

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**210365Orig1s000**

**OTHER REVIEW(S)**

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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)

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<b>Date of This Memorandum:</b>	June 20, 2018
<b>Requesting Office or Division:</b>	Division of Neurology Products
<b>Application Type and Number:</b>	NDA 210365
<b>Product Name and Strength:</b>	Epidiolex (cannabidiol) oral solution 100 mg/mL
<b>Applicant/Sponsor Name:</b>	GW Research Ltd
<b>FDA Received Date:</b>	June 20, 2018
<b>OSE RCM #:</b>	2018-114-2
<b>DMEPA Safety Evaluator:</b>	Briana Rider, PharmD
<b>DMEPA Team Leader:</b>	Lolita White, PharmD

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#### 1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) 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.<sup>a</sup>

#### 2 CONCLUSION

The revised container label and carton labeling for Epidiolex are acceptable from a medication error perspective. We have no further recommendations at this time.

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<sup>a</sup> Rider, B. Human Factors Results and Label and Labeling Review Memorandum for Epidiolex (NDA 210365). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 15. RCM No.: 2018-114-1.

**APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JUNE 20, 2018**

**Container label**



(b) (4)

## Carton labeling

(b) (4)



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/s/  
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BRIANA B RIDER  
06/21/2018

LOLITA G WHITE  
06/21/2018

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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)

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<b>Date of This Memorandum:</b>	June 15, 2018
<b>Requesting Office or Division:</b>	Division of Neurology Products
<b>Application Type and Number:</b>	NDA 210365
<b>Product Name and Strength:</b>	Epidiolex (cannabidiol) oral solution 100 mg/mL
<b>Applicant/Sponsor Name:</b>	GW Research Ltd
<b>FDA Received Date:</b>	May 18, 2018
<b>OSE RCM #:</b>	2018-114-1
<b>DMEPA Safety Evaluator:</b>	Briana Rider, PharmD
<b>DMEPA Team Leader:</b>	Lolita White, PharmD

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## 1 PURPOSE OF MEMORANDUM

The Division of Neurology Products (DNP) requested that we review the revised container label, carton labeling, Prescribing Information (PI), Medication Guide (MG), and Instructions for Use (IFU) 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.<sup>a</sup> The Sponsor also proposes language in the PI and IFU for the introduction of a 1 mL oral syringe.

## 2 CONCLUSION

The revised labels and labeling are unacceptable from a medication error perspective.

- We note the following statement under the “How should I take EPIDIOLEX?” section of the Medication Guide lacks clarity: “Measure each dose of EPIDIOLEX using the bottle adapter and dosing syringes that come with EPIDIOLEX”. We are concerned users may be confused if both 5 mL and 1 mL oral syringes are provided.

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<sup>a</sup> Rider, B. Human Factors Results and Label and Labeling Review for Epidiolex (NDA 210365). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 27. RCM No.: 2018-114 and 2018-898.

- [REDACTED] (b) (4)
- [REDACTED] (b) (4)

### 3 RECOMMENDATIONS FOR THE DIVISION

#### A. Medication Guide

1. We note the following statement under the “How should I take EPIDIOLEX?” section of the Medication Guide lacks clarity: “Measure each dose of EPIDIOLEX using the bottle adapter and dosing syringes that come with EPIDIOLEX”. [REDACTED] (b) (4)

[REDACTED]. To minimize the risk of wrong dose medication errors, we recommend revising the statement to read:

“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.”

### 4 RECOMMENDATIONS FOR GW RESEARCH LTD

We recommend the following be implemented prior to approval of this NDA:

#### A. Carton labeling

1. [REDACTED] (b) (4)

#### B. Container label

1. [REDACTED] (b) (4)

## **APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 18, 2018 AND JUNE 14, 2018**

### **A.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>b</sup> along with postmarket medication error data, we reviewed the following Epidiolex labels and labeling submitted by GW Research Ltd.

- Container label received on May 18, 2018
- Carton labeling received on May 18, 2018
- Instructions for Use (Image not shown) received on June 14, 2018
- Prescribing Information (Image not shown) received on June 14, 2018
- Medication Guide (Image not shown) received on June 14, 2018

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<sup>b</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## A. 2 Labels and Labeling Images

### Container label



## Carton labeling

(b) (4)



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/s/  
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BRIANA B RIDER  
06/15/2018

LOLITA G WHITE  
06/15/2018

**Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)  
Epidemiology: ARIA Sufficiency Templates  
Version: 2018-01-24**

Date: June 12, 2018

Reviewer(s): Hongliu Ding, MD, PhD, MPH  
Division of Epidemiology I

Team Leader: Kira Leishear, PhD, MS  
Division of Epidemiology I

Division Deputy Director: Sukhminder K. Sandhu, PhD, MS, MPH  
Division of Epidemiology I

Subject: ARIA Sufficiency Memo for Pregnancy Safety Concerns

Drug Name(s): Epidiolex (Cannabidiol)

Application Type/Number: NDA 210365

Applicant/sponsor: GW Research Ltd

OSE RCM #: 2018-868



## Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

### 1. BACKGROUND INFORMATION

#### 1.1. Medical Product

Epidiolex oral solution contains the active ingredient cannabidiol (CBD) and the proposed indication is for the adjunctive treatment of seizures associated with Dravet syndrome (DS) or Lennox-Gastaut syndrome (LGS) in patients 2 years and older. The precise mechanism of CBD anticonvulsant effect in humans is not clear. Although CBD interacts with cannabinoid receptors, it does not exert its anticonvulsant effects through this pathway<sup>1</sup>. According to the Sponsor, CBD modulates intracellular calcium via GPR55<sup>2,3</sup> and TRPV1<sup>4,5</sup> channels and also modulates adenosine-mediated signaling<sup>6-9</sup>, which might lead to reduced neuronal hyperexcitability and inflammation.

#### 1.2. Describe the Safety Concern

Epidiolex (Cannabidiol) exposure to females affected by Dravet or Lennox Gastuat syndromes who are pregnant or of childbearing potential is possible. However, as the sponsor stated, no studies have been conducted with cannabidiol in pregnant women. While pregnant women were excluded in the clinical trials, one pregnancy was reported 4 weeks after the last exposure in the cannabidiol clinical development programs, and the subject delivered 'a full-term baby without complications'. In animal studies, the administration of cannabidiol up to a dose of 250 mg/kg/day in rats did not show adverse effects on fertility and early embryonic development, and a dose up to 75 mg/kg/day in a pre- and post-natal rat study did not observe adverse effects on offspring. Taken together, there are no adequate data on the developmental risk associated with the use of cannabidiol in pregnant women and the effect of cannabidiol on pregnancy outcomes is not known at this time.

#### 1.3. FDAAA Purpose (per Section 505(o)(3)(B))

*- Please ensure that the selected purpose is consistent with the other PMR documents in DARRTS*

*Purpose (place an "X" in the appropriate boxes; more than one may be chosen)*

Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	X

### 2. REVIEW QUESTIONS

#### 2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

- ☐ Specific FDA-approved indication in pregnant women exists and exposure is expected
- ☐ No approved indication, but practitioners may use product off-label in pregnant women

- ☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized
- ☒ No approved indication, but use in women of child bearing age is a general concern

## 2.2. Regulatory Goal

- ☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty
- ☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty.<sup>†</sup>
- ☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review).<sup>†</sup>

<sup>†</sup> **If checked, please complete General ARIA Sufficiency Template.**

## 2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

- ☐ Pregnancy registry with internal comparison group
- ☐ Pregnancy registry with external comparison group
- ☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
- ☐ Electronic database study with chart review
- ☒ Electronic database study without chart review
- ☐ Other, please specify: [Click here to enter text.](#)

## 2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

- ☒ Study Population
- ☐ Exposures
- ☒ Outcomes
- ☐ Covariates
- ☒ Analytical Tools

*For any checked boxes above, please describe briefly:*

Study Population and Outcomes: ARIA is insufficient to identify the study population (babies that experienced in utero exposure or postpartum exposure through lactation) because the mother and baby records are not currently linked in Sentinel. Thus, the exposure corresponding to the mother and potential outcomes corresponding to the infant cannot be connected. This lack of linkage between mother and baby records renders ARIA insufficient for both the study population and outcome identification.

Analytical Tools: ARIA analytic tools are not sufficient to assess the regulatory question of interest because data mining methods have not been tested for birth defects and other pregnancy outcomes.



We did not formally assess the other parameters given that the mother-infant linkage is not currently available in ARIA.

**2.5. Please include the proposed PMR language in the approval letter.**

The following language has been proposed by Division of Neurology Products for PMRs related to pregnancy outcomes:

*“Conduct a pregnancy outcomes study using a different study design than provided for in the North American Antiepileptic Drug (NAAED) Pregnancy Registry (for example, a retrospective cohort study using claims or electronic medical record data or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, and small-for-gestational-age births in women exposed to Epidiolex during pregnancy compared to an unexposed control population.”*

Please note that the Division of Neurology Products (DNP) is only requesting an electronic database PMR study, not a pregnancy registry PMR, because this drug product will be part of the North American Anti-Epileptic Drug (NAAED) pregnancy registry.



### 3. References

1. McPartland JM, Duncan M, Di Marzo V, et al. Are cannabidiol and Delta(9)-tetrahydrocannabinol negative modulators of the endocannabinoid system? A systematic review. *Br J Pharmacol.* 2015;172(3):737-753.
2. Ryberg E, Larsson N, Sjogren S, et al. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol.* 2007;152(7):1092-1101.
3. Sylantsev S, Jensen TP, Ross RA, et al. Cannabinoid- and lysophosphatidylinositol-sensitive receptor GPR55 boosts neurotransmitter release at central synapses. *Proc Natl Acad Sci U S A.* 2013;110(13):5193-5198.
4. De Petrocellis L, Ligresti A, Moriello AS, et al. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol.* 2011;163(7):1479-1494.
5. Iannotti FA, Hill CL, Leo A, et al. Nonpsychotropic plant cannabinoids, cannabidivarin (CBDV) and cannabidiol (CBD), activate and desensitize transient receptor potential vanilloid 1 (TRPV1) channels in vitro: potential for the treatment of neuronal hyperexcitability. *ACS Chem Neurosci.* 2014;5(11):1131-1141.
6. Liou GI, Auchampach JA, Hillard CJ, et al. Mediation of cannabidiol anti-inflammation in the retina by equilibrative nucleoside transporter and A2A adenosine receptor. *Invest Ophthalmol Vis Sci.* 2008;49(12):5526-5531.
7. Mijangos-Moreno S, Poot-Ake A, Arankowsky-Sandoval G, et al. Intrahypothalamic injection of cannabidiol increases the extracellular levels of adenosine in nucleus accumbens in rats. *Neurosci Res.* 2014;84:60-63.
8. Pandolfo P, Silveirinha V, dos Santos-Rodrigues A, et al. Cannabinoids inhibit the synaptic uptake of adenosine and dopamine in the rat and mouse striatum. *Eur J Pharmacol.* 2011;655(1-3):38-45.
9. Friedman D, Devinsky O. Cannabinoids in the Treatment of Epilepsy. *N Engl J Med.* 2015;373(11):1048-1058.

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/s/  
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HONGLIU DING  
06/13/2018

KIRA N LEISHEAR  
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SUKHMINDER K SANDHU  
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JUDITH W ZANDER  
06/13/2018

MICHAEL D NGUYEN  
06/14/2018

CLAUDIA B MANZO on behalf of ROBERT BALL  
06/15/2018

**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: June 8, 2018

To: Billy Dunn, MD  
Director  
**Division of Neurology Products (DNP)**

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, RPh  
Regulatory Review Officer  
**Office of Prescription Drug Promotion (OPDP)**

Subject: Review of Patient Labeling: Medication Guide (MG) and  
Instructions for Use (IFU)

Drug Name (established name): EPIDIOLEX (cannabidiol)

Dosage Form and Route: oral solution, CX

Application Type/Number: NDA 210365

Applicant: Greenwich Biosciences

## 1 INTRODUCTION

On October 26, 2017 Greenwich Biosciences submitted for the Agency's review, an Initial New Drug Application (NDA)-Rolling Submission Part 4 of 5 for EPIDIOLEX (cannabidiol) oral solution, CX. This rolling submission includes the proposed Prescribing Information (PI) and associated labeling documents. The proposed indication for EPIDIOLEX (cannabidiol) is for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome 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 Products (DNP) on October 30, 2017 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for EPIDIOLEX (cannabidiol).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

## 2 MATERIAL REVIEWED

- Draft EPIDIOLEX (cannabidiol) MG and IFU received on October 26, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 1, 2018.
- Draft EPIDIOLEX (cannabidiol) PI received on October 26, 2017, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 1, 2018.

## 3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6<sup>th</sup> to 8<sup>th</sup> grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8<sup>th</sup> 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. We have reformatted the MG document using the Arial font, size 10 and 11 respectively.

In our collaborative review of the MG and IFU we have:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information

- ensured that the MG and IFU are 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 and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

#### **4 CONCLUSIONS**

The MG and IFU are 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 and IFU 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 and IFU.

Please let us know if you have any questions.

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NYEDRA W BOOKER  
06/08/2018

DHARA SHAH  
06/08/2018

MARCIA B WILLIAMS  
06/08/2018

**FOOD AND DRUG ADMINISTRATION**  
**Center for Drug Evaluation and Research**  
**Office of Prescription Drug Promotion**

**\*\*\*Pre-decisional Agency Information\*\*\***

## Memorandum

**Date:** June 07, 2018

**To:** Teresa Buracchio, M.D.  
Division of Neurology Products (DNP)  
  
Stephanie Parncutt, Regulatory Project Manager, (DNP)  
  
Tracy Peters, Associate Director for Labeling, DNP

**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

**NDA:** 210365

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In response to the DNP consult request dated October 30, 2017, OPDP has reviewed the proposed product labeling (PI), Medication Guide and Instructions for Use (IFU), and carton and container labeling for the original NDA EPIDIOLEX® (cannabidiol) oral solution (Epidiolex).

**PI:** OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail DNP (Stephanie Parncutt) on June 1, 2018, and are provided below.

**Medication Guide and IFU:** A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

**Carton and Container Labeling:** OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on May 18, 2018, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Dhara Shah (240) 402-2859 or [Dhara.Shah@fda.hhs.gov](mailto:Dhara.Shah@fda.hhs.gov).

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/s/  
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DHARA SHAH  
06/07/2018

## Clinical Inspection Summary

<b>Date</b>	5/16/2018
<b>From</b>	Cara Alfaro, Clinical Analyst Good Clinical Practice Assessment Branch Division of Clinical Compliance Evaluation Office of Scientific Investigations
<b>To</b>	Stephanie Parncutt, Regulatory Project Manager Natalie Getzoff, Medical Officer Division of Neurology Products
<b>BLA #</b>	210365
<b>Applicant</b>	GW Research LTD
<b>Drug</b>	cannabidiol
<b>NME</b>	Yes
<b>Proposed Indication</b>	Adjunctive treatment of seizures associated with Dravet syndrome or Lennox Gastaut syndrome in patients 2 years and older
<b>Consultation Request Date</b>	12/4/2017
<b>Summary Goal Date</b>	4/27/2018, Extension granted to 5/18/2018
<b>Advisory Committee Meeting</b>	4/19/2018
<b>Action Goal Date</b>	6/27/2018
<b>PDUFA Date</b>	6/27/2018

### I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Barron, Devinsky, Flamini, Frost, Laux, and Patel and the sponsor, GW Research Ltd., were inspected in support of this NDA. Although regulatory compliance violations were noted at Dr. Flamini's and Patel's sites, the findings are unlikely to significantly impact data reliability.

The sponsor inspection, coupled with findings from the clinical investigator inspections, revealed issues consistent with inadequate oversight and monitoring by the sponsor for the three clinical studies (Protocols GWEP1332B, GWEP1414, and GWEP1423). The sponsor's monitoring plan specifies that monitoring visits were to occur within two weeks after the first subject is enrolled with interim monitoring visits every 4 to 6 weeks. However, for one of the sites inspected (Site #1078/Flamini), no monitoring visits were conducted during active subject participation at this site. For all inspected sites, the majority of monitoring visits were conducted after the last subject's last study visit.

In addition, for all six clinical investigator inspections, data clarification forms (DCFs) correcting seizure type and/or count were sent to the sites approximately one year after the seizure event in question. At most of the sites, however, there was email documentation

between the site and sponsor regarding the seizure events requiring DCFs at the time of the event.

Despite the above inspectional findings, the studies appear to have been conducted adequately and the data generated by these sites and submitted by the sponsor appear acceptable in support of the respective indications.

The compliance classification of the inspections of Drs. Barron, Devinsky, Frost, and Laux is No Action Indicated (NAI). The classification of the inspections of Drs. Flamini and Patel as well as the sponsor, GW Research Ltd, is Voluntary Action Indicated (VAI).

## II. BACKGROUND

Cannabidiol oral solution is being developed, under NDA 210365, for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) in patients 2 years of age and older (b) (4). The sponsor has submitted one Phase 2/3 study in DS (GWEP1332B) and two Phase 3 studies in LGS (GWEP1414 and GWEP1423) to support the efficacy and safety of cannabidiol for the adjunctive treatment of seizures in patients with LGS and DS.

### Protocol GWEP1332B

*Title:* “A double-blind, placebo-controlled, two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P) in children and young adults with Dravet syndrome”

*Subjects:* 120 subjects enrolled

*Sites:* 22 sites in 4 countries; United States (13 sites), France (4 sites), England (3 sites), and Poland (2 sites)

*Study Initiation and Completion Dates:* 3/30/2015 – 11/26/2015

This was a Phase 2/3 study conducted in two parts, Part A (safety/pharmacokinetic) and Part B (safety/efficacy). Part B was a randomized, double-blind study evaluating cannabidiol or placebo added to current antiepileptic medication in subjects with DS.

The study consisted of a screening period, a 4-week baseline period, 14-week double-blind treatment period, and a tapering period. Subjects must have had  $\geq 4$  convulsive seizures during the baseline period to be eligible for randomization. Subjects were randomized (1:1) to cannabidiol or placebo solution administered twice daily for a 14-week double-blind treatment period. The dose of investigational product was titrated to 20 mg/kg/day over 11 days and subjects remained at this dose for the remainder of the treatment period.

The primary efficacy endpoint was the percentage change from baseline in total convulsive seizure frequency during the 14-week treatment period. Seizure information, including number and type of seizure, was recorded daily using an interactive voice response system.

#### Protocol GWEP1414

*Title:* “A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults”

*Subjects:* 225 subjects enrolled

*Sites:* 29 sites in 4 countries; United States (20 sites), Spain (5 sites), England (3 sites), and France (1 site)

*Study Initiation and Completion Dates:* 6/8/2015 – 5/19/2016

This was a randomized, double-blind study evaluating cannabidiol or placebo added to current antiepileptic medication in subjects with LGS. The study consisted of a screening period, a 4-week baseline period, 14-week double-blind treatment period, and a tapering period. Subjects must have had  $\geq 2$  drop seizures each week during the baseline period to be eligible for randomization.

Subjects were randomized (1:1:1) to one of three groups, and investigational product was administered twice daily (morning and evening):

- Cannabidiol solution 10 mg/kg/day
- Cannabidiol solution 20 mg/kg/day
- Placebo solution

The primary efficacy endpoint was the percentage change from baseline in number of drop seizures during the 14-week treatment period. Seizure information, including number and type of seizure, was recorded daily using an interactive voice response system.

#### Protocol GWEP1423

*Title:* A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003-P; CBD) as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome in children and adults”

*Subjects:* 171 subjects enrolled

*Sites:* 24 sites in 3 countries; United States (17 sites), Poland (6 sites), and Netherlands (1 site)

*Study Initiation and Completion Dates:* 4/28/2015 – 3/18/2016

The study design was the same as GWEP1414 with the exception that subjects were randomized (1:1) to two treatment groups, cannabidiol 20 mg/kg/day or placebo.

Interactive Voice Response System (IVRS)

According to the sponsor, during the protocol design stage for these protocols, The Epilepsy Study Consortium (ESC), an independent advisory panel, was enlisted. The process at study entry was that the clinical investigator submitted the subject's documented history of seizures directly to the ESC for verification of seizure types. Confirmation of seizure types from the ESC was required prior to randomization.

During the conduct of these studies (date not provided), it was identified by ESC that some of the IVRS reported seizure types differed from the seizure types agreed to by the ESC during the baseline assessment period of the study. Clinical investigators were given a summary of discrepant seizure types and were asked to discuss the discrepancies with caregivers. If the original entry was deemed correct and to be a new seizure type, then this description was sent to the ESC for review and verification. If the discrepant seizure type was identified by the clinical investigator and caregiver to be an error, the correct seizure data was recorded on a Data Clarification Form (DCF). The clinical investigator signed the DCF to confirm the seizure type and then returned it to the sponsor for inclusion in the data analysis process.

**Rationale for Site Selection**

The clinical sites were chosen primarily based on numbers of enrolled subjects, site efficacy, active complaints for associated INDs, and prior inspectional history. The sponsor, GW Research Ltd, was also inspected as part of a data audit inspection and a complaint related to the protocols under review for this NDA submission.

**III. RESULTS**

<b>Site #/ Name of CI/ Address</b>	<b>Protocol #/ # of Enrolled Subjects</b>	<b>Inspection Dates</b>	<b>Classification</b>
Site #1191  <b>Todd Barron, M.D.</b> 228 St. Charles Way, Suite 200 York, PA 17402	Protocol GWEP1414  Subjects: 13	12-16 Feb 2018	NAI
Site #1078  <b>Orrin Devinsky, M.D.</b> 223 E 34th Street New York, NY 10016	Protocol: GWEP1332B  Subjects: 7	22-25 Jan 2018	NAI

<b>Site #/ Name of CI/ Address</b>	<b>Protocol #/ # of Enrolled Subjects</b>	<b>Inspection Dates</b>	<b>Classification</b>
Site #1087  <b>J. Robert Flamini, M.D.</b> 5887 Glenridge Suite 140 Atlanta, GA 30328	Protocol GWEP1423  Subjects: 11	20-26 Feb 2018	VAI
Site #1147  <b>Michael Frost, M.D.</b> 225 Smith Avenue North St. Paul, MN 55102	Protocol GWEP1423  Subjects: 14	21 Jan – 7 Feb 2018	NAI
Site #1083  <b>Linda Laux, M.D.</b> 225 E. Chicago Avenue Chicago, IL 60611	Protocol GWEP1332B  Subjects: 13	14-21 Feb 2018	NAI
Site #1090  <b>Anup Patel, M.D.</b> 700 Children's Drive Columbus, OH 43205	Protocol GWEP1414  Subjects: 20	23-30 Jan 2018	VAI
Sponsor  <b>GW Research Ltd.</b> Sovereign House, Vision Park, Chivers Way, Cambridge, CB24 9BZ United Kingdom	Protocol GWEP1332B  Protocol GWEP1414  Protocol GWEP1423	29 Jan 2018 to 2 Feb 2018	VAI

Compliance Classifications

NAI = No Action Indicated, no deviation from regulations.

VAI = Voluntary Action Indicated, deviation(s) from regulations.

OAI = Official Action Indicated, significant deviations from regulations. Data may be unreliable.

**1. Todd Barron, M.D.**

At this site for Protocol GWEP1414, 15 subjects were screened, 13 subjects were randomized, and 12 subjects completed the study. One subject (# (b) (6)) withdrew due to the SAE of respiratory failure/respiratory syncytial virus (this subject recovered).

Informed consent forms were signed by all screened subjects prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Subject and study specific records reviewed included, but were not limited to, source documents, case report forms (paper), monitoring documents, training records, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and the primary efficacy endpoint.

The primary efficacy endpoint was the change from baseline in the number of drop seizures during the treatment period. An interactive voice response system (IVRS) was used by caregivers to record the type and number of daily seizures. The FDA field investigator verified the data line listings of the type and number of daily seizures against a printout of IVRS data available at the clinical site. The IVRS printout was provided by the sponsor, but no audit trails were included in these printouts. There were interim IVRS printouts that were printed by the site and used by study staff during subject study visits. Not all of the interim IVRS printouts were reviewed during the inspection, but for the few that were reviewed, no discrepancies between these and the sponsor line listings were noted. The FDA investigator noted some discrepancies between the sponsor line listings and the IVRS printout provided by the sponsor, however, when the Data Clarification Forms (DCFs) were reviewed, these discrepancies were reconciled.

DCFs were used to change the *type of seizure* in two of thirteen randomized subjects on three occasions during the study (Table 1). DCFs were used to change the *seizure counts* in three of thirteen randomized subjects (Table 2). The reason for the changes, as documented on the DCFs, were “caregiver error”.

Table 1. Change in Seizure Type (GWEP1414, Site #1191)

Subject/ Arm	Date	Recorded Seizure Type	Corrected Seizure Type	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Day 66	Other Partial	Countable Partial	(b) (6)
(b) (6) Placebo	(b) (6) Screening	Clonic	Tonic Associated Drops	
	(b) (6) Screening	Atonic Associated drops	Tonic Associated Drops	

Table 2. Changes in Seizure Counts (GWEP1414, Site #1191)

Subject/ Arm	Date	Recorded Seizure Type	Recorded Seizure Count	Corrected Seizure Count	Recorded Drop Seizure Count	Corrected Drop Seizure Count	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Screening	Myoclonic	1	0	-	-	(b) (6)
	(b) (6) Day 14	Clonic	1	0	-	-	
(b) (6) Placebo	(b) (6) Screening	Atonic	1	0	1	0	
(b) (6) Placebo	(b) (6) Day 6	Atonic	4	0	4	0	

There was no evidence of underreporting of adverse events.

*Reviewer's comment: DCFs were not signed by the clinical investigator until approximately one year after the seizure events occurred. It is not known when the site received the DCFs from the sponsor.*

## 2. Orrin Devinsky, M.D.

At this site for Protocol GWEP1332B, 9 subjects were screened, 7 subjects were randomized, and 6 subjects completed the study. One subject was discontinued from the study due to the SAE "worsening of seizure clusters."

Informed consent forms were signed by all screened subjects prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Subject and study specific records reviewed included, but were not limited to, source documents, case report forms (paper), monitoring documents, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, concomitant medications, protocol deviations, and the primary efficacy endpoint.

The FDA field investigator verified the primary efficacy endpoint data line listings against a CD provided by the sponsor to the clinical site. There was no evidence of underreporting of adverse events.

Of note, the IVRS system was originally designed to allow a maximum of 99 seizures per day for any one seizure type to be recorded by the caregivers/subjects. This caused a problem when the sponsor realized that some subjects were having >99 seizures per day of a particular type. Caregivers/subjects were instructed to document seizure counts in a paper diary and then the clinical investigator would transcribe the data onto a newly created CRF page (>99 Seizure Log). The >99 Seizure Log CRF pages were collected during the inspection for two of three subjects who had >99 seizures/day at this site (Table 3). As seen in this table, the data from the >99 Seizure Log CRF pages are not reflected in the data line listings, which uniformly show 99 seizures.

Table 3. Seizure Discrepancies Between &gt;99 Seizure Log and Data Listings (GWEP1332B, Site #1078)

Subject/Arm	Seizure Type	Date	Study Day	Seizure Count	
				>99 Log	Data Listing
(b) (6) Placebo	Myoclonic	(b) (6)	screening	390	99
			screening	115	99
			screening	39	99
			Day 5	123	99
			Day 17	110	99
			Day 35	200	99
			Day 44	35	99
			Day 49	114	99
			screening	84	99
# (b) (6) Placebo	Atonic	(b) (6)	Day 6	100	99
			Day 52	Unknown*	99
			Day 67	Unknown	99
			Day 84	Unknown	99
			Day 89	Unknown	99

\* “Unknown” was entered on &gt;99 Seizure Log

*Reviewer Comment: Please see inspection results for GW Research Ltd. (below) for comments on this issue. Note that some seizure counts recorded on the >99 Seizure Log were less than 99; presumably an error by the clinical investigator.*

DCFs were available at the site documenting change in *seizure type* for 4 of 7 randomized subjects. The reason for the change in seizure type was noted as “caregiver error.” The corrected seizure type was consistent with the data line listings.

Table 4. Changes in Seizure Types (GWEP1332B, Site #1078)

Subject/ Arm	Date	Recorded Seizure Type	Corrected Seizure Type	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Screening	Non-Convulsive	Myoclonic	(b) (6)
	(b) (6) Screening	Non-Convulsive	Myoclonic	
	(b) (6) Screening	Non-Convulsive	Myoclonic	
	(b) (6) Screening	Non-Convulsive	Myoclonic	
(b) (6) Cannabidiol	(b) (6) Screening	Tonic	Tonic-Clonic	
(b) (6) Placebo	(b) (6) Day 37	Tonic	Countable Partial	
(b) (6) Cannabidiol	(b) (6) Screening	Non-Convulsive status	Tonic-Clonic	

*Reviewer Comment: DCFs were not signed by the clinical investigator until approximately 10 months after the seizure events occurred. It is not known when the site received the DCFs from the sponsor.*

### Complaint Follow-up

OSI had received a complaint on 5/5/2017 alleging that this site was “reporting positive clinical results through manipulation of staff and alteration of study results for a study evaluating the efficacy of cannabis in Dravet syndrome”. The FDA field investigator stated that after review of the data and interviewing site staff, no evidence was found to support these allegations.

### **3. J. Robert Flamini, M.D**

At this site for Protocol GWEP1423, 13 subjects were screened, 11 subjects were randomized, and 10 subjects completed the study. One subject (# (b) (6)) was withdrawn from the study approximately two weeks after randomization since the subject had a G-tube and could not receive the study drug orally.

Informed consent forms were signed by all screened subjects prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Subject and study specific records reviewed included, but were not limited to, source documents, case report forms (paper), monitoring documents, training records, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, protocol deviations, and the primary efficacy endpoint.

The FDA field investigator verified the primary efficacy endpoint data line listings against a certified CD provided by the sponsor to the clinical site. There was no evidence of underreporting of adverse events.

Examples of DCFs were included in the EIR, but not all DCFs were collected (Table 5). The corrected seizure type was consistent with the data line listings.

**Table 5. Changes in Seizure Types (GWEP1423, Site #1087)**

Subject/ Arm	Date	Recorded Seizure Type	Corrected Seizure Type	Date DCF Signed by
(b) (6) Cannabidiol	(b) (6) Treatment	Atonic with drop	Tonic with drop	(b) (6)
(b) (6) * Cannabidiol	(b) (6) to Screening	Atonic with and without drops	Atonic all with associated drops	(b) (6)
	(b) (6) to Screening and Treatment	Tonic with and without drops	Tonic all with associated drops	

\*Note on DCF: Caregiver reported drop seizures incorrectly due to the subject being wheelchair bound

No Form FDA 483 was issued at the conclusion of the inspection. However, the FDA investigator discussed the finding that protocol-required urine samples (including at screening) for determination of THC were not collected for 8 of 11 randomized subjects. The clinical investigator stated that the subjects enrolled in the study had diminished cognition, and many were incontinent, which made it difficult to obtain urine samples.

The collection of urines samples at screening for THC analysis was used to determine eligibility for the study. According to the protocol (exclusion criterion 6.2.9), patients currently using or have in the past used recreational or medicinal cannabis or synthetic cannabinoid based medications within three months prior to study entry should be excluded. Additionally, section 9.1.9 of the protocol (Clinical Laboratory Sampling) states that “the THC results will be reported back to the study site to permit confirmation of eligibility...” Finally, although not part of the protocol itself, the CRF for the screening visit (Visit 1) includes a “Yes” or “No” checkbox after the question: “Was a urine sample collected for THC?” Next to the “No” checkbox is the following: “The patient is NOT eligible without lab results.”

