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.

I. Draft Points to Consider

FOOD AND DRUG ADMINISTRATION (FDA)

Center for Drug Evaluation and Research (CDER)

Peripheral and Central Nervous System Drugs Advisory Committee Meeting

DRAFT POINTS TO CONSIDER

April 19, 2018

Discuss the adequacy of the efficacy and safety data from the clinical trials in Lennox-Gastaut syndrome and Dravet syndrome to support the approval of cannabidiol for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older.

II. Consult Review for Potential Drug Induced Liver Injury

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION
DIVISION OF GASTROENTEROLOGY AND INBORN ERRORS PRODUCTS

Medical Officer Consult Review for Potential Drug Induced Liver Injury

NDA	210365
Sponsor	GW Research Ltd.
Drug	(b) (4) (cannabidiol) 100 mg/ml oral solution
Proposed Indication	Treatment of seizures associated with Lennox-Gastaut Syndrome and Dravet Syndrome
Consulting Division	Division of Neurology Products Stephanie Parncutt, MHA, Senior Regulatory Project Teresa Buracchio, MD, Team Leader Billy Dunn, MD, Division Director
Consult Due Date	3/28/2018
Date review Completed	3/20/2018
Clinical Reviewer	Lara Dimick-Santos, MD
Team Leader	Stephanie O. Omokaro, MD
Associate Division Director	Lisa Soule, MD
Associate Office Director, OPE/OSE	Mark Avigan, MD, CM
Project Manager	CDR. Cheronda Cherry-France, RN, BSN, MHA

Contents

1 Introduction

NDA 210365 was submitted on October 27, 2017, for cannabidiol (CBD) for the treatment of seizures associated with Lennox-Gastaut Syndrome and Dravet

Syndrome. During clinical development, a signal for drug-induced liver injury (DILI) was identified.

The Division of Neurology Products (DNP) requests assistance in the description of the liver findings in product labeling and recommendations regarding any further investigations that should be conducted in the post-approval setting.

CBD, the active ingredient of Cannabidiol Oral Solution (CBD-OS), is comprised of highly purified CBD; a naturally occurring component of Cannabis sativa L. (marijuana). In pivotal 14-week placebo-controlled trials, adjunctive CBD-OS was tested for the treatment of convulsive seizures associated with Dravet Syndrome (DS) in children (1 controlled trial), and drop seizures associated with Lennox-Gastaut Syndrome (LGS) in children and adults (2 controlled trials). In addition, other smaller clinical trials in other populations and an expanded access program that enrolled patients with uncontrolled seizures were conducted.

The review below summarizes the clinical trial data as related to the findings of CBD-induced aminotransferase elevations and concerns surrounding a potential signal for liver injury associated with this product.

2 Clinical Pharmacology

CBD rapidly appears in plasma with little or no lag time following oral administration of CBD-OS. Generally, there is slow attainment of maximum measured plasma concentration (Cmax), within 4-6 hours after a single dose, but at steady state, time to maximum plasma concentration (tmax) is around 3 hours. Food (a high-fat meal) significantly increases exposure to CBD (4- to 5-fold). CBD appears to reach steady state within 4 days of twice-daily dose administration. When CBD-OS is administered twice daily, the accumulation of CBD following multiple dosing for 7 days was approximately 3-fold based on the area under the concentration-time curve (AUC).

CBD has 2 major metabolites, 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOH-CBD). A third metabolite, 6-hydroxy-cannabidiol (6-OH-CBD) is found at relatively low levels. CBD is primarily eliminated from systemic circulation through hepatic phase 1 metabolism by CYP2C19 and CYP3A4. The major route of excretion is the feces. Between 30–35% of the CBD dose is eliminated by the fecal route and a further 10–15% is excreted in the urine over 72 hours.

CBD and major metabolites follow a multi-phasic decline and model-based predictions suggest a long terminal elimination phase. Model predictions of the CBD terminal (elimination) half-life (t½) (following discontinuation of CBD-OS dosing) show a tendency for t½ to increase with duration of dosing. In healthy subjects, terminal t½ was 85 hours, in DS patients, t½ was 139 hours, and in

LGS patients, t½ was 196 hours. The long elimination phase may indicate a depot effect from deep compartments, or may suggest there is time dependency (auto-inhibition) mediated by time-dependent inhibition (TDI) of CYP3A4.

Evaluation of the potential for CBD-OS to increase exposure to concomitant anti-epileptic drugs (AEDs), commonly administered to patients with DS or LGS, has led the sponsor to conclude that CBD-OS administration does not lead to any pharmacokinetically relevant increases in the systemic circulatory exposure for valproate, stiripentol, or clobazam. It should be noted that this conclusion by itself does not rule out potential drug-drug interactions that may occur due to intra-hepatic effects related to metabolism, apical secretion or mitochondrial functions.

3 Preclinical Findings

There were signals of liver injury with elevated aminotransferases in all nonclinical studies; however, there were no associated deaths. The liver was identified as a site of histopathological change (characterized by centrilobular hypertrophy) in rodents and dogs given CBD orally (as gavage) as CBD-OS, purified CBD, or CBD botanical drug substance (BDS), and this was associated with adaptive thyroid hypertrophy. Hepatic microsomal enzymes that are induced to metabolize the test material also increased clearance of thyroid hormones, resulting in thyroid stimulation and follicular cell hypertrophy. These findings were not adverse (i.e., there was an absence of inflammation and/or necrosis). At the end of the recovery period, there was a tendency towards reversal of treatment-related findings noted at the terminal kill, with reductions in incidence and severity levels of all such changes. Based on the data presented, the sponsor has concluded that there is an adequate margin of safety for CBD at a daily dose of 20 mg/kg/day in both juvenile and adult preclinical animal populations using multiple different models of seizures using mice and rats.

Reviewer Comments:
Based on a preliminary assessment by DNP, there appears to be efficacy in preventing seizures associated with these two debilitating and rare seizure disorders that typically present in pediatric age groups. Much of this review will draw primarily from clinical analyses presented in the Liver Safety Report (LSR) that was submitted by the sponsor and prepared in consultation for GW Research Ltd. by Dr. Paul Watkins, MD, who is a hepatologist with recognized expertise in the assessment of DILI.

4 Summary of Clinical Trials

Table 1: Overall Summary of Unique CBD-OS Exposures in the Clinical Development Program Included in the Liver Safety Report

Population Source	Number of unique CBD-OS exposures
Placebo-Controlled Trials in the Target Indications	
GWEP 1332 Part A (3 weeks)	27
Pool DS/LGS (Pivotal DS and LGS) (14 weeks) GWEP1332 Part B (DS), GWEP1414 (LGS), GWEP1423 (LGS)	296
Open-label Trial in the Target Indications	
GWEP1415 (includes patients who received placebo in previous controlled trials listed above).	217
Total Unique Exposures in Target Indications (Pool LT-DS/LGS)	**540**
Phase 1 Clinical Pharmacology Trials	
Pool H-SD (Healthy-Single Dose)	110
Pool H-MD (Healthy-Multiple Dose)	125
Pool PP1-SD (Special Patient Populations-Single Dose)	87
Total Unique Exposures in Clinical Pharmacology Trials	**322**
EAP (Expanded Access Program)	
Pool EAP patients with drug-resistant epilepsy enrolled in the EAP or other compassionate use programs (months to years)	**684**
Trials in Other Epilepsy Patient Populations	
GWEP1428 (DDI trial in patients with epilepsy)	**16**
GWEP1428 OLE	**4**
Trials in Other Exploratory Indications	
GWAP1241 (schizophrenia or related psychotic disorder) (6 weeks)	**43**
Total Unique Exposures to CBD-OS	**1609**
Total Unique Exposures to Multiple Doses of CBD-OS	**1412**

From Table 7.1 – sponsor LSR

Four placebo-controlled trials of CBD-OS have been completed in patients with DS or LGS and 1 placebo-controlled trial is ongoing in patients with DS (See Table 1). In addition, an open-label extension (OLE) trial is ongoing, which allowed patients who participated in the controlled trials to continue or begin treatment with CBD-OS. The NDA cutoff date for safety data from the OLE trial was November 3, 2016.

The LSR provides an evaluation of the liver safety data that have been acquired from the 540 patients with DS or LGS who were treated in the controlled trials in conjunction with findings in an OLE trial (See Table 1). The number of DS and LGS patients exposed to CBD-OS included: 478 (88.5%) exposed for over 12 weeks; 443 (82.0%) exposed for over 26 weeks; and 203 (37.6%) exposed for over 1 year at the time of the NDA data cutoff (November 3, 2016). In addition, liver safety data were acquired from CBD-OS trials conducted in subjects (treated under an Expanded Access Program) with epilepsy (n=20), schizophrenia or related psychotic disorder (n=43). In addition, healthy subjects were chronically administered twice-daily doses of CBD-OS (n=125). The LSR also summarizes the “real world” experience that was reported to the sponsor for

684 patients with DS, LGS, and a variety of severe epilepsy conditions who received chronic administration of CBD-OS in the Expanded Access Program (EAP) for compassionate use led by individual investigators.

A. Completed Placebo-controlled Trials

Pilot Trial - GWEP1332 Part A

A 3-week blinded pilot trial where patients with DS were randomized to adjunctive treatment with 5 mg/kg/day (n=10), 10 mg/kg/day (n=8), 20 mg/kg/day (n=9) CBD-OS or placebo (n=7). After 3 weeks on blinded study medication (BSM), patients were tapered by decreasing the BSM daily dose by 10% each day for 10 days. Following conclusion of the trial and result analysis, participating patients were offered the opportunity to enroll into an OLE trial (GWEP1415).

Pivotal Dravet Syndrome and Lennox-Gastaut Syndrome Trials

GWEP1332 Part B

A 14-week blinded trial where patients with DS were randomized to adjunctive treatment with 20 mg/kg/day CBD-OS (n=61) or placebo (n=59). Concomitant AEDs and doses were to remain constant during the treatment period. After 14 weeks on BSM, patients were eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415.

GWEP1414

A 14-week blinded trial where patients with LGS were randomized to adjunctive treatment with 10 mg/kg/day CBD-OS (n=67), 20 mg/kg/day CBD-OS (n=82) or placebo (n=76). Concomitant AEDs and doses were to remain constant during the treatment period. After 14 weeks on BSM, patients were eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415.

