Overview of Efficacy and Safety of Cannabidiol in Patients with Lennox-Gastaut Syndrome and Dravet Syndrome

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Overview of Clinical Studies and Efficacy

Summary of Clinical Studies

- Randomized, placebo-controlled safety and efficacy trials:
  - Lennox-Gastaut syndrome (LGS): Studies 1414 and 1423
  - Dravet syndrome (DS): Study 1332B
- Other sources for safety data:
  - Study 1332A
  - Study 1415 (OLE)
  - Expanded Access Program (EAP)

Primary Efficacy Results

	CBD 10 mg/kg/day	CBD 20 mg/kg/day	Placebo
Study 1414 (LGS)	**(n=73)**	**(n=76)**	**(n=76)**
Median percentage change in drop seizures	−37.2	-41.9	-17.2
p-value	0.002	0.005	
Study 1423 (LGS)	**N/A**	**(n=86)**	**(n=85)**
Median percentage change in drop seizures		-43.9	-21.8
p-value		0.014	
Study 1332B (DS)	**N/A**	**(n=61)**	**(n=59)**
Median percentage change in convulsive seizures		-38.9	-13.3
p-value		0.012	

Overview of Safety

Safety Populations

Population	Number of patients
All patients/subjects exposed	1756
Controlled trials	323
DS (Study 1332, parts A and B)	88
LGS (Studies 1414 and 1423)	235
Extension trial (Study 1415)	353
Expanded Access Program	684
DS or LGS patients	161
Additional subjects or patients	396

Deaths and Discontinuations

- 1 death in the controlled trials (CBD 20 mg/kg/day group): due to acute respiratory distress syndrome (ARDS)
- 19 additional deaths occurred in the OLE study and EAP
  - 7 deaths in the OLE study: 2 SUDEP, 1 seizure disorder, 4 others
  - 12 deaths in EAP (none were LGS or DS): 2 SUDEP, 1 status epilepticus, 3 seizures (various types); 6 others
- Causes of death were varied and not unexpected for the patient population and not clearly linked to the drug.
- Rate of discontinuation associated with AEs in the controlled trials was higher in the cannabidiol group (9.3%) than the placebo group (1.3%)

Treatment-emergent Serious Adverse Events*

	CBD 10 mg (N=75)	CBD 20 mg (N=238)	Placebo (N=227)
Transaminases ↑, hepatic failure	3%	4%	0
Infection, all	7%	7%	2%
Pneumonia	5%	4%	0.4%
Somnolence, lethargy	0	3%	0
Respiratory failure	1%	2%	1%
Fatigue, asthenia	0	1%	0
Bleeding	0	1%	0
Constipation	0	1%	0
Fever	3%	0.4%	0.4%

*Data from Studies 1332A, 1332B, 1414, and 1423

Treatment-emergent Adverse Events*

Adverse Event System/Organ/Class	Preferred Term	CBD 10 mg (N=75)	CBD 20 mg (N=238)	Placebo N=227
Hepatic	Transaminases ↑	8%	16%	3%
Gastrointestinal	Decreased appetite	16%	22%	5%
	Diarrhea	9%	20%	9%
	Weight decreased	5%	3%	1%
CNS	Somnolence, sedation	25%	30%	9%
	Seizure	15%	15%	13%
	Fatigue, malaise, asthenia	11%	12%	4%
	Irritability, agitation	9%	5%	2%
	Aggression, anger	3%	5%	0.4%
	Insomnia, sleep disturb, abn dreams	11%	5%	5%
Other	Infection, all	41%	40%	31%
	Rash	7%	11%	3%

*Data from Studies 1332A, 1332B, 1414, and 1423

Conclusions

Conclusions

- Substantial evidence of effectiveness of cannabidiol in the treatment of seizures associated with LGS and DS.
- Safety profile appears acceptable. Identified risks can be mitigated with labeling and monitoring.


