CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

210365Orig1s005s006s007

Trade Name:	EPIDIOLEX
Generic or Proper Name:	cannabidiol
Sponsor:	Jazz Pharmaceuticals Research UK Limited
Approval Date:	July 31, 2020
Indication:	EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older. EPIDIOLEX is contraindicated for Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
REMS	
Summary Review	**X**
Officer/Employee List	
Office Director Memo	
Cross Discipline Team Leader Review	
Clinical Review(s)	**X**
Product Quality Review(s)	**X**
Non-Clinical Review(s)	
Statistical Review(s)	
Clinical Microbiology / Virology Review(s)	
Clinical Pharmacology Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

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APPROVAL LETTER

U.S. FOOD & DRUG ADMINISTRATION

NDA 210365/S-005, S-006 & S-007

SUPPLEMENT APPROVAL

GW Research Ltd.
Attention: Christine Schulteis, Ph.D.
Senior Director, Global Regulatory Affairs
5750 Fleet Street, Suite 200
Carlsbad, CA 92008

Dear Dr. Schulteis:

Please refer to your supplemental new drug applications (sNDAs), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA), for the following:

Application	Product Name	Submitted on:	Received on:
NDA 210365/S-005	Epidiolex (cannabidiol) 100 mg/mL oral solution	January 31, 2020	January 31, 2020
This supplement proposes:			
To support addition of treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older to the Prescribing Information.			

Application	Product Name	Submitted on:	Received on:
NDA 210365/S-006	Epidiolex (cannabidiol) 100 mg/mL oral solution	January 31, 2020	January 31, 2020
This supplement proposes:			
To extend the indications for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome down to patients 1 year of age and older.			

Application	Product Name	Submitted on:	Received on:
NDA 210365/S-007	Epidiolex (cannabidiol) 100 mg/mL oral solution	April 6, 2020	April 6, 2020
This supplement proposes:			
To update final Prescribing Information and Medication Guide, Instructions for Use, Carton, and Bottle/Container labels to indicate that Epidiolex (cannabidiol) is no longer a controlled substance.			

APPROVAL & LABELING

We have completed our review of these applications. They are approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at FDA.gov.[1] Content of labeling must be identical to the enclosed labeling (text for the Prescribing Information, Instructions for Use, and Medication Guide), with the addition of any labeling changes in pending "Changes Being Effected" (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling. If the content of labeling in SPL format initially submitted with this CBE-0 labeling supplement is identical to the attached approved labeling, an additional submission of content of labeling in SPL format is not required.

Information on submitting SPL files using eList may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that include labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(l)(1)(i)] in Microsoft Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

CARTON AND CONTAINER LABELING

Submit final printed carton and container labeling that are identical to the carton and container labeling submitted on April 6, 2020, as soon as they are available, but no more than 30 days after they are printed. Please submit these labeling electronically according to the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. For administrative purposes, designate this submission "**Final Printed Carton and Container Labeling for approved**

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm
[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

NDA 210365/S-007." Approval of this submission by FDA is not required before the labeling is used.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[3]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[4] Information and Instructions for completing the form can be found at FDA.gov.[5]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, contact Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

ENCLOSURE(S):

- Content of Labeling
  - Prescribing Information
  - Medication Guide
  - Instructions for Use

[3] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[4] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[5] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
07/31/2020 08:00:05 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use EPIDIOLEX® safely and effectively. See full prescribing information for EPIDIOLEX.

EPIDIOLEX® (cannabidiol) oral solution
Initial U.S. Approval: 2018

----------RECENT MAJOR CHANGES ----------

Indications (1)	07/2020
Dosage and Administration (2.2, 2.3, 2.4, 2.6)	07/2020
Warnings and Precautions (5.1, 5.2, 5.4)	07/2020

----------INDICATIONS AND USAGE----------

EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older (1)

----------DOSAGE AND ADMINISTRATION----------

- Obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment. (2.1, 5.1)
- See Full Prescribing Information for titration. (2.2, 2.3)

Seizures Associated with Lennox-Gastaut Syndrome or Dravet Syndrome

- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). (2.2)
- Based on individual clinical response and tolerability, EPIDIOLEX can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).

Seizures Associated with Tuberous Sclerosis Complex

- The recommended starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day). Increase the dose weekly by 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day). (2.3)

Patients with Impaired Hepatic Function

- Dosage adjustment is recommended for patients with moderate or severe hepatic impairment. (2.6, 8.6)

----------DOSAGE FORMS AND STRENGTHS----------

Oral solution: 100 mg/mL (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to cannabidiol or any of the ingredients in EPIDIOLEX (4)

----------WARNINGS AND PRECAUTIONS----------

- Hepatocellular Injury: EPIDIOLEX can cause transaminase elevations. Concomitant use of valproate and higher doses of EPIDIOLEX increase the risk of transaminase elevations. See Full Prescribing Information for serum transaminase and bilirubin monitoring recommendations. (5.1)
- Somnolence and Sedation: Monitor for somnolence and sedation and advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX. (5.2)
- Suicidal Behavior and Ideation: Monitor patients for suicidal behavior and thoughts. (5.3)
- Hypersensitivity Reactions: Advise patients to seek immediate medical care. Discontinue and do not restart EPIDIOLEX if hypersensitivity occurs. (5.4)
- Withdrawal of Antiepileptic Drugs: EPIDIOLEX should be gradually withdrawn to minimize the risk of increased seizure frequency and status epilepticus. (5.5)

----------ADVERSE REACTIONS----------

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) in patients with Lennox-Gastaut Syndrome or Dravet Syndrome are: somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections. (6.1)

The most common adverse reactions (10% or more for EPIDIOLEX and greater than placebo) in patients with tuberous sclerosis complex are: diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Greenwich Biosciences at 1-833-424-6724 (1-833-GBIOSCI) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Strong inducer of CYP3A4 or CYP2C19: Consider dose increase of EPIDIOLEX. (7.1)
- Consider a dose reduction of substrates of UGT1A9, UGT2B7, CYP2C8, CYP2C9, and CYP2C19 (e.g., clobazam). (7.2)
- Substrates of CYP1A2 and CYP2B6 may also require dose adjustment. (7.2)

----------USE IN SPECIFIC POPULATIONS----------

Pregnancy: Based on animal data, may cause fetal harm. (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 07/2020

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

- EPIDIOLEX is indicated for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), or tuberous sclerosis complex (TSC) in patients 1 year of age and older.

2 DOSAGE AND ADMINISTRATION

2.1 Assessments Prior to Initiating EPIDIOLEX

Because of the risk of hepatocellular injury, obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment with EPIDIOLEX *[see Warnings and Precautions (5.1)]*.

2.2 Dosing for Seizures Associated with Lennox-Gastaut Syndrome or Dravet Syndrome

- The starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).
- After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day).
- Patients who are tolerating EPIDIOLEX at 5 mg/kg twice daily and require further reduction of seizures may benefit from a dosage increase up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day), in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated. For patients in whom a more rapid titration from 10 mg/kg/day to 20 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day. Administration of the 20 mg/kg/day dosage resulted in somewhat greater reductions in seizure rates than the recommended maintenance dosage of 10 mg/kg/day, but with an increase in adverse reactions.

2.3 Dosing for Seizures Associated with Tuberous Sclerosis Complex

- The starting dosage is 2.5 mg/kg by mouth twice daily (5 mg/kg/day).
- Increase the dose in weekly increments of 2.5 mg/kg twice daily (5 mg/kg/day), as tolerated, to a recommended maintenance dosage of 12.5 mg/kg twice daily (25 mg/kg/day). For patients in whom a more rapid titration to 25 mg/kg/day is warranted, the dosage may be increased no more frequently than every other day.
- The effectiveness of doses lower than 12.5 mg/kg twice daily has not been studied in patients with TSC.

2.4 Administration Instructions

Food may affect EPIDIOLEX levels *[see Clinical Pharmacology (12.3)]*. Consistent dosing of EPIDIOLEX with respect to meals is recommended to reduce variability in cannabidiol plasma exposure.

A calibrated measuring device (either 5 mL or 1 mL oral syringe) will be provided and is recommended to measure and deliver the prescribed dose accurately *[see How Supplied/Storage and Handling (16.1)]*. A household teaspoon or tablespoon is not an adequate measuring device.

Oral administration is recommended. When necessary, can be enterally administered via feeding tubes, such as nasogastric or gastrostomy tubes. Do not use with tubes made of polyvinyl chloride (PVC).

Discard any unused EPIDIOLEX remaining 12 weeks after first opening the bottle *[see How Supplied/ Storage and Handling (16.2)]*.

2.5 Discontinuation of EPIDIOLEX

When discontinuing EPIDIOLEX, the dose should be decreased gradually. As with most antiepileptic drugs, abrupt discontinuation should be avoided when possible, to minimize the risk of increased seizure frequency and status epilepticus *[see Warnings and Precautions (5.5)]*.

2.6 Patients with Hepatic Impairment

Dose adjustment is recommended in patients with moderate (Child-Pugh B) hepatic impairment or severe (Child-Pugh C) hepatic impairment *[see Warnings and Precautions (5.1), Use in Specific Populations (8.6), and Clinical Pharmacology (12.3)]*. It may be necessary to have slower dose titration in patients with moderate or severe hepatic impairment than in patients without hepatic impairment (see Table 1).

EPIDIOLEX does not require dose adjustment in patients with mild (Child-Pugh A) hepatic impairment.

Table 1: Dose Adjustments in Patients with Hepatic Impairment

Hepatic Impairment	Starting Dosage	In Patients with LGS or DS	In Patients with TSC
		Maintenance Dosage Range	Maintenance Dosage
Mild	2.5 mg/kg twice daily (5 mg/kg/day)	5 to 10 mg/kg twice daily (10 to 20 mg/kg/day)	12.5 mg/kg twice daily (25 mg/kg/day)
Moderate	1.25 mg/kg twice daily (2.5 mg/kg/day)	2.5 to 5 mg/kg twice daily (5 to 10 mg/kg/day)	6.25 mg/kg twice daily (12.5 mg/kg/day)
Severe	0.5 mg/kg twice daily (1 mg/kg/day)	1 to 2 mg/kg twice daily (2 to 4 mg/kg/day)	2.5 mg/kg twice daily (5 mg/kg/day)

3 DOSAGE FORMS AND STRENGTHS

Cannabidiol oral solution: 100 mg/mL for oral administration. Each bottle contains 100 mL of a clear, colorless to yellow solution.

4 CONTRAINDICATIONS

EPIDIOLEX is contraindicated in patients with a history of hypersensitivity to cannabidiol or any of the ingredients in the product *[see Description (11) and Warnings and Precautions (5.4)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Hepatocellular Injury

EPIDIOLEX can cause dose-related elevations of liver transaminases (alanine aminotransferase [ALT] and/or aspartate aminotransferase [AST]). In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages) and TSC (25 mg/kg/day), the incidence of ALT elevations above 3 times the upper limit of normal (ULN) was 13% (10 and 20 mg/kg/day dosages) and 12% (25 mg/kg/day dosage) in EPIDIOLEX-treated patients compared with 1% in patients on placebo. Less than 1% of EPIDIOLEX-treated patients had ALT or AST levels greater than 20 times the ULN. There were cases of transaminase elevations associated with hospitalization in patients taking EPIDIOLEX. In clinical trials, serum transaminase elevations typically occurred in the first two months of treatment initiation; however, there were some cases observed up to 18 months after initiation of treatment, particularly in patients taking concomitant valproate. Resolution of transaminase elevations occurred with discontinuation of EPIDIOLEX or reduction of EPIDIOLEX and/or concomitant valproate in about two-thirds of the cases. In about one-third of the cases, transaminase elevations resolved during continued treatment with EPIDIOLEX, without dose reduction.

Risk Factors for Transaminase Elevation

Concomitant Valproate and Clobazam

The majority of ALT elevations occurred in patients taking concomitant valproate *[see Drug Interactions (7.3)]*. Concomitant use of clobazam also increased the incidence of transaminase elevations, although to a lesser extent than valproate *[see Drug Interactions (7.2)]*. In EPIDIOLEX-treated patients with LGS or DS (10 and 20 mg/kg/day dosages), the incidence of ALT elevations greater than 3 times the ULN was 30% in patients taking both concomitant valproate and clobazam, 21% in patients taking concomitant valproate (without clobazam), 4% in patients taking concomitant clobazam (without valproate), and 3% in patients taking neither drug. In EPIDIOLEX-treated patients with TSC (25 mg/kg/day), the incidence of ALT elevations greater than 3 times the ULN was 20% in patients taking both concomitant valproate and clobazam, 25% in patients taking concomitant valproate (without clobazam), 0% in patients taking concomitant clobazam (without valproate), and 6% in patients taking neither drug. Consider discontinuation or dose adjustment of valproate or clobazam if liver enzyme elevations occur.

Dose

Transaminase elevations are generally dose-related. In patients with DS or LGS (10 and 20 mg/kg/day) or TSC (25 mg/kg/day), ALT elevations greater than 3 times the ULN were reported in 17% and 12% of patients taking EPIDIOLEX 20 or 25 mg/kg/day, respectively, compared with 1% in patients taking EPIDIOLEX 10 mg/kg/day. The risk of ALT elevations was higher (25%) in patients with TSC receiving a dosage above the recommended maintenance dosage of 25 mg/kg/day in Study 4.

Baseline Transaminase Elevations

Patients with baseline transaminase levels above the ULN had higher rates of transaminase elevations when taking EPIDIOLEX. In the DS and LGS controlled trials (Studies 1, 2, and 3) in patients taking EPIDIOLEX 20 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 times the ULN was 30% when ALT was above the ULN at baseline, compared to 12% when ALT was within the normal range at baseline. No patients taking EPIDIOLEX 10 mg/kg/day experienced ALT elevations

greater than 3 times the ULN when ALT was above the ULN at baseline, compared with 2% of patients in whom ALT was within the normal range at baseline. In the TSC controlled trial (Study 4) in patients taking EPIDIOLEX 25 mg/kg/day, the frequency of treatment-emergent ALT elevations greater than 3 and 5 times the ULN were both 11% when ALT was above the ULN at baseline, compared to 12% and 6%, respectively, when ALT was within the normal range at baseline.

Monitoring

In general, transaminase elevations of greater than 3 times the ULN in the presence of elevated bilirubin without an alternative explanation are an important predictor of severe liver injury. Early identification of elevated liver enzymes may decrease the risk of a serious outcome. Patients with elevated baseline transaminase levels above 3 times the ULN, accompanied by elevations in bilirubin above 2 times the ULN, should be evaluated prior to initiation of EPIDIOLEX treatment.

Prior to starting treatment with EPIDIOLEX, obtain serum transaminases (ALT and AST) and total bilirubin levels. Serum transaminases and total bilirubin levels should be obtained at 1 month, 3 months, and 6 months after initiation of treatment with EPIDIOLEX, and periodically thereafter or as clinically indicated. Serum transaminases and total bilirubin levels should also be obtained within 1 month following changes in EPIDIOLEX dosage and addition of or changes in medications that are known to impact the liver. Consider more frequent monitoring of serum transaminases and bilirubin in patients who are taking valproate or who have elevated liver enzymes at baseline.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX, as appropriate. Discontinue EPIDIOLEX in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Patients with sustained transaminase elevations of greater than 5 times the ULN should also have treatment discontinued. Patients with prolonged elevations of serum transaminases should be evaluated for other possible causes. Consider dosage adjustment of any co-administered medication that is known to affect the liver (e.g., valproate and clobazam).

5.2 Somnolence and Sedation

EPIDIOLEX can cause somnolence and sedation. In controlled studies for LGS and DS (10 and 20 mg/kg/day dosages), the incidence of somnolence and sedation (including lethargy) was 32% in EPIDIOLEX-treated patients (27% and 34% of patients taking EPIDIOLEX 10 or 20 mg/kg/day, respectively), compared with 11% in patients on placebo and was generally dose-related. The rate was higher in patients on concomitant clobazam (46% in EPIDIOLEX-treated patients taking clobazam compared with 16% in EPIDIOLEX-treated patients not on clobazam). In the controlled study for TSC, the incidence of somnolence and sedation (including lethargy) was 19% in EPIDIOLEX-treated patients (25 mg/kg/day), compared with 17% in patients on placebo. The rate was higher in patients on concomitant clobazam (33% in EPIDIOLEX-treated patients taking clobazam compared with 14% in EPIDIOLEX-

treated patients not on clobazam). In general, these effects were more common early in treatment and may diminish with continued treatment. Other CNS depressants, including alcohol, could potentiate the somnolence and sedation effect of EPIDIOLEX. Prescribers should monitor patients for somnolence and sedation and should advise patients not to drive or operate machinery until they have gained sufficient experience on EPIDIOLEX to gauge whether it adversely affects their ability to drive or operate machinery.

5.3 Suicidal Behavior and Ideation

Antiepileptic drugs (AEDs), including EPIDIOLEX, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with an AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, or any unusual changes in mood or behavior.

Pooled analyses of 199 placebo-controlled clinical trials (mono- and adjunctive therapy) of 11 different AEDs showed that patients randomized to one of the AEDs had approximately twice the risk (adjusted Relative Risk 1.8, 95% CI:1.2, 2.7) of suicidal thinking or behavior compared to patients randomized to placebo. In these trials, which had a median treatment duration of 12 weeks, the estimated incidence rate of suicidal behavior or ideation among 27863 AED-treated patients was 0.43%, compared to 0.24% among 16029 placebo-treated patients, representing an increase of approximately one case of suicidal thinking or behavior for every 530 patients treated. There were four suicides in drug-treated patients in the trials and none in placebo-treated patients, but the number is too small to allow any conclusion about drug effect on suicide.

The increased risk of suicidal thoughts or behavior with AEDs was observed as early as 1 week after starting drug treatment with AEDs and persisted for the duration of treatment assessed. Because most trials included in the analysis did not extend beyond 24 weeks, the risk of suicidal thoughts or behavior beyond 24 weeks could not be assessed.

The risk of suicidal thoughts or behavior was generally consistent among drugs in the data analyzed. The finding of increased risk with AEDs of varying mechanisms of action and across a range of indications suggests that the risk applies to all AEDs used for any indication. The risk did not vary substantially by age (5–100 years) in the clinical trials analyzed. Table 2 shows absolute and relative risk by indication for all evaluated AEDs.

Table 2: Risk of Suicidal Thoughts or Behaviors by Indication for Antiepileptic Drugs in the Pooled Analysis

Indication	Placebo Patients with Events Per 1000 Patients	Drug Patients with Events Per 1000 Patients	Relative Risk: Incidence of Events in Drug Patients/Incidence in Placebo Patients	Risk Difference: Additional Drug Patients with Events Per 1000 Patients
Epilepsy	1.0	3.4	3.5	2.4

Psychiatric	5.7	8.5	1.5	2.9
Other	1.0	1.8	1.9	0.9
Total	2.4	4.3	1.8	1.9

The relative risk for suicidal thoughts or behavior was higher in clinical trials in patients with epilepsy than in clinical trials in patients with psychiatric or other conditions, but the absolute risk differences were similar for the epilepsy and psychiatric indications.

Anyone considering prescribing EPIDIOLEX or any other AED must balance the risk of suicidal thoughts or behaviors with the risk of untreated illness. Epilepsy and many other illnesses for which AEDs are prescribed are themselves associated with morbidity and mortality and an increased risk of suicidal thoughts and behavior. Should suicidal thoughts and behavior emerge during treatment, consider whether the emergence of these symptoms in any given patient may be related to the illness being treated.

5.4 Hypersensitivity Reactions

EPIDIOLEX can cause hypersensitivity reactions. Some subjects in the EPIDIOLEX clinical trials had pruritus, erythema, and angioedema requiring treatment, including corticosteroids and antihistamines. Patients with known or suspected hypersensitivity to any ingredients of EPIDIOLEX were excluded from the clinical trials. If a patient develops hypersensitivity reactions after treatment with EPIDIOLEX, the drug should be discontinued. EPIDIOLEX is contraindicated in patients with a prior hypersensitivity reaction to cannabidiol or any of the ingredients in the product, which includes sesame seed oil *[see Description (11)]*.

5.5 Withdrawal of Antiepileptic Drugs (AEDs)

As with most antiepileptic drugs, EPIDIOLEX should generally be withdrawn gradually because of the risk of increased seizure frequency and status epilepticus *[see Dosage and Administration (2.5) and Clinical Studies (14)]*. But if withdrawal is needed because of a serious adverse event, rapid discontinuation can be considered.

6 ADVERSE REACTIONS

The following important adverse reactions are described elsewhere in labeling:

- Hepatocellular Injury *[see Warnings and Precautions (5.1)]*
- Somnolence and Sedation *[see Warnings and Precautions (5.2)]*
- Suicidal Behavior and Ideation *[see Warnings and Precautions (5.3)]*
- Hypersensitivity Reactions *[see Warnings and Precautions (5.4)]*
- Withdrawal of Antiepileptic Drugs *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

In controlled and uncontrolled trials in patients with LGS and DS, 689 patients were treated with EPIDIOLEX, including 533 patients treated for more than 6 months, 391 patients treated for more than 1 year. In controlled and uncontrolled trials in patients with TSC, 223 patients were treated with EPIDIOLEX, including 151 patients treated for more than 6 months, 88 patients treated for more than 1 year, and 15 patients treated for more than 2 years.

In an expanded access program and other compassionate use programs, 271 patients with DS, LGS, or TSC were treated with EPIDIOLEX, including 237 patients treated for more than 6 months, 204 patients treated for more than 1 year, and 140 patients treated for more than 2 years.

Patients with LGS or DS

In placebo-controlled trials of patients with LGS or DS (includes Studies 1, 2, 3, and a Phase 2 controlled study in DS), 323 patients received EPIDIOLEX *[see Clinical Studies (14.1, 14.2)]*. Adverse reactions are presented below; the duration of treatment in these trials was up to 14 weeks. Approximately 46% of patients were female, 83% were Caucasian, and the mean age was 14 years (range 2 to 48 years). All patients were taking other AEDs.

In controlled trials in LGS or DS, the rate of discontinuation as a result of any adverse reaction was 2.7% for patients taking EPIDIOLEX 10 mg/kg/day, 11.8% for patients taking EPIDIOLEX 20 mg/kg/day, and 1.3% for patients on placebo. The most frequent cause of discontinuations was transaminase elevation. Discontinuation for transaminase elevation occurred at an incidence of 1.3% in patients taking EPIDIOLEX 10 mg/kg/day, 5.9% in patients taking EPIDIOLEX 20 mg/kg/day, and 0.4% in patients on placebo. Somnolence, sedation, and lethargy led to discontinuation in 3% of patients taking EPIDIOLEX 20 mg/kg/day compared to 0% of patients taking EPIDIOLEX 10 mg/kg/day or on placebo.

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with LGS or DS (incidence at least 10% and greater than placebo) were somnolence; decreased appetite; diarrhea; transaminase elevations; fatigue, malaise, and asthenia; rash; insomnia, sleep disorder, and poor quality sleep; and infections.

Table 3 lists the adverse reactions that were reported in at least 3% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trials in LGS and DS.

Table 3: Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trials of LGS and DS (Studies 1, 2, and 3)

Adverse Reactions	**EPIDIOLEX**		**Placebo**
	10 mg/kg/day	**20 mg/kg/day**	
	N=75 %	**N=238 %**	**N=227 %**
Hepatic Disorders			

Transaminases elevated	8	16	3
Gastrointestinal Disorders			
Decreased appetite	16	22	5
Diarrhea	9	20	9
Weight decreased	3	5	1
Gastroenteritis	0	4	1
Abdominal pain, discomfort	3	3	1
Nervous System Disorders			
Somnolence	23	25	8
Fatigue, malaise, asthenia	11	12	4
Lethargy	4	8	2
Sedation	3	6	1
Irritability, agitation	9	5	2
Aggression, anger	3	5	<1
Insomnia, sleep disorder, poor quality sleep	11	5	4
Drooling, salivary hypersecretion	1	4	<1
Gait Disturbance	3	2	<1
Infections			
Infection, all	41	40	31
Infection, other	25	21	24
Infection, viral	7	11	6
Pneumonia	8	5	1
Infection, fungal	1	3	0
Other			
Rash	7	13	3
Hypoxia, respiratory failure	3	3	1

Adverse reactions were similar across LGS and DS in pediatric and adult patients.

Patients with TSC

In a placebo-controlled trial of patients with TSC (Study 4), 148 patients received EPIDIOLEX *[see Clinical Studies (14.3)]*. Adverse reactions are presented below; the duration of treatment in this trial was up to 16 weeks. Approximately 42% of patients were female, 90% were Caucasian, and the mean age was 14 years (range 1 to 57 years). All patients but one (25 mg/kg/day group) were taking other AEDs.

In the controlled trial in TSC, the rate of discontinuation as a result of any adverse reaction was 11% for patients taking EPIDIOLEX 25 mg/kg/day and 3% for patients on placebo. The most frequent cause of discontinuation was rash (5%).

The most common adverse reactions that occurred in EPIDIOLEX-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting.

Table 4 lists the adverse reactions that were reported in at least 3% of EPIDIOLEX-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trial in TSC.

Table 4: Adverse Reactions in Patients Treated with EPIDIOLEX in Controlled Trial of TSC (Study 4)

Adverse Reactions	EPIDIOLEX 25 mg/kg/day N = 75 %	Placebo N = 76 %
Hematological changes		
Anemia	7	1
Platelet count decreased	5	1
Eosinophil count increased	5	0
Hepatic Disorders		
Transaminases elevated	25	0
Gastrointestinal Disorders		
Diarrhea	31	25
Decreased appetite	20	12
Vomiting	17	9
Nausea	9	3
Gastroenteritis	8	7
Weight decreased	7	0
Nervous System Disorders		
Somnolence	13	9
Gait disturbance	9	5
Fatigue, malaise, asthenia	5	1
Infections		
Ear infection	8	3
Urinary tract infection	5	0
Pneumonia	4	1
Other		
Pyrexia	19	8
Rash	8	4
Rhinorrhea	4	0

Adverse reactions were similar in pediatric and adult patients with TSC.

Additional Adverse Reactions in Patients with LGS, DS, or TSC

Decreased Weight

EPIDIOLEX can cause weight loss. In the controlled trials of patients with LGS or DS (10 and 20 mg/kg/day), based on measured weights, 16% of EPIDIOLEX-treated patients had a decrease in weight of at least 5% from their baseline weight, compared to 8% of patients on placebo. The decrease in weight appeared to be dose-related, with 18% of patients on EPIDIOLEX 20 mg/kg/day experiencing a decrease in weight ≥5%, compared to 9% in patients on EPIDIOLEX 10 mg/kg/day. In the controlled trial of patients with TSC (25 mg/kg/day), 31% of EPIDIOLEX-treatment patients had a decrease in weight of at least 5%

from their baseline weight, compared to 8% of patients on placebo. In some cases, the decreased weight was reported as an adverse event (see Tables 3 and 4).

Hematologic Abnormalities

EPIDIOLEX can cause decreases in hemoglobin and hematocrit. In controlled trials of patients with LGS or DS, the mean decrease in hemoglobin from baseline to end of treatment was −0.42 g/dL in EPIDIOLEX-treated patients receiving 10 or 20 mg/kg/day and -0.03 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of −1.5% in EPIDIOLEX-treated patients, and −0.4% in patients on placebo. In trial of patients with TSC, the mean decrease in hemoglobin from baseline to end treatment was -0.37 g/dL in EPIDIOLEX-treated patients receiving 25 mg/kg/day and 0.07 g/dL in patients on placebo. A corresponding decrease in hematocrit was also observed, with a mean change of -1.2% in EPIDIOLEX-treated patients, and -0.2% in patients on placebo.

There was no effect on red blood cell indices. Thirty percent (30%) of EPIDIOLEX-treated patients with LGS and DS and 38% of EPIDIOLEX-treated patients with TSC developed a new laboratory-defined anemia during the course of the study (defined as a normal hemoglobin concentration at baseline, with a reported value less than the lower limit of normal at a subsequent time point), versus 13% of patients with LGS and DS on placebo and 15% of patients with TSC on placebo.

Increases in Creatinine

EPIDIOLEX can cause elevations in serum creatinine. The mechanism has not yet been determined. In controlled studies in healthy adults and in patients with LGS, DS and TSC, an increase in serum creatinine of approximately 10% was observed within 2 weeks of starting EPIDIOLEX. The increase was reversible in healthy adults. Reversibility was not assessed in studies in LGS, DS or TSC.

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on EPIDIOLEX

Strong CYP3A4 or CYP2C19 Inducers

Coadministration with a strong CYP3A4 and CYP2C19 inducer (rifampin 600 mg once daily) decreased cannabidiol and 7-OH-CBD plasma concentrations by approximately 32% and 63%. The impact of such changes on efficacy of EPIDIOLEX are not known *[see Clinical Pharmacology (12.3)]*. Consider an increase in EPIDIOLEX dosage (based on clinical response and tolerability) up to 2-fold, when coadministered with a strong CYP3A4 and/or CYP2C19 inducer.

7.2 Effect of EPIDIOLEX on Other Drugs

UGT1A9, UGT2B7, CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 Substrates

In vitro data predict drug-drug interactions with CYP1A2 substrates (e.g., theophylline, caffeine), CYP2B6 substrates (e.g., bupropion, efavirenz), uridine 5'-diphospho-glucuronosyltransferase 1A9 (UGT1A9) substrates (e.g., diflunisal, propofol, fenofibrate), and UGT2B7 substrates (e.g., gemfibrozil, lamotrigine, morphine, lorazepam) when coadministered with EPIDIOLEX. Coadministration of EPIDIOLEX is also predicted to cause clinically significant interactions with CYP2C8 and CYP2C9 (e.g., phenytoin) substrates. Because of potential inhibition of enzyme activity, consider a reduction in dosage of substrates of UGT1A9, UGT2B7, CYP2C8, and CYP2C9, as clinically appropriate, if adverse reactions are experienced when administered concomitantly with EPIDIOLEX. Because of potential for both induction and inhibition of enzyme activity, consider adjusting dosage of substrates of CYP1A2 and CYP2B6 as clinically appropriate.

Sensitive CYP2C19 Substrates

In vivo data show that coadministration of EPIDIOLEX increases plasma concentrations of drugs that are metabolized by (i.e., are substrates of) CYP2C19 (e.g., diazepam) and may increase the risk of adverse reactions with these substrates *[see Clinical Pharmacology (12.3)]*. Consider a reduction in dosage of sensitive CYP2C19 substrates, as clinically appropriate, when coadministered with EPIDIOLEX.

Clobazam

Coadministration of EPIDIOLEX produces a 3-fold increase in plasma concentrations of N-desmethylclobazam, the active metabolite of clobazam (a substrate of CYP2C19), with no effect on clobazam levels *[see Clinical Pharmacology (12.3)]*. The increase in N-desmethylclobazam may increase the risk of clobazam-related adverse reactions *[see Warnings and Precautions (5.1, 5.2)]*. Consider a reduction in dosage of clobazam if adverse reactions known to occur with clobazam are experienced when co-administered with EPIDIOLEX.

7.3 Concomitant Use of EPIDIOLEX and Valproate

Concomitant use of EPIDIOLEX and valproate increases the incidence of liver enzyme elevations *[see Warnings and Precautions (5.1)]*. If such elevations occur, discontinuation or reduction of EPIDIOLEX and/or concomitant valproate should be considered. Insufficient data are available to assess the risk of concomitant administration of other hepatotoxic drugs and EPIDIOLEX.

7.4 Concomitant Use of EPIDIOLEX and Mammalian Target of Rapamycin (mTOR) or Calcineurin Inhibitors

No dedicated drug-drug interaction studies have been conducted with mTOR inhibitors (e.g., everolimus) or calcineurin inhibitors (e.g., tacrolimus). Reports in the literature suggest that cannabidiol administration resulted in increased serum levels of everolimus, sirolimus, or tacrolimus. The mechanism

of increase in mTOR or calcineurin inhibitors concentrations is not clearly understood. Consider a reduction in dosage of everolimus, sirolimus, or tacrolimus, if adverse reactions known to occur with those medications are experienced when co-administered with EPIDIOLEX.

7.5 CNS Depressants and Alcohol

Concomitant use of EPIDIOLEX with other CNS depressants (including alcohol) may increase the risk of sedation and somnolence *[see Warnings and Precautions (5.2)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to antiepileptic drugs (AEDs), such as EPIDIOLEX, during pregnancy. Encourage women who are taking EPIDIOLEX during pregnancy to enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry by calling the toll free number 1-888-233-2334 or visiting http://www.aedpregnancyregistry.org/.

Risk Summary

There are no adequate data on the developmental risks associated with the use of EPIDIOLEX in pregnant women. Administration of cannabidiol to pregnant animals produced evidence of developmental toxicity (increased embryofetal mortality in rats and decreased fetal body weights in rabbits; decreased growth, delayed sexual maturation, long-term neurobehavioral changes, and adverse effects on the reproductive system in rat offspring) at maternal plasma exposures similar to (rabbit) or greater than (rat) that in humans at therapeutic doses *(see Animal Data)*. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2–4% and 15–20%, respectively. The background risks of major birth defects and miscarriage for the indicated populations are unknown.

Data

Animal Data

Oral administration of cannabidiol (0, 75, 150, or 250 mg/kg/day) to pregnant rats throughout the period of organogenesis resulted in embryofetal mortality at the highest dose tested. There were no other drug-related maternal or developmental effects. The highest no-effect dose for embryofetal toxicity in rats was associated with maternal plasma cannabidiol exposures (AUC) approximately 16 and 9 times that in humans at the recommended human doses (RHD) of 20 and 25 mg/kg/day, respectively.

Oral administration of cannabidiol (0, 50, 80, or 125 mg/kg/day) to pregnant rabbits throughout organogenesis resulted in decreased fetal body weights and increased fetal structural variations at the highest dose tested, which was also associated with maternal toxicity. Maternal plasma cannabidiol exposures at the no-effect level for embryofetal developmental toxicity in rabbits were less than that in humans at the RHDs.

When cannabidiol (75, 150, or 250 mg/kg/day) was orally administered to rats throughout pregnancy and lactation, decreased growth, delayed sexual maturation, neurobehavioral changes (decreased activity), and adverse effects on male reproductive organ development (small testes in adult offspring) and fertility were observed in the offspring at the mid and high dose. These effects occurred in the absence of maternal toxicity. The no-effect dose for pre- and post-natal developmental toxicity in rats was associated with maternal plasma cannabidiol exposures approximately 9 and 5 times that in humans at the RHDs of 20 and 25 mg/kg/day, respectively.

8.2 Lactation

Risk Summary

There are no data on the presence of cannabidiol or its metabolites in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EPIDIOLEX and any potential adverse effects on the breastfed infant from EPIDIOLEX or from the underlying maternal condition.

8.4 Pediatric Use

Safety and effectiveness of EPIDIOLEX for the treatment of seizures associated with LGS, DS, or TSC have been established in patients 1 year of age and older. The use of EPIDIOLEX in these indications is supported by adequate and well-controlled studies in patients 2 years of age and older with LGS and DS and in patients 1 year of age and older with TSC *[see Clinical Studies (14.1, 14.2, 14.3)]*.

Safety and effectiveness of EPIDIOLEX in pediatric patients below 1 year of age have not been established.

Juvenile Animal Data

Administration of cannabidiol (subcutaneous doses of 0 or 15 mg/kg on Postnatal Days (PNDs) 4-6 followed by oral administration of 0, 100, 150, or 250 mg/kg on PNDs 7-77) to juvenile rats for 10 weeks resulted in increased body weight, delayed male sexual maturation, neurobehavioral effects (decreased locomotor activity and auditory startle habituation), increased bone mineral density, and liver hepatocyte vacuolation. A no-effect dose was not established. The lowest dose causing developmental toxicity in juvenile rats (15 sc/100 po mg/kg) was associated with cannabidiol exposures (AUC) approximately 15 and 8 times that in humans at the RHDs of 20 and 25 mg/kg/day, respectively.

8.5 Geriatric Use

Clinical trials of EPIDIOLEX in the treatment of LGS, DS, and TSC did not include a sufficient number of patients aged above 55 years to determine whether or not they respond differently from younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of

concomitant disease or other drug therapy *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*.

8.6 Hepatic Impairment

Because of an increase in exposure to EPIDIOLEX, dosage adjustments are necessary in patients with moderate or severe hepatic impairment *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. EPIDIOLEX does not require dosage adjustments in patients with mild hepatic impairment.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

EPIDIOLEX is not a controlled substance.

9.2 Abuse

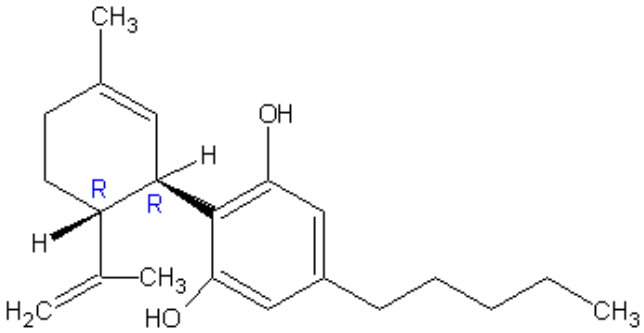
Animal abuse-related studies show that cannabidiol does not produce cannabinoid-like behavioral responses, including generalization to delta-9-tetrahydrocannabinol (THC) in a drug discrimination study. Cannabidiol also does not produce animal self-administration, suggesting it does not produce rewarding effects. In a human abuse potential study, acute administration of cannabidiol to non-dependent adult recreational drug users at therapeutic and supratherapeutic doses of 750, 1500, and 4500 mg in the fasted state (equivalent respectively to 10, 20, and 60 mg/kg in a 75 kg adult) produced responses on positive subjective measures such as Drug Liking and Take Drug Again that were within the acceptable placebo range. In contrast, 10 and 30 mg of dronabinol (synthetic THC) and 2 mg alprazolam produced large increases on positive subjective measures compared to placebo that were statistically significantly greater than those produced by cannabidiol. In other Phase 1 clinical studies conducted with cannabidiol, there were no reports of abuse-related adverse events.

9.3 Dependence

In a human physical dependence study, administration of cannabidiol 1500 mg/day (750 mg twice daily) to adults for 28 days did not produce signs or symptoms of withdrawal over a 6-week assessment period beginning three days after drug discontinuation. This suggests that cannabidiol likely does not produce physical dependence.

11 DESCRIPTION

Cannabidiol is a cannabinoid designated chemically as 2-[(1R,6R)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol (IUPAC/CAS). Its empirical formula is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. The chemical structure is:



Cannabidiol, the active ingredient in EPIDIOLEX, is a cannabinoid that naturally occurs in the *Cannabis sativa* L. plant.

Cannabidiol is a white to pale yellow crystalline solid. It is insoluble in water and is soluble in organic solvents.

EPIDIOLEX (cannabidiol) oral solution is a clear, colorless to yellow liquid containing cannabidiol at a concentration of 100 mg/mL. Inactive ingredients include dehydrated alcohol (7.9% w/v), sesame seed oil, strawberry flavor, and sucralose. EPIDIOLEX contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The precise mechanisms by which EPIDIOLEX exerts its anticonvulsant effect in humans are unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.

12.2 Pharmacodynamics

There are no relevant data on the pharmacodynamic effects of cannabidiol.

12.3 Pharmacokinetics

Cannabidiol demonstrated an increase in exposure that was less than dose-proportional over the range of 5 to 25 mg/kg/day in patients.

Absorption

Cannabidiol has a time to maximum plasma concentration (T_{max}) of 2.5 to 5 hours at steady state (C_{ss}).

Effect of Food

Coadministration of EPIDIOLEX with a high-fat/high-calorie meal increased C_{max} by 5-fold, AUC by 4-fold, and reduced the total variability, compared with the fasted state in healthy volunteers *[see Dosage and Administration (2.4)]*.

Distribution

The apparent volume of distribution in healthy volunteers was 20963 L to 42849 L. Protein binding of the cannabidiol and its metabolites was >94% in vitro.

Elimination

The half-life of cannabidiol in plasma was 56 to 61 hours after twice-daily dosing for 7 days in healthy volunteers. The plasma clearance of cannabidiol following a single EPIDIOLEX 1500 mg dose (approximately equal to the 20 mg/kg/day dosage) is 1111 L/h.

Metabolism

Cannabidiol is metabolized in the liver and the gut (primarily in the liver) by CYP2C19 and CYP3A4 enzymes, and UGT1A7, UGT1A9, and UGT2B7 isoforms.

After repeat dosing, the active metabolite of cannabidiol, 7-OH-CBD, has a 38% lower AUC than the parent drug. The 7-OH-CBD metabolite is converted to 7-COOH-CBD, which has an approximately 40-fold higher AUC than the parent drug. Based on preclinical models of seizure, the 7-OH-CBD metabolite is active; however, the 7-COOH-CBD metabolite is not active.

Excretion

EPIDIOLEX is excreted in feces, with minor renal clearance.

Specific Populations

Patients with Hepatic Impairment

No effects on the exposures of cannabidiol or metabolite exposures were observed following administration of a single dose of EPIDIOLEX 200 mg in patients with mild (Child-Pugh A) hepatic impairment. Patients with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment had an approximately 2.5 to 5.2-fold higher AUC, compared with healthy volunteers with normal hepatic function *[see Dosage and Administration (2.6), Warnings and Precautions (5.1), Use in Specific Populations (8.6)]*.

Drug Interaction Studies

In Vitro Assessment of Drug Interactions

Drug Metabolizing Enzymes *[see Drug Interactions (7.1, 7.2)]*

Cannabidiol is a substrate for CYP3A4 and CYP2C19. Cannabidiol has the potential to inhibit CYP2B6, CYP2C8, CYP2C9, and CYP2C19 at clinically relevant concentrations.

Cannabidiol may induce or inhibit CYP1A2 and CYP2B6 at clinically relevant concentrations.

Cannabidiol inhibits uridine 5'-diphospho-glucuronosyltransferase (UGT) enzymes UGT1A9 and UGT2B7, but does not inhibit the UGT1A1, UGT1A3, UGT1A4, UGT1A6, or UGT2B17 isoforms.

Transporters

Cannabidiol and the cannabidiol metabolite, 7-OH-CBD, are not anticipated to interact with BCRP, BSEP, MDR1/P-pg, OAT1, OAT3, OCT1, OCT2, MATE1, MATE2-K, OATP1B1, or OATP1B3. The cannabidiol metabolite, 7-COOH-CBD, is not a substrate of BCRP, OATP1B1, OATP1B3, or OCT1. However, 7-COOH-CBD is a substrate for P-gp. 7-COOH-CBD is an inhibitor of transport mediated via BCRP and BSEP at clinically relevant concentrations.

In Vivo Assessment of Drug Interactions

Drug Interaction Studies with AEDs

Clobazam and Valproate

The interaction potential with other AEDs (clobazam and valproate) was evaluated in dedicated clinical studies following coadministration of EPIDIOLEX (750 mg twice daily in healthy volunteers and 20 mg/kg/day in patients). Coadmininistration with clobazam in healthy volunteers increased the cannabidiol active metabolite 7-OH-CBD mean C_{max} by 73% and AUC by 47%; and increased the clobazam active metabolite, N-desmethylclobazam, C_{max} and AUC by approximately 3-fold, with no effect on clobazam levels *[see Drug Interactions (7.2)]*. When EPIDIOLEX was coadmininistered with valproate, there was no effect on valproate exposure.

Effect of EPIDIOLEX on Midazolam

Coadministration of EPIDIOLEX with midazolam (a sensitive CYP3A4 substrate) did not result in changes in plasma concentrations of midazolam compared to midazolam administered alone.

Effect of CYP3A4 and CYP2C19 Inducers and Inhibitors Coadministered with EPIDIOLEX on Exposure to Cannabidiol

Coadministration of EPIDIOLEX with potent inhibitors of CYP3A4 and CYP2C19 had the following effects on exposure to cannabidiol and its metabolites. The potent CYP3A4 inhibitor, itraconazole, increased exposure by < 10% for cannabidiol and < 20% for 7-OH-CBD and 7-COOH-CBD for both AUC and C_{max}. Although the effects of the potent CYP2C19 inhibitor fluconazole were slightly more marked, they are still considered not to be clinically meaningful (cannabidiol increased by 22% and 24% for AUC and C_{max}, respectively; 7-OH-CBD decreased by 28% and 41% for AUC and C_{max}; 7-COOH-CBD decreased by 33% and 48% for AUC and C_{max}).

Coadministration with the potent CYP3A4 and CYP2C19 inducing agent rifampin caused a decrease in cannabidiol exposure of 32% and 34% for AUC and C_{max} *[see Drug Interactions (7.1)]*. There were moderate changes in exposure to the active metabolite (7-OH-CBD decreased by 63% and 67% for AUC and C_{max}, 7-COOH-CBD decreased by 48% for AUC, whereas there was no change in C_{max}).

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis and Mutagenesis

Carcinogenesis

Adequate studies of the carcinogenic potential of cannabidiol have not been conducted.

Mutagenesis

Cannabidiol was negative for genotoxicity in *in vitro* (Ames) and *in vivo* (rat Comet and bone marrow micronucleus) assays.

Impairment of Fertility

Oral administration of cannabidiol (0, 75, 150, or 250 mg/kg/day) to male and female rats, prior to and throughout mating and continuing in females during early gestation, produced no adverse effects on fertility. The highest dose tested was associated with plasma exposures (AUC) approximately 60 and 34 times that in humans at the RHDs of 20 and 25 mg/kg/day, respectively.

14 CLINICAL STUDIES

14.1 Lennox–Gastaut Syndrome

The effectiveness of EPIDIOLEX for the treatment of seizures associated with LGS was established in two randomized, double-blind, placebo-controlled trials in patients aged 2 to 55 years (Study 1, NCT02224690; and Study 2, NCT02224560).

Study 1 (N=171) compared a dose of EPIDIOLEX 20 mg/kg/day with placebo. Study 2 (N=225) compared a 10 mg/kg/day dose and a 20 mg/kg/day dose of EPIDIOLEX with placebo. In both studies, patients had a diagnosis of LGS and were inadequately controlled on at least one AED, with or without vagal nerve stimulation and/or ketogenic diet. Both trials had a 4-week baseline period, during which patients were required to have a minimum of 8 drop seizures (≥ 2 drop seizures per week). The baseline period was followed by a 2-week titration period and a 12-week maintenance period.

In Study 1, 94% of patients were taking at least 2 concomitant AEDs. The most frequently used concomitant AEDs (> 25%) in Study 1 were clobazam (49%), valproate (40%), lamotrigine (37%), levetiracetam (34%), and rufinamide (27%). In Study 2, 94% of patients were taking at least 2 concomitant AEDs. The most frequently used concomitant AEDs (>25%) in Study 2, were clobazam (49%), valproate (38%), levetiracetam (31%), lamotrigine (30%), and rufinamide (29%).

The primary efficacy measure in both studies was the percent change from baseline in the frequency (per 28 days) of drop seizures (atonic, tonic, or tonic-clonic seizures) over the 14-week treatment period. Key secondary endpoints in both studies included analyses of change in total seizure frequency and changes from baseline in the Subject/Caregiver Global Impression of Change (S/CGIC) score at the last visit. For the S/CGIC, the following question was rated on a 7-point scale: “Since [you/your child] started treatment, please assess the status of [your/your child’s] overall condition (comparing [your/their] condition now to [your/their] condition before treatment) using the scale below.” The 7-point scale was as follows: “Very

Much Improved" (1); "Much Improved" (2); "Slightly Improved" (3); "No Change" (4); "Slightly Worse" (5); "Much Worse" (6); "Very Much Worse" (7).

In Studies 1 and 2, the median percent change from baseline (reduction) in the frequency of drop seizures was significantly greater for both dosage groups of EPIDIOLEX than for placebo (Table 5). A reduction in drop seizures was observed within 4 weeks of initiating treatment with EPIDIOLEX, and the effect remained generally consistent over the 14-week treatment period.

Table 5: Change in Drop Seizure Frequency in Lennox–Gastaut Syndrome during the Treatment Period (Studies 1 and 2)

Drop Seizure Frequency (per 28 Days)	**Placebo**	**EPIDIOLEX 10 mg/kg/day**	**EPIDIOLEX 20 mg/kg/day**
Study 1	**N=85**	**—**	**N=86**
Baseline Period Median Seizure Frequency	75	—	71
Median Percentage Change from Baseline During Treatment	−22	—	−44
p-value compared to placebo[a]			0.01
Study 2	**N=76**	**N=73**	**N=76**
Baseline Period Median Seizure Frequency	80	87	86
Median Percentage Change from Baseline During Treatment	−17	−37	−42
p-value compared to placebo[a]		<0.01	<0.01

[a]Obtained from a Wilcoxon rank-sum test.

Figure 1 displays the percentage of patients by category of reduction from baseline in drop seizure frequency per 28 days during the treatment period in Study 1.

