FDA Briefing Document

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

April 19, 2018

NDA 210365
Cannabidiol

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the panel members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We have brought these issues to this Advisory Committee in order to gain the Committee's insights and opinions, and the background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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I. Memorandum to the Committee

MEMORANDUM

DATE:	March 23, 2018
FROM:	Teresa Buracchio, M.D. Clinical Team Leader Division of Neurology Products, CDER, FDA
THROUGH:	Eric Bastings, M.D. Deputy Director Division of Neurology Products, CDER, FDA Billy Dunn, M.D. Director Division of Neurology Products, CDER, FDA
TO:	Members and Invited Guests of the Peripheral and Central Nervous System Drug Advisory Committee (PCNS AC)
SUBJECT:	Memorandum for New Drug Application (NDA) 210365, for the use of (b) (4) (cannabidiol) for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older

1) Introduction

The Peripheral and Central Nervous System Drugs Advisory Committee will meet on April 19, 2018, to discuss a New Drug Application (NDA) for [redacted] (b) (4) (cannabidiol), submitted by GW Pharmaceuticals, 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 and is a new molecular entity. It is structurally unrelated to other drugs approved for the treatment of seizures. CBD is currently a Schedule I drug. The exact mechanism of the anticonvulsant effect of CBD is unknown, but does not appear to involve an interaction with cannabinoid receptors.

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).

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. 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.

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, but not all, patients with the clinical syndrome have a gene mutation affecting the sodium channel (SCN1A). There are currently no drugs approved specifically for the treatment of seizures in DS.

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 INDs in refractory epilepsy populations

This memo summarizes the findings of efficacy and safety from these sources. Additionally, a signal of drug-induced liver injury (DILI) was identified in the clinical trials and expanded access programs. A detailed evaluation of the liver safety signal was conducted by the Division of Gastroenterology and Inborn Errors Products (DGIEP) and the Office of Surveillance and Epidemiology (OSE). Their consultation memo is provided in Section III of this briefing document.

In support of this application, the applicant also conducted nonclinical and clinical studies to assess the abuse potential of cannabidiol. A summary of the data related to the abuse potential of cannabidiol is provided by the Controlled Substances Staff in Section IV of the briefing document.

2) Summary of Efficacy

The results of the applicant's efficacy analyses for the controlled studies conducted in LGS and DS were independently confirmed by the FDA review team. This section of the memo will discuss the clinical and statistical review team's findings regarding the efficacy results from these studies.

A. Lennox-Gastaut Syndrome

Study 1414

Study 1414 was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with LGS. The study consisted of a 4-week baseline period and a 14-week treatment period (2-week titration plus 12-week maintenance). There were 225 patients randomized in a 1:1:1 ratio to either CBD 10 mg/kg/day (divided BID), CBD 20 mg/kg/day (divided BID), or placebo. CBD (or the equivalent volume of placebo) was started at 2.5 mg/kg/day and increased by 2.5 mg/kg/day every other day over a 7-day period to 10 mg/kg/day, or over an 11-day period to 20 mg/kg/day, respectively. 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: a clinical diagnosis of LGS (including documentation of having met EEG diagnostic criteria) not completely controlled by current "antiepileptic drugs" ("AEDs"), experience ≥ 2 drop seizures per week during a 28-day baseline period, taking one or more AEDs at a stable dose, and age between 2 and 55 years. Concomitant AEDs and doses were to remain constant during the treatment period.

The primary endpoint for Study 1414 was the percentage change from baseline in drop seizure frequency (average per 28 days) during the 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 endpoints controlled for multiplicity were:

- Number of patients considered treatment responders, defined as those with a ≥ 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)
- Changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score at the last visit. (A caregiver assessment of the change in status of overall condition compared to pre-treatment baseline. It is rated using a 7-point scale (1 = very much improved; 7 = very much worse).

Other endpoints were exploratory.

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.

The primary endpoint of percentage change from baseline in seizure frequencies was analyzed using a Wilcoxon rank-sum test. 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 score, 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 than the end of treatment) were analyzed using ordinal logistic regression.