GWEP1423

A 14-week blinded trial where patients with LGS were randomized to adjunctive treatment with 20 mg/kg/day CBD-OS (n=86) or placebo (n=85). Concomitant AEDs and doses were to remain constant during the treatment period. After 14 weeks on BSM, patients were eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415.

Ongoing DS Placebo-controlled Trial - GWEP1424

An ongoing 14-week blinded trial where patients with DS are planned for randomization to adjunctive treatment with 10 mg/kg/day CBD-OS (n=62), 20 mg/kg/day CBD-OS (n=62) or placebo (n=62). Concomitant AEDs and doses are to remain constant during the treatment period. After 14 weeks on BSM, patients are eligible to enter a transition to open-label treatment with CBD-OS in OLE trial GWEP1415. Due to the blinded nature of ongoing trial GWEP1424, data for patients from this trial and any GWEP1424 patient who subsequently participated in trial GWEP1415 will not be presented in this LSR. GWEP1424 will not be mentioned in subsequent sections of the LSR.

B. Ongoing Open-label Extension Trial - GWEP1415

This is an extended duration trial that enrolled patients who had been transitioned from trials GWEP1332 Part B, GWEP1414, GWEP1423, and GWEP1332 Part A. Patients were to be titrated beginning with 2.5 mg/kg/day CBD-OS on Day 1 up to a dose of 20 mg/kg/day beginning on Day 11. Subsequently the CBD-OS dose could be lowered or titrated to up to 30 mg/kg/day based on investigator assessment. Likewise, AEDs and doses could be changed in OLE trial GWEP1415 based on investigator assessment. Trial GWEP1415 remains open. The data cutoff date for the current NDA was November 3, 2016. The GWEP1415 data for 136 patients from the blinded, ongoing trial GWEP1424 have not been integrated into the GWEP1415 data analyses. Thus, data from 494 patients who were originally evaluated in GWEP1332 Part B, GWEP1414, GWEP1423, and GWEP1332 Part A and received CBD-OS in GWEP1415 were available for analysis.

C. CBD-OS Dose Escalation, Maintenance, and Taper Regimens

Dosing was started at a low 2.5 mg/kg/day and tapered upward over an 11-14 days period to the target dose of 10 or 20 mg/kg/day. Subsequently, dosing was tapered slowly over 10 days when completing or discontinuing drug. If an unacceptable AE developed at any time during the titration period, dosing was to be suspended or amended, at the investigator's discretion, until the event resolved or the AE became well tolerated. If that dose became poorly tolerated, the investigator could temporarily or permanently reduce the dosage for the remainder of the maintenance period.

D. Inclusion/Exclusion Criteria Related to Liver

Based on the results of liver biochemical tests, a patient was not to receive treatment in a trial if one or more of the following exclusion criteria shown in Table 2 below were met. It should be noted that, in recognition of the range of background laboratory abnormalities inherent in the DS and LGS populations with uncontrolled seizures, the liver test-related exclusion criteria were quite liberal.

Table 2: Liver Test-Related Exclusion Criteria for Placebo-Controlled Trials and the OLE Trial in Patients with DS and LGS

Trial Number	Exclusion Criteria
GWEP1332	ALT > 5 ×ULN and bilirubin > 2×ULN ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5.
GWEP1414 GWEP1415 GWEP1423	ALT or AST > 5 × ULN. ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5). ALT or AST > 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).

Source: Sponsor's Table 8.6-1 LSR: Protocols for GWEP1332, GWEP1414, GWEP1423, GWEP1415

E. Monitoring during Clinical Trials

The monitoring of liver tests in clinical trials appeared to be sufficiently frequent and thorough to characterize the CBD-OS risk for producing acute DILI. In the DS and LGS placebo-controlled trials, there was a systematic acquisition of liver test data at baseline and beginning at the time of steady-state for the assigned CBD-OS dose (2 weeks), then after 4 weeks, 8 weeks, and 14 weeks of treatment. For patients who subsequently entered the long-term OLE trial, liver tests were again acquired at 2 weeks following initiation of dosing, then at 4 weeks and 12 weeks and subsequently at 12 week intervals (See Table 3).

Table 3: Timing of Planned Liver Test Acquisition in Placebo- Controlled DS and LGS Trials and Open-label Extension Trial

	Planned Dosing Day[a] for Liver Test Acquisition[b]										
Trial Number	8	15	22	29	57	85	99	109[c]	169	253	337
Pilot											
GWEP1332 Part A	X		X								
Pivotal											
GWEP1332 Part B		X		X	X		X	X			
GWEP1414		X		X	X		X	X			
	Planned Dosing Day[a] for Liver Test Acquisition[b]										
Trial Number	8	15	22	29	57	85	99	109[c]	169	253	337
GWEP1423		X		X	X		X	X			
Open-label Extension											
GWEP1415		X		X		X			X	X	X

Source: Protocols for GWEP1332, GWEP1414, GWEP1423, GWEP1415.

[a] Windows used for summary statistical analyses of controlled trials. Day 8 (2-11); Day 15 (12-18); Day 22 (19-25); Day 29 (26-36); Day 57 (37-81); Day 99 (82-103).

[b] CBD-OS doses of 10 mg/kg/day and 20 mg/kg/day reached on Dosing Days 7 and 11, respectively.

[c] Follow-up off BSM

F. Withdrawal Criteria

The protocol-specified withdrawal criteria in each trial, including the EAP, included the following:

- ALT or AST > 3 × ULN with (or the appearance of) fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia > 5%.
- ALT or AST > 8 × ULN.
- ALT or AST > 5 × ULN for or more than 2 weeks.
- ALT or AST > 3 × ULN and bilirubin > 2 × ULN or INR > 1.5.

Following completion of the pilot trial GWEP1332 Part A, the following directions were agreed with the FDA and added to CBD-OS protocols:

- If a patient met one of the above criteria, the investigator was to arrange for the patient to return to the investigational site as soon as possible (within 24 hours of notice of abnormal results) for repeat assessment of ALT, AST, bilirubin and alkaline phosphatase (ALP), detailed history, and physical examination. Patients were to be followed in this way until all abnormalities had normalized (in the investigator's opinion) or returned to the baseline state. If the patient could not return to the investigational site, repeat assessments could be performed at a local laboratory (and the results were then to be sent to the sponsor by the investigator).
- Elevations in ALT or AST > 3 × ULN or bilirubin > 2 × ULN alone, i.e., when not concomitant, were not grounds for withdrawal but were to be followed up, as above, within 72 hours of notice of abnormal results. As will be described below, treatment with CBD was either paused or discontinued in some study subjects because of treatment-related elevations of liver test results that met the criteria described above.

G. Pooling Strategy

The 14-week placebo-controlled trials in patients with DS (GWEP1332 Part B) or LGS (GWEP1414 and GWEP1423) were pooled for the liver safety analyses (Pool DS/LGS, N=296). Due to its short duration, the 3-week pilot placebo-controlled trial in DS (GWEP1332 Part A) was analyzed separately.

Pool LT-DS/LGS (N=540) included all DS and LGS patients exposed to CBD-OS in the preceding 3 trials listed above (Pool DS/LGS, in GWEP1332 Part A, and/or during participation in the OLE trial GWEP1415). Thus, a patient (taking CBD-OS) with a liver test elevation or AE observed in a placebo-controlled trial would also have that event represented in analyses for Pool LT-DS/LGS.

H. Demographics

In Pool DS/LGS, the mean age of patients in the 3 treatment groups ranged from 13.8–14.7 years. The 6–11 years and 12–17 years age brackets accounted for nearly 60% of patients in the pool. Age, sex, race, body weight, BMI and region distribution were similar across CBD-OS 10 mg/kg/day, CBD-OS 20 mg/kg/day, and placebo groups.

Patient demographics for Pool LT-DS/LGS show that overall, the mean age of patients was 13.8 years (range: 2.3–48.0 years of age) with the greatest proportion of patients within the 6–11 years age bracket. There were similar proportions of males and females.

Liver Test Results at Baseline

Over 20% of the CBD-OS and placebo patients had an ALT value > ULN and 11 patients across groups had a baseline ALT value > 2 × ULN. The frequency of elevated (> ULN) baseline ALP values ranged from 16.4% to 17.9% across the 3 treatment groups. A lower but consistent frequency of elevation (> ULN) in AST was also observed at the baseline assessment across the treatment groups and ranged from 6.4% to 11.8%. All enrolled patients had normal total bilirubin levels at baseline.

INR, a marker for liver synthetic function, was elevated to > ULN at baseline in 4.5% of the patients randomized to 10 mg/kg/day, 3.2% of the patients randomized to CBD-OS 20 mg/kg/day, and 5.0% of patients randomized to placebo. The GGT results were quite variable. Across the 3 treatment groups, the frequency of a baseline GGT value > 3 × ULN ranged from 7.4% to 10.5% and across groups.

I. Disposition

Overall, 3.0%, 14.4%, and 3.6% of the patients in the CBD-OS 10 mg/kg/day, CBD-OS 20 mg/kg/day, and placebo groups, respectively, discontinued prematurely from their study. In the same respective groups, a total of 1.5%, 8.7%, and 1.4% were discontinued due to an AE.

A higher rate of discontinuation in the higher 20 mg/kg/day dose is notable.

J. Exposure

Table 4: Exposure in Pool LT-DS/LGS

Parameter	Statistics	All CBD-OS (N=540)
Safety Analysis Data Set	**n (%)**	**540 (100.0)**
GWEP1332A	n (%)	31 (5.7)
GWEP1332B	n (%)	117 (21.7)
GWEP1414	n (%)	222 (41.1)
GWEP1423	n (%)	170 (31.5)
Total number days:		
On Treatment[a] n (%)	N (missing)	540 (0)
	Mean ± SD	304.4 ± 136.0
	Median	327.5
	Q1 ; Q3	234.0 ; 396.0
	Min ; Max	7.0 ; 555.0
On Treatment[a] n (%)	1–14 days	3 (0.6)
	15–28 days	15 (2.8)
	29–42 days	23 (4.3)
	43–84 days	21 (3.9)
	85–182 days	35 (6.5)
	183–364 days	240 (44.4)
	365–729 days	203 (37.6)
	≥ 730 days	0

Source: Sponsor Table 10.4.2-1 LSR

a - Total number of days on treatment includes the titration and taper periods, up to last dose date. Compliance with dosing is based on completion of a daily paper diary. If the diary was not fully completed then this may result in inaccurate compliance.