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Review of Liver Safety for Cannabidiol

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Baseline Liver Data

Liver Test-Related Baseline 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 >2x 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

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**

Sponsor LSR Table 7.1

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

Withdrawal Criteria

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

Frequency of Baseline Liver Value Elevations by Treatment Groups 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* (%)	All CBD-OS (N=296) *n* / *N* (%)	Placebo (N=220) *n* / *N* (%)
ALT	> 1 x	11 / 67 (16.4)	52 / 229 (22.7)	63 / 296 (21.3)	45 / 220 (20.5)
	> 2 x	0 / 67	5 / 229 (2.2)	5 / 296 (1.7)	6 / 220 (2.7)
	> 3 x	0 / 67	2 / 229 (0.9)	2 / 296 (0.7)	1 / 220 (0.5)
	> 5 x	0 / 67	0 / 229	0 / 296	0 / 220

Source: LSR Table 11.5-1

Concomitant Anti Epileptic Drugs (AEDs)

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)

Source: LSR Table 10.5-1

Controlled Clinical Trial(s) Results

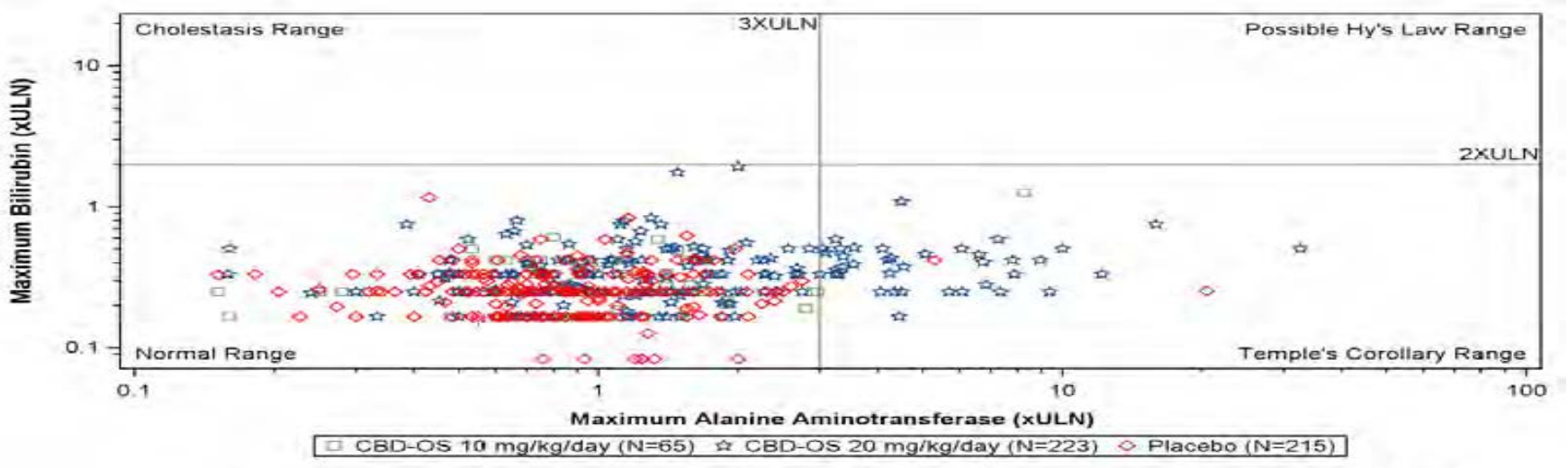
Specific to Liver Injury

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)

Source: LSR Table DSLGS.5.1.4.