<u>Results in the ITT population</u>

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. 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 percentage change from

baseline in drop seizure frequency in favor of CBD treatments (p=0.0047 and p=0.0016, respectively). **Table 1** presents the results of the analysis of the primary endpoint:

Table 1: 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)
Comparison over Placebo			
Estimated Median Difference (CI)*	−21.6 (−34.8, −6.7)	−19.2 (−31.2, −7.7)	
p-value by Wilcoxon rank-sum test	0.0047	0.0016	

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

Sensitivity analyses yielded similar results to the primary analysis.

The analysis of the secondary endpoint of ≥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=0.0006) and the 10 mg/kg/day group (OR =3.3; p = 0.0030).

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=0.0091 and p=0.0015, 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=0.0439 and p=0.0020, respectively).

Table 2: Analyses of the Secondary Endpoints from Study 1414 (LGS)

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

Source: FDA clinical/statistical review

*based on Hodges-Lehmann estimator, confirmed by FDA statistical reviewer

Study 1423

Study 1423 was a 14-week, multicenter, randomized, double-blind, placebo-controlled trial in patients with LGS. The study consisted of a 4-week baseline period and a 14-week treatment period (2-week titration plus 12-week maintenance). There were 171 patients randomized in a 1:1 ratio to CBD 20 mg/kg/day (divided BID) 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 every other day over an 11-day period to 20 mg/kg/day. 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: a clinical diagnosis of LGS (including documentation of having met EEG diagnostic criteria) not completely controlled by current AEDs, experience ≥ 2 drop seizures per week during a 28-day baseline period, taking one or more AEDs at a stable dose, and age between 2 and 55 years. Concomitant AEDs and doses were to remain constant during the treatment period.

The study population and statistical analysis of the primary endpoint were identical to those of Study 1414. The study contained the same secondary endpoints as Study 1414; however, hierarchical testing of the secondary endpoints to control for Type-I error was specified only in the European Union (EU) statistical analysis plan (SAP) and not in the United States (US) SAP. All statistical tests were 2-sided and used the 5% significance level.

Results in the ITT population

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. There was a statistically significant difference between the groups in the percentage change from baseline in drop seizure frequency during the treatment period, in favor of CBD treatment (p=0.0135). **Table 3** presents the results of the analysis of the primary endpoint:

Table 3: 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

Sensitivity analyses yielded similar results to the primary analysis.

During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline drop seizure frequency was greater in the CBD group (44.2%), compared with the placebo group (23.5%). The odds ratios (OR) was 2.6 (p=0.0043).

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 difference between the CBD group and placebo group was statistically significant (p=0.0005).

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 statistically significant (p=0.0012).

Table 4: Analyses of the Secondary Endpoints from Study 1423 (LGS)

Variable	CBD (N=86)	Placebo (N=85)
≥ 50% Reduction in Drop Seizure Frequency		
n (%)	38 (44.2)	20 (23.5)
Odds Ratio (CI)	2.6 (1.3, 5.0)	
p-value by CMH test	0.0043	
Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period		
Median Percentage Change During Treatment	−41.2	−13.7
Estimated Median Difference (CI*)	−21.1 (−33.3, −9.4)	
p-value by Wilcoxon rank-sum test	0.0005	
Subject/Caregiver Global Impression of Change Score at the Last Visit		
Mean	3.0	3.7
Odds Ratio (CI)	2.5 (1.5, 4.5)	
p-value by Logistic Regression	0.0012	

Source: FDA clinical/statistical review
*based on Hodges-Lehmann estimator,

B. Dravet Syndrome

Study 1332B

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 BID) 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 every other day over an 11-day period 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: a documented history of DS not completely controlled by current AEDs, experience ≥ 4 convulsive seizures during a 28-day baseline period, taking one or more AEDs at a stable dose, and age between 2 and 18 years. Concomitant AEDs and doses were to remain constant during the treatment period.

The primary endpoint was the percentage change from the baseline in total convulsive seizure frequency during the entire treatment period of the study. Patients or caregivers recorded the number and type of convulsive seizures (tonic, clonic, tonic–clonic, or atonic) 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 secondary endpoint was the number of patients considered treatment responders, defined as those with a ≥50% reduction in convulsive seizures from baseline during the treatment period. Hierarchical testing of the secondary endpoint was specified in the EU SAP but not in the US SAP.