Table 5: Common (≥ 10% in All CBD-OS group) Concomitant AEDs in Pivotal Trials (Pool DS/LGS)

Type of AED	CBD-OS 10 mg/kg/day (N=67) N (%)	CBD-OS 20 mg/kg/day (N=229) N (%)	All CBD-OS (N=296) N (%)	Placebo (N=220) N (%)
Clobazam	35 (52.2)	119 (52.0)	154 (52.0)	118 (53.6)
Valproic Acid	23 (34.3)	105 (45.9)	128 (43.2)	97 (44.1)
Levetiracetam	19 (28.4)	67 (29.3)	86 (29.1)	74 (33.6)
Lamotrigine	19 (28.4)	57 (24.9)	76 (25.7)	58 (26.4)
Rufinamide	18 (26.9)	55 (24.0)	43 (19.5)	43 (19.5)
Topiramate	13 (19.4)	38 (16.6)	51 (17.2)	39 (17.7)
Clonazepam	10 (14.9)	29 (12.7)	39 (13.2)	30 (13.6)
Zonisamide	8 (11.9)	31 (13.5)	39 (13.2)	26 (11.8)
Lacosamide	9 (13.4)	22 (9.6)	31 (10.5)	22 (10.0)
Stiripentol	0	30 (13.1)	21 (9.5)	21 (9.5)

Note: Safety analysis set.
Note: Patients from study GWEP1332 Part A are excluded.
Percentages based on column header N. Dictionary Coding: WHO Drug version June 2014 Source: LSR Table DSLGS.3.1.2.

5 Analyses and Results

A. Controlled Trial Results

Controlled trial results showed that CBD-OS was associated with dose-related ALT elevations in a subset of patients who manifested less pronounced AST elevations. Evaluation of the liver test results and adverse event (AE) reports from the 540 patients with DS or LGS who were administered chronic CBD-OS did not identify any patient as meeting published consensus criteria for severe drug-induced liver injury (DILI) (i.e., ALT > 3 x ULN and TB > 2x ULN). None of the clinical trial patients were identified as meeting the DILI laboratory criteria for Hy's Law (ALT ≥ 3 × ULN and bilirubin > 2 × ULN).

Among the 540 CBD-OS patients, there were 50 (9.3%) who had a treatment-emergent (TE) ALT > 3 and < 5 × ULN and 37 (6.9 %) who met the DILI biochemical criterion of TE ALT ≥ 5 × ULN. These ALT elevations were generally accompanied by normal ALP (a marker of bile duct injury) and bilirubin values. For the 37 patients with TE ALT ≥ 5 × ULN, the CBD-OS doses at the time of peak ALT elevation were: 5 (n=1); 10 (n=2); 18 (n=1); 20 (n=30); 23 (n=1); and 25 (n=2) mg/kg/day. A total of 32 of the 37 (86.5%) CBD-OS patients with TE ALT ≥ 5 ULN were taking concomitant valproate., which is also associated with hepatotoxicity. Eighteen of the patients with TE ALT ≥ 5 × ULN were discontinued from treatment, including 16 who had a TE ALT > 8 × ULN, one of the prespecified withdrawal criteria included in each trial protocol.

Table 6 shows that for the CBD-OS 20 mg/kg/day group, TE ALT > 3 × ULN (16.3%) was about twice as common as AST > 3 × ULN (7.9%). This difference suggests that the origin of the ALT elevation is the liver and not other organ sources. Amino transferase levels (either ALT or AST, AT) > 3 × ULN were observed at only a slightly higher rate (18.1%) than ALT alone (16.3%). For this reason, subsequent analyses in text will focus on ALT; however, analysis results will also be provided for AST and AT in supporting tables.

Table 6: Frequency of TE Liver Test Elevations (Observed Peak Levels) Any Time Post-baseline in Pool DS/LGS

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

AT = ALT or AST. N corresponds to the total number of patients in the treatment group. n / N : n = number of patients who had 1 or more elevations above the criterion any time post-baseline but not at baseline. N = number of patients who did not have an elevation above the criterion at baseline.
Source: LSR Table DSLGS.5.1.4.

The frequency of ALT elevations was dose-related. The frequencies of ALT > 3 × ULN and > 5 × ULN in the placebo group (both 0.9%) were only slightly lower than those in the CBD 10 mg/kg/day group (1.5% for each). The CBD-OS 20 mg/kg/day group exhibited higher frequencies, as 16.3% of these patients had TE ALT values > 3 × ULN and 7.4% had TE ALT values > 5 × ULN.

There was a similar frequency of TE ALP > 1.5 × ULN and ALP > 2 × ULN across all 3 treatment groups (Table 7).

Table 7: Frequency of Treatment-Emergent Liver Test Elevations (Observed Peak) Any Time Post-Baseline in Pool DS/LGS

Liver Test	Multiple of ULN	CBD-OS 10 mg/kg/day (N=67) *n / N* (%)	CBD-OS 20 mg/kg/day (N=229) *n / N* (%)	Placebo (N=220) *n / N* (%)
ALP	> ULN	5 / 56 (8.9)	13 / 188 (6.9)	17 / 181 (9.4)
	> 1.5 × ULN	1 / 64 (1.6)	8 / 222 (3.6)	5 / 212 (2.4)
	> 2 × ULN	1 / 65 (1.5)	3 / 227 (1.3)	5 / 219 (2.3)
	> 3 × ULN	0 / 67	0 / 229	3 / 220 (1.4)

Source: Sponsor Table 11.4-2 LSR - Table LSR DSLGS.5.1.2, Table LSR DSLGS.5.1.21.

Table 8: Frequency of Treatment-Emergent Liver Test Elevations (Observed Peak) Any Time Post-Baseline During Exposure to CBD-OS (Pool LT-DS/LGS)

Liver Test	Multiple of ULN	All CBD-OS (N=540) *n / N* (%)
ALT (U/L)	> 1×	223 / 426 (52.3)
	> 2×	134 / 534 (25.1)
	> 3×	84 / 538 (15.6)
	> 5×	33 / 540 (6.1)
	> 8×	15 / 540 (2.8)
	> 10×	10 / 540 (1.9)
	> 20 ×	2 / 540 (0.4)
AST (U/L)	> 1×	191 / 488 (39.1)
	> 2×	93 / 537 (17.3)
	> 3×	42 / 539 (7.8)
	> 5×	16 / 540 (3.0)
	> 8×	7 / 540 (1.3)
	> 10×	2 / 540 (0.4)
	> 20 ×	0 / 540

Source: sponsor Table LSR Table 11.5-1 LSR - LTDSLGS.5.2.4.

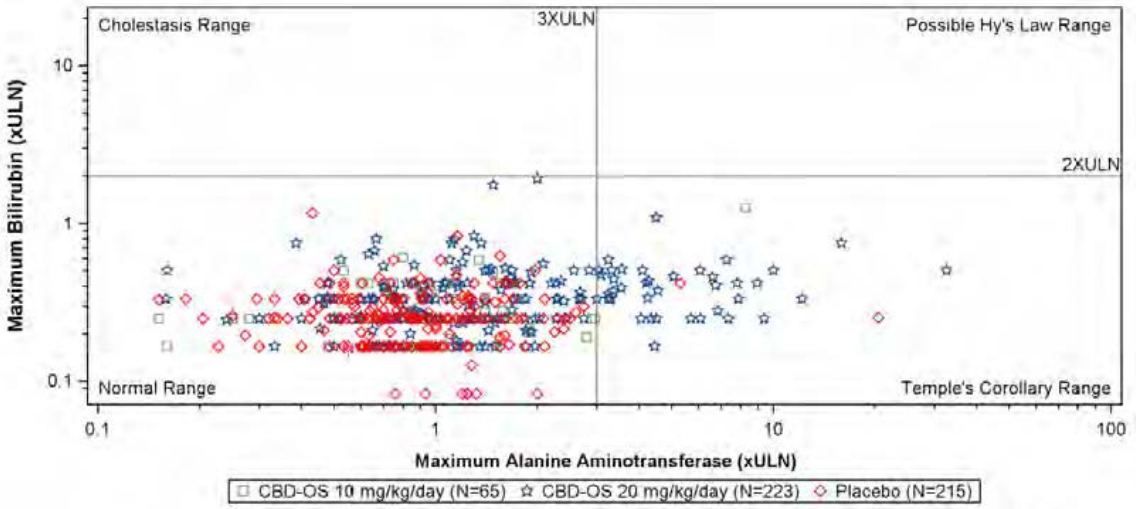
B. eDISH Plots

Figure 1 below

IN the eDISH plot, no CBD-OS or placebo patient was charted in the upper right quadrant, thus demonstrating the absence of any potential TE Hy's Law case, defined as one with peak ALT levels > 3 × ULN in conjunction with peak bilirubin levels >2 × ULN. Likewise, the absence of points in the upper left quadrant showed the absence of cases with potential TE severe cholestasis.

As illustrated in the lower left quadrant, approximately 91% of the CBD-OS and placebo patients combined did not exhibit a TE ALT value > 3 × ULN during treatment. Points in the lower right quadrant represent the 0.9% of placebo patients, the 1.5% of CBD-OS 10 mg/kg/day patients, and the 17.0% of CBD-OS 20 mg/kg/day patients who had a TE maximum ALT value > 3 × ULN.