Figure 1: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Lennox–Gastaut Syndrome (Study 1)

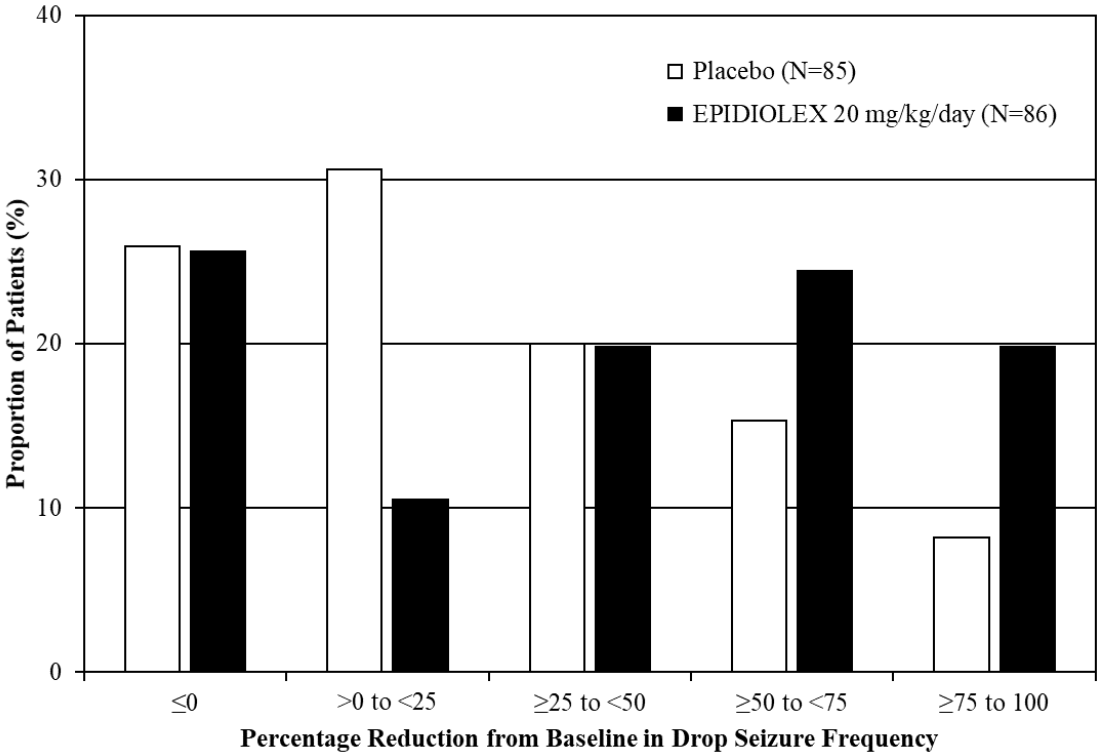
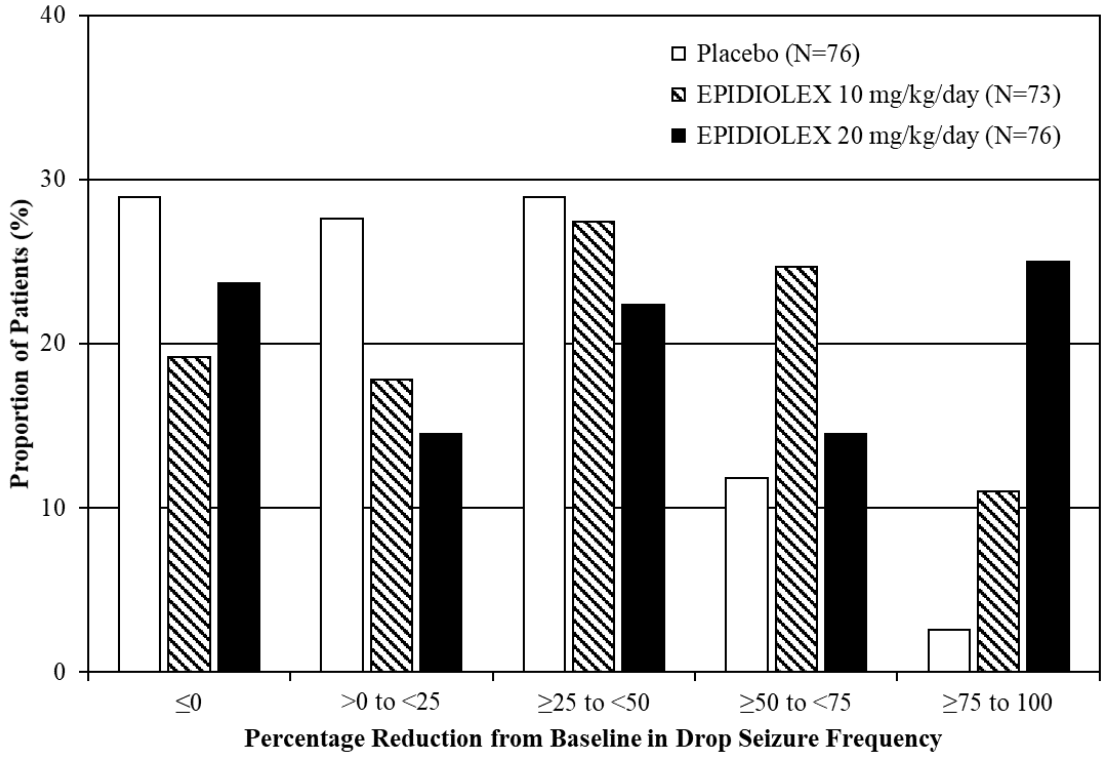


Figure 2 displays the percentage of patients by category of reduction from baseline in drop seizure frequency (per 28 days) during the treatment period in Study 2.

Figure 2: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Lennox–Gastaut Syndrome (Study 2)



In Study 1, 3 of 85 (4%) patients in the EPIDIOLEX 20 mg/kg/day group reported no drop seizures during the maintenance period, compared to 0 patients in the placebo group. In Study 2, 3 of 73 (4%) patients in the EPIDIOLEX 10 mg/kg/day group, 5 of 76 (7%) patients in the EPIDIOLEX 20 mg/kg/day group, and 1 of 76 (1%) patients in the placebo group reported no drop seizures during the maintenance period.

In LGS patients, EPIDIOLEX was associated with significant reductions in total seizure frequency (drop and non-drop seizures) versus placebo. During the treatment period in Study 1, the median percent reduction in total seizure frequency (per 28 days) was 41% in patients taking EPIDIOLEX 20 mg/kg/day compared to 14% in patients taking placebo ($p<0.01$). In Study 2, the median percent reduction in total seizure frequency (per 28 days) was 36% in the 10 mg/kg/day group, 38% in the 20 mg/kg/day group, and 18% in the placebo group ($p<0.01$ for both groups).

A greater improvement on the Subject/Caregiver Global Impression of Change (S/CGIC) was reported in patients treated with EPIDIOLEX compared with placebo in Studies 1 and 2. In Study 1, the mean S/CGIC score at last visit was 3.0 in the 20 mg/kg/day EPIDIOLEX group (corresponding to “slightly improved”) compared with 3.7 (most closely associated with “no change”) in the placebo group ($p<0.01$). In Study 2, the mean S/CGIC score at last visit was 3.0 and 3.2 in the 10 mg/kg/day and 20 mg/kg/day EPIDIOLEX groups, respectively (“slightly improved”), compared with 3.6 (“no change”) in the placebo group ($p<0.01$ and $p=0.04$, respectively).

14.2 Dravet Syndrome

The effectiveness of EPIDIOLEX for the treatment of seizures associated with DS was demonstrated in a single randomized, double-blind, placebo-controlled trials in 120 patients aged 2 to 18 years (Study 3, NCT02091375). Study 3 compared a dose of EPIDIOLEX 20 mg/kg/day with placebo. Patients had a diagnosis of treatment-resistant DS and were inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During the 4-week baseline period, patients were required to have at least 4 convulsive seizures while on stable AED therapy. The baseline period was followed by a 2-week titration period and a 12-week maintenance period. The primary efficacy measure was the percent change from baseline in the frequency (per 28 days) of convulsive seizures (all countable atonic, tonic, clonic, and tonic-clonic seizures) over the 14-week treatment period.

In Study 3, 93% of patients were taking at least 2 concomitant AEDs during the trial. The most commonly used concomitant AEDs (greater than 25%) in Study 3 were clobazam (65%), valproate (57%), stiripentol (43%), levetiracetam (28%), and topiramate (26%).

The median percent change from baseline (reduction) in the frequency of convulsive seizures was significantly greater for EPIDIOLEX 20 mg/kg/day than for placebo (Table 6). A reduction in convulsive seizures was observed within 4 weeks of initiating treatment with EPIDIOLEX and the effect remained generally consistent over the 14-week treatment period.

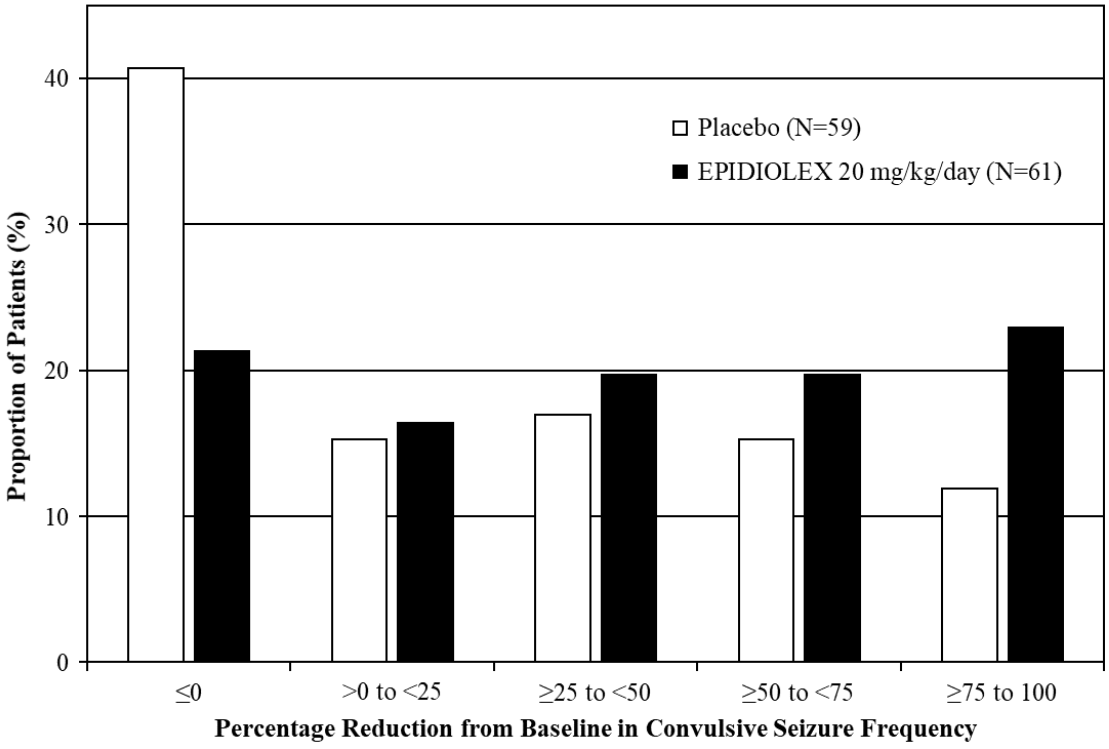
Table 6: Change in Convulsive Seizure Frequency in Dravet Syndrome during the Treatment Period (Study 3)

Total Convulsive Seizures (per 28 Days)	**Placebo**	**EPIDIOLEX 20 mg/kg/day**
Study 3	N=59	N=61
Baseline Period Median Seizure Frequency	15	12
Median Percentage Change from Baseline During Treatment	−13	−39
p-value compared to placebo[a]		0.01

[a]Obtained from a Wilcoxon rank-sum test.

Figure 3 displays the percentage of patients by category of reduction from baseline in convulsive seizure frequency (per 28 days) during the treatment period in Study 3.

Figure 3: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Dravet Syndrome (Study 3)



In Study 3, 4 of 60 (7%) patients treated with EPIDIOLEX 20 mg/kg/day reported no convulsive seizures during the maintenance period, compared to 0 patients in the placebo group.

14.3 Tuberous Sclerosis Complex

The effectiveness of EPIDIOLEX for the treatment of seizures associated with TSC was demonstrated in a randomized, double-blind, placebo-controlled trial in 224 patients aged 1 to 65 years (Study 4; NCT02544763).

Study 4 (N=224) compared doses of EPIDIOLEX 25 mg/kg/day and 50 mg/kg/day (2 times the recommended maintenance dosage) with placebo. Patients had a diagnosis of TSC and seizures inadequately controlled with at least one concomitant AED, with or without vagal nerve stimulation or ketogenic diet. During the 4-week baseline period, patients had at least 8 seizures, with at least 1 seizure occurring in at least 3 of the 4 weeks (focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures [tonic–clonic, tonic, clonic or atonic seizures]). The baseline period was followed by a 4-week titration period and a 12-week maintenance period.

In Study 4, all patients but 1 (in EPIDIOLEX 25 mg/kg/day group) were taking 1-2 concomitant AEDs during the trial. The most commonly used concomitant AEDs (greater than 25%) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%). The baseline median TSC-associated seizure frequency was 57 per 28 days for the combined groups. The primary efficacy measure was the change in seizure frequency of TSC-associated seizures over the 16-week treatment period compared with baseline.

In Study 4, the percentage change from baseline (reduction) in the frequency of TSC-associated seizures was significantly greater for patients treated with EPIDIOLEX than for placebo (Table 7). A reduction in TSC-associated seizures was observed within 4 weeks of initiating treatment with EPIDIOLEX and the effect remained generally consistent over the 12-week maintenance period.

Table 7: Change in TSC-Associated Seizure Frequency during the Treatment Period (Study 4)

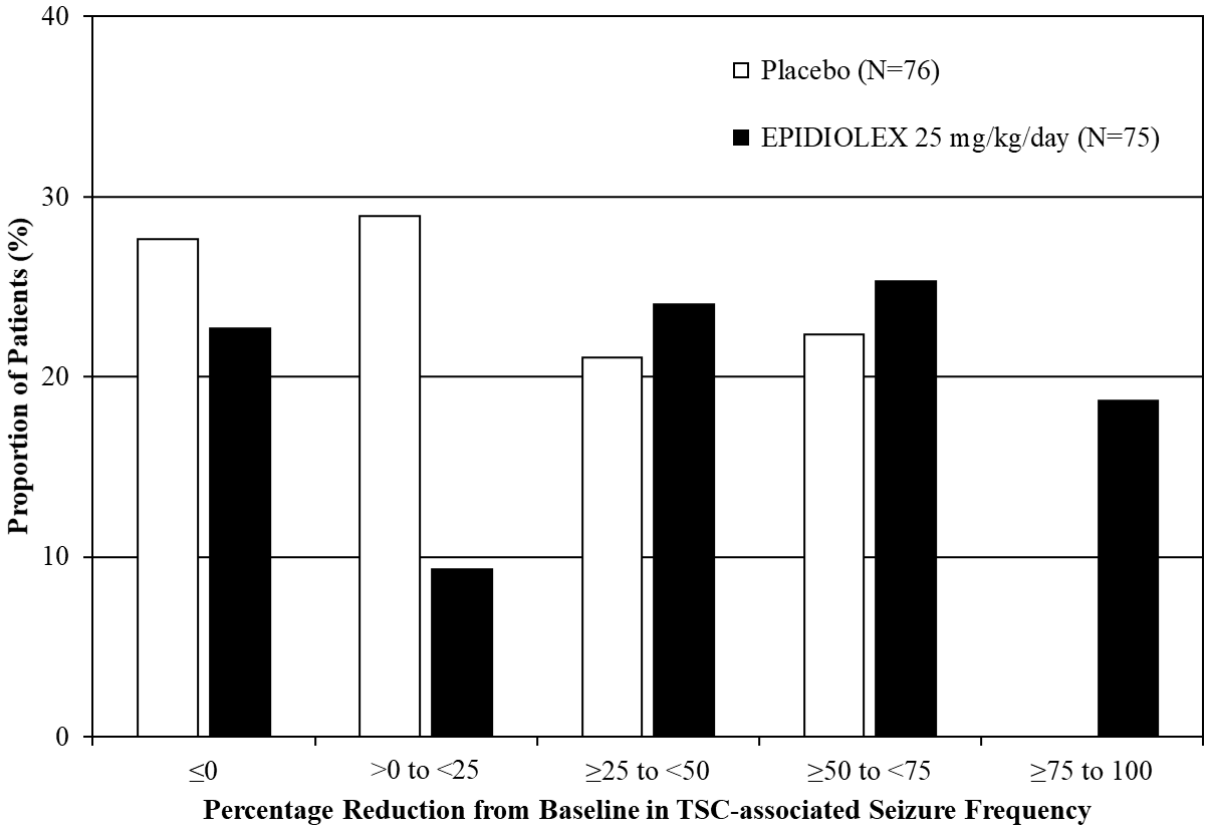
Total TSC-Associated Seizures (per 28 Days)	**Placebo**	**EPIDIOLEX 25 mg/kg/day**
Study 4	N=76	N=75
Baseline Period Median Seizure Frequency	54	56
Median Percentage Change from Baseline During Treatment	−20	−43
p-value compared to placebo[a]		<0.01
Percentage Change from Baseline During Treatment in Estimated Mean Seizure Frequency[b]	−24	−48
p-value compared to placebo[b]		<0.01

[a]Obtained from a Wilcoxon rank-sum test.

[b]Obtained from a log-transformed ANCOVA.

Figure 4 displays the percentage of patients by category of reduction from baseline in TSC-associated seizure frequency (per 28 days) during the treatment period in Study 4.

Figure 4: Proportion of Patients by Category of Seizure Response for EPIDIOLEX and Placebo in Patients with Tuberous Sclerosis Complex (Study 4)



In Study 4, 4 of 75 (5%) patients treated with EPIDIOLEX 25 mg/kg/day reported no TSC-associated seizures during the maintenance period, compared to 0 patients in the placebo group.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

EPIDIOLEX is a strawberry flavored clear, colorless to yellow solution supplied in a 105 mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution (NDC 70127-100-01). Each mL contains 100 mg of cannabidiol. EPIDIOLEX is packaged in a carton with two 5 mL calibrated oral dosing syringes and a bottle adapter (NDC 70127-100-10). The pharmacy will provide 1 mL calibrated oral dosing syringes when doses less than 1 mL are required.

16.2 Storage and Handling

Store EPIDIOLEX in an upright position at 20°C to 25°C (68°F to 77°F); excursions are permitted between 15°C to 30°C (59°F to 86°F) *[see USP Controlled Room Temperature]*. Do not freeze. Keep the cap tightly closed. Use within 12 weeks of first opening the bottle, then discard any remainder.

17 PATIENT COUNSELING INFORMATION

Advise the caregiver or patient to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Information

Advise patients who are prescribed EPIDIOLEX to use the adapter and oral dosing syringes provided *[see Dosage and Administration (2.4) and Instructions for Use]*.

Instruct patients to discard any unused EPIDIOLEX oral solution after 12 weeks of first opening the bottle *[see Dosage and Administration (2.4)]*.

Hepatocellular Injury

Inform patients about the potential for elevations of liver enzymes. Discuss with the patient the importance of measuring hepatic laboratory values and having them evaluated by the healthcare provider before treatment with EPIDIOLEX and periodically during treatment *[see Warnings and Precautions (5.1)]*.

Advise patients of the clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine) and to contact a healthcare provider promptly if these signs or symptoms occur.

Somnolence and Sedation

Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that EPIDIOLEX does not affect them adversely (e.g., impair judgment, thinking or motor skills) *[see Warnings and Precautions (5.2)]*.

Suicidal Thinking and Behavior

Counsel patients, their caregivers, and their families that antiepileptic drugs, including EPIDIOLEX, may increase the risk of suicidal thoughts and behavior and advise them to be alert for the emergence or worsening of symptoms of depression, any unusual changes in mood or behavior, or the emergence of suicidal thoughts, behavior, or thoughts of self-harm. Instruct patients, caregivers, and families to report behaviors of concern immediately to healthcare providers *[see Warnings and Precautions (5.3)]*.

Withdrawal of Antiepileptic Drugs (AEDs)

Advise patients not to discontinue use of EPIDIOLEX without consulting with their healthcare provider. EPIDIOLEX should normally be gradually withdrawn to reduce the potential for increased seizure frequency and status epilepticus *[see Dosage and Administration (2.5), Warnings and Precautions (5.4)]*.

Pregnancy Registry

Advise patients to notify their healthcare provider if they become pregnant or intend to become pregnant during EPIDIOLEX therapy. Encourage women who are taking EPIDIOLEX to enroll in the North

American Antiepileptic Drug (NAAED) Pregnancy Registry if they become pregnant. This registry is collecting information about the safety of antiepileptic drugs during pregnancy *[see Use in Specific Populations (8.1)]*.

Drug Testing

Advise patients of the potential for positive cannabis drug screens.

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MEDICATION GUIDE
EPIDIOLEX® (EH-peh-DYE-oh-lex)
(cannabidiol)
oral solution

Read this Medication Guide before you start taking EPIDIOLEX and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

What is the most important information I should know about EPIDIOLEX?

EPIDIOLEX can cause serious side effects, including:

1. EPIDIOLEX may cause liver problems. Your healthcare provider may order blood tests to check your liver before you start taking EPIDIOLEX and during treatment. In some cases, EPIDIOLEX treatment may need to be stopped. Call your healthcare provider right away if you develop any of these signs and symptoms of liver problems during treatment with EPIDIOLEX:
   - loss of appetite, nausea, vomiting
   - fever, feeling unwell, unusual tiredness
   - yellowing of the skin or the whites of the eyes (jaundice)
   - itching
   - unusual darkening of the urine
   - right upper stomach area pain or discomfort
2. EPIDIOLEX may cause you to feel sleepy, which may get better over time. Using certain medicines with EPIDIOLEX such as clobazam or alcohol may increase sleepiness. **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you.
3. Like other antiepileptic drugs, EPIDIOLEX may cause suicidal thoughts or actions in a very small number of people, about 1 in 500.

   Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you:
   - thoughts about suicide or dying
   - attempt to commit suicide
   - new or worse depression
   - new or worse anxiety
   - feeling agitated or restless
   - panic attacks
   - trouble sleeping (insomnia)
   - new or worse irritability
   - acting aggressive, being angry, or violent
   - acting on dangerous impulses
   - an extreme increase in activity and talking (mania)
   - other unusual changes in behavior or mood

   How can I watch for early symptoms of suicidal thoughts and actions?
   - Pay attention to any changes, especially sudden changes in mood, behaviors, thoughts, or feelings.
   - Keep all follow-up visits with your healthcare provider as scheduled.
4. Do not stop taking EPIDIOLEX without first talking to your healthcare provider. Stopping a seizure medicine such as EPIDIOLEX suddenly can cause you to have seizures more often or seizures that do not stop (status epilepticus).

Call your healthcare provider between visits as needed, especially if you are worried about symptoms.

What is EPIDIOLEX?

- EPIDIOLEX is a prescription medicine that is used to treat seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in people 1 year of age and older.
- It is not known if EPIDIOLEX is safe and effective in children under 1 year of age.

Who should not take EPIDIOLEX?

Do not take EPIDIOLEX if you are allergic to cannabidiol or any of the ingredients in EPIDIOLEX. See the end of this Medication Guide for a complete list of ingredients in EPIDIOLEX.

Before taking EPIDIOLEX, tell your healthcare provider about all of your medical conditions, including if you:

- have or have had depression, mood problems or suicidal thoughts or behavior.
- have liver problems.
- have abused or been dependent on prescription medicines, street drugs or alcohol.
- are pregnant or plan to become pregnant. Tell your healthcare provider right away if you become pregnant while taking EPIDIOLEX. You and your healthcare provider will decide if you should take EPIDIOLEX while you are pregnant.
  - If you become pregnant while taking EPIDIOLEX, talk to your healthcare provider about registering with the North American Antiepileptic Drug Pregnancy Registry. You can enroll in this registry by calling 1-888-233-2334. The purpose of this registry is to collect information about the safety of antiepileptic medicines during pregnancy.
- are breastfeeding or plan to breastfeed. It is not known if EPIDIOLEX passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby while taking EPIDIOLEX.

Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, herbal supplements, and any cannabis-based products.

EPIDIOLEX may affect the way other medicines work, and other medicines may affect how EPIDIOLEX works. Do not start or stop taking other medicines without talking to your healthcare provider. Know the medicines you take. Keep a list of them to show your healthcare provider and pharmacist when you get a new medicine.

Tell your healthcare provider if you are planning to have a cannabis drug screen because EPIDIOLEX may affect your test results. Tell the person giving the drug test that you are taking EPIDIOLEX.

How should I take EPIDIOLEX?

- Read the **Instructions for Use** at the end of this Medication Guide for information on the right way to use EPIDIOLEX.
- Take EPIDIOLEX exactly as your healthcare provider tells you.
- Your healthcare provider will tell you how much EPIDIOLEX to take and when to take it.
- Measure each dose of EPIDIOLEX using the bottle adapter and 5 mL dosing syringes that come with EPIDIOLEX. If your dose of EPIDIOLEX is less than 1 mL, your pharmacist will provide you with 1 mL syringes to take your medicine.
- Use a dry syringe each time you take EPIDIOLEX. If water is inside the syringe, it could cause the oil-based medicine to look cloudy.

What should I avoid while taking EPIDIOLEX?

- **Do not** drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you. EPIDIOLEX may cause you to feel sleepy.

What are the possible side effects of EPIDIOLEX?

EPIDIOLEX can cause serious side effects, including:

- See "**What is the most important information I should know about EPIDIOLEX?**"

The most common side effects of EPIDIOLEX include:

- sleepiness
- decreased appetite
- diarrhea
- increase in liver enzymes
- feeling very tired and weak
- rash
- sleep problems
- fever
- vomiting
- infections

These are not all of the possible side effects of EPIDIOLEX. For more information ask your healthcare provider or pharmacist.

Tell your healthcare provider about any side effect that bothers you or that does not go away.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

You may also contact Greenwich Biosciences at 1-833-424-6724 (1-833-GBIOSCI).

How should I store EPIDIOLEX?

- Store EPIDIOLEX at room temperature between 68ºF to 77ºF (20ºC to 25ºC).
- Always store EPIDIOLEX in an upright position.
- **Do not** freeze.
- Keep the child-resistant cap tightly closed.
- Use EPIDIOLEX within 12 weeks of first opening the bottle. Throw away (dispose of) any unused medicine after 12 weeks.

Keep EPIDIOLEX and all medicines out of the reach of children.

General Information about the safe and effective use of EPIDIOLEX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use EPIDIOLEX for a condition for which it was not prescribed. Do not give EPIDIOLEX to other people, even if they have the same symptoms that you have. It may harm them.

You can ask your pharmacist or healthcare provider for information about EPIDIOLEX that is written for health professionals.

What are the ingredients in EPIDIOLEX?

Active ingredient: cannabidiol

Inactive ingredients: dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose

EPIDIOLEX does not contain gluten (wheat, barley or rye).

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For more information, go to www.EPIDIOLEX.com or call 1-833-424-6724 (1-833-GBIOSCI).

This Medication Guide has been approved by the U.S. Food and Drug Administration Revised:07/2020

INSTRUCTIONS FOR USE
EPIDIOLEX® (EH-peh-DYE-oh-lex)
(cannabidiol)
oral solution
100 mg/mL

Be sure that you read, understand and follow these instructions carefully to ensure proper dosing of the oral solution.

Important:

- Follow your healthcare provider's instructions for the dose of EPIDIOLEX to take or give.
- Ask your healthcare provider or pharmacist if you are not sure how to prepare, take, or give the prescribed dose of EPIDIOLEX.
- Always use the oral syringe provided with EPIDIOLEX to make sure you measure the right amount of EPIDIOLEX.
- Do not use EPIDIOLEX after the expiration date on the package and each bottle.
- Use EPIDIOLEX within 12 weeks of first opening the bottle.
- After 12 weeks, safely throw away (dispose of) any EPIDIOLEX that has not been used.

Each package contains:

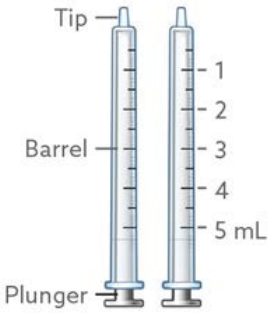
Child-resistant cap

Bottle adapter

1 bottle of EPIDIOLEX oral solution (100 mg/mL)

2 reusable 5 mL oral syringes:

- 1 syringe to take or give the dose of EPIDIOLEX
- 1 extra syringe (included as a spare if needed)



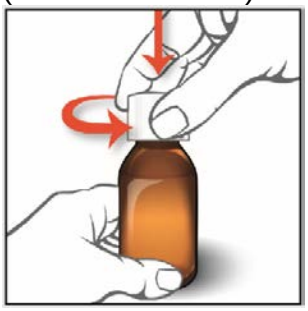
Supplies not included in the package:

- **If your dose of EPIDIOLEX is less than 1 mL**, your pharmacist will provide you with 1 mL syringes to take your medicine.
- Call your pharmacist right away if your dose of EPIDIOLEX is less than 1 mL and you do not receive 1 mL syringes with your medicine.

Note: If you lose or damage an oral syringe, or cannot read the markings, use the spare syringe.

Prepare The Bottle- to use EPIDIOLEX for the first time

1. Remove the child-resistant cap by pushing down while turning the cap to the left (counter-clockwise).



2. Push the bottle adapter firmly into the bottle. **Make sure the bottle adapter is fully inserted**. If not fully inserted, small parts such as the bottle adapter may become a choking hazard for children and pets.

   Note: **Do not** remove the bottle adapter from the bottle after it is inserted.

Prepare The Dose

Your healthcare provider will tell you how much EPIDIOLEX to take or give.

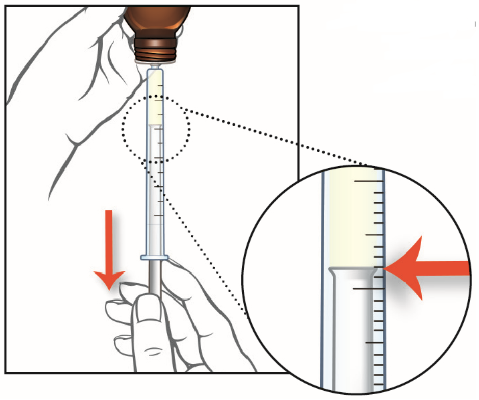
3. Use this table to measure the total dose of EPIDIOLEX to be given.

Dose	**How to measure**
5 mL or less	Use the oral syringe **1 time**
More than 5 mL	Use the oral syringe more than 1 time

4. Push the plunger all the way down and insert the tip of the oral syringe fully into the bottle adapter. With the oral syringe in place, turn the bottle upside down.

5. Slowly pull the plunger of the oral syringe to withdraw the dose of EPIDIOLEX needed. See **Step 3** for how to measure the total dose of EPIDIOLEX.

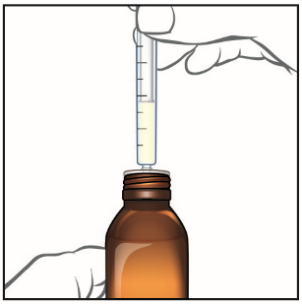
Line up the end of the plunger with the marking for your dose of EPIDIOLEX.



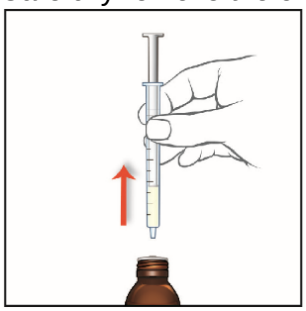
What to do if you see air bubbles:

If there are air bubbles in the oral syringe, keep the bottle upside down and push the plunger so that all of the liquid flows back into the bottle. Repeat **Step 5** until the air bubbles are gone.

6. When you have measured the correct dose of EPIDIOLEX, leave the oral syringe in the bottle adapter and turn the bottle right side up.

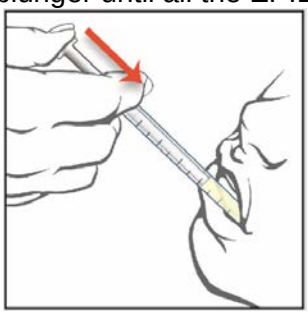


7. Carefully remove the oral syringe from the bottle adapter.



Give EPIDIOLEX

8. Place the tip of the oral syringe against the inside of the cheek and gently push the plunger until all the EPIDIOLEX in the syringe is given.



Do not forcefully push on the plunger.

Do not direct the medicine to the back of the mouth or throat. This may cause choking.

If the dose of EPIDIOLEX prescribed by the healthcare provider is more than 5 mL, repeat **steps 4 through 8** to complete the dose.

For example:

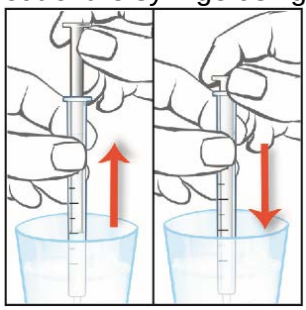
If your dose of EPIDIOLEX is 8 mL, withdraw 5 mL of medicine into the syringe and give the medicine. Insert the tip of the oral syringe back into the bottle adapter and withdraw 3 mL of medicine. Give the medicine to receive a total dose of 8 mL.

Clean Up

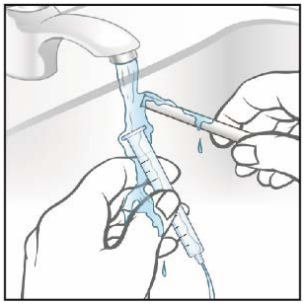
9. Screw the child-resistant cap back on the bottle tightly by turning the cap to the right (clockwise).

Do not remove the bottle adapter. The cap will fit over it.

10. Fill a cup with warm soapy water and clean the oral syringe by drawing water in and out of the syringe using the plunger.



11. Remove the plunger from the barrel of the oral syringe and rinse both parts under tap water.



Do not wash the oral syringe in the dishwasher.

12. Shake off any extra water from the plunger and oral syringe barrel, and allow them to air dry until next use.

Make sure the oral syringe is completely dry before the next use. If water is inside the syringe, it could cause the oil-based medicine to look cloudy.

Do not throw away the oral syringe.

How should I store EPIDIOLEX?

- Store EPIDIOLEX at room temperature between 68°F to 77°F (20°C to 25°C).
- Always store EPIDIOLEX in an upright position.
- **Do not** freeze.
- Keep the child-resistant cap tightly closed.
- Use EPIDIOLEX within 12 weeks of first opening the bottle. Dispose of any unused EPIDIOLEX after 12 weeks.
- **Keep EPIDIOLEX and all medicines out of the reach of children.**

Helpline Details

For additional assistance, call the toll-free helpline at 1-833-426-4243 (1-833-GBNGAGE).

Hours:
Monday-Friday 08:00am – 08:00pm EST

Frequently Asked Questions

Q: What if there are air bubbles in the oral syringe?

A: Push the liquid back into the bottle and repeat **Step 5** until the air bubbles are gone.

Q: What should I do if the liquid in the bottle has turned cloudy?

A: The liquid in the bottle may turn cloudy if water gets in the bottle. This does not change the safety or how well the medicine works. Continue to use the cloudy liquid as prescribed by your healthcare provider.

Always make sure the oral syringes are completely dry before each use.

Q: What should I do if the oral syringe is not completely dry before use?

A: If the oral syringe is not completely dry, use the spare syringe provided in the pack.

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This Instructions for Use has been approved by the U.S. Food and Drug Administration.

Revised: 04/2020

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

SUMMARY REVIEW

Summary Review

Date	July 31, 2020
From	Philip H. Sheridan, MD Nick Kozauer, MD
Subject	Summary Review
NDA/BLA # and Supplement#	NDA 210365 Suppl 05, 06, 07
Applicant	GW Pharmaceuticals PLC
Dates of Submission	January 31, 2020 (S05) January 31, 2020 (S06) April 6, 2020 (S07)
PDUFA Goal Dates	July 31, 2020 (S05) July 31, 2020 (S06) October 6, 2020 (S07)
Proprietary Name	Epidiolex
Established or Proper Name	Cannabidiol
Dosage Form(s)	Oral solution (100 mg/mL)
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with Dravet syndrome, Lennox Gastaut syndrome, and tuberous sclerosis complex in patients 1 year of age and older
Applicant Proposed Dosing Regimen(s)	(b) (4)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Epidiolex is indicated for the treatment of seizures associated with Dravet syndrome, Lennox Gastaut syndrome, and tuberous sclerosis complex in patients 1 year of age and older
Recommended Dosing Regimen(s) (if applicable)	For Dravet syndrome (DS) and Lennox Gastaut syndrome (LGS): 10 to 20 mg/kg/day (divided BID); For tuberous sclerosis complex (TSC): 25 mg/kg/day (divided BID) .

1. Benefit-Risk Assessment

Benefit-Risk Assessment Framework

Benefit-Risk Integrated Assessment

Cannabidiol (CBD) [proprietary name Epidiolex] is a cannabinoid prepared from the *Cannabis Sativa* L. plant and is structurally unrelated to other currently marketed antiepileptic drugs. It is currently indicated for the treatment of seizures in patients with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) in patients 2 years of age, and older. CBD is an oral solution given twice daily by mouth.

Tuberous sclerosis complex (TSC) is a genetic disorder characterized by the widespread development of nonmalignant tumors in multiple organs. Seizures are the most common neurological manifestation and most frequent presenting feature of TSC, with infantile spasms the most common seizure type at initial diagnosis. The seizures usually present early in childhood and are frequently resistant to medications and other treatments. Cognitive impairment is also a primary clinical feature of TSC. Early management of seizures is important, as it may prevent or mitigate the cognitive and neuropsychiatric impairment associated with epileptic encephalopathy. Patients with TSC are almost always significantly disabled by their seizures and cognitive impairment. There is one approved seizure treatment for patients with TSC(everolimus).

The efficacy of CBD for treatment of seizures associated with TSC was demonstrated in a single randomized clinical trial (Study 1521). There is evidence of clinical benefit based on reduction of monthly TSC-associated seizure frequency. Other outcome measures were supportive.

CBD at 25 and 50 mg/kg/day demonstrated reduction in TSC-associated seizures as compared to placebo. Patients had median baseline seizure frequency ranging from 54 to 61 TSC-associated seizures/month. The patients in the CBD groups had approximately 43 and 36% reductions in monthly TSC-associated seizure frequency, respectively, compared to 20% in the placebo group. Additionally, patients in the CBD groups had greater reductions in total seizure frequency and impression of improvement based upon a patient/caregiver assessment. A greater proportion of patients in the CBD groups were considered responders (50% reduction in seizure frequency). Because of hierarchical testing, many of the secondary efficacy endpoints were considered nominally but not statistically significant. There was no added benefit of the 50 mg/kg/day dose when compared to the 25 mg/kg/day dose.

Risks identified in the clinical safety data include liver injury; somnolence; decreased appetite, decreased weight, and weight loss; and rash. Liver injury may be monitored with baseline and interval lab tests. Somnolence and rash are observable and decreased appetite with weight loss may be observed and measured. When necessary, an intervention of CBD dose reduction or discontinuation can take place. There were additional safety findings at the 50 mg/kg/day dose; therefore, in the context of the lack of any added benefit of the 25 mg/kg/day dose, only the 25 mg/kg/day dose will be approved for the treatment of seizures associated with TSC in patients 1 year of age, and older.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Tuberous sclerosis complex (TSC) is a genetic disorder characterized by widespread development of nonmalignant tumors in multiple organ systems, including the brain, heart, skin, eyes, kidney, lung, and liver. It presents during childhood and is characterized neurologically by nonmalignant brain tumors, refractory epilepsy, cognitive impairment, and behavioral disorders. The epilepsy associated with TSC is a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities. • Epilepsy is reported in 80-90% of patients with TSC. Onset of epilepsy in patients with TSC typically occurs in the first year of life. Many patients (44-65%) have evidence of delayed intellectual development, and severity of patients' cognitive and behavior impairments vary from minimally affected (rare) to profoundly impaired. Cognitive impairment is more frequently seen in patients with TSC and refractory epilepsy. • A variety of seizure types are reported in patients with TSC and epilepsy. Refractory epilepsy is reported in 60% of patients with TSC, regardless of AED or other epilepsy treatments.	TSC is a serious disease. Seizures are a prominent manifestation of the condition and can result in severe morbidity and, rarely, mortality.
Current Treatment Options	• The primary objective of treatment of seizures in patients with TSC is reduction in frequency of the most incapacitating and injurious seizures (e.g., tonic-clonic seizures, focal seizures with or without alteration in awareness, and secondarily generalized seizures). • One drug is approved for reduction of seizures in patients with TSC: everolimus. Many other drugs are used to treat seizures in patients with TSC, especially valproic acid (which is generally considered a first-line agent) clobazam, vigabatrin, and levetiracetam. Seizures in TSC are often resistant to antiepileptic drugs (AEDs) (even when used as polytherapy) and complete seizure control with resolution of intellectual and psychosocial dysfunction is infrequently achieved.	One drug has been shown in controlled clinical trials to reduce seizures in patients with TSC. Other drugs are used off-label. Yet even when taking multiple AEDs, most patients still have frequent seizures. No AEDs have been shown to alter the cognitive impairment in patients with TSC. Serious and severe adverse drug effects have been reported with the approved drug and all the commonly-used drugs and must be

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Severe adverse drug reactions are reported with everolimus (pneumonitis, stomatitis, infections).	considered when choosing an AED treatment, especially in children and adolescents. The treatment armamentarium in TSC would benefit from therapeutic options that are more efficacious and potentially better tolerated. A drug that is better tolerated may improve compliance.
Benefit	• One pivotal trial (Study 1521) demonstrated the efficacy of CBD given orally (25 and 50 mg/kg/day) in patients with TSC. The primary endpoint the percentage reduction in TSC-associated seizure frequency from baseline to treatment period as compared to placebo. In Study 1521, CBD reduced the median seizure frequency by approximately 43% in the 25 mg/kg group, 36% in the 50 mg/kg group, as compared to 20% in the placebo group placebo. • Three key secondary endpoints favored CBD over placebo and were nominally significant for both CBD dose groups except for proportion of 50% responders in the 25 mg/kg group. These findings were generally consistent with the findings of the primary endpoint. These key secondary endpoints assessed the proportion of patients who were 50% responders, the percentage change in total seizure frequency from baseline to treatment period and the Subject/Caregiver Global Impression of Change.	CBD 25 mg/kg/day and 50 mg/kg/day were both found to be effective in reducing TSC-associated seizure frequency in patients with TSC. The treatment effect was robust statistically and clinically meaningful. Fewer seizures in these patients may lead to fewer injuries and days of disability. The benefit of treatment with CBD on seizures in patients with TSC is persuasive, justifies the modest and manageable risk) and justifies approval of the 25 mg dose; the 50 mg dose did not give additional therapeutic benefit and had a higher incidence of adverse events.
Risk and Risk Management	• Liver injury ○ 32% of patients in the pooled 25 mg/kg/day and 50 mg/kg/day CBD treatment group and 0% of patients in placebo (PBO) group had liver-related TEAEs (all but one were elevations in liver tests). A dose-response relationship was evident with 25% and 38% in the 25 mg/kg and 50 mg/kg groups, respectively. ○ Elevated transaminases were the most frequently reported treatment emergent adverse events (TEAE) in the 25 mg/kg group and 2nd in	Elevations of transaminases were at times very high and led to discontinuation of treatment. This adverse effect may be monitored. There is already a warning in the label. Depression of appetite and weight loss may be severe and require discontinuation of treatment. This may be monitored.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	the 50 mg/kg group. ○ 6 patients had liver-related serious adverse events (SAEs) (2 in the 25 mg/kg group and 4 in the 50 mg/kg group). ○ 4 patients in the 50 mg/kg group discontinued early due to liver test abnormalities. ○ Alanine aminotransferase (ALT) >3x the upper limit of normal (ULN) reported in 9 patients (12%), 18 patients (25%), and 0 patients in the 25 mg/kg, 50 mg/kg, and PBO groups, respectively. ALT >5x ULN reported in 7%, 11%, and 0%. ○ Concomitant VPA a risk factor for increased ALT by ~6x. • Decreased appetite/weight decreased ○ Decreased appetite: 20% of patients in 25 mg/kg group, 23% of the 50 mg/kg group, compared to 12% in PBO. ○ Weight decreased: 7%, 8%, and 0%, of patients in the 25 mg/kg, 50 mg/kg, and PBO groups, respectively. 1 patient discontinued early due to weight decreased TEAE (25 mg/kg). • Weight loss ○ Measured weight loss during the controlled trials: 16% of each of the CBD groups and 4% of the PBO group lost ≥7% of their baseline weight by the final visit of the controlled studies. • Rash ○ Reported in 8%, 11%, and 4% of patients in the 25 mg/kg, 50 mg/kg, and PBO groups, respectively. ○ Seen in 7% of patients in the OLE phase. ○ Most common reason for early discontinuation: 5% in 25 mg/kg group and 7% in 50 mg/kg group, compared to 0 in PBO. • Somnolence ○ 13% of 25 mg/kg and 26% of 50 mg/kg groups reported, compared to 9% in PBO. ○ Led to discontinuation in 2 patients in the 50 mg/kg group.	Rash was at times serious or severe and led to discontinuation in some patients. It is observable and may be monitored. Somnolence, sedation, and lethargy are effects of central nervous system depression seen frequently in antiseizure drug treatment. These are generally reversible upon discontinuation of treatment. This adverse reaction may be monitored.

2. Background

Cannabidiol (CBD) [proprietary name Epidiolex] is currently marketed in the US as an oral solution of 100 mg/ml for the following indications: treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older.

The efficacy supplements discussed in this review (05 and 06) propose a new indication for CBD, the treatment of seizures associated with tuberous sclerosis complex in (TSC) patients 1 year of age and older. They also propose to expand the age ranges for the currently-approved indications for LGS and DS to include younger pediatric patients 1 to less than 2 years of age.

(b) (4)

Supplement 06 also includes the final study report for Study 1424, a second safety and efficacy study with DS patients, which provides additional safety data for the DS population and which is discussed in Section 8 of this summary review.

Supplement 07 is a Changes Being Effected (CBE) supplement concerning the recent decision of the Drug Enforcement Agency that CBD is no longer controlled under the Controlled Substances Act. This is addressed in Section 13 of this summary review.

The applicant received orphan designation in April 2016 for the development program for seizures associated with TSC.

Supplements 05 and 06 were reviewed under a priority review timeline as they proposed dosing down to age 1 year for the TSC, DS, and LGS populations, which addressed an unmet medical need in each of the respective populations (i.e., the current LGS/DS indication for CBD is down to 2 years of age, as is the indication for everolimus in TSC).

3. Product Quality

No review was written by the Office of Product Quality (OPQ) review team since no new chemistry, manufacturing, and control (CMC) data were submitted.

4. Nonclinical Pharmacology/Toxicology

No review was written by the nonclinical pharmacology/toxicology review team since no new nonclinical data were submitted.

5. Clinical Pharmacology

An integrated Office of Clinical Pharmacology (OCP) review was written by Dr. Jagan Parepally (clinical pharmacology reviewer), Dr. Angela Men (clinical pharmacology team lead), Dr. Michael Bewernitz (pharmacometrics reviewer), and Dr. Atul Bhattaram (pharmacometrics team lead).

The clinical pharmacology of CBD was previously described in the clinical pharmacology review of the original NDA submission.

The application included exploratory exposure-response analyses for both safety and efficacy from Study 1521 in TSC; however, the OCP review notes a number of deficiencies in these analyses that make them uninformative. Additionally, efficacy and safety information for the sought indication are adequately derived from the clinical efficacy and safety data. Therefore, these analyses were not considered as part of the OCP review.

(b) (4)

6. Clinical Microbiology

Not applicable.

7. Clinical/Statistical- Efficacy

Dr. Jinnan Liu was the biometrics reviewer and Dr. Kun Jin was the biometrics team lead. Dr. Natalie Getzoff was the clinical reviewer.

TSC Efficacy Trial (Study 1521)

The effectiveness of CBD for the treatment of seizures associated with TSC was demonstrated in Study 1521, a randomized, double-blind, placebo-controlled trial of CBD as add-on therapy with TSC patients 1 to 65 years of age.

Study 1521 (N=224) compared doses of CBD 25 mg/kg/day and 50 mg/kg/day with placebo.

During the 4-week baseline period, patients were required to have at least 8 seizures, with at least 1 seizure occurring in at least 3 of the 4 weeks (seizure types acceptable for this purpose included focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures [tonic–clonic, tonic, clonic or atonic seizures]). The baseline median TSC-associated seizure frequency was 57 per 28 days for the combined groups.

The baseline period was followed by a 4-week titration period (with dosing initiated at 5 mg/kg/day and increased by 5 mg/kg/day every other day until the target dose of 25 or 50 mg/kg/day was reached) and a 12-week maintenance period.

The primary efficacy measure was the change in seizure frequency per 28 days of TSC-associated seizures over the 16-week treatment period (titration and maintenance periods) compared with baseline.

Efficacy analyses were based on the mITT population, which included the 224 patients who were randomized, received CBD or placebo in the study and had post-baseline efficacy data, and were analyzed according to their randomized treatment group.

Efficacy Results

Of the 224 subjects in the mITT population, the majority were men (58.1%), White (89.6%), and the mean age was 13.66 (1 to 57) years. The three treatment groups were balanced for these baseline demographic characteristics. All patients but 1 (in the CBD 25 mg/kg/day group) were taking 1-2 concomitant antiepileptic drugs (AEDs) during the trial. The most commonly used concomitant AEDs (greater than 25%) were valproate (45%), vigabatrin (33%), levetiracetam (29%), and clobazam (27%). The baseline median TSC-associated seizure frequency was 57 per 28 days for the combined groups.

In the applicant's study report for Study 1521, the primary endpoint [percentage change from baseline in TSC-associated seizure frequency (28-day average) during the treatment period] was analyzed using a negative binomial regression (NBR) model, giving the results shown in the Table 1 below.

Table 1: Change in TSC-Associated Seizure Frequency during the Treatment Period (Study 1521)

Total TSC-Associated Seizures	Placebo	CBD 25 mg/kg/day	CBD 50 mg/kg/day
Study 1521	N=76	N=75	N=73
Baseline Estimated Mean Seizure Rate	55	52	66
Treatment Estimated Mean Seizure Rate	40	27	35
Percentage Change from Baseline During Treatment in Estimated Mean Seizure Rates[a]	−27	−49	−48
p-value compared to placebo[b]		0.0009	0.0018

[a]Estimated from a negative binomial regression model.
[b]Obtained from negative binomial regression model.

However, the biometrics review team does not agree that the negative binomial regression is an appropriate method for this trial for the following reasons:

1. The previous efficacy studies (Study 1, 2, and 3 in labeling) that led to the approval of this CBD for other closely related seizure indications (DS and LGS) used the Wilcoxon rank-sum test with Hodges-Lehmann p-value. Seizure count data usually has rather large variations and seizure trials usually have relatively small to medium sample sizes; therefore, a non-parametric approach such as the Wilcoxon rank sum test is generally more appropriate.

2. The negative binomial mixed effects repeated measure model proposed by the applicant contains more than 10 parameters; it may or may not converge numerically to produce any results for a trial of small to medium size. The interpretation (clinical meaning) of the interaction terms in the model is problematic. It is common to add or lose a few terms/covariates from the model just to allow it to converge, which is acceptable for the purpose of exploring the data, which is why such method is more often used in the exploratory phase such as for Phase 2 study, but not for a Phase 3 study.

3. The Agency raised concerns about the negative binomial regression in the pre-NDA meeting and asked the applicant to "Please include a discussion of whether the assumptions of the negative binomial regression for the primary analysis are met."

