of CBD, and concomitant AEDs in response to transaminase elevations, and rechallenge with CBD that is described below.

In the pivotal studies, liver function tests were generally assessed after 2, 4, 8, and 12 weeks of treatment. Liver function tests were also assessed after 24, 36, and 48 weeks of treatment in the open-label extension study. Patients were withdrawn from the studies for the following criteria:

- 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.

However, it is noted that these criteria were inconsistently applied in the EAP.

In general, most patients “recovered” from the transaminase elevations within two weeks; however, recovery is defined as ALT elevation < 3X ULN, and does not indicate a complete

return to baseline. Of 37 patients in the controlled trials who experienced a ALT elevation > 5X ULN, 17 (45.9%) recovered from the ALT elevation without, or prior to, stopping CBD. Of these, 12 patients recovered without any dose reduction of CBD, and 5 patients recovered after dose reduction or during the taper of CBD. A total of 6 patients had their valproate reduced after such an ALT elevation.

There were 11 patients in the EAP who were rechallenged with CBD following a transaminase elevation that led to discontinuation of CBD for more than two days. Of these, 4 patients experienced a recurrence of the transaminase elevation of similar severity to the preceding event, and 7 patients experienced no recurrence.

There does not appear to be a PK interaction between CBD and VPA, so the mechanism by which VPA increases the risk for transaminase elevations is unclear. However, the liver consult notes the following:

“...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)

The liver consultants have provided the following recommendations for further evaluation and risk management of the transaminase elevations:

- The indication should be limited to the studied population of patients with LGS or DS (although restricted distribution is not necessary).
- The lowest effective dosage of CBD (10 mg/kg/day) should be used, when possible.
- Product labeling should provide specific recommendations for monitoring transaminases, similar to those used in the clinical studies.
- Labeling should indicate increased risk for transaminase elevations with VPA (Dr. Unger also recommends labeling for increased risk with clobazam.)
- Labeling should include recommendations for dose modification or interruption of treatment with CBD.
- Enhanced pharmacovigilance should be initiated.
- A post-marketing requirement (PMR) for a non-invasive study (e.g., liver ultrasound, biomarkers of liver injury) in CBD users to assess the long-term effects of CBD on the liver should be considered.

Dr. Unger and I agree with these recommendations.

#### Vital Signs

There were no notable differences in heart rate, blood pressure, or temperature. The frequency of weight decreases ( $\geq 5\%$ ) was 9.3%, 18.5% and 8.4% in the CBD 10 mg/kg/day,

CBD 20 mg/kg/day, and placebo groups, respectively. A similar trend was also noted for body mass index (BMI) decrease. Per Dr. Unger's review, there appeared to be some concordance with patients who reported decreased appetite and decreased weight as an adverse event, as seen in Table 16.

#### ECG/QT

There were no significant mean effects on the mean QTcB (corrected QT; Bazett's formula), PR, or QRS intervals. Please refer to the Clinical Pharmacology section for a discussion of the TQT study.

#### Subgroup analyses

Dr. Unger performed an assessment of important safety signals by demographic characteristics, baseline weight, dose, and use/non-use of VPA and clobazam. Diarrhea, weight loss, somnolence/sedation/lethargy, and ALT elevations were all dose-related. Somnolence, sedation, and lethargy occurred more frequently with concomitant clobazam use (44% in patients taking clobazam only compared to 13% in patients taking neither clobazam or VPA).

#### Other Events of Interest

##### *Hypersensitivity reactions*

There were two reports of hypersensitivity reactions in studies with CBD. One case occurred in Study 1414 in an 8 year-old patient with a limited description of the event. The patient continued the study drug and the symptoms resolved. The second case occurred in a healthy adult in the abuse liability study. The subject experienced swelling of the cheeks, generalized redness, and pruritus, all of which were moderate in severity, and occurred approximately 3 hours after receiving CBD. The subject was treated with diphenhydramine. The second case appears consistent with a hypersensitivity reaction. Dr. Unger recommends that "hypersensitivity reactions" be described in the PI. The sponsor has proposed that hypersensitivity reactions be listed as a contraindication in the label.

##### *Suicidal behavior/ideation*

The Columbia-Suicide Severity Rating Scale (C-SSRS) was included in the controlled studies. Analysis of the scales did not identify a signal for suicidal ideation or behavior; however, there were two serious adverse events of suicidal ideation or behavior in the EAP.

The applicant has included a warning for suicidal behavior and ideation in the proposed product label, which is a class warning for all drugs for the treatment of seizures. Dr. Unger supports the inclusion of this warning in labeling and I agree.

##### *Abuse Potential*

Since CBD is derived from the *Cannabis sativa* plant and is currently a Schedule I drug, a thorough evaluation of the abuse potential was conducted. Dr. Katherine Bonson from the Controlled Substances Staff performed the review of the data to evaluate abuse potential.

Please refer to Dr. Bonson's review for a detailed discussion of the assessment of abuse potential of CBD.