Figure 1: eDISH Plot of Maximum Treatment-Emergent ALT and Bilirubin Values for Individual Patients During Treatment in Pool DS/LGS (Pivotal DS and LGS)

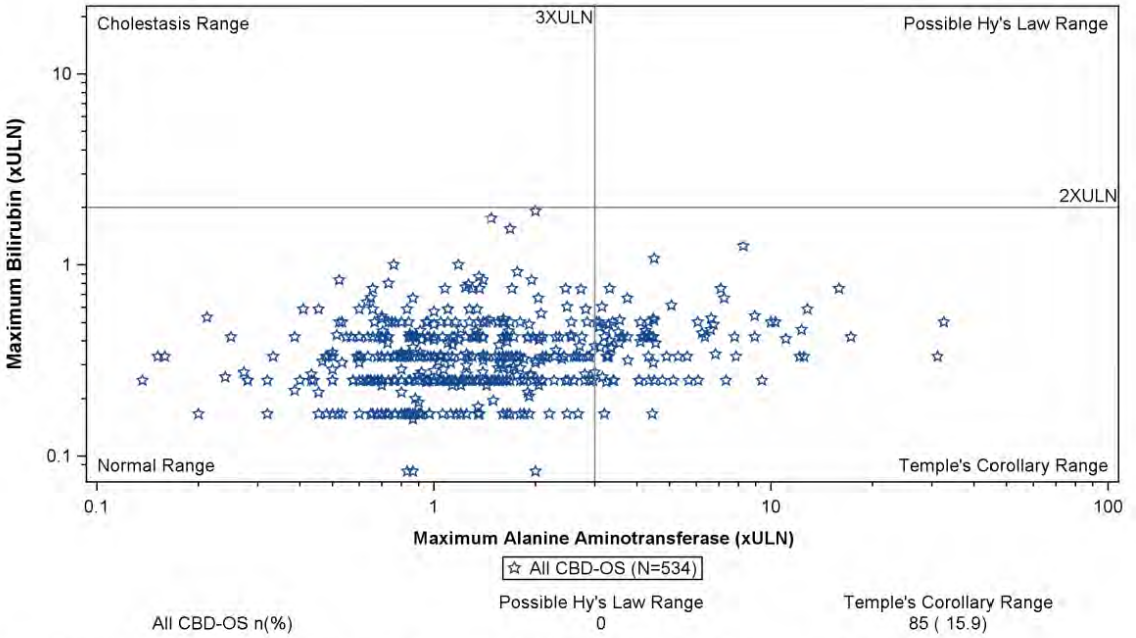


	Possible Hy's Law Range	Temple's Corollary Range
CBD-OS 10 mg/kg/day n(%)	0	1 (1.5)
CBD-OS 20 mg/kg/day n(%)	0	38 (17.0)
Placebo n(%)	0	2 (0.9)

Normal patients are on the lower left quadrant, while possible Hy's Law cases appear on the right upper quadrant.
Data from the studies 1332 Part B, 1414 and 1423 are included.

A similar picture is seen with the LT safety data where no Hy's law cases were observed; however, ALT elevations were frequent.

Figure 2: eDISH Plot of Maximum Treatment-Emergent ALT and Bilirubin Values for Individual Patients During CBD-OS Treatment in Pool LT-DS/LGS



	Possible Hy's Law Range	Temple's Corollary Range
All CBD-OS n(%)	0	85 (15.9)

Normal patients are on the lower left quadrant, while possible Hy's Law cases appear on the right upper quadrant.

Source: sponsor Figure 11.3-3 LSR:

A total of 36 of the 37 patients with TE ALT ≥ 5 × ULN had an R value[1] of ≥ 5, indicating a hepatocellular pattern of DILI. One patient had an R value of 2, suggesting a cholestatic pattern of DILI.

Reviewer Comments:
On review of the 30 narratives in the LSR appendix where transaminases were elevated, several cases are noted where the total bilirubin (TB) also increased from baseline in conjunction with the transaminase elevations (cases S195, V182, P033). None of the changes in TB resulted in the TB being above the ULN, but several of the patients with changes from baseline in TB were also noted to have symptoms consistent with DILI (cases V182, Q072, P033). It is noted that in the expanded access program (EAP), most patients did not have TB values measured. It would be prudent to include in the prescriber labeling, instructions to discontinue drug for development of symptoms (e.g., abdominal pain, anorexia, nausea or vomiting, fatigue) and for significant increases in TB from baseline, even if the TB does not rise above ULN.

Note that secondary to the relatively limited treatment periods of the controlled clinical trials (<14 weeks), little data are available to rule out whether continuous CBD exposure with or without mild elevations of aminotransferase levels over a longer term period is associated with a potential to cause chronic liver injury, or the slow development of liver fibrosis. While some patients have been treated for up to 2 years in open-label or uncontrolled studies, no screening for development of chronic liver injury has apparently been performed (e.g., histopathology or elastography).

It is also not clear from the available data if patients would adapt if they were kept on the drug after developing acute aminotransferase elevations, as study subjects, based on protocol stop rules, were supposed to be discontinued from treatment when ALT or AST were > 8 x ULN.

By-and-large we agree with the causality assessments provided in the LSR.

C. Time to Onset of TE Liver Test Elevations

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

The risk window was wider for patients taking concomitant valproate. In the 20mg/kg/day group, after 30 and 60 days of treatment with CBD-OS, 8 of 14

[1] The R-value is defined as serum ALT/upper limit of normal (ULN) divided by serum ALP/ULN. By common convention, R≥5 is labeled as hepatocellular DILI, R<2 is labeled as cholestatic DILI, and 2<R<5 is labeled as “mixed” DILI.

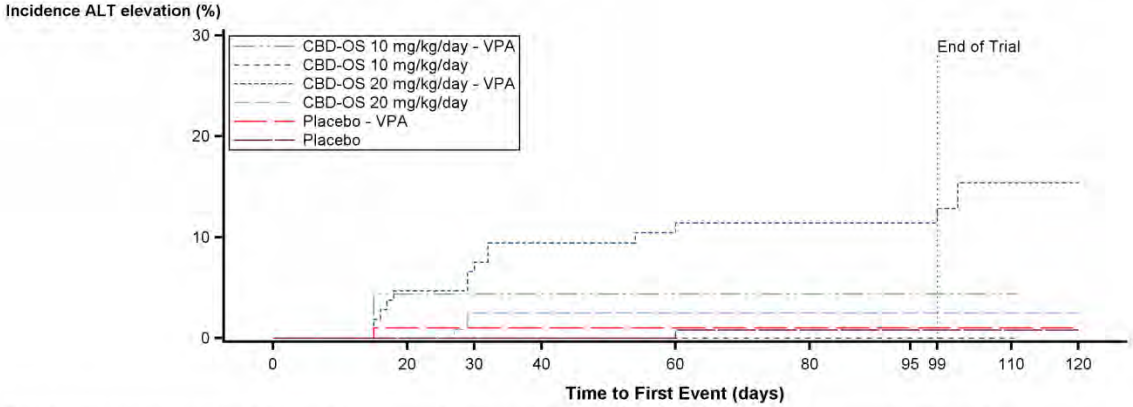
(57.1%) and 12 of 14 (85.7%) elevations of ALT > 5 × ULN had been observed, respectively. At the same respective times, 21 of 31 (67.7%) and 27 of 31 (87.1%) elevations of ALT > 3 × ULN had been observed. The single observations of ALT elevation to > 3 and > 5 × ULN in the CBD-OS 10 mg/kg/day group and placebo group occurred during the first 30 days of treatment. Both patients were taking concomitant valproate.

In the Pool LT-DS/LGS, the pattern of the Kaplan-Meier plots shows that the majority of ALT elevations occurred during the first 60 days of treatment with CBD-OS in patients regardless of their use of concomitant valproate.

For CBD-OS patients not taking concomitant valproate, all 5 of the elevations of TE ALT > 5 × ULN (100%) were observed in less than 100 days (~3 months) of treatment. For the same group, 12 of the 13 elevations of TE ALT > 3 × ULN (92%) were observed in less than 100 days (~3 months) of treatment.

For CBD-OS patients taking concomitant valproate, 24 of the 28 elevations (85.7%) of TE ALT > 5 × ULN were observed in less than the first 100 days (~3 months) of treatment, and the remaining 4 elevations were observed prior to the first 200 days (~6 months) of treatment. For the same group, 49 of the 71 elevations (69.0%) of TE ALT > 3 × ULN were observed in less than the first 100 days (~3 months) of treatment, and 61 of the 71 elevations (86%) were observed during the first 200 days (~6 months) of treatment.

Figure 3: Kaplan-Meier Plot of Incidence of ALT Elevations to > 5 × ULN for Patients Taking or Not Taking Concomitant Valproate in Pool DS/LGS (Pivotal DS and LGS)



Patients without events/censoring before or at the corresponding timepoint (Patients with events on or before the corresponding timepoint)

CBD-OS 10 mg/kg/day - VPA	23(0)	22(1)	22(1)	22(1)	22(1)	22(1)	22(1)	1(1)	0(1)
CBD-OS 10 mg/kg/day	44(0)	44(0)	44(0)	44(0)	44(0)	44(0)	44(0)	1(0)	0(0)
CBD-OS 20 mg/kg/day - VPA	106(0)	101(5)	97(8)	93(10)	87(12)	81(12)	77(12)	14(14)	0(14)
CBD-OS 20 mg/kg/day	123(0)	122(0)	116(3)	116(3)	113(3)	111(3)	107(3)	7(3)	0(3)
Placebo - VPA	97(0)	96(1)	96(1)	96(1)	95(1)	95(1)	94(1)	5(1)	0(1)
Placebo	123(0)	123(0)	123(0)	123(0)	120(1)	120(1)	116(1)	8(1)	0(1)

Valproate=VPA
Subjects from study GWEP1332 Part A are excluded.
Censoring is done at last known date or Day 120, whichever comes first.

Source: LSR Figure DSLGS.7.1.11.

D. DILI Defined as TE ALT ≥ 5 × ULN

Controlled Trials (Pool DS/LGS and GWEP1332 Part A):

TE ALT ≥ 5 × ULN was observed in a total of 23 patients who (at the time of their peak ALT elevation) were taking CBD-OS [5 mg/kg/day (n=1); 10 mg/kg/day (n=1); 20 mg/kg/day (n=19] or placebo (n=2) in the controlled trials. It should be noted that 18 of the 21 CBD-OS patients and 1 of the 2 placebo patients were taking valproate concomitantly.

The time to onset of the ALT elevation was similar across patients. Seventeen of the 21 patients (80.9%) taking CBD-OS had peak ALT values ≥ 5 × ULN first observed ≤ 36 days after the initiation of treatment. Four patients (all taking concomitant valproate) had peak ALT observed at Day 54, Day 77, Day 99, and Day 102. The 2 placebo elevations occurred on Day 15 and Day 60.

The remaining CBD-OS patients continued to receive CBD-OS for the duration of the trials, including 2 patients with TE ALT values = 15.9 × ULN and 10.0 × ULN. Thirteen of the 21 CBD-OS patients with TE ALT ≥ 5 × ULN continued to take CBD-OS after the elevation; 9 entered the OLE trial after the conclusion of their controlled trial.
The bilirubin value remained in the normal range for 20 of the 21 CBD-OS patients and was 1.3 × ULN in 1 patient. The ALP value remained within the normal range for 17 of the 21 CBD-OS patients, and was 1.1, 1.2, 1.3, and 2.9 × ULN in the remaining four patients.