   However, the applicant did not address the Agency's concern directly. The document (Module 5.3.5.3) submitted by the applicant as part of the NDA efficacy supplement was mainly on the goodness of fit of the overall model, and the residual QQ plot to show normality; both are data driven instead of "clinical meaning -based".

4. Numerically, for the same study data, the negative binomial regression model produced a much smaller p value comparing to the Hodges–Lehmann p value (b) (4) . A very small p value may appear to be

stronger evidence of efficacy although it might be merely a result of an overfitted model.

Therefore, the biometrics review team has calculated the efficacy findings using both Wilcoxon analyses as well as a log-ANCOVA (Tables 2 and 3).

Table 2: Primary Endpoint Analyses- Wilcoxon Rank Sum Test – ITT - Study 1521

	CBD 25 mg/kg/day N=75	**50 mg/kg/day N=73**	**Placebo N=76**
TSC – associated Seizures			
Baseline Period Median	56 (21.24, 101)	61 (36, 117)	54.04 (26.42, 102)
Treatment Period Median	32.35 (8.99, 56)	31.25 (13.63, 81.87)	41.06 (17.35, 76.12)
Median Percentage Change from Baseline (Q1, Q3)	-43.36 (-67.81, -13.64)	-36.55 (-67.03, -5.53)	-20.08 (-47.06, 3.05)
Estimated Median Difference (CI) *	-18.77 (-31.32, -6.28)	-16.95 (-29.51, -4.45)	
Hodges–Lehmann P-value by Wilcoxon rank-sum test	.0038	.0094	-

Source: FDA statistical reviewer's analysis and applicant's analysis Table 8.2.2

Table 3: Primary Endpoint Analyses-Log-transformed ANCOVA Analysis– ITT - Study 1521 (25 mg/kg/day dose only)

Total TSC-Associated Seizures (per 28 Days)	**Placebo**	**EPIDIOLEX 25 mg/kg/day**
	N=76	N=75
Baseline Period Median Seizure Frequency	54	56
Percentage Change from Baseline During Treatment in Estimated Mean Seizure Frequency	−24	−48
p-value compared to placebo		<0.01

These findings were both consistent with each other and the applicant's primary efficacy analysis using the NBR method, and they all support the efficacy of CBD for the treatment of seizures associated with TSC at the studied doses. (b) (4)

In both of the preceding analyses, there was no additional efficacy benefit of the 50 mg/kg/day dose compared to the 25 mg/kg/day dose.

In Study 1521, 4 of 75 (5%) patients treated with CBD 25 mg/kg/day reported no TSC-associated seizures during the maintenance period, compared to 0 patients in the placebo group.

Key Secondary Endpoints

As. Dr. Liu notes in her review, the following key secondary endpoints were analyzed in a prespecified hierarchical manner:

- Proportion of patients with a 50% reduction in TSC-associated seizures (50% responders)
- Subject/Caregiver Global Impression of Change (S/CGIC)
- Change in total seizure frequency

Because the results of the first key secondary endpoint (50% reduction from baseline in the 25 mg/kg group compared to placebo) did not achieve statistical significance, all subsequent analyses were reported as nominally significant. However, all of the key secondary endpoints numerically favored CBD (both groups) over placebo and are generally supportive of the primary efficacy endpoint as shown in Table 4.

Table 4: Analyses of the Key Secondary Endpoints (Study 1521)

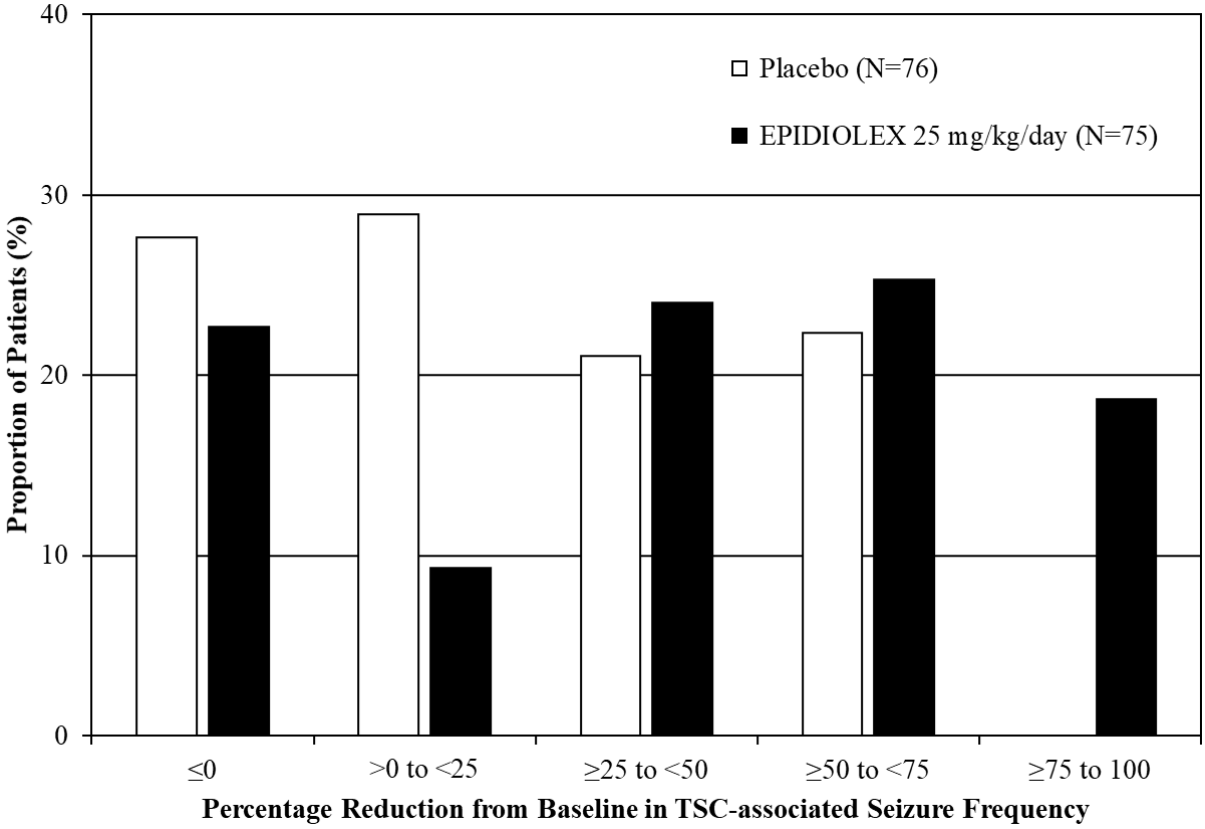
Variable	25 mg/kg/day (N=75)	50 mg/kg/day (N=73)	Placebo (N=76)
≥ 50% Reduction in Drop Seizure Frequency			
n (%)	27 (36.0)	29 (39.7)	17 (22.4)
Odds Ratio (95% CI)	1.95 (0.95, 4.00)	2.29 (1.12, 4.67)	
Nominal p-value[1]	0.0692	0.0245 (nominal)	
Subject/Caregiver Global Impression of Change Score at the Last Visit			
Mean	3.0	3.2	3.6
Odds Ratio (95% CI)	2.25 (1.24, 4.07)	1.77(0.98, 3.20)	
Nominal p-value[2]	0.0074	0.0580	
Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period			
Baseline (median)	56.00	70.00	56.48
Treatment (median)	32.96	32.25	44.03
Median Percentage Change During Treatment (95%CI)	−34.5 (−58.2, 0.5)	−33.3 (−58.3, −3.9)	−14.11 (−37.6, −2.5)
Estimated Percentage Reduction (95%CI)	−48.1 (39.8, 55.3)	−47.6 (39.3, 54.8)	−26.9 (15.4, 36.8)
Nominal p-value[3]	0.0013	0.0018	

Source: Table 8.4.1.2.1.3-1, Figure 8.4.1.2.1.2-2, and Table 9.3.1.2, Study 1521 CSR

1 - calculated using Cochran-Mantel-Haenszel test stratified by age group (1-6, 7-11, 12-17 and 18-65 years)
2 - calculated using ordinal logistic regression model with treatment group as a fixed factor
3 - calculated using a negative binomial regression model

Figure 1 displays the proportion of patients by category of seizure reduction from baseline in TSC-associated seizure frequency (per 28 days) during the treatment period in Study 1521.

Figure 1: Proportion of Patients by Category of Seizure Response for CBD and Placebo in Patients with TSC (Study 1521)



Applicant's Proposed Unified Dosing for DS, LGS, and TSC

(b) (4)

Therefore, we agree with Dr. Getzoff's conclusion that the recommended dosing in labeling for the treatment of seizures associated with TSC (i.e., 25 mg/kg/day) (b) (4)

(b) (4)

Efficacy Conclusion:

The applicant has provided substantial evidence of effectiveness to support the efficacy of CBD for the treatment of seizures associated with TSC in patients 1 year of age and older. The applicant provided data from a single adequate and well-controlled trial that demonstrated that CBD, as compared to placebo, reduces the frequency of seizures in patients with TSC. The applicant showed this effect for one dose (25 mg/kg/day). A higher dose (50 mg/kg/day) demonstrated no increased efficacy over the 25 mg/kg dose but did show some increased adverse effects in comparison to the 25 mg/kg/day dose. The treatment effect observed in these trials was comparable to what has been demonstrated with other approved drugs for seizures associated other epileptic encephalopathies. In addition, a single positive study is sufficient to support approval for this indication given the confirmatory evidence derived from the already established efficacy of CBD for the treatment of seizures in DS/LGS. Therefore, we agree with the biometrics and clinical reviewers that the efficacy data supports approval of CBD for the indication of seizures associated with TSC.

8. Clinical - Safety

Dr. Natalie Getzoff performed the clinical safety review of this application.

(b) (4)

Study 1521

To support the safety of CBD in the treatment of seizures associated with TSC in patients 1 year of age and older, the applicant has provided safety data primarily from one controlled efficacy trial (Study 1521) which included a long-term open-label extension (OLE) period.

Overall Patient Exposure:

The total number of unique TSC patients who were exposed to CBD during the TSC

development program prior to the cutoff date for the 120-day safety update (October 1, 2019) was 223 (one placebo patient in Study 1521 did not transition to the OLE phase). To support the new indication, the applicant performed safety analyses on Study 1521. The primary FDA safety analyses were also performed on the controlled safety population from Study 1521.

In Study 1521, 224 patients were enrolled and randomized into Study 1521 and received at least one dose of either CBD (n=148) or placebo (n=76) during the double-blind period. Mean duration of treatment with either dose of CBD during the blinded phase of Study 1521 was 102 days.

At the time of data cutoff for Study 1521 (26 Feb 2019), 223 patients with TSC had received at least one dose of CBD during Study 1521, and 88 patients had been exposed to CBD for at least 12 months at any dose. By the end of the cutoff for the 120-day Safety Update (October 1, 2019), 110 patients and 28 patients had been exposed to CBD for at least 1 year and at least 2 years, respectively.

In the context of a rare disease such as TSC, these exposures are adequate to allow for a clinical safety review of the application.

Deaths:

One patient (# (b) (6)) died during the OLE period of Study 1521. She was an 11-year-old girl with a history of idiopathic dilated cardiomyopathy, congestive heart failure, left ventricular hypertrophy, hypertension, and renal/cardiac involvement of her TSC. She was found dead in bed on day 74/75 of the OLE period of Study 1521. She had been randomized to the CBD 25 mg/kg/day group during the blinded portion of the trial, although the dose of CBD had been decreased to 10 mg/kg/day because of increased seizures and agitation on Day 19 of the OLE study and then increased to 20 mg/kg/day on Study Day 34. The cause of death was determined to be cardiopulmonary failure due to TSC.

Sixteen deaths occurred in the OLE study for DS/LGS (Study 1415) as of the cutoff date for the 120-day safety update (01 OCT 2019). Eight of these deaths were reviewed in the original NDA submission. The most frequently reported cause of death in these patients was sudden unexplained death in epilepsy (SUDEP), which occurred in 7 (0.8%) of patients. SUDEP is more commonly reported in pediatric patients with DS (and LGS to a lesser degree) than in the general epilepsy population. These deaths were not likely to be due to treatment with CBD.

We agree with Dr. Getzoff's conclusion that the incidences of death (and SUDEP) observed are consistent with the expected rates in patients with DS, LGS, and TSC.

Serious Adverse Events:

The overall incidence of treatment-emergent SAEs was 12.5% in the controlled safety population with a greater incidence in the pooled CBD group (18%) as compared to the placebo group (2%). The SAEs that occurred most frequently in the pooled CBD group was elevated hepatic enzymes, which was reported in 6 patients (4.1%). Five patients in the pooled CBD group experienced a serious TEAE of rash (3.4%), while 3 patients each (2%) experienced SAEs of gastroenteritis or seizure. The types and frequencies of SAEs reported in Study 1521 are similar to those seen in other trials of refractory epilepsy in pediatric patients, although the underlying reason for the imbalance between CBD and placebo in Study 1521 is unclear.

The nature and frequency of the observed SAEs are similar to those reported in other trials in pediatric patients with refractory epilepsy.

Discontinuations Due to Adverse Events:

A total of 18 patients in the pooled CBD group (12%) discontinued early because of adverse events from Study 1521 during the blinded phase, 8 (11%) and 10 (14%) in the 25 mg/kg and 50 mg/kg groups, respectively. No patients in the placebo group discontinued due to an adverse event. TEAEs leading to discontinuation which occurred in more than one patient included rash (n=9, 6.1%), hepatic enzyme increased (n=4, 2.7%), and somnolence/sedation (n=2, 1.4%). Nine of these events were adjudicated as serious and 6 as severe. Most patients who withdrew due to adverse events (n=11) did so during the titration period.

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

The most common adverse reactions that occurred in CBD-treated patients with TSC (incidence at least 10% at the recommended dosage and greater than placebo) were diarrhea; transaminase elevations; decreased appetite; somnolence; pyrexia; and vomiting.

Table 5 lists the adverse reactions that were reported in at least 3% of CBD-treated patients, and at a rate greater than those on placebo, in the placebo-controlled trial in TSC (Study 1521).

Table 5: Adverse Reactions in Patients Treated with CBD in Controlled Trial of TSC (Study 1521)

Adverse Reactions	**CBD 25 mg/kg/day**	**CBD 50 mg/kg/day**	**Placebo**
	N = 75 %	**N = 73 %**	**N = 76 %**
Hematological changes			
Anemia	7	4	1
Platelet count decreased	5	3	1
Eosinophil count increased	5	1	0
Hepatic Disorders			

Adverse Reactions	CBD 25 mg/kg/day	CBD 50 mg/kg/day	Placebo
	N = 75 %	N = 73 %	N = 76 %
Transaminases elevated	25		0
Gastrointestinal Disorders			
Diarrhea	31	38	25
Decreased appetite	20	23	12
Vomiting	17	18	9
Nausea	9	3	3
Gastroenteritis	8	8	7
Weight decreased	7	8	0
Nervous System Disorders			
Somnolence	13	26	9
Gait disturbance	9	7	5
Seizure	8	18	7
Fatigue, malaise, asthenia	5	5	1
Infections			
Ear infection	8	7	3
Urinary tract infection	5	1	0
Pneumonia	4	3	1
Other			
Pyrexia	19	16	8
Rash	8	11	4
Rhinorrhea	4	4	0

Adverse reactions were similar in pediatric and adult patients with TSC.

This pattern of TEAEs is largely consistent with those observed with many approved AEDs.

Safety Concerns of Special Interest:

Certain adverse events of special interest were specifically evaluated.

Hepatic TEAEs were of special interest due to the CBD-associated hepatocellular injury seen in the LGS and DS trials. In the controlled phase of Study 1521, transaminase elevations were reported as serious adverse events in 4% vs. 0% of patients in the CBD and placebo groups, respectively and led to discontinuation of approximately 4% of patients taking CBD during the blinded phase of Study 1521. For adverse events of any severity, elevated transaminases were reported in 25%, 38%, and 0% in patients taking CBD 25 mg, 50 mg, and placebo, respectively. The frequency of hepatic TEAEs in the OLE phase of Study 1521 was 18%, and it was 10% among patients combined from the American Expanded Access Program (EAP)

and the Australian Compassionate Access Scheme (CAS).

ALT elevations >3x upper limit of normal (ULN) were reported in 18% vs. 0% of subjects in the pooled 25 and 50 mg/kg day CBD groups and placebo groups, respectively, and >5x ULN in 7% and 1% of patients. For the 25 and 50 mg/kg/day doses, there was a clear dose-response with ALT >3x ULN reported in 12% of patients taking CBD 25 mg/kg and 25% of patients taking 50 mg/kg. A similar dose effect was seen in ALT >5x ULN (11% and 7%, respectively). Concomitant use of valproate increased the likelihood of significant ALT elevations by a factor of 5. There were no Hy's Law cases and no cases of overt hepatic failure.

During the controlled trial, somnolence (including sedation and lethargy) and fatigue (including malaise and asthenia) were reported notably more frequently in patients taking CBD (20% and 5%, respectively) than in patients taking placebo (9% and 1%, respectively). A dose response was seen with somnolence but not fatigue. Two patients in the 50 mg group discontinued participation in the study due to a TEAE of somnolence.

Rash occurred in 10% of CBD patients and 4% of placebo patients, leading to discontinuation in 9 patients (4 in the 25 mg/kg/day group and 5 in the 50 mg/kg/day group). 3% of patients in the pooled CBD group reported a SAE related to rash.

Review of adverse events in pediatric patients less than 2 years of age did not identify any new safety signal and the safety profile was reasonably similar to that of patients 2 years of age and older. Please see the additional discussion in Section 13 of the review with respect to the acceptability of the applicant's proposal to extend the currently approved indication for DS/LGS down to 1 year of age from 2 years of age.

Laboratory Findings:

In general, the shift values for hematology parameters were similar between CBD dose groups and placebo There was an imbalance between pooled CBD and pooled placebo groups with respect to reported TEAE of anemia, with 8 (5.4%) in the CBD group, compared to 1 (1.3%) patient in the placebo group. There was no apparent dose-response, as anemia was reported in a greater percentage of patients in the 25 mg/kg group (6.7%) than in the 50 mg/kg group (4.1%).

Serum chemistry values showed no clinically significant differences between CBD dose groups and placebo with the exception of the hepatic transaminase elevations discussed above in the Safety Concerns of Special Interest section of this summary review.

Vital Signs:

Vital signs including height, body weight, body mass index, respiratory rate, heart rate, systolic and diastolic blood pressure, and body temperature were monitored during Study

1521.

The most notable change from baseline was in weight. A larger percentage of patients on CBD had a clinically significant decreased in weight than placebo: 16.0%, 16.4% and 3.9% of patients in the 25 mg/kg, 50 mg/kg, and placebo groups, respectively, experienced a ≥7% reduction in weight from baseline at any time post-baseline.

Decreased weight, decreased appetite, and measured weight loss were seen in the previous pivotal trials in LGS and DS and are already described as adverse reactions in the current labeling.

Overdosage:

No overdoses were reported during the CBD development program.

Safety Conclusion:

The adverse event profile of CBD in the current application is consistent with that in the currently approved labeling.

CBD's most serious safety concern is the risk of liver injury. Although there were no Hy's Law cases and no patients in the development program developed acute liver failure, the program was modest in size. It remains possible that the drug could, in fact, cause severe acute and/or chronic liver injury in the marketed setting, when patient exposure markedly increases, and the magnitude of this risk is unknown. The currently approved labeling recommends monitoring of transaminases, including baseline and interval assessment, which should mitigate the risk of severe hepatic toxicity to some degree.

We agree with Dr. Getzoff that the risks associated with CBD for the treatment of seizures associated with TSC in patients 1 year of age and older are consistent with the approved product labeling for DS/LGS, and are acceptable, given the demonstrated benefit of significantly improved seizure control for the TSC patient population.

9. Advisory Committee Meeting

This application was not referred to an Advisory Committee for review because the clinical trial designs were acceptable, the efficacy findings were clear, and the safety profile was acceptable in light of the serious nature of the disease being treated.

10. Other Relevant Regulatory Issues

- No Good Clinical Practice (GCP) issues were identified in Dr. Getzoff' s clinical review.
- Dr. Getzoff concludes in her clinical review that the applicant has adequately disclosed financial interests/arrangements with clinical investigators.
- The Division of Medical Policy Programs (DMPP) (Reviewer Nyedra Booker, PharmD) and Office of Prescription Drug Promotion (OPDP) (Reviewer Dhara Shah, PharmD) edited the Medication Guide for clarity.
- The Division of Medication Error Prevention and Analysis (DMEPA) (Safety Evaluator John C. Morris, PharmD and Team Leader Briana Rider, PharmD, CPPS) reviewed label and labeling making recommendations to reduce potential medication errors.

11. Pediatrics

The studies for TSC were conducted in a pediatric population down to one years of age. Because the product has orphan designation for LGS, DS, and TSC, the Pediatric Research Equity Act (PREA) is not triggered.

12. Office of Scientific Integrity (OSI) Review

The OSI review team did not write a review since no inspections were required.

13. Labeling

Please refer to the final negotiated product label. Labeling negotiations with the applicant have been completed and the applicant has accepted all recommended changes.

In its proposed labeling, the applicant has also proposed to expand the age range for use in treatment of seizures associated with LGS or DS to include patients 1 to less than 2 years of age (the focus of supplement 06). There are no controlled efficacy data in the DS or LGS populations for patients 1 to less than 2 years of age; however, it is expected that, based on the pathophysiology of these two disorders, CBD would be as efficacious in reducing seizures in patients 1 to less than 2 years of age with DS or LGS as in patients 2 years and older with DS or LGS. Review of safety data from the controlled trial (Study 1521) of TSC-related seizures (another epilepsy syndrome) found a similar safety profile for patients 1 to less than 2 years of age as for patients 2 years and older. Review of safety data from an uncontrolled population of

patients with a variety of underlying seizure disorders (including 3 with DS or LGS) also identified no unexpected safety signal. As there is an expectation of efficacy and no expectation of a different safety profile in a similar epilepsy population, there is sufficient clinical information to support the proposed expansion of the age range in the DS and LGS populations to include patients 1 to less than 2 years of age.

In Supplement 07 (a Changes Being Effected supplement), the applicant cites a recent Drug Enforcement Agency Communication to the applicant (dated March 20, 2020) stating that CBD [Epidiolex] is no longer controlled under the Controlled Substances Act as a result of the enactment of the hemp provisions of the Agricultural Improvement Act of 2018, pub. L. 115-334, § 297A. Therefore, in this submission, the applicant submits updated final Prescribing Information and Medication Guide, Instructions for Use, Carton, and Bottle/Container labels to indicate that CBD is no longer a controlled substance. The Agency concurs with these proposed changes.

14. Postmarketing Recommendations

There are no further postmarketing requirements or commitments beyond those imposed in the original July 5, 2018 approval letter.

15. Recommended Comments to the Applicant

See action letter.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

PHILIP H SHERIDAN
07/31/2020 07:58:44 PM

NICHOLAS A KOZAUER
07/31/2020 07:59:46 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

CLINICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	210365/S-005, S-006, S-007
Priority or Standard	Priority
Submit Date(s)	1/31/2020 (S-05) 1/31/2020 (S-06) 4/06/2020 (S-07)
Received Date(s)	1/31/2020 (S-05) 1/31/2020 (S-06) 4/06/2020 (S-07)
PDUFA Goal Date	7/31/2020 (S-05) 7/31/2020 (S-06) 10/06/2020 (S-07)
Division/Office	DN2/ON
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	7/31/2020
Established/Proper Name	Cannabidiol
(Proposed) Trade Name	Epidiolex
Applicant	GW Pharmaceuticals PLC
Dosage Form(s)	Oral solution
Applicant Proposed Dosing Regimen(s)	(b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older Dosing • 10-20 mg/kg/day in patients with Lennox-Gastaut or Dravet syndromes and • 25 mg/kg/day in patients with tuberous sclerosis complex (all divided BID)

Table of Contents

Table of Tables

Table of Figures

Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
AR	adverse reaction
AST	aspartate aminotransferase
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBD	cannabidiol
CBER	Center for Biologics Evaluation and Research
CBZ	carbamazepine
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CLB	clobazam
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DEE	developmental and/or epileptic encephalopathy
DMC	data monitoring committee
DN2	Division of Neurology 2
DS	Dravet syndrome
DSMC	Data Safety Monitoring Committee
EAP	expanded access program
ECG	electrocardiogram
eCTD	electronic common technical document
EEG	electroencephalogram
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice

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

Primary FDA text, ***reviewer comments***, *extracted from Applicant documents, extracted from other discipline reviews or FDA documents*

1. Executive Summary

1.1. Product Introduction

The Applicant proposes to expand the indication for cannabidiol (proprietary name Epidiolex) in the United States (U.S.) to include treatment of seizures associated with tuberous sclerosis complex in patients 1 year of age and older (Supplement 05) and expand the age range for Lennox-Gastaut syndrome and Dravet syndrome to include patients 1 to < 2 years of age (Supplement 06). (b) (4) Supplement 07 is a Changes Being Effected supplement concerning the recent decision of the Drug Enforcement Agency that CBD is no longer controlled under the Controlled Substances Act.

Cannabidiol (investigational name GWP43003-P) is a cannabinoid prepared from the *Cannabis sativa* L. plant. Although the mechanism of action remains unclear and may depend on multiple factors, it is theorized that cannabidiol modulates adenosine and intracellular calcium, potentially reducing excitability of certain neurons.

Epidiolex is currently marketed in the US as an oral solution of 100 mg/ml for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients 2 years of age and older.

(b) (4) See Section 7.1.4 for discussion of Applicant's proposed dosing regimen and the dosing regimen recommended by the clinical reviewer.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant has provided substantial evidence of effectiveness to support approval. The Applicant provided data from a single adequate and well controlled trial that demonstrated that cannabidiol, as compared to placebo, reduces the frequency of seizures in patients with tuberous sclerosis complex. The Applicant showed this effect for one dose (25 mg/kg/day). A higher dose (50 mg/kg/day) demonstrated no increased efficacy over the 25 mg/kg dose but did show some increased adverse effects in comparison to the 25 mg/kg/day dose. The primary endpoint was statistically significant for both doses. Key secondary endpoints, except one were nominally significant. The treatment effect observed in these trials was comparable to what has been accepted in other FDA approved drugs for other epileptic encephalopathies.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

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

Tuberous sclerosis complex is a genetic disorder characterized by the widespread development of nonmalignant tumors in multiple organs. Seizures are the most common neurological manifestation and most frequent presenting feature of tuberous sclerosis complex, with infantile spasms the most common seizure type at initial diagnosis. The seizures usually present early in childhood and are frequently resistant to medications and other treatments. Cognitive impairment is a primary clinical feature of tuberous sclerosis complex. Early management of seizures is important, as it may prevent or mitigate the cognitive and neuropsychiatric impairment associated with epileptic encephalopathy. Patients with tuberous sclerosis complex are almost always significantly disabled by their seizures and cognitive impairment. There is one approved seizure treatment for patients with tuberous sclerosis complex (everolimus), which is moderately effective but has significant adverse effects.

The efficacy of cannabidiol for treatment of seizures associated with tuberous sclerosis complex was demonstrated in a single randomized clinical trial. There is evidence of clinical benefit based on reduction of monthly TSC-associated seizure frequency. Other outcome measures were supportive.

Cannabidiol at 25 and 50 mg/kg/day demonstrated reduction in TSC-associated seizures as compared to placebo. Patients had median baseline seizure frequency ranging from 54 to 61 TSC-associated seizures/month. The patients in the cannabidiol groups had 43% and 36% reduction in monthly TSC-associated seizure frequency, compared to 20% in the placebo group. There was no added benefit of the 50 mg/kg/day dose when compared to the 25 mg/kg/day dose. Additionally, patients in the cannabidiol groups had numerically greater reductions in total seizure frequency and impression of improvement based upon a patient/caregiver assessment. A greater proportion of patients in the cannabidiol groups were considered responders (50% reduction in seizure frequency). Because of hierarchical testing, many of the secondary efficacy endpoints were considered nominally but not statistically significant.

Risks identified in the clinical safety data include liver injury; somnolence; decreased appetite, decreased weight, and weight loss; and rash. Liver injury may be monitored with baseline and interval lab tests. Somnolence and rash are observable and decreased appetite with weight loss may be observed and measured. When necessary, an intervention of cannabidiol dose reduction or discontinuation can take place.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Tuberous sclerosis complex (TSC) is a genetic disorder characterized by widespread development of nonmalignant tumors in multiple organ systems, including the brain, heart, skin, eyes, kidney, lung, and liver. It presents during childhood and is characterized neurologically by nonmalignant brain tumors, refractory epilepsy, cognitive impairment, and behavioral disorders. The epilepsy associated with TSC is a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities. • Epilepsy is reported in 80-90% of patients with TSC. Onset of epilepsy in patients with TSC typically occurs in the first year of life. Many patients (44-65%) have evidence of delayed intellectual development, and severity of patients' cognitive and behavior impairments vary from minimally affected (rare) to profoundly impaired. Cognitive impairment is more frequently seen in patients with TSC and refractory epilepsy. • A variety of seizure types are reported in patients with TSC and epilepsy. Refractory epilepsy is reported in 60% of patients with TSC, regardless of AED or other epilepsy treatments.	Tuberous sclerosis complex is a genetic disorder characterized by widespread development of nonmalignant tumors in multiple organ systems, including the brain, heart, skin, eyes, kidney, lung, and liver. Epilepsy is reported in 80-90% of patients with TSC, 60% of whom develop refractory epilepsy. Onset of seizures is usually in the first year of life (infantile spasms, most commonly) but seizures are usually lifelong and require treatment. Delayed intellectual development is frequently seen and may be due in part to the underlying seizure disorder.
Current Treatment Options	• The primary objective of treatment of seizures in patients with TSC is reduction in frequency of the most incapacitating and injurious seizures (e.g., tonic-clonic seizures, focal seizures with or without alteration in awareness, and secondarily generalized seizures). • One drug is approved by FDA for reduction of seizures in patients with TSC: everolimus. Many other drugs are used to treat seizures in patients with TSC, especially valproic acid (which is generally considered a first-line agent) clobazam, vigabatrin, and levetiracetam. Seizures in TSC are often resistant to AEDs (even when used as polytherapy) and complete seizure	One drug has been shown in controlled clinical trials to reduce seizures in patients with TSC. Other drugs are used off-label. Yet even when taking multiple AEDs, most patients still have frequent seizures. No AEDs have been shown to alter the cognitive impairment in patients with TSC. Serious and severe adverse drug effects have

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	control with resolution of intellectual and psychosocial dysfunction is infrequently achieved. • Severe adverse drug reactions are reported with everolimus (pneumonitis, stomatitis, infections) and with many of the frequently used drugs to treat seizures in TSC, such as hepatic failure (lamotrigine and valproic acid), serious skin reactions (lamotrigine, clobazam), and hematologic abnormalities (lamotrigine).	been reported with the approved drug and all the commonly-used drugs and must be taken into account when choosing an AED treatment, especially in children and adolescents. The treatment armamentarium in TSC would benefit from therapeutic options that are more efficacious and potentially better tolerated. A drug that is better tolerated may improve compliance.
Benefit	• One pivotal trial (Study 1521) demonstrated the efficacy of cannabidiol in treatment of seizures given orally in patients with TSC. This study demonstrates efficacy of the 25 and 50 mg/kg/day doses. The primary endpoint the percentage reduction in TSC-associated seizure frequency from baseline to treatment period as compared to placebo. In study 1521, cannabidiol reduced the median seizure frequency by 43.4% in the 25 mg/kg group, 36.3% in the 50 mg/kg group, as compared to 13.3% in the placebo group placebo. The findings of the primary endpoint were statistically significant for both CBD groups tested (p=0.0038 and p=0.0094, respectively, in the 25 and 50 mg/kg/day groups). • Three key secondary endpoints favored CBD over placebo and were nominally significant for both CBD dose groups except for proportion of 50% responders in the 25 mg/kg group (p=0.069). These findings were generally consistent with the findings of the primary endpoint. These key secondary endpoints assessed the proportion of patients who were 50% responders, the percentage change in total seizure frequency from baseline to treatment period	Cannabidiol 25 mg/kg/day and 50 mg/kg/day were both found to be effective in reducing TSC-associated seizure frequency in patients with TSC. The treatment effect was robust statistically and clinically meaningful. Fewer seizures in these patients may lead to fewer injuries and days of disability. The benefit of treatment with cannabidiol on seizures in patients with TSC is persuasive, justifies the modest and manageable risk (see safety reviews) and justifies approval of the 25 mg dose. See risk discussion below for issues related to the 50 mg dose.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and the Subject/Caregiver Global Impression of Change.	
Risk and Risk Management	• Liver injury ○ 32% of patients in pooled 25 and 50 mg/kg CBD treatment group and 0% of patients in placebo (PBO) group had liver-related TEAEs (all but one were elevations in liver tests). Dose-response with 25% and 38% in the 25 mg/kg and 50 mg/kg groups, respectively. ○ Elevated transaminases the most frequently reported TEAE in the 25 mg/kg group and 2nd in the 50 mg/kg group. ○ 6 patients had liver-related SAEs (2 in the 25 mg/kg group and 4 in the 50 mg/kg group). ○ 4 patients in the 50 mg/kg group discontinued early due to liver test abnormalities. ○ Alanine aminotransferase (ALT) >3x the upper limit of normal (ULN) reported in 9 patients (12%), 18 patients (25%), and 0 patients in the 25 mg/kg, 50 mg/kg, and PBO groups, respectively. ALT >5x ULN reported in 7%, 11%, and 0%. ○ Concomitant VPA a risk factor for increased ALT by ~6x. • Decreased appetite/weight decreased ○ Decreased appetite: 20% of patients in 25 mg/kg group, 23% of the 50 mg/kg group, compared to 12% in PBO. ○ Weight decreased: 7%, 8%, and 0%, of patients in the 25 mg/kg, 50 mg/kg, and PBO groups, respectively. 1 patient discontinued early due to weight decreased TEAE (25 mg/kg). • Weight loss ○ Measured weight loss during the controlled trials: 16% of each of the CBD groups and 4% of the PBO group lost ≥7% of their baseline weight by the final visit of the controlled studies.	Elevations of transaminases were at times very high and led to discontinuation of treatment. This adverse effect may be monitored. There is already a warning in the label. Depression of appetite and weight loss may be severe and require discontinuation of treatment. This may be monitored. Rash was at times serious or severe and led to discontinuation in some patients. It is observable and may be monitored. Somnolence, sedation, and lethargy are effects of central nervous system depression seen frequently in antiseizure drug treatment. These are generally reversible upon discontinuation of treatment. This adverse reaction may be monitored. All of the frequently-observed adverse events in the TSC trial were also observed in the LGS and DS trials and are already included in the labeling.

Dimension	Evidence and Uncertainties	Conclusions and Reasons

	• Rash
	  ○ Reported in 8%, 11%, and 4% of patients in the 25 mg/kg, 50 mg/kg, and PBO groups, respectively.
	  ○ Seen in 7% of patients in the OLE phase.
	  ○ Most common reason for early discontinuation: 5% in 25 mg/kg group and 7% in 50 mg/kg group, compared to 0 in PBO.
	• Somnolence
	  ○ 13% of 25 mg/kg and 26% of 50 mg/kg groups reported, compared to 9% in PBO.
	  ○ Led to discontinuation in 2 patients in the 50 mg/kg group.	

1.4. Patient Experience Data

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

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

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

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant proposes a new indication for this application: treatment of seizures in patients ≥1 year of age with tuberous sclerosis complex. Additionally, the Applicant proposes expansion down to 1 year of age for treatment of seizures associated with Dravet syndrome or Lennox-Gastaut syndrome. While these disorders have some clinical similarities, they are sufficiently different that they will be discussed separately in sections 2.1 and 2.2.

Tuberous Sclerosis Complex

TSC is a multisystem, autosomal dominant genetic disorder characterized by the widespread development of nonmalignant tumors (tubers) in multiple organs. The expression of the disease varies considerably, and the diagnosis of TSC is made clinically or through genetic testing.[1]

Clinically, TSC is characterized by the development of a variety of benign tumors in multiple organs, including the brain, heart, skin, eyes, kidney, lung, and liver.[2,3] The clinical

[1] Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med 2006;355(13):1345–56
[2] DiMario FJ Jr, Sahin M, Ebrahimi-Fakhari D. Tuberous sclerosis complex. Pediatr Clin North Am. 2015;62(3):633.
[3] Curatolo P, Bombardieri R, Jozwiak S. Tuberous sclerosis. Lancet. 2008;372(9639):657

manifestations of TSC appear at fairly distinct developmental points (Table 1). There is an increased risk of malignancy in TSC. Most patients with TSC have epilepsy, and more than half have cognitive deficits and learning disabilities.[4] Other common neurological and/or psychiatric manifestations include autism, behavioral problems, and psychosocial difficulties. However, there is a wide variety of phenotypes between and within families regarding the number and severity of TSC manifestations.[4,5]

Table 1: Diagnostic Criteria and Age at Onset, Tuberous Sclerosis Complex

Diagnostic Criteria	Age at Onset
Major	
Facial angiofibroma	Infancy to adulthood
Ungual fibroma	Adolescence to adulthood
Shagreen patch	Childhood
Hypomelanotic macule	Infancy to childhood
Cortical tuber	Fetal life
Subependymal nodule	Childhood to adolescence
Subependymal giant-cell tumor	Childhood to adolescence
Retinal hamartoma	Infancy
Cardiac rhabdomyoma	Fetal life
Renal angiomyolipoma	Childhood to adulthood
Lymphangiomyomatosis	Adolescence to adulthood
Minor	
Multiple pits in dental enamel, Hamartomatous rectal polyps, Bone cysts, Cerebral white-matter radial migration lines, Gingival fibromas, Retinal achromic patch, "Confetti" skin lesions (groups of small, lightly pigmented spots), Multiple renal cysts	

Source: (Crino 2006[1])

Nearly all patients with TSC have one or more of the skin lesions typical of the disorder.[6] In population-based studies, 81-95% of patients with TSC have one of the characteristic skin lesions[6,7]. The most common lesions are hypopigmented macules, also known as ash-leaf spots; angiofibromas (sometimes called fibroadenomas); Shagreen patches; and a distinctive brown fibrous plaque on the forehead. Hypomelanotic macules and fibrous forehead plaques typically

[4] Curatolo P, Moavero R, de Vries PJ. Neurological and neuropsychiatric aspects of tuberous sclerosis complex. Lancet Neurol. 2015 Jul;14(7):733-745
[5] Northrup H, Wheless JW, Bertin TK, Lewis RA. Variability of Expression in Tuberous Sclerosis. J Med Genet 1993 Jan;30(1):41-3
[6] Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol. 1996;135(1):1
[7] Yates JR, Maclean C, Higgins JN, et al, Tuberous Sclerosis 2000 Study Group. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. Arch Dis Child. 2011 Nov;96(11):1020-5

appear earlier than facial angiofibromas or ungual fibromas (Table 1).

Central nervous system lesions characteristic of TSC include glioneuronal hamartomas, also called cortical tubers; subependymal nodules, subependymal giant cell tumors (SGCTs), also known as subependymal giant cell astrocytomas (SEGAs); and white matter heterotopia (dysplastic and dysmyelinated white matter lesions). Both cortical glioneuronal hamartomas and subependymal nodules are considered hamartomas. Cortical glioneuronal hamartomas are composed histologically of enlarged atypical and disorganized neuronal and glial elements with astrocytosis. Cortical hamartomas and subependymal nodules are seen on brain magnetic resonance imaging (MRI) in ~90% of children with TSC.[7] The characteristic brain tumor in TSC is the SGCT or SEGA, a benign, slow-growing tumor that usually arises in the periventricular area.[8] SGCTs are symptomatic in a small percentage (6-9%) of patients with TSC[8], and usually become symptomatic in adolescence or young adulthood (10-30 years of age).[9]

Seizures are the most common neurological manifestation and most frequent presenting feature of TSC, affecting 79-90%.[10] Seizures occur in the first year of life in ~60% of patients; however, new-onset seizures may occur in adulthood in patients with TSC.[10,11] In a natural history study of patients with TSC who had a single seizure, 99% eventually developed epilepsy.[10] Infantile spasms are the most common seizure type at initial diagnosis, occurring in up to 69% of patients.[10,12,13] Patients with TSC experience a variety of other seizure types, including partial onset seizures (POS), secondarily generalized seizures, subclinical seizures, and generalized onset seizures. The majority (~75%) of patients with TSC have epileptiform abnormalities on routine electroencephalography (EEG), including focal or multifocal discharges, hypsarrhythmia, and generalized spike-wave abnormalities. Most patients with TSC-associated epilepsy have seizures that are refractory and lifelong. Approximately 60% of patients with TSC-associated seizures develop medically intractable epilepsy.[10]

Cognitive impairment is a primary clinical feature of TSC, reported in 44-65% of TSC patients in population studies[7], in approximately 60% of TSC patients with a history of seizures, and in

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[8] Goh S, Butler W, Thiele EA. Subependymal giant cell tumors in tuberous sclerosis complex. Neurology. 2004;63(8):1457
[9] Webb DW, Fryer AE, Osborne JP. Morbidity associated with tuberous sclerosis: a population study. Dev Med Child Neurol. 1996;38(2):146
[10] Chu-Shore CJ, Major P, Camposano S, Muzykewicz D, Thiele EA. The natural history of epilepsy in tuberous sclerosis complex. Epilepsia. 2010;51(7):1236
[11] Yates JR, Maclean C, Higgins JN, et al, Tuberous Sclerosis 2000 Study Group. The Tuberous Sclerosis 2000 Study: presentation, initial assessments and implications for diagnosis and management. Arch Dis Child. 2011 Nov;96(11):1020-5.
[12] Riikonen R, Simell O. Tuberous sclerosis and infantile spasms. Dev Med Child Neurol. 1990;32(3):203.
[13] Curatolo P, Seri S, et al. Infantile spasms in tuberous sclerosis complex. Brain Dev 2001;23(7):502-7

nearly 75% of TSC patients with a history of refractory epilepsy.[10] Early management of seizures is important, as it may prevent or mitigate the cognitive and neuropsychiatric impairment associated with epileptic encephalopathy.[14]

The incidence of TSC is approximately 1 in 5000 to 10,000 live births [3-7].[3,15] TSC is caused by a mutation in either the *TSC1* gene (encoding hamartin) or the *TSC2* gene (encoding tuberin). About 80% of TSC cases are due to de novo mutations.[16] *TSC2* mutations are approximately four times as frequent as *TSC1* mutations in de novo cases, while the prevalence of *TSC1* and *TSC2* mutations is about equal in familial TSC cases.[16] Once a "de novo" mutation occurs in an individual, their offspring may inherit TSC, which then appears as a familial trait in subsequent generations.[17] TSC is highly variable in phenotypic expression, with significant variability in age of onset, severity of disease, and different signs and symptoms resulting from a specific genotype. Severity of disease in TSC may vary considerably from one family to another and even among affected individuals within the same family.[5,18]

Lennox-Gastaut syndrome

Lennox-Gastaut syndrome (LGS) is a severe form of epilepsy which presents during childhood. An epileptic encephalopathy and electroclinical syndrome with a childhood onset, diffuse slow spike-wave complexes, and several types of seizures was first described by Lennox and Davis in 1950[19], and the syndrome was further defined by Gastaut et al in 1966[20]. It is characterized by a triad of electro-clinical findings: multiple refractory seizure types, developmental delay and an interictal EEG pattern of diffuse, slow spike-wave complexes[21]. LGS is considered a developmental and/or epileptic encephalopathy, in which the seizures and the epileptic activity contribute to the developmental delay and behavioral abnormalities[22].

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[14] Wang S, Fallah A. Optimal management of seizures associated with tuberous sclerosis complex: current and emerging options. Neuropsychiatr Dis Treat 2014;10:2021–30

[15] Hong CH, Tu HP, Lin JR, Lee CH. An estimation of the incidence of tuberous sclerosis complex in a nationwide retrospective cohort study (1997-2010). Br J Dermatol. 2016 Jun;174(6):1282-9

[16] Au KS, Williams AT, Roach ES, et al. Genotype/phenotype correlation in 325 individuals referred for a diagnosis of tuberous sclerosis complex in the United States. Genet Med. 2007;9(2):88

[17] Rose VM, Au KS, Pollom G, et al. Germ-line mosaicism in tuberous sclerosis: how common? Am J Hum Genet. 1999;64(4):986

[18] Smalley SL, Burger F, Smith M. Phenotypic Variation of Tuberous Sclerosis in a Single Extended Kindred. J Med Genet. 1994 Oct;31(10):761-5

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

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

[21] Hancock EC, Cross JH. Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev. 2013 Feb 28;(2)

[22] Camfield PR. Definition and natural history of Lennox-Gastaut syndrome. Epilepsia, 52(Suppl. 5):3–9, 2011

Etiology of LGS can be identified in 60-75% of patients and include a wide variety of causes, such as hypoxic-ischemic insults (most common), tuberous sclerosis complex, brain malformations, and traumatic brain injuries[22]. Seizures associated with LGS might occur de novo or might follow severe infantile seizure disorders, such as infantile spasms. A variety of genetic anomalies have been reported in patients with the diagnosis of LGS, including variants or mutations in the SCN1A, FOXG1, DNM1, and CHD2 genes.

LGS accounts for 1-10% of childhood epilepsies.[23] Children and adolescents with LGS have a higher mortality rate than age-matched cohorts, with an up to 14 times increased risk of death during childhood and adolescence[24], mostly due to SUDEP, status epilepticus, or seizures[24].

Onset of LGS typically occurs before 8 years of age, with peak presentation occurring between ages 3 and 5 years,[19,22] and it has been reported in patients as young as 1 year of age.[19] LGS is an electroclinical syndrome characterized by a triad of findings: multiple seizure types, developmental delay, and an interictal EEG pattern of diffuse, slow spike-wave complexes. The hallmark EEG feature in LGS is slow (2.5 Hz) spike-and-wave bursts with abnormal background activity,[21]. Some patients (20-60%)[19] have evidence of delayed intellectual development at the time of diagnosis, especially those who present later. Cognitive impairment becomes more obvious over time, with intellectual dysfunction in 75-95% of patients within 5 years of initial diagnosis.[25] Severity of patients' cognitive and behavior impairments vary from minimally affected (rare) to profoundly impaired.

Drop attacks occur in more than 50% of patients with LGS and are the most disabling of the seizure types[19]. The most basic definition of a drop attack is a seizure that leads to a fall or would have caused a fall. In patients with LGS, drop attacks are often but not always preceded by a myoclonic jerk but occur too quickly for intervention, thus frequently leading to injury. Other seizure types seen in patients with LGS include tonic seizures, atypical absence seizures, myoclonic seizures, focal seizures with or without secondary generalization, generalized tonic-clonic seizures, and hemiclonic seizures. Non-convulsive status epilepticus has been reported in 50-70% of patients.[19]

Dravet syndrome

Dravet syndrome (DS) is a developmental and/or epileptic encephalopathy (DEE), as defined by

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[24] Autry AR, Trevathan E, et al. Increased Risk of Death Among Children with Lennox-Gastaut Syndrome and Infantile Spasms. J Child Neuro 25(4) 441-447
[25] Hancock EC, Cross HJ. (2009) Treatment of Lennox-Gastaut syndrome. Cochrane Database Syst Rev 2013 Feb 28; (2):CD003277

the International League Against Epilepsy (ILAE).[26] Clinically, it is characterized by refractory seizures of multiple types, febrile seizures, frequent episodes of status epilepticus, and developmental arrest or regression.[27,28] The syndrome typically presents prior to 1 year of age as frequent febrile seizures[29], and patients then develop hemi-clonic, bilateral clonic, and/or generalized tonic-clonic (GTC) seizures before age 2 years.[28,30,31] Other seizure types exhibited by patients with DS include clonic, tonic, atonic, absence, and/or focal seizures. Patients typically present with developmental delay by age 2 years.[28,30] Other neurologic findings include ataxia, pyramidal signs, and interictal myoclonus. Brain imaging is generally normal or non-specific.

As the patient ages, the course of the disease changes. Seizures in patients with DS evolve over time, seizures of variable frequency related to fever in the first year, seizures increasing in frequency and types from ages 1 to 5 years (a "catastrophic phase"), and stabilization of seizures after age 5 years.[31] Mortality during childhood and adolescence in patients with DS is about 15% (5-20%), primarily due to status epilepticus in the early years and sudden unexpected death in epilepsy patients (SUDEP) in adolescence and adulthood with SUDEP rates of 9.32/1000 person-years.[32] Other causes of death are usually indirectly related to the consequences of seizure, especially status epilepticus, and include drowning and traumatic injuries.[33] Seizure-freedom almost never occurs, but most seizures do become less frequent.