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 analysis specified in the SAP was a Wilcoxon rank-sum test. An estimate of the median difference between CBD and placebo, together with approximate 95% CI, was calculated using the Hodges-Lehmann approach.

Results in the ITT population

The primary efficacy analysis population comprised a total of 120 patients: 61 patients in the CBD group and 59 patients in the placebo group. There was a statistically significant difference between the groups in the percentage change from baseline in total convulsive seizure frequency, in favor of CBD treatment (p=0.0123). **Table 5** presents the results of the analysis of the primary endpoint:

Table 5: 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

Sensitivity analyses yielded similar results to the primary analysis.

The analysis of the secondary endpoint of ≥50% reduction from baseline in convulsive seizures showed a numerical trend favoring CBD treatment (p=0.0784). **Table 6** presents the results of this analysis:

Table 6: Secondary Responder Analysis from Study 1332B (DS)

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

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

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 studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS.

3) Summary of Safety

A. Sources of Safety Data

Because patients with DS and LGS are similar in many respects, and because the study designs and cannabidiol doses were comparable in the two indications, the applicant and FDA agreed to pool subjects across both indications for the conduct of safety analyses.

The principal safety data were generated in two trials in DS (1332, Parts A and B) and two trials in LGS (1414 and 1423). (Studies 1332 Parts A and B were independent, and enrolled entirely different subjects.) The data from these 4 double-blind, placebo-controlled studies constitute the controlled safety database and serve as the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs.

Subjects in studies for both indications had the option of continuing (or switching to) open-label cannabidiol treatment in an ongoing open-label extension trial (Study 1415). A separate double-blind, placebo-controlled phase 3 trial is ongoing in patients with DS (Study 1424) for which only limited safety data have been submitted (treatment assignment remains blinded).

An expanded access program (EAP) and compassionate access scheme (CAS) are ongoing at 38 sites in the US and Australia, respectively, for patients with drug-resistant epilepsy. The applicant exerted no control over these programs; site physicians were responsible for specific

treatment plans and actions. Safety data from these programs were examined and serve a secondary role.

B. Adequacy of drug exposure

At the time of the original NDA submission, 1756 subjects had been exposed to cannabidiol oral solution in the applicant's development program; 1391 of these subjects had been treated for epilepsy. Exposure by use is summarized in **Table 7**. Approximately one-fourth of the subjects were exposed in the placebo-controlled trials for DS (Study 1332, Parts A and B) and LGS (Studies 1414 and 1423); a similar number were exposed in the extension study (Study 1415). Approximately half of the subjects with epilepsy (684) were exposed in the uncontrolled EAP or CAS for drug-resistant epilepsy. This experience included 64 patients with DS and 97 patients with LGS. (The vast majority of patients in the EAP and CAS had other types of treatment-resistant seizures.) Newly exposed subjects in the extension study included subjects who had been assigned to placebo in the initial trials and switched to open-label cannabidiol, as well as new subjects who were enrolled directly in Study 1415 and begun on cannabidiol.

Table 7: Overall Cannabidiol Exposure in the Clinical Development Program

All subjects exposed to cannabidiol	1756		
Subjects with epilepsy	1391		
Controlled trials		323	
DS (Study 1332, Parts A and B)		88	
LGS (Studies 1414 and 1423)		235	
Extension trial* (Study 1415)		353	
DS		196	
LGS		157	
Expanded access for refractory epilepsy		684	
DS		64	
LGS		97	
other seizure disorders		523	
Other epilepsy		31	not in ISS
Subjects without epilepsy	365		
Phase 1 clinical pharmacology (healthy subjects and special patient populations)		322	
Other conditions (schizophrenia, diabetes, fatter liver disease)		43	not in ISS

*Includes new patients, or those who had received placebo in controlled studies
Adapted from Table 5-1 of applicant's ISS

The duration of exposure is summarized in **Table 8** for the important studies in the development program. At the time of the original submission, 165 and 314 subjects with DS and LGS, respectively, had been treated for > 6 months; 96 and 21 subjects, respectively, with DS and LGS had been treated for > 12 months.