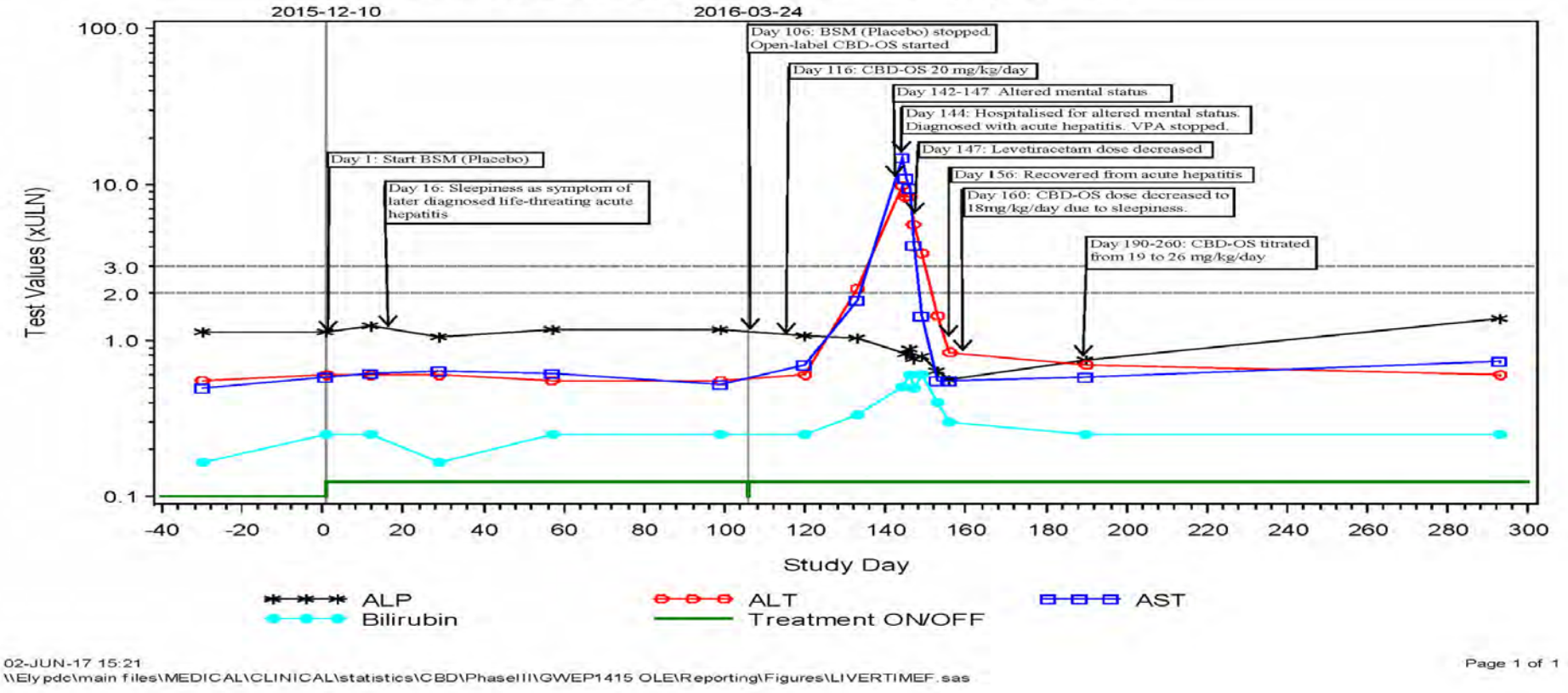
eDISH Plot of Maximum Treatment-Emergent ALT and Bilirubin Values for Individual Patients During Treatment in Pool DS/LGS (Pivotal DS and LGS)