The syndrome is rare, occurring in 1 per 15,700 to 40,000 live births in the United States[34,35]. Dravet syndrome accounts for less than 2% of epilepsy in children less than 15 years old[36]. A majority (70-80%) of patients with the clinical syndrome have one or more mutations in the alpha-1 subunit of the voltage-gated sodium channel (*SCN1A*) gene.[27]

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[27] Brunklaus A, Zuberi S. Dravet syndrome—From epileptic encephalopathy to channelopathy. Epilepsia, 55(7):979–984, 2014
[28] Dravet C. Dravet syndrome history. Dev Med Child Neurol. 2011 Apr;53 Suppl 2:1-6
[29] Wang JW, Shi XY, et al. Prevalence of SCN1A mutations in children with suspected Dravet syndrome and intractable childhood epilepsy. Epilepsy Res. 2012 Dec;102(3):195-200
[30] Dravet C, Bureau M, Oguni H, et al. Severe myoclonic epilepsy in infancy (Dravet syndrome). In Roger J, Bureau M, Dravet C, Genton P, Tassinari CA, Wolf P (Eds) Epileptic syndromes in infancy, childhood and adolescence. London: John Libbey, 2005:89–113
[31] Dravet C. The core Dravet syndrome phenotype. Epilepsia 2011;52 Suppl 2:3-9
[32] Cooper MS, Mcintosh A, et al. Mortality in Dravet syndrome. Epilepsy Res. 2016 Dec;128:43-47
[33] Genton P, Velizarova R, Dravet C. Dravet syndrome: the long-term outcome. Epilepsia 2011;52 Suppl 2:44-49.
[34] Hurst DL. Epidemiology of severe myoclonic epilepsy of infancy. Epilepsia 1990;31(4):397-400
[35] Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet Syndrome in a US Population. Pediatrics 2015 Nov; 136(5):e1310-5
[36] Dura-Trave T, Yoldi-Petri ME, Gallinas-Victoriano F. Epilepsy in children in Navarre, Spain: epileptic seizure types and epileptic syndromes. J Child Neurol 2007;22(7):823-828

Although treatment of seizures in some patients with DEEs may lead to improved cognition, seizures in patient with DS are generally refractory to antiepileptic drugs (AEDs). Some sodium channel blocking AEDs and GABA re-uptake or GABA enzyme inhibitors may exacerbate the seizures and are generally avoided.[37,38]

2.2. Analysis of Current Treatment Options

Tuberous Sclerosis Complex

Management of TSC is directed at its neurologic and systemic manifestations: seizures, TSC-associated neuropsychiatric disorders, brain tumors, skin lesions, renal disease, pulmonary disease, cardiac involvement, and an increased risk of malignant tumors. As noted above, epilepsy is reported in most patients with TSC and can be difficult to manage. Seizures are often refractory to AEDs and complete seizure control is uncommon.[10]

Infantile spasms (IS) in the setting of TSC is most often treated with adrenocorticotropic hormone (ACTH), with a benefit similar to patients without TSC. Vigabatrin is another option for treatment of IS in the TSC population.[12,13]

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, is only drug approved by U.S. FDA for treatment of seizures associated with TSC. It significantly reduced seizure frequency in pediatric and adult patients with TSC and refractory epilepsy, as demonstrated in a randomized, double-blind, controlled trial of 366 patients. Patients were randomized 1:1:1 to low-exposure (trough 3 to 7 ng/mL), high-exposure (trough 9 to 15 ng/mL), or placebo. The median reduction in seizure frequency was significantly greater for the low- and high-exposure everolimus groups (29% and 40%, respectively), compared with 15% for placebo).[39] Serious treatment emergent adverse events were more frequent in the low- and high-exposure everolimus groups (both 14%), compared with placebo (3%). Treatment discontinuation rates were low in all groups (5%, 3%, and 2%, respectively). The most common adverse events associated with everolimus were stomatitis, diarrhea, and pyrexia, which is similar to other studies. As with other epileptic encephalopathies and epilepsy in general, many AEDs are used to treat the variety of seizure types associated with TSC.

[37] Guerrini R, Dravet C, et al. Lamotrigine and seizure aggravation in severe myoclonic epilepsy. Epilepsia 1998;39(5):508-12
[38] Brunklaus A, Ellis R, et al. Prognostic, clinical and demographic features in SCN1A mutation-positive Dravet syndrome. Brain 2012;135:2329–2336
[39] French JA, Lawson JA, Yapici Z, et al. Adjunctive everolimus therapy for treatment-resistant focal-onset seizures associated with tuberous sclerosis (EXIST-3): a phase 3, randomised, double-blind, placebo-controlled study. Lancet. 2016;388(10056):2153

Lennox-Gastaut Syndrome

Seizures in LGS are usually resistant to AEDs and complete seizure control with resolution of intellectual and psychosocial dysfunction is almost never achieved. The primary objective of treatment of seizures in patients with LGS is reduction in frequency of the most incapacitating and injurious seizures (e.g., drop attacks and tonic-clonic seizures).[40]

Seven drugs are approved by the US Food and Drug Administration (FDA) for reduction of seizures in patients with LGS: cannabidiol, clobazam, rufinamide, topiramate, lamotrigine, felbamate, and clonazepam (see Table 2). Cannabidiol, clobazam, felbamate, lamotrigine, rufinamide, and topiramate were studied in patients with LGS in randomized controlled trials.

In two randomized, controlled, add-on treatment trials of cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome, there were statistically significant decreases in median percentage change in drop seizure frequency from baseline in cannabidiol treatment groups compared to placebo. Specifically, in Study 1414 there were 42%, 37%, and 17% reductions in median drop seizure frequencies in the CBD 20 mg/kg (p=0.0016), CBD 10 mg/kg (p=0.0047), and PBO groups, respectively. In Study 1423, the reduction in median percentage change in drop seizure frequency also favored the CBD 20 mg/kg/day group (-44%) over placebo (-22%), also a statistically significant (p=0.0135).[41]

Non-pharmacologic treatments for patients with LGS include corpus callosotomy as palliative treatment for intractable drop attacks[19], vagus nerve stimulation[19,42], and ketogenic diet[42].

Dravet Syndrome

Prior to 2018, there were no approved treatments of seizures associated with DS in the U.S. In June 2018, cannabidiol (CBD) was approved for treatment of seizures associated with Dravet syndrome based on safety and efficacy data collected from a randomized, placebo-controlled pivotal trial of Epidiolex 20 mg/kg/day as compared to placebo. The primary endpoint was the percentage reduction in convulsive seizure frequency from baseline to treatment period as compared to placebo. In patients with DS, CBD reduced the median percentage seizure frequency from baseline to treatment period by 38.9% in the CBD group and 13.3% in the placebo group (p=0.0123).[41] The proportion of 50% responders (key secondary endpoint) was numerically greater in the CBD group (42.6%), compared with the placebo group (27.1%) with an OR=2.0 (p=0.0784).

Stiripentol (STP) was approved for treatment of seizures associated with DS in patients 2 years

[40] Michoulas A, Farrell K (2010) Medical management of Lennox-Gastaut syndrome. CNS Drugs 24(5):363–374
[41] NDA 210365 Epidiolex clinical review (Natalie Getzoff, MD), dated 6/14/2018

of age and older taking clobazam by the U.S. FDA in September 2018. This approval was on the basis of 2 randomized, placebo-controlled trials comparing STP 50 mg/kg/day to placebo in the reduction of seizures associated in patients with DS. Almost all patients were taking concomitant valproate and clobazam. Both of these were small studies with a total of 64 patients. In the STICLO France study, the responder rate for STP treatment arm was 71.4% compared to 5% in the PBO arm ($p<0.00001$). In the STICLO Italy study the responder rate in the STP treatment arm was 67% compared to 9% in the PBO arm ($p=0.009$).[43]

Fintepla, or fenfluramine, was approved on June 25, 2020 for treatment of seizures associated with Dravet syndrome, based on safety and efficacy data collected from two randomized, placebo-controlled pivotal trials of Fintepla at doses of 0.2 to 0.8 mg/kg/day as compared to placebo. The primary endpoint was the percentage reduction in convulsive seizure frequency from baseline to treatment period as compared to placebo. In patients with DS, the percentages of difference for fenfluramine relative to placebo were -31.7%, -70.0%, and -59.5% for the fenfluramine 0.2 mg/kg, 0.8 mg/kg, and 0.5 mg/kg groups, respectively. These results statistically favored fenfluramine over placebo.[44]

A number of drugs are used off label as part of standard of care with varying degrees of effectiveness. The most commonly used AEDs in the treatment of seizures are clobazam (CLB) and valproic acid (VPA). Adjunctive treatment with VPA and/or CLB results in a 50% reduction in seizures in about 25% of patients[45,46]. In an open-label study of adjunctive valproic acid and clobazam therapy in patients with DS, 1/24 and 2/16 patients treated with VPA or CLB respectively were seizure free for a 12-week trial period[46]. Levetiracetam was studied in a small open-label single arm study in patients with DS with a reported responder rate of 64%.[47] The ketogenic diet may be helpful[48] and is typically used as an adjunct to drug treatment(s).

[43] NDA 206709 Diacomit clinical review (Steven Dinsmore, MD), dated 5/29/2018
[44] NDA 212102 Fintepla clinical review (Natalie Getzoff, MD), dated 6/24/2020
[45] Inoue Y, Ohtsuka Y, et al. Stiripentol open study in Japanese patients with Dravet syndrome. Epilepsia 2009;50(11):2362-2368.
[46] Inoue Y, Ohtsuka Y. Effectiveness of add-on stiripentol to clobazam and valproate in Japanese patients with Dravet syndrome: additional supportive evidence. Epilepsy Res 2014;108(4):725-731.
[47] Striano P, Coppola A, Pezzella M, et al. An open-label trial of levetiracetam in severe myoclonic epilepsy of infancy. Neurology 2007;69:250-254
[48] Caraballo RH, Cersosimo RO, et al. Ketogenic diet in patients with Dravet syndrome. Epilepsia 2005;46(9):1539-1544.

Table 2: Summary of Treatments of Seizures in Patients with Tuberous Sclerosis Complex, Dravet Syndrome, or Lennox-Gastaut Syndrome

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
FDA approved treatment for seizures associated with tuberous sclerosis complex					
Everolimus	Adjunctive treatment of adult and pediatric patients aged 2 years and older with TSC-associated partial-onset seizures	2018	Tablets and tablets for oral suspension 5 mg/m^2 orally once daily; adjust dose to attain trough concentrations of 5 15 ng/mL	Primary endpoint was percentage reduction of median frequency of POS (baseline to treatment) in 1 study: Target 3-7 ng/mL: -29.3% (p=0.003) Target 9-15 ng/mL: -39.6% (p<0.001) PBO: -14.9%	Warnings: Non-Infectious Pneumonitis, Infections, Severe Hypersensitivity Reactions, Angioedema, Stomatitis, Renal Failure, Impaired Wound Healing, Metabolic Disorders, Myelosuppression, Risk of Infection or Reduced Immune Response with Vaccination, Embryo-Fetal Toxicity Most common AR's in the TSC seizure study: stomatitis, pneumonia, and irregular menstruation
FDA approved treatment for seizures associated with Lennox-Gastaut syndrome					
Cannabidiol (CBD)	Treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients 2 years and older	2018	Oral Solution Start 5 mg/kg/day, titrate to 10-20 mg/kg/day	Primary endpoint was median change in drop seizure frequency (baseline to treatment) in 2 studies: Study 1414: CBD 20 mg/kg -42% (p=0.0016) CBD 10 mg/kg -37% (p=0.0047) PBO -17%. Study 1423: CBD 20 mg/kg -44% PBO -22% (p=0.0135).	Transaminase elevations identified in 13% of pooled CBD patients compared to 1% of pooled PBO patients. Somnolence and sedation noted in 32% of pooled CBD compared to 11% of pooled PBO patients.

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Clobazam	Adjunctive treatment of seizures associated with LGS in patients ≥ 2 years of age	2011	Patients ≤30 kg: 5-20 mg PO daily (divided BID) Patients >30 kg: 20-40 mg/day PO (divided BID)	Statistically significant reduction in mean percent reduction from baseline in weekly drop seizure frequency: Low dose: p<0.05 Med dose: (p<0.01) High dose: (p<0.01)	Somnolence/sedation, withdrawal symptoms, skin reactions (Stevens-Johnson Syndrome [SJS], toxic epidermal necrolysis [TEN])
Rufinamide	adjunctive treatment of seizures associated with LGS in pediatric patients 1 year of age and older, and in adults	2008	45 mg/kg per day, divided BID, maximum 3200 mg per day	• Median percent change in total seizure frequency per 28 days (p=0.0015) • Median percent change in tonic-atonic seizure frequency per 28 days (p<0.0001) • Improvement in Seizure Severity Rating from Global Evaluation (p=0.0041)	Shortening of the QT interval (unknown clinical risk) Somnolence or fatigue, and coordination abnormalities, dizziness, gait disturbances, and ataxia Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Leukopenia
Lamotrigine	adjunctive therapy for generalized seizures of Lennox-Gastaut syndrome in patients aged 2 years and older:	Initial: 1994 LGS: 1998	> 12 years: 100-500 mg divided BID (depending on concomitant AEDs esp., VPA) ≤12 years: 1-15 mg/kg/day, divided BID depending on concomitant AEDs (esp. VPA)	• Median percentage reduction from baseline in major motor seizures (p<0.05) • Drop attacks and tonic-clonic seizures were "significantly reduced" by lamotrigine	Serious skin rashes (including SJS), greater in pediatric than adult patients DRESS Hepatic failure Blood dyscrasias: neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia, and, rarely, aplastic anemia and pure red cell aplasia Aseptic meningitis SUDEP and status epilepticus

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
Topiramate	adjunctive therapy for patients ≥2 years of age with seizures associated with Lennox-Gastaut syndrome	Initial: 1996 LGS: 2001	Adults: 200-400 mg/day PO divided BID Pediatrics: 5 to 9 mg/kg/day PO divided BID	• Median percent reduction in drop attacks ($p<0.05$) • Parental global rating of seizure severity ($p<0.05$)	Acute Myopia and Secondary Angle Closure Glaucoma; Visual Field Defects; Metabolic Acidosis; Cognitive-related dysfunction; depression or mood problems; Fetal anomalies (cleft lip and/or cleft palate and small for gestational age); hyperammonemia with or without encephalopathy; nephrolithiasis;
Felbamate	adjunctive therapy in children with seizures associated with Lennox-Gastaut syndrome	Initial: 1993 LGS: ??	45 mg/kg/day PO QID	• Statistically significant reductions in total, atonic, and tonic-clonic seizures	Aplastic anemia; hepatic failure;
Clonazepam	useful alone or as an adjunct in the treatment of the Lennox-Gastaut syndrome (petit mal variant)	Initial: 1975 LGS: 1997?	Adults: maintenance dose dependent on response, max 20 mg/day PO (divided TID) Pediatric: infants/children (≤10 years or 30 kg) maintenance dose of 0.1 to 0.2 mg/kg PO divided TID	• N/A	CNS depression, withdrawal symptoms; Worsening of Seizures especially in patients with multiple seizure types;
FDA approved treatment for seizures associated with Dravet syndrome					
Cannabidiol (CBD)	Treatment of seizures associated with DS or Lennox-Gastaut syndrome (LGS) in patients 2 years and older	2018	Oral Solution Start 5 mg/kg/day, titrate to 10-20 mg/kg/day	Primary endpoint was median change in convulsive seizure frequency (baseline to treatment) CBD -39%, PBO -13% ($p=0.0123$). Key secondary endpoint: ≥50% Responder	Transaminase elevations identified in 13% of pooled CBD patients compared to 1% of pooled PBO patients. Somnolence and sedation noted in 32% of pooled CBD compared to 11% of pooled PBO patients.

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
				Analysis PBO 27%, CBD 43% (p=0.078)	
Stiripentol (STP)	Treatment of seizures associated with DS in patients 2 years and older taking clobazam	2018	Capsules and packet for oral suspension Dose: 50 mg/kg/day	Primary endpoint was ≥50% Responder Analysis (baseline to treatment): STICLO France STP 71%, PBO 5% (p=0.0123) STICLO Italy STP 67%, PBO 9% (p=0.009)	Warning for somnolence, decreased appetite/weight loss, and neutropenia/ thrombocytopenia.
Other Treatments for Dravet syndrome, 1st Line					
Clobazam (CLB)	Adjunctive treatment of seizures associated with LGS in patients 2 years of age or older	2011	Begin 5 mg/day, titrate up to 20 mg/day	Limited amount of data on the efficacy of clobazam in DS, single retrospective study	Behavioral disinhibition, sedation, ataxia and increased salivation.
Valproic acid (VPA)	Monotherapy and adjunctive therapy of complex partial seizures; sole and adjunctive therapy of simple and complex absence seizures; adjunctive therapy in patients with multiple seizure types that include absence seizures	1978	Start at 10 to 15 mg/kg/day, increasing at 1-week intervals by 5 to 10 mg/kg/week until seizure control or limiting side effects	There is minimal literature on its use in DS (level 4), and in retrospective studies responder rates (>50% reduction in seizure frequency) were 22.2-48%.	Potential for several severe adverse effects, including hepatotoxicity (particularly with underlying mitochondrial disease), hyperammonemia, pancreatitis and thrombocytopenia. Additionally, other adverse effects may include decreased or increased appetite, tremor (at higher doses), hair loss and sedation.
Other Treatments for Dravet syndrome, 2nd and 3rd line options					
Topiramate (TPM)	Initial monotherapy for treatment of partial-onset seizures (POS) or primary generalized tonic-clonic (PGTC) seizures in patients ≥2 years	1996	250-400 mg daily, divided BID, weight-based dosing for pediatric patients	Observational, open label, and retrospective study have shown responder rates of 35-78%.	Warnings for adult and pediatric patients: Acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Cognitive/ Neuropsychiatric Adverse Reactions (lower in peds than adults), Hyperammonemia and

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues
	Adjunctive therapy for the treatment of POS, PGTC, or seizures associated with LGS in patients 2 years of age and older				Encephalopathy, Kidney Stones,
Levetiracetam (LEV)	POS in patients one month of age and older with epilepsy, myoclonic seizures in patients 12 years of age and older with juvenile myoclonic epilepsy, PGTC seizures in patients 6 years of age and older with idiopathic generalized epilepsy.	1999	Starting at 7mg/kg twice daily in children 1 month to < 6 months Up to 500mg BID in adults	Reported to have a responder rate of 64% in a single open label prospective study	Warnings: Behavioral abnormalities and psychotic symptoms, somnolence and fatigue, anaphylaxis and angioedema, SJS and TEN, coordination difficulties, reduction in WBC and neutrophil counts (statistically sig worse in Keppra-treated pediatric patients than those on placebo), hypertension (particularly in the 1 mo to 4 yr study)

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Epidiolex® (cannabidiol oral solution) was approved 25 Jun 2018 in the United States and was launched on 01 Nov 2018. Epidiolex is indicated for the treatment of seizures associated with LGS or DS in patients 2 years of age and older. Since 01 Nov 2018, patient exposure to Epidiolex in the US is estimated at (b) (4) (based on Periodic Adverse Drug Experience Report #7, cutoff date 24 Mar 2020).

3.2. Summary of Presubmission/Submission Regulatory Activity

IND 120055 was submitted to FDA on March 31, 2014 for a study of the safety and efficacy of cannabidiol in the treatment of convulsive seizures associated with Dravet syndrome. A second trial of the safety and efficacy of cannabidiol in the treatment of convulsive seizures associated with Dravet syndrome was started in April 2015 (Study 1424) but was not completed prior to the original NDA submission in 2017. Two clinical trials evaluating safety and efficacy of cannabidiol in the treatment of drop seizures in patients with Lennox-Gastaut syndrome were started in June 2015 (Study 1414) and April 2015 (Study 1423). One clinical trial evaluating safety and efficacy of cannabidiol in the treatment of seizures associated with tuberous sclerosis complex was started in April 2016 (Study 1521).

Significant clinical interactions between FDA and the Applicant for the TSC indication include the following:

- Orphan Designation (15-5107) for treatment of TSC-associated seizures, granted April 2016
- Type B Pre-NDA Meeting (October 2019): Important clinical issues discussed in this meeting included the following:
  - (b) (4)
  - The Sponsor proposed that the results of Studies 1521 and (b) (4) plus the entirety of the development program, would support efficacy and safety of CBD-OS for treatment of seizures associated with TSC in patients 1 year of age and older. The adequacy of the data would be a matter of review, but the approach seemed reasonable. The Sponsor was requested to include a discussion of whether the assumptions of the negative binomial regression for the primary analysis are met in the sNDA submission.

- The proposal to submit Summaries of Clinical Efficacy (SCE) and Safety (SCS) in lieu of Integrated Summaries of Efficacy (ISE) and Safety (ISS) was considered acceptable, provided that each contained sufficient details and was concise enough to meet the suggested size limit.

- The division stated that the primary safety analyses should be performed in the "Pool TSC" and Pool OLE-TSC" datasets for the TSC sNDA. The Sponsor's proposal to combine safety data from the non-GW-sponsored expanded access program (EAP) into a single dataset with summaries within the SCS was also acceptable.

3.3. Foreign Regulatory Actions and Marketing History

Epidyolex received full EC marketing authorization approval in Europe on 23 Sep 2019. Epidyolex is indicated as adjunctive therapy of seizures associated with LGS or DS, in conjunction with clobazam, for patients 2 years of age and older. No postmarketing data are available from Europe as of the data cutoffs for this sNDA.

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

4.1. Office of Scientific Investigations (OSI)

No inspections were performed for this submission

4.2. Product Quality

Not applicable, as no new Chemistry, Manufacturing and Control data were submitted.

4.3. Clinical Microbiology

Not applicable.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable, as no new nonclinical data were submitted.

4.5. Clinical Pharmacology

For a full assessment of the clinical pharmacology issues, please see the review from the Office of Clinical Pharmacology (OCP).

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The Applicant included 6 studies in the tabular listing of all clinical studies in section 5.2 of the NDA application that included new data in this sNDA submission. One pivotal trial was in patients with TSC (Study 1521), and the other was in patients with DS (Study 1424); two were long-term, open-label extension (OLE), safety studies in patients with TSC (Study 1521, OLE phase) and DS (Study 1415). One was a pilot study in patients with infantile spasms that was terminated early for futility but contributed some safety data. The was a pharmacokinetic (PK) study conducted in patients with TSC to assess population PK parameters of CBD, 7-OH-CBD, and 7-COOH-CBD.

See Table 3 below for a summary of the clinical studies reviewed for efficacy and safety.

Table 3: Clinical Studies in Patients with TSC Contributing Efficacy and/or Safety Data

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
Controlled Studies to Support Efficacy and Safety							
GWEP1521 / NCT02544763	Randomized, double blind, placebo-controlled	CBD oral solution 25 or 50 mg/kg/day (divided BID) vs equal volume of placebo. Titration schedule: Initial dose of CBD 2.5 mg/kg/day increasing 2.5 mg/kg QOD to 25 or 50 mg/kg/day.	Primary: Percentage change from baseline in convulsive seizure frequency during the treatment period	Baseline: 28 days Titration: 2 weeks Maintenance: 12 weeks Follow-up: 4 weeks (or enrollment in OLE)	255 screened 224 randomized CBD 25 mg/kg/day: 75 CBD 50 mg/kg/day: 73 Placebo: 76 Screen failures: 31	1-65 years with a clinical diagnosis of TSC and refractory seizures, ≥ 8 convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks	44 centers in 6 countries: US (23), Spain (5), Poland (6), Australia (4), UK (4), Netherlands (2)
Other studies pertinent to the review of efficacy or safety							
GWEP1424 / NCT02224703	Randomized, double blind, placebo-controlled	CBD oral solution 10 or 20 mg/kg/day (divided BID) vs equal volume of placebo. Titration schedule: Initial dose of CBD 2.5 mg/kg/day increasing 2.5 mg/kg QOD to	Primary: Percentage change from baseline in convulsive seizure frequency during the treatment period	Baseline: 28 days Titration: 2 weeks Maintenance: 12 weeks Follow-up: 4 weeks (or enrollment in OLE)	285 screened 199 randomized CBD 10 mg/kg/day: 67 CBD 20 mg/kg/day: 67 Placebo: 65 Screen failures: 86	2-18 years with a clinical diagnosis of DS and refractory seizures, ≥ 4 convulsive seizures during baseline period while on ≥ 1 AED at a stable dose for ≥ 4 weeks	38 centers in 6 countries: US (23), Spain (7), Israel (1), Poland (3), Australia (2), the Netherlands (2)

Trial Identity/ NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		10 or 20 mg/kg/day.					
Other studies pertinent to the review of safety							
GWEP1521 / NCT02544763	Open-label safety	CBD oral solution 25 to 50 mg/kg/day (divided BID)	To evaluate the long-term safety and tolerability of CBD-OS in children and adults with TSC and inadequately controlled seizures.	3-week titration followed by maintenance period (1 to 4 years, depending on country)	199 patients	1-65 years with a clinical diagnosis of TSC and refractory seizures	
GWEP1415 / NCT02224573	Open-label safety	CBD oral solution 10 to 20 mg/kg/day (divided BID)	To evaluate the long-term safety and tolerability of CBD-OS in children and adults with DS or LGS and inadequately controlled seizures.	2-week titration followed by maintenance period (up to 4 years)	681 patients	DS: 2-18 years with a clinical diagnosis of DS and refractory seizures LGS: 2-55 years with refractory seizures	
GWEP15100 / NCT02953548	Pilot safety study	CBD oral solution 40 mg/kg/day (divided BID). Titration schedule: Initial dose of CBD 10 mg/kg/day increasing 10 mg/kg QD to 40 mg/kg/day	To determine the maximum safe, tolerable dose and dosing regimen of CBD in infants with infantile spasms (IS), to be utilized in the pivotal phase and OLE.	4-day titration followed by 2-week maintenance period, followed by OLE phase	9 patients enrolled and treated. No-Go criteria reached after 9th patient as 0 patients had resolution of spasms and hypsarrhythmia	1-24 months with documented hypsarrhythmia and IS on prolonged video-EEG monitoring	

Sources: Module 5.2; also clinical study reports from Studies 1521, 1424, and 1415.

Safety information was also collected from patients enrolled in studies in the Expanded Access Program (EAP, a multitude of small uncontrolled studies of CBD in a variety of refractory epilepsy syndromes).

Table 4: Pediatric Enrollment Data

Study#	Trial Type	Trial Design	# of Pediatric Patients Randomized
1521	Efficacy, safety	Randomized, double blind, placebo-controlled	166
1424	Efficacy, Safety	Randomized, double blind, placebo-controlled	199

5.2. Review Strategy

An efficacy determination was made by evaluating the results from one double-blind, placebo-controlled trial in patients with TSC. This reviewer assessed the primary endpoint by examining the source data provided by the Applicant.

Statistical analysis of the data was performed and reported by Dr. Jinnan Liu.

Safety analyses were performed primarily on a dataset of patients from the blinded phase of Study 1521. Other analyses were performed on a pooled dataset of patients from the blinded and OLE phases of Study 1521.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study 1521

6.1.1. Study Design

Title

GWEP1521 – A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures.

Overview and Objective

GWEP1521 (Study 1521) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study of cannabidiol in patients with refractory seizures and TSC.

The objectives of this study were as follows:

- Primary: *"To evaluate the efficacy of GWP42003-P as add-on therapy in reducing the frequency of seizures* when compared with placebo in patients with tuberous sclerosis complex (TSC)."*
  ** Seizures included: focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic-clonic, tonic, clonic or atonic) that are countable.*
- Secondary:
  - *To evaluate the effect of GWP42003-P compared with placebo on antiepileptic measures.*

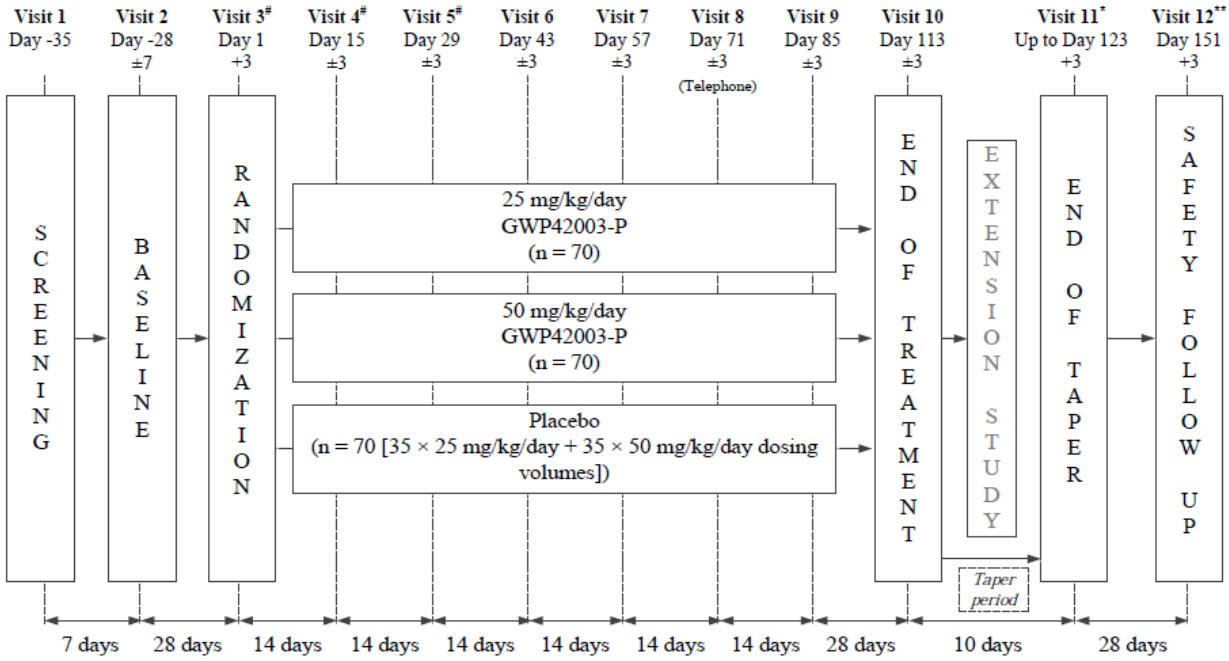
- *To evaluate the effect of GWP42003-P on growth and development (in patients less than 18 years old) compared with placebo.*
- *To evaluate the effects of GWP42003-P on quality of life compared with placebo.*
- *To evaluate the safety and tolerability of GWP42003-P compared with placebo.*

Trial Design

- **Basic Study Design**
  Study 1521 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study of CBD conducted at 44 centers worldwide. Approximately 210 patients were to be randomized into the study. This study was conducted to test the clinical efficacy, safety, and PK of CBD oral solution in patients with tuberous sclerosis complex and inadequately controlled seizures. The total duration of subject participation in the study was 4-5 months (Figure 1). The study consisted of a Screening Period (1 week), Baseline Period (4 weeks), a Treatment Period (titration [2 weeks] plus maintenance [12 weeks]), and a Taper Period (2 weeks), and a follow-up period (4 weeks). Alternatively, patients enrolled in a long-term, OLE study after the treatment period.

  The general design of Study 1521 was similar to other pivotal trials evaluating efficacy of AED treatments.

Figure 1: Trial Design and Treatment Schematic (Study 1521)



Source: Figure 5.1-1, Study 1521 CSR

- **Trial location**
  Study 1521 was conducted in the United States, Europe (Spain, Poland, Netherlands,

and United Kingdom [UK]) and Australia. The patient population and treatment regimen in Europe and Australia are expected to be similar to that in the United States.

- **Choice of control group**
  The Applicant used a concurrent add on "placebo" control as the comparator group, as recommended in FDA Guidelines for the Clinical Evaluation of Antiepileptic Drugs (Adults and Children)[49]. As all patients were receiving at least one AED during the trial, comparison to add-on/placebo is appropriate.

- **Diagnostic criteria**
  Patients were enrolled if they had a "clinical diagnosis of TSC according to the criteria agreed by the 2012 International TSC Consensus Conference" and a documented history of epilepsy.

- **Key inclusion/exclusion criteria**
  Inclusion Criteria:
  1. Willing and able to give informed assent/consent
  2. Age between 1 and 65 years
  3. Clinical diagnosis of TSC according to the criteria agreed by the 2012 International Tuberous Sclerosis Complex Consensus Conference
  4. Documented history of epilepsy with seizures not completely controlled by current AEDs.
  5. Taking at least 1 AED at a dose which has been stable for at least four weeks prior to screening.
  6. All medications or interventions for epilepsy (including ketogenic diet and vagus nerve stimulation [VNS]) must have been stable for 1 month prior to screening and patient and caregiver are willing to maintain a stable regimen throughout the study.

  Randomization Inclusion Criteria
  1. Must have experienced ≥8 TSC-associated seizures during the first 28 days of the baseline period with at least 1 seizure during at least 3 of the 4 weeks. (TSC-associated seizures included focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized convulsive seizures and generalized seizures (tonic-clonic, tonic, clonic or atonic) that were countable.
  2. Completed calls to the interactive voice response system (IVRS) telephone diary on at least 25 days of the baseline period.

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

Exclusion Criteria:

1. History of pseudo-seizures.
2. Significant unstable medical conditions other than epilepsy.
3. Illness in the 4 weeks prior to screening or randomization, other than epilepsy, which in the opinion of the investigator could affect seizure frequency.
4. Undergone general anesthetic in the 4 weeks prior to screening or randomization.
5. Undergone surgery for epilepsy in the 6 months prior to screening.
6. Being considered for epilepsy surgery or any procedure involving general anesthesia during the blinded phase of the trial.
7. Taking felbamate for less than one year prior to screening.
8. Taking an oral mTOR inhibitor.
9. Clinically significantly abnormal laboratory values.
10. Hypersensitivity to cannabinoids or any of the excipients of the IMP, such as sesame oil.
11. History of suicidal behavior or any suicidal ideation of type 4 or 5 on the C-SSRS in the last month or at screening.
12. Currently using or in the past used recreational or medicinal cannabis, or cannabinoid-based medications, within the 3 months prior to screening and was unwilling to abstain for the duration for the trial.
13. Tumor growth which, in the opinion of the investigator, could affect the primary endpoint.
14. Significant abnormalities in the ECG measured at screening or randomization or any concurrent cardiovascular conditions, which would interfere with the ability to read their ECGs.
15. Patient had significantly impaired hepatic function at the screening visit (Day −35) or the randomization visit (Day 1), defined as any of the following:
    i. *Serum ALT or AST > 5 × ULN.*
    ii. *TBL* ≥ 2 × ULN or INR > 1.5 (*TBL ≥ 2 × ULN exclusion did not apply for patients diagnosed with Gilbert's disease).*
    iii. *Serum ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%).*
16. Patient was female and of child-bearing potential or was male whose partner was of child-bearing potential, unless willing to ensure that they or their partner used a highly effective method of birth control during the trial and for 3 months thereafter.
17. Female patient who was pregnant (positive pregnancy test), lactating or planning pregnancy during the course of the trial and for 3 months thereafter.
18. Known or suspected history of alcohol or substance abuse.

Reviewer's comment: The eligibility criteria for Study 1521 were generally similar to

those in other AED treatment trials.

- **Dose selection**
  The 25 and 50 mg/kg/day doses of CBD and the titration (dose escalation) regimen used in Study 1521 were evaluated doses of CBD considered most likely to reduce the multiple seizure types in TSC and to allow demonstration of a possible dose response in TSC. CBD doses of 5, 10, and 20 mg/kg/day were explored a PK study of patients with DS and 10 and 20 mg/kg/day doses were deemed like to be efficacious in patients with DS. Other cannabidiol products have been used in patients with refractory seizures at doses of 10-50 mg/kg/day in published literature. As no significant or unanticipated safety issue occurred in Study 1332A, it was decided to study the higher doses in the TSC pivotal trial.

- **Study treatments**
  Subjects randomized to the CBD treatment groups received daily doses of CBD oral solution (100 mg/mL) at 25 or 50 mg/kg/day. All doses were divided BID. The study drug (or the equivalent volume of placebo) was started at 5 mg/kg/day and increased by 5 mg/kg/day every other day to 25 mg/kg/day (day 9) or to 50 mg/kg/day (day 29). Patients in the 25 mg and 50 mg placebo arms received equal volumes of placebo oral solution using an identical titration schedule.

Reviewer's comment: The titration schedule in Study 1521 was similar to those used in the previous CBD pivotal trials for DS and LGS. The primary difference between Studies 1521 and 1414/1332B/1423 was that those studies titrated CBD by 2.5 mg/kg/day up to 10 mg/kg, then by 5 mg/kg increases. Please see Section 7.1.4 for discussion of the dosing regimen proposed by the Applicant in the draft prescribing information.

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

- **Assignment to treatment**
  At the start of Visit 3, a unique patient number was assigned to each patient using the IVRS/IWRS, and patients were randomly allocated in a 2:2:1:1 manner to 25 mg/kg/day, 50 mg/kg/day, 25 mg placebo, or 50 mg placebo using the IVRS/IWRS.

Reviewer's comment: Patients were randomized after completion of the 28-day baseline period, as they were required to have at least 8 seizures during this time. Patients who did not have sufficient seizures (or were non-compliant with seizure recording) during the baseline were considered screen failures. This is consistent with other AED trials. Randomization was stratified by age group (1-6 years, 7-11 years, 12-

17 years, and 18-65 years) and was performed globally.

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

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

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

- **Administrative structure**
  Investigators at 46 study centers worldwide received IRB/IEC approval to participate in this study, and 44 centers enrolled and treated subjects. Safety data were reviewed on an ongoing basis by the Applicant's Medical Monitor and by an independent Data Safety Monitoring Committee (DSMC). An independent study consortium evaluated all patients for the TSC diagnosis and verified the seizure types of screened patients.

- **Procedures and schedule**
  Table 5 summarizes the schedule of study visits during the baseline period, treatment period, taper period, and follow-up period.

Table 5: Schedule of Assessments (Study 1521)

Visit Number	1	2	3	4	5	6	7	8	9	10	11	12 (Tel.)
Day Number (Visit Window	-35	−28 (±7)	1 (+3)	15 (±3)	29 (±3)	43 (±3)	57 (±3)	71 (±3)	85 (±3)	113 (±3)	123 (±3)	151 (±3)
Informed consent/assent	X											
Eligibility Criteria	X	X	X									
Randomization			X									
Demographics	X											
Medical history	X											
Vital signs and BP	X		X	X	X	X	X		X	X	X	
Postural BP	X		X		X							
Physical examination (incl height and body weight)	X		X	X	X	X	X		X	X	X	
ECG	X		X§	X	X	X	X		X	X	X	
Laboratory blood sampling	X		X	X	X	X	X		X	X	X	
Laboratory IGF-1 testing			X							X		
Urinalysis	X		X	X	X	X	X		X	X	X	
Urine/serum THC screen	X											
Pregnancy tests (if appropriate)	X		X		X		X		X	X		
Pharmacokinetic blood sampling			X							X		
AED concentration			X		X		X		X	X		
TSC1 and *TSC2* mutation status (if unknown and consented)	X											
AEs	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Inpatient epilepsy-related		X	X	X	X	X	X	X	X	X	X	X
hospitalizations												
Suicidality/C-SSRS/Children's C-SSRS	X		X	X	X	X	X		X	X	X	
Vineland-II			X							X		
SGIC/CGIC			X							X		
PGIC			X							X		
SGIC-SD/CGIC-SD			X							X		
QOLCE/QOLIE-31-P			X							X		
Wechsler Tests			X							X		
CBCL/ABCL			X							X		

Visit Number	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 (Tel.)**
Day Number (Visit Window	**-35**	**−28 (±7)**	**1 (+3)**	**15 (±3)**	**29 (±3)**	**43 (±3)**	**57 (±3)**	**71 (±3)**	**85 (±3)**	**113 (±3)**	**123 (±3)**	**151 (±3)**
SCQ			X							X		
Tanner Staging (where appropriate)			X							X		
Menstruation question (where appropriate)			X							X		
Patient IVRS and paper diary review (seizures, AE information, concomitant AEDs, rescue medication, IMP dosing)			X	X	X	X	X		X	X	X	
IVRS and diary training		X										
IMP dispensing			X	X	X	X	X		X	X		
Collection of IMP				X	X	X	X		X	X	X	
IMP compliance review				X	X	X	X		X	X	X	
Study Medication Use and Behavior Survey										X†		

Source: from Table 5.5.1-1, Study 1521 CSR

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

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

  Prohibited therapies during the study period were as follows:
  - *Any new medications or interventions for epilepsy (including ketogenic diet and VNS) or changes in dosage.*
  - *Recreational or medicinal cannabis or synthetic cannabinoid-based medications (including Sativex) within 3 months prior to or during the study.*
  - *Any other IMP taken as part of a clinical trial within six months or during the study.*
  - *Felbamate if taken for less than 1 year prior to screening.*
  - *Oral mTOR inhibitor*

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

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

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

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

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

Other potential withdrawal criteria included:

- Did not meet eligibility criteria.
- Patient non-compliance.
- AE which, in the opinion of the investigator, would compromise the continued safe participation of the patient in the study.
- Suicidal ideation or behavior of type four or five during the treatment period, as evaluated with the C-SSRS.

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

If a patient withdrew from the study during the treatment period, *"the primary analysis variable will be calculated from all the available data, during the treatment period, including any data available after the patient withdraws."* (1521 SAP, pg. 14) Sensitivity analyses to account for missing data arising from unreported days in the IVRS and missing data arising from patients withdrawing during the treatment period were prespecified in the SAP and performed.

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

Study Endpoints

Primary Efficacy Endpoint

The primary endpoint for Study 1521 was *"change in number of TSC associated seizures* during the treatment period (maintenance and titration) compared to baseline in patients taking GWP42003-P compared with placebo."*

The seizure types included in the primary endpoint analysis include countable:

- focal motor seizures without impairment of consciousness or awareness (Type 1 Focal);
- focal seizures with impairment of consciousness or awareness (Type 2 Focal);
- focal seizures evolving to bilateral generalized TSC-associated seizures (Type 3 Focal); and
- generalized seizures (tonic–clonic, tonic, clonic or atonic).

The primary efficacy endpoint was not assessed at one specific time but was rather a measure of change in seizure frequency over the entire treatment period, which included the 4-week titration period and the 12-week maintenance period.

Patients or caregivers were to record the number and type of seizures each day from screening until completion of dosing using the Interactive voice response system (IVRS).

Reviewer's comment: The primary outcome measure used in Study 1521 (percentage change from baseline in seizure frequency) is the most common efficacy endpoint AED treatment trials, though the outcome variable may differ depending on the underlying type of epilepsy and method of analysis. For example, in a study evaluating a drug intended to treat partial onset seizures (POS), the primary efficacy endpoint would likely be percentage change from baseline in frequency of POS. Patients with TSC have multiple seizure types, with seizures ranging in severity from generalized tonic-clonic seizures to atypical absence seizures, so careful definition of the primary outcome variable was important. The Applicant separated the seizure types into two broad categories: "TSC-associated seizures" and "other seizures". TSC-associated seizures were defined in the protocol as focal motor seizures without impairment of consciousness or awareness; focal seizures with impairment of consciousness or awareness; focal seizures evolving to bilateral generalized TSC-associated seizures and generalized seizures (tonic–clonic, tonic, clonic or atonic) that are countable. Seizures other than those above (absence seizures, myoclonic seizures, focal sensory seizures, and infantile/epileptic spasms) were considered "other" for the purpose of the primary efficacy analysis. These definitions were discussed with FDA prior to study commencement. Because the TSC-associated seizures are the most disabling and most likely to lead to patient injury, efficacy of CBD in TSC was measured by reduction in frequency of TSC-associated seizures.

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

Secondary Efficacy Endpoints

Key Secondary Endpoints

- *Treatment Responder Rate*
  Number of patients considered treatment responders, defined as those with a ≥50%

reduction in TSC-associated seizures from baseline during the treatment period.

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

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

Reviewer's comment: The CGI-C is a patient/caregiver reported outcome that aims to quantify disease activity against an anchor point. It is meant to provide an assessment of more global effects than only change in seizure frequency but is related to that measure to some degree.

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

Other Secondary Efficacy Endpoints

A number of secondary efficacy endpoints were evaluated in Study 1521. There was significant redundancy in these endpoints, and only a select number of secondary endpoints will be discussed.

- TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom
- Other (non-TSC-associated") Seizures
- Number of TSC-associated Seizure Free Days
- Individual Seizure Types
- Caregiver Global Impression of Change
- Status Epilepticus

- Quality of Life in Childhood Epilepsy
- Use of Rescue Medication

Secondary endpoints of particular clinical interest will be discussed below.

TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom

The number of patients experiencing a >25% worsening, +25 to -25% change, 25 to 50% improvement, 50 to 75% improvement or >75% improvement in TSC-associated seizure frequency from baseline during the treatment period will be summarized by treatment group. Additionally, the proportion of patients considered treatment responders, defined as those with a ≥25% or ≥75% reduction in TSC-associated seizure frequency from baseline, as well as the proportion of patients who have no TSC-associated seizures (100% reduction in TSC-associated seizure frequency from baseline during the treatment period), will be summarized by treatment group and analyzed.

Other Seizures

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

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

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

Safety Parameters

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

- Potential cases of Drug-induced Liver Injury
- Plasma concentrations of concomitant AEDs before and after treatment with CBD, where available.

Reviewer's comment: The planned safety assessments are acceptable.

Statistical Analysis Plan

The primary endpoint is the change in number of TSC-associated seizures during the treatment period (titration + maintenance) compared to baseline period in patients taking CBD compared with placebo.

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

The Applicant used a negative binomial regression model with the total number of TSC-associated seizures during the baseline period and treatment period as the response variables to analyze the primary endpoint. As noted in Section 3.2, the Agency had concerns about this statistical approach and informed the Applicant during the pre-NDA meeting that discussion of whether the assumptions of the negative binomial regression for the primary analysis are met would need to be included in the sNDA submission.

The following sensitivity analyses were specified for the primary endpoint:

- Primary endpoint analysis on the per-protocol (PP) dataset.
- Wilcoxon rank-sum test on percentage change from baseline in TSC-associated seizure frequency during the treatment period. An estimate of the median differences between each CBD arm and placebo, together with 95% Cis using the Hodges–Lehmann approach.
- Rank analysis of covariance (ANCOVA) on percentage change from baseline in TSC-associated seizure frequency during the treatment period.
- ANCOVA model on log-transformed TSC-associated seizure frequency during the treatment period.
- ANCOVA on percentage change from baseline in TSC-associated seizure frequency during the treatment period.
- ANCOVA on percentage change from baseline in TSC-associated seizure frequency during the treatment period including baseline and stratified age group as covariates and treatment arm as a fixed factor. The estimated least squares means and treatment differences, together with the 95% CIs and p-values, will be presented.
- Primary endpoint analysis on the maintenance period and each 4-week period of the maintenance period (Weeks 1–4, 5–8, and 9–12 of the 12-week maintenance period).
- Primary endpoint analysis, using the worst case of last observation carried forward

(LOCF), next observation carried backward (NOCB), and the mean from the non-missing data for each patient to impute intermittent missing data arising from unreported days during the treatment period only.

- Primary endpoint analysis using multiple imputation (MI) to impute data under the missing not at random (MNAR) assumption for CBD patients who discontinued for certain reasons.

Protocol Amendments

There were 7 submitted protocol amendments. Important modifications to the protocol are summarized in Table 6 below.

Table 6: Summary of Major Protocol Amendments (Study 1521)

Amendment Number	Date	Major Changes
1	21 OCT 2015	• Added generalized seizures to the primary efficacy outcome. • Added secondary endpoint of Total seizures • Age range changed from 2-65 years to 1-65 years. • Sample size increased from 144 to 192 (44 to 64 per arm)
2	25 AUG 2016	• Increased sample size to 210 • The primary analysis updated from an analysis of covariance to a Wilcoxon rank-sum test. • *A modified description has been included to describe how type I error will be controlled. Equal standing is to be given to 25 mg and 50 mg groups. An adjusted p value for significance ($p<0.025$) will be required if one of the comparisons is >0.05.* • Key secondary endpoint of 50% responder rate specified • Added a criterion to exclude patients with a history of suicidal behavior or suicidal ideation of type 4 or 5 on the C-SSRS at screening in both parts of the study
4	27 JUN 2017	• Revised withdrawal criteria to reflect FDA DILI guidelines • Recategorized secondary endpoints to Key, Other, and Exploratory. • Revised SAP to reflect revised secondary endpoints • Added administration via gastrostomy tube.
5	7 AUG 2018	• Added inclusion criterion that patients must be taking ≥1 AED at a stable dose prior to screening and documented history of epilepsy not completely controlled by current AEDs. • Revised treatment allocation to 2:2:1:1 to 25 mg/kg/day, 50 mg/kg/day, placebo 25 mg, or placebo 50 mg. • Allowed use of mTOR inhibitors and general anesthesia during OLE phase.
6	6 SEP 2018	• Changed primary endpoint analysis method from the Wilcoxon rank-sum test to a negative binomial regression analysis. • Added evaluation of primary efficacy endpoint analysis via Wilcoxon rank-sum test as a secondary endpoint (not key)
7	23 APR 2019	• Changed hierarchy of endpoints so the all TSC-associated seizure endpoints are tested first (before Global Impression of Change (GIC) and total seizure endpoints)

Data Quality and Integrity: Applicant's Assurance

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

Prior to trial initiation, during the trial, and after trial completion, the investigational site was visited by GW clinical research associates (CRAs), and a visit log was maintained. CRAs were responsible for reviewing adherence to the protocol, compliance with ICH GCP and any additional national legislation, and the completeness, accuracy, and consistency of the data. Direct access to the patient's medical and laboratory records was permitted to verify entries on the trial-specific CRFs. The original CRFs and other essential documents (for only 19 subjects as described in Section 5.6.2) were submitted to GW and copies were retained by each trial site…

GW's Clinical Quality Assurance (CQA) department provided quality assurance support for this trial. Audits of the quality systems that support the preparation, conduct and reporting of this trial were conducted periodically in accordance with audit plans. These audits were conducted to assure compliance with the regulations, guidelines, and standard operating procedures in place at the time of the trial. All findings were reported to appropriate personnel for corrective and preventative action (CAPA). All CAPAs relating to the audits have been completed.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant stated that Study 1332B was conducted in in compliance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines for conducting, recording, and reporting trials, as well as for archiving essential documents. The Applicant additionally stated that informed consent and assent, if possible, were obtained prior to carrying out any study procedures. The informed consent forms (ICF), protocol, and amendments for this trial were submitted to and approved by the IRB or independent ethics committee (IEC) at each participating trial site.

Financial Disclosure

In the financial disclosure summary, the Applicant identified 9 investigators with disclosable financial interests, primarily related to funding to support data collection in their EAP INDs. The Applicant states *"To minimize the potential bias of clinical study results by any of the disclosed arrangements or interests, the Phase 3 safety and efficacy studies were randomized, placebo-controlled, double-blind trials, conducted across multiple study sites, and the Investigators were not given access to study results until after the database lock for each study. GW requirements for confidentiality and financial disclosure were outlined in the protocols and clinical trial agreements, in addition to the financial disclosure requirements specified in 21 CFR part 54."*

Reviewer's comment: Similar financial disclosures were presented in the original NDA for Epidiolex. In the review of those findings, it was considered that the monies did not appear to have influenced study outcomes. Similar conclusions may be drawn regarding the findings for the studies under review in this submission.

Patient Disposition

A total of 255 patients were screened for Study 1521, and 224 patients were randomized into the trial (Table 7). Thirty-one patients were excluded from the study prior to randomization and considered screen failures. The single most common reason for screen failure was "Did not meet inclusion criteria", which was reported in 17 patients (52%). The safety and ITT datasets were identical.