Table 8: Exposures During the Controlled Clinical Trials vs. Open-Label Extension Trial

			Controlled				Open-label Extension (1415)		Expanded Access
			Dravet		Lennox-Gastaut		Dravet	Lennox-Gastaut	
			Cannabidiol	Placebo	Cannabidiol	Placebo	Cannabidiol	Cannabidiol	Cannabidiol
Dravet	1332 Part A	n (%)	27 (31%)	7 (11%)			23 (9%)		
	1332 Part B	n (%)	61 (69%)	59 (89%)			105 (40%)		
	1424	n (%)					136 (52%)		
	Access								64 (9%)
Lennox-Gastaut	1414	n (%)			149 (63%)	76 (47%)		210 (57%)	
	1423	n (%)			86 (37%)	85 (53%)		156 (43%)	
	Access								97 (14%)
Other seizure									523 (76%)
Total	Total		88 (100%)	66 (100%)	235 (100%)	161 (100%)	264 (100%)	366 (100%)	684 (100%)
Time on Treatment	Patient-years	Total	18	17	60	44	181	252	690
	Days on treatment	Mean	74	92	94	99	251	252	369
		Median	99	100	99	99	274	263	275
		Min; Max	7; 131	17; 122	10; 114	17; 111	1; 512	3; 429	1; 1025
	Days on treatment, number (%)	1–14 d	2 (2%)	0 (0%)	1 (0%)	0 (0%)	7 (3%)	2 (1%)	7 (1%)
		15–28 d	8 (9%)	3 (5%)	6 (3%)	2 (1%)	9 (3%)	4 (1%)	14 (2%)
		29–42 d	24 (27%)	7 (11%)	10 (4%)	0 (0%)	23 (9%)	7 (2%)	19 (3%)
		43–84 d	2 (2%)	0 (0%)	8 (3%)	1 (1%)	22 (8%)	14 (4%)	57 (8%)
		85–182 d	52 (59%)	56 (85%)	210 (89%)	158 (98%)	38 (14%)	25 (7%)	146 (21%)
		183–364 d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	69 (26%)	293 (80%)	160 (23%)
		365–729 d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	96 (36%)	21 (6%)	158 (23%)
		≥ 730 d	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	121 (18%)

Adapted from applicant's Table 5.1.7-1 in the ISS

Cannabidiol was granted orphan-drug designation for the treatment of both DS (2013) and LGS (2014). Given the prevalence of these diseases, FDA finds the exposure adequate to support a reasonable assessment of safety.

Table 9: Demographic and Baseline Characteristics in the Controlled DS/LGS (Safety) Population

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

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

There were 550 subjects in the controlled DS plus LGS safety population (323 received cannabidiol; 227 placebo), enrolled from 58 sites in the US, UK, France, Spain, Poland, and The Netherlands. Demographic and important baseline characteristics are summarized in **Table 9**. Between the indications, there were notable differences in baseline age (median 8.4 and 13 years in DS and LGS, respectively), and corresponding differences in body mass (27 and 38 kg in DS and LGS, respectively). Other characteristics, however, were similar. Subjects were evenly distributed by sex. Eighty percent to 90% of subjects were white; 5% were black, and 2% were Asian. Three-quarters of subjects were enrolled at US sites. In both indications, approximately 95% of subjects were taking 2 or more AEDs. Approximately 25% of subjects were taking valproate alone, 33% were taking clobazam alone, 22% were taking both drugs, and 22% were taking neither drug.

C. Deaths

At the time of original submission of the NDA, there had been 20 deaths in the development program. In the controlled trials, there was 1 death in a patient in the cannabidiol 20 mg/kg group and no deaths in the placebo group. Seven (7) deaths were reported in the open-label extension trial, with 12 deaths in the EAP.

With respect to the EAP program, the 12 deaths were reported among 684 patients with refractory seizures (1.8%); none of these patients was reported to have had DS or LGS. Causes of death were given as: respiratory failure due to aspiration, probable SUDEP, severe progressive mitochondrial disorder, asphyxia, hypoxemia, respiratory failure/septic shock from human pneumovirus, respiratory arrest, status epilepticus with a working diagnosis of febrile infection-related epilepsy syndrome (FIRES), death due to progressive condition, Batten disease, Ohtahara syndrome with acquired epileptic encephalopathy, pulmonary edema due to prolonged seizure, and possible SUDEP (also hyponatremia).