Following are the key findings from Dr. Bonson's review:

- In receptor binding studies with CBD, there was no significant affinity of CBD of cannabinoid (CB1 or CB2) sites or other sites associated with abuse potential (e.g., mu, kappa, or delta).
- Based on the nonclinical studies evaluating general behavior, similarity to THC (tetrad test and drug discrimination study) and ability to produce rewarding effects (self-administration studies), CBD did not demonstrate meaningful abuse-related signals
- In Phase 1 clinical studies, there were no euphoria-related AEs or other abuse-related AEs. Phase 2/3 studies in LGS and DS patients could not be evaluated for abuse-related signals due to the concomitant use of other seizure drugs and the limited capacity of the patients.
- A Phase 1 human abuse potential (HAP) study assessed CBD (750, 1500, and 4500 mg) compared to dronabinol (THC; 10 and 30 mg), alprazolam 2 mg, and placebo.
  - Randomized, double-blind, placebo-controlled, crossover design in healthy recreational polydrug users (n = 40, with 35 completers)
  - CBD at the lower therapeutic dose (750 mg) produced a mean Drug Liking score that did not differentiate statistically from placebo on Drug Liking and was within the acceptable placebo range
  - CBD at 1500 and 4500 mg produced very small increases in mean Drug Liking scores that were statistically significantly different from placebo; however, the mean scores bordered on the placebo range and were substantially lower than the two positive drug controls, THC and alprazolam
  - CBD was not identified as THC or any substance
- A human physical dependence study showed that CBD does not produce withdrawal signs or symptoms three days after drug discontinuation following chronic administration.

Although the HAP study showed that the higher therapeutic dose (1500 mg) and suprathereapeutic dose (4500 mg) of CBD produced marginal signals of abuse potential from subjective measures and AEs, Dr. Bonson concluded that the overall evidence suggests that there is little evidence that CBD has meaningful abuse potential.

#### *Pediatric and Assessment of Effects on Growth*

Decreased weight was identified as a safety finding, as described above. No other adverse effects on growth and development were identified.

#### *Human Factors*

The applicant submitted a Human Factors (HF) Validation Study to assess the use of the 5 ml syringes and an adapter that are co-packaged with the product. The report was reviewed by Dr. Briana Rider in the Division of Medication Error Prevention and Analysis (DMEPA). Please refer to Dr. Rider's review for a detailed discussion of the human factors assessment.

The most concerning failure in the HF study was use errors associated with a critical dose measurement task. The majority of use errors associated with the dose measurement task resulted in ten-fold overdoses and the remainder of the use errors contributed to failure to clear air bubbles, resulting in minor underdose. DMEPA noted that users typically made errors on the first attempt, and were able to learn and correct the mistake on subsequent attempts. DMEPA provided a recommendation to change the language in the instructions for use for more clarity. Based on the applicant's assessment of the root causes, the subjective feedback, the information provided by the review team, and the learning effect demonstrated in the study, DMEPA found the residual risk to be acceptable for this product.

For all other failures, the applicant provided an assessment of each of the use errors observed with essential tasks, including the subjective feedback, root cause analysis, and the proposed mitigations. DMEPA agreed with the mitigation strategies.

It was also identified during the review that the 5 ml syringe that will be co-packaged with CBD will not be capable of measuring the small doses (<1 ml) that may be required for low-weight patients with moderate to severe hepatic impairment. As CBD will be distributed through a specialty pharmacy, the applicant proposes that the specialty pharmacy will distribute 1 ml syringes with the CBD if the prescribed dose is < 1 ml. The applicant provided updated labeling to address this issue. DMEPA agreed with this proposal.

DMEPA recommends approval of the supplement.

### **Safety Conclusions**

Safety data were derived primarily from four controlled trials in LGS and DS, with the open-label extension trial and EAP providing additional supportive data. There was adequate exposure to allow for an assessment of safety. The most commonly observed adverse events in controlled clinical trials that occurred with a greater incidence in CBD-treated patients than on placebo were in the following categories: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations), and infections (e.g., pneumonia). These events were generally mild to moderate in severity. Serious and/or severe adverse events were generally related to transaminase elevations, somnolence and lethargy, and infections. Discontinuations were greater in CBD-treated patients (9.3%) than on placebo (1.3%), with most of the discontinuations related to transaminase elevations or somnolence. There were 21 deaths in the development program; however, as the patients were generally ill with multiple comorbidities, none of the deaths could be attributed to CBD.

A signal for drug-induced liver toxicity was identified in the controlled trials and in the Expanded Access Program. Frequencies of adverse events of transaminase elevations were 14% and 3% in CBD-treated and placebo subjects, respectively. Some events of transaminase elevation were serious or severe; however, there were no events of liver failure or death related to liver injury. All transaminase elevations resolved, with some resolving during continued treatment with CBD.

### **Safety Conclusion**

The risks associated with CBD are acceptable. Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, and further characterization of the risk in the post-market setting.