Table 7: Disposition of Patients in controlled TSC population (Study 1521)

	CBD 25 mg/kg/day N=75 n (%)	CBD 50 mg/kg/day N=73 n (%)	Placebo N=76 n (%)
Treatment Phase			
Completed	65 (86.7%)	61 (83.6%)	75 (98.7%)
Withdrawn	10 (13.3%)	12 (16.4%)	1 (1.3%)
Adverse Event	8 (10.7%)	8 (11.0%)	
Met Withdrawal Criteria	0	2 (2.7%)	
Other	1 (1.3%)	0	
Physician Decision	0	1 (1.4%)	
Withdrawal by Parent/Guardian	1 (1.3%)	1 (1.4%)	1 (1.3%)
OLE Phase			
Transitioned to OLE Phase	64 (86.5%)	60 (82.2%)	75 (98.7%)

Source: FDA clinical reviewer

Out of the 224 patients who were randomized into Study 1521, 75 were randomized to the CBD 25 mg/kg/day group, 73 to the 25 mg/kg/day group, and 76 to the pooled placebo group. All patients received the correct treatment according to planned treatment allocation. As seen in Table 7 above, 10% of the 224 randomized patients discontinued participation prior to completion of the treatment period, 10 patients (13.3%) in the CBD 25 mg/kg group, 12 (16%) in the CBD 50 mg/kg group, and 1 (1%) in the placebo group. The majority of patients who discontinued participation in the CBD groups withdrew due to adverse events (11% in each CBD dose group), while no patients in the placebo group discontinued because of an adverse event. The placebo patient withdrew because of parent/guardian.

Reviewer's comment: Although the overall numbers and percent of patients who discontinued participation during the treatment period of Study 1521 were small, there was an imbalance

between the CBD groups and the placebo group. Specifically, the completion rate for the placebo group (98.7%) was notably greater than in the treatment groups (86.7% and 83.6% in the 25 mg/kg and 50 mg/kg groups, respectively), and the reasons for discontinuation differed between groups. The majority of the patients in the CBD groups who withdrew during the treatment period, did so because of adverse events, while no patients did so in the placebo group. This phenomenon is not uncommon in AED treatment trials.

Protocol Violations/Deviations

Overall, 209 patients (93.3%) were reported as having at least one protocol deviation during the study. The incidence of deviations in all three groups was very similar, with 66 in the CBD 25 mg/kg group (88%), 64 in the CBD 50 mg/kg group (88%), and 69 in the placebo group (91%). None of protocol deviations that were directly related to safety.

Reviewer's comment: The protocol deviations were minor from the perspective of not impacting the study results.

Table of Demographic Characteristics

The baseline demographics of the patients enrolled and randomized in Study 1521 were similar between groups (Table 8). The mean ages were 14.1, 12.8, and 13.8 in the 25 mg, 50 mg, and placebo groups, respectively, and the distribution among the predefined age groups was also similar among the treatment groups. A total of 10 patients were < 2 years of age at the time of enrollment into Study 1521, 6 were randomized to placebo, 1 to the 25 mg group and 2 to the 50 mg group. Half of the patients overall were from the U.S. with 48%, 47% and 55% from the U.S. in the 25 mg, 50 mg, and placebo groups, respectively. Overall, 90% of patients were white.

Table 8: Baseline demographics in controlled TSC population (Study 1521)

Subgroup	CBD 25 mg/kg/day (N = 75) n (%)	CBD 50 mg/kg/day (N = 73) n (%)	Placebo (N = 76) n (%)	Total (N = 224) n (%)
Sex				
Female	32 (42.7)	30 (41.1)	31 (40.8)	93 (41.5)
Male	43 (57.3)	43 (58.9)	45 (59.2)	131 (58.5)
Age				
Mean	14.11	12.78	13.79	13.57
SD	10.81	8.55	10.61	10.03
Min, Max	1.05, 56.78	1.8, 34.92	1.2, 55.77	1.05, 56.78
Age Group (years)				
Age 1-6	21 (28.0)	21 (28.8)	22 (28.9)	64 (28.6)
Age 7-11	18 (24.0)	18 (24.7)	18 (23.7)	54 (24.1)
Age 12-17	16 (21.3)	16 (21.9)	16 (21.1)	48 (21.4)
Age 18+	20 (26.7)	18 (24.7)	20 (26.3)	58 (25.9)

Subgroup	CBD 25 mg/kg/day (N = 75) n (%)	CBD 50 mg/kg/day (N = 73) n (%)	Placebo (N = 76) n (%)	Total (N = 224) n (%)
Race				
Native American or Alaska Native	1 (1.3)	0 (0.0)	0 (0.0)	1 (0.4)
Asian	1 (1.3)	0 (0.0)	3 (3.9)	4 (1.8)
Black	2 (2.7)	3 (4.1)	0 (0.0)	5 (2.2)
Other	3 (4.0)	4 (5.5)	6 (7.9)	13 (5.8)
White	68 (90.7)	66 (90.4)	67 (88.2)	201 (89.7)
Region				
Europe	34 (45.3)	30 (41.1)	24 (31.6)	88 (39.3)
Other	5 (6.7)	9 (12.3)	10 (13.2)	24 (10.7)
United States	36 (48.0)	34 (46.6)	42 (55.3)	112 (50.0)
Weight (kg)				
N	75	72	75	222
Mean	42.79	42.37	44.90	43.37
SD	23.988	23.747	27.972	25.240
Min, Max	12.1, 143.7	13.0, 130.0	10.4, 115.7	10.4, 143.7
Height (cm)				
N	75	70	75	220
Mean	142.1	138.5	138.7	139.8
SD	27.08	28.62	29.49	28.33
Min, Max	81.0, 196.0	85.0, 184.0	80.0, 182.0	80.0, 196.0
BMI				
n	75	70	75	220
Mean	19.66	20.07	20.90	20.21
SD	5.823	5.011	6.359	5.771
Min, Max	8.4, 44.4	12.6, 38.4	13.2, 40.5	8.4, 44.4

Source: Applicant's Table 8.2-1, modified by FDA clinical reviewer
*The age groups in my analysis differ slightly from those used by the Applicant, because I separated patients <2 years of age into defined group.

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

The patients' current seizure types, based on their medical history, are summarized in Table 9. The distribution of current seizure types reported at screening was similar across the treatment groups, with focal motor seizures with or without impairment of consciousness being most common. Number of current and prior AEDs were also similar between groups, as were specific concurrent AEDs.

Table 9: Baseline characteristics in controlled TSC population (Study 1521)

Characteristic	CBD 25 mg/kg (N=75)	CBD 50 mg/kg (N=73)	Placebo (N=76)
TSC-associated Seizures per 28 Days			
Median	56.0	61.0	54.1
Min, Max	7.7, 427.7	10.3, 478.8	8.0, 558.0
Baseline Seizure Subtype (TSC-associated seizures only)			
Focal motor seizures w/o impairment of consciousness	29 (38.7%)	39 (53.4%)	33 (43.4%)
Focal seizures with impairment of consciousness	46 (61.3%)	54 (74%)	50 (65.8%)
Focal seizures evolving to bilateral generalized seizures	17 (22.7%)	24 (32.9%)	24 (31.6%)
Tonic–clonic	22 (29.3%)	16 (21.9%)	14 (18.4%)
Tonic	27 (36%)	23 (31.5%)	15 (19.7%)
Clonic	3 (4%)	3 (4.1%)	2 (2.6%)
Atonic	10 (13.3%)	5 (6.8%)	13 (17.1%)
Number of Concurrent AEDs Patient (Continuous)			
Median	3	3	3
Min, Max	0, 4	1, 5	1, 5
Number of Concurrent AEDs Patient (Categorical)			
0	1 (1.3%)	0	0
1	9 (12%)	7 (9.6%)	8 (10.5%)
2	20 (26.7%)	24 (32.9%)	27 (35.5%)
3	30 (40%)	26 (35.6%)	32 (42.1%)
4	15 (20%)	11 (15.1%)	7 (9.2%)
5	0	5 (6.8%)	2 (2.6%)
Number of Prior AEDs (failed)			
Median	4	4	4
Min, Max	0, 13	0, 13	0, 15
Concurrent AEDs (in at least 20% of patients)			
Clobazam	17 (22.7)	19 (26.0)	25 (32.9)
Valproic acid	29 (38.7)	36 (49.3)	35 (46.1)
Vigabatrin	28 (37.3)	29 (39.7)	17 (22.4)
Levetiracetam	19 (25.3)	22 (30.1)	24 (31.6)
Lamotrigine	17 (22.7)	15 (20.5)	18 (23.7)
Lacosamide	16 (21.3)	15 (20.5)	12 (15.8)

Source: Tables 8.2-2 and 8.2-6, Study 1521 CSR

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

The median baseline TSC-associated seizure frequency (median per 28 days) was similar

between groups, allowing for comparison between groups of the primary efficacy endpoint, although more TSC-associated seizures were reported in the CBD 50 mg/kg group (61.0) than in the 25 mg/kg (56.0) and placebo (54.1) groups.

Reviewer's comment: Although there were some differences between the groups with respect to baseline characteristics, the similarity of the baseline characteristics overall suggests that the underlying seizure disorders in the three groups are reasonably similar.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

A total of 43 patients (19.2%) had 1 or more days during the treatment period during which at least 1 dose of IMP was recorded as not being taken, 15 patients (20%) in the 25 mg/kg/day CBD group, 12 patients (16.4%) in the 50 mg/kg/day group, and 16 (21.1%) in the placebo group. In most of these patients (38/43, 88%), the number of days in which at least 1 dose was missed was less than 7 days. The maximum number of days during the treatment period in which no IMP was taken was 26 days, reported for 1 patient in the 50 mg/kg/day CBD group.

Use of rescue medications during the treatment period was most frequent in the 50 mg/kg group (32.9%), as compared to the 25 mg/kg (21.3%) and placebo (26.3%) groups.

Reviewer's comment: Treatment compliance was reasonably similar amongst the treatment groups. Rescue medication usage did not predispose towards increased efficacy in the CBD groups, as the there was no obvious dose effect.

Efficacy Results - Primary Endpoint

All patients who were randomized, received at least 1 dose of study drug, and had at least one post-baseline efficacy endpoint were included in the ITT analysis dataset, according to their allocated treatment group. The primary efficacy analyses were conducted on the ITT analysis set, which comprised a total of 224 patients: 75 patients in the 25 mg CBD group, 73 patients in the 50 mg CBD group, and 76 patients in the placebo group.

As noted above, the primary efficacy endpoint was the change from baseline in TSC-associated seizure frequency per 28 days during the treatment (titration + maintenance) period. The Applicant had previously planned to use the Wilcoxon rank-sum test with the Hodges–Lehmann p-value to estimate median difference between treatments for the primary endpoint analysis, which the Division of Biometrics 1 (DB1) generally prefers for analysis of non-parametric data such as seizure counts over time. In the background material for the pre-NDA meeting submitted in Sept 2018, the applicant stated that the primary endpoint would be analyzed using a negative binomial regression (NBR) model. At the pre-NDA meeting, DB1 expressed some concerns about this approach and noted that the adequacy of this method would be a

matter of review. DB1 said that the Applicant would need to provide a justification for the NBR in the sNDA submission. The Applicant included a justification in the sNDA submission, which was reviewed by DB1.

In the CSR for Study 1521, the Applicant analyzed the primary endpoint using a negative binomial regression (NBR) model and performed a sensitivity analysis of the primary endpoint using the Wilcoxon rank-sum test (Table 11).

As noted in their review of the sNDA submission, DB1 did not agree with the acceptability of this model for the following reasons:

- There is the lack of independence of one of the parameters (seizure count) within the model. *"The underlying assumption of negative binomial distribution is that the individual event counts are independent. It is not certain that seizure events would be considered independent of each other."* ***[Clinical reviewer's comment: From the clinical perspective, patients who have many seizures on one day are more likely to have many seizures on other days. Note that this relationship is not completely dependent, as patients may have no seizures one day and several the next day.]***
- *"The Primary Endpoint for study 1521 was defined as "Average 28-day measure" which is not actual count measure anymore. For example, if patient only have 10 days, it will be scaled up to 28 days. We don't think this type of data can be appropriate for NBR model****." [Clinical reviewer's comment: The clinical significance of this factor is unclear.]***
- *"The discrepancy between the observed sample means and the NBR model estimated means was quite large…"* which suggests potential overfitting of the model.

For these reasons, DB1 analyzed the primary efficacy endpoint using the Wilcoxon rank-sum test (based on Hodges-Lehmann estimator). Of note, the change to the negative binomial model was made in the last version of the SAP and submitted to FDA only a few days before the unblinding. Although not a reason for lack of acceptability of the model, it was not feasible for the division to review and provide any feedback on such major change prior to the unblinding. For these reasons, DB1 analyzed the primary efficacy endpoint using the Wilcoxon rank-sum test (based on Hodges-Lehmann estimator).

There were statistically significant differences between each CBD group (25 mg/kg/day and 50 mg/kg/day) and the placebo group in the percentage change from baseline in TSC-associated seizure frequency during the treatment period, in favor of CBD treatments (p=0.0038 and p=0.0094, respectively; Table 10). The estimated median difference was −18.77% and -16.95%, respectively, highlighting the treatment effect in both CBD groups.

Table 10: FDA Analysis of the Primary Endpoint Using Wilcoxon Rank-Sum Test (Study 1521)

	CBD 25 mg/kg N=75	CBD 50 mg/kg N=73	Placebo N=76
Baseline Period Median	56 (21.24, 101)	61 (36, 117)	54.04 (26.42, 102)
Treatment Period Median	32.35 (8.99, 56)	31.25 (13.63, 81.87)	41.06 (17.35, 76.12)
Median Percentage Change from Baseline (Q1, Q3)	-43.36 (-67.81, -13.64)	-36.55 (-67.03, -5.53)	-20.08 (-47.06, 3.05)
Estimated Median Difference (CI) *	-18.77 (-31.32, -6.28)	-16.95 (-29.51, -4.45)	
p-value	0.0038	0.0094	

Source: Table 8.2.2, GWEP1521-tables.pdf, confirmed by FDA statistical reviewer
*based on Hodges-Lehmann estimator

Table 11: Applicant's Analysis of the Primary Endpoint Using Negative Binomial Regression Model (Study 1521)

	CBD 25 mg/kg (N=75)	CBD 50 mg/kg (N=73)	Placebo (N=76)
Estimated Mean Seizure Rate per 28 Days			
Baseline Period (95% CI)	51.6 (40.8, 65.3)	66.3 (52.3, 84.2)	54.8 (43.4, 69.3)
Treatment Period (95% CI)	26.5 (21.0, 33.5)	34.9 (27.5, 44.2)	40.3 (31.9, 50.8)
Estimated Ratio [Percentage Reduction] Treatment / Baseline	0.514 [48.6]	0.525 [47.5%]	0.735 [26.5%]
Estimated Ratio [Percentage Reduction] Drug / Placebo (CI)	0.699 [30.1%]	0.715 [28.5%]	
Percentage Reduction Difference (CI)* Treatment / Baseline	48.6 (40.4, 55.8)	47.5 (39.0, 54.8)	26.5 (14.9, 36.5)
Effect Size	*22%*	*21%*	
p-value	0.0009	0.0018	

Source: FDA statistical review
Effect size = the extra reduction in the percentage of change from baseline in the 28-days TSC - associated seizure frequency compared to placebo
*based on Applicant's negative binomial regression model

Sensitivity analyses using ANCOVA yielded similar results to the primary analysis (Table 12).

Table 12: Sensitivity Analyses – ANCOVA (Study 1521)

	CBD 25 mg/kg N=75	CBD 50 mg/kg N=73	Placebo N=76
Baseline Period Mean (SD)	77.95 (83.39)	92.95 (89.78)	89.22 (101.78)
Treatment Period Mean (SD)	46.07 (58.15)	58.83 (65.78)	74.45 (105.21)
Percentage Change from Baseline Mean (SD)	-35.22 (46.02)	-34.91 (43.54)	-20.20 (33.83)
LS Mean Percentage Change from Baseline (CI)	-35.55 (-44.98, -26.13)	-35.16 (-44.69, -25.62)	-20.42 (-29.77, -11.07)
LS Mean Difference (CI) *	-15.13 (-28.38, -1.88)	-14.73 (-28.06, -1.40)	
P-value	0.0254	0.0350	

Source: Study 1521 CSR, Table 8.2.5 verified by the FDA statistical reviewer

Consistent results were seen for the maintenance period and each 4-week period of the maintenance period (Table 13).

Table 13: Sensitivity Analyses of Time Periods, Primary Efficacy Endpoint (Study 1521)

Analysis Period Statistics	CBD 25 mg/kg/day (N=75)	CBD 50 mg/kg/day (N=73)	Placebo (N=76)
Titration Period			
n	75	73	76
Percentage Reduction	36.5	35.6	17.9
95% CI	28.4, 43.8	27.4, 42.9	7.6, 27.0
Maintenance Period			
n	71	66	76
Percentage Reduction	55.8	55.8	30.0
95% CI	47.0, 63.2	46.8, 63.3	16.6, 41.2
Maintenance Period (Weeks 1–4)			
n	71	66	76
Percentage Reduction	50.5	53.4	29.0
95% CI	41.3, 58.3	44.6, 60.9	16.5, 39.7
Maintenance Period (Weeks 5–8)			
n	66	63	76
Percentage Reduction	55.9	55.8	28.7
95% CI	46.1, 63.9	45.9, 63.9	14.2, 40.7
Maintenance Period (Weeks 9–12)			
N	64	62	75
Percentage Reduction	56.6	60.3	34.8
95% CI	46.3, 64.9	50.8, 68.0	20.6, 46.4

Source: Study 1521 CSR, Table 8.4.1.1.1-2

Reviewer's comment: Compared with the placebo group, both CBD groups demonstrated a statistically significant decrease in percent change in TSC-associated seizures from baseline to

the treatment period. As noted above in the discussion of the primary efficacy outcome, this is the same primary efficacy endpoint used in most AED treatment trials, although the seizure types counted toward the primary endpoint may differ based on the underlying disease. The findings are both statistically significant (p=0.0038 and p=0.0094 for the 25 mg/kg and 50 mg/kg groups, respectively) and clinically meaningful. As noted by the FDA statistician, the sensitivity analyses on original data, ranked data, and log-transformed data all yielded similar results to the primary analysis. Similar results were seen for the titration period, maintenance period, and each 4-week period of the maintenance period. These are all supportive of the primary efficacy results. Although the Applicant's choice of analysis method for the primary efficacy endpoint was problematic, the primary endpoint was statistically significant using the Wilcoxon rank-sum test, which is FDA's preferred method for this type of analysis.

Missing data

Results of the primary analysis after imputing unreported days in the IVRS were evaluated (Table 14). For this analysis, missing data from the treatment period arising from unreported days in the IVRS were imputed using the worst (highest number of seizures) of the following for each CBD patient who withdrew during the treatment period: LOCF, NOCB, and the mean daily number of seizures during the treatment period (using the non-missing data).

Table 14: Statistical Reviewer's Worst-Case Analysis of the Primary Endpoint (Study 1521)

	CBD 25 mg/kg/day (N=75)	CBD 50 mg/kg/day (N=73)	Placebo (N=76)
Baseline Period Median	56 (21.24, 101)	61 (36, 117)	54.04 (26.42, 102)
Treatment Period Median	32.96 (10.14, 59.96)	31.25 (13.63, 86.23)	41.26 (20.00, 76.39)
Median Percentage Change from Baseline (Q1, Q3)	-35.46 (-61.22, -9.39)	-36.18 (-67.03, -2.56)	-16.91 (-43.51, 6.04)
Estimated Median Difference (CI) *	-19.92 (-32.43, -7.29)	-18.77 (-31.63, -6.19)	-
Hodges–Lehmann P-value by Wilcoxon rank-sum test	.0022	.0065	-

Source: FDA statistical reviewer

**= the worst (highest number of seizures) of LOCF (last observation carried forward), NOCB (next observation carried backward), and the mean daily number of seizures during the treatment period (using the non-missing data).*

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

Subgroup Analyses of the Primary Efficacy Endpoint

Subgroup analyses were performed on the primary efficacy endpoint for age group, sex, and region in the CBD and placebo groups. The sample sizes for each subgroup are small, making it difficult to derive any substantive conclusions of efficacy in a specific subgroup; however, all results trended in favor of CBD, compared to placebo (see Table 15). Subgroup analyses were also performed on the primary efficacy endpoint for concomitant drugs of interest, specifically clobazam, valproic acid, levetiracetam, and vigabatrin. Concomitant use of clobazam was associated with better reduction in seizure frequency for both the CBD groups, as was levetiracetam use in the CBD 25 mg/kg group. but not the 50 mg group. The percentage reduction of TSC-associated seizures in patients not taking concomitant vigabatrin (both CBD dose groups) and levetiracetam and valproate (CBD 50 mg/kg only) was greater than in patients taking these drugs. The results favored CBD over placebo for all AED subgroups.

Reviewer's comment: The results of the subgroup analyses of the primary efficacy endpoint favored both CBD dose groups over placebo in all cases and did not raise any clinical concerns.

Table 15: Subgroup Analysis of the Primary Endpoint, Demographics and Concomitant AEDs (Study 1521)

Treatment	Factor level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	Interaction p-value
Age Group						
25 mg/kg	1-6 years	21 / 22	0.567 [43.3%] / 0.813 [18.7%]	0.698 [30.2%]	(0.472, 1.032)	0.9287
	7-11 years	18 / 18	0.534 [46.6%] / 0.688 [31.2%]	0.776 [22.4%]	(0.504, 1.192)	
	12-17 years	16 / 16	0.506 [49.4%] / 0.808 [19.2%]	0.626 [37.4%]	(0.394, 0.995)	
	18-65 years	20 / 20	0.447 [55.3%] / 0.652 [34.8%]	0.686 [31.4%]	(0.453, 1.039)	
50 mg/kg	1-6 years	21 / 22	0.603 [39.7%] / 0.813 [18.7%]	0.742 [25.8%]	(0.502, 1.096)	0.7737
	7-11 years	18 / 18	0.529 [47.1%] / 0.688 [31.2%]	0.769 [23.1%]	(0.501, 1.180)	
	12-17 years	16 / 16	0.463 [53.7%] / 0.808 [19.2%]	0.572 [42.8%]	(0.360, 0.910)	
	18-65 years	18 / 20	0.494 [50.6%] / 0.652 [34.8%]	0.758 [24.2%]	(0.498, 1.152)	
Sex						
25 mg/kg	Female	32 / 31	0.513 [48.7%] / 0.668 [33.2%]	0.768 [23.2%]	(0.554, 1.063)	0.4653
	Male	43 / 45	0.514 [48.6%] / 0.784 [21.6%]	0.655 [34.5%]	(0.498, 0.863)	
50 mg/kg	Female	30 / 31	0.570 [43.0%] / 0.668 [33.2%]	0.853 [14.7%]	(0.614, 1.186)	0.1673
	Male	43 / 45	0.495 [50.5%] / 0.784 [21.6%]	0.631 [36.9%]	(0.480, 0.830)	
Region						
25 mg/kg	USA	36 / 42	0.469 [53.1%] / 0.806 [19.4%]	0.583 [41.7%]	(0.435, 0.781)	0.0813
	Rest of World	39 / 34	0.558 [44.2%] / 0.660 [34.0%]	0.846 [15.4%]	(0.627, 1.141)	
50 mg/kg	USA	34 / 42	0.522 [47.8%] / 0.806 [19.4%]	0.648 [35.2%]	(0.482, 0.870)	0.3193
	Rest of World	39 / 34	0.528 [47.2%] / 0.660 [34.0%]	0.801 [19.9%]	(0.595, 1.079)	
Clobazam Use						
25 mg/kg	No	58 / 51	0.556 [44.4%] / 0.738 [26.2%]	0.753 [24.7%]	(0.589, 0.963)	0.1535
	Yes	17 / 25	0.389 [61.1%] / 0.729 [27.1%]	0.534 [46.6%]	(0.356, 0.800)	
50 mg/kg	No	54 / 51	0.576 [42.4%] / 0.738 [26.2%]	0.780 [22.0%]	(0.609, 1.001)	0.1070
	Yes	19 / 25	0.389 [61.1%] / 0.729 [27.1%]	0.534 [46.6%]	(0.361, 0.789)	
Valproic Acid Use						
25 mg/kg	No	46 / 41	0.529 [47.1%] / 0.760 [24.0%]	0.696 [30.4%]	(0.528, 0.919)	0.9776
	Yes	29 / 35	0.490 [51.0%] / 0.707 [29.3%]	0.692 [30.8%]	(0.501, 0.957)	
50 mg/kg	No	37 / 41	0.495 [50.5%] / 0.760 [24.0%]	0.652 [34.8%]	(0.487, 0.872)	0.3734
	Yes	36 / 35	0.558 [44.2%] / 0.707 [29.3%]	0.789 [21.1%]	(0.582, 1.069)	

Treatment	Factor level	n (Active / Placebo)	Ratio to Baseline [Percentage Reduction] (Active / Placebo)	Treatment Ratio [Percentage Reduction]	95% CI	Interaction p-value
Levetiracetam Use						
25 mg/kg	No	56 / 52	0.527 [47.3%] / 0.737 [26.3%]	0.715 [28.5%]	(0.558, 0.916)	0.7079
	Yes	19 / 24	0.478 [52.2%] / 0.731 [26.9%]	0.654 [34.6%]	(0.441, 0.970)	
50 mg/kg	No	51 / 52	0.486 [51.4%] / 0.737 [26.3%]	0.660 [34.0%]	(0.513, 0.849)	0.2617
	Yes	22 / 24	0.624 [37.6%] / 0.731 [26.9%]	0.855 [14.5%]	(0.587, 1.245)	
Vigabatrin Use						
25 mg/kg	No	47 / 59	0.458 [54.2%] / 0.739 [26.1%]	0.619 [38.1%]	(0.481, 0.797)	0.1646
	Yes	28 / 17	0.623 [37.7%] / 0.723 [27.7%]	0.861 [13.9%]	(0.582, 1.273)	
50 mg/kg	No	44 / 59	0.512 [48.8%] / 0.739 [26.1%]	0.692 [30.8%]	(0.537, 0.894)	0.7156
	Yes	29 / 17	0.546 [45.4%] / 0.723 [27.7%]	0.755 [24.5%]	(0.512, 1.112)	

Source: Study 1521 CSR, Table 9.19.1

Efficacy Results – Secondary and other relevant endpoints

The key secondary endpoints were analyzed in a hierarchical manner (Table 16).

Key Secondary Endpoints

- Proportion of patients with a 50% reduction in TSC-associated seizures (50% responders)
  During the treatment period, the proportion of patients with a reduction of 50% or more in their baseline TSC-associated seizure frequency was greater in the 25 mg/kg and 50 mg/kg CBD groups (36.0% and 39.7% respectively), compared with the placebo group (22.4%). The odds ratios (ORs) were in favor of the CBD groups but did not reach statistical significance for the 25 mg/kg group (OR=1.95; p=0.069); therefore, the p-value for the 50 mg/day group was considered nominally significant (OR =3.29; p=0.025).

- Subject/Caregiver Global Impression of Change (S/CGIC)
  For the analysis of S/CGIC score, the 7-point scale scores (1 = very much improved; 7 = very much worse) at the last visit (if different to the end of treatment) were analyzed using ordinal logistic regression. The treatment differences were in favor of both the 25 mg/kg/day and 50 mg/kg/day CBD groups (OR= 2.25 and OR=1.77, respectively), and was nominally significant for the 25 mg/kg group (p=0.0074) but not for the 50 mg/kg group (p=0.058).

- Change in total seizure frequency
  A greater median percent reduction in total seizure frequency (28-day average) during the treatment period was seen in both the 25 mg/kg/day (−34.5%) and 50 mg/kg/day (−33.3%) CBD groups, compared with the placebo group (−14.1%). The difference between each CBD group and placebo was nominally significant (p=0.0013 and p=0.0018, respectively).

Table 16: Analyses of the Key Secondary Endpoints (Study 1521)

Variable	25 mg/kg/day (N=75)	50 mg/kg/day (N=73)	Placebo (N=76)
≥ 50% Reduction in Drop Seizure Frequency			
n (%)	27 (36.0)	29 (39.7)	17 (22.4)
Odds Ratio (95% CI)	1.95 (0.95, 4.00)	2.29 (1.12, 4.67)	
Nominal p-value[1]	0.0692	0.0245 (nominal)	
Subject/Caregiver Global Impression of Change Score at the Last Visit			
Mean	3.0	3.2	3.6
Odds Ratio (95% CI)	2.25 (1.24, 4.07)	1.77(0.98, 3.20)	
Nominal p-value[2]	0.0074	0.0580	

Variable	25 mg/kg/day (N=75)	50 mg/kg/day (N=73)	Placebo (N=76)
Percentage Change from Baseline in Total Seizure Frequency During the Treatment Period			
Baseline (median)	56.00	70.00	56.48
Treatment (median)	32.96	32.25	44.03
Median Percentage Change During Treatment (95%CI)	−34.5 (−58.2, 0.5)	−33.3 (−58.3, −3.9)	−14.11 (−37.6, −2.5)
Estimated Percentage Reduction (95%CI)	−48.1 (39.8, 55.3)	−47.6 (39.3, 54.8)	−26.9 (15.4, 36.8)
Nominal p-value[3]	0.0013	0.0018	

Source: Table 8.4.1.2.1.3-1, Figure 8.4.1.2.1.2-2, and Table 9.3.1.2, Study 1521 CSR
1 - calculated using Cochran-Mantel-Haenszel test stratified by age group (1-6, 7-11, 12-17 and 18-65 years)
2 - calculated using ordinal logistic regression model with treatment group as a fixed factor
3 - calculated using a negative binomial regression model

Reviewer's comment: The key secondary endpoints were analyzed hierarchically. Because the results of the 1st key secondary endpoint (50% reduction from baseline in the 25 mg/kg group compared to placebo) did not achieve statistical significance, all subsequent analyses were reported as nominally significant. One clinical issue with the 50% responder analysis is the underlying supposition that a patient who has a 40% reduction in seizure frequency from baseline is considered a treatment failure. While complete resolution of seizures Is the ultimate goal of seizure management, a reduction of even 30% of seizures from baseline would be considered clinically meaningful in the setting of seizures associated with TSC, due to the general refractoriness of seizures in this population. Therefore, the lack of statistical significance for the 50% responder endpoint in the 25 mg/kg/day group does not mean that CBD is ineffective in the treatment of seizures associated with TSC at that dose.

All of the key secondary endpoints numerically favored CBD (both groups) over placebo and are generally supportive of the primary efficacy endpoint. The ≥ 50% reduction in TSC-associated seizure frequency analysis (50% responder analysis) is not independent of the primary efficacy outcome and, while helpful in defining a subset of patients who might be considered responders, does not provide information separate from the primary efficacy endpoint.

The comparative reduction in the percentage change in total seizure frequency is somewhat related to the primary efficacy but does include the full range of seizures assessed in Study 1414 and suggests a broad efficacy in seizures in patients with TSC.

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

Other Secondary Endpoints of Clinical Interest

- **Non-TSC-associated Seizures**
  Non-TSC-associated seizures were reported during baseline in 16% of patients in the 20 mg/kg group, 32.9% of the 50 mg/kg/day patients, and 19.7% of placebo patients in the ITT analysis set. There was a median reduction from baseline in non-TSC-associated seizure frequency during the treatment period for all three treatment groups. This reduction was larger in the 50 mg/kg group (−89.9%) and the placebo group (−77.7%) than in the 25 mg/kg group (-39.7%) (Table 17).

Table 17: Percentage Change in Non-TSC-Associated Seizure Frequency (Study 1521)

	CBD 25 mg/kg/day (N=75)	CBD 50 mg/kg/day (N=73)	Placebo (N=76)
Total Non-TSC-associated Seizure Frequency (per 28 Days) n (%)	12 (16.0)	24 (32.9)	15 (19.7)
Median Percentage Change During Treatment	−39.67	−89.92	−77.73
Q1, Q3	−100.0, 14.6	−100.0, −51.4	−100.0, −32.9

Source: Table 8.4.1.2.2.3-1, Study 1414, CSR

Reviewer's comment: Although not pre-specified in the SAP as a hierarchical secondary endpoint for the purposes of statistical analysis, change in non-TSC-associated seizures is an important endpoint from the clinical perspective. A general concern with epilepsy disorders, in which there are frequent multiple seizure types, is that a treatment may improve one type of seizures and worsen another. Non-TSC-associated seizures, while not as disabling as TSC-associated attacks, still cause significant morbidity for patients with TSC. There was a median reduction from baseline in non-TSC-associated seizure frequency during the treatment period for all three treatment groups, although the median reduction did not favor the 25 mg/kg group over placebo.

- **TSC-associated Seizure Treatment Responders and TSC-associated Seizure Freedom**
  A higher proportion of patients in both the 25 mg/kg and 50 mg/kg CBD groups had a ≥25% reduction in TSC-associated seizure frequency from baseline during the treatment period compared with patients in the placebo group (57.3% and 58.9% vs. 43.4%, respectively). Sixteen percent (16%) of patients in the CBD 25 mg/kg group and 17.8% of patients in the CBD 50 mg/kg/day group achieved a ≥75% reduction in TSC-associated seizure frequency during the treatment period compared with 0% in the placebo group. Only one patient had no TSC-associated seizures during the treatment period (25 mg/kg group). The proportion of patients with a >25% worsening in TSC-associated seizure frequency was similar amongst the treatment groups (8.0%, 11.0% and 7.9% in the CBD

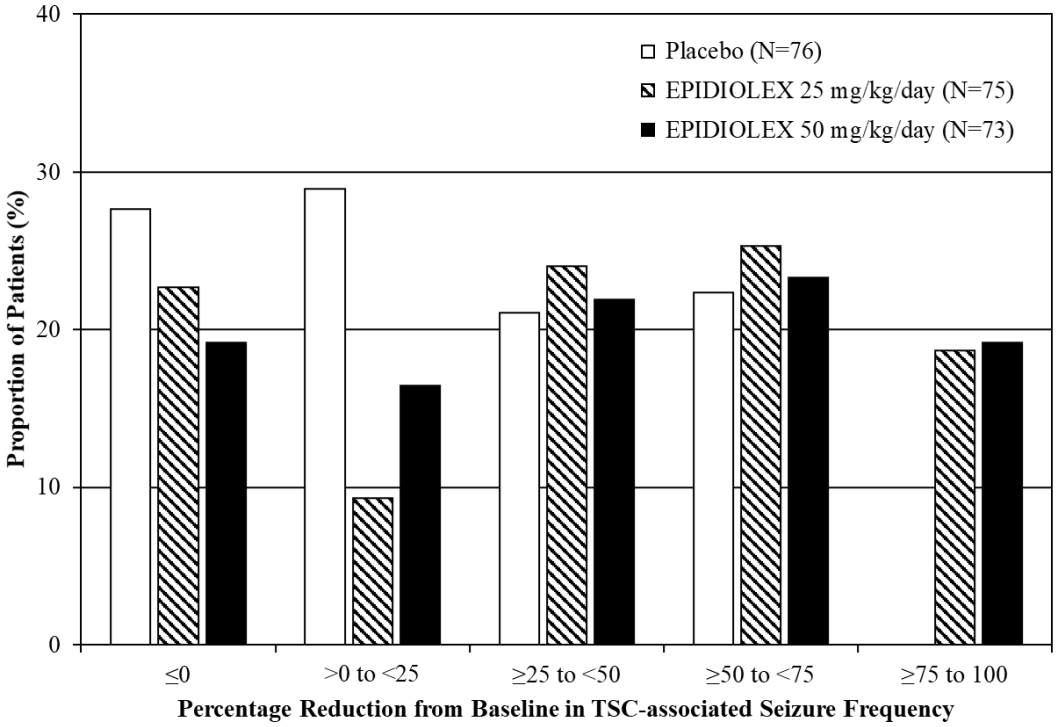
25 mg/kg, CBD 50 mg/kg, and placebo groups, respectively). See Table 18 and Figure 2 below for specifics.

Table 18: Summary and Analysis of TSC-associated Seizure Treatment Responders (Study 1521)

	25 mg/kg (N=76)	50 mg/kg (N=73)	Placebo (N=76)
>25% (Worsening)	6 (8.0%)	8 (11.0%)	6 (7.9%)
≥0% to ≤25% (Worsening)	11 (14.7%)	6 (8.2%)	15 (19.7%)
>25% to <0% (Improvement)	7 (9.3%)	12 (16.4%)	22 (28.9%)
>50% to ≤25% (Improvement)	18 (24.0%)	16 (21.9%)	16 (21.1%)
>75% to ≤50% (Improvement)	19 (25.3%)	17 (23.3%)	17 (22.4%)
≤75% (Improvement)	14 (18.7%)	14 (19.2%)	0
≥25% Reduction			
Yes	43 (57.3%)	43 (58.9%)	33 (43.4%)
No	32 (42.7%)	30 (41.1%)	43 (56.6%)
Difference in Proportions (95% CI) [Active-Placebo]	0.139 (-0.019, 0.297)	0.155 (-0.004, 0.313)	
Odds Ratio (95% CI) [Active/Placebo]	1.75 (0.92, 3.33)	1.87 (0.97, 3.58)	
≥50% Reduction			
Yes	27 (36.0%)	29 (39.7%)	17 (22.4%)
No	48 (64.0%)	44 (60.3%)	59 (77.6%)
Difference in Proportions (95% CI) [Active-Placebo]	0.136 (-0.007, 0.280)	0.174 (0.027, 0.320)	
Odds Ratio (95% CI) [Active/Placebo]	1.95 (0.95, 4.00)	2.29 (1.12, 4.67)	
p-value (nominal)	0.069	0.025	
≥75% Reduction			
Yes	12 (16.0%)	13 (17.8%) 0	0
No	63 (84.0%)	60 (82.2%)	76 (100.0%)
Difference in Proportions (95% CI) [Active/Placebo]	0.013 (-0.013, 0.039)		

Source: Applicant's Table 9.1.1, Study 1521

Figure 2: Continuous Response Analysis for TSC-Associated Seizures, Treatment Period (Study 1521)



Source: Applicant proposed PI

Reviewer's comment: Overall, the responder analysis favored CBD (both dose groups) over placebo. However, this is complicated by the greater proportion of patients in the placebo group (28.9%) with a 0 to ≤25% reduction of TSC-associated seizures when compared to patients in the 25 mg/kg (9.3%) and 50 mg/kg (16.4%) groups. Because of the small numbers of patients in all of these responder analyses, it is difficult to draw any meaningful clinical conclusions from the individual analyses, but the overall analysis is supportive of CBD over placebo.

- **Seizure Subtypes**
  The Applicant assessed outcomes for the following seizure types: type 1 focal, type 2 focal, type 3 focal, tonic-clonic, and tonic. All seizure subtype outcomes favored the CBD groups over placebo, except for type 1 focal, which slightly favored placebo. The baseline mean seizure rate was higher in the 25 mg/kg group (14.3) than in the placebo group (8.1), which may have been a factor in this discrepant result.

Reviewer's comment: Analysis of the median percentage change in seizure frequency of most seizure subtypes favored the CBD treatment groups over placebo and are

generally supportive of the primary efficacy endpoint.

Dose/Dose Response

Study 1521 evaluated two doses of CBD in the treatment of seizures associated with TSC: 25 mg/kg/day and 50 mg/kg/day. Analysis of the primary efficacy endpoint established that both CBD doses were statistically significantly superior over placebo. However, the reduction in TSC-associated seizures was greater in the 25 mg/kg group (−43.4%) than in the 50 mg/kg (−36.6%). Similar findings were seen for reduction of total seizures (−48.1% and −47.6%, respectively), as well as S/CGIC (OR= 2.25 and OR=1.77, respectively). These results suggest that the 50 mg/kg dose does not confer any added benefit over the 25 mg/kg/day dose.

Please also see Section 7.1.4.

Durability of Response and Persistence of Effect

Sensitivity analyses of the primary endpoint were performed on the maintenance period and each 4-week period of the maintenance. Consistent results were seen for each of these time periods in Study 1521. There are no controlled efficacy data in reduction of seizures in patients with TSC beyond 16 weeks.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This application contains data from one pivotal trial to support a new indication – treatment of seizures associated with tuberous sclerosis complex. The Applicant also included a summary of experience of treatment response in patients <2 years of age with a variety of underlying seizure disorders (including 10 patients in Study 1521) to support the expansion of the LGS and DS indications down to 1 year of age. Given the differences between the TSC, LGS, and DS populations and the lack of controlled efficacy data to support the expansion of the LGS and DS indications, direct comparison of the primary efficacy results cannot be made for the three indications. As efficacy for the TSC indication is dependent on a single pivotal trial which is summarized in Section 6.1.2 above, a summary of the efficacy results from Study 1521 will not be repeated here.

7.1.1. Primary Endpoints

See Section 6.1.2 for discussion of the primary endpoint in the TSC pivotal trial.

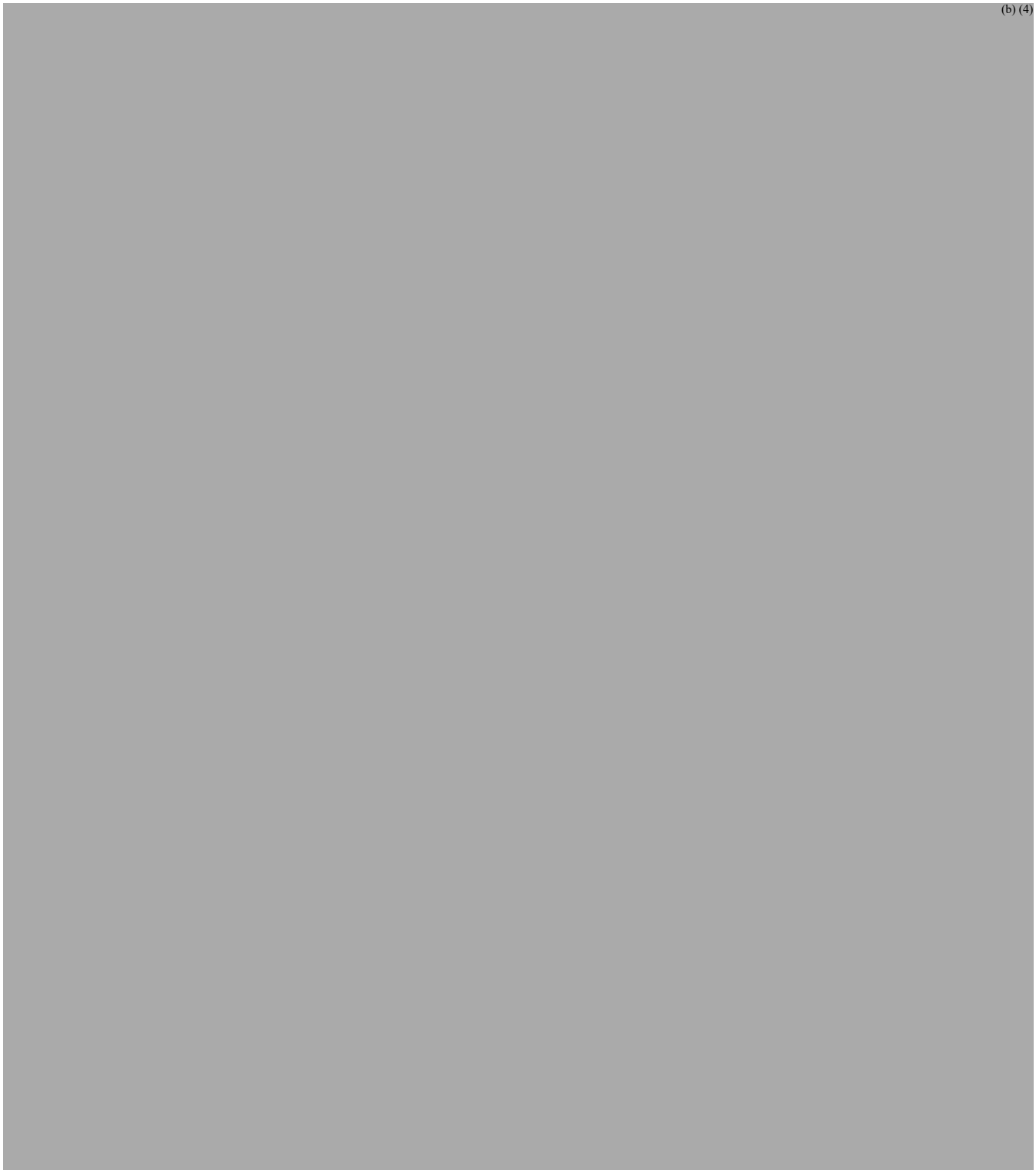
7.1.2. Secondary and Other Endpoints

See Section 6.1.2 for discussion of secondary endpoints in the TSC pivotal trial.

7.1.3. Subpopulations

See Section 6.1.2 for discussion of efficacy in the subpopulations in the TSC pivotal trial.

(b) (4)



7.1.5. Onset, Duration, and Durability of Efficacy Effects

See Section 6.1.2 for discussion of onset, duration, and effect durability in the TSC pivotal trial.

7.1.6. Efficacy in Patients < 2 Years of Age with LGS or DS

The Applicant has proposed to expand the indications for LGS and DS to include patients 1 to < 2 years of age. There are no controlled efficacy data in these populations, as the pivotal trials included only patients 2 years and older. There were 21 patients with various seizure etiologies in the expanded access program with baseline seizure frequencies available for comparison to seizure frequencies while taking CBD, 10 of whom were reported to have "clinically meaningful reductions in seizure frequency." Out of the 21 patients, there were 2 with LGS and 1 with DS. The patient with DS had a reduction of seizure frequency from baseline that persisted for ~30 weeks. He discontinued treatment due to "lack of efficacy" after approximately 1 year. One patient with LGS did not have any initial reduction in seizure frequency (actually increased seizures were reported). After addition of concomitant CLB, her convulsive seizure frequency dropped significantly. The second patient with LGS had an increase in seizure frequency over the first 30 weeks of treatment.

Reviewer's comments: As noted by the Applicant in the 14 Apr 2020 response to an IR, there are no available controlled efficacy data for CBD in the treatment of patients with LGS or DS < 2 years of age in the development program. There are too few patients with LGS or DS < 2 years of age in the EAP (all uncontrolled) from whom to derive any efficacy information.

Many patients with DS or LGS present prior to the age of 2 with seizures, although the clinical diagnosis of the underlying disorder may lag due to incomplete clinical picture, lack of genetic testing, other illnesses, etc. Recruitment of these youngest patients with LGS or DS into seizure drug treatment trials is complicated by small numbers, delayed diagnosis, and the need to have failed at least one drug treatment. Although recruitment of very young patients into DS or LGS may be challenging, the underlying pathophysiology of patients with DS is quite similar between 1 and 4 years of age, such that patients with DS < 2 years of age are expected to respond in a similar fashion to a treatment for seizures as those 2-4 years of age. The expectation is the same for patients with LGS. For these reasons, the efficacy for CBD as a treatment for seizures associated with DS and LGS in pediatric patients older than 2 years of age are supportive of efficacy in patients 1 to < 2 years of age.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

None at this time. While there is some off-label use reported in the postmarket setting, there are no data available to determine efficacy (or lack thereof) of off label use in the postmarket

setting. There have been no reports to suggest lack of efficacy in the approved indications.

7.2.2. Other Relevant Benefits

Not applicable

7.3. Integrated Assessment of Effectiveness

The Applicant provided results from a single randomized, double-blind, placebo-controlled pivotal trial to support cannabidiol in the treatment of seizures associated with tuberous sclerosis complex in patients 1 year of age and older. The trial used a primary efficacy outcome measure (reduction in frequency of prespecified seizures) and primary efficacy endpoint (change from baseline in seizure frequency [average per 28 days] during the treatment period) that are considered to be a standard measure of efficacy in antiepileptic drug trials. The analysis method used by the Applicant to assess the primary efficacy endpoint (negative binomial regression analysis model) was problematic primarily because of the assumption that individual event counts are independent, when they may actually be a dependent parameter. However, more standard analysis methods of the primary efficacy endpoint provided similar results.

Study 1521 provides statistical and clinical evidence for the efficacy of CBD in the treatment of seizures associated with TSC. Both doses of CBD (25 and 50 mg/kg/day) showed statistical superiority over placebo in the reduction of convulsive seizure frequency over the treatment period with the 25 mg/kg group demonstrating slightly better efficacy than the 50 mg/kg group (-18.77 and -16.95 in the 25 mg/kg and 50 mg/kg groups, respectively, compared to placebo). These results were statistically significant (p=0.0038 and p=0.0094, respectively) and clinically meaningful. Additionally, similar results were seen for each 4-week period during the maintenance period, suggesting no effect drop off during the trial.

The key secondary endpoints were analyzed hierarchically. Because the results of the 1st key secondary endpoint (50% reduction from baseline in the 25 mg/kg group compared to placebo) did not achieve statistical significance, all subsequent analyses were reported as nominally significant. CBD was numerically superior over placebo in all of the key secondary endpoints and nominally significant in all but the 50% responder analysis of the 25 mg/kg group, providing more support for the efficacy of CBD in treating seizures in patients with seizures associated with TSC.

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

8. Review of Safety

8.1. Safety Review Approach

The primary safety data used to support this sNDA were generated from a single, randomized, double-blind, placebo-controlled, add-on therapy trial in patients with TSC (Study 1521), which is described in Section 6 above. Supportive long-term safety data were derived from a chronic open-label safety study of CBD in patients with TSC (OLE phase of Study 1521). Other supportive safety data, particularly to explore safety in patients < 2 years of age, were derived from a pilot study of CBD for treatment of infantile spasm (Study 15100) and the EAP.

Other Controlled Data:

- Study 1424: This was a randomized, double-blind, placebo-controlled, add-on trial of CBD to evaluate safety and efficacy in the treatment of seizures associated with DS in patients 2-18 years of age. Patients were randomized to 10 or 20 mg/kg/day of CBD or placebo. These safety data were pooled by the Applicant with safety data from studies submitted to support the original NDA submission.

Uncontrolled Safety Data:

- Study 15100: This was an open-label safety study of CBD in patients with infantile spasms ages 1 to 24 months. A total of 9 patients were enrolled in two cohorts (5 patients in the initial cohort and 4 in the second cohort) and treated with CBD 40 mg/kg/day for 2 weeks. Patients were titrated to the target dose over 4 days (started at 10 mg/kg/day and increased by 10 mg/kg/day daily for 3 days to 40 mg/kg/day). The study was stopped for futility after the 9th patient was treated, as no patient had demonstrated resolution of hypsarrhythmia on EEG or clinical seizures. All 9 patients entered an optional OLE phase.
- Expanded Access Program: this program consists of data derived from a variety of compassionate use programs and is used primarily to explore safety in patients < 2 years of age as well as to provide supporting safety data for the proposed TSC indication and liver safety data.