These patients were generally quite ill, with complex, chronic multisystem diseases and complicated courses. In the absence of a plausible drug adverse effect, it is therefore not possible to attribute the deaths to cannabidiol; conversely, it is not possible to rule out the possibility that the drug was in some way contributory. As noted by the applicant, however, the proximate causes of death were typical for these patient populations; there was no suggestion that an off-target drug effect was responsible. Moreover, the numbers of deaths did not seem to differ importantly from the numbers that would be expected in the DS or LGS patient populations. In conclusion, therefore, it would not seem reasonable to attribute these deaths to the investigational drug. Causality is certainly possible, but the cases do not have features that suggest a specific off-target drug effect.

D. Serious Treatment-emergent Adverse Events

Serious adverse events (and groupings of related serious adverse events) are tabulated in **Table 10**. Serious adverse events that were reported in ≥2 more cannabidiol-treated subjects than placebo subjects are shown; the relative risk (RR) is shown on the right.

Transaminase elevations are clearly drug-related and are discussed below. Although there were two serious adverse events identified as "hepatic failure," neither patient met accepted criteria for liver failure, as neither patient had hyperbilirubinemia or INR elevation. Somnolence and lethargy also appear to show a signal. Infections appear to show a signal.

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

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

E. Discontinuations Due to Adverse Events

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

F. Severe Treatment-emergent Adverse Events

Severe treatment-emergent adverse events (and groupings of closely related severe adverse events) are shown in **Table 11** from the DS and LGS controlled trials. The "All Cannabidiol" column has been replaced by a 10 + 20 mg/kg/d column, because these are the to-be-marketed doses. The table shows the RR with its 95% CI, and the absolute risk difference (Δ Risk, right). Signals are evident for infections, particularly pneumonia, somnolence/lethargy, and hepatic toxicity, with weaker signals for decreased appetite and rash.

Table 11: Severe Treatment-emergent Adverse Events in the Controlled Safety Database (DS and LGS)

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

G. Treatment-Emergent Adverse Events – All Severities/Seriousness

All of the treatment-emergent adverse events (and groupings of closely related adverse events) from the controlled trials in DS and LGS are shown in **Table 12**. Events that occurred at a frequency of ≥2% in cannabidiol-treated patients with a risk difference of ≥2% (cannabidiol minus placebo) are included in the table. The table shows the RR with its 95% CI, and the simple risk difference (right).

Table 12: Treatment-emergent Adverse Events in the Controlled Trials (DS and LGS)