## **9. Advisory Committee Meeting**

The Peripheral and Central Nervous System Drugs (PCNS) Advisory Committee met on April 19, 2018, to discuss the efficacy and safety findings from the NDA submission for CBD.

The committee was asked to vote on the following question:

“Is the benefit-risk profile of cannabidiol favorable for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older?”

The committee voted unanimously (13 Yes, 0 No) that the risk-benefit profile was favorable for CBD for the treatment of seizures associated with LGS and DS.

## **10. Pediatrics**

The studies in LGS and DS were conducted in a pediatric population down to 2 years of age. Issues specific to the pediatric population are discussed within the review. Because the product has orphan designation for both LGS and DS, the Pediatric Research Equity Act (PREA) is not triggered.

## **11. Other Relevant Regulatory Issues**

- No Good Clinical Practice (GCP) issues were identified in Dr. Getzoff’s review.
- Dr. Getzoff concludes that the applicant has adequately disclosed financial interests/arrangements with clinical investigators. Dr. Getzoff noted that some of the remunerations to investigators were large; however, there was no evidence that that this influenced data integrity.
- The Office of Scientific Investigations (OSI) has inspected six clinical sites and the applicant. Regulatory compliance violations were noted at two sites; however, OSI feels that the findings are unlikely to impact data reliability. The applicant inspection revealed issues consistent with inadequate oversight and monitoring by the applicant for the three pivotal studies. The applicant and the two sites received a compliance

classification of Voluntary Action Indicated (VAI). Despite these findings, OSI states that “the studies appear to have been conducted adequately and the data generated by these sites and submitted by the applicant appear acceptable in support of the respective indications.”

## 12. Labeling

Labeling negotiations with the sponsor have been completed and the sponsor has accepted all recommended changes.

## 13. Postmarketing Recommendations

### Risk Evaluation and Management Strategies (REMS)

The Division of Risk Management (DRISK) reviewer for this application is Dr. Yasmeen Abou-Sayed. Dr. Abou-Sayed concludes that a risk evaluation and mitigation strategy (REMS) is not necessary for CBD.

### Postmarketing Requirements (PMRs) and Commitments (PMCs)

The following studies are recommended as PMRs:

- An embryofetal development study of 7-COOH-cannabidiol in rat.
- A pre- and postnatal development study of 7-COOH-cannabidiol in rat.
- A juvenile animal toxicology study of 7-COOH-cannabidiol in rat.
- A 2-year carcinogenicity study of cannabidiol in mouse.
- A 2-year carcinogenicity study of cannabidiol and 7-COOH-cannabidiol, both directly administered, in rat.
- Assess whether the effect of Epidiolex on serum creatinine reflects an effect on glomerular filtration rate.
- Assess the potential for chronic liver injury with Epidiolex, with evaluation including physical exam, serum/blood biomarkers and other noninvasive measures of liver fibrosis, such as MRI or ultrasound based elastography. Patients should be evaluated yearly for five years.
- Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Epidiolex during pregnancy compared to an unexposed control population.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of caffeine in healthy volunteers.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2B6 substrate in healthy volunteers.

- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive CYP2C9 substrate in healthy volunteers.
- Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP2C19 inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.
- Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of a strong CYP3A inhibitor on the pharmacokinetics of Epidiolex in healthy volunteers.
- Submit the complete results for the ongoing drug-drug interaction trial to evaluate the effects of rifampin on the pharmacokinetics of Epidiolex in healthy volunteers.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGT1A9 substrate in healthy volunteers.
- A drug-drug interaction trial to evaluate the effects of Epidiolex on the pharmacokinetics of a sensitive UGTB7 substrate in healthy volunteers.
- A thorough QT trial at the maximum tolerable dose of Epidiolex that is feasible (e.g. dosing in the fed state), with appropriate controls (i.e., placebo and positive control).

Additional comments will be conveyed to the applicant regarding recommended enhanced postmarketing pharmacovigilance, as described in Section 14 of this review.

## **14. Recommended Comments to the Applicant**

We request that you perform postmarketing surveillance for liver toxicity after exposure to Epidiolex. Submit 15-day expedited reports to the Division of Neurology Products and to the NDA with sufficient data to assess causality including duration of Epidiolex administration, symptoms, whether the patient was hospitalized or had organ dysfunction, failure, transplant, or death. Include comprehensive summaries and analyses of these events quarterly as part of your required postmarketing safety reports [e.g., periodic safety update reports (PSURs)]. In the analysis of each case, provide an assessment of causality, with documentation of risk factors and results of all assessments that support the diagnosis or the causality, along with duration of Epidiolex therapy, concomitant therapies, treatment given for the event, range of severity, and of each event, and incidence.

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/s/  
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TERESA J BURACCHIO  
06/25/2018

WILLIAM H Dunn  
06/25/2018

ELLIS F UNGER on behalf of ROBERT TEMPLE  
06/25/2018