*Reviewer Comments: For 8 of 11 randomized subjects, urine samples for THC analysis were not collected as required by protocol (including at screening). Email communication between the site and sponsor regarding this issue was available at the site; however, the date of this communication was six months after the last subject’s last study visit. There was no documentation of contemporaneous discussions between the site and sponsor regarding subject eligibility in the absence of urine samples for THC analysis. Since no monitoring visits occurred during the period of active study participation, this issue was not identified in real time. However, the probability of cannabis use in this population is very low. In addition, the clinical investigator may have questioned the subject’s parents/caregivers regarding use of cannabis for these 8 subjects, which should have been sufficient to determine whether the subjects had been given cannabis within the three months prior to screening. Because of these findings, this inspection was upgraded from NAI to VAI.*

### Complaint Follow-up

OSI had received a complaint alleging inadequate monitoring of this clinical site by the sponsor, GW Research. Sponsor monitoring activities were reviewed during the inspection.

The site initiation visit date for this site is unknown. The site stated that the sponsor had conducted initial training on (b) (6) but no documentation was available at the site. Monitoring visits occurred from (b) (6). The first subject was screened on (b) (6), the first subject was randomized on (b) (6) and the last subject last visit was (b) (6). During this period of active study participation, no clinical monitoring was conducted. There were 17 monitoring visits occurring after the last subject’s study visit, including study close-out visits in (b) (6) and four “Pre-Approval Inspection” visits occurring after study close-out.

*Reviewer Comments: The sponsor was responsible for clinical monitoring for this protocol. The sponsor’s monitoring plan, obtained during the sponsor inspection (refer to inspection*

*results for GW Research Ltd.), specified the frequency of monitoring visits including within two weeks of subject enrollment with interim monitoring visits every 4 to 6 weeks. However, according to the monitoring log, no monitoring visits were conducted between the first subject's screening visit and the last subject's last study visit. At least 17 monitoring visits were conducted after all subjects had completed the study, but these monitoring visits were not contemporaneous to the active conduct of the study. The FDA investigator was able to verify adverse events and primary efficacy endpoint data. Therefore, despite what appears to be inadequate monitoring during the conduct of the study, there is no evidence of issues with data integrity or human subject protection.*

#### **4. Michael Frost, M.D**

At this site for Protocol GWEP1423, 14 subjects were screened, all of whom were randomized, and 12 subjects completed the study. Two subjects (# (b) (6)), both randomized to cannabidiol 20 mg/kg, withdrew from the study due to abnormal liver function test results (these LFTs were reported by the sponsor). Of note, one subject who completed GWEP1423 and enrolled in the open-label extension study, GWEP1415, died secondary to Sudden Unexplained Death in Epilepsy (SUDEP). This death was reported by the sponsor.

Informed consent forms were signed by all screened subjects prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Subject and study specific records reviewed included, but were not limited to, source documents, case report forms (paper), monitoring documents, training records, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, protocol deviations, and the primary efficacy endpoint.

With respect to the primary efficacy endpoint, the field investigator verified the sponsor line listings against a IVRS spreadsheet supplied by the sponsor and available at the clinical site. No discrepancies were noted.

There was no evidence of under-reporting of adverse events by the site. However, one SAE (status epilepticus) occurred in Subject # (b) (6) who was randomized to cannabidiol. This SAE was noted in CRFs available at the site, but did not appear in sponsor adverse event line listings. Of note, while the sponsor AE line listings do not include the SAE "status epilepticus", the subject narrative does. That is, the subject narrative was provided in the NDA submission since this subject had an SAE of pneumonia ("likely due to aspiration during seizures") that required hospitalization and was associated with the status epilepticus.

The only DCF at this site was for Subject # (b) (6), who was randomized to cannabidiol 20 mg/kg (Tables 6 and 7). The FDA investigator noted that the data listings submitted with the NDA do not include these corrected seizure counts. The site provided documentation from the sponsor, dated 2/6/2018 (during the inspection), that data from this DCF was not forwarded by GW Pharma to their data management department.

In their response, dated 5/11/18, to our information request, GW Pharma stated:

GW acknowledges that the data clarification form (DCF) for subject (b) (6) (study GWEP 1423) was not logged and sent to data management which resulted in the associated changes not being implemented in the database. GW is not aware of any further cases in randomized subjects for the pivotal studies contained in the NDA.

The root cause of the issue was that we did not have a unique identifier allocated to track each DCF recording seizure data. As part of the review of data to ensure no additional DCFs remained unreported, GW has further reviewed the Trial Master Files for these studies. This review indicates that only the one instance described above was not submitted to data management.

The DCF process for clarifying seizure data will not be implemented for ongoing studies or future studies as the sponsor concluded the process was not value added.

In addition, although the DCF forms were not signed by the clinical investigator until approximately 10 months after the seizure events occurred (it is not known when the site received the DCF forms from the sponsor), email correspondence between the site and Epilepsy Study Consortium (dated 8/15/2015) close to the time that the events occurred documents the corrected numbers of seizures.

Table 6. Change in Seizure Type (GWEP1423, Site #1147)

Subject/ Arm	Date	Recorded Seizure Type	Corrected Seizure Type	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Screening	Clonic	Myoclonic	(b) (6)

Table 7. Changes in Seizure Counts (GWEP1423, Site #1147)

Subject/ Arm	Date	Recorded Seizure Type	Recorded Seizure Count	Corrected Seizure Count	Recorded Drop Seizure Count	Corrected Drop Seizure Count	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Screening	Tonic	8	20	8	20	(b) (6)
	(b) (6) Screening		6	28	6	28	
	(b) (6) Screening		9	29	9	29	
	(b) (6) Screening		7	21	7	21	
	(b) (6) Screening		9	32	9	32	
	(b) (6) Screening		8	29	8	29	
	(b) (6) Screening		0	40	0	40	
	(b) (6) Screening		0	8	0	NA	
	(b) (6) Screening	Myoclonic	0	8	0	NA	

*Reviewer Comments: The inspectional findings noted by the FDA investigator pertain to the sponsor and not the clinical site. The sponsor acknowledged that the DCF for Subject # (b) (6) was not sent to data management. The NDA submission does not, therefore, contain the correct number of seizures occurring during this time interval. This reviewer provided the corrected seizure data to the review division. The statistician, Xiang Ling, stated that the corrected seizure counts were unlikely to affect the overall efficacy since these seizure counts are used to calculate baseline seizure frequency and would have shown an even greater reduction in seizure frequency for cannabidiol.*

*One SAE, status epilepticus, occurring on Study Day 39 (treatment phase) in a subject randomized to cannabidiol (b) (6), was not reported by the sponsor. The subject narrative was provided in the NDA submission since this subject had an SAE of pneumonia that required hospitalization (and was associated with the status epilepticus). The narrative includes pneumonia and status epilepticus as preferred terms and includes descriptions of the clinical events in the body of the narrative. However, neither the adverse event line listing nor the AE dataset includes status epilepticus. The review division should include this additional event in their analyses of efficacy and safety.*

## **5. Linda Laux, M.D.**

At this site for Protocol GWEP1332B, 14 subjects were screened, 13 subjects were randomized, and 13 subjects completed the study.

Informed consent forms were signed by all screened subjects prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Subject and study specific records reviewed included, but were not limited to, source documents, case report forms (paper), monitoring documents, training records, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and the primary efficacy endpoint.

The FDA field investigator verified the primary efficacy endpoint data line listings against a certified copy of the IVRS data that was sent to the site by the CRO, (b) (4). There was no evidence of under-reporting of adverse events.

DCFs for changes in seizure type and seizure number were present at the site. Emails between the site and CRA (monitor) were reviewed. It appears that the CRA queried the site via email on 12/15/2015 to address potential seizure misclassifications. Based on responses from the site, a DCF was then sent to the site to make these changes in seizure classification and/or number. Some of the email communications include verification from the site that they had been informed of the caregiver's error in seizure information at the time the seizure occurred.

Table 8. Changes in Seizure Types (GWEP1332B, Site #1083)

Subject/ Arm	Date	Recorded Seizure Type	Corrected Seizure Type	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Screening	Clonic	Tonic	(b) (6)
	(b) (6) Screening			
	(b) (6) Screening			
	(b) (6) Screening			
(b) (6) Cannabidiol	(b) (6) Screening	Tonic	Tonic/Clonic	
(b) (6) Placebo	(b) (6) Screening	Countable Partial	Tonic/Clonic	
	(b) (6) Screening			
	(b) (6) Day 19			
	(b) (6) Day 20			
	(b) (6) Day 26			
	(b) (6) Day 28			
	(b) (6) Day 55			
	(b) (6) Day 67			
	(b) (6) Day 80			
	(b) (6) Day 85			
(b) (6) Placebo	(b) (6) Screening	Non-convulsive status	Myoclonic	
	(b) (6) Screening			

Table 9 shows the changes in seizure counts for this site. Most of the changes in seizure counts were due to tonic seizures that had been included already in tonic/clonic seizure counts. For Subject # (b) (6), it should be noted that:

- A total of 172 myoclonic seizures during Screening was changed to 0. On the DCF, the reason for this change was “caregiver error, subject does not have myoclonic seizures, mother was mistakenly reporting eyelid flutters as myoclonics.”
- The DCF notes that the reason for the changes in countable partial and other partial seizures to 0 was that the school nurse was reporting the seizures to the mother, and the mother was reporting them as partial seizures. Upon review with Dr. Laux, these were noted to be consistent with eyelid flutters.
- Although these seizure counts for Subject # (b) (6) were changed to zero, the data listings for this subject do include significant numbers of other types of seizures [atonic (143) and absence (213)] that occurred during the screening phase.

Table 9. Changes in Seizure Counts (GWEP1332B, Site #1083)

Subject/ Arm	Date	Recorded Seizure Type	Recorded Seizure Count	Corrected Seizure Count	Date DCF Signed by Investigator
(b) (6) Placebo	(b) (6) Screening	Tonic	1	0	(b) (6)
(b) (6) Cannabidiol	(b) (6) Screening	Tonic	1	0	
(b) (6) Cannabidiol	(b) (6) Screening	Clonic	1	0	
(b) (6) Placebo	(b) (6) Screening	Tonic	1	0	
(b) (6) Placebo	(b) (6) Treatment Day 36	Tonic	1	0	
(b) (6) Cannabidiol	(b) (6) Screening	Non-convulsive status	1	0	
(b) (6) Placebo	(b) (6) to Screening	Myoclonic	172	0	
	(b) (6) Screening and Treatment	Countable Partial	13	0	
	(b) (6) Screening	Other Partial	2	0	
	(b) (6) Screening	Non- Convulsive	1	0	
(b) (6) Placebo	(b) (6) Screening	Tonic	1	0	

*Reviewer Comments: For changes in seizure classification and seizure counts, it appears that the CRA (monitor) contacted the site in 12/15/2015, approximately 8 months after these seizure events. The DCFs were signed a few months after the queries. Although there was a delay in the CRA queries, there was documentation at the site of communications occurring between the CRA and site close to the time that the seizures occurred.*

## 6. Anup Patel, M.D.

At this site, for Protocol GWEP1414, 22 subjects were screened, 20 subjects were randomized, and 19 subjects completed the study. One subject withdrew from the study due to an adverse event (drowsiness). Sponsor line listings include this adverse event, but the reason for discontinuation is listed as “guardians withdrew consent for the study”.

Informed consent forms were signed by all screened subjects prior to participation in any study procedures. An audit of the study records of all subjects enrolled was conducted. Subject and study specific records reviewed included, but were not limited to, source documents, case report forms (paper), monitoring documents, training records, IRB/sponsor communications, financial disclosure, test article storage and accountability, inclusion/exclusion criteria, adverse event reports, laboratory results, concomitant medications, protocol deviations, and the primary

efficacy endpoint.

The FDA field investigator verified the primary efficacy endpoint data line listings against a certified copy of the IVRS data that was sent to the site by the sponsor after study closeout.

DCFs for changes in seizure type (Table 10) and seizure number (Table 11) were present at the site.

Table 10. Changes in Seizure Types (GWEP1414, Site #1090)

Subject/ Arm	Date	Recorded Seizure Type	Corrected Seizure Type	Date DCF Signed by Investigator
(b) (6) Placebo	(b) (6) Treatment	Atonic and Associated Drops	Tonic and Associated Drops	(b) (6)
	(b) (6) Treatment	Tonic/clonic and Associated Drops	Tonic and Associated Drops	
(b) (6) Cannabidiol	(b) (6) Screening	Non-convulsive Status	-	

DCFs for changes in seizure counts were noted in 10 of 20 randomized subjects, the reasons for which were listed as “caregiver error”. Subjects who had changes in the number of drop seizures (the primary efficacy endpoint) are listed in Table 11. In particular, there was a significant decrease in seizure counts, including drop seizures, for Subject # (b) (6). On the DCF, the reason for the change was “caregiver error, a long-term video EEG was obtained to characterize these episodes and none were epileptic seizures. Mother was noting events that she thought were seizures that were not.” This was supported by documentation from Dr. Patel to the sponsor. Of note, this subject did have significant numbers of other types of seizures [tonic-clonic (488) and associated drops (469); atonic and associated drops (1565)] during the study.

Table 11. Changes in Seizure Counts (GWEP1414, Site #1090)

Subject/ Arm	Date	Recorded Seizure Type	Recorded Seizure Count	Corrected Seizure Count	Recorded Drop Seizure Count	Corrected Drop Seizure Count	Date DCF Signed by Investigator
(b) (6) Cannabidiol	(b) (6) Screening - Treatment	Tonic	68	0	68	0	(b) (6)
		Countable Partial	477	0	NA	NA	
		Other Partial	233	0	NA	NA	
(b) (6) Cannabidiol	(b) (6) Screening	Atonic	11	0	11	0	
(b) (6) Placebo	(b) (6) Treatment	Tonic/Clonic	3	0	3	0	

A Form FDA 483 was issued at the conclusion of the inspection with the observation that the investigation was not conducted in accordance with the investigational plan. Specifically, nine of 20 (45%) randomized subjects did not have a urine sample obtained at screening for THC analysis as required by protocol. The reason for lack of a urine sample was documented on the CRF pages as “unable to obtain” or “unable to collect”.

The collection of urines samples at screening for THC analysis was used to determine eligibility for the study. According to the protocol (exclusion criterion 6.2.9), patients currently using or have in the past used recreational or medicinal cannabis or synthetic cannabinoid based medications within three months prior to study entry should be excluded. Additionally, section 9.1.9 of the protocol (Clinical Laboratory Sampling) states that “the THC results will be reported back to the study site to permit confirmation of eligibility....” Finally, although not part of the protocol itself, the CRF for the screening visit (Visit 1) includes a “Yes” or “No” checkbox after the question: “Was a urine sample collected for THC?” Next to the “No” checkbox is the following: “The patient is NOT eligible without lab results.”

Dr. Patel submitted a response, dated 2/12/2018, to the inspectional findings. He acknowledged the findings and stated that there was incomplete documentation of communication with the sponsor and IRB regarding the THC urine testing. He stated that, during the screening process, he had conversations with the Medical Monitor regarding the difficulty in obtaining urine samples in this population. Based on these conversations, Dr. Patel thought that parent report was sufficient to determine eligibility. In his response, Dr. Patel included an email from the sponsor dated 1/30/2018 (during the inspection) that states the GW Medical Monitor was made aware of randomization of subjects after the inability of staff to obtain urinalysis for urine THC analysis as specified in the protocol. This email further states that Dr. Patel was advised to notify his IRB of the protocol deviation and to continue the subjects in the study.

*Reviewer Comments: Screening urine samples for THC analysis were required per protocol. The site had difficulty obtaining these samples, but there is no documentation that the clinical investigator contacted the sponsor to discuss protocol-acceptable alternatives to address exclusion criterion 6.2.9. In addition, these protocol deviations should have been identified during interim monitoring visits but were not noted until approximately one month before the last subject's last study visit. However, the probability of cannabis use in this population is very low. In addition, Dr. Patel stated that he had questioned parents regarding subjects' use of cannabis prior to subject enrollment, which should have been sufficient to determine whether the subjects had been given cannabis within the three months prior to screening.*

## **7. GW Research Ltd.**

This inspection covered sponsor practices related to Protocols GWEP1332B, GWEP1414, and GWEP1423 and to investigate a complaint alleging inadequate monitoring by the sponsor for these protocols.

Records reviewed during this inspection included, but were not limited to, Form FDA 1572s, financial disclosure forms, monitoring reports, the study-specific monitoring guidelines, the monitoring SOPs, the source data verification SOP, the source data validation plan, CRF

completion guidelines, Epilepsy Study Consortium (ESC) committee charter, IVRS/ePRO systems, ePRO data transfer process, Data Safety Monitoring Committee charters and meeting minutes, Abuse Adjudication Committee charter and final report, safety reporting, and test article accountability.

For these clinical studies, the primary efficacy endpoint was change from baseline in total convulsive seizures (GWEP1332B) or change from baseline in total drop seizures (GWEP1414, GWEP1423). Per protocol, caregivers called the IVRS daily to report the types and numbers of seizures experienced by subjects. Initially, the IVRS system was designed to record a maximum value of 99 seizures per day for any one seizure type. Once GWEP1332B (the first study initiated) was underway, the sponsor became aware that some subjects were experiencing >99 seizures per day that could not be recorded. Caregivers/subjects were instructed to document seizure counts on a paper diary and then the clinical investigator would transcribe the data onto a newly created CRF page (>99 Seizure Log). The sponsor stated that they did not receive any further information regarding numbers of seizures >99/day and decided that the count for reported seizures that may have been >99 would remain 99 in the database. Of note, when this issue was discovered, the IVRS was updated for the other two studies (GWEP1414, GWEP1423) to enable capturing seizure counts >99/day.

*Reviewer Comment: Two >99 Seizure Log pages were available for two subjects at inspected Site #1078 (see Table 3). There were a total of 4 subjects in GWEP1332B with tonic and/or clonic seizures (primary endpoint) = 99 in the data listings:*

- (b) (6) (placebo) tonic clonic during screening, seizure log = 84 seizures, data listings = 99
- (b) (6) (placebo) atonic seizures during treatment phase, seizure log = 100 or “unknown”, data listings = 99
- (b) (6) (placebo) clonic seizures during screening, no seizure log available to quantitate number of seizures
- (b) (6) (cannabidiol) multiple (11) days of tonic seizures during screening and multiple (19) days of tonic seizures during treatment phase, no log available to quantitate number of seizures

*Therefore, the only data available quantifying the numbers of seizures >99/day for convulsive seizures (primary endpoint) is one value of 100 seizures on one treatment day for Subject # (b) (6). Of note, the value of 84 for the tonic-clonic seizure in Subject # (b) (6) was an error and should not have been recorded on this seizure log; however, the data listings show a seizure count of 99. These minor changes in seizure counts are not thought to have an impact on the primary efficacy analysis.*

*There were a total of 14 subjects in GWEP1332B with non-convulsive seizures = 99 in the data listings. One >99 Seizure Log page was available for one subject (Subject # (b) (6)) experiencing myoclonic seizures (see Table 3). Recorded on this seizure log were seizure counts >99 and, in error, seizure counts <99; all were recorded as seizure counts = 99 in the sponsor data listings. Per the data listings, this subject experienced 766 seizures during the screening period and 1918 seizures during the treatment phase. If you correct those seizure*

*counts according to the >99 Seizure log, this subject had 1013 seizures during the screening phase and 2005 seizures during the treatment phase. The corrected seizure counts impact seizure counts during the screening phase ( $\Delta$  247) more than the treatment phase ( $\Delta$  87). Compared to the seizure counts on the >99 Seizure Log, the data listings include a lower seizure count in the screening phase, which would have made it more difficult to show efficacy (difference from baseline), no matter the group. Additionally, since these were non-convulsive seizures, there is no impact on the primary efficacy analysis.*

Monitoring files were reviewed for 7 sites for GWEP1332B (including inspected sites #1083 and #1087), 10 sites for GWEP1423 (including inspected site #1147), and 9 sites for GWEP1414 (including inspected site #1090). GW Research used their employees or contracted employees to perform monitoring for all three clinical trials. The sponsor did not have a formalized procedure for selection of monitors.

A Form FDA 483 was not issued at the conclusion of the inspection, but several issues related to monitoring were discussed with the sponsor:

1. A review of the monitoring reports revealed that the sponsor was not always following their monitoring guidelines and/or procedures. There were several instances where the sponsor had not conducted the monitoring visits at the specified timeframes.
2. Monitoring guidelines were not in place prior to the first subjects being screened in each of the studies.
  - GWEP1332B: Monitoring Guidelines (Version 1) dated 6/9/2015; first subjects screened (b) (6)
  - GWEP1414: Monitoring Guidelines (Version 1) dated 1/26/2016; first subject screened (b) (6)
  - GWEP1423: Monitoring Guidelines (Version 1) dated 1/12/2016; first subject screened (b) (6)

Per the sponsor, prior to implementation of the Monitoring Guidelines, the CRAs (monitors) followed the Monitoring SOP, Source Data Verification SOP, Source Data Validation Plan, and the CRF completion guidelines. The FDA investigator reviewed the SOPs and found them to be adequate. The sponsor also stated that the CRAs were trained on the draft monitoring plan prior to the first subjects being randomized.

3. Monitoring reports were not submitted, reviewed, and finalized within the 15-day, and subsequently 30-day, windows as specified in the monitoring guidelines and/or procedures. The Global Clinical Operations Director acknowledged that, due to the rapid pace of enrollment into these three studies and the significant increase in sample size, in combination with the paper-based CRFs and manual tracking logs, there was a backlog resulting in monitoring non-compliance.

*Reviewer Comments: As outlined in the clinical investigator inspection summaries above, a number of issues identified at these sites appear to have been primarily sponsor-related and*

*were likely the result of inadequate clinical monitoring. Inadequate monitoring was noted for one inspected site (Site #1087/Flamini) in that no monitoring visits were conducted from the first subject's screening visit to the last subject's last study visit. Additionally, for all clinical investigator sites that were inspected, significantly more monitoring visits (approximately 70% of all visits) were conducted after the last subject's last study visit as compared to the time period of subjects' active study participation. Based on the monitoring discussion items for the sponsor inspection as well as the issues noted during the clinical investigator inspections that appear to be related to inadequate oversight and monitoring by the sponsor, OSI upgraded the inspection classification for the sponsor from NAI to VAI.*

*{See appended electronic signature page}*

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05/17/2018

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05/17/2018



**MEMORANDUM**  
**Department of Health and Human Services**  
**Food and Drug Administration**  
**Center for Drug Evaluation and Research**

**Date:** May 7, 2018

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

**Through:** Dominic Chiapperino, Ph.D., Director  
Silvia Calderon, Ph.D., Senior Pharmacologist  
Controlled Substance Staff (CSS)

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

**Subject:** Cannabidiol  
NDA 210365 (IND 120055)  
Indication: adjunctive treatment for Dravet syndrome and  
Lennox-Gastaut syndrome  
Dosage: (b) (4)-20 mg/kg oral solutions  
Sponsor: GW Pharma, Ltd  
PDUFA Goal Date: June 27, 2018

**Materials reviewed:**

- NDA 210365, a rolling submission, with final portion received 10/27/17
- Statistical Review and Evaluation of Human Abuse Potential Study with CBD (Dr. Anna Sun, Office of Biostatistics, CDER/FDA, 3/26/18)

**Table of Contents**

<b>1</b>	<b>BACKGROUND.....</b>	<b>2</b>
<b>2</b>	<b>CONCLUSIONS.....</b>	<b>3</b>
<b>3</b>	<b>RECOMMENDATIONS .....</b>	<b>4</b>
<b>4</b>	<b>DISCUSSION.....</b>	<b>5</b>
<b>5.</b>	<b>REFERENCES.....</b>	<b>37</b>

## **1. BACKGROUND**

This memorandum responds to a consult request by the Division of Neurology Products (DNP) to CSS to evaluate abuse-related preclinical and clinical data submitted by GW Pharmaceuticals, Inc. in NDA 210365 for cannabidiol (CBD) oral solution under the tradename Epidiolex. The drug product is prepared as a solution of CBD (b) (4) sesame oil containing (b) (4) sucralose) and flavoring (strawberry).

The Sponsor is proposing oral administration of CBD at (b) (4) and 20 mg/kg as an adjunct treatment of two epilepsy conditions in children: Dravet syndrome (also known as severe myoclonic epilepsy of infancy) and Lennox-Gastaut syndrome in treatment-resistant patients aged 2 years and older (b) (4). Patients in these studies remained on their current antiepileptic medications and were not allowed to change their regimen.

The Sponsor states that CBD is created from “extracts of Cannabis sativa L. plants (b) (4) are processed to yield a purified (b) (4) % w/w) CBD, which typically contains less than (b) (4) % (w/w) THC [ $\Delta^9$ -tetrahydrocannabinol].” The limits of THC in the CBD product during clinical testing was < (b) (4) %, although the THC limits of the CBD used in the human abuse potential study was (b) (4) % as an average of tested samples for the reported test result of these drug substance batches.

CBD is currently controlled as a Schedule I substance under the Controlled Substances Act (CSA) because it is a chemical constituent of the cannabis plant [see 21 U.S.C. 802(16) defining “Marihuana”]. For this reason, an Eight Factor Analysis (8FA) for CBD was required in order to recommend a change in control status of CBD under the CSA so that it may be removed from Schedule I, a necessity in order for it to be a marketed drug product if this NDA is approved. The 8FA was conducted by CSS in parallel with our review of the NDA 210365. At this time, a complete draft of CSS’ 8FA is under review and clearance within FDA and, thus, has not yet been transmitted to the Drug Enforcement Administration (DEA).

### **Sponsor-Proposed Drug Label**

(b) (4)

In the following proposed text (latest revision of which was submitted on January 8, 2018), the Sponsor uses the tradename (b) (4) for their drug product. Although the Sponsor originally proposed Epidiolex as the tradename for their CBD product, FDA initially rejected the name and the Sponsor proposed “(b) (4)” as a substitute name. The Sponsor subsequently requested restoration of Epidiolex as the tradename and FDA granted approval of the Epidiolex trade name on April 23, 2018. Thus, the text below

reflects the earlier presumed tradename. The secondary endpoints for “perception” refer to the VAS for the modified Bowdle scale, which evaluates 11 internal and external perceptions.

## **9 DRUG ABUSE AND DEPENDENCE**

### **9.1 Controlled Substance**

(b) (4)

### **9.2 Abuse**

(b) (4)

### **9.3 Dependence**

(b) (4)

## **2. CONCLUSIONS**

CSS has reviewed the nonclinical and clinical abuse-related data submitted in NDA 210365 for CBD and concludes that the drug has negligible abuse potential. This conclusion is based on the data described below:

- In receptor binding studies, CBD did not have affinity to any receptor sites currently associated with abuse potential, including cannabinoid CB1 and CB2 sites.
- In tests of general behavior, CBD produced some slight signs of CNS activity, but these behavioral changes were transient and observed only at higher doses.

- In the tetrad test (a measure of cannabinoid effects), CBD did not produce a pattern of producing the 4 behaviors associated with cannabinoid agonists.
- In a drug discrimination studies in rats, intravenous administration of CBD did not produce full generalization to either the THC interoceptive cue or the midazolam interoceptive cue. This shows CBD does not produce sensations similar to a cannabinoid or a depressant.
- In a self-administration studies in rats and monkeys, CBD did not produce self-administration in animals trained to self-administer cocaine, midazolam or heroin.
- In a human abuse potential study, oral administration of CBD at therapeutic (1500 mg) and/or supratherapeutic (4500 mg) doses produced small but statistically significant increases compared to placebo on positive subjective responses such as Drug Liking, Overall Drug Liking, Take Drug Again, Good Effects, High, and Stoned. However, these responses were typically just outside the acceptable placebo range and were statistically significantly less, by a substantial margin, than responses on these measures produced by the two positive control drugs, THC and alprazolam.
- No abuse-related AEs were reported in Phase 1 clinical safety studies. Phase 2/3 clinical safety and efficacy studies could not be evaluated for abuse-related AEs because of the incapacity of the children with epilepsy and because they remained on other antiepileptic drugs.
- The human physical dependence study showed that CBD did not produce withdrawal signs or symptoms three days after drug discontinuation following chronic administration.

### **3. RECOMMENDATIONS**

Based on the CSS determinations that CBD has negligible abuse potential, will have currently accepted medical use upon NDA approval, and does not appear to produce physical dependence:

- a) CSS concludes that CBD could be recommended for decontrol under the Controlled Substances Act. However, there are circumstances outside the scope of the submitted studies that must be considered in determining the final scheduling recommendation.
- b) CSS recommends that the necessity for and content of Section 9 (Drug Abuse and Dependence) be determined after the availability of the DEA's interim final rule regarding changes to the control status of CBD under the CSA.

## **4. DISCUSSION**

### **A. Chemistry of CBD**

#### **1. Drug Substance**

##### **a. Chemical Properties**

Cannabidiol (USAN name) is a new molecular entity identified by CAS registry number: 13956-29-1. It is chemically known as 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol. It has a molecular formula of  $C_{21}H_{30}O_2$  and a molecular weight of 314. (b) (4) It is a white to pale yellow crystalline solid with a melting point of 65-67 °C. It is soluble in methanol, ethanol, acetone, dichloromethane, sesame oil, and other oils, but insoluble in water.

The drug product is a 100 mg/ml oral solution of CBD (b) (4) in sesame oil, (b) (4) (b) (4) (sucralose (b) (4) and flavoring agent. It is available in (b) (4) mL amber glass bottles with child-resistant screw caps.

##### **b. Manufacturing of CBD for the Drug Product**



Stability studies conducted by the Sponsor confirm that the drug product will remain within specification limits up to 24 months when stored at the conditions tested (25°C at 60% relative humidity, and 30°C at 75% relative humidity). Additionally, no evident degradation was observed during the photostability study.

## **2. Conversion of CBD to THC**

CBD can act as an immediate precursor to both  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) and to  $\Delta^8$ -tetrahydrocannabinol ( $\Delta^8$ -THC) through cyclization of CBD under acidic conditions (Adams et al. 1941, Gaoni and Mechoulam 1966, Gaoni and Mechoulam 1971). Although there are no reports that this synthesis takes place in clandestine laboratories, the Sponsor conducted studies to understand the feasibility of converting CBD to  $\Delta^9$ -THC. Based on internet drug forum discussions (Bluelight.com), the Sponsor attempted the conversion using commercially available acids at various concentrations and volumes, and studied the effects of temperature, agitation, and reaction time. Under the best conditions of reaction identified by the Sponsor, the maximum amount of CBD that could be converted to  $\Delta^9$ -THC was approximately 40%.

It is important to point out that the conversion appeared to peak at a certain reaction time, after which  $\Delta^9$ -THC may start to degrade. Isolation of  $\Delta^9$ -THC from the reaction mixture did not prove difficult when using nonpolar organic solvents; however, the  $\Delta^9$ -THC formed could not be separated from other cannabinoids (including unchanged CBD) and other components (i.e., sesame oil present in the formulation) by readily available extraction or filtration methods.

Even though the possibility of converting the CBD present in the product to  $\Delta^9$ -THC or  $\Delta^8$ -THC exists, there may be practical reasons (knowledge of the best reaction conditions to avoid degradation of the THC product, limited reaction yields, and purity of the THC product upon isolation, among other possible reasons) that may deter initiation of this laborious route to obtain the drug. Thus, it would seem unlikely that CBD would act as an immediate precursor to THC for abuse purposes.