In the LSR, Dr. Watkins conducted un-blinded reviews of individual narratives for each of the 37 CBD-OS patients with TE ALT ≥ 5 × ULN. He assessed that CBD-OS probably caused or contributed to the elevations in 35 of the 37 patients (94.6%) and that this was possible for the remaining 2 (5.4%). Dr. Watkins noted that he would also have assessed one of the placebo elevations as probable and the other as possible had the patients been taking CBD-OS. The probable assessment represents a 50-100% likelihood of causation and possibly represents a 25-49% likelihood. By-and-large, we agree with the conclusions of this causality analysis.

E. Recovery Times

Estimated recovery times were calculated for the period from an ALT elevation ≥ 5 × ULN to a value of 2.9 × ULN. Notably, the endpoints of ALT reversal do not represent full resolution of the abnormalities to a normal range. When defined in the manner, the estimated recovery times were commonly less than 2 weeks for patients who had treatment with CBD-OS abruptly discontinued, tapered then discontinued, or CBD-OS continued at the same or lower daily dose.

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

The occurrence of DILI (defined as TE ALT ≥ 5 × ULN) was also observed in multiple-dose phase 1 studies in healthy subjects and phase 2 studies in adult epilepsy patients administered CBD-OS for several weeks. The frequency and pattern of ALT elevations in these trials was similar to those observed in the DS and LGS trials. There was also a relevant 6-week phase 2 pilot trial of adjunctive CBD-OS for schizophrenia or related psychotic disorder in which initiation and continuation of CBD-OS 500 mg twice daily (~11.9 mg/kg/day in 43 adults 19-64 years of age) did not result in any observations of TE ALT ≥ 5 × ULN. This may be secondary to the lower dose and duration.

Recovery of treatment-emergent ALT ≥ 5 × ULN without stopping CBD-OS: Pooled Controlled Studies:

37/540 patients (6.9%) in Pool LT-DS/LGS[2] had treatment-emergent (TE) ALT ≥ 5 × ULN. Of the 37 patients in Pool LT-DS/LGS who had TE ALT ≥ 5 × ULN during treatment with CBD-OS, 17 patients (45.9%) recovered from this ALT elevation without, or prior to, stopping CBD-OS. Of these 17 patients:

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

F. Expanded Access Program:

30/647 patients (4.6%) in Pool Expanded Access Program (EAP) had TE ALT ≥ 5 × ULN. Of the 30 patients in Pool EAP who had TE ALT ≥ 5 × ULN during treatment with CBD-OS, 24 patients (80%) recovered from this ALT elevation without, or prior to, stopping CBD-OS. Of the 24 patients:

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

It is notable that protocol CBD stop rules were inconsistently adhered to by practitioners managing these patients. Several patients had reduction in dose of other concomitant medications, especially valproate.

Thirteen patients with ALT > 8 × ULN recovered without stopping CBD-OS, including patients with peak ALT elevations up to 40.3 × ULN ((b) (6)) and 21.1 × ULN (b) (6)).

[2] Pool LT-DS/LGS included all DS and LGS patients exposed to CBD-OS in trials GWEP1332A and B, GWEP1414 and GWEP1423, and/or during participation in the OLE trial GWEP1415. Thus, a patient (taking CBD-OS) with a liver test elevation or AE observed in a placebo-controlled trial would also have that event represented in analyses for Pool LT-DS/LGS.

One patient ([redacted] (b) (6)) in study GWEP1428 (phase 2 drug-drug interaction trial with clobazam) experienced a peak ALT elevation to 5.1 × ULN on Day 32 of CBD-OS dosing. This 36-year-old male patient with epilepsy was on 20 mg/kg/day at the time of the peak ALT elevation, as well as concomitant valproate. The day after the peak ALT elevation, the patient completed the double-blind phase of study GWEP1428, enrolled in the GWEP1428 OLE and commenced open-label CBD-OS, titrating up to 20 mg/kg/day over an 11-day period. Nine days after the peak ALT elevation, the patient's ALT returned to < 3 × ULN. On that same day, the patient withdrew from the GWEP1428 OLE.

Reviewer Comments:
While CBD clinical trial protocols stipulate that CBD should be discontinued if ALT levels rise above 8 x ULN, the above-mentioned patients were continued on CBD and apparently showed improvement of ALT levels (as defined above). However, these data are sparse and more data should be obtained to clarify if reversal of injury acceleration or full adaptation would occur in most or all patients with continued treatment. These data could be obtained in an open-label trial with very close monitoring of patients who developed ALT elevations on treatment, with drug discontinuation rules for patients who developed significant elevations in bilirubin or clinical symptoms of DILI.

In an uncontrolled investigator-initiated study of 14 patients with Parkinson's disease, 2 patients (aged 69 and 70) developed evidence of cholestasis (ALP > 2 × ULN) and one also had elevated transaminases. An additional 2 patients (both aged 68) had elevations of ALP (< 2 × ULN) without elevated transaminases. The patients were exposed to doses of CBD-OS in the range of 20 to 25 mg/kg/day for 25 to 30 days. All elevations resolved.

G. Re-challenge experience:

Eleven patients with uncontrolled epilepsy were re-challenged with CBD-OS after experiencing a liver enzyme elevation (TE ALT or AST > 3 × ULN) which resulted in CBD-OS discontinuation for more than 2 days. Of these:

- 4 patients experienced a recurrence of ALT or ALT > 3 × ULN – in 3 patients, the recurrence was observed within 29 days of restarting CBD-OS. In the 4 patients with a recurrence of transaminase elevations after CBD-OS re-challenge, the nature and characteristics of the recurrence was not significantly different from the initial elevations in terms of magnitude, time to onset, or the continued absence of functional impairment. None of the 4 patients with elevated transaminases after re-challenge were Hy's law cases.
- 7 did not experience a recurrence of ALT or ALT > 3 × ULN

H. Recovery from elevated ALT while still taking CBD

As noted in Section F, 37/540 patients (6.9%) in Pool LT-DS/LGS had TE ALT ≥ 5 × ULN. Examination of these 37 patients shows that 17 patients (45.9%)

recovered from this ALT elevation without, or prior to, stopping CBD-OS. Of these 17 patients:

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

Valproate was the most common concomitant medication where dose reduction occurred after observation of ALT ≥ 5 × ULN. A total of 6 patients had their valproate dose reduced after such an ALT elevation.

There were 4 patients who recovered from ALT > 8 × ULN without stopping CBD-OS. Of note, patient (b) (6) had ALT 15.9 × ULN on day 54; however, the patient recovered from the ALT elevation while continuing in study GWEP1423, and later enrolled into the OLE.

I. Intrinsic/Extrinsic Factors

- The frequency of ALT elevations when expressed as multiples of baseline values were similar for males and females (> 3 x baseline males (24.8%) and females (20.0%) in the CBD-OS 20 mg/kg/day group).
- Age did not appear to be a significant contributing risk factor; however, few children in the 2-5 year age range were included.
- Comparison of the CBD-OS 20 mg/kg/day groups showed that when ALT was > ULN at baseline, there was a higher frequency of TE ALT > 3 × ULN (30.0%) compared to when ALT was within the normal range at baseline (12.4%). Similarly, patients with an ALT > ULN at baseline were twice as likely to exhibit a TE ALT > 5 × ULN.
- Although the sample size for the CBD-OS 10 mg/kg/day group with baseline ALT > ULN (n=11) was relatively small, it was notable than none of the patients in the group exhibited even an ALT > 2 × ULN during treatment.
- The number of patients in the LGS CBD-OS 20 mg/kg/day group (n=168) was approximately 2.8 times larger than the corresponding DS group (n=61).
    - The frequencies of TE ALT > 3 × ULN (17.5%) and 5 × ULN (8.9%) in the LGS CBD-OS 20 mg/kg/day group were higher than the frequencies of 13.1% and 3.3%, respectively, observed in the corresponding DS group. None of the DS patients had a TE ALT > 8 × ULN compared with 3.6% for the LGS patients.
    - The Pool LT-DSLGS results suggest that, although there is an imbalance in the number of patients in the 2 groups, patients with DS and patients with LGS appeared to have a similar risk for TE ALT elevations > 3 × ULN and > 5 × ULN when administered CBD-OS 20 mg/kg/day.

MO Comment:
The liver injury associated with CBD appears to be relatively mild and reversible on drug discontinuation. It is dose-related, with a much higher incidence on the 20 mg/kg/day dose. Liver injury is noted most frequently in the first 30-90 days of treatment and is rare after 200 days of treatment. Therefore, it is recommended that patients be monitored frequently for 3 months and then at regular intervals for 1 year of treatment and then at 6-12 month intervals thereafter.

J. Concomitant AEDs

Both valproate and felbamate have previously been associated with elevations of liver test results.

Valproate

Table 9 shows a clear association between treatment with valproate plus CBD-OS and an increased frequency of ALT elevations. The use of valproate was common in the populations studied. Across groups, ~44% (n=225) of patients were being treated with concomitant valproate at the time of randomization and during the trial.

Comparison of the CBD-OS 20 mg/kg/day groups showed that patients with concomitant valproate treatment had a higher frequency of TE ALT > 3 × ULN (29.2%) than patients not taking valproate (5.0%). Similarly, patients taking concomitant valproate exhibited a higher frequency of TE ALT > 5 × ULN (13.2%) and > 8 × ULN (5.7%) compared to patients not taking valproate, at 2.4% and 0%, respectively.

Patients taking concomitant valproate exhibited TE ALT > 5 × ULN in 1/23 (4.3%) in the CBD-OS 10 mg/kg/day group, 14 /106 (13.2%) in the CBD-OS 20 mg/kg/day group, and 1/97 (1.0%) in the placebo group.

In contrast, in the groups of patients not taking concomitant valproate, TE of ALT > 5 x ULN was observer in 0%. 2.4% and 0.8% of patients taking CBD-OS 10 mg/kg/day, 20 mg/kg/day, or placebo. ALT > 8 × ULN was observed in 4.3%, 5.7%, and 1.0% of patients not taking concomitant valproate and taking CBD-OS 10 mg/kg/day, 20 mg/kg/day, or placebo (Table 10).