120-Day Safety Update:
A 120-day safety update was submitted on 29 May 2020 and included no additional patients enrolled into Studies 1521 or 1415 (cutoff date of 01 OCT 2019).

Pooling Data across Studies:
The analyses in this section are based primarily on the controlled safety dataset from Study 1521. Other analyses were performed on the uncontrolled safety dataset and the pooled dataset of patients < 2 years of age (from Study 1521, Study 15100, and the EAP with exposure to CBD (uncontrolled).

Analyses of Adverse Event Data:
The adae.xpt datafile was examined for accuracy of translation from verbatim to preferred term through manual review of all unique pairs of verbatim and preferred terms. Some AEs were coded under slightly different terms, although the underlying events were very similar and/or related. Therefore, several AE terms were recoded to avoid underestimating prevalence of a specific adverse event. Some terms were also recoded for ease of review, although none rose to the level of a new safety concern. The following table shows the original AE code on the left, and revised codes on the right. Terms that only resulted in the addition of one or two cases after recoding are not included in the table.

Where *additions* were made, the original record from the adverse event data file was duplicated (e.g., time of onset, intensity, severity, relatedness), and the new preferred term(s) was used. For example, the Applicant translated the verbatim term "HEAD BUMP (DUE TO FALL(DUE TO SEIZURE))" to the preferred term "Head Injury," but the seizure itself had not generated a preferred term. In such cases, the record for the fall was duplicated, and the newly inserted preferred term ("Seizure") was added on a new line below the original AE.

Grouping of related preferred terms: Applicants typically tabulate preferred terms individually, markedly reducing the apparent magnitude of safety signals. I assessed ~200 groupings of related preferred terms in my safety analyses. For example, the preferred terms "Atonic seizures", "Complex partial seizures", "Clonic convulsion", "Generalised tonic-clonic seizure", "Partial seizures", "Seizure cluster", and "Tonic convulsion" were included in the "Seizure" grouping. "Somnolence," "Sedation," and "Lethargy" were combined in a grouping, as were "Fatigue", "Asthenia", and "Malaise". See Table 22 below for specific changes and revised groupings.

8.2. Brief Review of Other Studies Contributing to Safety

8.2.1. GWEP1424

A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome.

- **Basic Study Design**
  Study 1424 was a Phase 3, multicenter, double-blind, randomized, placebo-controlled study of 2 doses of CBD (10 mg/kg/day and 20 mg/kg/day). This study was conducted to test the clinical efficacy, safety, and PK of CBD oral solution in patients with inadequately controlled seizures due to Dravet syndrome. The study consisted of a Screening Period (1 week), Baseline Period (4 weeks), a Treatment Period (titration [2 weeks] plus maintenance [12 weeks]), and a Taper Period (2 weeks), and a follow-up period (4 weeks). Alternatively, patients enrolled in a long-term, OLE study (Study 1415) after the treatment period.

The primary efficacy outcome was the change in total convulsive seizure frequency during the treatment period of the trial compared to baseline in patients taking CBD compared with placebo. The key secondary efficacy endpoints were change in total seizure frequency, proportion of patients with a ≥ 50% reduction from baseline in convulsive seizure frequency, and change in Caregiver Global Impression of Change (CGIC) score. The primary efficacy endpoint was analyzed using a negative binomial regression model.

Patients were 2-18 years of age with a documented history of DS with seizures incompletely controlled by their current AEDs. In order to randomized, patients were required to have ≥4 convulsive seizures (i.e., tonic–clonic, tonic, clonic, atonic seizures) during the first 28 days of the baseline period.

The general design of Study 1424 was similar to other the other pivotal trial evaluating and safety of efficacy of CBD in the treatment of seizures associated with DS.

- **Results**

  199 patients were randomized to double-blind treatment: 67 to CBD 20 mg/kg/day, 67 to CBD 10 mg/kg/day, and 65 to placebo. 190 patients (95%) completed the treatment period (61 [91%] in the CBD 20 mg/kg group, 64 [97%] in the CBD 100 mg/kg group, and 65 [100%] in the placebo group). 186 (93%) entered the OLE study.

  Similar issues with the negative binomial regression analysis method of the primary efficacy endpoint were identified with Study 1424 as were seen in Study 1521 (Section 6.1.2). When estimated using the Applicant's complex negative binomial regression model, the percentage reduction from baseline in convulsive seizures during the treatment period (primary endpoint period) was greater for the 20 mg/kg/day and 10 mg/kg/day groups compared with placebo (45.7% and 48.7% vs. 26.9%) and the treatment ratios were statistically significant (20 mg/kg: 0.743; 95% CI: 0.568, 0.971; p=0.0299; 10 mg/kg: 0.702, 95% CI: 0.538, 0.916, p=0.0095). When analyzed using the more standard Wilcoxon Rank-Sum test, the Hodges-Lehmann estimated median difference between treatments numerically favored both CBD groups over placebo. However, this difference was only statistically significant for the 20 mg/kg group (-19.88, p=0.0082), not the 10 mg/kg group (-15.74, p=0.1051).

  A similar percentage of patients in each treatment group experienced TEAEs: 89.9%, 87.5%, and 89.2% in the 20 mg/kg, 10 mg/kg, placebo groups, respectively. In the Applicant's analysis, the most frequently reported TEAEs during the treatment period (20 mg/kg and 10 mg/kg vs. placebo) were decreased appetite (29% and 17% vs. 17%), diarrhea (26% and 17% vs. 12%), somnolence (23% and 25% vs. 14%), pyrexia (22% and 23% vs. 17%), fatigue (22% and 8% vs. 11%), vomiting (16% and 6% vs. 6%), nasopharyngitis (12% vs. 6% vs. 8%), ALT increased (13% and 5% vs. 0%), AST increased (12% and 5% vs. 0%), and status epilepticus (10% and 8% vs. 12%). Some TEAEs

demonstrated a dose response (decreased appetite, diarrhea, fatigue, elevated ALT and AST), while others did not (somnolence, pyrexia). All of the commonly reported TEAEs in Study 1424 were also identified in the review of the pooled safety dataset from Studies 1414, 1423, and 1332B.

No patients died during Study 1424. Treatment emergent SAEs were more frequently seen in the CBD groups (25% and 20% in the 20 mg and 10 mg groups, respectively) than in the placebo group (15%). TEAEs led to discontinuation in 5 patients in the 20 mg/kg group and none in the 10 mg/kg or placebo groups. Fatigue and abnormal liver tests each were reported in 3 patients who discontinued due to AEs (2 had both).

Elevations in serum transaminases (ALT or AST) to levels >3x ULN occurred 19% of patients in the 20 mg/kg group, and 5% of patients in the 10 mg/kg group (4.7%) and no patients in the placebo group. All of these patients were also taking concomitant VPA. Elevated transaminases >3x ULN led to discontinuation in 3 patients in the 20 mg/kg group (1 patient also had reductions in CLB and VPA doses). Of the 13 with elevated transaminases who completed the trial, 4 patients had no change to the CBD or other AED doses, 1 patient had an interruption study drug dose, 3 patients had their VPA dose reduced, 1 patient stopped their concomitant CLB, and 1 patient their CLB dose reduced. Most elevations (62.5%) resolved spontaneously or resolved following adjustment of concomitant AED dosing or after discontinuation of CBD. There were no cases that met Hy's law criteria. Liver-related TEAEs were reported in 20%, 11%, and 5% of patients in the 20 mg/kg, 10 mg/kg, and placebo groups, respectively.

Rashes were reported in more patients in the 20 mg/kg group (7.2%) and 10 mg/kg (9.4%) than the placebo group (3.1%).

Reviewer's comments: Safety results of Study 1424 were reviewed but not independently confirmed, as no new signals were identified by the Applicant. Additionally, the results of this study were neither intended nor expected to change dosing recommendations for patients with DS.

(b) (4)

8.2.2. GWEP15100

A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of

cannabidiol (CBD; GWP42003-P) in infants with infantile spasms following an initial open-label pilot study.

- **Basic Study Design**
  Study 15100 was a Phase 2, multicenter, open-label, 2-cohort pilot study to test the clinical efficacy, safety, and PK of CBD 40 mg/kg/day in patients with infantile spasms (IS) and hypsarrhythmia. The first cohort enrolled patients 6-24 months of age, and the second cohort enrolled patients 1-24 months of age, based on safety of the first cohort. Patients were titrated to 40 mg/kg/day of CBD over 4 days and remained on the drug for two weeks. All patients were offered the opportunity to enroll in a long-term, OLE study after the 2-week treatment period.

  Treatment success was considered to be freedom from spams and resolution of hypsarrhythmia at the end of the 2-week treatment, determined by video-EEG.

  Patients had documented hypsarrhythmia and IS on prolonged video EEG monitoring, were 6-24 months of age (inclusive) in the first cohort or 1-24 months of age (inclusive) in the second cohort, had failed to respond adequately to treatment with 1 or more approved IS therapies, and had been stable for all non-pharmacological interventions for epilepsy for 2 weeks prior to screening.

- **Results**
  9 patients with IS and hypsarrhythmia were enrolled in the study. None of the patients had resolution of the spasms or hypsarrhythmia; therefore, the pivotal phase was not initiated.

  All patients were under 2 years of age (range 6 to 23 months).

  Safety results of the treatment and OLE phases were reviewed. Eight patients (89%) experienced a total of 75 TEAEs during the treatment and long-term extension periods. Three patients experienced 21 serious TEAEs, 1 of which occurred during the treatment period (status epilepticus on day #3). No TEAE led to discontinuation and no fatalities were reported. Only 3 TEAEs occurred in more than 2 patients: diarrhea, upper respiratory congestion, and urinary tract infection. The rest occurred in only 1 or 2 two patients. TEAEs of interest included status epilepticus, rash, respiratory failure, urinary retention (severe), and deafness. No elevations in transaminases were reported during the study.

Reviewer's comments: This was an open label pilot study of CBD 40 mg/kg/day in patients with infantile spasms. It consisted of a short-term treatment phase (2 weeks) followed by a long-term extension phase. When all TEAEs in the study were analyzed, the most frequently reported TEAEs were diarrhea, upper respiratory congestion, and urinary tract infection. Three patients (33%) experienced SAEs, but no patients

discontinued early due to a TEAE. In general, the drug appeared well-tolerated in this population, although the study was terminated early for futility due to lack of efficacy.

8.3. Review of the Safety Database

8.3.1. Overall Exposure

(b) (4)

All of the safety data in the primary safety analyses were generated in Study 1521. The data from this study provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs. The primary NDA safety database includes a total of 224 patients who were exposed to at least one dose of cannabidiol. The primary uncontrolled safety dataset is comprised of data from the OLE phase of Study 1521. Further analyses were performed on a dataset of patients less than 2 years of age from Studies 1521 and 15100 and the EAP.

Table 19: Overall Summary of CBD-OS Exposures in the GW Epilepsy Clinical Development Program

Population Source	Total CBD-OS Exposures	Number of Unique CBD-OS Exposures
Controlled trials in the target indications		
Pool TSC (controlled portion of GWEP1521)	148	148
Pool DS/LGS	456	—[a]
Pool DS	221	221
Pool LGS	235	235
Pool DS/LGS/TSC	604	—[a]
Long-term open-label trials in the target indications		
GWEP1521 OLE (TSC)	199	75[b]
GWEP1415 (DS/LGS)	681	282
Phase 1 clinical pharmacology trials (healthy patients and special patient populations)[c]		
(b) (4)		
Trials in other patient populations with epilepsy[d]		
GWEP1428 (DDI study in patients with epilepsy)	16	16
GWEP1447	28	28
GWEP15100[e]	9	9
Total for GW clinical development	(b) (4)	

Population Source	Total CBD-OS Exposures	Number of Unique CBD-OS Exposures
EAP and other compassionate use programs (drug-resistant epilepsy)		
Pool EAP	(b) (4)	

Source: Modified from Table 1-2, Summary of Clinical Safety (SCS)
a - Exposures in pools with combined indications are not considered unique.
b - Total number of unique exposures in the TSC program is 223, as 75 patients from the placebo group transitioned to the OLE study.
c - Includes patients from crossover trials (GWEP1544, (b) (4), GWEP1431) having multiple treatment periods separated by washout periods
(b) (4)
e – Study 15100 was not included in the Applicant's summary of CBD exposure in the development program.

As seen in Table 20 below, 224 patients were enrolled and randomized into Study 1521 and received at least one dose of either CBD (n=148) or placebo (n=76) during the double-blind period. Mean duration of treatment with either dose of CBD during the blinded phase of Study 1521 was 102 days.

At the time of data cutoff for Study 1521 (26 Feb 2019), 223 patients with TSC had received at least one dose of CBD during Study 1521, and 88 patients had been exposed to CBD for ≥12 months at any dose (see Table 21). By the end of the cutoff for the 120-day Safety Update, 110 patients and 28 patients had been exposed to CBD for ≥1 year and ≥2 years, respectively.

Table 20: Summary of CBD exposure by Dose Group (Study 1521)

CBD Exposures				
Controlled phase	**CBD-OS**			
	25 mg/kg/day (N = 75)	**50 mg/kg/day (N = 73)**	**All CBD-OS (N = 148)**	**Placebo (N = 76)**
Patient-years (on treatment)	21.11	20.34	41.45	23.61
Mean ± SD time on study (weeks)	15.2 ± 3.0	15.3 ± 3.0	15.2 ± 3.0	16.3 ± 0.6
Open-label phase	**CBD-OS Modal Dose**			
	≤ 20 mg/kg/day (N = 19)	**> 20-30 mg/kg/day (N = 150)**	**> 30 mg/kg/day (N = 30)**	**All CBD-OS (N = 199)**
Patient-years (on treatment)	18.12	103.89	30.90	152.91
Mean ± SD time on study (weeks)	49.8 ± 34.2	36.4 ± 27.5	53.8 ± 30.0	40.3 ± 29.3

Source: Table 2-1, Summary of Clinical Safety (SCS)

Table 21: Duration of Exposure in all TSC Safety Populations (Study 1521)

	Study 1521 Double-Blind Period[1] (N=224)			Study 1521 Open-Label Period[2] (N=199)				All TSC patients with CBD exposure (N=223)	
	CBD 50 mg/kg (N=75)	CBD 50 mg/kg (N=73)	Pool DB CBD (N=148)	CBD ≤20 mg/kg (N=19)	CBD 20-30 mg/kg (N=150)	CBD 20-30 mg/kg (N=30)	Pool OLE CBD (N=199)	Pool CBD (not incl 120-day update)[3]	Pool CBD (incl 120-day update)[4]
Summary Statistics									
n	75	73	148	19	150	30	199	223	223
Mean (days)	102.8	101.8	102.3	348.3	253.0	376.3	280.7	317.8	445.7
SD	28.8	29.7	29.1	239.3	193.5	210.4	205.6	225.2	278.6
Median	113	113	113	372	232	340	267	307	434
Min, Max	9, 124	10, 125	9, 125	18, 862	26, 876	69, 910	18, 910	9, 988	9, 1205
Duration of Exposure n (%)									
<1 month	5 (6.7)	5 (6.8)	10 (6.8)	1 (5.3)	1 (0.7)	0	2 (1.0)	12 (5.4)	12 (5.4)
1 to <3 months	5 (6.7)	6 (8.2)	11 (7.4)	2 (10.5)	33 (22.0)	1 (3.3)	36 (18.1)	25 (11.2)	15 (6.7)
3 to <6 months	65 (86.7)	62 (84.9)	127 (85.8)	3 (15.8)	29 (19.3)	2 (6.7)	34 (17.1)	35 (15.7)	15 (6.7)
6 to <12 months	0	0	0	3 (15.8)	54 (36.0)	15 (50.0)	72 (36.2)	63 (28.3)	43 (19.3)
12 to <24 months	0	0	0	8 (42.1)	26 (17.3)	8 (26.7)	42 (21.1)	73 (32.7)	110 (49.3)
≥24 months	0	0	0	2 (10.5)	7 (4.7)	4 (13.3)	13 (6.5)	15 (6.7)	28 (12.6)

[1] Duration of exposure is the number of days from the date of first active CBD dose in Study 1521, to the date of last dose in the double-blind period. Placebo patients are not included.
[2] Duration of exposure is calculated from date of first dose in the OLE study to the last date of treatment or data cutoff date, whichever is earlier.
[3] Total duration of active CBD exposure is based on exposure time in the core study plus time in study 1521. For Placebo group patients, first exposure begins in the OLE period
[4] Total duration of active CBD exposure is based on exposure time in the double-blind period plus time in in the OLE period of Study 1521. For patients in the placebo group, first exposure begins in the OLE period.

8.3.2. Relevant characteristics of the safety population:

The baseline demographics and underlying disease characteristics of the patients enrolled and randomized in Study 1521 were similar between groups (Table 8 and Table 9). The safety and efficacy (ITT) populations were identical; see pages 54-57 for a discussion of the relevant characteristics of the study population.

8.3.3. Adequacy of the safety database

Based on the characteristics of the safety population described in Section 6.1.2, the development program provides generally adequate representation across the TSC population; however, the studies enrolled only 4 black patients and only 5 Asian patients. The course of TSC, a genetic disease, is not known to differ importantly in these minority populations. It is unclear if race or ethnicity are factors that would predispose these populations to CBD-associated liver injury. Given the rarity of these diseases, the patient demographic exposure seems adequately diverse and generalizable to the to-be-marked U.S. patient population.

8.4. Adequacy of Applicant's Clinical Safety Assessments

8.4.1. Issues Regarding Data Integrity and Submission Quality

No significant issues with the data were identified during the course of the clinical review.

Routine clinical safety evaluations were scheduled (and generally occurred) at the following timepoints: On-treatment visits were scheduled on Days 15, 29, 43, 57, 71, 85, 113, and 123 with additional safety telephone calls every 2 days during titration, 1 week after the end of titration and, for patients not entering the OLE, weekly from Visit 10 to Visit 12.

8.4.2. Categorization of Adverse Events

The Applicant used standard procedures to collect and analyze adverse event data. Adverse events were recorded at all subject visits, and subjects were to be monitored for adverse events through 28 days after the last dose of the study drug. Investigators were asked to decide on causality and to provide their opinion on intensity (mild, moderate, severe) of each AE.

The standard definition of serious adverse event was used in the development program. A treatment emergent adverse event (TEAE) was defined as an AE *"that started, or worsened in severity or seriousness, following the first dose of IMP."* Status epilepticus was considered to be a medically significant event was to be reported as a serious AE. Clinically significant abnormalities in clinical laboratory tests were to be documented as adverse events.

Multiple occurrences of adverse events were counted once, per specific Medical Dictionary for Regulatory Activities (MedDRA) preferred term. In the OLE period of Study 1521, AEs that were

continuing from the blinded period were carried over as medical history and not classified as adverse events unless they worsened. MedDRA (version 19.1) was used for coding of adverse events for all the clinical studies.

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

Characterization of seizures as AEs in an efficacy trial of a seizure treatment drug is at times complicated by reporting of specific types of seizures. As the incidence of any type of seizure is most important when assessing seizures as AEs, all subtypes of seizures were recoded as "Seizure", except for status epilepticus. The preferred terms preferred terms "Atonic seizures", "Complex partial seizures", "Clonic convulsion", "Generalised tonic-clonic seizure", "Partial seizures", "Seizure cluster", and "Tonic convulsion" were included in the "Seizure" grouping. "Somnolence," "Sedation," and "Lethargy" were combined in a grouping, as were "Fatigue", "Asthenia", and "Malaise". See Table 22 below for specific changes and revised groupings.

Table 22: Recoded AE Codes (Study 1521)

Original Coded Preferred Term(s)	Recoded Term
Abdominal pain upper, Abdominal discomfort	Abdominal pain
Otitis media acute, Otitis media, Ear infection bacterial	Ear infection
Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, Liver function test increased	Elevated transaminase
Viral gastroenteritis	Gastroenteritis
Urticaria, Rash erythematous, Rash papular, Rash maculo-papular, Rash generalized, Rash macular	Rash
Atonic seizures, Complex partial seizures, Clonic convulsion, Generalised tonic-clonic seizure, Partial seizures, Seizure cluster, and Tonic convulsion	Seizures
Upper respiratory tract infection viral	Upper Respiratory Tract Infection

A few seizures were omitted through incomplete translation from the verbatim term to the preferred term. These events were added to the dataset.

The Applicant designated adverse events of special interest (AESI), and these received specific attention. The initial list of AESI is as follows:

- Liver-related TEAEs
- Rashes
- Worsening of seizures and development of new seizure types
- Self-injurious ideation/behavior
- Euphoria
- Pregnancy

8.4.3. Routine Clinical Tests

Assessments of vital signs and laboratory monitoring were performed at screening, randomization and multiple timepoints throughout both trials. The laboratory monitoring performed during Study 1521 is summarized below.

Serum Biochemistry		Hematology	Urinalysis	Additional Tests
Albumin	Glucose	Hematocrit	Bilirubin	Pregnancy (serum and urine)
ALP	HDL-C	Hemoglobin	Blood	THC (serum and urine)
ALT	IGF-1*	MCV	Glucose	
AST	Potassium	MCH	Ketones	
BUN	Prolactin	Platelets	Nitrites	
Calcium	Prothrombin time	RBC count	pH	
Creatine Kinase	Sodium	WBC count	Protein	
Creatinine	TBL		Specific gravity	
GFR	Total protein		Urobilinogen	
GGT	Triglycerides			

Missing data were sparse. There was no indication that laboratory data were obtained in the fasting state. The Applicant evaluated laboratory values based on the Common Terminology Criteria for Adverse Events grading scheme (version 4.03).

8.5. Safety Results

8.5.1. Deaths

One patient (# (b) (6)) died during the OLE period of Study 1521. She was an 11-year-old girl with a history of idiopathic dilated cardiomyopathy, congestive heart failure, left ventricular hypertrophy, hypertension, and renal/cardiac involvement of her TSC. She was found dead in bed on day 74/75 of the OLE period of Study 1521. She had been randomized to the CBD 25 mg/kg/day group during the blinded portion of the trial, although the dose of CBD had been decreased to 10 mg/kg/day because of increased seizures and agitation on day 19 of the OLE study and then increased to 20 mg/kg/day on Study day 34. The cause of death was determined to be cardiopulmonary failure due to TSC.

Sixteen deaths occurred in the OLE study for DS/LGS (Study 1415) as of the cutoff date for the 120-day safety update (01 OCT 2019). These deaths are summarized in Table 23 below. Eight of these deaths were reviewed in the original NDA submission. None of the deaths were adjudicated as due to CBD. The most frequently reported cause of death in these patients was sudden unexplained death in epilepsy (SUDEP), which occurred in 7 (0.8%) of patients. SUDEP is more commonly reported in pediatric patients with DS (and LGS to a lesser degree) than in the general epilepsy population.

Table 23: Fatal TEAEs in DS/LGS and TSC Patients (Studies 1415 and 1521-OLE)

System Organ Class/Preferred Term	CBD ≤20 mg/kg/day (N=350) n (%)	CBD >20-30 mg/kg/day (N=500) n (%)	CBD >30 mg/kg/day (N=30) n (%)	All CBD-OS (N=880) n (%)
Patients with at least 1 fatal TEAE	**10 (2.9)**	**6 (1.2)**	**0**	**16 (1.8)**
Cardiac disorders	2 (0.6)	1 (0.2)	0	3 (0.3)
Cardiac arrest	0	1 (0.2)	0	1 (0.1)
Cardio-respiratory arrest	1 (0.3)	0	0	1 (0.1)
Cardiopulmonary failure	1 (0.3)	0	0	1 (0.1)
Gastrointestinal disorders	1 (0.3)	1 (0.2)	0	2 (0.2)
Gastrointestinal necrosis	1 (0.3)	0	0	1 (0.1)
Intestinal ischemia	0	1 (0.2)	0	1 (0.1)
Intestinal obstruction	1 (0.3)	0	0	1 (0.1)
General disorders and administration site conditions	4 (1.1)	2 (0.4)	0	7 (0.8)
Sudden unexplained death in epilepsy	4 (1.1)	3 (0.6)	0	7 (0.8)
Infections and infestations	1 (0.3)	0	0	1 (0.1)
Peritonitis	1 (0.3)	0	0	1 (0.1)
Septic shock	1 (0.3)	0	0	1 (0.1)
Nervous system disorders	1 (0.3)	2 (0.4)	0	3 (0.3)
Seizure	1 (0.3)	1 (0.2)	0	2 (0.2)
Hypoxic-ischemic encephalopathy	0	1 (0.2)	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	2 (0.6)	0	0	2 (0.2)
Acute respiratory failure	1 (0.3)	0	0	1 (0.1)
Pneumonia aspiration	1 (0.3)	0	0	1 (0.1)
Respiratory failure	1 (0.3)	0	0	1 (0.1)

Source: SCS, Table 4-1 verified in JMP, including one more patient reported during in the 120-day safety update

Reviewer's comment: Patients these studies were often ill, with complex, chronic multisystem diseases and complicated courses. It is not possible to attribute the deaths to CBD, but it is not possible to be certain that the drug did not contribute in some way. The most frequently reported or suspected cause of death (7 patients) is SUDEP, which is common in the DS population (9.32/1000 person-years), more so than in the epilepsy population at large (1.5-5.1/1000 person-years).[32] Therefore, it would not seem appropriate to attribute these deaths to the investigational drug.

8.5.2. Serious Adverse Events

Controlled Trial

A total of 44 serious TEAEs occurred in 28 patients during the treatment period in Study 1521 (Table 24). The incidence of serious TEAEs was notably greater in patients in the pooled CBD group compared to placebo, with 26 patients (17.6%) in the pooled CBD treatment group and only 2 patients (2.6%) in the combined placebo group reporting at least 1 serious TEAE. More

Sixteen patients (21%) in the 25 mg/kg group and 10 (14%) in the 50 mg/kg group reported serious TEAEs.

The most frequently reported serious TEAEs in the pooled CBD group occurred in the Investigations SOC (7 patients [4.7%]). Five (3.4%) patients each experienced serious TEAEs in the Gastrointestinal SOC, Infections and infestations SOC, Nervous system SOC, and Skin and subcutaneous tissues SOC. The serious TEAE that occurred most frequently in the pooled CBD group was elevated hepatic enzymes, which was reported in 6 patients (4.1%). Five patients in the pooled CBD group experienced a serious TEAE of rash (3.4%), while 3 patients each (2%) experienced serious TEAEs of gastroenteritis or seizure and 2 patients each reported serious TEAEs of status epilepticus or vomiting. All other serious TEAEs in the pooled CBD group occurred in a single patient only (abdominal pain, acute respiratory failure, angioedema, blood bilirubin increased, dehydration, diarrhea, ear infection, electrolyte imbalance, fatigue, hypophagia, laceration, liver injury, nausea, pneumonia, pneumonia aspiration, toxicity to various agents). The two serious TEAEs in the placebo group were pneumonia and status epilepticus, each of which occurred in one patient.

Reviewer's Comments: The types and frequencies of serious TEAEs reported in Study 1521 are similar to those seen in the studies of CBD in patients with DS and LGS, as well as in other trials of refractory epilepsy in pediatric patients. Transaminase elevations are clearly drug-related and are discussed in Section 8.5.6 and Section 8.6.1. The underlying reason for the imbalance in serious TEAEs between the CBD groups and the placebo group is not clear.

Table 24: Serious Treatment-Emergent Adverse Events, TSC Controlled Population (Study 1521)

	CBD 25 mg/kg (N=75)		CBD 50 mg/kg (N=73)		Pool CBD (N=148)		PBO (N=76)		Pooled CBD vs. Pooled PBO	
	n	%	n	%	n	%	n	%	RR	Δ Risk (%)
Any TEAE	**16**	**25%**	**10**	**13.7%**	**26**	**17.6%**	**2**	**1.6%**		
Elevated hepatic enzymes	2	2.7%	4	5.5%	6	4.1%	0		4.05	6.72
Rash	3	4.0%	2	2.7%	5	3.4%	0		3.38	5.69
Gastroenteritis	2	2.7%	1	1.4%	3	2.0%	0		2.03	3.62
Seizure	1	1.3%	2	2.7%	3	2.0%	0		2.03	3.62
Status epilepticus	2	2.7%	0		2	1.4%	1	1.3%	0.04	1.03
Vomiting	2	2.7%	0		2	1.4%	0		1.35	2.59
Abdominal pain	0		1	1.4%	1	0.7%	0		0.68	1.55
Acute respiratory failure	1	1.3%	0		1	0.7%	0		0.68	1.55
Angioedema	0		1	1.4%	1	0.7%	0		0.68	1.55
Blood bilirubin increased	1	1.3%	0		1	0.7%	0		0.68	1.55
Dehydration	0		1	1.4%	1	0.7%	0		0.68	1.55
Diarrhea	0		1	1.4%	1	0.7%	0		0.68	1.55
Ear infection	1	1.3%	0		1	0.7%	0		0.68	1.55

	CBD 25 mg/kg (N=75)		CBD 50 mg/kg (N=73)		Pool CBD (N=148)		PBO (N=76)		Pooled CBD vs. Pooled PBO	
	n	%	n	%	n	%	n	%	RR	Δ Risk (%)
Electrolyte imbalance	1	1.3%	0		1	0.7%	0		0.68	1.55
Fatigue/Malaise/Asthenia	1	1.3%	0		1	0.7%	0		0.68	1.55
Hypophagia	1	1.3%	0		1	0.7%	0		0.68	1.55
Laceration	0		1	1.4%	1	0.7%	0		0.68	1.55
Liver injury	1	1.3%	0		1	0.7%	0		0.68	1.55
Nausea	1	1.3%	0		1	0.7%	0		0.68	1.55
Pneumonia	1	1.3%	0		1	0.7%	1	1.3%	-0.64	0.514
Pneumonia aspiration	1	1.3%	0		1	0.7%	0		0.68	1.55
Toxicity to various agents	0		1	1.4%	1	0.7%	0		0.68	1.55

Uncontrolled Safety Data

Twenty-nine patients experienced 59 serious TEAEs during the OLE period of Study 1521 (Table 25). Nervous system and infectious serious adverse TEAEs occurred most frequently (7% and 4.5%, respectively). The most frequently reported serious TEAE in the uncontrolled patient population was seizures, which occurred in 7 patients (3.5%). Other serious TEAEs reported in at least 2% of patients during the OLE period were status epilepticus (2.5%) and hepatic enzyme increased (2%). All other serious TEAEs occurred in only 1 or 2 patients during the OLE period

Table 25: Serious Treatment-Emergent Adverse Events, Uncontrolled TSC Population (Study 1521 OLE)

	All CBD (N=199)	
	n	%
Any serious TEAE during the OLE period	**29**	**14.6%**
Blood and lymphatic system disorders	**1**	**0.5%**
Neutropenia	1	0.5%
Thrombocytopenia	1	0.5%
Cardiac disorders	**1**	**0.5%**
Cardiopulmonary failure	1	0.5%
Gastrointestinal disorders	**1**	**0.5%**
Diarrhea	1	0.5%
General disorders and administration site conditions	**2**	**1.0%**
Pyrexia	1	0.5%
Soft tissue inflammation	1	0.5%
Infections and infestations	**9**	**4.5%**
Influenza	2	1.0%
Gastroenteritis	2	1.0%
Adenoiditis	1	0.5%
Adenovirus infection	1	0.5%
Enterovirus infection	1	0.5%
Infective myositis	1	0.5%
Parainfluenzae virus infection	1	0.5%

	All CBD (N=199)	
	n	%
Pneumonia	1	0.5%
Respiratory tract infection	1	0.5%
Rhinovirus infection	1	0.5%
Upper respiratory tract infection	1	0.5%
Injury, poisoning and procedural complications	**1**	**0.5%**
Toxicity to various agents	1	0.5%
Investigations	**6**	**3.0%**
Hepatic enzyme increased	4	2.0%
Platelet count decreased	2	1.0%
Astrovirus test positive	1	0.5%
Blood bilirubin increased	1	0.5%
Sapovirus test positive	1	0.5%
Metabolism and nutrition disorders	**2**	**1.0%**
Dehydration	2	1.0%
Musculoskeletal and connective tissue disorders	**1**	**0.5%**
Myositis	1	0.5%
Nervous system disorders	**14**	**7.0%**
Seizure	7	3.5%
Status epilepticus	5	2.5%
Somnolence	2	1.0%
Epileptic encephalopathy	1	0.5%
Psychiatric disorders	**2**	**1.0%**
Mental status changes	2	1.0%
Reproductive system and breast disorders	**1**	**0.5%**
Spontaneous penile erection	1	0.5%
Respiratory, thoracic and mediastinal disorders	**3**	**1.5%**
Asthma	1	0.5%
Lung infiltration	1	0.5%
Pneumonitis	1	0.5%

Source: ADAE, revised and analyzed in JMP

Reviewer's Comments: The most frequently reported serious TEAEs in the uncontrolled population were seizures (of any type) and status epilepticus, both of which are frequently reported in this population and are likely related to the underlying diagnosis of TSC. Elevated transaminases (hepatic enzyme increased) were reported in 4 (2%) of patients. Lower frequency serious TEAEs seem generally consistent with expected frequencies in the patient population.

8.5.3. Dropouts and/or Discontinuations Due to Adverse Effects

Controlled Trials

A total of 18 patients (8.9%) discontinued early because of adverse events from Study 1521 during the blinded phase, 8 (10.7%) in the 25 mg/kg group and 10 (13.7%) in the 50 mg/kg group. Two patients in the placebo group developed TEAEs (ataxia and agitation) during the blinded phase that persisted into the OLE phase and eventually led to discontinuation, but these patients are not included in this discussion. One of the patients (# (b) (6)) in the 25 mg/kg group completed the treatment period but withdrew during the taper period (vomiting, weight decreased, decubitus ulcer) and is included in the discussion below.

These 18 patients experienced 31 adverse events leading to discontinuation, with 8 patients experiencing more than one AE (Table 26). Nine of these events were adjudicated as serious and 6 as severe. TEAEs leading to discontinuation which occurred in more than one patient included rash (n=9, 6.1%), hepatic enzyme increased (n=4, 2.7%), and somnolence/sedation (n=2, 1.4%). The rest of the events occurred in one patient each. All but one patient who discontinued participation due to an adverse event did so during the maintenance period. Eleven patients withdrew due to AEs which occurred the titration period, five patients withdrew due to AEs that occurred during the maintenance period, and one patient withdrew during the transition/taper period. One patient withdrew during the maintenance period due to AEs that occurred in titration and maintenance periods. Five events in three patients were reported as not recovered (eosinophil count increased; somnolence and hepatic enzyme increased; blepharospasm and restlessness).

Table 26: Treatment-Emergent AEs Leading to Discontinuation, Controlled TSC Safety Population (Study 1521)

	25 mg/kg (N=75)		50 mg/kg (N=73)		Pool CBD (N=148)		Placebo (N=76)
	n	%	n	%	n	%	
Any TEAE leading to discontinuation	**8**	**10.7%**	**10**	**13.7%**	**18**	**12.2%**	**0**
Rash	4	5.30%	5	6.8%	9	6.1%	0
Hepatic enzyme increased	0		4	5.5%	4	2.7%	0
Somnolence	0		2	2.7%	2	1.4%	0
Blepharospasm	1	1.3%	0		1	0.7%	0
Decubitus ulcer	1	1.3%	0		1	0.7%	0
Electrocardiogram abnormal	1	1.3%	0		1	0.7%	0
Eosinophil count increased	1	1.3%	0		1	0.7%	0
Liver injury	1	1.3%	0		1	0.7%	0
Restlessness	1	1.3%	0		1	0.7%	0
Vomiting	1	1.3%	0		1	0.7%	0
Weight decreased	1	1.3%	0		1	0.7%	0
Angioedema	0		1	1.4%	1	0.7%	0
Diarrhea	0		1	1.4%	1	0.7%	0

	25 mg/kg (N=75)		50 mg/kg (N=73)		Pool CBD (N=148)		Placebo (N=76)
	n	%	n	%	n	%	
Diet refusal	0		1	1.4%	1	0.7%	0
Eye swelling	0		1	1.4%	1	0.7%	0
Lip swelling	0		1	1.4%	1	0.7%	0
Musculoskeletal chest pain	0		1	1.4%	1	0.7%	0

Source: ADAE, ADSL (JMP)

Reviewer's Comments: The discontinuation rate due to AEs in my analysis differ from that in the Applicant's analyses, due to pooling of related preferred terms and exclusion of the placebo patients.

The rate of early termination due to AEs was notably greater in the pooled CBD group (12%) than in the pooled placebo group (0%). Most patients who terminated early due to AEs did so during the titration period (11/18, 61%), which is typical of AED treatment trials. The rest discontinued during the maintenance or taper periods.

There was also a mild dose-response in discontinuations, as 11% of patients in the 25 mg/kg group and 14% of patients in the 50 mg/kg group withdrew early due to adverse events. In the analysis of the pooled safety data from the DS/LGS trials submitted to the original NDA for Epidiolex, there was also an imbalance in discontinuations in the CBD group (9.3%) as compared to placebo (1.3%), although it was not as notable. A dose-response was seen with respect to discontinuation due to AEs in those trials, with 3% and 12% of patients discontinuing early due to AEs in the 10 mg/kg and 20 mg/kg groups, respectively. The dose-response to discontinuations was more prominent in the LGS/DS trials than in the TSC trial.

Rash and hepatic enzymes increased were most frequent AEs leading to discontinuation all CBD group. Rash was not an identified reason for discontinuation in the DS/LGS studies of CBD, which evaluated lower doses. It is unclear if the increased incidence of rash overall and of rash leading to discontinuation are dose-related.

In general, the TEAEs leading to discontinuation were consistent with AEs seen in similar circumstances in other AED studies and to the AEs leading to discontinuation in the DS/LGS trials.

8.5.4. Significant Adverse Events

A total of 17 patients (7.6%) experienced 22 TEAEs during the treatment phase of Study 1521 that were adjudicated as severe. One patient experienced 3 severe TEAEs and two patients experienced 2 severe TEAEs each while the rest of the patients each experienced a single severe TEAE. The severe TEAEs that occurred in more than one patient were rash (3), seizure

(2), and gait disturbance (2). The severe TEAEs that occurred in one patient each were acute respiratory failure, angioedema, decreased appetite, dehydration, diarrhea, drooling, electrolyte imbalance, fatigue, hepatic enzyme increased, liver injury, nausea, pneumonia, somnolence, and vomiting. Seven severe TEAEs contributed to drug discontinuation in 6 patients and drug interruption or dose reduction in 6 other patients.

8.5.5. Treatment Emergent Adverse Events and Adverse Reactions

Controlled population

A total of 1123 treatment emergent adverse events (TEAEs) occurred in 215/224 (96%) patients in the controlled TSC safety database. Overall, the incidence of TEAEs in patients taking any dose of CBD (143, 95%) was similar to that in patients taking placebo (71, 95%) during the treatment period. Overall TEAE rates were slightly lower in the 25 mg/kg group (93%) than in the 50 mg/kg group (100%). A summary of the percentages of subjects with TEAEs that occurred in at least 2% of patients in the any CBD group are presented in Table 27 below.

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

- Hepatic adverse events - elevated transaminases (as detected as adverse events – transaminase elevations detected in the laboratory data are discussed in Section 8.5.6 and Section 8.6.1, below). Frequencies are 32% and 0% in CBD-treated and placebo subjects, respectively, and there is a clear dose-response in the TSC controlled trial, i.e., 25% and 38% in the 25 mg/kg and 50 mg/kg groups, respectively (Table 27).
- Central nervous system events. These include seizures, fatigue/malaise/asthenia, somnolence, and ataxia/balance disorders/gait disturbances. There is an apparent dose-response for somnolence (19% and 30% in the 25 mg/kg and 50 mg/kg groups, respectively) and seizure (8% and 18%), but the reverse was true (higher frequency at lower dose) for ataxia/balance disorders/gait disturbances making CNS adverse events, making overall interpretation difficult.
- Decreased appetite (22% vs. 12%) and weight decreased (7% vs. 0%) in the CBD and placebo groups, respectively, with a dose-response for both (greater frequencies in the 50 mg/kg group than the 25 mg/kg group).
- Other gastrointestinal events, including diarrhea, vomiting, abdominal pain, and retching. Diarrhea is notable because of the risk difference (18%) and apparent dose-response (31% and 56% in the 25 mg/kg and 50 mg/kg groups, respectively).
- Infections with imbalances in ear infections and urinary tract infections. However, incidences of other infections (nasopharyngitis, upper respiratory tract infection) were higher in the placebo group, making any interpretation difficult.
- Rash was more frequently seen in the pooled CBD group (10%) as compared to placebo (4%) with an apparent dose-response (11% and 8% in the 50 mg/kg and 25 mg/kg groups, respectively; and 9 patients discontinued participation early due to rash.

Reviewer's comment:
In general, the overall incidence of TEAEs were similar in the CBD and placebo groups. Some TEAEs had notable dose-responses (elevated transaminases, decreased appetite and weight, diarrhea, somnolence, and seizure, although the reverse was true for other frequently-reported AEs. The overall adverse event profile was also similar to that seen in the analysis of the pooled DS/LGS controlled safety dataset in the original NDA submission. No new safety signals were identified during review of the controlled TSC safety dataset.

There are differences between my results and the Applicant's, primarily due to grouping of similar AEs, additions of uncoded AEs found in review of the verbatim terms, and some changes to preferred terms based on verbatim terms. These differences are described in Sections 8.1 and 8.3.2 above.

Please see Section 8.6.1 for a broader discussion of hepatic adverse events.

Table 27: All Treatment-Emergent Adverse Events (≥2% CBD and Δ risk ≥2%), Controlled TSC Safety Population (Study 1521)

	CBD 25 mg/kg (N=75)			CBD 50 mg/kg (N=73)			Pool CBD (N=148)			Pool PBO (N=76)			Pooled CBD vs. Pooled PBO		
PT	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Δrisk (%)**	**RR**	**OR**
Any TEAE	**433**	**70**	**93.3**	**411**	**73**	**100**	**844**	**143**	**96.6**	**279**	**72**	**94.7**			
Gastrointestinal															
Diarrhea	36	23	30.7	55	41	56.2	91	64	43.2	26	19	25	18.24	1.73	2.29
Hepatic enzyme increased[1]	30	19	25.3	50	28	38.4	80	47	31.8	0	0	0	31.76	49.09	71.60
Decreased appetite	17	15	20	19	17	23.3	36	32	21.6	9	9	11.8	9.78	1.83	2.14
Vomiting	22	13	17.3	22	13	17.8	44	26	17.6	13	7	9.2	8.36	1.91	2.10
Weight decreased	5	5	6.7	6	6	8.2	11	11	7.4	0	0	0	7.43	11.89	12.8
Abdominal pain	2	2	2.7	5	4	5.5	7	6	4.1	1	1	1.3	2.74	3.11	3.17
Retching	3	2	2.7	1	1	1.37	4	3	2.0	0	0	0	2.0	3.62	3.68
Nervous System															
Somnolence/Sedation/ Lethargy	15	14	18.7	24	22	30.2	39	36	24.3	14	13	17.1	7.22	1.42	1.56
Somnolence	10	10	13.3	21	19	26.0	31	29	19.6	8	7	9.2	10.38	2.13	2.40
Seizure[2]	7	6	8	14	13	17.8	21	19	12.8	8	5	6.6	6.26	1.95	2.09
Gait disturbance[3]	9	7	9.3	5	5	6.9	14	12	8.1	8	4	5.3	2.84	1.54	1.59
Fatigue[4]	5	4	5.3	4	4	5.45	9	8	5.4	1	1	1.3	4.09	4.11	4.29
General disorders and administration site conditions															
Pyrexia	23	14	18.7	14	12	16.4	37	26	17.6	6	6	7.9	9.7	2.23	2.49
Nausea	9	7	9.3	2	2	2.7	11	9	6.1	2	2	2.6	3.45	2.31	2.40
Infections and Infestations															
Ear infection	7	6	8	5	5	6.9	12	11	7.4	2	2	2.6	4.8	2.82	2.97
Urinary tract infection	4	4	5.3	2	1	1.4	6	5	3.4	0	0	0	3.38	5.69	5.86
Blood and lymphatic system disorders															
Anemia	5	5	6.7	3	3	4.1	8	8	5.4	1	1	1.3	4.09	4.11	4.29
Eosinophil count increased	4	4	5.3	1	1	1.4	5	5	3.4	0	0	0	3.38	5.69	5.86
Platelet count decreased[5]	4	4	5.3	2	2	2.7	6	6	4.1	1	1	1.3	2.14	3.01	2.89
Skin and subcutaneous tissue disorders															
Rash[6]	6	6	8	8	8	11.0	14	14	9.5	4	3	4.0	5.51	2.40	2.54
Respiratory, thoracic and mediastinal disorders															
Rhinorrhea	3	3	4	3	3	4.1	6	6	4.1	0	0	0	4.1	6.72	6.98
Asthma	1	1	1.3	2	2	2.7	3	3	2.0	0	0	0	2.0	3.62	3.68

	CBD 25 mg/kg (N=75)			CBD 50 mg/kg (N=73)			Pool CBD (N=148)			Pool PBO (N=76)			Pooled CBD vs. Pooled PBO		
PT	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Events**	**n**	**%**	**Δrisk (%)**	**RR**	**OR**
Ear and labyrinth disorders															
Ear pain	2	2	2.7	1	1	1.4	3	3	2.0	0	0	0	2.0	3.62	3.68
Vascular disorders															
Hypertension	2	2	2.7	1	1	1.4	3	3	2.0	0	0	0	2.0	3.62	3.68
Metabolism and nutrition disorders															
Dehydration	1	1	1.3	2	2	2.7	3	3	2.0	0	0	0	2.0	3.62	3.68
Injury, poisoning and procedural complications															
Laceration	0	0	0	3	3	4.1	3	3	2.0	0	0	0	2.0	3.62	3.68

Source: ADAE (Study 1521), MAED/JMP
[1]Hepatic enzyme also includes Alanine aminotransferase increased, Aspartate aminotransferase increased, Gamma-glutamyltransferase increased, and Transaminases increased;
[2]Seizure also includes Atonic seizures, Complex partial seizures, Partial seizures, Seizure cluster, Tonic convulsion; Generalised tonic-clonic seizure;
[3]Gait disturbance also includes Ataxia and Balance disorder;
[4]Fatigue also includes Malaise;
[5]Platelet count decreased includes Thrombocytopenia
[6]Rash also includes Rash maculo-papular, Rash erythematous, Rash macular, and Urticaria;

Uncontrolled population

The uncontrolled TSC safety population includes 199 patients from the OLE phase of Study 1521. As seen in Table 28 below, 184 patients (92.5%) in the uncontrolled TSC safety population experienced 1322 TEAEs. Most of these events were nonserious (n=1263). The most frequently reported TEAEs during the uncontrolled study periods were diarrhea (42%), seizure (24%), decreased appetite (20%), somnolence (18%), pyrexia (16%), vomiting (16%), upper respiratory tract infection (16%), nasopharyngitis (14%), and hepatic enzyme increased (14%).

Most of the TEAEs reported in the uncontrolled population were mild (n=1026 in 171 patients, 93%). A total of 266 moderate TEAEs occurred in 108 patients (54%), and 18 patients (9%) experienced 30 severe TEAEs.

Table 28: Treatment-Emergent Adverse Events (>3%), TSC Uncontrolled Safety Population (Study 1521 OLE)

	All CBD (N=199)	
Dictionary-Derived Term	**n**	**%**
Any TEAE	**184**	**92.4%**
Diarrhea	83	41.7%
Seizure	47	23.6%
Decreased appetite	39	19.6%
Somnolence	36	18.1%
Pyrexia	32	16.1%
Vomiting	32	16.1%
Upper respiratory tract infection	31	15.6%
Nasopharyngitis	28	14.1%
Hepatic enzyme increased	27	13.6%
Fatigue	16	8.0%
Pharyngitis	16	8.0%
Ear infection	14	7.0%
Fall	14	7.0%
Rash	14	7.0%
Cough	12	6.0%
Gait disturbance	12	6.0%
Constipation	11	5.5%
Gastroenteritis	11	5.5%
Influenza	11	5.5%
Nasal congestion	11	5.5%
Abdominal pain	10	5.0%
Aggression	10	5.0%
Weight decreased	10	5.0%
Headache	9	4.5%
Oropharyngeal pain	9	4.5%
Insomnia	8	4.0%
Laceration	8	4.0%
Rhinorrhea	8	4.0%

Source: ADAE 1521 (JMP)

Reviewer's Comments: Significant TEAEs are discussed in Sections 8.5.4 and 8.6. In general, the TEAEs reported in the uncontrolled safety population also occurred during the blinded phases of Study 1521, and most of the frequently-reported TEAEs in the open-label extension study were seen frequently in the blinded phases, as well. Many of the TEAEs observed in the OLE study are seen fairly frequently in the general pediatric population (e.g., pyrexia, nasopharyngitis, upper respiratory tract infection), may be considered due to the underlying condition (seizure, status epilepticus), or may be related to the drug (somnolence, decreased appetite, diarrhea, hepatic enzyme increased).

8.5.6. Laboratory Findings

Hematology

- Anemia:
  Mean decreases from baseline to end of treatment in red blood cells (RBCs), hemoglobin, and hematocrit and mean increases from baseline to end of treatment in mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV) were seen in patients receiving CBD as shown in Table 29 (CBD 25 mg/kg and 50 mg/kg vs. placebo). These changes were small but persistent and similar to the changes observed in the DS/LGS pivotal trials.[50]

Table 29: Mean Changes from Baseline at the End of Treatment Visit for Red Blood Cell Parameters, TSC Controlled Population (Study 1521)

	Absolute Change from Baseline		
Parameter (Unit)	**CBD 25 mg/kg/day (n=73)**	**CBD 50 mg/kg/day (n=71)**	**Pooled Placebo (n=75)**
RBC count ($\times 10^{12}$/L)	−0.192	−0.162	0.003
Hemoglobin (g/L)	−3.5	−3.8	0.7
Hematocrit (L/L)	−0.0112	−0.0115	−0.0016
MCH (pg)	0.49	0.25	0.11
MCV (fL)	1.4	0.7	−0.5

Source: Study 1521 CSR, Table 9.4.1.1.1.1-1

In general, the shift values for hematology parameters were similar between CBD dose groups and placebo. However, there were more patients in the CBD groups than in the placebo group with >5% shifts from normal at baseline to above or below normal at the end of treatment for some parameters, as summarized below:

[50] NDA 210365 Epidiolex safety review (Ellis Unger, MD), dated May 22, 2018, pgs. 32-33

- *RBC normal to low at end of treatment*: 8 patients (10.7%) in the 25 mg/kg/day group and 11 patients (15.1%) in the 50 mg/kg/day group vs. 4 patients (5.3%) in the pooled placebo group.
- *Hemoglobin normal to low at end of treatment*: 6 patients (8.0%) in the 25 mg/kg/day group and 9 patients (12.3%) in the 50 mg/kg/day group vs. no patients in the pooled placebo group.
- *Hematocrit normal to low at end of treatment*: 13 patients (17.3%) in the 25 mg/kg/day group and 14 patients (19.2%) in the 50 mg/kg/day group vs. 5 patients (6.6%) in the pooled placebo group.