## **B. Preclinical Abuse-Related Studies with CBD**

### **1. Receptor Binding and Functional Studies**

Receptor Binding Studies with CBD (Study #100023994, 11105, 1216, 8148, 1562 and 15104)

In receptor binding studies with CBD, there was no significant affinity of CBD for cannabinoid (CB1 or CB2) sites. There was also no significant affinity for sites associated with abuse potential (opioids ( $\mu$ ,  $\kappa$ ,  $\delta$ ), GABA/ benzodiazepine, dopamine (D1 and D2), serotonin (1A, 1B, 2A, 3, 5A, 6, and 7), NMDA/glutamate, channels (calcium, potassium, sodium, chloride), transporters (dopamine, norepinephrine)) or for sites that are not associated with abuse potential (acetylcholine

(muscarinic and nicotinic), adenosine, norepinephrine (alpha and beta), histamine, and neurokinin).

However, CBD does inhibit the transient receptor potential cation channel subfamily M member 8 (TRPM8) channel and activates TRPV1, TRPV2, TRPV3, and TRPV4 and TRPA1 channels. This receptor is not well understood at this time, so the implications of this activity are unclear.

## **2. Animal Behavioral Studies**

Note that all of the doses of CBD used in animal behavioral studies produced plasma levels that are similar to or greater than the plasma levels produced in humans at therapeutic doses.

### **a. General Behavioral Observations**

#### **i. Rat Irwin Test (Acute Oral Administration) (Study #GWOR10109)**

Rats were evaluated in the Irwin test following acute oral doses of CBD (10, 50, and 100 mg/kg) or vehicle. Detailed observations were performed at 30, 60, 120, 240, and 360 minutes post-dose.

There were no observable unusual behaviors produced by any of these doses of CBD or by vehicle. There were also no changes observed in body temperature after these doses of CBD or vehicle. These data show that oral CBD does not induce overt behavioral effects in rats.

#### **ii. Mouse Irwin Test (Acute Intravenous Administration) (Study #GPA002/000159)**

Mice were evaluated in the Irwin test following acute i.v. doses of CBD (3, 10, and 30 mg/kg) or vehicle. Detailed observations were performed at 5, 20, and 60 minutes post-dose.

In the first 5 minutes after drug administration at all doses, animals appeared to walk lower on their limbs, but this returned to normal within 20 minutes. There was a decreased pain response when the 30 mg/kg dose of CBD was tested in response to the phenylquinone writhing test. Although animals that received the 3 mg/kg dose returned to normal within 20 minutes, mice that received the higher two doses still exhibited a decreased pain response 60 minutes after drug administration. All animals showed reductions in body temperature between 5 to 60 minutes after drug administration.

These data show that intravenous CBD induces transient abnormal gait, analgesia, and reductions in body temperature.

iii. Mouse Spontaneous Locomotor Behavior (Acute Intraperitoneal Administration) (Study # GWOR0904)

Mice were pretreated with i.p. CBD (120 mg/kg) or vehicle and placed into an observation cage. Over a 15-minute observation period, CBD did not produce any changes in locomotor activity or general behavior compared to vehicle. This included no changes in time spent in the center of the cage, as a measure of reductions in anxiety. There was also no change in muscle strength, as measured by a hanging wire test. However, CBD did produce a reduction in fecal boli.

These data show that i.p. CBD does not produce changes in behavior in mice, but may produce some constipation.

Mouse Open Field Test (Acute Intraperitoneal Administration) (Study # GWOR08229)

Mice were treated with i.p. CBD (30 or 100 mg/kg) or vehicle and placed into an observation cage. The 30 mg CBD dose did not alter locomotor activity, but the 100 mg dose reduced locomotor activity, especially during the first 10 minutes of observation.

These data show that locomotor activity is not affected in mice by CBD until a very high dose is administered.

iv. Rat Open Field Test (Acute Intraperitoneal Administration) (Study #GWOR0901 and GWOR0897)

Rats were treated with i.p. CBD (60 and 120 mg/kg) or vehicle and placed into an observation cage. CBD decreased locomotor activity, especially in terms of impairment of rearing and exploratory behavior. CBD also increased time spent on the periphery of the cage, suggesting that it did not induce a reduction in anxiety. There was also a reduction in fecal boli.

These data show that CBD reduces locomotor activity but may induce constipation.

v. Rat Rotorod Test (Acute Intraperitoneal Administration) (Study #GWOR1161)

Rats received i.p. administration of CBD (200 mg/kg), THC (0.4, 1.2, 2.4, and 4.8 mg/kg) or vehicle and were placed on a rotarod that increased in speed from 4 to 40 rpm over a 300 second period. Each of three tests per animal ended when the animal fell from the rotarod, with each animal performing three accelerating rotarod runs per experimental day.

Neither CBD or THC had an effect on the latency of rats to fall in the rotorod test compared to vehicle-treated animals.

### Overall Conclusions from General Behavioral Studies

The results from the general behavioral studies show that CBD has some CNS activity at higher doses, but the effects are transient. However, in order to determine if CBD produces *abuse-related* CNS effects, specific abuse-related behavioral studies were conducted.

#### **b. Abuse-Related Behavioral Studies (Tetrad Test, Drug Discrimination, and Self-Administration)**

##### i. Mice Tetrad Test (Acute Intraperitoneal Administration) (Study #GWOR1211 and GWPP1370)

The Tetrad Test is a series of four behavioral tests (ambulation and rearing, immobility, hypothermia, and antinociception) that are known to produce positive results in rodents when they receive a drug that has cannabinoid agonist activity. Thus, test drugs that produce positive results in the Tetrad Test may also have activity as cannabinoid agonists.

##### *Method*

Mice were evaluated for ambulation and rearing (activity meter test), immobility (bar test), hypothermia (rectal temperature), and antinociception (hot plate test), after receiving THC, CBD, THC:CBD (1:1 mixture), or one of three CBD metabolites (6-OH-CBD, 7-OH-CBD, and 11-OH-CBD) using i.p. doses of 1, 10, 50, and 100 mg/kg.

##### *Results*

R-(+)-WIN 55,212-2 (10 mg/kg, i.p.), a cannabinoid agonist that served as the positive control, decreased the number of crossings and rearings, increased the latency to remove forelimbs, decreased rectal temperature, and increased the foot-licking latency.

THC did not alter behavior in the four tests at the two lower doses of 1 and 10 mg/kg. At 50 and 100 mg/kg, it decreased the number of crossings and the number of rearings in the activity meter test, decreased rectal temperature, and increased the foot-licking latency. However, it did not affect the latency to remove forelimbs in the bar test.

THC:CBD did not alter behavior in the four tests at 1 mg/kg. At higher doses, it dose-dependently decreased the number of crossings and rearings (10, 50, and 100 mg/kg), increased the latency to remove forelimbs in the bar test (at 100 mg/kg), decreased rectal temperature (at 50 and 100 mg/kg) and increased the foot-licking latency.

CBD did not alter behavior in the four tests at 1, 10, and 50 mg/kg. At 100 mg/kg, there was a decrease compared to vehicle in the number of rearings (but not the number of crossings) and decreased rectal temperature. However, it did not affect the latency to remove forelimbs in the bar test or the foot-licking latency in the hot plate test.

The CBD metabolite, 6-OH-CBD, did not produce any changes in the four behavioral tests at 1, 10, 50, and 100 mg/kg. However, another CBD metabolite, 7-OH-CBD, did not significantly affect the number of crossings and rearings at 1, 10, 50, and 100 mg/kg, but at 50 and 100 mg/kg, it significantly increased the latency to remove forelimbs and decreased the rectal temperature. It had no effects on the foot-licking latency. A behavioral profile similar to 7-OH THC was seen for 11-OH THC.

These data suggest that CBD and two of its metabolites (7-OH THC and 11-OH THC) have slight cannabinoid effects at very high doses.

## ii. Drug Discrimination Studies

### *Drug Discrimination Study with Oral CBD (Study #GWTX1554)*

Drug discrimination is an experimental method of determining whether a test drug produces physical and behavioral responses that are similar to a training drug with specific pharmacological effects. Any centrally-acting drug can serve as the training drug. When the training drug is a known drug of abuse, drug discrimination in animals serves as an important method for predicting whether the effects of a new drug will similarly have abuse potential. Drugs that produce a response similar to known drugs of abuse in animals are also likely to be abused by humans.

In drug discrimination, an animal learns to press one bar when it receives the training drug and another bar when it receives a placebo. Once responding to the training drug and placebo is stable, an animal is given a challenge session with the test drug. A test drug is said to have "full generalization" to the training drug when the test drug produces bar pressing  $\geq 75\%$  on the bar associated with the training drug.

### *Method*

Rats ( $n = 7$ ) were trained to lever press for food reward using a fixed ratio (FR) 1 schedule of reinforcement, which was then increased to FR2. After responding was stable, animals were trained to discriminate THC (3 mg/kg, i.p., 15-minute pretreatment time) from vehicle. During training, the schedule of reinforcement was gradually raised to FR10. Vehicle and THC were administered across sessions according to alternating sequences of single and double alternation (e.g., THC, vehicle, vehicle, THC, THC, vehicle, vehicle, THC, vehicle, THC), 5 days a week. The session continued until a rat obtained 50 food pellets or 15 minutes had elapsed, whichever occurred first.

During test sessions, 10 responses on either lever resulted in delivery of a food pellet, with the FR value being reset to zero if an animal responded on the other lever prior to completion of FR10 (rats had to make 10 consecutive responses on a given lever in order to receive a food pellet). When rats could stably discriminate THC from vehicle, challenge sessions with CBD began. Full generalization was defined as 80% accuracy on the drug-associated lever.

CBD (in vehicle containing (b) (6)), sucralose, strawberry flavoring, and sesame oil) was administered orally at doses of 20, 75 and 150 mg/kg two hours before the test session. These animal doses are known through pharmacokinetic studies to produce CBD plasma levels that are equivalent to 0.6-0.9X, 1.7-2.7X, and 2.5-3.7X (respectively) of the plasma levels produced in humans after the two therapeutic doses of 10 and 20 mg/kg/day. The Sponsor justifies the oral route for testing on the basis that this is the human therapeutic route of administration.

### *Results*

Rats discriminated THC (71% accuracy on THC-associated lever) from vehicle (<10% on THC-associated lever) at both the beginning and end of the study. Notably, however, responding for THC never met the full generalization criterion of 80% on the THC-associated lever. No explanation is provided for this discrepancy.

CBD did not produce a mean generalization of 80% or greater to THC at any dose:

- At the 20 mg/kg dose of CBD, THC-responding was only 14%. This was similar to the 11% generalization produced by vehicle to the THC cue.
- At the 75 mg/kg dose of CBD, there was a mean responding of 46% THC-lever, while vehicle produced 11% THC-lever responding.
- At the 150 mg/kg dose of CBD, the mean generalization fell to 27% THC-lever responding, while vehicle produced 11% THC-lever responding.

Another way to look at the data is to look at the animal responses on the lever associated with placebo. These data can be interpreted as showing that the partial generalization at 75 and 150 mg/kg was >50% for the placebo cue (54% for 75 mg/kg and 73% for 150 mg/kg). These data suggest that CBD is more like placebo than THC.

A separate group of rats was used to determine plasma concentrations of CBD-associated and THC-associated compounds at each of the three CBD doses (sampled at the 2 hour timepoint of behavioral testing).

- Plasma levels of CBD and its metabolites (7-COOH-CBD, 7-OH-CBD, and 6-OH-CBD,) increased in a dose-dependent manner after a single oral administration of CBD at 20, 75, and 150 mg/kg.
- At 20 mg/kg CBD, plasma levels of THC and its metabolites were not quantifiable.
- At 75 mg/kg CBD, the mean plasma level concentration THC was 0.47 ng/ml, but 11-COOH-THC and 11-OH-THC were not quantifiable.

- At 150 mg/kg CBD, the mean plasma level concentration of THC was 0.70 ng/ml but 11-COOH-THC and 11-OH-THC were not quantifiable.

The plasma levels of THC produced in rats by the two higher doses of THC (0.47 and 0.70 ng/ml) are higher than those produced in humans at therapeutic (10 and 20 mg/kg) and supratherapeutic (60 mg/kg) doses (plasma levels of 0.27, 0.38, and 0.40 ng/ml, respectively).

### *Conclusions*

These data show that CBD does not produce significant interoceptive cues similar to those produced by THC. This suggests that CBD does not produce cannabinoid agonist effects.

### *Drug Discrimination Study with CBD and Its Metabolites Comparing Oral and Intraperitoneal Administration (Study #10136)*

#### *Method*

Rats (n = 7) were trained to lever press for food reward using a fixed ratio (FR) 1 schedule of reinforcement, which was then increased to FR2. After responding was stable, animals were trained to discriminate i.p. THC (3 mg/kg, 15-minute pretreatment time) from vehicle. During training, the schedule of reinforcement was gradually raised to FR10. Full generalization was defined as 80% accuracy on the drug-associated lever.

Rats were first tested with oral THC at 1, 3, and 10 mg/kg (90 minutes pretreatment time). After these sessions were complete, testing was conducted with oral administration of CBD and its metabolites (tetrahydrocannabivarin (THCV), cannabidivarin (CBDV), cannabigerol (CBG)) (in vehicle containing (b) (6) ) was administered orally at doses of 1, 3, and 10 mg/kg two hours before the test session. The Sponsor justifies the oral route for testing on the basis that this is the human therapeutic route of administration.

#### *Results*

As expected, oral THC resulted in dose-dependent THC-lever responding (54%, 100%, and 96%, at 1, 3, and 10 mg/kg, respectively), compared to 1% for oral vehicle

In contrast, oral CBD did not result in THC-lever responding (9%, 9% and 8% at 1, 3, and 10 mg/kg, respectively) compared to 1% for vehicle.

Oral administration of the three CBD metabolites (THCV, CBDV and CBG at 1, 3, and 10 mg/kg) did not result in THC-lever responding (<21%).

### *Conclusions*

These data show that oral administration of CBD or its metabolites do not produce generalization to the THC interoceptive cue. The data also show that similar results with respect to generalization are obtained by both oral and i.p. administration of CBD and THC.

### *Drug Discrimination with CBD in Benzodiazepine-Trained Rats (Study #15110)*

Female, Lister Hooded rats were trained to discriminate between midazolam (0.5 mg/kg, i.p.) and saline. Rats were trained to lever press for food reward where the schedule of reinforcement was gradually raised to FR10. Full generalization was defined as 80% accuracy on the drug-associated lever. Following stabilization of responses, rats (n = 6/group) were tested with the test compounds.

### *Results*

Midazolam (0.5, 1.0, and 1.5 mg/kg, p.o.), which produced dose-dependent generalization to the midazolam interoceptive cue: 53%, 74%, and 91%, respectively. Alprazolam (0.125, 0.25, 0.50, and 1.0 mg/kg, p.o.) produced a similar dose-dependent generalization to the midazolam interoceptive cue: 11%, 38%, 86%, and 89%, respectively.

CBD was then tested at 20, 75 and 150 mg/kg (p.o.). These doses produce CBD plasma levels that are equivalent to 2.3-3.6X, 5.8-9.1X, and 11.1-17.7X (respectively) of the plasma levels produced in humans after the two therapeutic doses of 10 and 20 mg/kg/day. These doses of CBD did not produce any generalization to the midazolam interoceptive cue: 11%, 4%, and 6%, respectively.

### *Conclusions*

CBD does not produce benzodiazepine-like interoceptive responses.

### iii. Self-Administration Studies

#### *Self-Administration Study in Rats Trained with Cocaine (Study # GWTX1551)*

A self-administration study was conducted in rats (n = 5-7/group, n = 44 total) to evaluate whether CBD produces sufficient reward to be reinforcing.

Animals were initially trained to press a lever to receive cocaine (0.32 mg/kg/infusion, i.v.). The animals were trained initially using a FR1 schedule of reinforcement, which was gradually increased to FR3 and then finally FR10. A stable response was defined as “80% or greater drug-paired lever responding while exhibiting a sustained pattern of reinforced behavior (>30 rewards), over at least three consecutive sessions”.

After cocaine self-administration was stable, substitution sessions began. The positive control was amphetamine (0.05 mg/kg/infusion, i.v.) while CBD was tested at 0.1, 0.5, and 1.5 mg/kg/infusion (i.v.). Each test drug was made available to each rat on 3 consecutive days.

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

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

### *Conclusions*

The data from this study suggest that CBD produced insufficiently rewarding properties to sustain reinforcement.

### *Self-Administration Study in Rats Trained with Heroin (Study # GWTX1663)*

#### *Method*

Rats were trained to self-administer heroin (0.015 mg/kg/injection, i.v.) on a FR3 reinforcement schedule using methods detailed above for the self-administration study with cocaine.

#### *Results*

Rats tested with heroin, midazolam, diazepam, CBD, and saline produced the following self-administration:

- Heroin (0.015 mg/kg/injection i.v.) produced ~18 infusions/session
- Cannabidiol (0.1, 0.2, and 0.5 mg/kg i.v.) produced <7 infusions/session
- Midazolam (0.0003, 0.0010, 0.0015, 0.0030 mg/kg i.v.) produced <7 infusions/session
- Diazepam (0.001, 0.003, 0.0045, and 0.01 mg/kg i.v.) produced <6 infusions/session
- Saline produced < 4 infusions/session.

The  $C_{\max}$  of accumulated mean drug intake for CBD ranged between 11% and 411% of the reported clinical  $C_{\max}$  values (750 mg and 1500 mg p.o. doses).

The data from this study suggests that CBD produced insufficiently rewarding properties to sustain reinforcement.

*Self-Administration Study in Monkeys Trained with Midazolam (Study # GWTX1664)*

Rhesus monkeys (n = 5) were trained to self-administer the benzodiazepine, midazolam (0.032 mg/kg/infusion in two monkeys and 0.01 mg/kg/infusion in three monkeys), using an FR3 schedule of reinforcement. Animals were also presented with vehicle to confirm they would not self-administer a substance without rewarding properties. Once midazolam self-administration was stable, midazolam and CBD were substituted, interspersed with vehicle sessions.

Midazolam (0.01 mg/kg/infusion in three monkeys and 0.032 mg/kg/infusion in two monkeys) produced <13 infusions/session

CBD (0.1, 0.32, 1.0, and 3.2 mg/kg/infusion) produced <1 infusions/session  
Vehicle produced <1 infusions/session

The data from this study suggest that CBD produced insufficiently rewarding properties to sustain reinforcement.

**3. Physical Dependence Studies in Animals**

Rat Physical Dependence Study (Study #1555 and 15114)

*Methods*

Male and female rats (n = 7-13 animals/sex/treatment group, using both juvenile rats (n = 1-5/treatment) and adult rats (n = 6-10)) received daily oral administration of the study treatments twice per day (b.i.d.) for 19 days and once on Day 20. The treatments included: CBD (20 and 100 mg/kg = 40 and 200 mg/kg/day), diazepam (40 mg/kg = 80 mg/kg/day), morphine (64 mg/kg = 128 mg/kg/day), and placebo.

The 20 mg/kg dose is known through pharmacokinetic studies to produce CBD plasma levels that are equivalent on the last day of treatment to 1.8-2.8X (female juveniles), 3.1-4.9X (male juveniles), 2.6-41.X (female adults), and 2.4-3.9X (male adults) of the plasma levels produced in humans after the 10 and 20 mg/kg/day therapeutic doses. The 100 mg/kg dose is known through pharmacokinetic studies to produce CBD plasma levels that are equivalent on the last day of treatment to 21-33X (female juveniles), 24-38X (male juveniles), 19-28X (female adults), and 14-23X (male adults) of the plasma levels produced in humans after the 10 and 20 mg/kg/day therapeutic doses.

Animals were observed daily for behavioral changes and for changes in food consumption, body weight, and rectal temperature on the last three days of treatment (Days 18-20) as well as during the 8 days after treatment discontinuation (Days 21-28). During the withdrawal period, animals received a once-daily administration of distilled water. Behavioral and physiological manifestations including the following items: jumping, sniffing, wet dog shakes, writhing, ptosis, tremor, genital licks, scratching, hyperactivity, grooming, Straub tail, tiptoe gait, teeth-chattering, dyspnea, diarrhea, and burying.

An additional 12 rats were used in a satellite group to determine plasma levels of CBD (20 and 100 mg/kg, p.o.) in both juvenile and adult rats.

## **Results**

### **Body Weight**

*Juvenile Rats.* There was no effect on body weight following placebo, CBD (20 mg/kg, BID), or diazepam either during the last 3 days of treatment or during the withdrawal period. In males, there was also no effect from 100 mg/kg CBD, but this dose produced a 10% increase in body weight during the last 3 days of treatment as well as during the withdrawal period. In contrast, morphine decreased body weight in the last 3 days of treatment period (5-7% in females, 18-19% in males,  $p < 0.001$ ) and during the withdrawal period (28% at Day 22,  $p < 0.001$ ).

*Adult Rats.* Body weight increased over treatment period and withdrawal period in the placebo group. CBD (20 and 100 mg/kg) and DZP did not affect body weight before or after treatment. In contrast, morphine decreased body weight in the last 3 days of treatment period (14-15%,  $p < 0.001$ ) and during the withdrawal period (16% in females, 23% in males at Days 22-23,  $p < 0.001$ ).

### **Food Consumption**

*Juvenile Rats.* There was an increase in food consumption in the withdrawal period (compared to the last 3 days of treatment) in the placebo group ( $p < 0.001$ ) in both males (25%) and females (36%). Food consumption during the last 3 days of treatment was not affected by the 20 mg/kg dose, but was increased by 10% (males) and 35% (females) at the 100 mg/kg dose ( $p < 0.001$ ). During the withdrawal period, there was an increase in food consumption in both the 20 mg/kg group (19% in males, 34% in females) and the 100 mg/kg group (18% in males and 16% in females) (both  $p < 0.001$ ). DZP treatment increased food consumption in the last 3 days of treatment (27-31%,  $p < 0.001$ ). During the withdrawal period, diazepam produced a decrease (16%,  $p < 0.001$ ) in food consumption at Day 21, with recovery in the days afterwards. Morphine did not affect food consumption in the last 3 days of treatment. During the withdrawal period, morphine produced a decrease in food consumption (41%,  $p < 0.001$ ) on Day 20, with recovery in the days afterwards.

*Adult Rats.* There was an 74% increase in food consumption in the withdrawal period (compared to the last 3 days of treatment) in the placebo group ( $p < 0.01$ ). CBD (20 and 100 mg/kg) treatment increased food consumption on Day 20 (14% and 11%, respectively,  $p < 0.01$ ), and further increased consumption during the withdrawal period (58% and 67%, on Day 28,  $p < 0.001$ ). DZP treatment increased food consumption in the last 3 days of treatment (37-67%,  $p < 0.001$ ). During the withdrawal period, diazepam produced an initial trend in decrease in food consumption, following by a 24% increase ( $p < 0.001$  on Day 23). Morphine increased food consumption in the last 3 days of treatment (46%,  $p < 0.001$ ). During the withdrawal period, morphine produced an increase in food consumption (36%,  $p < 0.001$ ) on Day 27, with recovery in the days afterwards.

#### Rectal temperature

*Juvenile Rats.* Placebo produced a slight but significant increase in rectal temperature during the withdrawal period ( $0.3-0.4^{\circ}\text{C}$ ,  $p < 0.05$ ). CBD (20 and 100 mg/kg) did not affect rectal temperature either during the last 3 days of treatment. During the withdrawal period, the 20 mg/kg dose of CBD did not affect temperature, but there was a slight but significant increase in temperature ( $+0.4^{\circ}\text{C}$ ,  $p < 0.05$ ). The 100 mg/kg did not produce changes before or after drug treatment. Diazepam increased rectal temperature during the last 3 days of treatment ( $0.5-0.8^{\circ}\text{C}$ ,  $p < 0.001$ ) and during the withdrawal period ( $+0.3-0.5^{\circ}\text{C}$ ,  $p < 0.05$ ). Morphine did not alter temperature during the last 3 days of treatment, but did increase it during the withdrawal period ( $0.3-0.5^{\circ}\text{C}$ ,  $p < 0.05-0.001$ ).

*Adult Rats.* Placebo produced a slight but significant decrease in rectal temperature during the withdrawal period ( $0.4^{\circ}\text{C}$ ,  $p < 0.01$ ). CBD (20 mg/kg) did not affect rectal temperature either during the last 3 days of treatment but decreased temperature during the withdrawal period ( $-0.5^{\circ}\text{C}$ ,  $p < 0.01$ ). CBD (100 mg/kg) caused a slight increase in temperature during the last days of treatment ( $0.2-0.3^{\circ}\text{C}$ ,  $p < 0.05$ ), but decreased temperature during the withdrawal period ( $0.3-0.7^{\circ}\text{C}$ ,  $p < 0.01$ ). Diazepam increased rectal temperature during the last 3 days of treatment ( $0.5-0.6^{\circ}\text{C}$ ,  $p < 0.001$ ), but decreased it during the withdrawal period ( $0.3-0.5^{\circ}\text{C}$ ,  $p < 0.05$ ). Morphine increased temperature during the last 3 days of treatment ( $0.2^{\circ}\text{C}$ ,  $p < 0.05$ ), but decreased it during the withdrawal period ( $0.3-0.5^{\circ}\text{C}$ ,  $p < 0.01-0.05$ ).

#### Behavioral and physiological symptoms.

*Juvenile and Adult Rats.* There were no changes in behavior or physiological signs in rats during treatment or following discontinuation of placebo or CBD (at either 20 or 100 mg/kg). In contrast, diazepam produced a slight increase in sniffing, appearance of occasional wet-dog shakes, genital licks, and hyperactivity, but there were no additional signs during drug discontinuation. Morphine did not produce any changes in behavior during the last 3 days of treatment, but it produced occasional writhes, jumping, hyperactivity, ptosis, and wet dog shakes during the withdrawal period.

## Conclusions

In this laboratory, CBD at 20 and 100 mg/kg (BID) did not produce a clear withdrawal syndrome following chronic administration and subsequent drug discontinuation. Diazepam produced the same lack of withdrawal-associated responses. Morphine produced a slight but significant increase in opioid-related withdrawal responses.

Since the two positive control drugs did not produce a clear withdrawal syndrome, this study cannot be considered valid for definitively determining whether CBD produces physical dependence.

## C. Animal and Human Pharmacokinetics of CBD

### 1. Rodent Pharmacokinetics

When mice and rats were given 120 mg/kg CBD through oral or intraperitoneal administration, they produced varied peak plasma levels ( $C_{\max}$ ) and time to  $C_{\max}$  ( $T_{\max}$ ), as shown in Table 1 (below):

**Table 1: Pharmacokinetics for CBD in mice (120 mg/kg, oral and i.p.)**

#### Mice

PK Parameter	Oral	IP
$C_{\max}$ (µg/ml)	2.0	14.3
$T_{\max}$ (minutes)	60	120

#### Rats

PK Parameter	Oral	IP
$C_{\max}$ (µg/ml)	2.0-3.2	2.4-2.6
$T_{\max}$ (minutes)	120-360	30-120

### 2. Human Pharmacokinetics (Study #GWEP1544)

The pharmacokinetics of CBD and its metabolites (7-hydroxy-cannabidiol [7-OH-CBD], 6-hydroxy-cannabidiol [6-OH-CBD], and 7-carboxy-cannabidiol [7-COOH-CBD]) were characterized in a single ascending dose and multiple dose study following administration of CBD oral liquid formulation with an open label two period cross-over part to study food effects in healthy subjects.

Following a single oral dose (1500, 3000, 4500, and 6000 mg), CBD appeared rapidly in the plasma, with  $C_{\max}$  typically occurring within 3-5 hours post dosing and remaining detectable up to 72 hours post-dose. CBD concentrations in plasma declined with an elimination half-life of 30 hours, with CBD metabolites generally decreasing with a slightly shorter half-life.

Following multiple bi-daily administration (750 or 1500 mg CBD for 7 days) exposures to CBD and its metabolites increased with dose in a manner that was almost dose proportional. Steady state for CBD was reached by Day 2 to 3.

The terminal elimination of CBD after multiple dosing was approximately 56 to 61 hours and slightly longer than that observed following a single dose. Following a single oral dose of 300 mg [<sup>14</sup>C] CBD in healthy male subjects, 82.2% of the total radioactivity was recovered in feces within 336 hours and less than 1% was recovered in urine within 192 hours.

There was a statistically significant food effect when 1500 mg CBD was administered to healthy volunteers after a high-fat breakfast. Both mean C<sub>max</sub> and AUC of CBD and its metabolites increased by approximately 4- to 5-fold.

Additional pharmacokinetic evaluations were conducted during the human abuse potential study (see Section D.1, below).

#### **D. Clinical Abuse-Related Studies**

##### **1. Oral Administration Human Abuse Potential Study with CBD (Study #GWEP1431)**

This was a randomized, double-blind, double-dummy, placebo- and active-controlled, 6-period, crossover study that evaluated the oral abuse potential, safety, tolerability, and PK of CBD versus placebo and alprazolam in healthy nondependent recreational polydrug users. The study consists of a Screening Phase, the Main Study (Qualification Phase and Treatment Phase), and a Follow-Up Visit (up to 2 weeks after last treatment). In the Treatment Phase, subjects were confined to the unit the day prior to the first study drug administration (at check-in).

#### **Subjects**

##### *Number of Subjects*

During the Qualification Study, 95 subjects participated. During the Main Study, 43 adult subjects (age 18-55 years; 31 men, 12 women) who passed the Qualification Phase were randomized from the Qualification Phase into the Treatment Phase. There were 35 study completers (81%). Subjects had to have a body mass index (BMI) within 19.0 to 30.0 kg/m<sup>2</sup>.

*Inclusion Criteria*, for participation in either study phase, are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject had at least 10 lifetime non-therapeutic experiences (i.e., for psychoactive effects) with central nervous system (CNS) depressants (e.g., benzodiazepines, barbiturates, zolpidem, zopiclone, propofol/fospropofol, gamma-hydroxybutyrate);

- Subject had at least 10 lifetime non-therapeutic experiences with cannabinoids (e.g., cannabis, hashish, dronabinol, nabilone);
- Subject had at least 1 lifetime non-therapeutic use of another drug class of abuse (i.e., opioids, stimulants, dissociatives, hallucinogens); and
- Subject had at least 1 non-therapeutic use of a CNS depressant and a cannabinoid within the previous 12 weeks.

*Exclusion Criteria* are standard but include the following criteria that are relevant for a human abuse potential study:

- Subject had a positive urine drug screen (UDS) or breath alcohol test;
- Subject had a urine carboxy-THC/creatinine ratio > 100 ng/mg;
- Subject had used intravenous drugs within the past 2 years;
- Subject had a history or current diagnosis of substance dependence (excluding caffeine and nicotine), as assessed by the investigator using the DSM-IV-TR criteria;
- Subject had participated in, was currently participating in, or planned to seek treatment for substance-related disorders (excluding nicotine and caffeine); and
- Subject had a risk of significant respiratory depression.

**Main Study:**

Subjects must pass the following criteria in the Qualification Phase to be eligible to enter the Treatment Phase:

1. Ability to distinguish alprazolam and dronabinol from placebo on Drug Liking visual analog scale (VAS), with a 15 point peak increase (of at least 65 points) for Drug Liking relative to placebo;
2. Acceptable placebo response on Drug Liking VAS between 40 to 60, inclusive;
3. Ability to tolerate study treatments and ability to produce acceptable responses; and
4. General behavior suggestive that they could successfully complete the study, as judged by the clinic staff.