Reviewer Comments: The combined effects of liver injury signaling with concomitant CBD and valproate treatment pose an important challenge with regard to the sequencing of treatment adjustments in patients treated with these agents who manifest TE high levels of ALT. It is well recognized that valproate alone is an idiosyncratic hepatotoxic agent that can cause severe liver injury. Given that CBD either contributed to the resulting liver injuries or was the primary cause of DILI in the study subjects who were receiving both agents, it will be important to establish a decision tree for the triggering and agent-specific

sequencing of dose modification, drug discontinuation and patient observation when monitoring indicates acute injury.

Table 9: Frequency of ALT Elevations for Patients Taking or Not Taking Concomitant Valproate in Pool DS/LGS (Pivotal DS and LGS)

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

Source: Sponsor Table 13.2.2.1-1 LSR - LSR Table DSLGS.5.1.7.

Felbamate

The small numbers of patients taking felbamate limit interpretation of the results. Across groups, only ~10% (n=50) of patients were being treated with concomitant felbamate. In the CBD-OS 20 mg/kg/day group, patients taking concomitant felbamate exhibited a higher frequency (22.2%) of ALT values >3 × ULN than patients not taking felbamate (15.8%). However, the apparent higher frequency in the felbamate group appears to be driven by the presence of concomitant valproate in patients exhibiting ALT elevations.

MO Comment:
The small number of patients on felbamate and not on valproate makes conclusions impossible. All patients on concomitant felbamate should be monitored closely and for longer periods when starting CBD.

Clobazam

Clobazam had been observed to be associated with a low frequency of AT elevations (3.1% and 2.8% for doses of 0.25 and 1.0 mg/kg/day in 1 LGS trial. However, there was an interest in exploring a potential transaminase elevation interaction between clobazam and CBD-OS because CBD-OS increases exposure to the major metabolite of clobazam (N-desmethylclobazam).

The overall results support that apparent increased frequencies in ALT elevations in CBD-OS patients taking clobazam may be explained by the fact that valproate

tended to be a concomitant AED in CBD-OS patients who exhibited ALT elevations to > 5 × ULN while taking clobazam.

MO Comment:
CBD inhibits CYP2C19 and has the potential to increase plasma concentrations of drugs that are metabolized by CYP2C19, which includes phenytoin and clobazam. While no increases in valproic acid, stiripentol or clobazam levels were seen in a dedicated drug-drug interaction study (GWEP1543), there was an active metabolite of clobazam, n-desmethylclobazam (aka., nor-clobazam), that did show a 3-fold increase. N-clobazam is thought to have 1/5 the activity of clobazam, so the clinical significance of this increase is not clear.

6 Exploration of Potential Mechanisms for Observed Elevations of ALT

CBD and its major plasma metabolite, 7-COOH-CBD, were incubated for 1 hour and 24 hours with HepG2 cells and analyzed for effects on mitochondrial function via the mitochondria stress test measured in the Seahorse XF Analyzer. Three independent experimental runs were completed.

These in vitro data suggest that 7-COOH-CBD could cause serum ALT elevations via direct action on hepatic mitochondria at concentrations achieved in vivo. Furthermore, the commonly used antiepileptic drug (AED), valproate, and its metabolite 4-ene-valproic acid, have been implicated as ETC inhibitors. Therefore, a potential interaction effect between CBD and valproate at the level of the mitochondria could underlie observations in the clinical data. This hypothesis is currently being investigated further via additional data collection and simulations in collaboration with DILIsym Services Inc., RTP, NC, USA.

7 SUMMARY

In summary, CBD-OS administration to the target DS and LGS population in controlled clinical trials and an open label extension trial (n=540), and the large EAP program (n=684) was causally associated with elevations in serum ALT, consistent with hepatocellular DILI, but cases of severe hepatocellular injury marked by coincidentally substantial rises of serum bilirubin or changes of other indicators of worsening liver cell function did not occur. There were no reports of severe DILI and no reports of Hy's Law cases among the 540 DS and LGS patients receiving CBD-OS treatment. Among these patients, 522 were exposed to CBD-OS for longer than 28 days. There was a higher frequency for aminotransferase elevations in the higher 20 mg/kg/day dose compared with 10 mg/kg/day dosing.

Because the intended population for treatment with adjunctive CBD-OS (patients with DS or LGS) is the same as the population evaluated in the phase 3 trials,

the frequency of TE ALT ≥ 5 × ULN post-marketing is expected to be similar to the frequencies observed in the CBD-OS controlled trials. Based on the rule of 3, the absence of serious liver injury in the 522 patients were studied in these trials excludes an incidence of Hy's law cases greater that 1 in 174 treated patients and likely excludes an incidence of acute liver failure due to CBD-induced DILI greater than 1 in 1740 treated patients treated in a similar fashion, with respect to dosing, duration of treatment, and use of concomitant medications.

However, trial protocol and guideline recommendations provided liver test-based withdrawal criteria including trial withdrawal for patients with ALT values > 8 × ULN and may have prevented cases of more serious liver injury in some instances in which the agent was promptly stopped. It is notable that several patients continued on drug despite significant elevations in transaminases and did not develop evidence of severe liver injury with hyperbilirubinemia.

Concomitant valproate is identified as the most common risk factor for elevations in transaminases. Some patients resolved transaminase elevations while on CBD, in some of these patients, the valproate dose may have been decreased. From these data, it appears that in addition to the hepatotoxic profile of CBD alone marked by elevations of aminotransferases, there can be an additive toxic effect in some instances when CBD is combined with valproic acid.

Most cases of aminotransferase (ALT) elevations occurred in the first 30 days and almost all in the first 90 days of treatment, though a few did occur after 100 days, but before 200 days. All cases of transaminase elevations for which data were available recovered, most within 2 weeks.
Unknowns now include the unknown risk for chronic liver injury even in patients who do not exhibit transaminase elevations or who recover from transaminase elevations in patients treated with CBD for long periods of time. Whether longer exposures could result in chronic liver injury, such as the development of liver fibrosis over time, has not been studied.

I. Memorandum from Controlled Substance Staff: Human Abuse Potential Study

M E M O R A N D U M
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: March 20, 2018

To: Billy Dunn, M.D., Director
Division of Neurology Products

Through: Dominic Chiapperino, Ph.D., Acting Director
Silvia Calderon, Ph.D., Senior Pharmacologist
Controlled Substance Staff

From: Katherine Bonson, Ph.D., Pharmacologist
Controlled Substance Staff

Subject: **OPEN SESSION BACKGROUND DOCUMENT ON**:
Oral Human Abuse Potential Study as submitted under NDA 210,365 (IND 120,055)

Document prepared for FDA Peripheral and Central Nervous System Drug Advisory Committee on April 19, 2018, regarding cannabidiol oral solution (CBD-OS), 10 and 20 mg/day, p.o., proposed adjunct treatment of two epilepsy conditions in children aged 2 years and older who remain on their current antiepileptic medication: Dravet Syndrome and Lennox-Gastaut Syndrome
Sponsor: GW Research, Ltd.

I. Background

Cannabidiol oral solution (CBD-OS) is a first-in-class antiepileptic drug product sponsored by GW Research, Ltd. (a subsidiary of GW Pharmaceuticals, plc that operates under Greenwich Biosciences, Inc. in the United States, the holder of the Investigational New Drug (IND) application for CBD-OS). CBD-OS contains a 100 mg/ml solution of cannabidiol (CBD) dissolved in sesame oil, ethanol, sweetener and flavoring agent. It is proposed as oral adjunct treatment (10 and 20 mg/kg/day) of two epilepsy conditions in children who remain on their current antiepileptic medication: Dravet Syndrome (DS; also known as severe myoclonic epilepsy of infancy) and Lennox-Gastaut Syndrome (LGS) in patients 2 years of age and older. CBD-OS was granted Orphan Drug Designation and Rare Pediatric Designation for the treatment of LGS and DS, as well as Fast-Track Designation for the treatment of DS.

CBD is considered to be a new molecular entity for regulatory purposes because there are currently no FDA-approved drug products containing CBD. Under the Controlled Substances Act (CSA), CBD is a Schedule I substance based on its derivation from the plant, *Cannabis sativa*, also known as marijuana (hereafter, cannabis). Given that CBD is proposed for the treatment of a central nervous system (CNS) condition (epilepsy), it was necessary to evaluate the abuse potential of CBD through both preclinical studies (chemistry, receptor binding, animal behavioral studies) and clinical studies (including a human abuse potential study, as well as analyses of abuse-related adverse events in all clinical studies). These studies (described below) often used dronabinol as a positive control drug because it is a major psychoactive cannabinoid present in the cannabis plant.. Dronabinol is the established name for (-)-*trans*-delta-9-tetrahydrocannabinol (THC) and will be the term used throughout this document.

II. Conclusions

Based on the following preclinical experimental data, CBD does not appear to have abuse potential:

- It does not bind to cannabinoid receptors or any other receptor associated with drugs of abuse, such as dronabinol
- It does not produce overt behaviors similar to those produced by drugs of abuse such as dronabinol
- It does not produce a cannabinoid agonist response in the tetrad test that is similar to that produced by dronabinol
- It does not generalize to dronabinol or to the depressant, midazolam, in separate drug discrimination studies, showing it does not produce effects similar to a cannabinoid agonist or to a benzodiazepine
- It does not produce self-administration, suggesting it does not have rewarding properties like many known drugs of abuse

Based on clinical experimental data, CBD does not appear to have abuse potential:

- In a Phase 1 human abuse potential study with CBD, there were some slight abuse-related signals from the positive subjective measures, but these responses were close to being within the acceptable placebo range and were much lower than the abuse-related signals produced by the positive control drugs with known abuse potential (dronabinol and alprazolam). CBD produced a low level of euphoria-related adverse events (AEs), but this was much lower than that produced by dronabinol and did not predict positive subjective responses.
- There were no euphoria-related AEs in other Phase 1 clinical studies conducted with CBD in a non-patient population that would be indicative of abuse potential. Drugs that have abuse potential typically produce euphoria-related AEs in clinical studies. Phase 2 clinical studies with CBD were not assessed for euphoria-related AEs because the antiepileptic medication patients were also taking can have known abuse potential that would confound the evaluation.

Therefore, an overall assessment of the abuse-related data from preclinical and clinical studies leads to the finding that CBD has negligible abuse potential.