Furthermore, there was an imbalance between pooled CBD and pooled placebo groups with respect to reported TEAE of anemia, with 8 (5.4%) in the CBD group, compared to 1 (1.3%) patient in the placebo group. There was no apparent dose-response, as anemia was reported in a greater percentage of patients in the 25 mg/kg group (6.7%) than in the 50 mg/kg group (4.1%).

Reviewer's comments: There are no signals for anemia in the animal toxicology studies, and no known mechanism of action that would account for the finding.

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

Chemistry

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

Transaminases, Bilirubin, and Alkaline Phosphatase Elevations

Transaminase elevations were obviously increased in CBD-treated patients in Study 1521, as they were in the pivotal trials of CBD in LGS and DS and were one of the applicant's adverse events of special interest. Prior to the original NDA submission in 2017, FDA asked the Applicant to address the hepatic safety by including evaluation of the data by an external expert in liver disease, and they Applicant has included an updated external report in this sNDA submission.

Alanine aminotransferase elevations >3 times the upper limit of normal (ULN) were reported in 18% of patients in the pooled CBD group, compared to 0% of patients in the placebo group (Table 30). For elevations >5x ULN, the corresponding frequencies were 9% and 0%. Elevations of ALT >3x ULN were more frequently reported in patients taking 50 mg/kg (25%) than in patients taking 25 mg/kg (12%). Similar dose effect was seen with ALT elevations >5x ULN (11% and 7%, respectively). Calculations of relative risk were not performed due to lack of ALT elevations > 3 or 5x ULN in the placebo group. No cases met the criteria for Hy's Law (ALT ≥ 3x ULN and bilirubin > 2x ULN) during the controlled TSC trial.

The highest elevation observed during Study 1521 was in a patient (# (b) (6)) in the 50 mg/kg group who, on study day 15, had an ALT of 603 U/L (30.2x ULN) and AST 536 U/L (17.3x ULN) in the setting of dehydration. The patient met liver stopping criteria and was withdrawn from the study.

Table 30: Frequency of Treatment Emergent ALT and AST Elevations by Treatment Groups, Controlled TSC Population (Study 1521)

		CBD			
Test	Criteria	25 mg/kg (N=75) n / N (%)	50 mg/kg (N=73) n / N (%)	Pooled CBD (N=148) n / N (%)	Placebo (N=76) n / N (%)
ALT (U/L)	>1xULN	20 / 66 (30.3)	29 / 62 (46.8)	49 / 128 (38.3)	14 / 69 (20.3)
	>2xULN	11 / 73 (15.1)	22 / 72 (30.6)	33 / 145 (22.8)	3 / 74 (4.1)
	>3xULN	9 / 75 (12.0)	18 / 73 (24.7)	27 / 148 (18.2)	0 / 75
	>5xULN	5 / 75 (6.7)	8 / 73 (11.0)	13 / 148 (8.8)	0 / 76
	>8xULN	2 / 75 (2.7)	3 / 73 (4.1)	5 / 148 (3.4)	0 / 76
	>10xULN	2 / 75 (2.7)	3 / 73 (4.1)	5 / 148 (3.4)	0 / 76
	>20xULN	1 / 75 (1.3)	1 / 73 (1.4)	2 / 148 (1.4)	0 / 76
AST (U/L)	>1xULN	25 / 72 (34.7)	29 / 68 (42.6)	54 / 140 (38.6)	9 / 74 (12.2)
	>2xULN	7 / 75 (9.3)	19 / 73 (26.0)	26 / 148 (17.6)	0 / 76
	>3xULN	5 / 75 (6.7)	8 / 73 (11.0)	13 / 148 (8.8)	0 / 76
	>5xULN	1 / 75 (1.3)	3 / 73 (4.1)	4 / 148 (2.7)	0 / 76
	>8xULN	1 / 75 (1.3)	1 / 73 (1.4)	2 / 148 (1.4)	0 / 76
	>10xULN	1 / 75 (1.3)	1 / 73 (1.4)	2 / 148 (1.4)	0 / 76
	>20xULN	0 / 75	0 / 73	0 / 148	0 / 76

Source: Table TSC.5.1.2, Ancillary Liver Safety Report

As seen in Table 31 below, ALT elevations to >3x ULN were more frequently seen in male patients compared to female patients in the CBD 25 mg/kg/day group (27.9% vs 18.8%, respectively) and in the 50 mg/kg group (39.5% vs.36.7%, respectively). Similarly, ALT >5x baseline was more frequently seen in male patients vs. females in the CBD 25 mg/kg (11.6% vs. 6.3%) and 50 mg/kg (25.6% vs. 16.7%) groups.

In the pediatric population, the 12-17 years age group had the highest frequency of TE ALT >3x ULN in the CBD 25 mg/kg/day (25%) and 50 mg/kg/day (37.5%) groups compared to other age ranges (Table 31). Similarly, TE ALT >5x ULN were seen most frequently in the 12-17 years age group for the 25 mg/kg/day dose group. However, the 2-5 years age group had the highest frequency (16.7%) in the 50 mg/kg/day dose compared to the other age groups.

Table 31: ALT Elevations by Subgroup, Controlled TSC Population (Study 1521)

Subgroup	Total CBD (N = 148) n (%)		↑ALT >3x ULN Pooled CBD (N=148) n (%)		↑ALT >5x ULN Pooled CBD (N=148) n (%)		Placebo (N=76)
	n	%	n	%	n	%	
All	148	100	27	18.2	13	8.8	0
Sex							
Female	62	41.9	9	14.5	1	1.6	0
Male	86	58.1	18	20.9	12	13.9	0
Age group							
< 2 years	3	2.0	0		0		0
2–5 years	34	23.0	5	3.4	4	2.7	0
6–11 years	41	27.7	5	3.4	2	1.4	0
12–17 years	32	21.6	10	6.8	4	2.7	0
≥ 18 years	38	25.7	7	4.7	3	2.0	0
Concomitant AEDs							
Valproic acid (Yes)	65	43.9	22	33.8	11	16.9	0
Valproic acid (No)	83	56.1	5	6.0	2	2.4	0

Tables TSC.5.1.2 and TSC.5.1.3, Ancillary Liver Safety Report

Overall, 197 patients (88%) had a baseline ALT value ≤ ULN and 27 patients (12%) had a baseline ALT value > ULN. As seen in Table 32 below, there was no effect of increased baseline ALT (≥ULN) in patients in the 25 mg/kg group who had a post-baseline ALT >3x ULN (12.1% vs. 11.1%). However, patients in the 50 mg CBD group who had an elevated baseline ALT (≥ULN) were more likely to have a post-baseline ALT >3x ULN than those with a baseline ALT less than ULN (45.5% vs. 21.0%, respectively). In the 25 mg/kg and 50 mg/kg CBD groups, patients with an ALT > ULN at baseline were more likely to have an ALT >5x ULN or >8x ULN than patients with ALT values in the normal range at baseline.

Table 32: Frequency of ALT Elevations by Baseline ALT, Controlled TSC Population (Study 1521)

Criteria	ALT ≤ ULN at Baseline			ALT > ULN at Baseline		
	CBD 25 mg/kg (N=66) [n / N (%)]	CBD 50 mg/kg (N=62) [n / N (%)]	Placebo (N=69) [n / N (%)]	CBD 25 mg/kg (N=9) [n / N (%)]	CBD 50 mg/kg (N=11) [n / N (%)]	Placebo (N=7) [n / N (%)]
>2x ULN	10/66 (15.2)	17/62 (27.4)	2/69 (2.9)	1/7 (14.3)	5/10 (50.0)	1/5 (20.0)
>3x ULN	8/66 (12.1)	13/62 (21.0)	0/69	1/9 (11.1)	5/11 (45.5)	0/6
>5x ULN	4/66 (6.1)	5/62 (8.1)	0/69	1/9 (11.1)	3/11 (27.3)	0/7
>8x ULN	1/66 (1.5)	2/62 (3.2)	0/69	1/9 (11.1)	1/11 (9.1)	0/7
>10x ULN	1/66 (1.5)	2/62 (3.2)	0/69	1/9 (11.1)	1/11 (9.1)	0/7
>20x ULN	0/66	0/62	0/69	1/9 (11.1)	1/11 (9.1)	0/7

Source: Table 12-6, Ancillary Liver Safety Report

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

Reviewer's comments: Patients in the CBD groups experienced significant elevations of transaminases, particularly ALT, during Study 1521. ALT elevations >3x ULN were reported in 18% of patients in the pooled CBD group, compared to 0 patients in the placebo. For ALT elevations >5x ULN, the corresponding frequencies were 9% and 0%. The incidence of significant AST elevations were also greater in the pooled CBD group (9%) as compared to placebo (0%). No cases meeting Hy's law criteria were identified.

For a more detailed discussion of the liver findings from Study 1521 and the CBD development program, see Section 8.6.1.

Renal Parameters

- Mean changes from baseline in blood urea nitrogen (BUN) over time were small, with no notable differences across the treatment groups.
- There were small increases from baseline in mean creatinine (Cr) levels in the CBD 25 mg/kg and 50 mg/kg groups throughout the treatment period (Figure 3). Most of the baseline creatinine levels were below the normal reference range and remained below the normal reference range at the end of the treatment period. Mean changes in Cr from baseline to end of treatment are summarized in Table 33.

Table 33: Mean Changes in Creatinine, TSC Controlled Population (Study 1521)

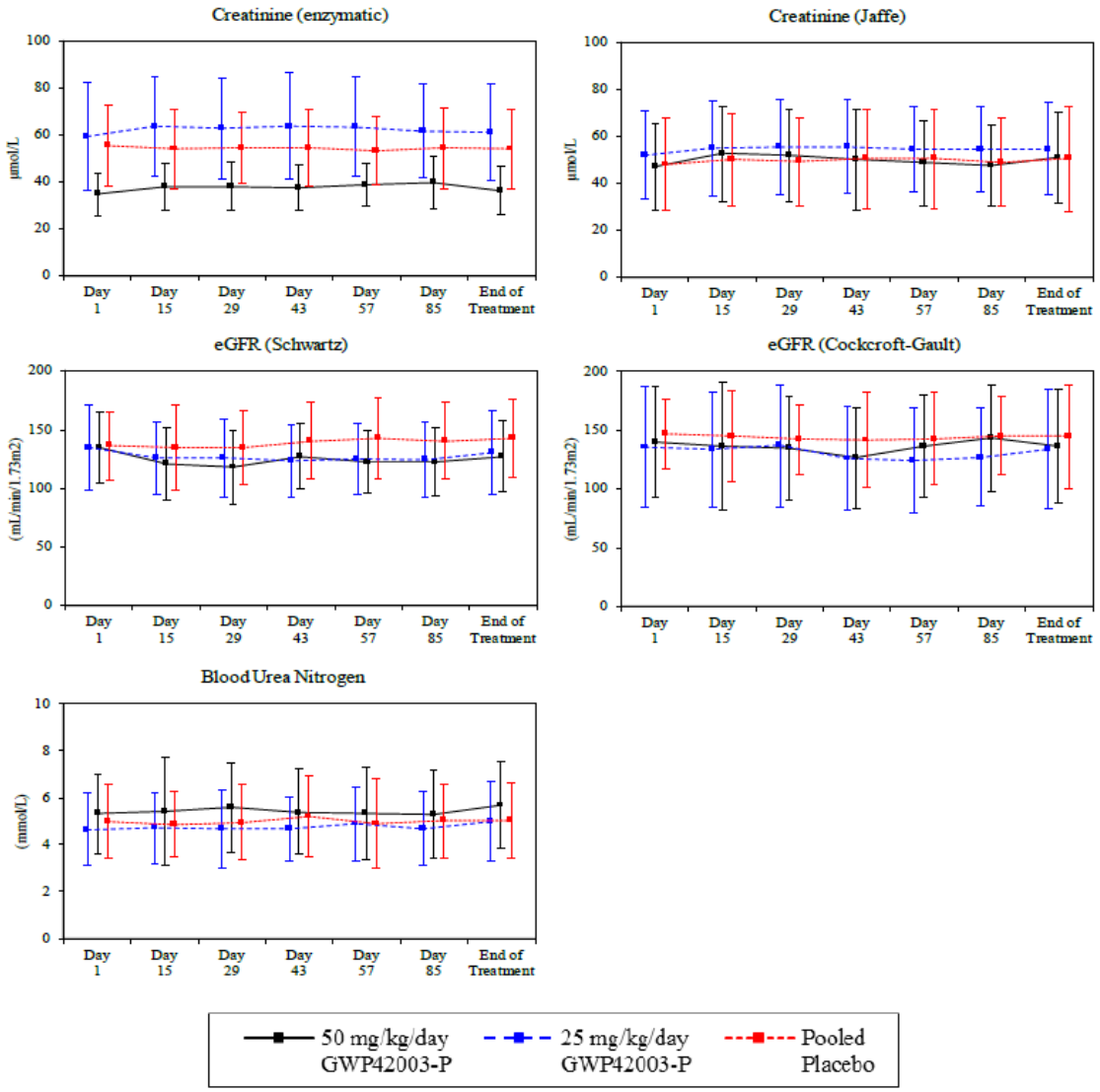
Change from baseline to end-of-treatment	CBD 25 mg/kg/day (n=73)	CBD 50 mg/kg/day (n=71)	Pooled Placebo (n=75)
Mean change in Cr (Jaffe method)	2.5 µmol/L	3.5 µmol/L	1.2 µmol/L
Mean change in Cr (Enzymatic method)	0.9 µmol/L	2.1 µmol/L	−1.1 µmol/L

- Estimated glomerular filtration rate (eGFR) was calculated using the Schwartz equation in the 166 patients who were <18 years old at screening. Small decreases in eGFR (Schwartz) over time were noted in the CBD 25 mg/kg and 50 mg/kg groups vs. pooled placebo. Fifty-eight patients were ≥18 years at screening; therefore, eGFR was calculated using the Cockcroft-Gault equation. Similar to the results in the pediatric patients, small decreases in mean eGFR for patients ≥18 years at screening were noted in the CBD 25 mg/kg and 50 mg/kg groups vs. pooled placebo (Figure 3).
- Four patients developed decreased eGFR from normal at screening to CTCAE grades 2 or 3 during the trial: 1 in the CBD 25 mg/kg/day group (Schwartz, dropped to grade 2 at

Day 14, recovered by Day 85 but returned to grade 2 by end of treatment [Day 119]), 1 patient in the CBD 50 mg/kg/day group (Schwartz, dropped to grade 2 at Day 30, recovered by Day 43) and 2 patients in the pooled placebo group (one, Cockcroft-Gault, the other: Schwartz) had shifts in eGFR to <60 mL/min/1.73m^2 during the blinded phase of Study 1521.

Reviewer's comments: The clinical laboratory data from Study 1521 again demonstrated decreased eGFR in 1 patient in each CBD dose group and 2 in the pooled placebo group, as well as decreases in the mean eGFR from baseline to end of study in the CBD groups. Lastly, there were mild increases in the mean serum Cr in the CBD groups using two different calculation methods, which was not seen to the same degree in the placebo group. Increases in creatinine, particularly early during the treatment period were identified in review of the safety data from the DS and LGS studies. It was unclear from the data in the LGS and DS studies whether these transient elevations in Cr were due to lack of accuracy of the calculated creatinine clearance or due to true elevations in serum creatinine and possibly nephropathy. A post-marketing requirement to study GFR and Cr in healthy volunteers, including measurement of GFR and cystatin C, was issued to resolve this issue. That PMR study is currently ongoing.

Figure 3: Mean Creatinine and Estimated Glomerular Filtration Rate Results Over Time, TSC Controlled Population (Study 1521)



8.5.7. Vital Signs

Vital signs including height, body weight, body mass index, respiratory rate, heart rate, systolic and diastolic blood pressure, and body temperature were monitored during Study 1521.

Some clinically significant changes from baseline in vital signs were observed during the double-blind treatment period in the CBD treatment groups and the combined placebo group, specifically in heart rate, blood pressure, and weight.

The most notable change from baseline was in weight. A larger percentage of patients on CBD

had a clinically significant decreased in weight than placebo: 16.0%, 16.4% and 3.9% of patients in the 25 mg/kg, 50 mg/kg, and placebo groups, respectively, experienced a ≥7% reduction in weight from baseline at any time post-baseline.

Table 34: Summary of Clinically Significant Changes from Baseline in Vital Signs Parameters Post Baseline, Controlled TSC population (Study 1521)

Parameter	CBD 25 mg/kg/day (N=75) n (%)	CBD 50 mg/kg/day (N=73) n (%)	Pooled Placebo (N=76) n (%)
Systolic BP < −20 mmHg	12 (16.0)	18 (24.7)	14 (18.4)
Systolic BP > 20 mmHg	12 (16.0)	11 (15.1)	13 (17.1)
Diastolic BP < −10 mmHg	31 (41.3)	36 (49.3)	24 (31.6)
Diastolic BP > 10 mmHg	21 (28.0)	20 (27.4)	27 (35.5)
Pulse Rate < −10 beats/min	35 (46.7)	39 (53.4)	37 (48.7)
Pulse Rate > 10 beats/min	42 (56.0)	37 (50.7)	51 (67.1)
Weight ≤ −7%	12 (16.0)	12 (16.4)	3 (3.9)
Weight ≥ 7%	6 (8.0)	12 (16.4)	18 (23.7)

Source: Table 9.5.2-1, Study 1521 CSR (verified in JMP)

Reviewer's comments: Decreased weight, decreased appetite, and measured weight loss were seen in the previous pivotal trials in LGS and DS and are adverse reactions in the FDA-approved labeling.

8.5.8. Electrocardiograms (ECGs) and QT

A thorough QT (TQT) study was submitted and reviewed in the original NDA submission.

In Study 1521, small increases from baseline in mean QT duration were reported in both CBD groups, peaking on Day 15. This increase was observed after correcting for heart rate on Day 15 in the 25 mg/kg and on Day 29 in the 50 mg/k group. Consistent, small decreases from baseline in mean ventricular rate were observed in the CBD 50 mg/kg group.

Overall, 6 patients had TEAEs related to ECG findings, 3 in the 25 mg/kg group, 2 in the 50 mg/kg group, and 1 in the placebo group. One patient in the 25 mg/kg group had a TEAE of electrocardiogram abnormal ("rhythm abnormalities on ECG" as per the narrative), increased ALT and increased AST. He discontinued participation in the study due to the abnormal ECG. A second patient in the 25 mg/kg group experienced a mild TEAE of QT prolongation (day 15) which resolved on day 54. He withdrew from study participation on Day 27 due to rash.

Reviewer's comments: The clinical significance of the ECG findings is unclear. It is possible that ECG changes due to CBD may not have been identified in the TQT study due to the lack of dosing with food to achieve supratherapeutic drug levels. A PMR for a clinical TQT study was issued at the time of the original approval for Epidiolex. The protocol for this study was recently agreed to by the Division.

8.5.9. Immunogenicity

Immunogenicity testing was not performed.

8.6. Analysis of Submission-Specific Safety Issues

8.6.1. Liver

Cannabidiol has been associated with liver injury, which was extensively evaluated during review of the original NDA. Non-clinical studies included in the original NDA submission showed increases in alkaline phosphatase and ALT with centrilobular hypertrophy on histopathological exam. Prior to submission of the original NDA, FDA asked the Applicant to address hepatic safety by including an evaluation of the data by an external expert in hepatic disease. In this supplemental NDA submission, the Applicant included an ancillary report by the outside expert and an updated global report on hepatic safety for the entire development program.

Study 1521 included an exclusion criterion for increases in transaminases, bilirubin, and INR at screening, specifically ALT or AST >5x ULN, bilirubin >2x ULN or INR >1.5, or ALT or AST ≥ 3 × ULN with the presence of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%). Transaminases, bilirubin, and INR were generally assessed at baseline, with monitoring at 2, 4, 6, 8, 10, and 12 weeks. Additional monitoring was conducted in the open-label extension study at 24, 36, and 48 weeks. Study 1521 also included termination for withdrawing patients from the trials for potential liver injury:

- ALT or AST >3x ULN with symptoms and/or eosinophilia (> 5%),
- ALT or AST >8x ULN,
- ALT or AST >5x ULN for more than 2 weeks,
- ALT or AST >3x ULN and bilirubin >2x ULN or INR >1.5.

Liver-related TEAEs

Transaminase elevations and other abnormalities of liver function testing were reported as TEAEs at the discretion of the site investigator in Study 1521; therefore, not all abnormalities in liver testing were captured as TEAEs. As seen in Table 35 below, when all preferred terms are analyzed separately in the blinded phase, there are notably more liver-related TEAEs in the CBD groups (25% and 38% in the 25 mg and 50 mg groups, respectively) than in the placebo group (0%). There was a dose response for all TEAEs, as well as for serious liver-related TEAEs: 3% in the 25 mg/kg group and 6% in the 50 mg/kg group. All patients (n=4) who exited the study early due to hepatic-related TEAEs were in the 50 mg/kg group. These values differ slightly from the incidence of elevated transaminases discussed in Section 6.1.2. The preferred terms combined in the analysis in the Applicant's liver report included elevations of alkaline phosphatase and total bilirubin, while those in the FDA analysis of TEAEs did not.

Table 35: Frequency of Liver-Related TEAEs, TSC Controlled population (Study 1521)

SOC PT	Treatment Group	N	TEAE	Serious TEAE	TEAE (D/C)
Investigations (liver-related)	**CBD-OS 25 mg/kg**	**75**	**19 (25.3)**	**2 (2.7)**	**0**
	CBD-OS 50 mg/kg	**73**	**28 (38.4)**	**4 (5.5)**	**4 (5.5)**
	Placebo	**76**	**0**	**0**	**0**
ALT Increased	CBD-OS 25 mg/kg	75	9 (12.0)	2 (2.7)	0
	CBD-OS 50 mg/kg	73	16 (21.9)	2 (2.7)	2 (2.7)
	Placebo	76	0	0	0
AST Increased	CBD-OS 25 mg/kg	75	8 (10.7)	2 (2.7)	0
	CBD-OS 50 mg/kg	73	14 (19.2)	2 (2.7)	1 (1.4)
	Placebo	76	0	0	0
GGT Increased	CBD-OS 25 mg/kg	75	12 (16.0)	0	0
	CBD-OS 50 mg/kg	73	10 (13.7)	0	0
	Placebo	76	0	0	0
Transaminases Increased	CBD-OS 25 mg/kg	75	1 (1.3)	0	0
	CBD-OS 50 mg/kg	73	3 (4.1)	2 (2.7)	1 (1.4)
	Placebo	76	0	0	0
Hepatic Enzyme Increased	CBD-OS 25 mg/kg	75	0	0	0
	CBD-OS 50 mg/kg	73	3 (4.1)	0	1 (1.4)
	Placebo	76	0	0	0
Blood Bilirubin Increased	CBD-OS 25 mg/kg	75	1 (1.3)	1 (1.3)	0
	CBD-OS 50 mg/kg	73	1 (1.4)	0	0
	Placebo	76	0	0	0
Blood ALP Increased	CBD-OS 25 mg/kg	75	1 (1.3)	0	0
	CBD-OS 50 mg/kg	73	0	0	0
	Placebo	76	0	0	0
Hepatobiliary Disorders	**CBD-OS 25 mg/kg**	**75**	**1 (1.3)**	**1 (1.3)**	**1 (1.3)**
	CBD-OS 50 mg/kg	**73**	**0**	**0**	**0**
	Placebo	**76**	**0**	**0**	**0**
Liver injury	CBD-OS 25 mg/kg	75	1 (1.3)	1 (1.3)	1 (1.3)
	CBD-OS 50 mg/kg	73	0	0	0
	Placebo	76	0	0	0

Source: LSR Table TSC.4.1.3.
D/C – discontinuation

When concomitant VPA was considered, 60% of patients taking concomitant VPA developed at least one liver-related TEAE, compared to 10% of patients not taking concomitant VPA. In the OLE phase of Study 1521, 68 patients (31%) experienced at least one liver-related TEAE, 9 had SAEs (4%), and 7 patients (3%) had at least one hepatic TEAE leading to discontinuation.

The frequency of adverse events for transaminase elevations of any severity in the OLE phase of Study 1521 was 18%, and 10% in the EAP/CAS.

Based on the laboratory data from Study 1521, ALT elevations >3x ULN were reported in 18% vs. 0% of subjects in the pooled CBD and placebo groups, respectively, and >5x ULN in 7% and 1% of subjects (Table 30). The incidences of elevated transaminase TEAEs were slightly higher than those seen in the LGS/DS pivotal studies (13% vs. 1% and 7% and 1% in the CBD and placebo groups with ALT >3x ULN and >5x ULN, respectively). For the 25 and 50 mg/kg/day doses, there was a clear dose-response with ALT >3x ULN reported in 12% of patients taking CBD 25 mg/kg and 25% of patients taking 50 mg/kg. A similar dose effect was seen in ALT >5x ULN (11% and 7%, respectively). This dose response is inconsistent when compared to the incidences in the LGS/DS pivotal trials, as ALT >3x ULN in that pooled analysis was 17% in patients taking CBD 20 mg/kg. No patient had a bilirubin increase >2x ULN, and there were no important increases in alkaline phosphatase in the controlled phase of Study 1521.

As noted in Section 8.5.6, the probability of ALT elevations was not related to age or sex (Table 31. There were too few non-white patients enrolled in Study 1521 to suggest differences by race. For patients taking CBD, concomitant use of valproate increased the likelihood of ALT elevations by a factor of 5 (Table 31). A similar effect was not seen in patients taking clobazam.

Plots of time-to-first ALT elevation >3x ULN show that transaminase elevations were generally reported within 2 to 3 months of initiating cannabidiol; however, a few patients experienced elevated transaminases even after 12 months. These findings are similar to those in the LGS/DS studies. Development of ALT elevations tended to occur earlier in patients taking concomitant VPA.

Transaminase elevations generally resolved with discontinuation of CBD or after dose decreases of CBD and/or VPA; however, some events resolved despite continued treatment with cannabidiol at the same dose, and few persisted even after CBD was discontinued.

Severe hepatic injury, with concurrent increases in bilirubin and INR, was not reported, i.e., there were no Hy's Law cases and no cases of overt hepatic failure. One patient in the 25 mg/kg group discontinued CBD during the blinded phase because of "liver damage". The case narrative indicated that he developed elevated transaminases and decreased appetite on treatment day 14. No other concomitant symptoms were reported. He was on concomitant VPA. His highest ALT was 10.2x ULN and highest AST was 4.1x ULN. INR, bilirubin, and eosinophils were all normal. Transaminase levels returned to normal ~15 days after CBD was discontinued.

The updated liver safety report included analyses on pooled datasets from the LGS/DS/TSC studies which included a total of 961 patients. The updated report did not identify any patients meeting the criteria for Hy's Law or drug-induced liver injury (DILI), although 2 patients did experience ALT >3x ULN and bili >1.5x ULN. Of the 961 patients, 80 met the DILI criteria for ALT >5x ULN without concurrent significant elevations in AST, bilirubin, or alkaline phosphatase. A dose response was noted in patients experiencing a >5x ULN increase in ALT: 1.5%, 6.7%, 6.7%, 11.0%, in the 10 mg, 20 mg, 25 mg, and 50 mg (pooled) CBD groups, compared to 0.6 in the

pooled placebo group. As noted in the liver safety review, 90% of these patients were taking concomitant valproate.

TEAEs related to abnormal liver testing were experienced by 18.7% of patients in the pooled CBD dataset, compared to 2.5% of patients taking placebo. As seen in the individual trials, there was a dose effect with 10%, 16%, 25%, and 38% of patients in the 10 mg, 20 mg, 25 mg, and 50 mg groups, respectively reporting elevated transaminase TEAEs. Other liver-related TEAEs reported in the combined dataset included acute hepatic failure and hepatic failure (although neither of these patients met the criteria for hepatic failure), hepatotoxicity, and liver injury. One patient reported hyperammonemia.

Reviewer's comments: Cannabidiol has been associated with liver injury, which was extensively evaluated during review of the original NDA. In this supplemental NDA submission, the Applicant included an ancillary report and an updated global report on hepatic safety for the entire development program by an outside expert in hepatic disease. Analysis of liver testing and adverse events in Study 1521, as well as GW's wider development program in patients with epilepsy, revealed that significantly elevated transaminases (most notably ALT >5x ULN) occur much more frequently in CBD-treated patients than in patients taking placebo; that liver-related TEAEs, SAEs, and AEs leading to discontinuation are much more common in patients taking CBD than placebo; that there is a prominent dose response with respect to the elevated transaminases and hepatic TEAEs; that most, but not all, elevated transaminases occur within the first 2-3 months of treatment; and that concomitant valproate is associated with a greater risk of these findings. These results are similar to those from the analysis of the original dataset from the LGS/DS trials, although the dose effect appears to be greatest with the 50 mg dose in the TSC trial.

Given the previous dose-response of liver injury in the LGS/DS studies at lower doses (10 and 20 mg/kg/day), the clear dose-response of elevated transaminases, particularly ALT, to the 25 mg/kg and 50 mg/kg doses, and the greater incidence of SAEs and discontinuations due to hepatic TEAEs in the 50 mg/kg group, the Applicant's decision not to pursue the 50 mg/kg dose is reasonable, especially in light of no added benefit based on the efficacy results.

The risk of long-term (3-5 years) treatment with CBD remains unknown (PMR study to explore the risks of chronic liver injury with long-term treatment will begin in 2020). Given the persistent dose-response of liver injury to CBD and the lack of efficacy data for the LGS/DS populations at the higher dose, I strongly recommend that we limit the maximum dosing in these populations to the currently-approved maximum dose of 20 mg/kg/day. The current PMR study for chronic liver injury is sufficient to address concerns in the TSC population. No changes are necessary to the monitoring recommendations for elevated transaminases and liver injury in the PI.

8.6.2. Central Nervous System TEAEs

As noted in Section 8.5.5, somnolence and fatigue (including malaise and asthenia) were notably more frequently reported in patients taking CBD than in patients taking placebo, during the controlled phase of Study 1521. Somnolence was reported in 20% and 9% of patients in the pooled CBD and placebo groups, respectively and had an attributable risk difference of 10%. Fatigue was reported in 5% of patients in the pooled CDB group and in 1% of patients in the placebo group for an attributable risk difference of 4%. A dose response was seen with somnolence but not with fatigue. A total of 36 patients (18%) in the OLE study reported somnolence, while 8% reported fatigue. Two patients in the 50 mg/kg group discontinued participation in the study due to a TEAE of somnolence. One patient discontinued due to somnolence or fatigue during the OLE study.

Gait disturbance (including ataxia, and balance disorder) events were also reported at higher frequencies in the CBD group than in the placebo group, and at a notable frequency in the OLE study. Given that the drug crosses the blood-brain barrier, and in light of the relatedness of some of the events, these are reasonably likely to be drug-related and should be included as adverse reactions in the description of the TSC adverse reactions in Section 6 of the PI.

8.6.3. Effects on Appetite and Weight

Dr. Unger discussed decreased appetite, decreased weight and measured weight loss in his review of the safety data in the original NDA submission. A dose-response was noted in the LGS/DS trials for all three of these findings, and similar results were identified in the review of the TSC trial. Decreased appetite was reported in 22% of patients taking CBD, as compared to 12% of patients in the placebo group during the blinded phase of Study 1521. Decreased weight was reported in 7% and 0% of patients in the CBD and placebo groups, respectively. The dose response for decreased appetite was small for both events (). Both decreased appetite and decreased weight were reported during the OLE phase (20% and 5%, respectively).

The frequencies of measured weight loss (≥ -7%) in the blinded phase of Study 1521 were 16% and 4% in the CBD and placebo groups, respectively. There were also fewer subjects with weight *gain* (≥ 7%) in CBD-treated subjects than placebo subjects: 12% vs. 24%, respectively. There was no apparent dose response for measured weight loss, but more patients in the 50 mg/kg group gained weight (16%) than in the 25 mg/kg group (8%). In general, these findings are similar to those seen in the LGS and DS trials.

8.6.4. Rash

Skin reactions were reviewed closely, as they were identified as AEs of interest during the development program. The term “rash” includes the following closely-related preferred terms: Rash, Rash maculo-papular, Rash erythematous, Rash macular, and Urticaria. Unlike the LGS/DS trials in the original submission, rash was more frequently reported as a serious adverse event in the pooled CBD group (3%) than in the placebo group (0%), and 3 patients in the CBD group

(2%) experienced rash events that were adjudicated as severe. When TEAEs of any seriousness or severity are considered, rash was reported in 10% and 4% of patients in the pooled CBD and placebo groups, respectively. Rash was more frequently seen in in the 50 mg/kg/day group (11%) as compared to the 25 mg/kg/day group (8%), although this difference was small. Additionally, rash was reported in 7% of patients taking CBD during the OLE phase of Study 1521. Lastly and as opposed to the prior experience with the LGS/DS trials, rash led to early drug discontinuation in 9 patients (6%) taking CBD and none taking placebo. Slightly greater percentage of patients in the in the 50 mg/kg group (7%) than in the 25 mg/kg group (5%) discontinued participation early because of rash. No findings were consistent with serious cutaneous adverse reactions (SCAR) such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia and systemic symptoms (DRESS). Given the current findings, no changes are recommended for the labeling, although if any cases of serious skin reactions are reported, it may be necessary to add a warning to the label.

8.6.5. Safety in Patients Less Than 1 Year of Age

The applicant has proposed to expand the indication for treatment of seizures associated with LGS or DS from patients 2 years of age and older to 1 year of age and older. The primary basis for their proposal is that safety in patients below 2 years of age is not significantly different from that in older pediatric patients. The safety database of patients <2 years of age is comprised of 51 patients from Study 15100 (9), Study 1521 (8), and the expanded access program (34). There were insufficient numbers of patients < 2 years of age in Study 1521 (2, 1, and 5 in the 25 mg/kg, 50 mg/kg, and placebo groups respectively) to perform useful analyses on safety data from the blinded phase.

As seen in Table 36 below, 44 patients < 2 years of age (86%) experienced 380 adverse events while taking CBD at any dose. Infection-related (65%), nervous system (53%), respiratory (49%), gastrointestinal (47%), and general disorders (45%) TEAEs were most frequently reported. The most frequently reported TEAEs in this population were pyrexia (33%), seizure (33%), upper respiratory tract infection (25%), diarrhea (24%), and vomiting (24%). SAEs of bronchiolitis, pyrexia, respiratory failure, and status epilepticus were each reported in 8% of patient under age 2 years.

Table 36: All Treatment-Emergent Adverse Events in ≥3 Patients < 2 Years of Age (Studies 1521 and 15100 and EAP)

	CBD any dose* (N=51)	
	n	%
Pyrexia	17	33.3%
Seizure	17	33.3%
Upper respiratory tract infection	13	25.4%
Diarrhea	12	23.5%
Vomiting	12	23.5%

	CBD any dose* (N=51)	
	n	%
Pneumonia	10	19.6%
Somnolence	10	19.6%
Rash	8	15.7%
Cough	7	13.7%
Urinary tract infection	6	11.8%
Bronchiolitis	5	9.8%
Irritability	5	9.8%
Hyponatremia	4	7.8%
Nasopharyngitis	4	7.8%
Respiratory failure	4	7.8%
Rhinorrhea	4	7.8%
Rhinovirus infection	4	7.8%
Status epilepticus	4	7.8%
Upper respiratory tract congestion	4	7.8%
Blood triglycerides increased	3	5.9%
Decreased appetite	3	5.9%
Dehydration	3	5.9%
Ear infection	3	5.9%
Enterovirus infection	3	5.9%
Sleep disorder	3	5.9%
Teething	3	5.9%

Source: ASAE ISS, AE Study 15100, analyzed in JMP
*Does not include TEAEs experienced by patients in placebo group of Study 1521 during the double-blind period

Twenty-three patients (45%) under the age of 2 years experienced a total of 136 serious TEAEs while taking CBD (Table 37). Most of these SAEs were in the infections and infestations SOC (31%), nervous system SOC (24%) or respiratory SOC (16%). The most frequently reported SAEs in this population were seizure (18%) and pneumonia (16%). SAEs of bronchiolitis, pyrexia, respiratory failure, and status epilepticus were each reported in 8% of patients < age 2 years.

Table 37: Serious Treatment-Emergent Adverse Events in ≥2 Patients < 2 Years of Age (Studies 1521 and 15100 and EAP)

	CBD any dose* (N=51)	
	n	%
Seizure	9	17.6%
Pneumonia	8	15.7%
Bronchiolitis	4	7.8%
Pyrexia	4	7.8%
Respiratory failure	4	7.8%
Status epilepticus	4	7.8%

	CBD any dose* (N=51)	
	n	%
Dehydration	3	5.9%
Enterovirus infection	3	5.9%
Rhinovirus infection	3	5.9%
Upper respiratory tract infection	3	5.9%
Hyponatremia	2	3.9%
Hypoxia	2	3.9%
Pneumonia aspiration	2	3.9%
Respiratory distress	2	3.9%
Vomiting	2	3.9%

Source: ASAE ISS, AE Study 15100, analyzed in JMP
*Does not include TEAEs experienced by patients in placebo group of Study 1521 during the double-blind period

Elevated transaminase levels were not observed in patients < 2 years of age.

Reviewer's comments: In general, the safety profile in the patients younger than 2 years of age similar to that of the older pediatric and adult patients in the CBD development program for epileptic encephalopathies. Assessment of the TEAEs and SAEs in this population revealed no new safety signals, although the small number of patients limits the potential to detect less frequent adverse events.

8.7. Safety Analyses by Demographic Subgroups

TEAEs were examined by age subgroup (<2, 2-6, 7-11, 12-17, and 18+ years) in the TSC controlled population. There were no clear age-related patterns in the distribution of TEAEs (Table 38).

Table 38: Frequent TEAEs by Age Group, TSC Controlled Population (Study 1521)

	Pool CBD (N=148)								PBO (N=76)							
	1-6 years		7-11 years		12-17 years		18-65 years		1-6 years		7-11 years		12-17 years		18-65 years	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Any TEAE	**41**	**27.7%**	**36**	**24.3%**	**31**	**20.9%**	**35**	**23.6%**	**21**	**27.6%**	**17**	**22.3%**	**15**	**19.7%**	**19**	**25%**
Diarrhea	20	13.5%	12	8.1%	9	6.1%	23	15.5%	6	7.9%	7	9.2%	1	1.3%	5	6.6%
Somnolence	13	8.8%	12	8.1%	6	4.1%	5	3.4%	5	6.6%	1	1.3%	1	1.3%	6	7.9%
Hepatic enzyme increased	9	6.1%	12	8.1%	14	9.5%	12	8.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Decreased appetite	7	4.7%	11	7.4%	5	3.4%	9	6.1%	2	2.6%	1	1.3%	3	3.9%	3	3.9%
Nasopharyngitis	6	4.1%	6	4.1%	3	2.0%	7	4.7%	2	2.6%	3	3.9%	2	2.6%	5	6.6%
Vomiting	8	5.4%	6	4.1%	8	5.4%	4	2.7%	1	1.3%	3	3.9%	2	2.6%	1	1.3%
Pyrexia	18	12.2%	4	2.7%	2	1.4%	2	1.4%	2	2.6%	2	2.6%	2	2.6%	0	0.0%
Upper respiratory tract infection	6	4.1%	3	2.0%	4	2.7%	1	0.7%	5	6.6%	3	3.9%	1	1.3%	2	2.6%
Seizure	3	2.0%	5	3.4%	8	5.4%	3	2.0%	2	2.6%	2	2.6%	0	0.0%	1	1.3%
Constipation	2	1.4%	7	4.7%	2	1.4%	2	1.4%	2	2.6%	2	2.6%	1	1.3%	1	1.3%
Rash	4	2.7%	4	2.7%	3	2.0%	5	3.4%	2	2.6%	1	1.3%	0	0.0%	0	0.0%
Gastroenteritis	7	4.7%	4	2.7%	0	0.0%	1	0.7%	5	6.6%	0	0.0%	0	0.0%	0	0.0%
Cough	5	3.4%	2	1.4%	2	1.4%	2	1.4%	2	2.6%	1	1.3%	1	1.3%	1	1.3%
Gait disturbance	3	2.0%	2	1.4%	2	1.4%	5	3.4%	3	3.9%	1	1.3%	0	0.0%	0	0.0%
Ear infection	8	5.4%	3	2.0%	0	0.0%	0	0.0%	1	1.3%	1	1.3%	0	0.0%	0	0.0%
Irritability	5	3.4%	1	0.7%	1	0.7%	2	1.4%	1	1.3%	0	0.0%	0	0.0%	3	3.9%
Fall	1	0.7%	2	1.4%	2	1.4%	1	0.7%	4	5.3%	1	1.3%	0	0.0%	0	0.0%
Increased appetite	3	2.0%	2	1.4%	0	0.0%	1	0.7%	1	1.3%	1	1.3%	2	2.6%	1	1.3%
Nausea	0	0.0%	2	1.4%	0	0.0%	7	4.7%	0	0.0%	0	0.0%	1	1.3%	1	1.3%
Weight decreased	1	0.7%	2	1.4%	5	3.4%	3	2.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
Headache	0	0.0%	2	1.4%	2	1.4%	2	1.4%	0	0.0%	1	1.3%	2	2.6%	1	1.3%
Insomnia	3	2.0%	1	0.7%	0	0.0%	1	0.7%	1	1.3%	3	3.9%	1	1.3%	0	0.0%
Anemia	3	2.0%	1	0.7%	1	0.7%	3	2.0%	1	1.3%	0	0.0%	0	0.0%	0	0.0%
Fatigue	2	1.4%	3	2.0%	2	1.4%	1	0.7%	0	0.0%	0	0.0%	0	0.0%	1	1.3%
Pharyngitis	1	0.7%	3	2.0%	1	0.7%	0	0.0%	2	2.6%	0	0.0%	2	2.6%	0	0.0%
Abdominal pain	1	0.7%	1	0.7%	3	2.0%	1	0.7%	1	1.3%	0	0.0%	0	0.0%	0	0.0%

Source: ADAE 1521 (JMP)

8.8. Specific Safety Studies/Clinical Trials

Suicidality was assessed using the Columbia-Suicide Severity Rating Scale (C-SSRS). Patients 7 years and older were administered the age-appropriate version of the C-SSRS if they were considered capable of completing the questionnaire by the investigator. The C-SSRS was assessed in Studies 1 and 1504-C2 at the screening visit (visit 1), at randomization (visit 3), titration period (at visit 6), maintenance period (at visits 8 and 10) and at EOS (visit 12). The proportion of patients who completed the C-SSRS ranged from 35% to 52.3%.

Suicidal ideation type 1 ("wish to be dead") was reported by 1 patient in the placebo group at the screening visit, but not at any other point during the trial. Non-suicidal self-injurious behavior was reported in 1 patient in the placebo group at the screening visit and 1 patient in the CBD 25 mg/kg group at screening and at End of Treatment (Day 115). One patient in the placebo was reported as engaging in self-injurious behavior described as "non-suicidal but was also of unknown intent" at screening, baseline, Day 15, Day 29 and Day 57. No TEAEs relating to suicidality were reported during the trial; the 1 patient who reported a mild TEAE of intentional self-injury had no record of self-injurious behavior reported in the C-SSRS.

8.9. Additional Safety Explorations

8.9.1. Human Carcinogenicity or Tumor Development

Not applicable

8.9.2. Human Reproduction and Pregnancy

No studies were conducted with fenfluramine in pregnant women to assess risks. No pregnancies were reported during the development program.

8.9.3. Pediatrics and Assessment of Effects on Growth

See Sections 8.5.7 and 8.5.3 above.

8.9.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No overdoses were reported during the development program.

Four patients reported TEAEs of interest for potential withdrawal phenomena: 1 patient (1.3%) in the 25 mg/kg group ('euphoria'), 2 patients (2.7%) in the 50 mg/kg group ('drunkenness' and 'behaviour change - aggressive outbursts') and 1 patient in the placebo group ('aggressive behaviour and anxiety'). None of these events led to alteration of study drug dosing. The patient in the 25 mg/kg group was reported to be "uncertain" about liking the TEAE, while the other 3 patients did not like the event.

8.10. Safety in the Postmarket Setting

8.10.1. Safety Concerns Identified Through Postmarket Experience

No new validated safety signals have been identified on review of the post-marketing data contained within the PADERs.

8.10.2. Expectations on Safety in the Postmarket Setting

In general, I expect that the patterns of adverse reactions in the postmarket setting will be similar to those seen during the controlled and uncontrolled clinical studies. There has been one report of a completed suicide in a patient taking Epidiolex in the postmarket setting. Confounding factors in the determination of causal relationship in that case are insufficient information and a long history of mental illness.

8.10.3. Additional Safety Issues from Other Disciplines

Not applicable.

8.11. Integrated Assessment of Safety

Cannabidiol (Epidiolex) was approved by U.S. FDA in 2018 as treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older. The current sNDA is for a new indication (treatment of seizures associated with tuberous sclerosis complex) and expansion of the age range for the current indications of Lennox-Gastaut syndrome or Dravet syndrome to 1 year of age and older.

The total number of unique patients who were exposed to cannabidiol during the TSC development program prior to the cutoff date for the 120-day safety update was 223. To support the new indication, the Applicant performed safety analyses on Study 1521. The primary FDA safety analyses were performed on the controlled safety population from Study 1521.

No deaths were reported in the TSC development program. Sixteen deaths have been reported in the DS/LGS development program, eight of which were included in the original NDA dataset. The most frequently reported cause of death in these patients was sudden unexplained death in epilepsy (SUDEP), which occurred in 7 (0.8%) of patients. None of the deaths were adjudicated as due to CBD. SUDEP is more commonly reported in pediatric patients with DS (and LGS to a lesser degree) than in the general epilepsy population.

The overall incidence of treatment-emergent SAEs was 12.5% in the controlled safety population with a greater incidence in the pooled CBD group (18%) as compared to the placebo group (2%). The SAEs that occurred most frequently in the pooled CBD group was elevated

hepatic enzymes, which was reported in 6 patients (4.1%). Five patients in the pooled CBD group experienced a serious TEAE of rash (3.4%), while 3 patients each (2%) experienced SAEs of gastroenteritis or seizure. The types and frequencies of SAEs reported in Study 1521 are similar to those seen in other trials of refractory epilepsy in pediatric patients, although the underlying reason for the imbalance between CBD and placebo in Study 1521 is unclear.

A total of 18 patients in the pooled CBD group (12%) discontinued early because of adverse events from Study 1521 during the blinded phase, 8 (11%) and 10 (14%) in the 25 mg/kg and 50 mg/kg groups, respectively. No patients in the placebo group discontinued due to an adverse event. TEAEs leading to discontinuation which occurred in more than one patient included rash (n=9, 6.1%), hepatic enzyme increased (n=4, 2.7%), and somnolence/sedation (n=2, 1.4%). Nine of these events were adjudicated as serious and 6 as severe. Most patients who withdrew due to adverse events (n=11) did so during the titration period.

Certain adverse events of special interest were specifically evaluated. Hepatic TEAEs were of especial interest due to the CBD-associated hepatocellular injury seen in the LGS and DS trials. In the controlled phase of Study 1521, transaminase elevations were reported as serious adverse events in 4% vs. 0% of patients in the cannabidiol and placebo groups, respectively and led to discontinuation of approximately 4% of patients taking CBD during the blinded phase of Study 1521. For adverse events of any severity, elevated transaminases were reported in 25%, 38%, and 0% in patients taking CBD 25 mg, 50 mg, and placebo, respectively. The frequency hepatic TEAEs in the OLE phase of Study 1521 was 18%, and 10% in the EAP/CAS.
Effects on weight and appetite were also specifically assessed. Decreased appetite and weight decrease were seen more frequently in the pooled CBD group (22% and 7%, respectively) than in the placebo group (12% and 0%, respectively). The dose response for these findings was small. The frequencies of measured weight loss (≥ -7%) in the blinded phase of Study 1521 were 16% and 4% in the CBD and placebo groups, respectively. There were also fewer subjects with weight *gain* (≥ 7%) in CBD-treated subjects than placebo subjects: 12% vs. 24%, respectively. In general, these findings are similar to those seen in the LGS and DS trials.

During the controlled trials, somnolence (including sedation and lethargy) and fatigue (including malaise and asthenia) were reported notably more frequently in patients taking CBD (20% and 5%, respectively) than in patients taking placebo (9% and 1%, respectively). A dose response was seen with somnolence but not fatigue. Two patients in the 50 mg group discontinued participation in the study due to a TEAE of somnolence.

Rash occurred in 10% of CBD patients and 4% of placebo patients, leading to discontinuation in 9 patients (4 in the 25 mg group and 5 in the 50 mg group). 3% of patients in the pooled CBD group reported a SAE related to rash.

ALT elevations >3x ULN were reported in 18% vs. 0% of subjects in the pooled CBD and placebo groups, respectively, and >5x ULN in 7% and 1% of patients. For the 25 and 50 mg/kg/day doses, there was a clear dose-response with ALT >3x ULN reported in 12% of patients taking

CBD 25 mg/kg and 25% of patients taking 50 mg/kg. A similar dose effect was seen in ALT >5x ULN (11% and 7%, respectively). Concomitant use of valproate increased the likelihood of significant ALT elevations by a factor of 5. There were no Hy's Law cases and no cases of overt hepatic failure.

Review of adverse events in patients a population of patients < 2 years of age in the controlled and uncontrolled studies did not identify any new safety signal and the safety profile was reasonably similar to that of patients ≥2 years of age.