On the bipolar Drug Liking VAS Emax, placebo responses were appropriate (mean =  $55 \pm 11$ ), as were responses to alprazolam 2 mg (mean =  $79 \pm 16$ ) and dronabinol 15 mg and 30 mg ( $74 \pm 19$  and  $87 \pm 14$ , respectively) for those subjects who were allowed to participate in the Treatment Phase.

### **Oral Drug Doses**

Subjects were required to abstain from food for at least 8 hours prior to dosing during the Qualification and Treatment Periods and for at least 4 hours post-dose. Subjects were required to abstain from smoking or use of nicotine replacement therapy for at least 2 hours prior to and 8 hours after trial drug administration.

### ***Main Study***

#### ***Blinding***

During the Qualification and Treatment Phases, treatments were matched so that the same number/type of capsules and same volume of oral solution (for the Treatment Phase) were administered. Dronabinol capsules, alprazolam tablets and lactose placebo tablets were overencapsulated in identical opaque gelatin capsules so they all had the same visual appearance and approximate weight. Placebos consisted of over-encapsulated placebo tablets to match alprazolam and dronabinol, and placebo oral solution to match CBD.

#### ***Qualification Phase (single blinded)***

The following treatments (2 capsules) were administered orally:

- Alprazolam 2 mg (2 X 1 mg tablet)
- Dronabinol 20 mg (2 X 10 mg Marinol capsule)
- Placebo (2 placebo tablets)

Alprazolam was selected as a positive control because it has similarities to CBD in terms of ability to produce anti-convulsant and anti-anxiety effects, proposed indication (seizure disorders) and half-life (9-11 hours).

Dronabinol (the generic name for (-)-*trans*- $\Delta^9$ -tetrahydrocannabinol (THC)) was selected as a positive control because CBD is also a cannabinoid.

The 2 mg dose of alprazolam was selected because it has been used in previous human abuse potential studies and does not produce the sedation often observed at 3 mg (which could interfere with subjective measure data collection).

The 20 mg dronabinol dose was selected because it has been used in previous human abuse potential studies and is between the 10 and 30 mg doses of dronabinol used in the Treatment Phase.

There was a washout period of 48 hours between treatments. This is not a sufficient period for washout (5 half-lives) given the following drug half-lives:

- alprazolam (11-26 hours X 5 half lives = 130 hours = 5.4 days)
- dronabinol (36 hours X 5 half lives = 180 hours = 7.5 days).

However, the Sponsor states that these washout periods “have been used successfully in previous studies of dronabinol and alprazolam”.

Subjects were discharged 24 hours after the last drug administration and returned for the Treatment Phase at least 8 days after the conclusion of the Qualification Phase.

*Treatment Phase (double-blind)*

Subjects who entered the Treatment Phase were assigned a unique Treatment randomization number. Subjects were randomized to 1 of 14 treatment sequences, according to two  $7 \times 7$  Williams squares. Randomization was stratified by sex, such that 1 complete block of sequences (i.e., 14 sequences) was planned to be filled with female subjects.

The following treatments (45 ml solution + 3 capsules) were administered orally:

- CBD 750 mg (7.5 ml drug solution + 37.5 ml placebo solution + 3 placebo capsules)
- CBD 1500 mg (15 ml drug solution + 30 ml placebo solution + 3 placebo capsules)
- CBD 4500 mg (45 ml drug solution + 3 placebo capsules)
- Alprazolam 2 mg (45 ml placebo solution + 2 X 1 mg tablet + 1 placebo tablet)
- Dronabinol 10 mg (45 ml placebo solution + 1 X 10 mg Marinol capsule + 2 placebo tablets)
- Dronabinol 30 mg (45 ml placebo solution + 3 X 10 mg Marinol capsule)
- Placebo (45 ml placebo solution + 3 placebo capsules)

CBD was provided as an oral solution in sesame oil with (b) (4) sucralose and strawberry flavoring. The Sponsor states that their purified CBD contains only trace amounts of THC ( $< (b) (6) \% w/w$ ).

The doses of CBD represent a therapeutic dose (750 mg) and a supratherapeutic dose of

4500 mg (6 times the therapeutic dose). A mid-dose (1500 mg) was also included in order to appropriately evaluate the dose-response of the drug. The Sponsor states that the high dose of 4500 mg is the maximum tolerated dose of CBD, based on clinical study data, in which a dose of 6000 mg was not well tolerated.

The 2 mg dose of alprazolam was selected because it has been used in previous human abuse potential studies and does not produce the sedation often observed at 3 mg (which could interfere with subjective measure data collection).

The dronabinol ranging from 10 to 30 mg were selected because they have been used in previous human abuse potential studies to produce low and moderate psychoactive cannabinoid responses.

There was a washout period of at least 8 days between treatments, which was calculated on the basis of an elimination period of 5 half-lives for the longest of the 3 study treatments, dronabinol:

- CBD (9-10 hours X 5 half lives = 50 hours = 2.1 days)
- alprazolam (11-26 hours X 5 half lives = 130 hours = 5.4 days)
- dronabinol (36 hours X 5 half lives = 180 hours = 7.5 days)

#### *Pharmacodynamic Variables*

All subjective endpoints were assessed at baseline, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, and 24 hours after drug administration, except for VAS for Overall Drug Liking and Take Drug Again, which was assessed at 12 and 24 hours. Drug Similarity was assessed at 12 hours. The cognitive/behavioral measures were assessed at baseline, 1, 2, 3, 6, 8, 12, and 24 hours after drug administration.

#### Primary Measure:

Drug Liking VAS ( $E_{max}$ )

#### Secondary Measures:

##### *Balance of effects:*

- ☐ Drug Liking VAS ( $E_{max}$ ,  $E_{min}$ , and TA\_AUE)
- ☐ Overall Drug Liking VAS ( $E_{max}$ ,  $E_{min}$ ; end-of-day, and next day scores)
- ☐ Take Drug Again VAS ( $E_{max}$ ; end-of-day, and next day scores)

##### *Positive effects:*

- ☐ High VAS ( $E_{max}$  and TA\_AUE)
- ☐ Good Effects VAS ( $E_{max}$  and TA\_AUE)
- ☐ Stoned VAS ( $E_{max}$  and TA\_AUE)

*Negative effects:*

- ☐ Bad Effects VAS ( $E_{\max}$  and TA\_AUE)

*Other drug effects:*

- ☐ Any Effects VAS ( $E_{\max}$  and TA\_AUE)
- ☐ Alertness/Drowsiness VAS ( $E_{\max}$  and TA\_AUE)
- ☐ Agitated/Relaxed VAS ( $E_{\max}$  and TA\_AUE)
- ☐ Hallucinations VAS ( $E_{\max}$  and TA\_AUE)
- ☐ Drug Similarity VAS (score at 12 hours)
- ☐ Bowdle VAS (internal and external perceptions,  $E_{\max}$  and TA\_AUE)

The modified Bowdle VAS consisted of 11 items:

1. My body or body parts seemed to change their shape or position
2. My surroundings seemed to change in size, depth, or shape
3. The passing of time was altered
4. I had feelings of unreality
5. It was difficult to control my thoughts
6. The intensity of colors changed
7. The intensity of sound changes
8. I heard voices or sounds that were not real
9. I had the idea that events, objects, or other people had particular meaning that was specific for me
10. I had suspicious ideas or the belief that others were against me
11. I felt anxious

*Cognitive-Behavioral Measures:*

- ☐ Hopkins Verbal Learning Test – Revised (HVLTR)
- ☐ Divided Attention test (DAT)
- ☐ Digit-Symbol Substitution Task (DSST; a test of processing speed and visual-motor coordination)

*Safety Variables*

- Adverse events
- Clinical laboratory parameters
- Vital signs measurements
- 12-lead ECG
- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Continuous pulse oximetry/telemetry monitoring

*Pharmacokinetic Evaluation:*

Venous blood samples (6 ml) were collected at 1, 2, 3, 4, 6, 8, 10, 12, and 24 hours after drug administration. Validated liquid chromatographic tandem mass spectrometric bioanalytical methods were used to quantify concentrations of CBD, THC, and their metabolites 6-hydroxy-cannabidiol (6-OH-CBD), 7-carboxy-cannabidiol (7-COOH-CBD), 7-hydroxy-cannabidiol (7-OH-CBD), 11-hydroxy- $\Delta^9$ -tetrahydrocannabinol (11-

OH-THC), and 11-*nor*-9-carboxy- $\Delta^9$ -tetrahydrocannabinol (11-COOH-THC) in human plasma.

The pharmacokinetic parameters evaluated included:

- time to maximum observed plasma concentration ( $T_{\max}$ )
- maximum observed plasma concentration ( $C_{\max}$ )
- area under the plasma concentration-time curve (AUC<sub>0–last</sub> and AUC<sub>0–∞</sub>)
- terminal elimination half-life ( $t_{1/2}$ )

## **Results**

### **Subjective Responses**

Table 2 below depicts the effects of study treatments on subjective measures used in this study. The mean and standard deviation numbers provided below were drawn from the Statistical Review and Evaluation of the present HAP study, as conducted by Dr. Anna Sun, FDA Office of Biostatistics (3/26/18). The primary measure of Drug Liking, as well as the secondary measures Overall Drug Liking, Good Drug Effects, and Take Drug Again, were evaluated for statistically significant differences between CBD, dronabinol, alprazolam, and placebo by both Dr. Sun as well as by the Sponsor. However, a statistical evaluation of the remaining secondary measures was only conducted by the Sponsor.

**Table 2: Effects of Oral Placebo, Alprazolam (2 mg), Dronabinol (DRO, 10 and 30 mg), and CBD (750, 1500, and 4500 mg) on Subjective Measures (VAS) –  $E_{\max}$  Scores (n = 35)**

<b>Measure</b>	<b>Placebo</b>	<b>ALZ 2</b>	<b>DRO 10</b>	<b>DRO 30</b>	<b>CBD 750</b>	<b>CBD 1500</b>	<b>CBD4500</b>
Drug Liking VAS bipolar	55 ± 11	79 ± 16 ^	74 ± 19 ^	87 ± 15 ^	57 ± 14	61 ± 17 *	64 ± 17 *
Overall Drug Liking VAS bipolar	50 ± 17	87 ± 16 ^	75 ± 21 ^	87 ± 19 ^	55 ± 16	57 ± 19	60 ± 26
Take Drug Again VAS	11 ± 25	85 ± 24 ^	65 ± 39 ^	85 ± 27 ^	20 ± 31	28 ± 37 *	42 ± 42 ^
Good Drug Effects VAS	11 ± 26	77 ± 25 ^	55 ± 39 ^	83 ± 22 ^	22 ± 33	29 ± 38 *	38 ± 38 #
High VAS	9 ± 22	55 ± 38 ^	38 ± 40 ^	71 ± 35 ^	10 ± 25	20 ± 35 *	31 ± 38 #
Stoned VAS	6 ± 19	45 ± 39 ^	37 ± 38 ^	78 ± 28 ^	14 ± 27	14 ± 29	24 ± 37 ^
Bad Drug Effects VAS	9 ± 23	23 ± 33 *	16 ± 30	26 ± 35 *	9 ± 21	11 ± 20	15 ± 26
Alert/	55 ± 12	57 ± 15	58 ± 15	65 ± 17	55 ± 14	54 ± 11	54 ± 11

Drowsy VAS	41 ± 17	10 ± 14 ^	26 ± 21 ^	14 ± 14 ^	33 ± 18 *	30 ± 20 *	29 ± 19 #
Agitated/ Relaxed VAS bipolar	50 ± 11 38 ± 19	54 ± 14 9 ± 13 ^	52 ± 14 22 ± 20 ^	58 ± 16 14 ± 16 ^	52 ± 12 34 ± 21	52 ± 9 32 ± 21	53 ± 10 29 ± 21 *
Any Drug Effect VAS bipolar	18 ± 31	75 ± 26 ^	55 ± 38 ^	87 ± 17 ^	23 ± 32	34 ± 36 *	46 ± 39 ^
Hallucinations VAS	1 ± 2	18 ± 29 ^	3 ± 11	15 ± 34 *	1 ± 2	1 ± 2	1 ± 3
Bowdle (Internal Perception) VAS	1 ± 0	1 ± 0 ^	1 ± 0 *	1 ± 0 ^	1 ± 0	1 ± 0	1 ± 0
Bowdle(External Perception) VAS	1 ± 0	1 ± 0 ^	1 ± 0	1 ± 1 ^	1 ± 0	1 ± 0	1 ± 0
Drug ID: Benzodiazepine	12 ± 27	<b>88 ± 24</b>	27 ± 39	29 ± 39	21 ± 35	23 ± 36	27 ± 36
Drug ID: THC	9 ± 24	24 ± 35	<b>58 ± 44</b>	<b>91 ± 22</b>	20 ± 33	18 ± 29	28 ± 37
Drug ID: Placebo	<b>71 ± 44</b>	2 ± 11	27 ± 42	3 ± 17	<b>54 ± 46</b>	<b>52 ± 48</b>	36 ± 44

\* p < 0.05; #p<0.001, ^ p < 0.0001 compared to placebo

Across all study treatments, there were wide variations in responses, suggesting that the data were not normally distributed. This led to very large standard error values that were often larger than the mean values themselves. This also meant that there were great overlaps in mean/standard error values between all treatment groups on each subjective measure.

Thus, even though statistical tests showed statistically significant differences between treatment groups (see below), the mean values between CBD and placebo were typically small – and the supratherapeutic CBD responses for Drug Liking (61 and 64) were just barely outside the accepted placebo range (40-60), while the responses for Overall Drug Liking (57 and 60) were inside the placebo range.

#### Statistical Analysis of Subjective Measures

As stated above, the primary measure of Drug Liking, as well as the secondary measures Overall Drug Liking, Good Drug Effects, and Take Drug Again were evaluated for statistically significant differences between CBD, dronabinol, alprazolam, and placebo by Dr. Sun in the FDA Office of Biostatistics, as well as by the Sponsor. However, a statistical evaluation of all remaining secondary measures was only conducted by the Sponsor.

On the primary subjective measure of Drug Liking, the two positive control drugs, alprazolam (2 mg) and dronabinol (10 and 30 mg), produced significantly higher maximum ( $E_{\max}$ ) scores compared to placebo ( $P < 0.001$  to  $0.0001$ ) (see Table 2, above) using the Sponsor's analysis. In contrast, Dr. Sun's analysis showed that the 10 mg dose of dronabinol did not differentiate from placebo. This is not critical when at least one dose of the positive control is significantly different from placebo.

Based on the Sponsor's statistical analysis, CBD at the two highest doses (1500 and 4500 mg) produced small but statistically significantly higher  $E_{\max}$  scores on Drug Liking compared to placebo ( $P < 0.05$  for both). For the FDA analysis of CBD responses compared to placebo, Dr. Sun used the statistical test  $H_0: \mu_T - \mu_P \geq 11$ , in which the treatments are not considered to be similar if the null hypothesis is not rejected. Using this analysis, the 1500 and 4500 mg doses of CBD produced P values of 0.07 and 0.31, respectively, which shows the responses from these two doses are not similar to placebo. However, it is important to note that both these doses produced responses that were just outside the placebo range (40-60, with 50 being "neutral" on a bipolar scale of 0 to 100) and had large standard deviations. CBD at the lowest dose (750 mg) was similar to placebo on Drug Liking in the analyses conducted by the Sponsor and by Dr. Sun. Additionally, the response to any dose of CBD was statistically significantly less, in many cases substantially less, than that produced by the positive control drugs, dronabinol and alprazolam.

Results from the secondary subjective measures by the Sponsor and Dr. Sun show that:

- The positive control drugs alprazolam (2 mg) and dronabinol (10 and 30 mg) produced statistically significantly increased scores compared to placebo on other positive subjective responses such as the VAS for Overall Drug Liking, Take Drug Again, Good Drug Effects, and High.
- Using a standard statistical analysis, the Sponsor reported that CBD at the high therapeutic and supratherapeutic oral doses (1500 and 4500 mg) produced small but statistically significant increases compared to placebo in positive subjective responses such as VAS for Take Drug Again, Good Drug Effects, and High. In contrast, using Dr. Sun's statistical test (above), all three CBD doses (750, 1500, and 4500 mg) were shown to not be similar to placebo for these three subjective measures. Notably, using the standard statistical analysis, the positive subjective responses to CBD were always statistically significantly less than those produced by either alprazolam or dronabinol. However, using Dr. Sun's evaluation, the 4500 mg dose of CBD was shown to not be statistically significantly different from 10 mg dronabinol on High, with scores of 31 and 38 out of 100, respectively.
- When Take Drug Again was evaluated for CBD (750-4500 mg) on an individual basis (see below), 46-66% of subjects reported a score of 0 out of 100, indicating the subject would never be inclined to take CBD again. In contrast, the positive control drugs would be taken again by 83% of those who received 2 mg

alprazolam and 60 and 77% of those who received 10 and 30 mg dronabinol (respectively).

- Using a standard statistical analysis, the Sponsor reported that the response to CBD at any dose did not produce Overall Drug Liking that was significantly different from placebo. In contrast, Dr. Sun's analysis showed that the 4500 mg dose of CBD was shown to not be similar to placebo on this measure. However, the value reported on Overall Drug Liking for the 4500 mg dose of CBD (60 out of 100) and for placebo (50 out of 100) were both within the acceptable placebo range (40-60, bipolar scale).

### ***Individual Response Analysis***

Although CBD produced some statistical evidence of being different from placebo on certain positive subjective measures, these differences numerically were typically small and only slightly outside the acceptable placebo range. The responses to CBD were also always statistically less than those produced by 2 mg alprazolam and 30 mg dronabinol. Additionally, each of the mean values had very large standard deviations reported for each subjective measure in response to the drug treatments. Thus, CSS determined that an individual analysis would provide useful information regarding whether CBD has meaningful abuse potential.

### ***Drug Liking***

On the primary measure of "Drug Liking" (a bipolar scale), 16 of the 35 (46%) had a positive subjective response (i.e., >60, which is outside the acceptable placebo range of 40-60) to at least one of the CBD doses (750 mg, 1500 mg, or 4500 mg). However, of these 16 subjects with a positive response, 3 of them also had placebo responses that were outside the placebo range, with scores that ranged from 64 to 84. (Overall, 30 of 35 subjects (86%) had an appropriate placebo response of 40-60, regardless of CBD response).

When the 13 subjects who had a positive response and an appropriate placebo response were evaluated, 11 of them produced a score on Drug Liking after any dose of CBD that was 15 points greater than that reported for placebo (the margin used in the Qualification Phase to allow subjects to proceed to the Treatment Phase). Thus, only 11 of 35 subjects (31%) who reported a 15-point increase in "Drug Liking" in response to any dose of CBD had an appropriate placebo response.

When this is evaluated by dose, a positive response on "Drug Liking" and an appropriate placebo response was reported by 3 of 35 subjects (9%) who received 750 mg CBD, 6 of 35 subjects (17%) who received 1500 mg of CBD, and 10 of 35 subjects (29%) who received 4500 mg CBD.

In contrast, when data from the positive control drugs were evaluated, the number of subjects who had an appropriate placebo response and a "Drug Liking" response that was

> 60 included 17 of 35 subjects (50%) who received alprazolam; 21 of 35 subjects (60%) who received 10 mg dronabinol; and 28 of 35 subjects (80%) who received 30 mg dronabinol.

Thus, all doses of CBD produced positive subjective responses on “Drug Liking” in a more limited number of study subjects (9-29%) that was reported after administration of the positive controls (50% after alprazolam, 60% after 10 mg dronabinol and 80% after 30 mg dronabinol).

### *Overall Drug Liking*

On the secondary measure of “Overall Drug Liking” (a bipolar scale), 17 of 35 subjects (49%) had a positive subjective response (i.e., >60, which is outside the acceptable placebo range of 40-60) to at least one of the CBD doses (750 mg, 1500 mg, or 4500 mg). However, of these 17 subjects, 4 of them also had placebo responses that were outside the placebo range, with scores that ranged from 0 to 100. Two of these scores were in the negative range (0 to 38) and 2 were in the positive range (80 to 100). This contrasts with a much narrower range of inappropriate placebo response for “Drug Liking”, where all 3 of the responses were in the positive range (64 to 84). (Overall, 29 of 35 subjects (83%) had an appropriate placebo response of 40-60, regardless of CBD response).

When the 13 subjects who had had a positive response and an appropriate placebo response were evaluated, 12 of them (92%) produced a score on “Overall Drug Liking” after any dose of CBD that was 15 points greater than that reported for placebo (the standard used in the Qualification Phase to allow subjects to proceed to the Treatment Phase). Thus, only 12 of 35 subjects (34%) who reported a 15-point increase in “Overall Drug Liking” in response to any dose of CBD had an appropriate placebo response.

When this is evaluated by dose, a positive response on “Overall Drug Liking” and an appropriate placebo response was reported by 2 of 35 subjects (6%) who received 750 mg CBD, 5 of 35 subjects (14%) who received 1500 mg of CBD, and 10 of 35 subjects (29%) who received 4500 mg CBD. These results are similar to those reported for “Drug Liking” (9%, 17%, 29%, respectively by dose).

In contrast, when data from the positive control drugs were evaluated, the number of subjects who had an appropriate placebo response and a “Overall Drug Liking” response that was > 60, included 26 of 35 subjects (74%) who received alprazolam; 18 of 35 subjects (51%) who received 10 mg dronabinol; and 24 of 35 subjects (69%) who received 30 mg dronabinol. These “Overall Drug Liking” results are slightly higher than those reported for “Drug Liking” after administration of alprazolam (50%) but slightly lower than that reported following 10 mg dronabinol (60%) and 30 mg dronabinol (80%).

Thus, all doses of CBD produced positive subjective responses on “Overall Drug Liking” in a more limited number of study subjects (6-29%) that was reported after administration

of the positive controls (74% after alprazolam, 51% after 10 mg dronabinol and 69% after 30 mg dronabinol).

### *Take Drug Again*

On the secondary measure of “Take Drug Again” (a unipolar scale), 20 of 35 subjects (57%) reported a score of >20 (outside the acceptable placebo range of 0-20) to at least one of the CBD doses (750 mg, 1500 mg, or 4500 mg). However, of these 20 subjects, 6 of them also had placebo responses that were outside the placebo range, with scores that ranged from 33 to 100. (Overall, 29 of 35 subjects (83%) had an appropriate placebo response <20, regardless of CBD response).

When the “Take Drug Again” data are evaluated by CBD dose, those indicating they would take the drug again (score of >50) and had an appropriate placebo score was reported by 8 of 35 subjects (23%) who received 750 mg CBD, 8 of 35 subjects (23%) who received 1500 mg of CBD, and 14 of 35 subjects (40%) who received 4500 mg CBD.

Conversely, a large percent of subjects who received CBD indicated they were not inclined to ever take it again by providing a score of 0 out of 100: 21 of 35 subjects (60%) who received 750 mg CBD, 21 of 35 subjects (60%) who received 1500 mg of CBD, and 15 of 35 subjects (43%) who received 4500 mg CBD.

When data from the positive control drugs were evaluated, the number of subjects who had an appropriate placebo response and indicated they would “Take Drug Again” (score of >20), included 29 of 35 subjects (83%) who received alprazolam; 21 of 35 subjects (60%) who received 10 mg dronabinol; and 27 of 35 subjects (77%) who received 30 mg dronabinol.

Thus, all doses of CBD produced positive subjective responses on “Take Drug Again” in a more limited number of study subjects (23-40%) than was reported after administration of the positive controls (83% after alprazolam, 60% after 10 mg dronabinol and 77% after 30 mg dronabinol). More importantly, a significant percent of subjects who received CBD indicated they would never want to take the drug again (43-60%).

### ***Drug Identification***

On the Drug Identification question:

- Alprazolam (2 mg) was identified as a benzodiazepine (88 out of 100).
- Dronabinol (10 and 30 mg) was identified as THC (58 and 91 out of 100).
- Placebo was identified as placebo (71 out of 100).
- CBD did not produce a strong signal for any substance except for placebo in response to the 750 and 1500 mg doses (54 and 52 out of 100).
- CBD at 4500 mg was not identified as any substance (<36 out of 100 on any scale) and was notably not identified as dronabinol.

This lack of identification of CBD as similar to dronabinol by human subjects parallels the animal drug discrimination data, where animals did not indicate that CBD produced THC-like sensations.

### Adverse Events

As provided in the Sponsor's study report, CBD (750, 1500 and 4500 mg) produced reports of the AE euphoria in a few subjects (5.3% (2 of 38 subjects); 5.1% (2 of 39 subjects), 7.5% (3 of 40 subjects), respectively) (see Table 3, below). Alprazolam (2 mg) produced a similarly low level of euphoria (7.5%, 3 of 40 subjects), while placebo produced no reports of euphoria (0%, 0 of 37 subjects). In contrast, dronabinol (10 and 30 mg) produced higher levels of euphoria (30.8% (12 of 39 subjects) and 62.5% (25 of 40 subjects)).

<b>Table 3: Treatment-related Adverse Events With <math>\geq</math> 5% Incidence Following Administration of Oral Placebo, Alprazolam (2 mg), Dronabinol (DRO, 10 and 30 mg), and CBD (750, 1500, and 4500 mg)</b>							
	<b>Treatment at Onset of Adverse Event</b>						
	<b>Placebo (N=37)</b>	<b>ALP 2 mg (N=40)</b>	<b>DRO 10 mg (N=39)</b>	<b>DRO 30 mg (N=40)</b>	<b>CBD 750 mg (N=38)</b>	<b>CBD 1500 mg (N=39)</b>	<b>CBD 4500 mg (N=40)</b>
<b>Psychiatric</b>							
Euphoric mood	0	3 (8%)	12 (1%)	25 (63%)	2 (5%)	2 (5%)	3 (8%)
<b>Nervous system</b>							
Somnolence	8 (22%)	35 (88%)	14 (36%)	22 (55%)	9 (24%)	12 (31%)	12 (30%)
Headache	3 (8%)	2 (5%)	5 (13%)	4 (10%)	5 (13%)	7 (18%)	3 (8%)
<b>Gastrointestinal</b>							
Nausea	4 (11%)	0	6 (15%)	7 (18%)	2 (5%)	4 (10%)	3 (8%)
Diarrhea	0	0	2 (5%)	0	1 (3%)	4 (10%)	8 (20%)
Dry mouth	0	0	3 (8%)	8 (20%)	1 (3%)	1 (3%)	1 (3%)
Abdominal pain	0	0	2 (5.1%)	1 (3%)	0	1 (3%)	4 (10%)
<b>General</b>							
Fatigue	2 (5%)	7 (18%)	3 (8%)	5 (13%)	2 (5%)	2 (5%)	2 (5%)
Relaxation	1 (3%)	5 (13%)	0	2 (5%)	0	1 (3%)	2 (5%)
Feeling	1 (3%)	1 (3%)	1 (3%)	2 (5%)	0	0	2 (5%)

When an individual analysis was conducted on CBD responses, a euphoria-related response for most subjects either did not predict whether the individual reported positive responses on the subjective measures, or the positive subjective response was equivalent to that reported following placebo. Conversely, a high rating on a positive subjective response by any subject did not predict a report of a euphoria-related AE. Thus, although two of the nine subjects who reported euphoria as an AE following 4500 mg CBD also reported a high degree of positive subjective response on Drug Liking or Take Drug Again, seven of the nine subjects did not. Thus, the small degree of euphoria signals following CBD administration were not consistent with any other reports of positive subjective responses to the drug.

The rate of somnolence from CBD ranged from 24-31% (n = 9-12 from 38-40 subjects at each dose), which is similar to that from placebo (22%, n = 8 of 37 subjects) and the low dose of dronabinol (36%, n = 14 of 39 subjects), but lower than that produced by the high dose of dronabinol (55%, n = 22 of 40 subjects) and by alprazolam (88%, n = 35 of 40 subjects). However, in the absence of “euphoria”-like AEs, “somnolence” is not interpreted as producing an abuse-related signal. None of the other AEs reported are signals of abuse potential.

### *Pharmacokinetics*

As reported by the Sponsor in the study report (Table 8.5.2.3.2.1), the  $C_{\max}$  values of CBD did not increase proportionally, despite 6-fold increases in CBD dose from 750 mg to 4500 mg. Instead, there was very little variation in plasma levels no matter which dose of CBD was administered. As was seen in Study #1544 (section C.2), the half-life of CBD in the HAP study ranges from 4-6 hours.

<b>Pharmacokinetic Parameters of CBD and THC (Data from Table 8.5.2.3.2.1)</b>			
<b>Analyte &amp; Pharmacokinetic Parameter</b>	<b>CBD 750 mg (N=38)</b>	<b>CBD 1500 mg (N=39)</b>	<b>CBD 4500 mg (N=40)</b>
<b>CBD</b>			
$C_{\max}$ (ng/mL)	336.2 (46.7)	524.5 (64.9)	426.9 (112.8)
$T_{\max}$ (h)	5.11 (2.18–8.23)	6.13 (3.13–8.17)	4.07 (2.15–12.20)
$t_{1/2}$ (h)	4.1 (83.2)	4.5 (50.2)	5.6 (47.6)
<b>THC</b>			
$C_{\max}$ (ng/mL)	0.27 (46.5)	0.38 (55.1)	0.40 (64.5)
$T_{\max}$ (h)	6.2 (3.15–12.18)	6.1 (2.17–6.22)	4.1 (2.2–12.2)
$t_{1/2}$ (h)	10.8 (57.0)	7.6 (86.3)	10.2 (98.8)

Similarly, the  $C_{\max}$  values of THC did not increase proportionally, and in fact showed very little variation in plasma levels no matter which dose of CBD was administered.

### *Subjective Responses in Relation to Residual THC Levels*

The CBD product studied in all clinical investigations contained <0.15% residual THC. In the HAP study, the CBD batches used contained 0.03% and 0.06% residual THC. This means that the amount of THC present in the test doses ranged from 0.3-0.45 mg (750 mg CBD) to 0.45-0.90 mg (1500 mg CBD) to 1.35-2.70 mg (4500 mg CBD). The lowest FDA-approved dose of dronabinol in the Marinol drug product (Schedule III) is 2.5 mg. Thus, it is possible that THC may have contributed to the subjective responses following CBD administration.

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

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

### Overall Conclusions

In this HAP study, the 750 mg dose of CBD (the low 10 mg/kg therapeutic dose) did not produce abuse potential signals. Although the two higher doses of CBD tested in this study (1500 and 4500 mg, representing the 20 mg/kg therapeutic dose and a supratherapeutic dose) produced some signals of abuse potential, they were small and often inside or just outside the acceptable placebo range. Additionally, these signals were always statistically significantly less, and often substantially less, than those produced by dronabinol or alprazolam. In a drug identification test, CBD at any dose was not identified as dronabinol and was most frequently identified as placebo. The low degree of the AE of euphoria produced by the higher doses of CBD did not predict reports of positive subjective responses. Thus, these data show that although CBD is a cannabinoid, it is not producing dronabinol-like responses that are indicative of abuse potential.

## 2. Abuse-Related Adverse Events in Clinical Studies

### i. Phase 1 Clinical Safety Studies (Excluding HAP Study)

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

None of the individuals in these Phase 1 studies with CBD reported that they experienced “euphoria”-related AEs, which are the key AEs in determining whether there are abuse-related signals from clinical studies.

There was a high rate of “somnolence” in the two pharmacokinetic studies. In one study, 750 and 1500 mg CBD produced “somnolence” in 2-4 of 9 subjects (22-44%) compared to 2 of 9 subjects (33%) from placebo. In the other study, 750 and 4500 mg CBD produced “somnolence” in 5-11 of 49 subjects (10-22%) compared to 4 of 50 subjects (8%) from placebo. However, in the absence of “euphoria”-like AEs, “somnolence” is not interpreted as producing an abuse-related signal. Interestingly, no subjects in the

sleep study (n = 18) reported “somnolence” in response to CBD or placebo. No other AEs that can be indicative of abuse were reported in any of these studies.