	Cannabidiol (mg/kg/day)				Placebo	RR	95% CI	Δ Risk (%)
	5	10	20	10 + 20				
	10	75	238	313	227			
Hepatic								
Transaminases increased; hepatic failure	1 (10%)	6 (8%)	39 (16%)	45 (14%)	6 (3%)	5.4	(2.4, 12.5)	11
Transaminases increased	1 (10%)	6 (8%)	37 (16%)	43 (14%)	6 (3%)	5.2	(2.3, 12)	11
Hepatic failure	0 (0%)	0 (0%)	2 (1%)	2 (1%)	0 (0%)	-	-	1
Other gastrointestinal								
Decreased appetite	0 (0%)	12 (16%)	53 (22%)	65 (21%)	11 (5%)	4.3	(2.3, 7.9)	16
Weight decreased	0 (0%)	2 (3%)	11 (5%)	13 (4%)	3 (1%)	3.1	(0.9, 10.9)	3
Abdominal pain, distension, discomfort	0 (0%)	2 (3%)	8 (3%)	10 (3%)	2 (1%)	3.6	(0.8, 16.4)	2
Gastroenteritis	1 (10%)	0 (0%)	10 (4%)	10 (3%)	3 (1%)	2.4	(0.7, 8.7)	2
Diarrhea	0 (0%)	7 (9%)	47 (20%)	54 (17%)	20 (9%)	2.0	(1.2, 3.2)	8
Dry mouth, thirst	0 (0%)	1 (1%)	4 (2%)	5 (2%)	1 (0%)	3.6	(0.4, 30.8)	2
Central nervous system								
Irritability, agitation	0 (0%)	7 (9%)	12 (5%)	19 (6%)	4 (2%)	3.4	(1.2, 10)	4
Somnolence, sedation	4 (40%)	19 (25%)	72 (30%)	91 (29%)	21 (9%)	3.1	(2, 4.9)	20
Somnolence, lethargy, disorientation, depressed level of consciousness	2 (20%)	19 (25%)	71 (30%)	90 (29%)	25 (11%)	2.6	(1.7, 3.9)	18
Fatigue, malaise, asthenia	0 (0%)	8 (11%)	28 (12%)	36 (12%)	9 (4%)	2.9	(1.4, 5.9)	8
Ataxia, coordination abnormal	2 (20%)	1 (1%)	5 (2%)	6 (2%)	0 (0%)	-	-	2
Tremor	0 (0%)	1 (1%)	4 (2%)	5 (2%)	0 (0%)	-	-	2
Agression, anger	0 (0%)	2 (3%)	11 (5%)	13 (4%)	1 (0%)	9.4	(1.2, 71.6)	4
Drooling, salivary hypersecretion	0 (0%)	1 (1%)	10 (4%)	11 (4%)	1 (0%)	8.0	(1, 61.4)	4
Insomnia, sleep disturbance, abnormal dreams	1 (10%)	8 (11%)	13 (5%)	21 (7%)	11 (5%)	1.4	(0.7, 2.8)	2
Insomnia	0 (0%)	4 (5%)	8 (3%)	12 (4%)	5 (2%)	1.7	(0.6, 4.9)	2
Fall, dizziness, balance disorder, gait disturbance, difficulty walking	0 (0%)	3 (4%)	21 (9%)	24 (8%)	13 (6%)	1.3	(0.7, 2.6)	2
Gait disturbance, difficulty walking,	0 (0%)	2 (3%)	5 (2%)	7 (2%)	1 (0%)	5.1	(0.6, 41)	2
Infectious								
Infection, all	4 (40%)	31 (41%)	96 (40%)	127 (41%)	70 (31%)	1.3	(1, 1.7)	10
Infection, viral	2 (20%)	5 (7%)	25 (11%)	30 (10%)	13 (6%)	1.7	(0.9, 3.1)	4
Pneumonia	0 (0%)	6 (8%)	12 (5%)	18 (6%)	2 (1%)	6.5	(1.5, 27.9)	5
Respiratory infections	2 (20%)	19 (25%)	54 (23%)	73 (23%)	46 (20%)	1.2	(0.8, 1.6)	3
Infection, fungal	0 (0%)	1 (1%)	6 (3%)	7 (2%)	0 (0%)	-	-	2
Other								
Urine output decreased	0 (0%)	2 (3%)	3 (1%)	5 (2%)	0 (0%)	-	-	2
Respiratory failure, disorder, hypoxemia	0 (0%)	2 (3%)	8 (3%)	10 (3%)	3 (1%)	2.4	(0.7, 8.7)	2
Rash	1 (10%)	5 (7%)	25 (11%)	30 (10%)	7 (3%)	3.1	(1.4, 7)	7

These adverse events can be divided into several broad categories, and some of the interrelations among adverse events within categories suggest that the adverse events are cannabidiol-related:

- Hepatic adverse events – elevated transaminases (as detected as adverse events and as laboratory abnormalities). Frequencies are 14% and 3% in cannabidiol-treated and placebo subjects, respectively, and there is a clear dose-response, i.e., 8% and 16% in the 10 mg/kg and 20 mg/kg groups, respectively (Table 12). (The frequency was 10% in the 5 mg/kg group, but the estimate is difficult to interpret with only 10 subjects in that group.) As previously noted, a review of the two adverse events of "hepatic failure" showed that neither patient met accepted criteria for liver failure, as neither patient had hyperbilirubinemia or INR elevation.
- Central nervous system events. These include irritability, agitation, somnolence, sedation, lethargy, disorientation, fatigue, malaise, asthenia, ataxia, tremor, aggression, anger, drooling, hypersalivation, insomnia and other sleep disturbances, falls, dizziness, balance disorders, and gait disturbances. There is an apparent dose-response for somnolence and drooling, but frequencies were similar in the 10 and 20 mg/kg groups for other CNS adverse events.
- Decreased appetite (21% vs. 5%) and weight decreased (4% vs. 1%) in the cannabidiol and placebo groups, respectively, with a dose-response (greater frequencies in the 20 mg/kg group than the 10 mg/kg group).
- Gastrointestinal events (non-hepatic), including diarrhea, abdominal pain, distension, and discomfort, gastroenteritis, and dry mouth. Diarrhea shows a dose-response.
- Infections, with imbalances in pneumonia and upper respiratory infections, as well as viral and fungal infections.
- Rash, reported in 10% vs. 3% of subjects in the cannabidiol and placebo groups, respectively, with an apparent dose-response.
- Urine output decreased.
- Respiratory failure, respiratory disorders, and hypoxemia.
- Infections. The difference in total infections shows a relative risk of 1.3, which seems borderline in significance, especially considering the multiplicity (numerous adverse events tested for differences) and the lack of an apparent mechanism of action that would account for the finding. Pneumonia and fungal infections stand out (the latter were non-serious), but there is no known mechanistic connection to the drug.