In summary, cannabidiol's most serious safety concern is the risk of liver injury. Although there were no Hy's Law cases and no patients in the development program developed acute liver failure, the program was modest in size. It remains possible that the drug could, in fact, cause severe acute and/or chronic liver injury in the marketed setting, when patient exposure markedly increases, and the magnitude of this risk is unknown. The currently approved labeling recommends monitoring of transaminases, including baseline and interval assessment, which should mitigate the risk of severe hepatic toxicity to some degree.

9. Advisory Committee Meeting and Other External Consultations

An Advisory Committee Meeting was not deemed necessary for this submission.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

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

As described in Section 7.1.6 and Section 8.6.1, the Applicant has proposed to expand the age range for use in treatment of seizures associated with LGS or DS to include patients 1 to < 2 years of age. There are no controlled efficacy data in the DS or LGS populations. However, it is expected that, based on the pathophysiology of the disorders, CBD would be efficacious in reducing convulsive and drop seizures in patients 1 to < 2 years of age with DS or LGS, respectively. Review of safety data from an uncontrolled population of patients with a variety of underlying seizure disorders (including 3 with DS or LGS) identified no unexpected safety signal. As there is an expectation of efficacy and no reported safety issues in a similar population, there is sufficient information to support the proposed expansion of the age range in the DS and LGS populations.

(b) (4)

(b) (4)

In Supplement 07 (a Changes Being Effected supplement), the Applicant cites a recent Drug Enforcement Agency Communication to the Applicant (dated March 20, 2020) stating that CBD [Epidiolex] is no longer controlled under the Controlled Substances Act as a result of the enactment of the hemp provisions of the Agricultural Improvement Act of 2018, pub. L. 115-334, § 297A. Therefore, in this submission, the Applicant submits updated final Prescribing Information and Medication Guide, Instructions for Use, Carton, and Bottle/Container labels to indicate that CBD is no longer a controlled substance. The Agency concurs with these proposed changes.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS was not needed.

12. Postmarketing Requirements and Commitments

No new post-marketing requirements or commitments were required.

13. Appendices

13.1. References

See footnotes throughout the review.

13.2. Financial Disclosure

See Section 6.1.2 for discussion of financial disclosures.

Covered Clinical Study (Name and/or Number): 1521, 1424

Was a list of clinical investigators provided:	Yes ☒ ☐	No ☐ (Request list from Applicant)
Total number of investigators identified: 1521: 54, 1424: 48		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 9		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1521 and 1424: 5		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATALIE B GETZOFF
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PHILIP H SHERIDAN
07/31/2020 07:52:07 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

PRODUCT QUALITY REVIEW(S)

Office of Lifecycle Drug Products
Division of Post-Marketing Activities I
Review of Chemistry, Manufacturing, and Controls

1. **NDA Supplement Number: NDA 210365 / S-005**

2. **Submission(s) Being Reviewed**:

Submission (Supp. Doc. No.)	Type	Submission Date	CDER Stamp Date	Assigned Date	PDUFA Goal Date	Review Date
Supplement (188)	PAS	01/31/2020	01/31/2020	02/05/2020	07/31/2020	06/30/2020

3. **Provides For from the Cover Letter:** addition of a new indication, namely for the treatment of seizures associated with tuberous sclerosis complex, to the prescribing information for the drug product Epidiolex® (cannabidiol) oral solution.

4. **Review #**: 1

5. **Clinical Review Division**: CDER/ON/DN2

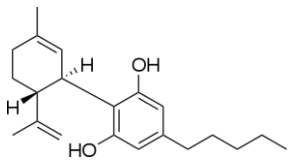
6. **Name and Address of Applicant**:
GW Research Ltd
C/O Greenwich Biosciences, Inc.
5750 Fleet Street / Suite 200
Carlsbad, California 92008

7. **Drug Product**:

Drug Name	Dosage Form	Strength	Route of Administration	Rx or OTC	Special Product
Epidiolex® (cannabidiol) oral solution, CV*	Solution	100 mg/mL	Oral	Rx	No

*CV stands for controlled substance

8. **Chemical Name and Structure of Drug Substance**:

	USAN: Cannabidiol CAS Number: 13956-29-1 Chemical name: 2-[(1*R*,6*R*)-3-Methyl-6-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol Molecular formula: $C_{21}H_{30}O_2$ MW: 314.46

9. **Indication**: Treatment of seizures associated with Lennox Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.

10. **Supporting/Relating Documents**: See pages 3-5.

11. Consults: None

12. Executive Summary:

In this supplemental submission, the applicant proposes to add a new indication, namely for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older, to the prescribing information for the drug product Epidiolex® (cannabidiol) oral solution.

The applicant claims categorical exclusion from the requirement to prepare an Environmental Assessment because approval will not increase the "estimated concentration of the drug substance at the point of entry into the aquatic environment" above 1 part per billion (in accordance with 21 CFR 25.31(b)). Based upon the calculations provided (see details in the body of the review), the claim of categorical exclusion appears to be warranted.

13. Conclusions & Recommendations:

This supplement is recommended for approval from a CMC point of view.

14. Comments/Deficiencies to be Conveyed to Applicant: None

15. Primary Reviewer:

Richard T. Matsuoka, CMC reviewer, Branch 3, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, Office of Pharmaceutical Quality (OPQ)

16. Secondary Reviewer:

David B. Lewis, Branch Chief, Branch 2, Division of Post-Marketing Activities I, Office of Lifecycle Drug Products, OPQ

CMC Assessment

I. Background Information

Epidiolex® (cannabidiol) oral solution is a clear, colorless to yellow liquid containing the drug substance cannabidiol at a concentration of 100 mg/mL. Epidiolex oral solution, approved on 06/25/2018, is supplied in a 105-mL amber glass bottle with a child-resistant closure containing 100 mL of oral solution. The drug product contains the following inactive ingredients: "dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose". The drug product is indicated for the treatment of seizures associated with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

This efficacy supplement, which was submitted on 01/31/2020, was split into two supplements, namely SUPPL-5 and SUPPL-6. This split is considered an administrative split and the same data is provided in the same submission in EDR (Electronic Data Room). The subject of SUPPL-5 is the proposed addition of a new indication, namely for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older, to the drug product's prescribing information. The subject of SUPPL-6 is the proposed extension of the patient age group, namely down to patients one year of age and older, for the currently indicated treatments of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) regarding the drug product.

II. Proposed Changes

The applicant proposes to add a new indication, namely for the treatment of seizures associated with tuberous sclerosis complex (TSC) in patients 1 year of age and older, to the prescribing information for the drug product Epidiolex® (cannabidiol) oral solution.

III. Data Submitted to Support the Proposed Changes

Module "1.2. Cover Letters"

Comments: No changes are being made to either the drug substance or the drug product. The applicant made minor changes to Module "3.2.P.2. Pharmaceutical Development" to include Development Pharmaceutics to include tuberous sclerosis complex (TSC) as an indication (SUPPL-5) in addition to Dravet syndrome (DS), Lennox-Gastaut syndrome (LGS), to adjust the lower age range for administration from 1 year of age, (b) (4)

Evaluation: ***Adequate***

Module "1.14. Labeling"

Comments: The applicant submitted a draft "prescribing information" document (annotated, tracked changes, and clean version) and a draft "instructions for use" document (tracked changes and clean version) to support the proposed change. The annotated prescribing information document showed only one minor change to the CMC-related information included in Sections "3 DOSAGE FORMS AND STRENGTHS", "11 DESCRIPTION", and "16 HOW SUPPLIED/STORAGE AND HANDLING". In Section "11 DESCRIPTION", the applicant added the term "(7.9% w/v)" to the description of the inactive ingredient dehydrated alcohol. Previously, no "w/v" value was associated with the description of the inactive ingredient dehydrated alcohol.

In Section "2 DOSAGE AND ADMINISTRATION", the applicant made one important CMC-related change; the applicant added information concerning the compatibility of the Cannabidiol (CBD) 100 mg/ml oral solution with gastric and the naso-gastric feeding tubes manufactured with different materials. More precisely, the applicant does not recommend using feeding tubes made of polyvinyl chloride (PVC) as shown below.

> Oral administration is recommended. When necessary, nasogastric and gastrostomy tubes may be acceptable routes of enteral administration. Do not use with tubes made of polyvinyl chloride (PVC).

(b) (4)

Evaluation: ***Adequate***

Module "1.12.14. Environmental Analysis"

Comments: The applicant has provided a request for a Categorical Exclusion under 21 CFR 25.31(b) as the EIC (Expected Introduction Concentration) "of cannabidiol (CBD) in the aquatic environment is < 1 ppb." Moreover, the applicant certifies that to the best of their knowledge "extraordinary circumstances exist that would significantly affect the quality of the human environment as a result of the proposed action." More specifically, the applicant calculates that the EIC into the aquatic environment for cannabidiol equals (b) (4); this value is based on the highest quantity of the active moiety (CBD) expected to be produced for direct use in any of the next five years (2020-2024) of (b) (4) (5^{th} year production). This value is well below the 1.0 ppb limit and, hence, the claim of categorical exclusion appears to be warranted.

Evaluation: ***Adequate***

Module "3.2.P.2. Pharmaceutical Development"

(b) (4)

(b) (4)

Evaluation: ***Adequate***

IV. Risk Associated with the Proposed Changes and Impact to Product Quality and Patient Safety: Low

Richard Matsuoka

Digitally signed by Richard Matsuoka
Date: 6/30/2020 09:56:53AM
GUID: 58405a2d00b8e6d18c2b669521269752

David Lewis

Digitally signed by David Lewis
Date: 6/30/2020 10:49:07AM
GUID: 508da72000029f287fa31e664741b577
Comments: concur; recommend approval from the standpoint of CMC

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

CLINICAL PHARMACOLOGY REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA#	**210365/S0088**
Submission Date:	1/31/2020
Generic Name:	Cannabidiol (Epidiolex)
Indication:	Treatment of Seizures Associated with Tuberous Sclerosis Complex (TSC)
Sponsor:	GW Pharma
Submission Type:	Efficacy Supplement sNDA 210365

BACKGROUND

Epidiolex (cannabidiol) was approved in 2018 for adjunctive treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) or Dravet syndrome (DS) in patients 2 years of age and older. The recommended starting dosage is 2.5 mg/kg taken twice daily (5 mg/kg/day). After one week, the dosage can be increased to a maintenance dosage of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, Epidiolex can be increased up to a maximum recommended maintenance dosage of 10 mg/kg twice daily (20 mg/kg/day).

This is a supplemental NDA (sNDA) to support the extension of cannabidiol (CBD) indication as for the treatment of seizures associated with tuberous sclerosis complex in patients 1 years of age and older. The efficacy and safety studies, GWEP1521 and GWEP1521OLE were conducted to support the proposed dosage. The proposed dose includes titration to a therapeutic dose based on individual clinical response and tolerability upto12.5 mg/kg twice daily (25 mg/kg/day). The recommended starting dose is 2.5 mg/kg taken twice daily (5 mg/kg/day).

Note: (b) (4) There are no new clinical pharmacology studies conducted in this sNDA.

Efficacy and Safety Studies

The supportive evidence of efficacy for TSC indication includes following clinical studies:

- GWEP1521: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P, CBD) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately-controlled seizures.

  Note: The effectiveness of CBD was demonstrated in 224 patients aged 1 to 65 years (50 mg/kg/day vs placebo) based on the results showing significant change in number of TSC-associated seizures during the treatment period (titration and maintenance) compared with baseline in patients taking CBD-OS compared with placebo.

  Open Label Extension Study

- GWEP1521 OLE: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) as add-on therapy in patients with tuberous sclerosis complex who experience inadequately controlled seizures.

Phamacometrics Summary

The Applicant conducted exposure-response analyses for efficacy (report gwpp19217-pharmacometrics-report.pdf, sequence 0088, module 5335). The following is a summary of the data relevant to the analyses:

a) The endpoint used in exposure-response analyses is proportion of responders, defined as subjects with ≥ 50% reduction from baseline in TSC-associated seizure frequency. For computing seizure frequency, the baseline period is Day -28 to Day 1 and the treatment period is Day 1 to Day 113.
b) PK data samples were acquired at Visit 3 (Day 1) and Visit 10 (Day 113; or early termination). PK samples were acquired pre-dose, and at two to three timepoints up to 6 hours post-dose. Patients 18 years and older provided a sample at 8 to 10 hours post-dose.
c) The Applicant utilized simulated Day 71 plasma AUC values as the input to the exposure-response model.

As was the case with the exposure-response analyses in the original submission (for Lennox-Gastaut Syndrome and Dravet Syndrome), the exposure-response analyses for efficacy in TSC patients were not reviewed as it is not clear that the simulated PK values used in the E-R analyses can be considered representative of the CBD-time profile throughout the duration of the study. The following reasons support this assertion:

1. The timing of CBD administration with respect to meals appears to affect CBD PK. In the original NDA submission, in Study 1544, a 3-fold difference in the mean CBD maximum concentration was observed between morning administration and the subsequent evening administration on Day 1. This 3-fold increase in mean CBD maximum concentration was likely due to a prandial effect (e.g. 10-hour overnight fast before morning dose versus the 2-hour fast before the subsequent dose in the evening). This suggests that that differences in the prandial state may cause CBD PK profile to vary widely from one administration to the next (page 64-65 of 114 of original Epidiolex OCP review [Clinical Pharmacology review of NDA 210365, archived on 05/16/2018]).
2. The current Epidiolex label states “Coadministration of EPIDIOLEX with a high-fat/high-calorie meal increased C_{max} by 5-fold, AUC by 4-fold, and reduced the total variability, compared with the fasted state in healthy volunteers”.

3. Like the original NDA submission, there were no restrictions on meals.
4. Observed PK data samples were collected over a period of 10 hours (less than one quarter of the 56-61-hour half-life) on Day 1 and again on Day 113.
5. Meal information was only collected at one time point; at Day 113 visit for PK sampling.
    - meal status information is available for only ~55% of subjects in the PPK dataset.

Overall, in consideration of the food effect on PK, meal timing effect on PK, the lack of meal restrictions in Trial 1521, and meal status is missing at all timepoints except on Day 113, it is not clear that the observed PK values used in the E-R analyses can be considered to be representative of the CBD-time profile throughout the duration of the study. As such it is not clear whether the E-R analyses for efficacy are informative and thus they will not be reviewed.

The Applicant also provided exposure-response analyses for safety (also in report gwpp19217-pharmacometrics-report.pdf, sequence 0088, module 5335). The exposure-response analyses for safety also will not be reviewed, for the same reason.

The sponsor updated labeling related to drug-drug interactions based on literature reports as follows.

7.4 Concomitant Use of EPIDIOLEX and Mammalian Target of Rapamycin (mTOR) or Calcineurin Inhibitors

No dedicated drug-drug interaction studies have been conducted with mTOR inhibitors (e.g., everolimus) or calcineurin inhibitors (e.g., tacrolimus). Reports in the literature suggest that cannabidiol administration resulted in increased serum levels of everolimus, sirolimus or tacrolimus upto 2-fold in some patients.

Consider a reduction in dosage of everolimus, sirolimus or tacrolimus, if adverse reactions are experienced when co-administered with EPIDIOLEX.

Note: Reports in the literatures suggest that concomitant administration of cannabidiol (CBD) with Mammalian Target of Rapamycin (mTOR inhibitors, e.g., everolimus, sirolimus) or Calcineurin Inhibitors (e.g., tacrolimus) increased plasma concentrations of these drugs (Appendix 1). The major enzyme involved in metabolism of everolimus, sirolimus or tacrolimus was found to be CYP3A. However, CBD and midazolam drug-drug interaction study (submitted previously) could not explain the conflicting results. An information request was sent to the sponsor to provide rationale for the observed increase in plasma concentrations of these drugs.

According to the sponsor, there are no definitive studies evaluating a drug-drug interaction between CBD and this class of molecules. Thus, the magnitude of such an effect, should it exist, has not been determined. The case reports in the literature were likely identified as a consequence of the standard clinical practice of monitoring trough

plasma concentrations of this class of drugs. The Sponsor is therefore planning to conduct a definitive drug-drug interaction study to evaluate the potential interaction between CBD and everolimus. The protocol for this study (GWCP19195) has been submitted to IND 120055 (Sequence 0529).

Rapamycin (mTOR inhibitors, e.g., everolimus, sirolimus) or Calcineurin Inhibitors (e.g., tacrolimus) are also substrates for P-glycoprotein (P-gp). Cannabidiol is not a substrate for P-gp but it has been shown to be a weak inhibitor. The Ki value for CBD was determined to be in excess of 1.83 μM. Therefore, the role of P-gp inhibition in the gastrointestinal tract as a potential mechanism for an interaction with P-gp substrates such as everolimus, especially given the high doses of CBD administered and the enhanced solubility in its oil formulation cannot be ruled out.

Inhibition of intestinal P-gp may increase absorption by blocking efflux transport and decrease total metabolism, resulting in a significant increase in intestinal bioavailability of these drugs.

CONCLUSIONS AND RECOMMENDATIONS:

Labeling recommendations-based literature reports should include following statement "Mechanism of increase in mTOR or calcineurin inhibitors concentrations is not clearly understood" until the study GWCP19195 report is submitted to the FDA's review.

Labeling Revisions:
7.4 Concomitant Use of EPIDIOLEX and Mammalian Target of Rapamycin (mTOR) or Calcineurin Inhibitors

No dedicated drug-drug interaction studies have been conducted with mTOR inhibitors (e.g., everolimus) or calcineurin inhibitors (e.g., tacrolimus). Reports in the literature suggest that cannabidiol administration resulted in increased serum levels of everolimus, sirolimus or tacrolimus. Mechanism of increase in mTOR or calcineurin inhibitors concentrations is not clearly understood. Consider a reduction in dosage of everolimus, sirolimus or tacrolimus, if adverse reactions are experienced when co-administered with EPIDIOLEX.

Jagan Mohan Parepally, M.S., Ph.D.
Reviewer
Division of Neuropsychiatric Pharmacology (DNP)

Michael Bewernitz, Ph.D.
Reviewer
Division of Pharmacometrics (DPM)

Concurrence:

Atul Bhattaram, Ph.D._____
Team Leader, DPM

Angela Men, M.D., Ph.D._____
Team Leader, DNP

Appendix 1: Literature Reports Summary

Ebrahimi-Fakhari et.al (2019)[1], noted that cannabidiol elevates mechanistic target of rapamycin inhibitor levels (everolimus, sirolimus) in patients with tuberous sclerosis complex. Clinical information, mechanistic target of rapamycin inhibitor and cannabidiol dosing, concomitant antiepileptic drugs, as well as laboratory and adverse events were reviewed before and after initiation of cannabidiol. All mechanistic target of rapamycin inhibitor levels were drawn as troughs. Levels were significantly higher in 76% patients after cannabidiol treatment (P ¼ 0.0003). Median change from baseline was +9.8 ng/mL for everolimus and +5.1 ng/mL for sirolimus. Adverse events occurred in 40%, with diarrhea being the most frequent adverse event occurring in three patients.

Tacrolimus is metabolized by the cytochrome P450 (CYP) 3A subfamily. Metabolic drug-drug interaction studies were conducted to provide information regarding the optimal usage of tacrolimus, and its metabolism was inhibited by known CYP3A inhibitors such as ketoconazole, cyclosporine A, and nifedipine[2].

Effect of various drugs on tacrolimus metabolism by human liver microsomes

Inhibition (%)	Drugs
>90	Ketoconazole*
70–61	Cyclosporin A, nifedipine
50–41	Diltiazem, ethinyl estradiol, nilvadipine
40–31	Astemizole, erythromycin, prednisolone, terfenadine
30–21	Fluconazole, rifampicin
20–10	Amphotericin B, cefixime, ciprofloxacin, licomycin, norethindrone, ofloxacin, omeprazole, quinidine, sulindac
<10	Acyclivir, azulene, cefalexine, cefotaxime, chlorpheniramine, cimetidine, clemastine, cycroheptadine, diclofenac, enoxacin, etizolam, fosfomycin, gentamycin**, homochlorcyclizine, hydroxyzine, indomethacin, kanamycin. ketotifen, loxoprofen, minocycline, phenobarbital, phenylbutazon, promethazine

Underlined drugs: clinically relevant drug interactions with tacrolimus were reported.[4]
Concentrations of tacrolimus and drugs were 10 and 100 μM, respectively.
*: Concentration of ketoconazole was 10 μM.
**: Concentration of gentamycin was 60 μg/mL.

Tacrolimus has a narrow therapeutic range, and its blood concentrations should be maintained at an optimal range in transplanted patients to prevent the rejection of transplanted organs due to insufficient concentrations of tacrolimus or the toxic events due to its excess concentrations. Tacrolimus is a substrate of CYP3A4, CYP3A5 and P-glycoprotein (PGP, MDR1).

Wiemer-Kruel et al. (2019)[3] in his literature report "Cannabidiol Interacts Significantly with Everolimus - Report of a Patient with Tuberous Sclerosis Complex" described a 6.5-year-old female patient with a TSC2 mutation had been given everolimus (EVE) for 3 years for pharmaco-resistant focal epilepsy and for life-threatening, severe ventricular dysrhythmia. EVE had been started with daily dose of 0.15 mg/kg/day and was increased up to 0.6mg/kg/day. Target blood trough levels of around 9 µg/L had been documented. Although EVE therapy revealed no effect on seizure activity, cardiac rhythm normalized completely. Thus, EVE was reduced to a dose of 0.3mg/kg/day leading to stable blood trough levels of 4 to 5 µg/L. Due to refractory tonic seizures with a frequency of 1 to 4 per day, we initiated cannabidiol (CBD) treatment, raising it to a daily dose of 200mg. After 6weeks, the EVE blood trough levels rose to 12.0 µg/L. Although we halved the EVE dose, her EVE blood trough level continued increasing up to 16.0 µg/L. The CBD dose was increased to 500mg/day (20.4 g/kg/day), but EEG parameters and seizures failed to respond. Serum concentrations of EVE were unstable under the comedication with CBD. Depending on the CBD dose, they varied between 1.7 and 12.3 µg/L, while EVE was always administered at the same dose.

Fukuda et al., (2015)[4] in his literature report "The impact of CYP3A5*3 polymorphism on sirolimus pharmacokinetics: insights from predictions with a physiologically-based pharmacokinetic model" noted that sirolimus metabolism was inhibited by over 90% by ketoconazole, a CYP3A specific inhibitor. The PBPK model developed based on CLint of recombinant CYP3A4, CYP3A5 and CYP2C8 predicted a small CYP3A5*3 effect on simulated sirolimus PK profiles. A subsequent power analysis based on these findings indicated that at least 80 subjects in an enrichment design, 40 CYP3A5 expressers and 40 nonexpressers, would be required to detect a significant difference in the predicted trough concentrations at 1 month of therapy ($P < 0.05$, 80% power).

In a review article Kirshner et al., (2015)[5] in his literature report "Clinical Pharmacokinetics of Everolimus" noted that the interindividual pharmacokinetic variability of everolimus can be explained by different activities of the drug efflux pump P-glycoprotein and of metabolism by cytochrome P450 (CYP) 3A4, 3A5 and 2C8. The critical role of the CYP3A4 system for everolimus biotransformation leads to drug-drug interactions with other drugs metabolised by this cytochrome system.

References

1 Ebrahimi-Fakhari D, Agricola KD, Tudor C, Krueger D, Franz DN. Cannabidiol Elevates Mechanistic Target of Rapamycin Inhibitor Levels in Patients with Tuberous Sclerosis Complex. Pediatric Neurology. 2020 Apr;105:59-61.

2 Iwasaki K. Metabolism of tacrolimus (FK506) and recent topics in clinical pharmacokinetics. Drug Metab Pharmacokinet. 2007;22(5):328-335.

3 Wiemer-Kruel A, Stiller B, Bast T. Cannabidiol Interacts Significantly with Everolimus-Report of a Patient with Tuberous Sclerosis Complex. Neuropediatrics. 2019;50(6):400-403. doi:10.1055/s-0039-1695786

4 Emoto C, Fukuda T, Venkatasubramanian R, Vinks AA. The impact of CYP3A5*3 polymorphism on sirolimus pharmacokinetics: insights from predictions with a physiologically-based pharmacokinetic model. Br J Clin Pharmacol. 2015;80(6):1438-1446.

5 Kirchner, G.I., Meier-Wiedenbach, I. & Manns, M.P. Clinical Pharmacokinetics of Everolimus. Clin Pharmacokinet 43, 83–95 (2004).

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JAGAN MOHAN R PAREPALLY
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs

PATIENT LABELING REVIEW

Date:	July 20, 2020
To:	Stephanie N. Parncutt, MHA Senior Regulatory Project Manager **Division of Neurology II (DN II)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Marcia Williams, PhD Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Nyedra W. Booker, PharmD, MPH Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Dhara Shah, PharmD, RAC Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	EPIDIOLEX (cannabidiol)
Dosage Form and Route:	oral solution, CV
Application Type/Number:	NDA 210365
Supplement Number:	S-005 and S-006
Applicant:	Greenwich Biosciences

1 INTRODUCTION

On January 31, 2020 Greenwich Biosciences submitted for the Agency's review, an Efficacy Supplement: Treatment of Tuberculosis Sclerosis Complex (TSC) to the New Drug Application (NDA) for EPIDIOLEX (cannabidiol) oral solution. The purpose of this submission is to support the addition of treatment of seizures associated with TSC to the Prescribing Information (PI) for EPIDIOLEX (cannabidiol) oral solution. EPIDIOLEX (cannabidiol) oral solution has an Orphan Designation for the treatment of TSC.

EPIDIOLEX (cannabidiol) oral solution was approved on June 25, 2018 for the treatment of seizures associated with Dravet syndrome (DS) and Lennox-Gastaut syndrome (LGS) in patients 2 years of age and older.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Neurology II (DN II) on March 10, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for EPIDIOLEX (cannabidiol) oral solution.

2 MATERIAL REVIEWED

- Draft EPIDIOLEX (cannabidiol) oral solution MG received on January 31, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 14, 2020.
- Draft EPIDIOLEX (cannabidiol) oral solution PI received on January 31, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on July 14, 2020.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG we have:

- simplified wording and clarified concepts where possible
- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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LASHAWN M GRIFFITHS
07/20/2020 09:44:22 AM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 17, 2020

To: Natalie Getzoff, Medical Officer
Division of Neurology II (DN II)

Stephanie Parncutt, Regulatory Project Manager, DN II

Tracy Peters, Associate Director for Labeling, DN II

From: Dhara Shah, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, Team Leader, OPDP

Subject: OPDP Labeling Comments for EPIDIOLEX® (cannabidiol) oral solution, CV
NDA: 210365 Supplements 05, 06

In response to the DN II consult request dated March 10, 2020, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the NDA submission for EPIDIOLEX® (cannabidiol) oral solution, CV (Epidiolex). These supplements pertain to a new indication (s5) and a new patient population (s6).

PI and Medication Guide: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DN II (Stephanie Parncutt) on July 14, 2020, and are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or Dhara.Shah@fda.hhs.gov.

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DHARA SHAH
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 26, 2020
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 210365/S-005 & S-006
Product Name and Strength:	Epidiolex (cannabidiol) oral solution, 100 mg/mL
Applicant/Sponsor Name:	GW Research Ltd
OSE RCM #:	2020-286-1
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on May 15, 2020 for Epidiolex. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Epidiolex (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a] The revised container label and carton labeling also incorporate the removal of the Schedule V designation, as implemented in the Changes Being Effected labeling supplement (S-007) submitted on April 6, 2020.

2 CONCLUSION

The Applicant implemented our previous recommendation, and the removal of the Schedule V designation from the container label and carton labeling is acceptable from a medication error perspective. We have no additional recommendations at this time.

[a] Morris, C. Label and Labeling Review for Epidiolex (NDA 210365/S-005 & S-006). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 17. RCM No.: 2020-286.


(b) (4)

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/s/

JOHN C MORRIS
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BRIANA B RIDER
05/26/2020 07:45:53 AM

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	April 17, 2020
Requesting Office or Division:	Division of Neurology 2
Application Type and Number:	NDA 210365/S-005 & S-006
Product Name and Strength:	Epidiolex (cannabidiol) oral solution, 100 mg/mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	GW Research Ltd
FDA Received Date:	January 31, 2020
OSE RCM #:	2020-286
DMEPA Safety Evaluator:	Chad Morris, PharmD, MPH
DMEPA Team Leader:	Briana Rider, PharmD, CPPS

1 REASON FOR REVIEW

GW Research Ltd submitted two efficacy supplements for Epidiolex (cannabidiol) oral solution to support:

- S-005, expanding the indication to include treatment of seizures associated with tuberous sclerosis complex (TSC), and
- S-006, extend the indications for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome down to patients 1 year of age and older.

Subsequently, the Division of Neurology 2 (DN 2) requested that we review the proposed revisions to the Epidiolex Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C (N/A)
FDA Adverse Event Reporting System (FAERS)*	D (N/A)
Other	E (N/A)
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 ASSESSMENT AND RECOMMENDATIONS

GW Research Ltd is proposing to expand the indication for Epidiolex to include treatment of seizures associated with tuberous sclerosis complex (TSC), and extend the indications for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) from 'patients 2 years of age and older' down to 'patients 1 year of age and older'.

We evaluated the proposed changes from a medication safety and usability perspective. We note the proposed changes to the indication do not require changes to the strength, dosage form, route of administration, or packaging configuration. We find the currently marketed strength and packaging configuration supports the dosage and administration for the proposed TSC indication and expanded age for LGS and DS.

Additionally, the use tasks required to use the product safely and effectively remain unchanged. We expect a caregiver will administer for pediatric patients with LGS and DS; thus,

the intended users will not change if the indications are expanded from 'patients 2 years of age and older' down to 'patients 1 year of age and older'.

Furthermore, the new user population (patients with TSC and their caregivers) is accustomed to using an oral syringe (for example, Afinitor Disperz tablet for oral suspension). As such, we do not require additional human factors validation data to support safe and effective use in the expanded user populations.

We note there are no changes proposed to the IFU, but the revision date has been updated to align with the updates to the PI and MG. Our review of the proposed revisions to the PI, MG, and IFU did not identify any concerns from a medication safety perspective related to the expanded indication and user population.

We note, additional instructions for enteral routes of administration (that is, nasogastric (NG) and gastrostomy (G) tubes) are proposed in Section 2.3 (Administration Instructions) of the PI. As part of our review, we considered whether this change, or the expansion of the indication/user population would require revisions to the carton labeling or container label to ensure consistency and decrease risk of confusion and medication errors. We find the route of administration statement (that is, for oral administration only) on the container label and carton labeling is inaccurate. We provide recommendations to GW Research Ltd below in Table 2 to address this concern.

Table 2. Identified Issues and Recommendations for GW Research Ltd (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	The route of administration statement on the Principal Display Panel (PDP) of the currently marketed container label and carton labeling states "for oral administration only."	Can be revised for accuracy since NG and G-tube administration can be used if necessary.	We recommend you revise the route of administration statement "for oral administration only" to read "for oral administration."

4 CONCLUSION

Our evaluation of the proposed revisions to the Epidiolex PI, MG, and IFU did not identify areas of vulnerability that may lead to medication errors. However, we identified areas of vulnerability with the currently marketed carton labeling and container label that may increase the risk for medication errors. We have provided recommendations, above, in Table 2 for GW Research Ltd. We ask the Division to convey Table 2 in its entirety to GW Research Ltd, so the recommendations are implemented prior to approval of this NDA Supplement.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Epidiolex that GW Research Ltd submitted on January 31, 2020.

<table>
<tr><th colspan="2">Table 3. Relevant Product Information for Epidiolex</th></tr>
<tr><td>Initial Approval Date</td><td>06/25/2018</td></tr>
<tr><td>Active Ingredient</td><td>Cannabidiol</td></tr>
<tr><td>Indication</td><td>Current: treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older

Proposed: treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients 1 year of age and older</td></tr>
<tr><td>Route of Administration</td><td>Oral, enteral (if necessary, via NG- or G-tube)</td></tr>
<tr><td>Dosage Form</td><td>Oral solution</td></tr>
<tr><td>Strength</td><td>100 mg/mL</td></tr>
<tr><td>Dose and Frequency</td><td>The starting dosage is 2.5 mg/kg twice daily (5 mg/kg/day).
(b) (4) [redacted]

Table 1: Dose Adjustments in Patients with Hepatic Impairment
<table><tr><th>Hepatic Impairment</th><th>Starting Dosage</th><th>(b) (4) [redacted]</th></tr><tr><td>Mild</td><td>2.5 mg/kg twice daily (5 mg/kg/day)</td><td></td></tr><tr><td>Moderate</td><td>1.25 mg/kg twice daily (2.5 mg/kg/day)</td><td></td></tr><tr><td>Severe</td><td>0.5 mg/kg twice daily (1 mg/kg/day)</td><td></td></tr></table></td></tr>
<tr><td>How Supplied</td><td>(b) (4) [redacted] amber glass multi-use bottle, a bottle adapter and two 5 mL oral syringes</td></tr>
<tr><td>Storage</td><td>Store at room temperature between 68°F to 77°F (20°C to 25°C)</td></tr>
<tr><td>Container Closure</td><td>Amber (b) (4) [redacted] glass bottle sealed with a child resistant cap.</td></tr>
</table>

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 18, 2020, we searched for previous DMEPA reviews relevant to this current review using the terms, Epidiolex, cannabidiol, and NDA 210365. Our search identified four previous reviews, and we considered our previous recommendations to see if they are applicable for this current review.

Table 4. Summary of Previous DMEPA Reviews for Epidiolex

OSE RCM #	Review Date	Summary of Recommendations
2016-545[a]	04/11/2016	IND 120055, Human Factors Protocol Review: We reviewed the HF Study Protocol and URRA, and identified several deficiencies in the Protocol, labels, labeling, and IFU. We provided recommendations to GW Research. Revisions were reviewed in 2018-114, 2018-898.
2018-114, 2018-898[b]	04/27/2018	Original NDA, Human Factors Study Results Review: We reviewed the Human Factors (HF) validation study results, proposed container label, carton labeling, and device design. The Human Factors (HF) validation study identified use errors associated the following tasks: push the bottle adapter firmly into the bottle and measure the dose. We also identified areas of the PI, carton labeling and container label that can be improved. Recommendations for the IFU were provided to the Division and carton labeling and container label to GW Research. Revisions were reviewed in 2018-114-1.
2018-114-1[c]	06/15/2018	Original NDA, Labels and Labeling Review MEMO: We reviewed the revised container label, carton labeling, PI, MG, and IFU. We provided MG recommendations to the Division and carton labeling and container label recommendations to GW Research. Revisions were reviewed in 2018-114-2.

[a] White, L. Label and Labeling Review for cannabidiol (IND 120055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APR 11. RCM No.: 2016-545.

[b] Rider, B. Label and Labeling Review for Epidiolex (cannabidiol) (NDA 210365). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 27. RCM No.: 2018-114, 2018-898.

[c] Rider, B. Label and Labeling Review for Epidiolex (cannabidiol) (NDA 210365). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 15. RCM No.: 2018-114-1.

Table 4. Summary of Previous DMEPA Reviews for Epidiolex		
OSE RCM #	Review Date	Summary of Recommendations
2018-114-2[d]	06/20/2018	Original NDA, Labels and Labeling Review MEMO: We reviewed the revised container label and carton labeling and found them acceptable.

APPEARS THIS WAY ON ORIGINAL

[d] Rider, B. Label and Labeling Review for Epidiolex (cannabidiol) (NDA 210365). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 20. RCM No.: 2018-114-2.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Epidiolex labels and labeling submitted by GW Research Ltd. on January 31, 2020.

- Instructions for Use (Image not shown)
- Medication Guide (Image not shown)
- Prescribing Information (Image not shown)

APPEARS THIS WAY ON ORIGINAL

[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

JOHN C MORRIS
04/17/2020 08:45:15 AM

BRIANA B RIDER
04/17/2020 08:54:56 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210365Orig1s005s006s007

ADMINISTRATIVE/CORRESPONDENCE

NDA 210365

MEETING MINUTES

GW Research Ltd.
Attention: Christine Schulteis, Ph.D.
Senior Director, Global Regulatory Affairs
5750 Fleet Street, Suite 200
Carlsbad, CA 92008

Dear Dr. Schulteis:[1]

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Epidiolex (cannabidiol) 100 mg/mL oral solution.

We also refer to the telecon between representatives of your firm and the FDA on October 1, 2019. The purpose of the meeting was to discuss results from the randomized, double-blind, placebo-controlled trial GWEP1521, in which CBD-OS was evaluated as treatment of seizures in patients with Tuberous Sclerosis Complex (TSC) as the basis of a proposed efficacy supplement to NDA 210365 for Epidiolex (cannabidiol) oral solution, CV to add treatment of seizures in patients with TSC to the indication.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Stephanie N. Parncutt, M.H.A., Senior Regulatory Health Project Manager, at (301) 796-4098 or email at Stephanie.Parncutt@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, M.D.
Acting Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Enclosure: Meeting Minutes

APPEARS THIS WAY ON ORIGINAL

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: October 1, 2019; 3:00 – 4:00 PM EST
Meeting Location: Teleconference

Application Number: NDA 210365
Product Name: Epidiolex (cannabidiol) 100 mg/mL oral solution

Indication: **The treatment of seizures in patients with Tuberous Sclerosis Complex (TSC).**

Applicant Name: GW Research Ltd.

Meeting Chair: Nick Kozauer, M.D.

Meeting Recorder: Stephanie N. Parncutt, M.H.A.

FDA ATTENDEES

Eric Bastings, M.D., Acting Director, DNP
Nick Kozauer, M.D., Acting Deputy Director, DNP
Philip Sheridan, M.D., Clinical Team Leader, DNP
Natalie Getzoff, M.D., Clinical Reviewer, DNP
Jagan Parepally, Ph.D., Clinical Pharmacology Reviewer, DNP
Xiang Ling, Ph.D., Statistics Reviewer, DNP
Stephanie Parncutt, M.H.A., Senior Regulatory Project Manager, DNP

SPONSOR ATTENDEES

Dennis Ahern, MS, Vice President, Global Regulatory Affairs
Daniel Checketts, MSc, Head of Biometrics
Eduardo Dunayevich, MD, Vice President, Clinical Science
Sigal Gal, PhD, Senior Director, Global Product Development
Thomas Grint, MS, Global Pharmacovigilance
Volker Knappertz, MD, Chief Medical Officer, Research and Development
Emma Lennon, Group Manager, Research and Development
Jie Li, MD, Senior Director, Global Pharmacovigilance

Gilmour Morrison, Director of Clinical Pharmacology
Farhad Sahebkar, MD, Medical Director, Clinical Sciences
Christine Schulteis, PhD, Senior Director, Global Regulatory Affairs
Kevan VanLandingham, MD, Senior Medical Director, Clinical Sciences
Benjamin J. Whalley, BPharm, PhD, MRPharmS, HonFBPhS, Director of Research, Nonclinical

1.0 BACKGROUND

GW Research Ltd. has submitted a Type B Pre-NDA Meeting Request - to discuss the results from the recently completed, randomized, double-blind, placebo-controlled trial GWEP1521, in which cannabidiol oral solution (CBD-OS) was evaluated as treatment of seizures in patients with tuberous sclerosis complex (TSC), and the proposed efficacy supplement to NDA 210365 to seek approval for treatment of seizures in patients with TSC as an indication for CBD-OS.

GW Research Ltd. also plans to add supportive information and additional labeling updates as part of the supplement.

The purpose of the proposed meeting is to reach alignment with the Division on the structure and contents of the planned supplemental NDA submission.

The Division sent Preliminary Comments to GW Research Ltd. on September 27, 2019.

2. DISCUSSION

QUESTION 1: The sponsor believes that the current comprehensive clinical pharmacology package, in combination with planned post-marketing studies, will be sufficient, pending FDA review, to support submission and review of an sNDA for CBD-OS for treatment of seizures associated with TSC at doses of 10 mg/kg/day to 25 mg/kg/day. Does FDA agree?

FDA Preliminary Response

(b) (4)

[redacted]

Meeting Minutes

No further discussion.

Post-meeting note:
The following are the general expectations for submitting pharmacometric data and models:

All datasets used for model development and validation should be submitted as a SAS transport files (*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA (1). Also provide in the summary of the report a description of the clinical application of modeling results.

In terms of where the code and data should be submitted, the following folders can be used as one example for population PK related codes and data. The codes should be submitted under "module5/datasets/poppk/analysis/programs/" folder (such as run1.ctl.txt, run1.lst.txt, plot1.R.txt) with a define pdf file to explain the role of each file and sometimes with a pdf file as the reviewerraid.pdf to explain the flow of running the code if necessary. The datasets should be submitted under "module5/datasets/poppk/analysis/datasets/" folder (such as poppk.xpt, pkpd.xpt) with a define pdf file to explain the variables within each data file.

QUESTION 2: The sponsor proposes that the results of GWEP1521, a Phase 3, double-blind, randomized placebo-controlled study of the efficacy and safety of CBD-OS for treatment of seizures in patients with TSC, in combination with supportive safety information from open-label data and the overall clinical development program for LGS and DS, (b) (4) , support the review of the efficacy and safety of CBD-OS for treatment of seizures associated with TSC in patients 1 year of age and older. Does FDA agree?

FDA Preliminary Response

The results Study GWEP1521 may be sufficient to support an indication for treatment of seizures associated with Tuberous Sclerosis Complex (TSC) in the context of the previous approval of Epidiolex for treatment of seizures associated with other epilepsy syndromes. The adequacy of the study results to support approval will be a matter of review. (b) (4) See response to Question 5.

In addition to the efficacy analyses identified in the pre-NDA submission, you should also provide the following information in your future sNDA(s):

- Please include a discussion of whether the assumptions of the negative binomial regression for the primary analysis are met.
- You performed your primary efficacy endpoint analysis on "TSC-associated seizures", which were defined as focal motor seizures without impairment of consciousness or awareness (Type 1 focal); focal seizures with impairment of consciousness or awareness (Type 2 focal); focal seizures evolving to bilateral generalized convulsive seizures (Type 3 focal) and tonic-clonic, tonic, clonic or atonic seizures. Please also perform an exploratory analysis of the change in seizure frequency from baseline of each treatment group for each of these "TSC-associated" seizure subtypes, as well as for the group of any seizures that do not meet your definition for "TSC associated seizures". Also, please perform an exploratory analysis of the change in seizure frequency from baseline of each treatment group for all seizures combined.

Meeting Minutes

(b) (4)

(b) (4)

QUESTION 3: **Is FDA in agreement with the safety analyses planned to support the sNDA and the 120-day safety update for CBD-OS for treatment of TSC, as outlined briefly below and described in greater detail in Appendix 4?**

FDA Preliminary Response

The primary safety analyses should be performed on data from the double-blind period of Study GWEP1521, which appears to be your "Pool TSC". Your proposal to analyze the safety data from the open-label extension of GWEP1521 ("Pool OLE-TSC") is also acceptable. Additionally, your plan to combine available safety data from the non-GW-sponsored expanded access program (EAP) into a single dataset with summaries within the Summary of Clinical Safety is also acceptable as you have described.

You should also include updates from ongoing clinical studies. These study updates should include a description of serious adverse events, deaths, and other important adverse events, as well as a tabular summary of these data. Narratives of such cases (SAEs and deaths) should also be provided. Please note that, although we do not object to analysis of other pooled safety datasets, such analyses do not appear to be critical to support approval of Epidiolex for treatment of seizures in patients with TSC.

Please also see the response to Question 5.

Meeting Minutes

The sponsor proposed submitting an ISS of all the clinical studies. The Division replied that primary safety should be as was stated in the preliminary responses: A summary of clinical safety (as in the 2nd paragraph of the preliminary responses) rather than an ISS.

QUESTION 4: **The sponsor plans to provide narrative descriptions of efficacy and safety for the TSC indication within Module 2.7.3, Summary of Clinical Efficacy, and Module 2.7.4, Summary of Clinical Safety, respectively, with supporting data tables and individual patient narratives (as appropriate) located in Module 5 as the Integrated Summaries of Efficacy and Safety. Module 2.7.3 will include a summary of the efficacy of the proposed TSC indication. Module 2.7.4, Summary of Clinical Safety, is proposed to describe the safety of CBD-OS across the three**

patient populations, including the approved LGS and DS indications and the proposed TSC indication. Does FDA agree with submission of the narrative descriptions of efficacy and safety as part of Modules 2.7.3 and 2.7.4, with supporting data tables and additional information provided in Module 5?

FDA Preliminary Response

Your proposed plan is acceptable, provided that the Summary of Clinical Safety (SCS) and the Summary of Clinical Efficacy (SCE) each contain details sufficient to allow them to serve as the narrative portion of the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), respectively, while still being concise enough to meet the suggested size limitation for Module 2. Analyses presented in the SCS or SCE should be linked to relevant analyses in Module 5. Links should function from the SCS or SCE to the appropriate information in Module 5, and there should be a link back to the corresponding original section in the SCS or SCE. We refer you to the "M4E(R2): The CTD — Efficacy Guidance for Industry"[2] and the Guidance for Industry "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document"[3]. See also Attachment 1 below for additional requests for safety information in Module 5.

Please also see the response to Question 5.

Meeting Minutes

No further discussion.

QUESTION 5: The planned efficacy supplement to support treatment of CBD-OS for seizures associated with TSC is based on the randomized, double-blind, placebo-controlled trial GWEP1521. In addition to the data supporting the additional indication, the sponsor also proposes to include supportive studies that will contribute to additional labeling updates, as described in Table 8.3-1.

In addition to the clinical study reports in Table 8.3-1, the following study reports will provide supportive safety information:

- **GWEP1415 OLE: An open-label extension study to investigate the safety of cannabidiol (GWP42003-P; CBD) in children and adults with inadequately controlled Dravet or Lennox-Gastaut syndromes. (synoptic, interim CSR [study remains ongoing])**
- **GWEP1521 OLE: A double-blind, randomized, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P) as add-on therapy in patients with tuberous sclerosis complex who experience**

[2] https://www.fda.gov/media/93569/download
[3] https://www.fda.gov/media/75783/download

inadequately controlled seizures. (synoptic, interim CSR [study remains ongoing])
- **Updated Liver Safety Report**
- **Gastrostomy Tube Administration Research Report**

(b) (4)

FDA Preliminary Response

(b) (4)

Meeting Minutes

(b) (4)

Attachment 1.

DNP Pre-NDA/BLA Meetings
General Clinical Safety Requests

Datasets:

1. Each individual subject should be assigned a single unique subject identifier across the entire application (e.g., including open label extensions of the trials). Include the unique subject identifier in the ISS and individual studies' datasets.
2. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.

For additional guidance refer to the FDA webpage on Study Data Standards Resources.

General Submission Contents:

1. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the Guideline for the Format and Content of the Clinical and Statistical Sections of an Application
2. Provide an assessment of safety as per the FDA Guidance for Industry: Premarketing Risk Assessment

3. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
4. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
5. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
    a) Title of the table or figure in the application
    b) A hyperlink to the location of the table or figure with page number
    c) A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
6. Format the tables of the ISS according to examples in FDA's Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review.
7. Include active hyperlinks from the lists of references to the referenced article.
8. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
9. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
10. Submit an annotated version of the pre-BLA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed "MedDRA Term Selection: Points to Consider" document accessible at MedDRA
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. The preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.

5. Ensure that all adverse events are presented, and not only events deemed “drug-related.”
6. Provide a table of treatment-emergent adverse events reported in ≥ 2% of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
7. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, adverse events leading to drug discontinuation, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request. Narratives should be integrated. For subjects who had more than one event requiring a narrative (whether in the same trial or in the core study and an extension) present a single narrative (rather than separate narratives for the various events).
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the narrative and CRF.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy’s Law laboratory criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them “CRFs”, e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide a tabular listing of all subjects with all discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for drug or study discontinuation. For reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation. The Division may want to request selected narratives/CRFs from some of these patients, but they do not need to be submitted at the time of the initial NDA/BLA submission.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
    a) Patient age and gender
    b) Adverse event onset and stop dates (presented as relative Study Day number)
    c) Signs and symptoms related to the adverse event being discussed
    d) An assessment of the relationship of exposure duration to the development of the adverse event

e) Pertinent medical history
f) Concomitant medications with start dates relative to the adverse event
g) Pertinent physical exam findings
h) Any abnormal vital sign measurements
i) Pertinent test results (e.g., lab data, ECG data, procedures, biopsy data, autopsy results)
j) Discussion of the diagnosis as supported by available clinical data
k) For events without a definitive diagnosis, a list of the differential diagnoses
l) Treatment provided
m) Re-challenge results (if performed)
n) Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests:
   SI Units.
2. Provide the normal reference ranges for every laboratory value.
3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs, and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
   - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
   - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
   - Pulse Rate: <60 bpm, >100 bpm
   - Body Weight: decrease of ≥7% from baseline and increase of ≥7% from baseline
   - Temperature: >38.0 °C, <36.0 °C
   - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

Other requests:

1. Patient profiles
   Submit individual patient profiles containing all laboratory and other study results in a single place for each patient. Provide this information for patients who died, had a serious adverse event, discontinued from the trial due to an adverse event, or had a medically significant event for which a narrative is submitted. Include all the information recorded for that patient, including but not limited to:
   a) Age

b) Sex
c) Dates of screening, randomization and starting therapy
d) Whether the patient completed or did not complete the study, with dates and reason for withdrawal
e) Adverse events (reported term, preferred term, start and stop date [with relative study day], seriousness, outcome, whether it resolved or not and action taken with drug)
f) Prior medications and concomitant medications with dates of start and end
g) Vital signs and laboratories, sorted by date, with reference ranges *
h) Autopsy reports for all deaths. (If an autopsy report is not available, explicitly state this.)
i) Full reports for radiologic studies, ECG, MRI, pathology results, special studies and procedures with dates and reference ranges
j) Provide relevant results obtained outside of clinical trial visits, including those obtained during hospitalization or emergency room visits, in each patient file. Also include baseline study results.
k) For patients who had IND safety report(s), include dates when the initial and follow up safety reports were submitted.

Create a PDF file for each patient and a table of contents with links to each assessment for each patient.

2. Please submit for Division comments an example narrative from a patient who had more than one serious adverse event and participated in the controlled and extension studies prior to submitting your NDA.
3. We request that you submit a sample integrated summary of safety datasets (with data definition file) for Division comments prior to submitting the NDA. This process could help to identify and resolve any potential issues of navigability or interpretability that could impact the review of your application.

3.0 PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements/ Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential:*

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[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NICHOLAS A KOZAUER
10/31/2019 06:22:47 PM