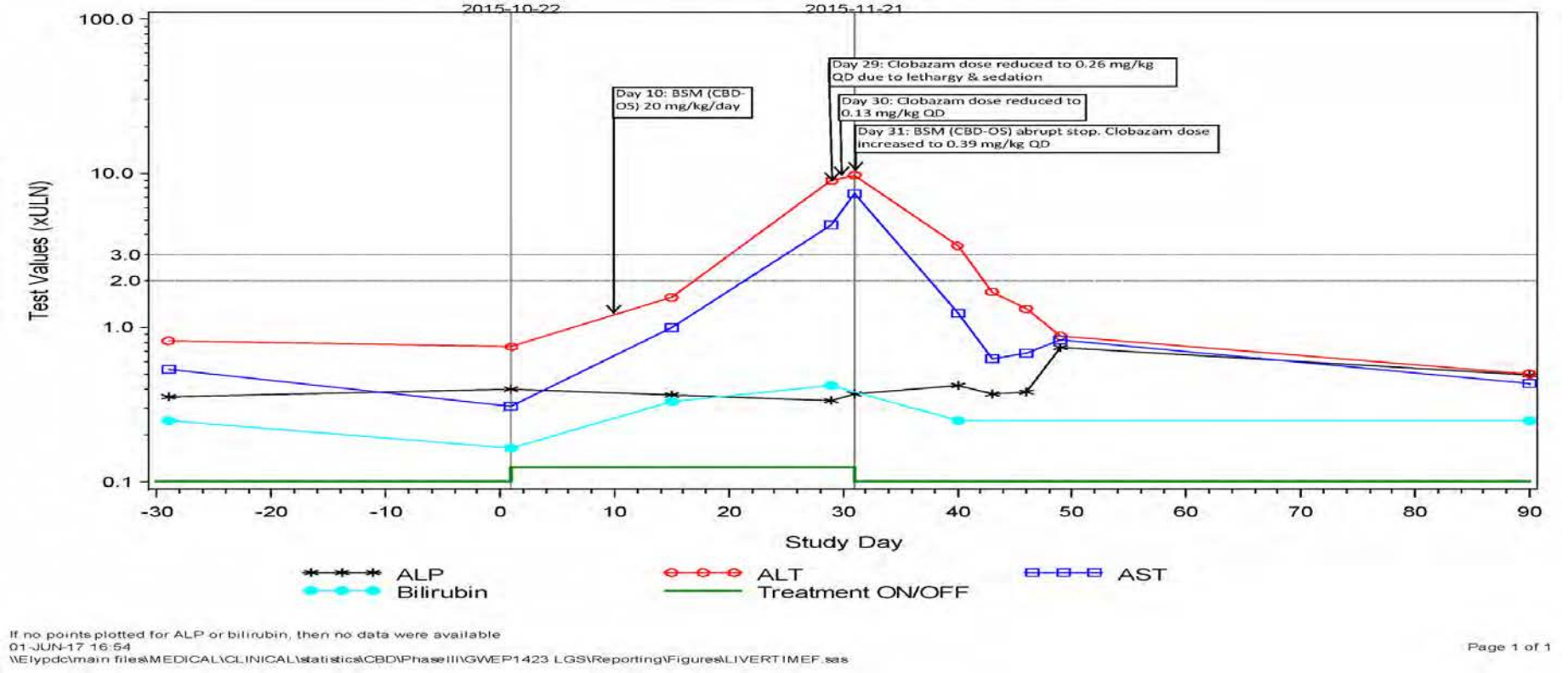
	Possible Hy's Law Range	Temple's Corollary Range
CBD-OS 10 mg/kg/day n(%)	0	1 (1.5)
CBD-OS 20 mg/kg/day n(%)	0	38 (17.0)
Placebo n(%)	0	2 (0.9)

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.