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

### ii. Phase 2/3 Clinical Efficacy Studies

Three Phase 2/3 clinical studies were conducted to support the efficacy and safety claim for CBD as an adjunct treatment of two epilepsy conditions in children: Dravet syndrome (also known as severe myoclonic epilepsy of infancy; (b) (4)) and Lennox-Gastaut syndrome (b) (4).

It is not possible to evaluate these Phase 2/3 studies for abuse signals related to CBD because of the underlying neurological impairment of patients and the confounding effects of other medications. Specifically, the children in the studies are too ill or too young to volunteer accurate information regarding psychiatric or neurological AEs indicative of abuse potential. Additionally, since CBD is proposed as an adjunctive treatment, children in these studies remained on their current antiepileptic medications.

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

### 3. Assessment of Human Physical Dependence (Study #GWEP1542)

A randomized, two-phase clinical study was conducted to assess the ability of CBD to produce physical dependence in an outpatient design. The Sponsor characterizes this as an “exploratory trial”, so they did not conduct prospective calculations of statistical power to determine sample size. This led to a very small sample size ( $\leq 12$  subjects per withdrawal condition).

The first single-blind phase consisted of a total of 30 subjects (n = 13 female) who received 1500 mg/day (750 mg b.i.d.) CBD for 4 weeks. In the second double-blind phase, subjects who completed the first phase (n = 21) were randomized to either continue receiving 1500 mg/day (750 mg b.i.d.) CBD for an additional 2 weeks (n = 9) or to receive placebo (n = 12). There was no positive control to validate the study procedures.

Subjects were healthy male and female subjects aged 18-45 years (inclusive), with a body mass index (BMI) of 18-28. During the 6-week study period, subjects returned to the clinical research center on Days 7, 14, 21, 28, 31, 35, and 42 for evaluations. Compliance was assessed by plasma concentrations of CBD and THC and their major metabolites.

Subjects were required to refrain from using medications (prescribed and OTC), dietary supplements, cannabinoids and tobacco during the study, but were allowed to use alcohol

as long as they stopped “before each clinic visit”, when they would receive blood draws and other intermediate evaluations. Although subjects were tested for drugs and alcohol on weekly visits during the initial 28 days of CBD administration, they were not tested again during the discontinuation period (Days 29-42) until Day 35.

Safety evaluations included the following:

- Incidence, type and severity of AEs (phone calls twice daily plus subject diary)
- Vital signs (baseline, Days 1, 7, 14, 21, 35, and 42)
- 12-lead electrocardiogram (ECG) (baseline, Days 1, 7, 14, 21, 35, and 42)
- Clinical laboratory parameters (baseline, Days 7, 14, 21, 35, and 42)
- Physical examination (screening)
- Sleep disruption scale and Epworth Sleepiness Scale (baseline, Days 1, 7, 14, 21, 35, and 42)
- Columbia-Suicide Severity Rating Scale (baseline, Days 7, 14, 21, 35, and 42)
- Hamilton Depression Rating Scale (baseline, Days 1, 7, 14, 21, 35, and 42)

Physical dependence was evaluated using two scales: the Cannabis Withdrawal Scale (CWS) and the Penn Physician Withdrawal Checklist (PWC-20). These two questionnaires were administered on Days 1, 21 and 28 during CBD administration, as well as Days 31, 35 and 42 after drug discontinuation (e.g., Days 3, 7, and 14 following completion of the 28 days of CBD administration) to capture withdrawal symptoms. Subjects were asked to indicate the extent to which each withdrawal symptom was experienced in the last 24 hours and also to rate the negative impact on normal daily activities. During drug administration, the questionnaires were completed 3-5 hours after the morning dose on ambulatory visits.

Possible CWS scores range from 0 to 190 points (0-10 points for 19 questions) for both withdrawal symptoms and (separately) for impact on daily living. After 28 days of CBD administration, the CWS score for all completers (n = 23) was 9.3 on the questionnaire and 5.8 for the daily negative impact. During the second phase, withdrawal scores in both groups decreased such that the CBD group had scores on the CWS that decreased from baseline (Day 28) by up to 6 points and the placebo group had scores that decreased by up to 4 points. A similar reduction in scores were seen for the impact on daily living scores, which decreased from baseline (Day 28) for the CBD group by up to 9 points and the placebo group had scores that decreased by up to 6 points.

Possible PWC-20 scores range from 0–60 points (0-3 points for 20 questions) for withdrawal symptoms. The scores for both groups were close to 0 during and immediately after 28 days of CBD administration. As observed with the CWS, withdrawal scores during the second phase decreased from baseline (Day 28) for the CBD group by up to 0.8 points and the placebo group had scores that decreased by up to 1.3 points.

### Other Subjective Measures

There were no changes recorded during discontinuation from CBD compared to CBD maintenance for evaluations on sleep disruption, Epworth Sleepiness Scale (ESS), Columbia-Suicide Severity Rating Scale (C-SSRS), or the Hamilton Depression Rating Scale (HAM-D).

### Adverse Events

During the physical dependence study, AEs were monitored both during CBD administration and after drug discontinuation.

<b>Table 4 All Causality TEAEs Experienced by &gt; 1 Subject</b>			
	<b>Part 1</b>	<b>Part 2</b>	
	<b>1500 mg/day CBD 28 days (n=30)</b>	<b>1500 mg/day CBD 14 days (n=9)</b>	<b>Placebo 14 days (n=12)</b>
	<b>n (%)</b>	<b>n (%)</b>	
<b>Gastrointestinal</b>			
Diarrhea	19 (63.3)	4 (44.4)	2 (16.7)
Abdominal pain	14 (46.7)	0 (0)	1 (8.3)
Nausea	13 (43.3)	2 (22.2)	0 (0)
Dyspepsia	4 (13.3)	0 (0)	0 (0)
Dry mouth	2 (6.7)	0 (0)	0 (0)
<b>Nervous system</b>			
Headache	15 (50.0)	2 (22.2)	7 (58.3)
Somnolence	7 (23.3)	1 (11.1)	0 (0)
Dizziness	7 (23.3)	0 (0)	0 (0)
Disturbance in attention	2 (6.7)	0 (0)	0 (0)
Dizziness postural	2 (6.7)	0 (0)	0 (0)
<b>General disorders</b>			
Fatigue	10 (33.3)	0 (0)	0 (0)
Influenza-like illness	2 (6.7)	0 (0)	1 (8.3)
<b>Psychiatric disorders</b>			
Nightmare	2 (6.7)	0 (0)	1 (8.3)
Insomnia	2 (6.7)	0 (0)	0 (0)
Mood altered	1 (3.3)	1 (11.1)	0 (0)

Adverse events reported during CBD administration included diarrhea (63%), abdominal pain (47%), nausea (43%), headache (50%), somnolence and fatigue (23% and 33%), dizziness (23%), and insomnia (7%). Notably for an abuse potential evaluation, there were no reported incidents of euphoria during the CBD administration phase.

During the drug discontinuation phase, there was only one adverse event for which the incidence was higher in the placebo group than the continued CBD administration group: headache was reported in 7 of 12 subjects (58%) who received placebo compared to 2 of 9 subjects (22%) who continued to receive CBD.

### Pharmacokinetics of CBD and THC

As expected, CBD levels in subjects who transitioned to placebo fell steadily over the discontinuation period and reached nearly predose levels by Day 42. In contrast, CBD levels continued to increase for subjects who were maintained on CBD.

The Sponsor reported that inter-subject variability was high, with standard deviations of the mean CBD plasma concentrations during the study ranging from 17 to 306 ng/ml. The concentration–time profiles of the major metabolites of CBD showed a similar pattern.

THC and its major metabolites were detected only at trace levels, with the mean plasma THC concentration on Day 42 in Arm 1 reaching 0.4 ng/ml (range: 0.1-1.0 ng/ml).

### Conclusions

CSS provided feedback to the Sponsor regarding the design of this study prior to its initiation and instructed the Sponsor to evaluate withdrawal signs and symptoms “at least daily for the first 5 days of the discontinuation phase”, based on the presumption that “withdrawal symptoms should be most prominent immediately following drug cessation” because the half-life of CBD is ~9 hours.

However, the Sponsor conducted the first assessment of withdrawal 3 days after CBD discontinuation. Thus, although the data show little evidence of withdrawal, it is not possible to conclude that CBD does not produce physical dependence from this study. The most circumspect conclusion is that if CBD produces a withdrawal syndrome, it has subsided by 3 days after drug discontinuation. The interpretation of this study is further complicated by the fact that there is no positive control to validate the procedures for producing withdrawal symptoms.

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/s/  
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KATHERINE R BONSON  
05/07/2018

SILVIA N CALDERON  
05/07/2018

DOMINIC CHIAPPERINO  
05/07/2018

## HUMAN FACTORS RESULTS 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\*\*\***

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<b>Date of This Review:</b>	April 27, 2018
<b>Requesting Office or Division:</b>	Division of Neurology Products (DNP)
<b>Application Type and Number:</b>	NDA 210365
<b>Product Name and Strength:</b>	Epidiolex (cannabidiol) oral solution, 100 mg/mL
<b>Product Type:</b>	Single-Ingredient Product
<b>Rx or OTC:</b>	Rx
<b>Applicant/Sponsor Name:</b>	GW Research Ltd
<b>Submission Date:</b>	August 4, 2017, October 26, 2017
<b>OSE RCM #:</b>	2018-114 and 2018-898
<b>DMEPA Safety Evaluator:</b>	Briana Rider, PharmD
<b>DMEPA Team Leader:</b>	Lolita White, PharmD
<b>DMEPA Associate Director for Human Factors:</b>	QuynhNhu Nguyen, MS
<b>DMEPA Deputy Director :</b>	Danielle Harris, PharmD, BCPS

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## **1 REASON FOR REVIEW**

This review is in response to a consultation request from the Division of Neurology Products (DNP) to review the Human Factors (HF) validation study results for cannabidiol (CBD) 100 mg/mL oral solution to determine if the validation data adequately supports the safe and effective use of the product. In addition, we reviewed the proposed labels, labeling, and device design for areas of vulnerability that may lead to medication error.

### **1.1 PRODUCT INFORMATION**

The proposed combination product is intended for at-home twice daily oral administration by a caregiver for adjunctive treatment of seizures associated with Dravet Syndrome (DS) and seizures associated with Lennox-Gastaut Syndrome (LGS). The product is provided in a carton containing:

- One (b) (4) mL glass bottle
- One bottle adapter
- Two 5 mL oral syringes
- One Instructions for Use (IFU)
- One Prescribing Information (PI)/Medication Guide (MG)

### **1.2 REGULATORY HISTORY**

As part of their August 12, 2015 Type C Chemistry, Manufacturing, and Controls (CMC) meeting for IND 120055, GW Research Ltd submitted their use-related risk analysis and rationale for not conducting a HF validation study. During the meeting, DMEPA disagreed with the Sponsor's risk assessment and identified several medication safety concerns with the proposed 1 mL and 5 mL oral syringes (see Appendix B). DMEPA noted that the Sponsor's proposed risk mitigation strategies rely heavily upon the information provided in the IFU and recommended that the Sponsor conduct a HF validation study to assess whether the IFU and other mitigation strategies effectively reduce the identified risks to an acceptable level.

On February 19, 2016, GW Research Ltd submitted an updated use-related risk analysis and a HF validation study protocol to the Agency for review under IND 120055. Within their submission, the Sponsor also detailed actions undertaken to address the medication safety concerns previously raised by DMEPA, including the elimination of the 1 mL oral syringe.

DMEPA noted deficiencies in their April 11, 2016 review of the Sponsor proposed HF validation study protocol and provided recommendations to be implemented prior to conducting the HF validation study.

On August 4, 2017 GW Research Ltd submitted the results of their HF validation study under NDA 210365 as part of their rolling submission.

## **2 MATERIALS REVIEWED**

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

<b>Table 1. Materials Considered for this Label and Labeling Review</b>	
<b>Material Reviewed</b>	<b>Appendix Section (for Methods and Results)</b>
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C
ISMP Newsletters	D – N/A
FDA Adverse Event Reporting System (FAERS)*	E – N/A
Information Requests Issued During the Review	F
Labels and Labeling	G

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 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED**

#### **3.1 HUMAN FACTORS VALIDATION STUDY DESIGN**

The objective of this Human Factors (HF) Validation Study was to demonstrate that the user interface is designed to ensure safe and effective use by the intended users in the intended use environment.

The HF validation study design methodology includes forty-eight untrained representative personal caregivers and vocational caregivers, including 15 oral syringe-experienced personal caregivers (PC), 15 oral syringe-naïve personal caregivers (NC), and 18 vocational caregivers (VC). According to the Sponsor, patients with Dravet Syndrome (DS) and Lennox Gastaut Syndrome (LGS) are unable to self-administer due to “intellectual impairment” and therefore are not intended users. The simulated use testing consisted of the following elements: simulated use scenario<sup>1</sup>, simulated titration scenario<sup>2</sup>, knowledge-based test of the IFU, and post-test interview. The user groups and use scenarios are representative of real world use. As such, we agree with the user groups and methodology used in the study (see Appendix C).

During the simulated use scenario, the Sponsor evaluated the two critical tasks (push the bottle adapter firmly into the bottle, and screw the child resistant cap back on the bottle) and 10 essential tasks (see below for Sponsor’s categorization of tasks).

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<sup>1</sup> Participants were required to prepare one dose of CBD 100 mg/mL oral solution and then clean the syringe as though preparing it for the next use.

<sup>2</sup> Participants were asked to prepare some doses that increase in amount. In real use, the dose titration will be determined by the health care provider, so this simulated representation aims to demonstrate that participants can prepare a range of doses.

<b>Sponsor's Task Categorization</b>	
Remove items from secondary packaging	Essential
Remove the child resistant cap	Essential
Push bottle adapter firmly into bottle	Critical
Insert the tip of syringe into the adapter	Essential
Turn the bottle and syringe upside down	Essential
Pull the plunger to measure the dose and check for air bubble	Essential**
Turn the bottle right side up and remove syringe	Essential
Place the tip of syringe in patients mouth and gently push plunger to release drug	Essential
Screw the cap back on the bottle. Do not remove bottle adapter	Critical
Fill a cup with soapy water and clean syringe	Essential
Remove the plunger from the barrel of the oral syringe and rinse with tap water	Essential
Shake off excess water and allow to air dry	Essential

\*\*We disagree with Sponsor's categorization of this task

However, we disagree with the Sponsor's categorization of the dose measurement task as essential. Therefore, we have recategorized this task and evaluated it as a critical task.

### **3.2 HUMAN FACTORS VALIDATION STUDY RESULTS AND ANALYSIS**

Failures observed in the HF Validation Study involved nine essential tasks and two critical tasks.

The Applicant provided their assessment of each of the use errors observed with essential tasks, including the subjective feedback, root cause analysis and their proposed mitigations. Details for these essential task failures may be found in the submission (See Appendix C). We reviewed the Sponsor's assessment and evaluated the use errors and difficulties pertaining to the nine essential tasks for risk of medication error. We agree with the Sponsor that no additional mitigation strategies are necessary for the essential tasks, and we determined that the residual risk is acceptable.

Our assessment of the failures observed during the critical tasks of pushing the bottle adapter firmly into the bottle and dose measurement are discussed in Table 2 and Table 3 below, respectively. A summary of the results, the Sponsor's provided root cause analysis and justification for no additional mitigation strategies is also provided in Table 2 and Table 3, along with our assessment.

**Table 2. Summary and Analysis of Critical Task Use Errors and Close Calls**

<b>Task Description</b>	<b>Number of Use Errors and Description of Use Errors/Subjective Feedback on First Attempt</b>	<b>Number and Description of Close Calls on First Attempt</b>	<b>Applicant's Root Cause Analysis</b>	<b>Applicant's Mitigation Strategies</b>	<b>DMEPA's Analysis and Recommendation</b>
Push the bottle adapter firmly into the bottle	<p><u>4 use errors</u></p> <ol style="list-style-type: none"> <li>1. PC did not insert adapter at first attempt. Not using IFU but did so at second attempt</li> <li>2. PC had initially not inserted bottle adapter at first attempt. Fitted the second time when using IFU but did not press into the bottle at first.</li> <li>3. PC did not use IFU and said that did not see the bottle adapter.</li> <li>4. VC did not insert adapter and drew and gave dose.</li> </ol>	<p><u>2 close calls</u></p> <ul style="list-style-type: none"> <li>• VC placed on top of bottle and did not insert fully into the bottle. Corrected this once it had leaked.</li> <li>• CV did not insert adapter, drew dose, saw adapter and wondered what it was and then looked at IFU and realized.</li> </ul>	<ul style="list-style-type: none"> <li>• Did not read the IFU</li> <li>• Prior experience with similar devices</li> <li>• Lack of focus during the task</li> <li>• Overlooked the step in the IFU</li> <li>• Perception</li> </ul>	<p>No further mitigation is required. No instances led to a scenario where the bottle adapter remained at the end of the syringe and could lead to choking. Participants who did not use the bottle adapter were able to successfully withdraw the dose from the bottle. When they referred to the IFU, all were able to successfully push the bottle adapter firmly into the bottle.</p>	<p>Failure to push the bottle adapter firmly into the bottle could lead to choking if it remains at the end of the syringe and given to a child at the dosing stage or could lead to spillage. Our review of the study results did not identify any instances which led to a scenario where the bottle adapter remained at the end of the syringe and could lead to choking. We also find that these risks are not unique to this product and exist with other oral liquid medications that are co-packaged with a bottle adapter.</p> <p>Our review of the instructions for adapter insertion and the participant subjective feedback finds the instructions are acceptable. In particular, we find the IFU instructions are prominent and provide clear instruction to, 'Push the bottle adapter firmly into the bottle'. The instruction is accompanied</p>


					<p>by a figure illustrating how to push the bottle adapter into the bottle opening. Furthermore, <sup>(b) (4)</sup></p>  <p>We agree that no additional mitigation is required to address risk of the failure to push the bottle adapter firmly into the bottle.</p>
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Table 3 below summarizes and focuses on the results observed with the critical dose measurement task that was evaluated in the HF Validation Study along with the Sponsor's provided root cause analysis and justification for no additional mitigation strategies. The table also includes our assessment of the failures associated with the critical dose measurement task. Each participant simulated the measurement of four different doses during the dose measurement task. Each participant was assigned 0.1 mL for their first dose (n = 49) and 9 mL for their fourth dose (n = 49). Participants were randomized to measure either 1.5 mL (n = 24) or 3.7 mL (n = 25) for their second dose and either 5.2 mL (n = 26) or 7.5 mL (n = 23) for their third dose. The following failures were observed during participants' first attempt at the following doses:

- 0.1 mL: 12 failures
- 1.5 mL: 1 failure
- 3.7 mL: 1 failure
- 5.2 mL: 1 failure
- 7.5 mL: 2 failures
- 9 mL: 1 failure

Table 3. Summary and Analysis of Failures Associated with Dose Measurement Task						
Dose	User	Description of use errors/close calls/use difficulties	Subjective Feedback	Applicant's Root Cause Analysis	Applicant's Rationale for no Additional Mitigations	DMEPA's Analysis and Recommendation
0.1 mL	PC04	Initially drew 1 mL (although had identified 0.1 mL on the syringe). Then drew 5 mL and at third attempt drew 0.1 mL.	Said that struggled to see the medication in the syringe with the small dose. Mentioned that thought it was a very small dose.	Action and Cognition. Read and understood the correct dose amount but struggled to draw the dose required partially because the participant thought it was such as small amount.	<ul style="list-style-type: none"> <li>• Graduations are clearly numbered at each 0.5 mL interval and labeling them at each 0.1 mL graduation would create a crowded interface and would cause even more difficulties in dose</li> </ul>	Our review of the HF validation results identified twelve participants who experienced use errors measuring the 0.1 mL dose. Ten participants mistakenly measured 1 mL, resulting in a 10-fold overdose. At the time of conducting the HF validation study, 0.1 mL was the lowest expected starting dose. However, the lowest

	PC05	Pushed air into bottle at first attempt and adapter came out with liquid leaking. Drew out 0.5 mL. Drew 0.1 mL on third attempt.	First attempt – participant said that they were following what was in IFU (not referring to pharmacy label and didn't understand where the pharmacy label was). Second attempt – said that they were confused by the numbers.	First attempt – Perception. Followed IFU exactly, did not realize that this was an example not the actual dose. Second attempt – cognition. Said that they were confused by the numbers. Participant's own understanding of the decimal point – 1 mL and 0.1 mL.	<p>measurements. So, no further changes are proposed.</p> <ul style="list-style-type: none"> <li>The ability of caregivers and patients to administer accurate doses of oral liquid medications in not without error in clinical practice, despite familiarity with this dosage form. Given the literature, it seems inevitable that some dosing errors will occur.</li> <li>A 10-fold overdose at the beginning of therapy still remains less than the overall target therapeutic dose.</li> <li>Healthy volunteer subjects well-tolerated the single doses in the range of 32X the highest starting dose of CBD and &gt;</li> </ul>	<p>expected starting dose for the proposed commercial product is 0.3 mL. Based on post-marketing experience, it is likely that 10-fold dosing errors may also occur with the 0.3 mL dose.</p> <p>We also note that among the twelve participants who experienced use errors, seven participants demonstrated an ability to identify the error, self correct, and successfully completed the task upon second attempt and the remaining five participants successfully completed the task upon third attempt, illustrating a learned effect.</p> <p>The Sponsor has determined that a 10-fold overdose would not cause serious harm to the proposed patient population (see Appendix F, response to Information Request #2) and categorized the severity of harm as minor. We consulted with the medical officer (MO) and confirmed that 10-fold overdoses are</p>
	PC09	Drew 1 mL as though this was the correct dose. Drew 0.1 mL dose at second attempt.	Initially said that thought 1 mL was the dose. When asked again did not know why had thought that as could read 0.1 mL.	Perception. Thought 1 mL was the correct dose but was not sure why she had thought this.		
	PC12	First attempt – drew 5 mL (approx.). Second attempt – drew 1 mL.	Said that 5 mg was dose that gave patient at home. (Also said this when asked about 1 mL dose).	Perception and Cognition – participant did not appear to be reading information and carrying out instructions. Mentioned the		

				patient they cared for had died recently and was on participant's mind while performing the tasks.		
	PC13	Drew 1 mL at both attempts although had correctly read aloud 0.1 mL on the pharmacy label and understood that to be the dose. When asked at end of session could correctly identify 0.1 mL marking on the syringe.	Said that was used to smaller syringes and unsure of measurement and so drew down to 1 mL.	Cognition – participant did not clearly understand how the dose would look in the syringe although they could understand the dose amount on the pharmacy label.		
	VC02	Drew 1 mL dose initially.	Participant said that not thinking too well and knew the dose was 0.1 mL, just did not put thoughts into action.	Action. Knew the correct dose to draw but did not put thoughts into action.		
	VC15	Drew 0.1 mL but syringe full of air. Did this twice. Drew 0.1 mL at third attempt.	Participant said that she was nervous and this added to the confusion.	Cognition. Re-read section 3 of IFU at the end of session and said that instructions were clear and it was the participant's own confusion. Also said that as a caregiver	<p>8X the expected daily dose without significant safety concerns. Similar AEs were recorded for multiple doses up to twice the expected daily dose.</p> <ul style="list-style-type: none"> <li>From the safety profile observed in patients with Dravet Syndrome/Lennox-Gastaut Syndrome to date, there does not appear to be a serious risk to patients who may incorrectly dose CBD 100 mg/mL oral solution and the benefit-risk remains favorable.</li> <li>The lowest dose tested in the validation study was 0.1 mL. However, the lowest expected starting dose for the proposed commercial</li> </ul>	<p>not expected to cause serious harm to patients. The MO's assessment is based on the greater clearance in younger patients (in whom the greater overdoses would be more likely to occur) and that 8X the expected daily dose has been administered (single doses) to healthy adult volunteers with no significant adverse events reported. Based on the Sponsors assessment, the information provided by the MO, and the learned effect demonstrated in the study, we find the residual risk is acceptable for this product.</p> <p>However, we have identified one aspect of the user interface that can be optimized to further decrease the risk of 10-fold overdose errors for prescribed doses less than 1 mL. Step 5 in the Instructions for Use (IFU) states "Slowly pull the plunger of the oral syringe to draw the (b) (4). We are concerned</p>

				would normally double check dose, which hadn't done today. Said she was nervous.		
	VC16	Drew 1 mL at first attempt. 0.1 mL at second attempt.	Could correctly identify different amounts.	Cognition. Said that own confusion as to why they had drawn down 1 mL initially as could correctly identify that the pharmacy label was 0.1 mL. Gives 1 mL dose to one of their patients.		
	VC17	Drew 1 mL at first attempt. Second attempt – 0.1 mL.	Said that thinking about insulin injections and got caught up in the dosage and markings on the syringe. Said that she was nervous.	Cognition. Participant knew what they had to do but thinking of past experience and other syringes. Also mentioned that nervous.		
	VC18	First attempt drew 1 mL and then changed to 0.5 mL. Second attempt drew 1 mL and then self-corrected to 0.1 mL.	Confused by scale/markings on the syringe initially and thought it started at 0.5 mL.	Perception. Participant did not initially read/understood the markings on the syringe.		
	NC04	Drew 1 mL dose initially. Drew 0.1 mL second attempt.	Participant said that she had been reading	Perception – participant reading	<ul style="list-style-type: none"> <li>product is 0.3 mL.</li> <li>The pharmacokinetics of CBD are nonlinear and are characterized by lower relative bioavailability as dose is increased, particularly at supra-therapeutic doses. This would have the effect of reducing the impact of an accidental overdose. From a healthy volunteer study, the nonlinearity observed estimates that an increase of 10-fold would lead to just a 5.4-fold increased <math>C_{max}</math>.</li> <li>In the youngest children, where the potential impact of an accidental overdose would be most likely, the</li> </ul>	that this statement may be misleading since prescribed doses may be less than 1 mL. <b><u>We provide specific recommendations to address this concern in section 4.1.</u></b>

			quickly and only saw the “1” on the pharmacy label. When re-read later, read more slowly and read full number.	quickly and misread the dose number.	clearance of CBD is slightly greater than in older children and adults, so exposures in that group are generally lower for a given dose compared to older children and adults.	
	NC16	Drew 1 mL dose for first two attempts. When looked at pharmacy label for the third time realized own error.	Said that overconfident and eyes drawn to the “1” on the pharmacy label.	Perception – participant misread the pharmacy label.	Based on these justifications, in light of these perspectives, the severity of the underlying condition, the relatively low impact of dosing errors with this particular medication (wide therapeutic index), and given the results of the summative study, we believe that the level of dosing errors observed in the study are acceptable and no further mitigation is required.	
3.7 mL	PC04	Drew plunger to correct level but with large air	Confused initially and used IFU to	Cognition. Confused initially and rushed.	<ul style="list-style-type: none"> <li>All participants</li> </ul>	Among the six use errors observed for the remaining

		bubble. Used IFU (section 3) and corrected on second attempt.	clarify. Participant said missed air bubbles because rushing to complete the task, not being attentive enough.	Read IFU and understood.	<ul style="list-style-type: none"><li>were able to identify correct graduations for each dose in the end.</li><li>Graduations are clearly numbered at each 0.5 mL interval and labeling them at each 0.1 mL graduation would create a crowded interface and would cause even more difficulties in dose measurements. So, no further changes are proposed.</li><li>The ability of caregivers and patients to administer accurate doses of oral liquid medications in not without error in clinical practice, despite familiarity with this dosage form. Given the</li></ul>	five doses, failure to clear air bubbles was described by the Sponsor as a potential root cause for all six cases.  According to the Sponsor's URRA, failure to clear air bubbles could result in a minor underdose. The Sponsor has determined that a minor underdose would not cause serious harm to the proposed patient population and categorized the severity of harm as negligible. The Sponsor provided the following rationale for the severity categorization: <ul style="list-style-type: none"><li>Cannabidiol is used as an add-on therapy to standard care, so patients will continue to receive their other anti-epileptic drugs.</li><li>CBD has a half-life of about 56 to 61 hours, so an underdose is unlikely to affect the therapeutic efficacy.</li><li>Withdrawal seizures or other withdrawal effects have not been</li></ul>
1.5 mL	PC07	Drew twice. First attempt had an air bubble.	Found syringe tricky to use. Plunger was slippery. Not sure why missed air bubble initially.	Action – not sure why missed air bubble but could see it.		
5.2 mL	PC13	5 mL correctly drawn up but air bubbles present for the 0.2 mL dose. Confused by 0.2 mL measurement.	Does not normally draw up partial dose (e.g., 0.1 mL). Air bubble in amount drawn up. Confused with the amounts.	Cognition. Could identify 0.2 mL mark on syringe but said not used to drawing partial doses which caused their confusion.		
7.5 mL and 9 mL	PC12	Measured 3.7 mL for first attempt at both doses. Not turning the bottle vertically upside down to remove air bubbles.	Participant said that they had broken wrist and unable to turn bottle. Therefore, struggled to remove air bubbles.	Cognition and Action. Could identify correct amounts in syringe but unable to measure correctly due to physical constraint of broken wrist and resulting lack of wrist		

				mobility. Was also distracted by recent death of the patient they cared for.	literature, it seems inevitable that some dosing errors will occur.	problematic in clinical trials.
7.5 mL	VC18	Had air bubbles. When used the IFU successfully removed air bubbles on second attempt.	Not read IFU so didn't think air bubbles were a problem.	Perception. Had not read IFU at first attempt but carried out task correctly when did so.	Based on these justifications, in light of these perspectives, the severity of the underlying condition, the relatively low impact of dosing errors with this particular medication (wide therapeutic index), and given the results of the summative study, we believe that the level of dosing errors observed in the study are acceptable and no further mitigation is required.	<p>We consulted with the MO and the MO agrees that minor underdoses due to air bubbles are unlikely to cause serious harm.</p> <p>Step 5 in the IFU instructs on what to do if there is an air bubble.</p> <p>We also note that among the six use errors observed, five participants successfully self corrected and completed the task upon second attempt and the remaining participant successfully completed the task upon a third attempt, illustrating a learned effect.</p> <p>Thus, we agree with the Sponsor's conclusion that the risk of underdose due to air bubbles has been mitigated to an acceptable level and no additional mitigations are required.</p>

### 3.3 LABELS AND LABELING

Our review of the proposed Prescribing Information (PI) labeling, Instructions for Use (IFU) labeling, container label and carton labeling identified areas which may be improved to decrease risk of medication error.

#### Instructions for Use

- Step 5 of the IFU states “Slowly pull the plunger of the oral syringe to draw the (b) (4) (b) (4).” We are concerned that (b) (4) resulting in wrong dose medication errors.

#### Carton Labeling and Container Label



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<sup>3</sup> Institute for Safe Medication Practices. Affirmative warnings (do this) may be better understood than negative warnings (do not do that). ISMP Med Saf Alert Acute Care. 2010;15(16):1-3.

### All Labels and Labeling

- We note the labels and labeling reference the proprietary name, (b) (4) however, the proprietary name, Epidiolex, is conditionally approved for this product.<sup>4</sup>

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur with the use of the combination product.

## **4 CONCLUSION & RECOMMENDATIONS**

The Human Factors (HF) validation study identified use errors associated with the following critical tasks: push the bottle adapter firmly into the bottle and dose measurement.