III. Abuse-Related Preclinical and Clinical Study Data

Receptor Binding Studies

In receptor binding studies with CBD, there was no significant affinity of CBD for cannabinoid (CB1 or CB2) sites. In contrast, dronabinol has high affinity for CB1 and CB2 receptors. There was also no significant affinity of CBD for other sites associated with abuse potential: opioids (mu, kappa, or delta), GABA/ benzodiazepine, dopamine (D1 or D2), serotonin (1A, 1B, 2A, 3, 5A, 6, or 7), NMDA/glutamate, channels (calcium, potassium, sodium, or chloride), transporters (dopamine or norepinephrine). Drugs such as opioids, sedatives, stimulants, and hallucinogens (among many others) have high affinity for these sites.

These data show that CBD does not have a mechanism of action similar to that of known drugs of abuse.

Animal Behavioral Effects

General Behavioral Studies

Administration of drugs with known abuse potential produce standard and predictable changes in overt observable behavior. If a test drug does not produce these behaviors, it is possible that the drug does not produce effects similar to known drugs of abuse. In the studies below, the CBD doses produce plasma levels of CBD that are equivalent to or greater than the plasma levels of CBD produced by therapeutic doses.

In an Irwin test of general behavior in rats (characterizing presence of certain behaviors), acute oral doses of CBD (10, 50 and 100 mg/kg) did not produce any changes in overt behavior or body temperature relative to vehicle. When the test was conducted in mice, acute intravenous doses of CBD (3, 10 and 30 mg/kg) produced a slight transient alteration in gait and a decrease in pain response and temperature relative to vehicle. However, when mice were given acute intravenous dose of CBD at 120 mg/kg, there were no changes in behavioral or muscular tone relative to vehicle.

In an open-field test in mice (in which animals are allowed to transverse a cage), acute intraperitoneal CBD (30 mg/kg) did not alter behavior, but the 100 mg/kg dose reduced locomotor activity, both relative to vehicle. When the test was conducted in rats, acute intraperitoneal CBD (60 and 120 mg/kg) both produced a decrease in locomotor activity relative to vehicle.

In the rotorod test (which evaluates the muscular coordination of an animal to maintain itself on a slowly rotating rod), an acute intraperitoneal CBD (200 mg/kg) produced no changes in latency to fall relative to vehicle.

These results show that CBD does not produce overt behavioral effects until doses that are equivalent to human supratherapeutic doses are administered. These effects are transient, however. Thus, CBD does not produce effects suggestive that the drug has abuse potential.

Cannabinoid-Specific Behavioral Tests

Mice were evaluated using the Tetrad Test, which measures changes in four behaviors that are known to be altered by dronabinol (locomotor activity, immobility, hypothermia and antinociception). In this study, mice received intraperitoneal doses of CBD or dronabinol, or vehicle prior to observation.

CBD did not alter locomotor activity, immobility, or antinociception at 1, 10, 50, or 100 mg/kg, but did produce hypothermia at 100 mg/kg, relative to vehicle. In contrast, dronabinol produced a decrease in locomotion as well as hypothermia and antinociception (but no changes in immobility) at 50 and 100 mg/kg, but produced no changes in response at 1 and 10 mg/kg, relative to vehicle.

These results show that CBD did not produce positive signs on all four of the tetrad test behaviors. In contrast, dronabinol produced positive signs in three of the four tetrad behaviors. These data suggest that CBD does not produce dronabinol-like effects.

Drug Discrimination Study (Evaluating Similarity to Known Drugs of Abuse)

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

Three drug discrimination studies were conducted with CBD, in rats that had been trained to discriminate dronabinol from vehicle or midazolam from vehicle. In the first two studies, rats (n = 7/study) were trained to discriminate dronabinol (3 mg/kg, i.p., 15 minute pretreatment time) from vehicle using a fixed ratio (FR) 10 schedule of reinforcement. When rats could stably discriminate dronabinol from vehicle, challenge sessions with CBD began. CBD was tested orally with a 2-hour pretreatment time at 20, 75, and 150 mg/kg (first study) and at 1, 3, and 10 mg/kg (second study). Dronabinol was tested as a positive control using oral administration (1, 3 and 10 mg/kg, p.o., 90-minute pretreatment time).

As expected, dronabinol (3 and 10 mg/kg) produced full generalization (70-99%) to the dronabinol cue. In contrast, CBD did not produce full generalization to the dronabinol

cue at any dose: 1 mg/kg (9%), 3 mg/kg (9%), 10 mg/kg, (8%), 20 mg/kg (14%), 75 mg/kg (46%), and 150 mg/kg (27%).

These data show that CBD does not produce similar interoceptive effects to those produced by dronabinol in rats.

In the third study, rats (n = 6) were trained to discriminate midazolam (0.5 mg/kg, i.p.) from vehicle. Once responding was stable, rats were challenged with midazolam (0.50, 1.0 and 1.50 mg/kg, p.o., 30-minute pretreatment time), alprazolam (0.125, 0.25, 0.50, and 1.0 mg/kg, p.o.), CBD (20, 75 and 150 mg/kg, p.o.) or vehicle. Full generalization to the midazolam cue was seen after administration of midazolam (1.0 and 1.5 mg/kg) and alprazolam (0.50 and 1.0 mg/kg). However, CBD produced no generalization to the midazolam cue at any dose. Notably, the highest dose of CBD produced plasma levels that were ~4X the highest human C_{max} value produced by therapeutic doses.

These data show that CBD does not produce similar interoceptive effects to those produced by midazolam in rats.

Overall, the data from these three studies show that CBD does not produce effects similar to those produced by a cannabinoid (dronabinol) or a benzodiazepine with depressant properties (midazolam).

Self-Administration Studies (Evaluating Rewarding Effects)

Self-administration is a method that assesses whether a drug produces rewarding effects that increase the likelihood of behavioral responses in order to obtain additional drug. Drugs that are self-administered by animals are likely to produce rewarding effects in humans, which is indicative that the drug has abuse potential.

A self-administration study was conducted in rats (n = 5-7/group) to evaluate whether CBD produces sufficient reward to be reinforcing. Animals were initially trained to press a lever to receive the Schedule II stimulant, cocaine (0.32 mg/kg/infusion, i.v.), using a fixed ratio (FR)10 final schedule of reinforcement. Once responding for cocaine was stable, animals were allowed to lever press for CBD (0.1, 0.5 and 1.5 mg/kg/infusion, i.v.), amphetamine (0.05 mg/kg/infusion, i.v.) or vehicle (i.v.). Rats were given access to each drug treatment for 3 consecutive days. To re-initiate lever pressing on each test day, animals received a non-contingent injection of cocaine (0.1 mg) at the start of the session.

As expected, cocaine produced a high degree of self-administration (~45 infusions/ session) and vehicle produced a low degree of self-administration (<5 infusions/session). The positive control, amphetamine (0.05 mg/kg/infusion) produced a moderate degree of self-administration (~25 infusions/session). Both the cocaine and amphetamine responses were statistically significantly different from vehicle.

In contrast, each of the three doses of CBD (0.1, 0.5, and 1.5 mg/kg/infusion) produced self-administration that was similar to that of saline (<10 infusions/session).

These data suggest that CBD produced insufficiently rewarding properties to sustain reinforcement. In contrast, drugs with known abuse potential (cocaine and amphetamine) did produce rewarding properties that maintained self-administration.

Human Behavioral Effects

Human Abuse Potential Study

Human abuse potential (HAP) studies evaluate the ability of a test drug to produce positive subjective responses in subjects compared to a known drug of abuse and to placebo. Subjects in HAP studies are individuals with a history of recreational drug use but not drug dependent. When the test drug produces consistently high responses on scales such as "Drug Liking," "Good Drug Effects," and "High" that are far outside the acceptable placebo range, it is likely that the test drug has abuse potential.

A HAP study was conducted to evaluate the oral abuse potential, safety, tolerability, and pharmacokinetics of CBD (750, 1500, and 4500 mg) compared to dronabinol (10 and 30 mg), alprazolam (2 mg), and placebo using a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-period, crossover design in healthy non-dependent recreational polydrug users (n = 40). The doses of CBD represent the two proposed therapeutic doses (10 mg/kg/day and 20 mg/kg/day, scaled up to a standard adult weight of 70 kg) and a supratherapeutic dose (3 to 6 times greater than the therapeutic doses, when scaled up to a standard adult weight of 70 kg).

Subjective Responses

As shown below in Table 1, on the primary subjective measure of Drug Liking visual analog scale (VAS), the two positive control drugs, alprazolam (2 mg) and dronabinol (10 and 30 mg), produced significantly higher maximum (E_{max}) scores compared to placebo ($P < 0.001$ to 0.0001), which validates the study.

CBD at the two highest doses (1500 and 4500 mg) produced small but statistically significantly higher E_{max} scores on Drug Liking compared to placebo ($P < 0.05$ for both). However, both of these responses were barely outside the placebo range (40-60, with 50 being "neutral" on a bipolar scale of 0 to 100) and had large standard deviations. CBD at the lowest dose (750 mg) did not differentiate statistically significantly from placebo on Drug Liking.