Source: LSR Figure 11.3-1

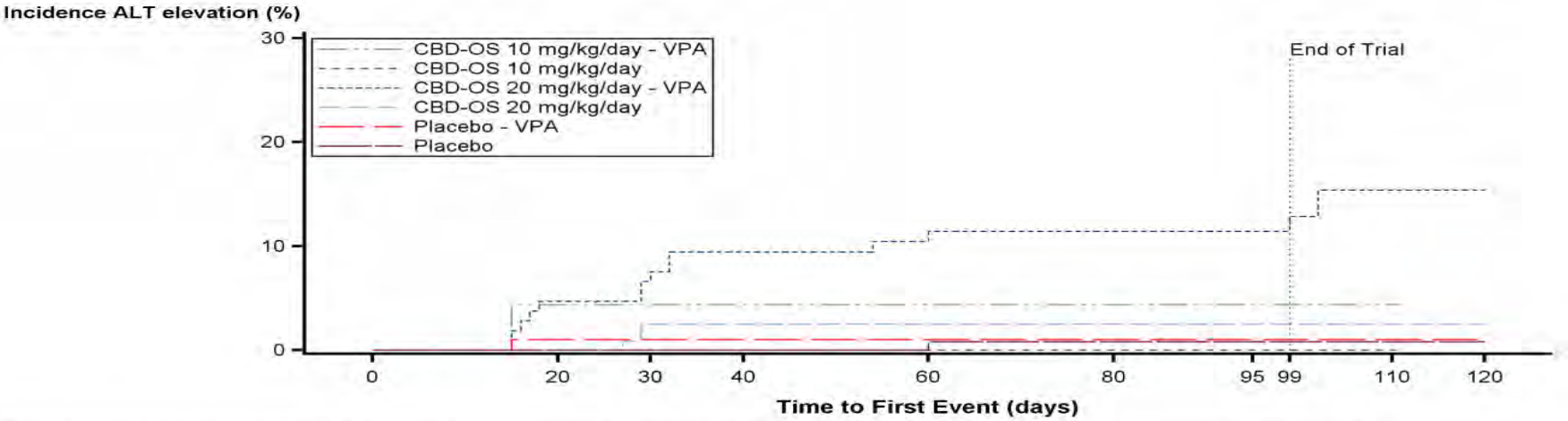


Source: LSR pg 1126



Source: LSR pg 760

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 14.1-1

Discontinuations

- Of the 540 CBD patients in the controlled trials
- 37 (6.9%) patients had ALT ≥5× ULN
  - 18 with ALT ≥5x ULN were discontinued from drug
    - 16 had ALT >8x ULN – discontinued

Recovery from Elevated ALT While Still Taking CBD

- 37/540 patients with ALT ≥5× ULN
  - 17 patients (45.9%) recovered without, or prior to, stopping CBD-OS.
    - 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

- 4 patients who recovered from ALT >8× ULN without stopping CBD-OS
  - this

Re-Challenge Experience

- Eleven patients were re-challenged with CBD-OS after experiencing 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
    - 3 patients, the recurrence was observed within 29 days of restarting CBD-OS
    - 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
  - 7 did not experience a recurrence of ALT or ALT >3× ULN

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: LSR Table 13.2.2.1-2

Other Contributing Factors

- Felbamate
- Clobazam
- Baseline liver enzyme elevations

- No significant influence of age, or underlying disease (DS vs. LGS)

Expanded Access Program

- 30/647 patients (4.6%) in Pool Expanded Access Program (EAP) had TE ALT ≥5× ULN:
  - 24 patients (80%) recovered without, or prior to, stopping CBD-OS:
    - 17 patients recovered without any dose reduction of CBD-OS
    - 7 patients recovered after dose reduction or during taper of CBD-OS

Conclusions

Conclusions

- There is a causal association with use of CBD and ALT elevations consistent with hepatocellular DILI
- No cases of severe liver injury, or cases meeting Hy's law
- Dose relationship with higher frequency in the 20mg/kg group

Conclusions (2)

- No patients with baseline underlying significant liver dysfunction have been studied
- The majority of patients with ALT >8x ULN were discontinued from drug
- Concomitant valproic acid was the most frequent risk factor for DILI
  - Potentially clobazam and felbamate
- Unknown if chronic liver injury could occur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Abuse Potential Assessment for Cannabidiol (CBD)

FDA Peripheral and Central Nervous System Drug Advisory Committee

April 19, 2018

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Assessing the Abuse Potential of CBD

- Under the FDA guidance for industry *Assessment of the Abuse Potential of Drugs* (2017), all CNS-active drugs need to undergo an abuse potential evaluation during drug development.
- CBD is controlled under the Controlled Substances Act as a Schedule I substance because it is a constituent of the *Cannabis* plant.
- Under the current NDA, CBD is proposed for the treatment of a central nervous system (CNS) disorder. Thus, it was necessary to conduct an abuse potential assessment for CBD.
- During drug development, CSS provided feedback to the Sponsor regarding which abuse-related studies in animals and humans would be required, as well as feedback on their appropriate design.