Based on our assessment of the root causes, subjective feedback, and user-interface associated with the 'push the bottle adapter firmly into the bottle' task, we believe that the risk for error to occur with this critical task has been minimized to as low as reasonably practical and we determined no further mitigation is necessary.

The HF validation study also identified use errors associated with the critical dose measurement task. We note the majority of use errors associated with the dose measurement task resulted in ten-fold overdoses and the remainder of the use errors were contributed to failure to clear air bubbles, resulting in minor underdose. Additionally, participants in the study who failed the dose measurement task on the first attempt demonstrated an ability to identify the error, self-correct, and successfully measure the dose on the second or third attempt, demonstrating a learned effect. We consulted with the medical officer who confirmed that 10-fold overdoses<sup>5</sup> and minor underdoses due to air bubbles are not expected to cause serious harm to patients. Based on the sponsor's assessment of the root causes, the subjective feedback, the information

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<sup>4</sup> Rider B. Proprietary Name Review for Epidiolex (NDA 210365). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 APR 19. Panorama No. 2018-21548356.

<sup>5</sup> The MO's assessment is based on the greater clearance in younger patients (in whom the greater overdoses would be more likely to occur) and that 8X the expected daily dose has been administered (single doses) to healthy adult volunteers with no significant adverse events reported.

provided by the MO, and the learned effect demonstrated in the study, we find the residual risk is acceptable for this product. However, based on the user-interface associated with this task, we identified one area of improvement in the IFU that could be further optimized to decrease the risk of wrong dose medication errors. See our recommendation number 1 in section 4.1 below.

Our review of the PI labeling, container label, and carton labeling has identified areas that are vulnerable to medication error and we provide recommendations in section 4.1 and 4.2 and recommend their implementation prior to approval of this NDA application.

#### **4.1 RECOMMENDATIONS FOR THE DIVISION**

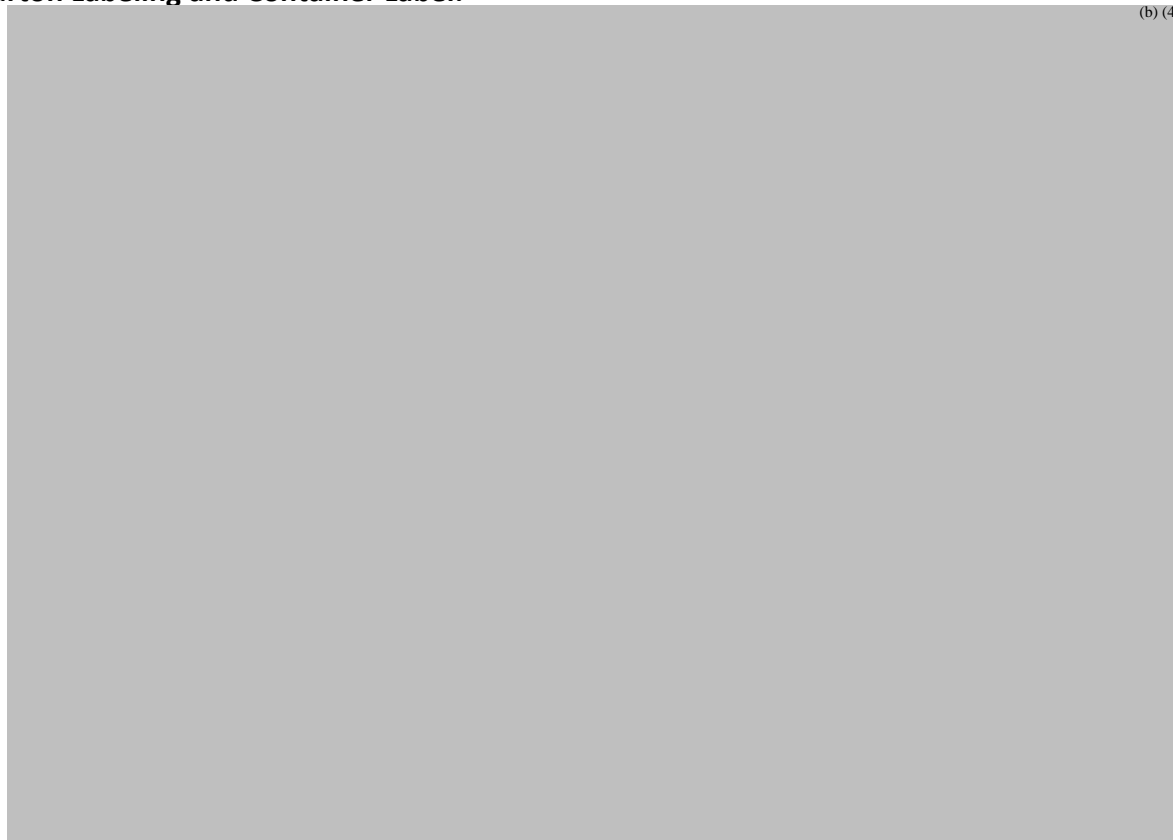
##### **A. Instructions for Use (IFU)**

1. Step 5 of the IFU states “Slowly pull the plunger of the oral syringe to draw the (b) (4).” We are concerned that (b) (4). We recommend revising the statement to read: “Slowly pull the plunger of the oral syringe to withdraw the prescribed dose.”

#### **4.2 RECOMMENDATIONS FOR GW RESEARCH LTD**

We recommend the following be implemented prior to approval of this NDA:

##### **A. Carton Labeling and Container Label:**



**D. All Labels and Labeling**

1. Revise all labels and labeling to reflect the conditionally approved proprietary name for this product, Epidiolex.

## APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

### APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Epidiolex that GW Research Ltd submitted on August 4, 2017 and September 12, 2017.

<b>Table 2. Relevant Product Information for Epidiolex</b>	
<b>Initial Approval Date</b>	N/A
<b>Active Ingredient</b>	Cannabidiol
<b>Indication</b>	Adjunctive treatment of seizures associated with Dravet Syndrome (DS) and seizures associated with Lennox-Gastaut Syndrome (LGS)
<b>Route of Administration</b>	Oral
<b>Dosage Form</b>	Solution
<b>Strength</b>	100 mg/mL
<b>Dose and Frequency</b>	<p>The recommended starting dose is 2.5 mg/kg twice daily (5 mg/kg per day) for 1 week. The daily dose should be increased weekly by 2.5 mg/kg administered twice daily (5 mg/kg per day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg per day). Based on individual clinical response and tolerability, the dose can be increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg per day) to 10 mg/kg twice daily (20 mg/kg per day). The maximum recommended effective dose is 20 mg/kg/day. (b) (4)</p> <p>(b) (4)</p>
<b>How Supplied</b>	(b) (4) mL amber glass multi-use bottle, a bottle adapter and two 5 mL oral syringes
<b>Storage</b>	Store at room temperature between 68°F to 77°F (20°C to 25°C)
<b>Container Closure</b>	Amber Type (b) (4) glass bottle sealed with a child resistant cap.

## APPENDIX B. PREVIOUS DMEPA REVIEWS

On September 18, 2017, we searched the L:drive and AIMS using the terms, cannabidiol, IND 120055, and NDA 210365 to identify reviews previously performed by DMEPA. We limited our search to reviews associated with the usability, label and labeling.

Our search identified 3 previous assignments in AIMS<sup>6</sup>, of which 1 previous review<sup>7</sup> was performed.

In OSE RCM # 2015-1433, DMEPA was consulted to a Type C CMC meeting with GW Research Ltd on August 12, 2015. During the meeting, DMEPA disagreed with the Sponsor's risk assessment and identified the following medication safety concerns with the proposed oral syringes:

- The wide range of doses (and volumes) and required dose titration may require the patient/caregiver to transition from the 1 mL to the 5 mL syringe
- The patient/caregiver may need to use both syringes to measure a dose or use a single syringe more than once
- The 1 mL and 5 mL have (b) (4)
- (b) (4)
- The numerical markings have commas rather than periods

During the meeting, DMEPA recommended that the Sponsor conduct a HF validation study to assess whether the IFU and other mitigation strategies effectively reduce the identified risks to an acceptable level. We confirmed that the Sponsor has addressed our previous medication safety concerns.

In OSE RCM # 2016-545, DMEPA reviewed the Sponsor's proposed HF validation study protocol, labels, labeling, and updated use-related risks analysis from a medication error perspective. DMEPA identified deficiencies with the proposed HF validation study protocol, labels, and labeling. We confirmed that our previous recommendations were implemented or considered.

In OSE RCM #2016-1098, DMEPA was consulted to attend a July 19, 2016 Pre-NDA meeting with the Sponsor. However, DMEPA did not attend the meeting.

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<sup>6</sup> OSE RCM # 2015-1433, 2016-545, and 2016-1098.

<sup>7</sup> White, L. Human Factors Protocol Review for cannabidiol oral solution (IND 120055). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 APR 11. RCM No.: 2016-545.

**APPENDIX C. REVISED HUMAN FACTORS STUDY (SUBMITTED SEPTEMBER 12, 2017)**

<\\cdsesub1\evsprod\nda210365\0003\m5\53-clin-stud-rep\535-rep-effic-safety-stud\dravet-syn\5354-other-stud-rep\human-fact\16-188-r2.pdf>

## **APPENDIX F. INFORMATION REQUESTS ISSUED DURING THE REVIEW**

### **Information Request #1**

#### **Request**

On August 29, 2017, we issued an Information Request (IR) requesting that the Sponsor clarify the intended dosage for the proposed product, provide the moderator transcript and five intend-to-market samples of the proposed product, provide root cause analysis and subjective feedback for all failures, close calls and difficulties, and update their use-related risk analysis to include several missing key elements.

#### **Response**

The Sponsor provided responses to the IR on September 12, 2017. The responses can be accessible in EDR via:

<\\cdsesub1\evsprod\nda210365\0003\m1\us\response-to-information-request.pdf>

### **Information Request #2**

#### **Request**

On October 23, 2017, we issued an IR requesting that the Sponsor explain the clinical significance of a 10-fold overdose in the proposed patient population, clarify the lowest expected starting dose for the proposed product, and clarify whether participants were told they measured the wrong dose after each failed attempt.

#### **Response**

The Sponsor provided responses to the IR on November 6, 2017. The responses can be accessible in EDR via: <\\cdsesub1\evsprod\nda210365\0007\m1\us\human-factors-fda-request.pdf>

#### **Clinical significance of a 10-fold overdose (excerpted from the Sponsor's response)**

- A 0.1 mL dose of CBD = 10 mg dose, while a 10-fold overdose (i.e., 1 mL instead of 0.1 mL) = 100 mg dose. The average 2-year-old weighs approximately 13 kg thus, a single dose of CBD at the target therapeutic dose of 20 mg/kg/day would be 130 mg. Hence, the worst-case overdose in this scenario represents less than the target therapeutic dose (100 mg overdose versus 130 mg maintenance dose).
- The pharmacokinetics of CBD are nonlinear and are characterized by lower relative bioavailability as dose is increased, particularly at supra-therapeutic doses. This would have the effect of reducing the impact of an accidental overdose. From a healthy volunteer study (GWEP1544), the nonlinearity observed estimates that an increase of 10-fold in dose would lead to just a 5.4-fold increased C<sub>max</sub>.

- In the youngest children, where the potential impact of an accidental exposure would be most likely, the clearance of CBD is slightly greater than in older children and adults.
- In the case of a single accidental overdose, the elevated plasma exposure would be transient due to the rapid distribution of CBD (apparent volume of distribution is greater than 20,000 L), and normal plasma concentrations would be achieved within a dosing interval.
- There have been large doses of CBD given to healthy volunteers with good to moderate tolerability. In study GWEP1544 healthy volunteer subjects well-tolerated the single doses in the range of 32X the highest likely starting dose of CBD and > 8X the expected daily dose without significant safety concerns. Similar AEs were recorded for multiple doses up to twice the expected daily dose.

## **APPENDIX G. LABELS AND LABELING**

### **G.1 List of Labels and Labeling Reviewed**

Using the principles of human factors and Failure Mode and Effects Analysis,<sup>8</sup> along with postmarket medication error data, we reviewed the following Epidiolex labels and labeling submitted by GW Research Ltd on October 26, 2017 and October 27, 2017.

- Container label
- Carton labeling
- 5 mL oral syringe
- Instructions for Use - no image

### **G.2 Label and Labeling Images**

#### **Container Label**



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<sup>8</sup> Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

## Carton Labeling

(b) (4)



## 5 mL Oral Syringe

(b) (4)



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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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BRIANA B RIDER  
04/27/2018

LOLITA G WHITE  
04/27/2018

QUYNHNHU T NGUYEN  
04/27/2018

DANIELLE M HARRIS  
04/30/2018

## Interdisciplinary Review Team for QT Studies Consultation: Thorough QT Study Review

<b>IND or NDA</b>	IND 120055 NDA 210365
<b>Brand Name</b>	(b) (4)
<b>Generic Name</b>	GWP42003-P (Cannabidiol)
<b>Sponsor</b>	GW Research, Ltd.
<b>Indication</b>	Adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older
<b>Dosage Form</b>	Oral solution
<b>Drug Class</b>	Antiepileptic
<b>Therapeutic Dosing Regimen</b>	Recommended starting dose is 2.5 mg/kg taken twice daily (5 mg/kg/day) for 1 week. After one week's treatment, each dose should be increased weekly by 2.5 mg/kg administered twice daily (5 mg/kg/day) to a therapeutic dose of 5 mg/kg twice daily (10 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 2.5 mg/kg administered twice daily (5 mg/kg/day) to 10 mg/kg twice daily (20 mg/kg/day).
<b>Duration of Therapeutic Use</b>	Chronic
<b>Maximum Tolerated Dose</b>	Unknown
<b>Submission Number and Date</b>	SDN#004, 9/25/2017
<b>Review Division</b>	DNP

Note: Any text in the review with a light background should be inferred as copied from the sponsor's document.

## 1 SUMMARY

### 1.1 OVERALL SUMMARY OF FINDINGS

The TQT study GWEP1541 is inadequate to support the QT risk assessment for the proposed dosing in the current indication because the exposure achieved in the study are substantially lower (e.g., likely 2-fold or more) than the therapeutic exposures of parent and the 7-COOH-CBD metabolite. Therefore, we recommend that the sponsor conducts another TQT study with appropriate dosing (e.g., dosing in fed state) to satisfy the

requirement for adequate characterization of QTc prolongation risk. The sponsor should submit the protocol for such a study for our review.

Our rationale for not accepting the results of the current TQT study GWEP1541 is as follows:

1. (b) (4) The food effect study showed 5-fold increase in  $C_{max}$  of CBD and 2-3-fold increase in  $C_{max}$  of metabolites when administered with high fat-high calorie meal compared to the fasted state. The suprathreshold dose (4500 mg) given in the fasted state in this TQT study would not cover the therapeutic exposures of CBD or one of its metabolites 7-COOH-CBD with the highest proposed dose of the drug administered with food.
2. Furthermore, in vitro hERG inhibition assay had a small safety margin with respect to clinically relevant free plasma concentrations of CBD (~57-fold for  $C_{max}$  in fasted state and ~11-fold for  $C_{max}$  with high fat-high calorie meal for therapeutic dosing) and the characterization of metabolites for hERG inhibition potential has not been done.

As shown in Table 1 below, for 750 mg BID dosing (i.e., therapeutic dosing for a 75 kg person with highest recommended 10 mg/kg twice daily dosing) with a normal meal, the steady state therapeutic  $C_{max}$  for CBD is expected to be between 732 ng/mL (fasted) and 3552 ng/mL (fed high fat-high calorie meal) and for 7-COOH-CBD it is expected to be between 9824 ng/mL (fasted) and 20434 ng/mL (fed high fat-high calorie meal). The  $C_{max}$  achieved with suprathreshold dose of 4500 mg in fasted state in this TQT study were 629 ng/mL for CBD and 4621 ng/mL for 7-COOH-CBD, which are lower than the above range of expected therapeutic exposures. As per the sponsor's development plan, a food effect study is being planned to evaluate impact of (b) (4) food on PK, which could better inform the exposure margin achieved in this TQT study vis-à-vis the therapeutic exposures expected with dosing with (b) (4) meal. Nonetheless, the highest exposures in this TQT study for these moieties are ~5-fold lower than the highest clinically relevant scenario exposures (dosing with high fat-high calorie meal).

**Table 1: Summary of Mean  $C_{max}$  for CBD and the Metabolites for Different Dosing Scenarios**

Dosing in HV	Food status for dos	Timing	Mean Cmax (ng/mL)			
			CBD	6-OH-CBD	7-OH-CBD	7-COOH-CBD
750 mg SD (TQT)	Fasted	Day 1	387	5	94	1872
4500 mg SD (TQT)	Fasted	Day 1	629	12	234	4621
1500 mg SD (FE)	Fasted	Day 1	335	10	135	2426
	Fed (High fat-high calorie meal)	Day 1	1628	27	393	5044
750 mg BID MD (10 mg/kg BID dosing for a 75 kg subject)	Fasted*	Day 1 AM	291	8	123	2785
		Day 1 PM	732	15	197	5307
		Day 7 AM (~Steady State AM sampling)	330	13	153	9824
	Fed (High fat-high calorie meal)**	Day 1 AM	1410	23	358	5793
		Day 1 PM	3552	43	574	11039
		Day 7 AM (~Steady State AM sampling)	1602	36	444	20434

HV= Healthy adult volunteers; SD= Single dose; MD= Multiple dosing; FE= Food effect Study GWEP1544; TQT= TQT Study GWEP1541

\*Data from Study GWEP1544 (MD)

\*\*Data estimated by the sponsor using fasting data from GWEP1544 and applying an analyte specific 'food effect factor' determined in GWEP1544 [CBD 4.85, 6-OH 2.80, 7-OH 2.91, 7-COOH 2.08]

Source: Collated from information in Summary of Clinical Pharmacology and sponsor's response to information request on 03/23/2018

## 2 PROPOSED LABEL

The Sponsor included the following QT related language in the proposed label:

### 12.2 Pharmacodynamics

(b) (4)

## 3 BACKGROUND

### 3.1 PRODUCT INFORMATION

GWP42003-P is a highly purified version of cannabidiol (CBD) which is being developed as a potential antiepileptic drug. CBD is a 21-carbon terpenophenolic compound found in the Cannabis sativa L. plant. CBD is reported to have analgesic properties and demonstrates significant anti-inflammatory activity. CBD also has anti-convulsant, neuroprotective, anxiolytic and anti-psychotic actions. The current clinical formulations contain (b) (4) CBD Botanical Drug Substance (BDS). CBD medicines may be presented as liquid, solid or topical dosage forms.

### 3.2 MARKET APPROVAL STATUS

CBD comprises approximately (b) (4) of the CB content of Sativex Oromucosal Spray (b) (4) ratio of THC:CBD, at a level of (b) (4) mg/mL THC and (b) (4) mg/mL CBD), which is approved in the United Kingdom and in over 20 countries worldwide.

### 3.3 PRECLINICAL INFORMATION

The effects of CBD BDS on the hERG encoded potassium channel were studied in trial GWOR10120 ZNA34345 using the whole cell patch clamp technique in HEK293 cells stably transfected with hERG cDNA (complementary DNA). Nominal CBD concentrations of 150, 300, 500 and 1500 ng CBD/mL were assessed. The CBD concentrations in the recording chamber were estimated to be 43, 92, 150 and 530 ng CBD/mL. CBD inhibited hERG tail current in a concentration-dependent manner, with a statistically significant inhibition of tail current observed at nominal concentrations of 300 ng CBD/mL and above ( $P < 0.01$ , compared to vehicle). The estimated nominal IC<sub>25</sub>, IC<sub>50</sub> and IC<sub>75</sub> values for CBD inhibition of hERG tail current were 220, 420 and 790 ng CBD/mL, respectively. When the concentration-response curve was plotted using the estimated achieved concentrations in the recording chamber, the IC<sub>25</sub>, IC<sub>50</sub> and IC<sub>75</sub> values were estimated to be 64, 130 and 250 ng CBD/mL, respectively. This IC<sub>50</sub> represents a margin of >16-fold relative to the free concentration of CBD (assuming >99% plasma protein binding) at a mean C<sub>max</sub> of 791 ng/mL which was reached after

4500 mg of GWP42003 (proposed supratherapeutic dose) as observed after a single dose in healthy volunteers.

For the effects of CBD BDS on isolated rabbit Purkinje fibers, estimated actual concentrations of 6, 19 and 22 ng CBD/mL had no effects on resting membrane potential, maximum rate of depolarization, upstroke amplitude, action potential duration at 60% and 90% (APD60 and APD90) or triangulation (APD60-90, 1 Hz only) when compared to vehicle treated fibers. The no observable adverse effect level (NOAEL) of 22 ng/mL represents a margin of > 2.8 fold relative to the free concentration of CBD with a C<sub>max</sub> of 791 ng/mL.

The cardiovascular effects of CBD BDS were evaluated in conscious, telemetered beagle dogs. A dose related decrease in heart rate and increase in systolic blood pressure were observed. No effects on QTcF were detected at any dosage (10, 50 or 100 mg/kg via oral gavage in labrafil).

*Reviewer's comments: The IC<sub>50</sub> value of 420 ng/mL for CBD for hERG inhibition represents a margin of ~57-fold and ~11-fold relative to the free concentration of CBD (assuming >99% plasma protein binding) corresponding to the mean C<sub>max</sub> of 732 ng/mL for dosing in fasted state and the mean C<sub>max</sub> of 3552 ng/mL for dosing with high fat-high calorie meal for the therapeutic dosing of 750 mg BID (10 mg/kg BID in a 75 kg weight adult). In vitro characterization of metabolites for hERG inhibition potential has not been done.*

### 3.4 PREVIOUS CLINICAL EXPERIENCE

As of a cut-off date of April 2015, approximately 278 subjects have been exposed to CBD in ongoing and completed company sponsored clinical trials. Of these, 152 were exposed to CBD BDS and 126 to purified CBD.

In addition, approximately 213 children and adults for drug resistant epilepsies were exposed to purified CBD in non-GW sponsored uncontrolled programmes through the United States (US) Expanded Access Programme (EAP) Emergency Investigational New Drug (IND) and Worldwide Named Patient Supply (NPS).

GW423003-P has been developed as a formulation in sesame oil and the pharmacokinetic properties of this formulation are being investigated currently in a program of studies including SAD, MAD, and food effect.

A Thorough QT/QTc study has been performed using Sativex. In this study, a 90-mg supratherapeutic dose of CBD as part of Sativex (36 sprays) for 5 days produced a mean C<sub>max</sub> of 4.79 ng/ml. No effect on cardiac repolarization was observed. However, it should be noted that the intended dose in Dravet and Lennox-Gastaut syndromes is in the range of 350-700 mg twice daily and much higher plasma exposure of CBD and metabolites will occur.

### 3.5 CLINICAL PHARMACOLOGY

Appendix 6.1 summarizes the key features of clinical pharmacology of GWP42003-P (cannabidiol).

## 4 SPONSOR'S SUBMISSION

### 4.1 OVERVIEW

The QT-IRT reviewed the protocol prior to conducting this study under IND 120055 (dated [09/28/2015](#) in DARRTS). The sponsor submitted the study report GWEP1541, including electronic datasets and waveforms to the ECG warehouse.

In the protocol review, the following comment regarding dosing was provided for conveying to the sponsor: *“Ultimately, the adequacy of the doses will be determined once the final therapeutic dose is established and the effects of all relevant intrinsic and extrinsic factors on the PK of CBD are determined.”*

In the protocol review, the reviewer's comment for the dose justification section was as follows: *“Drug accumulation at the steady state, food effect on drug absorption, hepatic and renal impairment on PK, and drug-drug interactions are unknown. Ultimately, the adequacy of the doses will be determined once the final therapeutic dose is established and the effects of all relevant intrinsic and extrinsic factors on the PK of CBD are determined.”*

### 4.2 TQT STUDY

#### 4.2.1 Title

A Single Oral Dose, Randomized, Double-Blind, Placebo and Positive-controlled, 4-Way Crossover Study to Investigate the Effect of Cannabidiol (GWP42003-P) on the QTc Interval in Healthy Subjects.

#### 4.2.2 Protocol Number

GWEP1541

#### 4.2.3 Study Dates

27-Oct-2015 to 16-Feb-2016

#### 4.2.4 Objectives

##### Primary:

To assess the effect of single oral dose administration of 750 mg and 4500 mg GWP42003-P on the QT/QTc-interval corrected for heart rate (QTc), relative to placebo, in healthy adult male and female subjects.

##### Secondary:

- To evaluate the safety and tolerability of a single therapeutic and supratherapeutic oral dose of GWP42003-P in healthy adult male and female subjects.
- To evaluate assay sensitivity (i.e. to evaluate the effect of a positive control, a single oral dose of moxifloxacin [400 mg], on the QT/QTc interval in healthy subjects).
- To assess the effects of a single therapeutic and supratherapeutic oral dose of GWP42003-P on non-QT interval electrocardiogram (ECG) parameters (heart rate [HR] and RR, PR and QRS intervals) in healthy subjects.

- To determine the pharmacokinetics (PKs) of CBD and its major metabolites following a single therapeutic and supratherapeutic oral dose of GWP42003-P.
- To determine the plasma concentration-effect relationship for CBD and its metabolites on the QT/QTc interval in healthy subjects.

## 4.2.5 Study Description

### 4.2.5.1 Design

This is a randomized, double-blind, placebo- and positive-controlled, 4-way crossover trial. All subjects were administered all 4 single dose treatments during 4 different treatment periods. Each dosing occasion will be followed by a 10-day washout period.

### 4.2.5.2 Controls

The Sponsor used both placebo and positive (moxifloxacin) controls.

### 4.2.5.3 Blinding

This was a double-blind trial, with the exception of the positive control (moxifloxacin), which was open-label.

## 4.2.6 Treatment Regimen

### 4.2.6.1 Treatment Arms

Subjects were randomized to receive 1 of 12 treatment sequences administered over 4 periods using a complete orthogonal set of three 4X4 Latin squares. The following treatments were administered under fasted conditions:

- Treatment A: A single therapeutic oral dose of 750 mg GWP42003-P.
- Treatment B: A single supratherapeutic oral dose of 4500 mg GWP42003-P.
- Treatment C: A single oral dose of 400 mg moxifloxacin.
- Treatment D: A single oral dose of GWP42003-P-matched placebo

### 4.2.6.2 Sponsor's Justification for Doses

A low (therapeutic) dose of 750 mg and a high (supratherapeutic) dose of 4500 mg GWP42003-P were studied to characterize the effect of GWP42003-P on the QT/QTc interval, as recommended by the ICH E14 guidance.

The GWP42003-P dose currently being used in Phase 3 clinical trials is an oral dose of 20 mg/kg/day, split between morning and evening. This equates to oral administration of approximately 750 mg twice daily in an average 75 kg person.

Based on results of a Phase 1 single ascending dose trial, there was moderate accumulation of CBD after 7 days of multiple b.i.d. dosing (Rac 1.8-fold after 750 mg and 2.6-fold after 1500 mg GWP42003-P). The therapeutic dose of GWP42003-P administered in this study was therefore a single oral dose of 750 mg.

The inter-subject variability of CBD exposure, as noted in the preliminary results of the single ascending dose trial was generally moderate. A study in rats did not show a clear sex difference in exposure for CBD. When GWP42003-P was co-administered with food there was a marked increase in  $C_{max}$  (4.85-fold) and area under the concentration-time

curve calculated to the last observable concentration at time t (AUC(0-t)) (4.2-fold). The  $t_{1/2}$  was 30 hours in the fasted state compared with 24 hours in the fed state. For the current trial, a margin of 3-4 fold increase in exposure for the supratherapeutic dose relative to the maximum therapeutic dose was selected based on a usually acceptable margin rather than indication of higher exposure due to specific intrinsic or extrinsic factors.

The maximum tolerated dose of GWP42003-P has not been established. From the single ascending dose trial,  $C_{max}$  and AUC(0-t) for CBD and metabolites increased with dose but with a trend to less than dose proportionality; 4500 mg GWP42003-P appeared to yield a  $C_{max}$  for CBD very close to that of the 6000 mg dose (722.1 and 782 ng/mL, respectively). Based on the results of the single ascending trial, 4500 mg GWP42003-P was well tolerated. A single 4500 mg oral dose, 6 times the anticipated therapeutic oral dose, was therefore utilized as the supratherapeutic dose. The supratherapeutic dose of 4500 mg is anticipated to yield a  $C_{max}$  of 700-800 ng/mL, which is anticipated to be 3-4 times higher than will be achieved with the therapeutic dose of 750 mg GWP42003-P.

*Reviewer's Comment: The supratherapeutic dose and dosing in fasted state employed in this study are inadequate to cover the therapeutic exposures ( $C_{max}$ )* (b) (4)  
*See Section 5.3 for detailed discussion.*

#### 4.2.6.3 Instructions with Regard to Meals

The study had dosing in fasted state.

*Reviewer's Comment: Not appropriate. The protocol review had the following comment, "Food effect on CBD absorption has not been determined.". See Section 5.3 for detailed discussion related to inadequacy of dosing in fasted state.*

#### 4.2.6.4 ECG and PK Assessments

**ECG:** Holter monitoring was carried out in each treatment period from 2 hours prior to IMP administration, up to 23 hours postdose. ECGs were extracted at the following time points: -0.75, -0.5 and -0.25 h predose for construction of a baseline, and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18 and 23 h postdose.

**PK:** Blood sampling for PK of CBD and its major metabolites in plasma was carried out in each treatment period at predose and 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 18 and 23 h postdose.

*Reviewer's Comment: The timing of ECG/PK sampling is adequate to capture effects at  $T_{max}$  (4-6 h for cannabidiol and its major metabolites) and delayed effects over 23 h.*

#### 4.2.6.5 Baseline

For each dosing period, baseline was defined as the average of three predose measurement.

#### 4.2.7 ECG Collection

Triplicate ECGs were extracted from the continuous 12-lead digital recording (holter) after the subject had been resting for at least 10 minutes in a supine position.

## 4.2.8 Sponsor's Results

### 4.2.8.1 Study Subjects

There were 50 subjects enrolled; all 50 were administered placebo and 400 mg moxifloxacin, 49 (98%) received 750 mg GWP42003-P and 48 (96%) received 4500 mg GWP42003-P. All enrolled subjects completed Period 1 of the trial, 49 (98%) completed Period 2, and 48 (96%) completed Periods 3 and 4. Two (4%) subjects withdrew from the trial before it completed. There were 22 males and 28 female subjects randomized. The majority of the subjects enrolled were White (96%); 1 (2.0%) subject each were Asian and Black or African American. The mean age was approximately 33 years and the mean body mass index was approximately 24 kg/m<sup>2</sup>.

### 4.2.8.2 Statistical Analyses

### 4.2.8.3 Primary Analysis

The time-matched analysis for QTcF was conducted as the primary endpoint as recommended by ICH E14. Assay sensitivity was a secondary objective for this trial but is included below as it relates to data generated from the time-matched results. Table displays the 2-sided 90% CI, or equivalent 1-sided 95% upper CI in ms for the  $\Delta\Delta$ QTcF analysis, which included the 750 and 4500 mg GWP42003-P and moxifloxacin groups.

The change from baseline, calculated as the [mean of the triplicate postdose] - [mean of the mean of 3 triplicates predose] per time point for each treatment were subjected to a linear mixed-effects model (using the SAS Procedure PROC MIXED with a diff option) with the following covariates: time (categorical), treatment, time-by-treatment interaction, sex, period and sequence as fixed effects. Subject was included as a random effect.