H. Laboratory Tests

Anemia

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

An FDA analysis was conducted to determine the numbers of subjects who developed anemia during the course of the study, i.e., subjects who had a normal hemoglobin concentration at baseline, with a value below the lower limit of normal (for sex and age) reported at a

subsequent time point. Twenty-four percent (24%) of cannabidiol-treated subjects developed a new anemia during the course of the study, versus 11% of patients who received placebo. Anemia was reported only twice as an adverse event (one in cannabidiol; one in placebo), and severity was mild.

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

Creatinine Clearance

FDA found a decrease in calculated creatinine clearance of approximately 10%, occurring soon after administration of cannabidiol, which appears to be reversible upon drug discontinuation. FDA is conducting additional analyses to try to better understand these changes and determine whether this finding should be mentioned in labeling.

Transaminase elevations

As previously noted, a signal for transaminase elevations was identified in the controlled trials. In the three pivotal trials (1332B, 1414, and 1423), the incidence of elevation of ALT or AST >3X the upper limit of normal (ULN) was 2/219 (0.9%) in placebo, 2/67 (3.0%) in CBD 10 mg/kg/day, and 18/228 (18.1%) in CBD 20 mg/kg/day. Elevations in ALT were more pronounced than AST, suggesting that the liver was the source of the transaminase elevations. Although small increases in total bilirubin were seen in a few cases, the bilirubin levels generally remained within normal limits and there were no cases that met Hy's law criteria (ALT ≥ 3X ULN and bilirubin > 2X ULN). Some events of transaminase elevation were serious or severe; however, there were no events of liver failure or death related to liver injury. Identified risk factors for transaminase elevation included concomitant valproic acid use, elevated baseline liver function tests, and higher doses of CBD. Most events of transaminase elevation occurred within 30 to 90 days after initiation of CBD treatment; however, rare cases were observed up to 200 days after initiation of treatment, particularly in patients taking concomitant valproic acid. Events of transaminase elevation generally resolved with discontinuation of CBD or dose decreases in CBD or valproic acid; however, some events resolved during continued treatment with CBD at the same dose.

Please refer to Section III for the consultation memo from DGIEP and OSE that provides a detailed evaluation of the transaminase elevations that were observed in the controlled clinical trials.

I. Abuse potential

The Controlled Substances Staff evaluated the abuse potential of cannabidiol in nonclinical studies and in a human abuse potential study, and has concluded that CBD has a negligible abuse potential. Please refer to the consultation memo from the Controlled Substances Staff in Section IV for a more detailed discussion of the assessment of abuse potential.

Safety Conclusions

Safety data was reviewed 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 20 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 are 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.

In general, the risks associated with cannabidiol appeared to be 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.

4) Conclusions

Clinically meaningful and statistically significant reductions in seizure frequency were demonstrated in three adequate and well-controlled trials in LGS and DS. The results from these three studies provide substantial evidence of the effectiveness of CBD for the treatment of seizures associated with LGS and DS. In general, the risks associated with CBD treatment appear 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 post-market setting. Although the review is still ongoing, the risk-benefit profile established by the data in the application appears to support approval of cannabidiol for the treatment of seizures associated with LGS and DS.