Abuse-Related Assessment

- Receptor binding (where drug acts neurochemically)
- Behavioral studies (using animal doses that produce plasma levels equivalent to or greater than human therapeutic plasma levels):
  - General behavior: Irwin test, open field test, rotorod test
  - Tetrad test (cannabinoid effects)
  - Drug discrimination (similar sensations to a known drug of abuse)
  - Self-administration (rewarding properties producing reinforcement)
- Clinical studies:
  - Assessment of adverse events (AEs) in clinical safety studies
  - Human abuse potential (HAP) study

Receptor Binding Studies

- No significant affinity of CBD for cannabinoid CB_1 or CB_2 sites, unlike (−)-*trans*-Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent of cannabis.
- No significant affinity of CBD for other abuse-related sites:
  - opioids (mu, kappa, or delta)
  - GABA/ benzodiazepine
  - dopamine (D_1 or D_2)
  - serotonin ($5HT_{2A}$)
  - NMDA/glutamate
  - ion channels (calcium, potassium, sodium, or chloride)
  - transporters (dopamine)

General Behavioral Studies

General behavioral tests are conducted as safety studies for all new drugs under development:

- In the **Irwin Test** of general behavior:
  - In mice, CBD (i.v.) produced a slight alteration in gait and a decrease in pain response, relative to vehicle, but these were transient effects
  - In rats, CBD (p.o.) produced no changes in behavior relative to placebo
- In the **Open-Field Test** of locomotion:
  - In mice, CBD (i.p.) reduced locomotor activity only at high dose, relative to vehicle
  - In rats, CBD (i.p.) reduced locomotor activity at moderate and high doses, relative to vehicle.
- In the **Rotorod Test** of motor activity:
  - In rats, CBD (i.p.) produced no changes in latency to fall off the slowly rotating rod, relative to vehicle.

General Behavioral Studies

- The data from the general behavioral studies show that CBD produces some CNS activity, but only at relatively high doses.
- However, in order to determine whether CBD produces ***abuse-related*** CNS-active effects in animals, additional preclinical studies were required that specifically address abuse potential:
    - Tetrad test
    - Drug discrimination study
    - Self-administration study

Tetrad Test

- The Tetrad Test is a screening test that measures changes in four behaviors that are known to be produced by THC:
    - decrease in locomotor activity
    - immobility
    - hypothermia and
    - antinociception (pain relief)
- CBD did not alter locomotor activity, immobility or antinociception, but produced some hypothermia at the highest dose.
- THC produced a decrease in locomotion, as well as an increase in hypothermia and antinociception, but little immobility.
- This shows that CBD does not produce an overt behavioral profile associated with a cannabinoid.

Drug Discrimination Studies

- 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.
- Test drugs that produce a response similar to a training drug with known abuse potential are also likely to be abused by humans.
- In rats trained to discriminate THC from vehicle, CBD produced $\leq$ 46% generalization to the THC cue. Full generalization is 80%.
- In rats trained to discriminate midazolam from vehicle, CBD produced $\leq$ 11% generalization to the midazolam cue.
- These data suggest that CBD does not produce sensations similar to THC or to a benzodiazepine.

Self-Administration Studies

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

Self-Administration Studies

- Animals were trained to lever-press for a rewarding substance: rats were trained with intravenous cocaine or heroin, while monkeys were trained with midazolam
- After self-administration of the training drug was stable, animals were allowed intravenous access to the following substances, which produced varying degrees of self-administration (infusions/session):
  - **cocaine** = ~ 45 infusions *vs.* **CBD** (range of doses) = < 10 infusions
  - **midazolam** = ~ 13 infusions *vs.* **CBD** (range of doses) = < 0.5 infusions
  - **heroin** = ~18 infusions *vs.* **CBD** (range of doses) = < 7 infusions
  - **vehicle** = < 5 infusions/session in each study
- These data suggest that CBD produces insufficiently rewarding properties to sustain positive reinforcement.

Assessment of Preclinical Abuse Studies

- As described in the *Assessment of the Abuse Potential of Drugs* (2017), following completion of preclinical abuse-related studies, the resulting data are evaluated to determine if there are sufficient abuse-related signals to justify the need for a human abuse potential (HAP) study.
- Based on the preclinical studies evaluating receptor binding, general behavior, similarity to THC (tetrad test and drug discrimination study) and ability to produce rewarding effects (self-administration studies), CBD did not produce meaningful abuse-related signals in rats.
- The next step in an abuse assessment is to examine the adverse event profile in the clinical studies to see if there is an abuse-related signal.