For both the therapeutic and suprathreshold doses of GWP42003-P, none of the time points demonstrated an upper 1-sided 95% CI that approached or exceeded 10 ms, demonstrating no effect of GWP42003-P (750 or 4500 mg) on cardiac repolarization.

**Table 2: Placebo-Corrected Change from Baseline Estimates from Mixed-Effects General Linear Model: QTcF(PD set)**

Time (hour)	750 mg GWP42003-P (n=49)			4500 mg GWP42003-P (n=48)			400 mg Moxifloxacin (n=50)		
	Estimate <sup>a</sup>	Lower Bound <sup>b</sup>	Upper Bound <sup>b</sup>	Estimate <sup>a</sup>	Lower Bound <sup>b</sup>	Upper Bound <sup>b</sup>	Estimate <sup>a</sup>	Lower Bound <sup>b</sup>	Upper Bound <sup>b</sup>
0.5	-0.3	-2.7	2.0	-1.4	-3.7	0.9	7.3	4.1	10.5
1	0.1	-2.2	2.5	-1.5	-3.8	0.8	12.6	9.5	15.8
2	-1.0	-3.3	1.3	-2.6	-5.0	-0.3	13.6	10.4	16.8
3	0.5	-1.9	2.8	-0.1	-2.5	2.2	15.0	11.9	18.2
4	0.5	-1.9	2.8	-1.2	-3.5	1.2	12.6	9.4	15.8
5	1.3	-1.0	3.6	-0.9	-3.3	1.4	14.6	11.4	17.8
6	0.1	-2.3	2.4	-0.1	-2.5	2.2	9.6	6.4	12.7

Time (hour)	750 mg GWP42003-P (n=49)			4500 mg GWP42003-P (n=48)			400 mg Moxifloxacin (n=50)		
	Estimate <sup>a</sup>	Lower Bound <sup>b</sup>	Upper Bound <sup>b</sup>	Estimate <sup>a</sup>	Lower Bound <sup>b</sup>	Upper Bound <sup>b</sup>	Estimate <sup>a</sup>	Lower Bound <sup>b</sup>	Upper Bound <sup>b</sup>
8	0.5	-1.8	2.9	-0.4	-2.8	1.9	8.6	5.4	11.7
12	-2.1	-4.4	0.3	-0.1	-2.5	2.2	6.9	3.7	10.1
18	-0.4	-2.7	1.9	2.2	-0.1	4.6	7.1	3.9	10.3
23	1.2	-1.2	3.6	-1.0	-3.4	1.3	5.4	2.2	8.7

Note: bounds were multiplicity adjusted for moxifloxacin only.

<sup>a</sup> Mixed Effect General Linear Model is fit for time-matched changes from baseline and includes terms for treatment, time, and interactions: treatment by time in addition to period and sequence.

<sup>b</sup> Lower/Upper Bound = lower or upper 2-sided 90% CI.

Sex main effect p-value = 0.3582.

Source: Clinical Study Report GWEP1541, Table 8.4.1-1.

**Reviewer's Comments:** FDA analysis results are presented in section 5.2. FDA conclusion matches with the sponsor's conclusion.

#### 4.2.8.4 Assay Sensitivity

The time-matched analysis for QTcF revealed that the moxifloxacin group met the assay sensitivity criteria outlined in the SAP; at all 4 predefined time points between 1 and 4 hours postdose the lower 1-sided 95% CI was  $\geq 5$  ms (range: 9.4-11.9 ms) (Table 8.4.1-1), with a typical moxifloxacin QTcF profile whereby the  $\Delta$ QTcF declined from 5 hours postdosing.

**Reviewer's Comments:** Both FDA's analysis and sponsor's analysis using QTcF confirm that the assay sensitivity was established. The FDA's analysis is presented in section 5.2.

#### 4.2.8.5 Categorical Analysis

Outlier analysis was performed to supplement the central tendency analysis by determining if there were subjects who had an exaggerated effect on any ECG interval. The outlier analysis was exploratory only since there is little power to detect genetically sensitive individuals to potential QT prolonging drugs in a small sample size in healthy volunteers (see Table 3).

**Table 3: Outlier Analysis (PD set)**

Outlier Criteria	750 mg GWP42003-P (n=49)	4500 mg GWP42003-P (n=48)	400 mg Moxifloxacin (n=50)	Placebo (n=49)
	Number of Subjects (%)			
Heart rate: bradycardia	1 (2.0)	0	0	0
Heart rate: tachycardia	0	0	0	0
PR	0	0	0	0
QRS	0	0	0	0
QT new > 500 ms	0	0	1 (2.0)	0
QTcF > 60 ms increase	0	0	0	0
QTcF new > 500 ms	0	0	0	0
QTcF new > 480 ms	0	0	0	0
<b>Nonspecific Criterion<sup>a</sup></b>				
QTcF > 30-60 ms increase	0	0	3 (6.0)	0

Note: “new” means not present at baseline and only seen after baseline.

Source: Clinical Study Report GWEP1541, Table 8.4.2.4-1.

No subjects met the QTcF defined outlier criteria.

One subject in the 750 mg GWP42003-P dose group met the bradycardic outlier criterion and no subjects met the tachycardic outlier criterion. These findings were considered to be of no clinical significance. No subjects met the PR or QRS outlier criteria.

#### 4.2.8.6 Safety Analysis

All AEs reported were TEADs of mild or moderate severity which is presented in Table 4: Summary of Adverse Events by Treatment, Relationship and Severity (Safety Set) Table 4. There were no SAEs or deaths but 1 early withdrawal due to TEAEs.

**Table 4: Summary of Adverse Events by Treatment, Relationship and Severity (Safety Set)**

	Placebo (N=50)	400 mg Moxifloxacin (N=50)	750 mg GWP42003-P (N=49)	4500 mg GWP42003-P (N=48)	Total Active GWP42003-P (N=49)	Total (N=50)
<b>Event</b>	<b>Number of Subjects that experienced adverse events (%)</b>					
Subjects with TEAEs (all severities)	23 (46.0)	21 (42.0)	29 (59.2)	38 (79.2)	44 (89.8)	46 (92.0)
Subjects with mild TEAEs <sup>a</sup>	22 (44.0)	20 (40.0)	27 (55.1)	36 (75.0)	40 (81.6)	40 (80.0)
Subjects with moderate TEAEs <sup>a</sup>	1 (2.0)	1 (2.0)	2 (4.1)	2 (4.2)	4 (8.2)	6 (12.0)
Subjects with treatment-related TEAEs (all severities)	18 (36.0)	10 (20.0)	19 (38.8)	35 (72.9)	39 (79.6)	40 (80.0)
Subjects with mild treatment-related TEAEs <sup>a</sup>	18 (36.0)	10 (20.0)	18 (36.7)	33 (68.8)	36 (73.5)	37 (74.0)
Subjects with moderate treatment-related TEAEs <sup>a</sup>	0	0	1 (2.0)	2 (4.2)	3 (6.1)	3 (6.0)
Subjects discontinued trial medication due to AE	0	1 (2.0)	0	0	0	1 (2.0)

Source: Clinical Study Report GWEP1541, Table 9.2.1-1.

#### 4.2.8.7 Clinical Pharmacology

##### 4.2.8.7.1 Pharmacokinetic Analysis

Plasma samples were analyzed for parent drug (CBD), and major metabolites (6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD). The PK parameters are presented in Table 5 and the concentration-time profiles are shown in Figure 1. C<sub>max</sub> and AUC for CBD did not increase in a dose proportional manner for the studied doses (750 and 4500 mg

GWP42003-P); for a 6-fold increase in dose there was only a 1.6-fold increase in  $C_{\max}$ ,  $AUC(0-t)$  and  $AUC(0-\infty)$ .

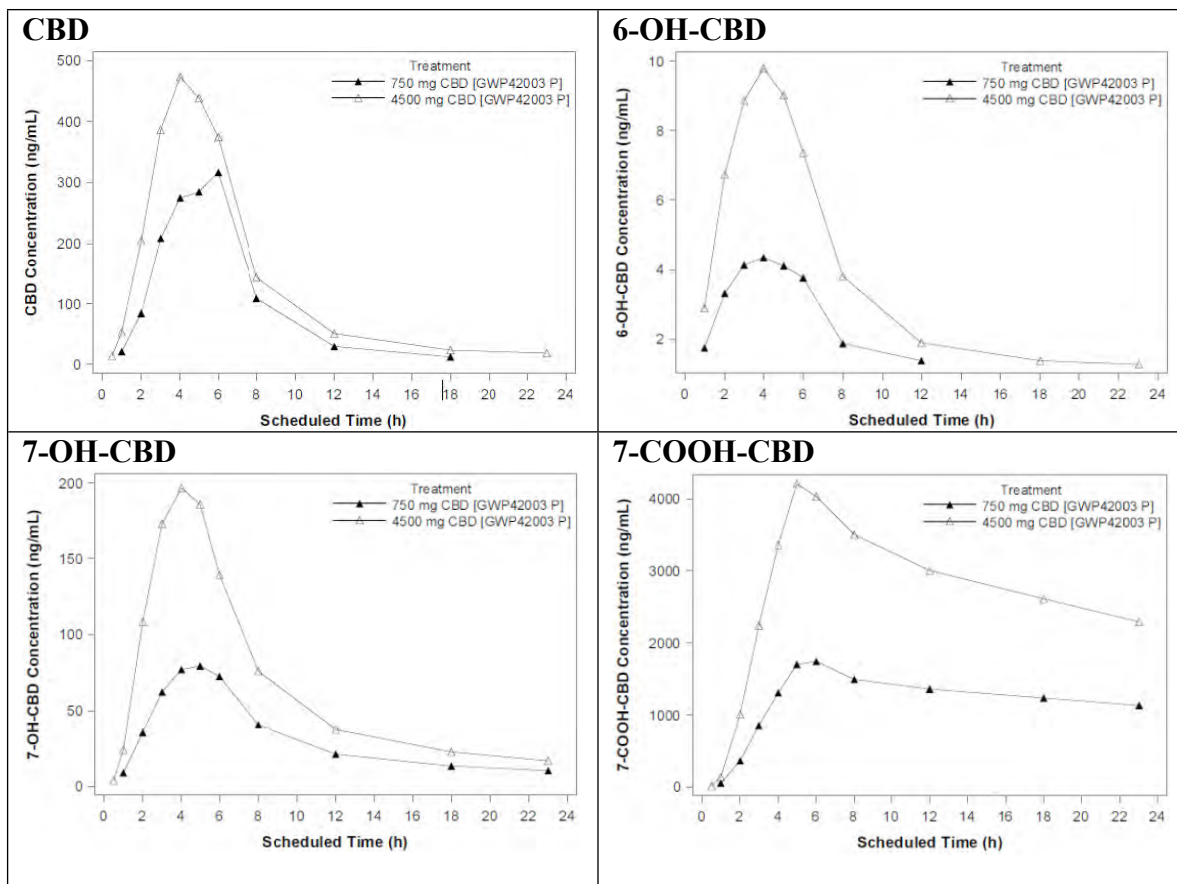
Amongst all moieties, 7-COOH-CBD was the most abundant analyte followed by parent drug CBD, 7-OH-CBD then 6-OH-CBD, respectively.

**Table 5: Pharmacokinetic Parameters of CBD, 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD**

GWP42003-P Dose (n)	$C_{\max}$ (ng/mL) <sup>a</sup>	$t_{\max}$ (h) <sup>b</sup>	$AUC(0-t)$ (ng.h/mL) <sup>a</sup>	$AUC(0-\infty)$ (ng.h/mL) <sup>a</sup>	% $AUC_{\text{extra}}$ <sup>c</sup>	CL/F (L/h) <sup>c</sup>	$V_z/F$ (L) <sup>c</sup>	$t_{1/2}$ (h) <sup>c</sup>
<b>CBD</b>								
750 mg (n=49)	387 (52.4)	5.00 (3.00–8.00)	1960 (43.4)	2150 (38.2) <sup>d</sup>	4.87 (49.0) <sup>d</sup>	375 (42.1) <sup>d</sup>	2820 (46.9) <sup>d</sup>	5.94 (53.2) <sup>d</sup>
4500 mg (n=48)	629 (74.5)	4.01 (2.00–12.00)	3143 (77.1)	3365 (75.6) <sup>d</sup>	7.21 (53.6) <sup>d</sup>	1729 (96.0) <sup>d</sup>	19261 (75.8) <sup>d</sup>	8.55 (38.0) <sup>d</sup>
<b>6-OH-CBD</b>								
750 mg (n=49)	5.34 (54.8)	4.00 (1.00–6.03)	38.7 (113.1)	55.5 (68.1) <sup>j</sup>	21.53 (27.7) <sup>j</sup>	NC	NC	13.9 (92.6) <sup>e</sup>
4500 mg (n=48)	11.9 (69.2)	4.02 (1.00–12.00)	74.9 (100.9)	97.6 (80.5) <sup>k</sup>	15.17 (38.1) <sup>k</sup>	NC	NC	9.30 (82.8) <sup>f</sup>
<b>7-OH-CBD</b>								
750 mg (n=49)	93.9 (57.2)	4.02 (2.00–6.03)	719 (47.3)	913 (43.9) <sup>l</sup>	18.16 (37.9) <sup>l</sup>	NC	NC	12.2 (49.9)
4500 mg (n=48)	234 (61.9)	4.52 (2.00–12.00)	1536 (63.7)	1872 (56.3) <sup>m</sup>	13.51 (45.9) <sup>m</sup>	NC	NC	11.3 (46.9) <sup>g</sup>
<b>7-COOH-CBD</b>								
750 mg (n=49)	1872 (49.1)	6.00 (4.00–23.02)	28109 (49.4)	NC	NC	NC	NC	33.3 (37.4) <sup>h</sup>
4500 mg (n=48)	4621 (63.5)	5.02 (4.00–18.03)	63603 (70.1)	NC	NC	NC	NC	25.1 (32.1) <sup>i</sup>

Source: Clinical Study Report GWEP1541, Table 8.4.3.1.3-1.

**Figure 1: Geometric Mean Plasma Concentration-Time Profiles for the Parent Drug (CBD) and Metabolites (6-OH-CBD, 7-OH-CBD and 7-COOH-CBD) after Administration of Single Dose of 750 mg and 4500 mg GWP42003-P**



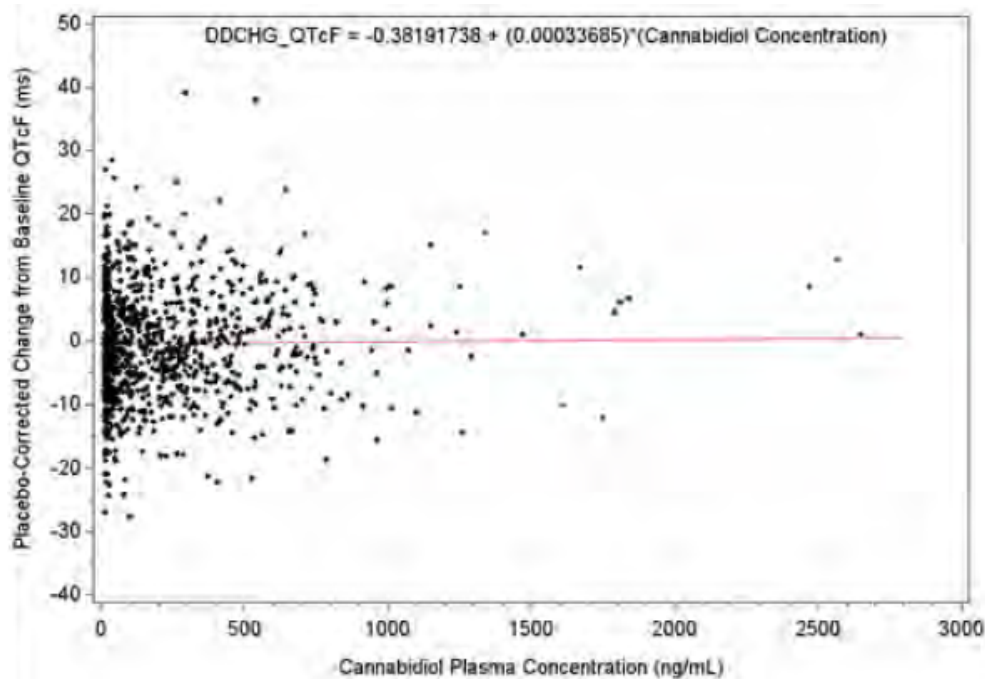
Source: Clinical Study Report GWEP1541, Figures 8.4.3.1.2.1-1, 8.4.3.1.2.2-1, 8.4.3.1.2.3-1, and 8.4.3.1.2.4-1.

#### 4.2.8.7.2 Exposure-Response Analysis

Figure 2 below shows the relationship between plasma concentration of CBD and  $\Delta\Delta\text{QTcF}$  (relationship for the metabolites are not shown here; available in sponsor's report). The results of the linear mixed effect model showed that the slope for  $\Delta\Delta\text{QTcF}$  vs. CBD and other metabolite was flat (slope estimates shown in Table 6 below), suggesting no effect of GWP42003-P on cardiac repolarization.

For CBD, 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD, the overall predicted placebo and baseline corrected values at arithmetic mean  $C_{\text{max}}$  for the supratherapeutic (4500 mg) dose of GWP42003-P were -0.12, -0.51, -0.40, and 0.63 ms, respectively (with respective 1-sided 95% upper CI of: 1.37, 1.00, 1.08 and 2.03 ms). These data suggest no effect of CBD or its metabolites on cardiac repolarization.

**Figure 2: Relationship between Plasma Concentration of CBD and  $\Delta\Delta\text{QTcF}$  Using Mixed-effects Model Regression (PD Set)**



Source: Clinical Study Report GWEP1541, Figure 8.4.3.2-1

**Table 6: Concentration-QTc Effect Analysis - Placebo-corrected Change from Baseline versus CBD, 6-OH-CBD, 7-OH-CBD or 7-COOH-CBD Concentration: Estimates from Linear Mixed Model - QTcF in ms (PD Set)**

QTc Parameter	Slope of Plasma Concentration-effect on $\Delta\Delta QTc$	Standard Error	p-value
<b>CBD</b>			
QTcF	0.00033685	0.00110410	0.7648
<b>6-OH-CBD</b>			
QTcF	-0.01916441	0.06707664	0.7771
<b>7-OH-CBD</b>			
QTcF	-0.00060669	0.00324624	0.8532
<b>7-COOH-CBD</b>			
QTcF	0.00025841	0.00017520	0.1508

Source: Clinical Study Report GWEP1541, Table 8.4.3.2-1.

Reviewer's Comments: The reviewer's analysis is in agreement with the sponsor's analysis results that there is no statistically significant positive slope for concentration-QTc relationship for CBD or its metabolites (see Section 5.3).

## 5 REVIEWERS' ASSESSMENT

### 5.1 EVALUATION OF THE QT/RR CORRECTION METHOD

There were no significant heart rate effects (>10 bpm) with the drug. QTcF was used for the primary statistical analysis and other analyses.

### 5.2 STATISTICAL ASSESSMENTS

#### 5.2.1 QTc Analysis

##### 5.2.1.1 The Primary Analysis for GWP42003-P

The statistical reviewer used mixed model to analyze the  $\Delta QTcF$  effect. The model includes treatment, time point, treatment-by-time point interaction, sequence, period as fixed effects and SUBJECT as a random effect. Baseline is included in the model as a covariate. Compound symmetry covariance structure is used. The analysis results are listed in the following table.

**Table 7: Analysis Results of  $\Delta QTcF$  and  $\Delta\Delta QTcF$  for Treatment Groups GWP42003-P 4500 mg and GWP42003-P 750 mg**

	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin			
	ΔQTcF	Placebo	ΔΔQTcF		ΔQTcF	Placebo	ΔΔQTcF		ΔQTcF	Placebo	ΔΔQTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)

	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin			
	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF		$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF		$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-3.5	-2.1	-1.4	(-3.4, 0.7)	-2.5	-2.1	-0.5	(-2.5, 1.6)	5.2	-2.1	7.3	(5.3, 9.3)
1	-4.4	-3.0	-1.5	(-3.5, 0.6)	-3.0	-3.0	0.0	(-2.0, 2.0)	9.7	-3.0	12.6	(10.6, 14.7)
2	-5.6	-3.0	-2.6	(-4.6, -0.5)	-4.2	-3.0	-1.1	(-3.2, 0.9)	10.6	-3.0	13.6	(11.6, 15.6)
3	-3.2	-3.1	-0.1	(-2.2, 1.9)	-2.8	-3.1	0.4	(-1.7, 2.4)	11.9	-3.1	15.1	(13.0, 17.1)
4	-2.9	-1.7	-1.1	(-3.2, 0.9)	-1.4	-1.7	0.3	(-1.7, 2.4)	10.9	-1.7	12.6	(10.6, 14.7)
5	-2.2	-1.2	-0.9	(-3.0, 1.1)	-0.1	-1.2	1.2	(-0.9, 3.2)	13.4	-1.2	14.6	(12.6, 16.7)
6	-4.7	-4.6	-0.1	(-2.2, 1.9)	-4.7	-4.6	-0.1	(-2.1, 2.0)	5.0	-4.6	9.6	(7.5, 11.6)
8	-12.0	-11.6	-0.4	(-2.4, 1.7)	-11.2	-11.6	0.4	(-1.6, 2.5)	-3.0	-11.6	8.6	(6.6, 10.6)
12	-7.3	-7.2	-0.1	(-2.2, 2.0)	-9.4	-7.2	-2.2	(-4.2, -0.1)	-0.3	-7.2	6.9	(4.9, 9.0)
18	6.9	4.6	2.3	(0.2, 4.3)	4.1	4.6	-0.5	(-2.6, 1.5)	11.8	4.6	7.1	(5.1, 9.2)
23	-4.8	-3.8	-1.0	(-3.0, 1.1)	-2.5	-3.8	1.2	(-0.8, 3.3)	1.7	-3.8	5.4	(3.4, 7.5)

The largest upper bounds of the 2-sided 90% CI for the mean difference between GWP42003-P 4500 mg and placebo, and between GWP42003-P 750 mg and placebo were 4.3 ms and 3.3 ms, respectively.

### 5.2.1.2 Assay Sensitivity Analysis

The statistical reviewer used the same statistical model to analyze moxifloxacin and placebo data. The results are presented in

Table 8. The largest unadjusted 90% lower confidence interval is 13.0. By considering Bonferroni multiple endpoint adjustment, the largest lower confidence interval is 12.3, which indicates that an at least 5 ms QTcF effect due to moxifloxacin can be detected from the study.

**Table 8: Analysis Results of  $\Delta$ QTcF and  $\Delta\Delta$ QTcF for Moxifloxacin**

Moxifloxacin					
Time (hrs)	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF		
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
0.5	5.2	-2.1	7.3	(5.3, 9.3)	(4.5, 10.1)
1	9.7	-3.0	12.6	(10.6, 14.7)	(9.9, 15.4)
2	10.6	-3.0	13.6	(11.6, 15.6)	(10.8, 16.4)

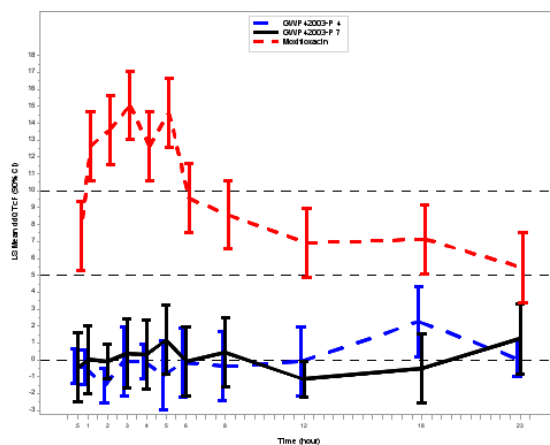
Moxifloxacin					
Time (hrs)	$\Delta$ QTcF	Placebo	$\Delta\Delta$ QTcF		
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	97.5% CI (ms)
3	11.9	-3.1	15.1	(13.0, 17.1)	(12.3, 17.8)
4	10.9	-1.7	12.6	(10.6, 14.7)	(9.9, 15.4)
5	13.4	-1.2	14.6	(12.6, 16.7)	(11.8, 17.4)
6	5.0	-4.6	9.6	(7.5, 11.6)	(6.8, 12.3)
8	-3.0	-11.6	8.6	(6.6, 10.6)	(5.8, 11.4)
12	-0.3	-7.2	6.9	(4.9, 9.0)	(4.1, 9.7)
18	11.8	4.6	7.1	(5.1, 9.2)	(4.4, 9.9)
23	1.7	-3.8	5.4	(3.4, 7.5)	(2.6, 8.3)

\* Bonferroni method was applied for multiple endpoint adjustment for 4 time points

### 5.2.1.3 Graph of $\Delta\Delta$ QTcF Over Time

The following figure displays the time profile of  $\Delta\Delta$ QTcF for different treatment groups.

**Figure 3: Mean and 90% CI  $\Delta\Delta$ QTcF Timecourse**



(Note: CIs are all unadjusted including moxifloxacin)

### 5.2.1.4 Categorical Analysis

Table 9 lists the number of subjects as well as the number of observations whose QTcF values are  $\leq 450$  ms, between 450 ms and 480 ms. No subject's QTcF was above 480 ms.

**Table 9: Categorical Analysis for QTcF**

Treatment Group	Total (N)		Value $\leq$ 450 ms		450 ms<Value $\leq$ 480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.

Treatment Group	Total (N)		Value≤450 ms		450 ms<Value≤480 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
GWP42003-P 4500 mg	48	526	45 (93.8%)	521 (99.0%)	3 (6.3%)	5 (1.0%)
GWP42003-P 750 mg	49	536	48 (98.0%)	534 (99.6%)	1 (2.0%)	2 (0.4%)
Moxifloxacin 400 mg	50	546	38 (76.0%)	499 (91.4%)	12 (24.0%)	47 (8.6%)
Placebo	49	534	48 (98.0%)	530 (99.3%)	1 (2.0%)	4 (0.7%)

**Table 10** lists the categorical analysis results for  $\Delta Q_{TcF}$ . No subject's change from baseline ( $\Delta Q_{TcF}$ ) was above 60 ms.

**Table 10: Categorical Analysis of  $\Delta Q_{TcF}$**

Treatment Group	Total (N)		Value≤30 ms		30 ms<Value≤60 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
GWP42003-P 4500 mg	48	526	48 (100%)	526 (100%)	0 (0.0%)	0 (0.0%)
GWP42003-P 750 mg	49	536	49 (100%)	536 (100%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	50	546	47 (94.0%)	540 (98.9%)	3 (6.0%)	6 (1.1%)
Placebo	49	534	49 (100%)	534 (100%)	0 (0.0%)	0 (0.0%)

## 5.2.2 HR Analysis

The same statistical analysis was performed based on HR. The point estimates and the 90% confidence intervals are presented in Table 11. The largest upper limits of 90% CI for the HR mean differences between GWP42003-P 4500 mg and placebo and GWP42003-P 750 mg and placebo are 3.5 bpm and 2.9 bpm, respectively.

None of the subjects experienced HR interval greater than 100 bpm across all treatment group.

**Table 11: Analysis Results of  $\Delta HR$  and  $\Delta\Delta HR$  for Treatment Groups GWP42003-P 4500 mg and GWP42003-P 750 mg**

Time (hrs)	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin 400 mg			
	$\Delta HR$	Placebo	$\Delta\Delta HR$		$\Delta HR$	Placebo	$\Delta\Delta HR$		$\Delta HR$	Placebo	$\Delta\Delta HR$	
	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
0.5	5.7	5.3	0.4	(-1.3, 2.0)	5.9	5.3	0.6	(-1.0, 2.3)	2.1	5.3	-3.1	(-4.8, -1.5)
1	5.9	6.3	-0.4	(-2.1, 1.2)	7.6	6.3	1.3	(-0.4, 2.9)	3.2	6.3	-3.1	(-4.8, -1.5)
2	5.6	5.8	-0.1	(-1.8, 1.5)	6.0	5.8	0.2	(-1.4, 1.9)	1.5	5.8	-4.2	(-5.9, -2.6)

	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin 400 mg			
	$\Delta$ HR	Placebo	$\Delta\Delta$ HR		$\Delta$ HR	Placebo	$\Delta\Delta$ HR		$\Delta$ HR	Placebo	$\Delta\Delta$ HR	
Time (hrs)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)	LS Mean (bpm)	LS Mean (bpm)	Diff LS Mean (bpm)	90% CI (bpm)
3	5.2	5.0	0.3	(-1.4, 1.9)	4.0	5.0	-1.0	(-2.6, 0.7)	0.8	5.0	-4.1	(-5.8, -2.5)
4	4.6	4.1	0.5	(-1.2, 2.1)	4.1	4.1	-0.0	(-1.7, 1.7)	-0.3	4.1	-4.3	(-6.0, -2.7)
5	4.7	3.7	1.0	(-0.7, 2.7)	4.5	3.7	0.7	(-0.9, 2.4)	1.3	3.7	-2.4	(-4.1, -0.8)
6	12.4	10.6	1.8	(0.1, 3.5)	11.1	10.6	0.5	(-1.2, 2.2)	10.2	10.6	-0.4	(-2.1, 1.2)
8	8.7	9.7	-1.0	(-2.7, 0.6)	9.4	9.7	-0.3	(-2.0, 1.3)	9.8	9.7	0.1	(-1.6, 1.7)
12	9.4	9.2	0.2	(-1.5, 1.9)	9.6	9.2	0.4	(-1.2, 2.1)	9.4	9.2	0.2	(-1.4, 1.9)
18	1.6	0.9	0.7	(-0.9, 2.4)	1.6	0.9	0.8	(-0.9, 2.4)	0.6	0.9	-0.2	(-1.9, 1.4)
23	3.1	5.0	-1.9	(-3.5, -0.2)	3.9	5.0	-1.1	(-2.7, 0.6)	2.5	5.0	-2.5	(-4.2, -0.8)

### 5.2.3 PR Analysis

The same statistical analysis was performed based on PR interval. The point estimates and the 90% confidence intervals are presented in Table 12. The largest upper limits of 90% CI for the PR mean differences between GWP42003-P 4500 mg and placebo and GWP42003-P 750 mg and placebo are 4.1 ms and 4.4 ms, respectively.

The outlier analysis results for PR are presented in Table 13. There were five subjects who experienced PR interval greater than 200 ms in GWP42003-P 4500 mg and GWP42003-P 750 mg treatment groups.