Table 1: Effects of Oral Placebo, Alprazolam (2 mg) , Dronabinol (THC, 10 and 30 mg) and CBD (750, 1500 and 4500 mg) on Subjective Measures (VAS) – Emax Scores

Measure	Placebo (n = 37)	ALZ 2 (n = 40)	THC 10 (n = 39)	THC 30 (n = 40)	CBD 750 (n = 38)	CBD 1500 (n = 39)	CBD4500 (n = 40)
Drug Liking VAS bipolar	55 ± 11	79 ± 16 ^	74 ± 19 #	87 ± 15 ^	57 ± 14	61 ± 17 *	64 ± 17 *
Overall Drug Liking VAS bipolar	50 ± 17	87 ± 16 ^	75 ± 21 ^	87 ± 19 ^	55 ± 16	57 ± 19 *	60 ± 26
Take Drug Again VAS	11 ± 25	85 ± 24 ^	65 ± 39 ^	85 ± 27 ^	20 ± 31	28 ± 37 *	42 ± 42 ^
Good Drug Effects VAS	11 ± 26	77 ± 25 ^	55 ± 39 ^	83 ± 22 ^	22 ± 33	29 ± 38 *	38 ± 38 ^
High VAS	7 ± 22	55 ± 38 ^	38 ± 40 ^	73 ± 33 ^	10 ± 25	20 ± 35 *	31 ± 38 #
Stoned VAS	6 ± 19	45 ± 39 ^	37 ± 38 ^	78 ± 28 ^	14 ± 27	14 ± 29	24 ± 37 ^
Bad Drug Effects VAS	9 ± 23	23 ± 33 *	16 ± 30	26 ± 35 *	9 ± 21	11 ± 20	15 ± 26
Alert/ Drowsy VAS	55 ± 12 41 ± 17	57 ± 15 10 ± 14 ^	58 ± 15 26 ± 21 ^	65 ± 17 14 ± 14 ^	55 ± 14 33 ± 18 *	54 ± 11 30 ± 20 #	54 ± 11 29 ± 19 #
Agitated/ Relaxed VAS bipolar	50 ± 11 38 ± 19	54 ± 14 9 ± 13 ^	52 ± 14 22 ± 20 ^	58 ± 16 14 ± 16 ^	52 ±12 34 ± 21	52 ± 9 32 ± 21	53 ± 10 29 ± 21 *
Any Drug Effect VAS bipolar	18 ± 31	75 ± 26 ^	55 ± 38 ^	87 ± 17 ^	23 ± 32	34 ± 36 *	46 ± 39 ^
Hallucinations VAS	1 ± 2	18 ± 29 ^	3 ± 11	15 ± 34 *	1 ± 2	1 ± 2	1 ± 3
Bowdle (Internal Perception) VAS	1 ± 0	1 ± 0 ^	1 ± 0 *	1 ± 0 ^	1 ± 0	1 ± 0	1 ± 0
Bowdle(External Perception) VAS	1 ± 0	1 ± 0 ^	1 ± 0	1 ± 1 ^	1 ± 0	1 ± 0	1 ± 0
Drug ID: Benzodiazepine	12 ± 27	88 ± 24	27 ± 39	29 ± 39	21 ± 35	23 ± 36	27 ± 36
Drug ID: THC	9 ± 24	24 ± 35	58 ± 44	91 ± 22	20 ± 33	18 ± 29	28 ±37
Drug ID: Placebo	71 ± 44	2 ± 11	27 ±42	3 ±17	54 ± 46	52 ±48	36 ±44

* $p < 0.05$; #$p<0.001$, ^ $p < 0.0001$ compared to placebo. All scales are unipolar (0-100 with 0 as neutral) unless marked as bipolar (0-100 with 50 as neutral).

Results from the secondary subjective measures show that:

- The positive control drugs, dronabinol (10 and 30 mg) and alprazolam (2 mg), produced statistically significantly increased scores compared to placebo on other positive subjective responses such as the VAS for Overall Drug Liking, Take Drug Again, Good Drug Effects, High, Stoned, Bowdle (Internal Perception).

These results validate the study by showing that known drugs of abuse can produce positive responses in this study.

- CBD at the high therapeutic and supratherapeutic oral doses (1500 and 4500 mg) produced small but statistically significant increases compared to placebo in positive subjective responses such as VAS for Take Drug Again, Good Drug Effects, and High. The positive subjective responses to CBD were always statistically significantly less than those produced by either alprazolam or dronabinol. Of specific interest in evaluation of whether CBD produces cannabinoid-like responses, no dose of CBD produced Overall Drug Liking that fell outside the placebo range (40-60, bipolar scale). Similarly, the response to CBD for Stoned was either within or just outside the placebo range (0-20, unipolar scale). Thus, these data do not show that CBD produces positive subjective responses that are similar to those produced by known drugs of abuse. Instead, CBD produces positive subjective responses that are close to the acceptable placebo range.

- Dronabinol (30 mg) and alprazolam (2 mg) produced small but statistically significant increases in VAS Bad Drug Effects and Hallucinations. In contrast, CBD did not produce a statistically significant increase in response on VAS Bad Drug Effects or Hallucinations at any dose.

On the Drug Identification question, alprazolam (2 mg) was identified as a benzodiazepine (88 out of 100). Dronabinol (10 and 30 mg) was identified as dronabinol (58 and 91 out of 100). Placebo was identified as placebo (71 out of 100). In contrast, CBD did not produce a strong signal for any substance except for placebo in response to the 750 and 1500 mg doses (54 and 52 out of 100). The 4500 mg dose of CBD was not identified as any substance (<36 out of 100 on any scale) and was notably not identified as dronabinol. Thus, CBD does not produce sensations that were identified as cannabinoid-like or sedative-like.

Although these subjective data produced some statistically significant signals of abuse potential at the two higher doses of CBD (1500 and 4500 mg), these responses were either inside or just outside of the acceptable placebo range and had large standard deviations. Most importantly, any positive subjective response to CBD was always much lower than that produced by the positive control drugs, alprazolam and dronabinol. Additionally, CBD was never identified as dronabinol.

Therefore, the subjective data from this study do not show that CBD produces meaningful signals of abuse potential.

Abuse-Related Adverse Events

Dronabinol (10 and 30 mg) produced high levels of the adverse event of euphoria (30.8% (12 of 39 subjects) and 62.5% (25 of 40 subjects)). Alprazolam (2 mg) produced a lower

level of euphoria (7.5%, 3 of 40 subjects) while placebo produced no reports of euphoria (0%, 0 of 37 subjects). When AEs were evaluated for CBD (750, 1500 and 4500 mg), the drug produced reports of euphoria in a few subjects (5.3% (2 of 38 subjects); 5.1% (2 of 39 subjects), 7.5% (3 of 40 subjects), respectively).

However, when an individual analysis was conducted on CBD responses, reports of euphoria did not correlate with reported scores on positive subjective measures of drug liking, take the drug again and overall drug liking. Additionally, in some subjects, placebo produced euphoria-related AEs. A euphoria-related response for most subjects either did not predict whether the individual reported positive responses on the subjective measures, or the positive subjective response was equivalent to that reported after administration of placebo. Conversely, a high rating on a positive subjective response did not predict whether a subject would report a euphoria-related AE. There were only two subjects who reported a euphoria response following 4500 mg CBD who also concurrently reported a high degree of positive subjective response on Drug Liking or Take Drug Again.

Overall, these data do not strongly support a conclusion that CBD produces a dose-dependent signal of euphoria that predicts a positive subjective response. However, given that the residual amount of dronabinol present in the 4500 mg dose of CBD could be as much as 2.7 mg (see below), this led to the question of whether dronabinol was responsible for the euphoric responses.

Residual Dronabinol Levels

In the HAP study, the CBD batches used contained 0.03% and 0.06% residual dronabinol. This means that the amount of dronabinol present in the test doses ranged from 0.3-0.45 mg (750 mg CBD) to 0.45-0.90 mg (1500 mg CBD) to 1.35-2.70 mg (4500 mg CBD). The lowest FDA-approved dose of dronabinol in the Marinol drug product is 2.5 mg. Thus, it is possible that dronabinol may have contributed to the subjective responses following CBD administration.

However, when plasma concentrations of dronabinol from subjects in the HAP study were evaluated following administration of CBD, they were low compared to the plasma levels produced in the same subjects following administration of the two doses of dronabinol. Following administration of CBD, the C_{max} levels of residual dronabinol were 0.30 ng/ml (750 mg CBD), 0.44 ng/ml (1500 mg CBD) and 0.48 ng/ml (4500 mg CBD), which demonstrates a nonlinear pharmacokinetics. These concentrations are much lower than the C_{max} reported following administration of 10 mg dronabinol in the HAP study (C_{max} = 7.90 ng/ml).

Thus, it is unlikely that dronabinol contributed to the slight positive responses on some of the subjective measures or contributed to the euphoric AE responses reported following the higher doses of CBD.

Overall Conclusions

The 750 mg dose of CBD (the low 10 mg/kg therapeutic dose) did not produce abuse potential signals. Although the two higher doses of CBD tested in this study (1500 and 4500 mg, representing the 20 mg/kg therapeutic dose and a supratherapeutic dose) produced some signals of abuse potential, they were small and often inside or just outside the acceptable placebo range. Additionally, these signals were always much less than those produced by dronabinol or alprazolam. CBD was not identified as dronabinol.

Thus, these data show that although CBD is present in the marijuana plant, it does not produce dronabinol-like responses or depressant-like responses that are indicative of abuse potential.

Adverse Events in Clinical Studies with CBD

Phase 1 Clinical Safety Studies (Excluding HAP Study)

Abuse-related AEs were evaluated from the Phase 1 studies with CBD, which included studies investigating pharmacokinetics, hepatically-impaired patients, renally-impaired patients, impact on sleep, and physical dependence.

None of the individuals in these Phase 1 studies with CBD reported that they experienced "euphoria"-related AEs, which are the key AEs in determining whether there are abuse-related signals from clinical studies. In the absence of a euphoria response in these individuals, CBD does not appear to produce an abuse-related signal.

There was a high rate of "somnolence" in the two pharmacokinetic studies. In one study, 750 and 1500 mg CBD produced "somnolence" in 2-4 of 9 subjects (22-44%) compared to 2 of 9 subjects (33%) from placebo. In the other study, 750 and 4500 mg CBD produced "somnolence" in 5-11 of 49 subjects (10-22%) compared to 4 of 50 subjects (8%) from placebo. However, in the absence of "euphoria"-like AEs, "somnolence" is not interpreted as producing an abuse-related signal. Interestingly, no subjects in the sleep study (n = 18) reported "somnolence" in response to CBD or placebo. No other AEs that can be indicative of abuse were reported in any of these studies.

Thus, it appears from the AE data in Phase 1 studies conducted with CBD that the drug does not produce abuse potential signals.

Phase 2/3 Clinical Efficacy Studies

Three Phase 2/3 clinical studies were conducted to support the efficacy and safety claim for CBD as an adjunct treatment of two epilepsy conditions in children. Since CBD is proposed as an adjunctive treatment, children in these studies remained on their current antiepileptic medications. Given that many drugs used to treat epilepsy often have known abuse potential and are scheduled under the CSA, it is not possible to determine whether

abuse-related signals from efficacy studies with CBD were due to CBD or to the other antiepileptic drugs. Additionally, individuals with these epilepsy conditions are extremely ill and often too young to provide accurate information regarding psychiatric or neurological AEs.

Thus, AE data from the Phase 2/3 clinical efficacy studies cannot be evaluated for abuse-related AEs directly related to CBD.