Adverse Events in Clinical Studies

Phase 1 Clinical Safety Studies

- In Phase 1 studies with CBD (evaluating pharmacokinetics, hepatically and renally-impaired patients, and impact on sleep) there were no reports of euphoria-related AEs.
- No other abuse-related AEs were reported in any of these studies.
- Thus, AE data from the Phase 1 studies (not including the HAP study) do not show that CBD produces signals of abuse potential.

Adverse Events in Clinical Studies

Phase 2/3 Clinical Efficacy Studies

- It is not possible to evaluate Phase 2/3 studies for abuse signals related to CBD because of the underlying neurological impairment in the patients and the presence of confounding drugs:
  - The children in the studies are too ill or too young to volunteer accurate information regarding psychiatric or neurological AEs indicative of abuse potential
  - The children in the 3 efficacy studies remained on their current antiepileptic drugs (AEDs)

Assessment of Preclinical Abuse Studies

- Based on the *Assessment of the Abuse Potential of Drugs* (2017), a human abuse potential (HAP) study is not typically conducted when there is:
  - a lack of strong preclinical abuse-related signals

  and

  - a lack of euphoria-related AE signals from clinical safety studies
- However, given that CBD is a Schedule I substance, and that it can produce sedative effects, FDA required that the Sponsor conduct a HAP study to provide additional experimental evidence of whether CBD has meaningful abuse potential in humans.

Human Abuse Potential Study

- 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 they are not drug dependent.
- When the test drug produces consistently large responses on positive subjective scales that are far outside the acceptable placebo range, it is likely that the test drug has abuse potential.

Human Abuse Potential Study

The HAP study with CBD evaluated the oral abuse potential of:

- CBD (750, 1500 and 4500 mg)
  This represents the two therapeutic doses (10 and 20 mg/kg, scaled up for 75 kg adults) and a supratherapeutic dose (3-6 X)
- dronabinol (THC; 10 and 30 mg)
- alprazolam (2 mg)
- placebo

This study used a randomized, double-blind, placebo-controlled, crossover design in healthy recreational polydrug users with a history of cannabis and benzodiazepine abuse (n = 40, with 35 completers).

Human Abuse Potential Study

Primary Measure:

VAS Drug Liking (bipolar scale of 0 to 100, with 50 as neutral)

- Dronabinol (10 and 30 mg) and alprazolam (2 mg) produced statistically significantly higher mean Drug Liking scores (74, 87 and 79, respectively) compared to placebo, which validates the study.
- CBD at the lower therapeutic dose (750 mg) produced a mean Drug Liking score (57) that did not differentiate statistically from placebo on Drug Liking and was within the acceptable placebo range of 40-60.
- CBD at 1500 and 4500 mg produced very small increases in mean Drug Liking scores that were statistically significantly different from placebo. However, the mean scores (61 and 64, respectively) are barely outside the placebo range.

Human Abuse Potential Study

Secondary Measures:

- On other positive subjective measures (VAS for Take Drug Again, Good Drug Effects, High, and Stoned), dronabinol and alprazolam produced statistically significant increases in mean scores (37-85 out of 100 on unipolar scales, where 0-20 is acceptable placebo range) compared to placebo.
- CBD at 750 mg produced mean scores (10-22) that were not significant on these measures. CBD at 1500 and 4500 mg produced small but significant increases in mean scores (14-42) compared to placebo on VAS Take Drug Again, Good Drug Effects, High, and Stoned.
- All subjective responses to CBD were statistically significantly less than those produced by either dronabinol or alprazolam.

Human Abuse Potential Study

Drug Identification:

After each session, subjects were asked how much the test drug felt like any of the drug classes in a list. On a scale of 0 ("not like drug class") to 100 ("very much like drug class"), the means scores show that:

- Dronabinol (10 and 30 mg) was identified as THC (58 and 91 out of 100).
- Alprazolam was identified as a benzodiazepine (88 out of 100).
- Placebo was identified as placebo (71 out of 100).
- CBD (750 and 1500 mg) was not identified as THC or any substance, except for placebo (54 and 52 out of 100). CBD at 4500 mg was not identified as THC or any substance (<36 out of 100 for any drug class or placebo).
- The lack of identifying CBD as THC parallels the animal drug discrimination study, where animals did not indicate that CBD produced THC-like sensations.

Human Abuse Potential Study

Abuse-Related Adverse Events:

- Dronabinol produced high levels of euphoria: 10 mg = 30.8% (12 of 39 subjects) and 30 mg = 62.5% (25 of 40 subjects).
- Alprazolam produced a low level of euphoria (7.5%, 3 of 40 subjects).
- CBD produced a similarly low rate of euphoria:
  - 750 mg = 5.3% (2 of 38 subjects)
  - 1500 mg = 5.1% (2 of 39 subjects)
  - 4500 mg = 7.5% (3 of 40 subjects)
- Placebo produced no euphoria (0%, 0 of 37 subjects)
- There were no other abuse-related AEs reported for any of the drug treatments.

Human Abuse Potential Study

Abuse-Related Adverse Events:

- Was the euphoria signal from CBD (5.3-7.5%) indicative of abuse?
- When an individual analysis was done on the subjects (n = 2-3 of 35) who had a euphoria-related AE following administration of CBD:
  - Euphoria-related AEs did not predict a high score on the positive subjective measures
  - A high score on positive subjective measures for *any* subject did not predict a report of a euphoria-related AE
- Thus, the concern regarding euphoria-related AEs does not appear to be valid, since they were not predictive of concurrent positive subjective responses in those same subjects.

Human Abuse Potential Study

Conclusions:

- CBD at the **lower therapeutic dose (10 mg/kg; 750 mg)** does not produce positive subjective responses indicative of abuse.
- CBD at the **higher therapeutic dose (20 mg/kg; 1500 mg)** and the **supratherapeutic dose (4500 mg)**:
  - produces some statistically significant increases in positive subjective responses, but these are statistically significantly less than the increases produced by alprazolam or dronabinol and were often very close to the acceptable placebo range
  - produces much lower levels of euphoria compared to dronabinol
  - was most often identified as placebo (1500 mg) or was not identified as any drug class at all (4500 mg)

Final Conclusions: Abuse Potential of CBD

- Preclinical data (receptor binding, general behavior, and behavioral studies) do not provide signals that CBD has abuse potential.
- There were no abuse-related AEs in the Phase 1 clinical study population outside of the HAP study.
- The HAP study showed that the higher therapeutic dose (1500 mg) and supratherapeutic dose (4500 mg) of CBD produced marginal signals of abuse potential from subjective measures and AEs.
- Thus, there is little evidence that CBD has meaningful abuse potential, even at supratherapeutic doses in adults.


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Backup Slides Shown

Human Abuse Potential Study: Residual THC

Could the low level of positive subjective responses from CBD be due to residual THC?

- The quantity of residual THC contained in the CBD drug substance batches used for the HAP study was **~ 0.03 to 0.06% (w/w)**
- This is less than the product spec limit of < 0.15%. Thus:
  - 750 mg CBD contains 0.3 to 0.5 mg of THC
  - 1500 mg CBD contains 0.5 to 0.9 mg of THC
  - 4500 mg CBD contains 1.4 to 2.7 mg of THC
- Since the lowest marketed dose of Marinol (dronabinol) is 2.5 mg, the 2.7 mg of residual THC in CBD might be of concern.

Human Abuse Potential Study: Residual THC

- Residual THC in the CBD solution did not appear to produce meaningful Cmax plasma concentrations of THC:
  - 750 mg CBD (w/ 0.3 to 0.5 mg of THC) = 0.27 ng/ml THC
  - 1500 mg CBD (w/ 0.5 to 0.9 mg of THC) = 0.38 ng/ml THC
  - 4500 mg CBD (w/ 1.4 to 2.7 mg of THC) = 0.40 ng/ml THC
- These plasma levels of THC after CBD administration are much lower than the THC levels after administration of dronabinol:
  - 5 mg dronabinol = 4.7 ng/ml THC
  - 10 mg dronabinol = 7.9 ng/ml THC
- Thus, it appears **unlikely** that any positive subjective responses after CBD are the result of the effects of residual THC.