**Table 12: Analysis Results of  $\Delta$ PR and  $\Delta\Delta$ PR for Treatment Groups GWP42003-P 4500 mg and GWP42003-P 750 mg**

	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin 400 mg			
	$\Delta$ PR	Placebo	$\Delta\Delta$ PR		$\Delta$ PR	Placebo	$\Delta\Delta$ PR		$\Delta$ PR	Placebo	$\Delta\Delta$ PR	
Time (hrs)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.8	-0.6	-0.2	(-2.0, 1.6)	0.6	-0.6	1.2	(-0.6, 2.9)	-1.3	-0.6	-0.7	(-2.5, 1.0)
1	-2.2	-3.2	1.1	(-0.7, 2.9)	-1.5	-3.2	1.7	(-0.0, 3.5)	-1.7	-3.2	1.5	(-0.2, 3.3)
2	-3.9	-4.0	0.1	(-1.7, 1.9)	-3.4	-4.0	0.6	(-1.2, 2.4)	-2.7	-4.0	1.3	(-0.5, 3.1)
3	-3.6	-5.7	2.1	(0.3, 3.9)	-3.1	-5.7	2.6	(0.8, 4.4)	-4.1	-5.7	1.6	(-0.2, 3.4)
4	-3.4	-5.8	2.3	(0.5, 4.1)	-3.8	-5.8	1.9	(0.1, 3.7)	-5.7	-5.8	0.0	(-1.7, 1.8)
5	-2.6	-4.5	1.9	(0.1, 3.7)	-3.3	-4.5	1.2	(-0.6, 3.0)	-5.0	-4.5	-0.5	(-2.3, 1.3)

Time (hrs)	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin 400 mg			
	ΔPR	Placebo	ΔΔPR		ΔPR	Placebo	ΔΔPR		ΔPR	Placebo	ΔΔPR	
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
6	-3.3	-4.8	1.5	(-0.3, 3.3)	-4.5	-4.8	0.3	(-1.5, 2.1)	-6.1	-4.8	-1.3	(-3.1, 0.5)
8	-4.4	-4.5	0.1	(-1.7, 1.9)	-5.9	-4.5	-1.4	(-3.2, 0.4)	-9.1	-4.5	-4.6	(-6.4, -2.9)
12	-4.0	-4.8	0.8	(-1.0, 2.6)	-5.0	-4.8	-0.2	(-2.0, 1.5)	-6.5	-4.8	-1.7	(-3.5, 0.1)
18	2.5	1.3	1.2	(-0.6, 3.0)	3.9	1.3	2.6	(0.8, 4.3)	1.3	1.3	-0.0	(-1.8, 1.7)
23	-0.5	-1.6	1.0	(-0.8, 2.9)	0.8	-1.6	2.3	(0.5, 4.2)	-0.8	-1.6	0.7	(-1.1, 2.5)

**Table 13: Categorical Analysis for PR**

Treatment Group	Total (N)		Value≤200 ms		200 ms<Value≤220 ms		Value>220 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
GWP42003-P 4500 mg	48	525	46 (95.8%)	523 (99.6%)	2 (4.2%)	2 (0.4%)	0 (0.0%)	0 (0.0%)
GWP42003-P 750 mg	49	536	46 (93.9%)	531 (99.1%)	2 (4.1%)	4 (0.7%)	1 (2.0%)	1 (0.2%)
Moxifloxacin 400 mg	50	546	48 (96.0%)	542 (99.3%)	2 (4.0%)	4 (0.7%)	0 (0.0%)	0 (0.0%)
Placebo	49	534	46 (93.9%)	530 (99.3%)	3 (6.1%)	4 (0.7%)	0 (0.0%)	0 (0.0%)

#### 5.2.4 QRS Analysis

The same statistical analysis was performed based on QRS interval. The point estimates and the 90% confidence intervals are presented in **Table 14**. The largest upper limits of 90% CI for the QRS mean differences between GWP42003-P 4500 mg and placebo and GWP42003-P 750 mg and placebo are 1.0 ms and 1.1 ms, respectively.

The outlier analysis results for QRS are presented in Table 15. One subject in GWP42003-P 4500 mg group experienced QRS interval greater than 110 ms.

**Table 14: Analysis Results of ΔQRS and ΔΔQRS for Treatment Groups GWP42003-P 4500 mg and GWP42003-P 750 mg**

Time (hrs)	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin 400 mg			
	ΔQRS	Placebo	ΔΔQRS		ΔQRS	Placebo	ΔΔQRS		ΔQRS	Placebo	ΔΔQRS	
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
0.5	-0.2	-0.2	-0.0	(-0.8, 0.7)	-0.5	-0.2	-0.3	(-1.1, 0.4)	0.3	-0.2	0.5	(-0.3, 1.2)

Time (hrs)	Treatment Group											
	GWP42003-P 4500 mg				GWP42003-P 750 mg				Moxifloxacin 400 mg			
	ΔQRS	Placebo	ΔΔQRS		ΔQRS	Placebo	ΔΔQRS		ΔQRS	Placebo	ΔΔQRS	
	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)	LS Mean (ms)	LS Mean (ms)	Diff LS Mean (ms)	90% CI (ms)
1	-0.9	-0.4	-0.5	(-1.3, 0.3)	-0.8	-0.4	-0.4	(-1.1, 0.4)	0.1	-0.4	0.5	(-0.2, 1.3)
2	-0.8	-0.0	-0.8	(-1.5, 0.0)	-0.0	-0.0	-0.0	(-0.8, 0.7)	0.5	-0.0	0.5	(-0.2, 1.3)
3	-0.4	-0.1	-0.3	(-1.1, 0.5)	-0.4	-0.1	-0.3	(-1.1, 0.4)	0.1	-0.1	0.2	(-0.5, 1.0)
4	-0.7	-0.7	-0.0	(-0.8, 0.7)	-0.7	-0.7	-0.0	(-0.8, 0.7)	0.4	-0.7	1.1	(0.3, 1.8)
5	-0.9	-0.4	-0.5	(-1.3, 0.3)	-0.4	-0.4	-0.0	(-0.8, 0.7)	0.2	-0.4	0.6	(-0.2, 1.3)
6	0.6	0.7	-0.1	(-0.8, 0.7)	0.5	0.7	-0.2	(-0.9, 0.6)	0.9	0.7	0.2	(-0.6, 1.0)
8	-0.3	-0.4	0.1	(-0.7, 0.8)	0.0	-0.4	0.4	(-0.4, 1.1)	-1.1	-0.4	-0.7	(-1.5, 0.1)
12	-1.0	-1.1	0.1	(-0.7, 0.8)	-1.1	-1.1	-0.0	(-0.8, 0.8)	-0.7	-1.1	0.4	(-0.4, 1.2)
18	0.7	0.5	0.2	(-0.5, 1.0)	0.6	0.5	0.2	(-0.6, 0.9)	0.9	0.5	0.4	(-0.3, 1.2)
23	-0.3	-0.3	0.1	(-0.7, 0.8)	-0.4	-0.3	-0.1	(-0.9, 0.7)	-0.1	-0.3	0.2	(-0.5, 1.0)

**Table 15: Categorical Analysis for QRS**

Treatment Group	Total (N)		Value≤100 ms		100 ms<Value≤110 ms		Value>110 ms	
	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.	# Subj.	# Obs.
GWP42003-P 4500 mg	48	526	29 (60.4%)	407 (77.4%)	18 (37.5%)	118 (22.4%)	1 (2.1%)	1 (0.2%)
GWP42003-P 750 mg	49	536	30 (61.2%)	397 (74.1%)	19 (38.8%)	139 (25.9%)	0 (0.0%)	0 (0.0%)
Moxifloxacin 400 mg	50	546	29 (58.0%)	409 (74.9%)	21 (42.0%)	137 (25.1%)	0 (0.0%)	0 (0.0%)
Placebo	49	534	31 (63.3%)	404 (75.7%)	18 (36.7%)	130 (24.3%)	0 (0.0%)	0 (0.0%)

### 5.3 CLINICAL PHARMACOLOGY ASSESSMENTS

The mean drug concentration-time profile is illustrated in Figure 1.

#### Evaluation of adequacy of exposure margin

(b) (4). In a food effect study with single 1500 mg dose, co-administration with food (high fat-high calorie meal) resulted in 5-fold increase in  $C_{max}$  of CBD and 2-3-fold increase in  $C_{max}$  of metabolites compared to the fasted state (Table 16).

The hepatic impairment study (Study GWEP1539 using 200 mg single oral dose 2 h after standardized, light, low protein breakfast) showed an increase in  $C_{max}$  for CBD and 6-OH-CBD by ~2-fold or more in moderate/severe hepatic impairment. There is also a potential for increase in exposure due to DDI with inhibitors of CYP3A4 or CYP2C19 (magnitude of effect not yet quantified). Administration of doses with high fat-high

calorie meal (5-fold increase in  $C_{max}$ ) likely represents the highest clinically relevant scenario.

As shown in Table 16 below, for 750 mg BID dosing (i.e., therapeutic dosing for a 75 kg person with highest recommended 10 mg/kg twice daily dosing) with a normal meal, the steady state therapeutic  $C_{max}$  for CBD is expected to be between 732 ng/mL (fasted) and 3552 ng/mL (fed high fat-high calorie meal) and for 7-COOH-CBD it is expected to be between 9824 ng/mL (fasted) and 20434 ng/mL (fed high fat-high calorie meal). The  $C_{max}$  achieved with supratherapeutic dose of 4500 mg in fasted state in this TQT study were 629 ng/mL for CBD and 4621 ng/mL for 7-COOH-CBD, which are lower than the above range of expected therapeutic exposures.

As per the sponsor's development plan, a food effect study is being planned to evaluate impact of (b) (4) food on PK, which could better inform the exposure margin achieved in this TQT study vis-à-vis the therapeutic exposures expected with dosing with a (b) (4) meal. Nonetheless, the highest exposures in this TQT study for these moieties are ~5-fold lower than the highest clinically relevant scenario exposures (dosing with high fat-high calorie meal).

In Clinical Overview, the sponsor states that systemic exposure to CBD after oral administration (10 to 20 mg/kg/day) is relatively low in patients (geometric mean  $C_{max}$  [of CBD] in the range 18.8 to 738 ng/mL). However, the dosing in these clinical studies was without regard to the food, (b) (4).

. Also, these studies had a broad population consisting of pediatric and adult patients and it seems the PK evaluation was done after morning dose, which likely under-represents the  $C_{max}$  values (See Table 16 for reported AM vs. PM values in a multiple dosing study).

Overall, the data suggests that the supratherapeutic dose in fasted state employed in this TQT study did not produce adequate exposures to cover the therapeutic exposures of CBD or one of its metabolites 7-COOH-CBD expected with the highest proposed dose of the drug administered with food to support the QT risk assessment in current indication.

**Table 16: Summary of Mean  $C_{max}$  for CBD and the Metabolites for Different Dosing Scenarios**

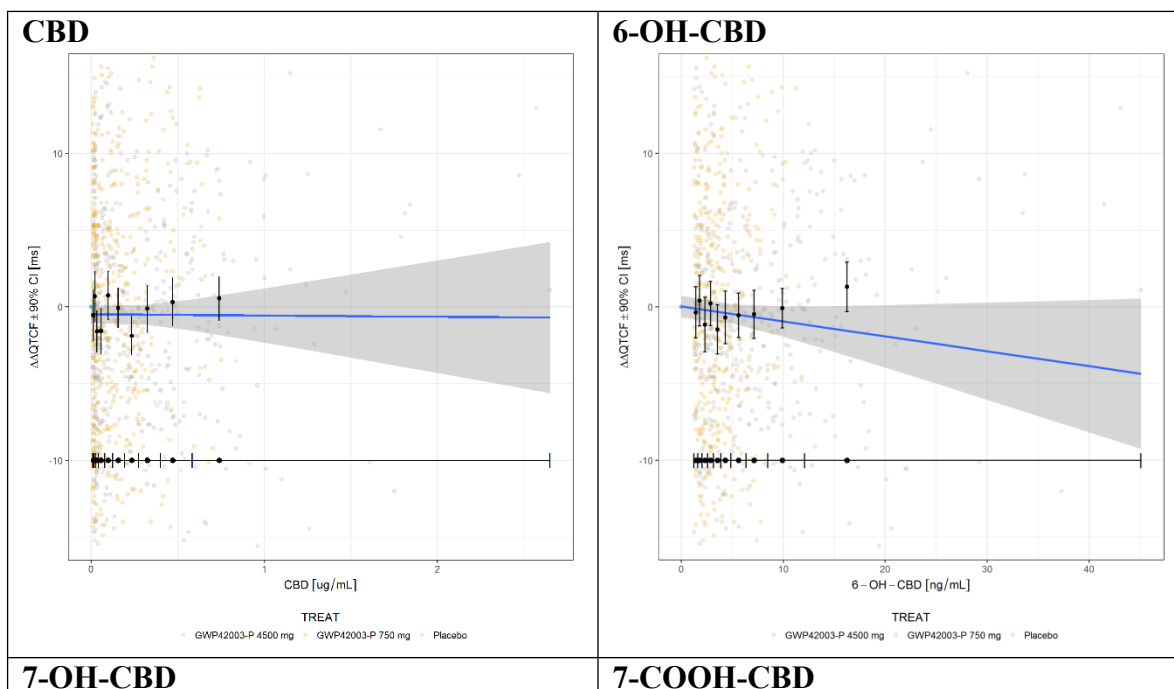
			Mean Cmax (ng/mL)			
Dosing in HV	Food status for dos	Timing	CBD	6-OH-CBD	7-OH-CBD	7-COOH-CBD
750 mg SD (TQT)	Fasted	Day 1	387	5	94	1872
4500 mg SD (TQT)	Fasted	Day 1	629	12	234	4621
1500 mg SD (FE)	Fasted	Day 1	335	10	135	2426
	Fed (High fat-high calorie meal)	Day 1	1628	27	393	5044
750 mg BID MD (10 mg/kg BID dosing for a 75 kg subject)	Fasted*	Day 1 AM	291	8	123	2785
		Day 1 PM	732	15	197	5307
		Day 7 AM (~Steady State AM sampling)	330	13	153	9824
	Fed (High fat-high calorie meal)**	Day 1 AM	1410	23	358	5793
		Day 1 PM	3552	43	574	11039
		Day 7 AM (~Steady State AM sampling)	1602	36	444	20434
HV= Healthy adult volunteers; SD= Single dose; MD= Multiple dosing; FE= Food effect Study GWEP1544; TQT= TQT Study GWEP1541						
*Data from Study GWEP1544 (MD)						
**Data estimated by the sponsor using fasting data from GWEP1544 and applying an analyte specific ‘food effect factor’ determined in GWEP1544 [CBD 4.85, 6-OH 2.80, 7-OH 2.91, 7-COOH 2.08]						

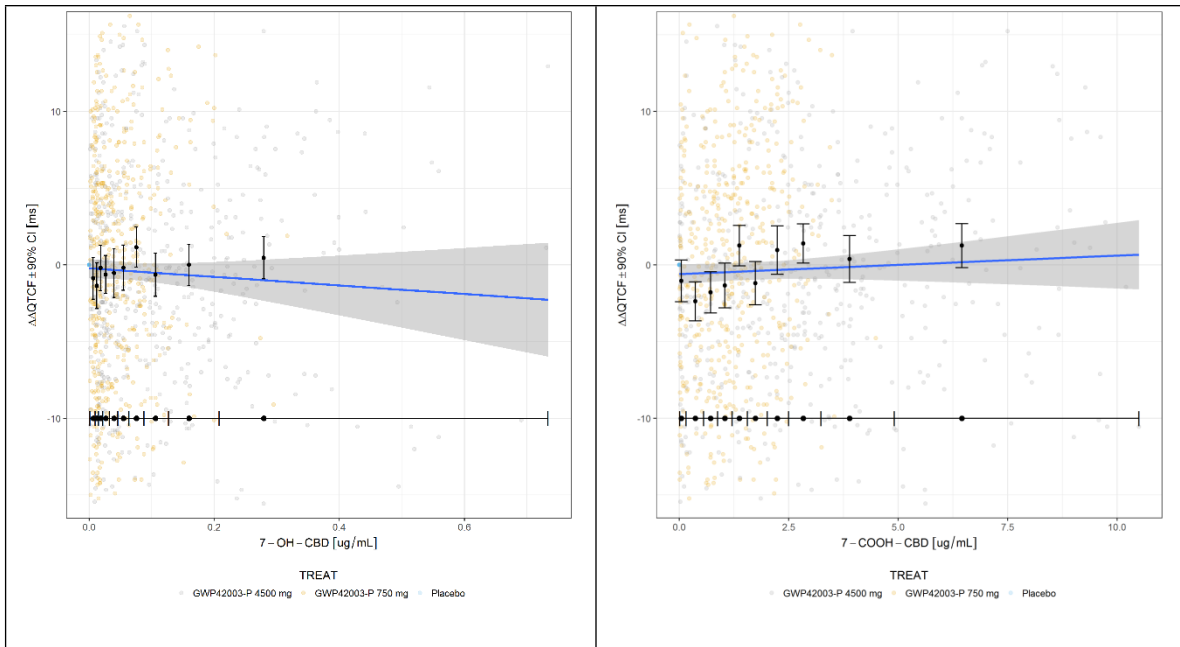
Source: Collated from information in Summary of Clinical Pharmacology and sponsor's response to information request on 03/23/2018

## Exposure-response analysis

The concentration-QTc relationship for data in this study was investigated using the recommended prespecified linear mixed-effects model for each of the parent drug (CBD) and metabolites (6-OH-CBD, 7-OH-CBD and 7-COOH-CBD) separately. The slope estimates from the model were -0.082 ms per  $\mu\text{g/mL}$  ( $p=0.9$ ) for CBD, -0.097 ms per  $\text{ng/mL}$  ( $p=0.2$ ) for 6-OH-CBD, -2.791 ms per  $\mu\text{g/mL}$  ( $p=0.4$ ) for 7-OH-CBD and 0.120 ms per  $\mu\text{g/mL}$  ( $p=0.4$ ) for 7-COOH-CBD. The relationship is visualized in Figure 4 with no statistically significant positive slope for exposure-response relationship for any of the 4 moieties. The upper bound of 90% CI for the mean predicted  $\Delta\Delta\text{QTcF}$  at the mean  $C_{\text{max}}$  of all 4 moieties for the suprathreshold dose (4500 mg) is well below the 10 ms regulatory threshold, as seen in Figure 4.

**Figure 4: Relationship between  $\Delta\Delta\text{QTcF}$  and Plasma Concentration of Parent Drug (CBD) and Metabolites (6-OH-CBD, 7-OH-CBD and 7-COOH-CBD)**





## 5.4 CLINICAL ASSESSMENTS

### 5.4.1 Safety assessments

None of the events identified to be of clinical importance per the ICH E14 guidelines (i.e. syncope, seizure, significant ventricular arrhythmias or sudden cardiac death) occurred in this study.

### 5.4.2 ECG assessments

Overall ECG acquisition and interpretation in this study appears acceptable.

### 5.4.3 PR and QRS Interval

There were no effects on the PR and QRS intervals.

## 6 APPENDIX

### 6.1 HIGHLIGHTS OF CLINICAL PHARMACOLOGY

Therapeutic dose	Anticipated clinical effective dose range = 350mg -750 mg bid CBD	
Maximum tolerated dose	<p><b>MTD (with CBD Botanical Drug Substances: CBD BDS):</b>  Rat: &gt;100mg/kg/day CBD (oral gavage: Study GWOR10109)  Dog: 10mg/kg/day CBD (oral gavage: Study GWOR10111)  <b>MTD (with Sativex Botanical Drug Substances (Tetrahydrocannabinol (THC) BDS: CBD BDS, 1:1 ratio,)</b>  Mouse: 10mg/kg/day CBD (oral gavage: Study GWTX1089)  Rabbit: 12.5mg/kg/day CBD (gavage; Study JJG0009)  <b>CBD NOAEL Rat: (with Sativex Botanical Drug Substances (THC BDS: CBD BDS 1:1 ratio); 6 weeks; Study JJG0023)</b></p> <ul style="list-style-type: none"> <li>• Males: 25 mg/kg/day</li> <li>• Females: 50 mg/kg/day</li> </ul> <p><b>CBD NOAEL Rat: (with Sativex Botanical Drug Substances (THC BDS: CBD BDS, 1:1 ratio); 13 weeks; Study GWTX10124)</b></p> <ul style="list-style-type: none"> <li>• 15 mg/kg/day</li> </ul> <p><b>CBD NOAEL Rat: (with Sativex Botanical Drug Substances (THC BDS: CBD BDS, 1:1 ratio); 26 weeks; Study GWTX0601)</b></p> <ul style="list-style-type: none"> <li>• 5mg/kg/day</li> </ul> <p><b>NOAEL Dog: (with Sativex Botanical Drug Substances THC BDS: CBD BDS, 1:1 ratio); 4 weeks; Study 2228/004)</b></p> <ul style="list-style-type: none"> <li>• 5 mg/kg/day CBD</li> </ul> <p><b>NOAEL Dog: (with Sativex Botanical Drug Substances THC BDS: CBD BDS, 1:1 ratio); 52 weeks; Study GWTX0602)</b></p> <ul style="list-style-type: none"> <li>• 2.5mg/kg/day</li> </ul> <p><b>HUMAN</b></p> <ul style="list-style-type: none"> <li>• Study GWEP 1544 (see below): 1500, 3000, 4500 &amp; 6000 mg CBD</li> <li>• Maximum dose tested 6000 mg CBD single dose</li> </ul>	
Safety Pharmacology Studies	<p><b>CBD BDS: Dog Safety Pharmacology study: 4 weeks (10, 50 &amp; 100mg/kg CBD; Study GWOR10111)</b></p> <ul style="list-style-type: none"> <li>• NOEL 10mg/kg/day</li> <li>• At 50 &amp; 100 mg/kg there were significant decreases in heart rate 4 hours post dose</li> <li>• At 100 mg/kg there were significant increases in systolic blood pressure 5 hours post dose</li> <li>• Changes at 50 &amp; 100 mg/kg were considered not adverse, but related to the pharmacodynamic activity of CBD</li> </ul>	
<i>In vitro</i> Zebrafish Acute Toxicology	<p><b>CBD BDS: ( 5, 25, 50, 100, 200 µM: Studies GWOR 0801/ GWP002) Cardiotoxicity</b></p> <ul style="list-style-type: none"> <li>• Cardiotoxic <math>\geq 25 \mu\text{M}</math></li> </ul>	
Human Studies	<p><b>GWEP 1544:</b> A randomized, double-blind, placebo-controlled, single ascending dose study to evaluate the safety, tolerability and pharmacokinetics of Cannabidiol (GWP42003-P) oral liquid formulation in sesame oil with an open-label two-period cross-over part to study food effects in healthy subjects</p> <p>This is an ongoing study that has only completed the single ascending dose part, but has not yet completed the multiple dose or food effect parts of the study. Therefore both the interim safety data and pharmacokinetic data from the single dose part remain blinded. The blinded adverse event profile is highlighted below.</p>	
Maximum dose tested	Single Dose	Study GWEP 1544 Part A: 4 dose Groups (1500, 3000, 4500 & 6000mg

Principal adverse events		<p>p.o. given as oral liquid formulation in sesame oil) Blinded Safety Data. Each cohort had 6 subjects receiving CBD and 2 receiving placebo orally (Total n=8)</p> <p><b>Group 1: 1500 mg CBD or placebo</b></p> <ul style="list-style-type: none"> <li>• 10 Treatment emergent adverse events (TEAEs) from 3 subjects</li> <li>• All TEAEs were mild and resolved</li> </ul> <p><b>Group 2: 3000 mg CBD or placebo</b></p> <ul style="list-style-type: none"> <li>• 11 TEAEs from 6 subjects</li> <li>• These consisted of gastrointestinal events (x8) sleepiness (x 2) and headache (x1)</li> <li>• All TEAEs were mild and resolved</li> </ul> <p><b>Group 3: 4500 mg CBD or placebo</b></p> <ul style="list-style-type: none"> <li>• 13 TEAEs from 7 subjects; 12 were considered related to the medication</li> <li>• 11 TEAEs were mild and 1 moderate (dizziness)</li> <li>• All TEAEs resolved</li> </ul> <p><b>Group 4: 6000 mg CBD or placebo</b></p> <ul style="list-style-type: none"> <li>• 27 TEAEs reported from all subjects</li> <li>• 4 of the TEAEs were moderate in intensity ( nausea x3, dizziness x1)</li> <li>• All other TEAEs were mild in intensity</li> <li>• All TEAEs resolved</li> </ul> <p>There were no withdrawals or serious adverse events from the study and there were no clinically significant changes in vital signs, 12-lead ECGs, clinical chemistry, hematology and urinalysis during the ascending single dose phase.</p>
	Multiple Dose	<p>GWEP 1544: Multiple dose and food effect part currently ongoing. Doses under test for multiple dose are 750 mg CBD b.i.d and 1500 mg CBD b.i.d in healthy volunteers.</p>

Exposures Achieved at Maximum Tested Dose	Single Dose	<p><b>Study GWEP 1544</b></p> <p><b>1500 mg CBD:</b></p> <ul style="list-style-type: none"> <li>- Mean C<sub>max</sub>: 292 ng/mL <ul style="list-style-type: none"> <li>o Min C<sub>max</sub> 87 ng/mL</li> <li>o Max C<sub>max</sub> 849 ng/mL</li> </ul> </li> <li>- Mean AUC<sub>0-∞</sub>: 1638 (ng/mL*min) <ul style="list-style-type: none"> <li>o Min AUC 604 ng/mL*min</li> <li>o Max AUC 4330 ng/mL*min</li> </ul> </li> <li>- T<sub>max</sub> 4.0 hours</li> <li>- T<sub>½</sub> 14.1 hours</li> </ul> <p><b>3000 mg CBD:</b></p> <ul style="list-style-type: none"> <li>- Mean C<sub>max</sub>: 533 ng/mL <ul style="list-style-type: none"> <li>o Min C<sub>max</sub> 393 ng/mL</li> <li>o Max C<sub>max</sub> 887 ng/mL</li> </ul> </li> <li>- Mean AUC<sub>0-∞</sub>: 2829 (ng/mL*min) <ul style="list-style-type: none"> <li>o Min AUC 2113 ng/mL*min</li> <li>o Max AUC 4579 ng/mL*min</li> </ul> </li> <li>- T<sub>max</sub> 4.5 hours</li> <li>- T<sub>½</sub> 14.8 hours</li> </ul> <p><b>4500 mg CBD:</b></p> <ul style="list-style-type: none"> <li>- Mean C<sub>max</sub>: 722 ng/mL <ul style="list-style-type: none"> <li>o Min C<sub>max</sub> 314 ng/mL</li> <li>o Max C<sub>max</sub> 1314 ng/mL</li> </ul> </li> <li>- Mean AUC<sub>0-∞</sub>: 3445 (ng/mL*min) <ul style="list-style-type: none"> <li>o Min AUC 1573 ng/mL*min</li> <li>o Max AUC 5466 ng/mL*min</li> </ul> </li> <li>- T<sub>max</sub> 5.0 hours</li> <li>- T<sub>½</sub> 16.6 hours</li> </ul> <p><b>6000 mg CBD:</b></p> <ul style="list-style-type: none"> <li>- Mean C<sub>max</sub>: 782 ng/mL <ul style="list-style-type: none"> <li>o Min C<sub>max</sub> 223 ng/mL</li> <li>o Max C<sub>max</sub> 1760 ng/mL</li> </ul> </li> <li>- Mean AUC<sub>0-∞</sub>: 3919 (ng/mL*min) <ul style="list-style-type: none"> <li>o Min AUC 1299 ng/mL*min</li> <li>o Max AUC 9389 ng/mL*min</li> </ul> </li> <li>- T<sub>max</sub> 4.3 hours</li> <li>- T<sub>½</sub> 15.1 hours</li> </ul>
	Multiple Dose	<p><b>Study GWEP 1544</b></p> <p>No multiple dose PK data available yet</p>
Range of linear PK	Single dose pharmacokinetics (1500, 3000, 4500 & 6000 mg CBD single dose range) fails to demonstrate linear kinetics for CBD.	
Accumulation at steady state	There are no data as yet for steady state plasma concentrations or data for accumulation. It is proposed that from the pharmacokinetic data from the single dose, there may be little accumulation of CBD on repeat dosing	
Preliminary Metabolites	<p>In humans and animals CBD is metabolized by the liver, with urinary and fecal excretion of many of its metabolites. The main metabolites from the GWEP 1544 single ascending dose study are 7-OH-CBD, 6-OH CBD</p> <p><b>1500 mg CBD: 6-OH CBD</b></p> <ul style="list-style-type: none"> <li>- Mean C<sub>max</sub>: 10.8 ng/mL</li> <li>- Mean AUC<sub>0-∞</sub>: 131 (ng/mL*min)</li> </ul>	

	<ul style="list-style-type: none"> <li>- Tmax 3.8 hours</li> <li>- T <math>\frac{1}{2}</math> 29.68 hours</li> </ul> <p><b>1500 mg CBD: 7-OH CBD</b></p> <ul style="list-style-type: none"> <li>- Mean Cmax: 181 ng/mL</li> <li>- Mean AUC<sub>0-∞</sub>: 1704 (ng/mL*min)</li> <li>- Tmax 3.0 hours</li> <li>- T <math>\frac{1}{2}</math> 18.7 hours</li> </ul> <p><b>3000 mg CBD: 6-OH CBD</b></p> <ul style="list-style-type: none"> <li>- Mean Cmax: 14.4 ng/ml</li> <li>- Mean AUC<sub>0-∞</sub>: 151 (ng/mL*min)</li> <li>- Tmax 4.1 hours</li> <li>- T <math>\frac{1}{2}</math> 19.3 hours</li> </ul> <p><b>3000 mg CBD: 7-OH CBD</b></p> <ul style="list-style-type: none"> <li>- Mean Cmax: 241 ng/mL</li> <li>- Mean AUC<sub>0-∞</sub>: 2029 (ng/mL*min)</li> <li>- Tmax 4.0 hours</li> <li>- T <math>\frac{1}{2}</math> 15.4 hours</li> </ul> <p><b>4500 mg CBD: 6-OH CBD</b></p> <ul style="list-style-type: none"> <li>- Mean Cmax: 14.6 ng/ml</li> <li>- Mean AUC<sub>0-∞</sub>: 128 (ng/mL*min)</li> <li>- Tmax 4.8 hours</li> <li>- T <math>\frac{1}{2}</math> 26.7 hours</li> </ul> <p><b>4500 mg CBD: 7-OH CBD*</b></p> <ul style="list-style-type: none"> <li>- T <math>\frac{1}{2}</math> 14.8 hours</li> </ul> <p><b>6000 mg CBD: 6-OH CBD</b></p> <ul style="list-style-type: none"> <li>- Mean Cmax: 23.6 ng/ml</li> <li>- Mean AUC<sub>0-∞</sub>: 208 (ng/ml*min)</li> <li>- Tmax 4.3 hours</li> <li>- T <math>\frac{1}{2}</math> 22.09 hours</li> </ul> <p><b>6000 mg CBD: 7-OH CBD*</b></p> <ul style="list-style-type: none"> <li>- T <math>\frac{1}{2}</math> 14.4 hours</li> </ul> <p>* Cmax, AUC<sub>0-∞</sub>, Tmax excluded from descriptive statistics (unreliable profile due to plasma concentrations &gt;ULOQ values). Samples currently under re-analyses to determine full PK profiles for 7-OH and 7-COOH CBD.</p>
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Absorption	Absolute/Relative Bioavailability	Literature reports of clinical pharmacokinetic studies demonstrate that the rate of absorption is dependent upon the route of administration (Huestis 2005). The cannabinoids distribute readily throughout the tissue, especially fatty tissue.
	Tmax	Study GWEP 1544 6000 mg CBD (single dose) <ul style="list-style-type: none"> <li>CBD <ul style="list-style-type: none"> <li>Median Tmax: 5 hours</li> </ul> </li> </ul>
Distribution	Vz/F	GWEP 1544 Study Apparent Vd from 6000mg CBD single dose (median) <ul style="list-style-type: none"> <li>33445 L</li> </ul>
	% bound	No formal clinical protein binding studies have been undertaken to date with CBD.
Pre-clinical <i>In Vitro</i> Data	% bound	Human, Rat & Dog Plasma (GWPP0933) <ul style="list-style-type: none"> <li>Pure CBD or CBD BDS is highly protein bound (&gt;99%)</li> </ul>
Elimination	Route	No human elimination data is currently available for CBD
	Terminal t <sub>1/2</sub>	14-16 h Based on single dose data from study GWEP 1544
	CL/F or CL	GWEP 1544 Study Apparent CL/F from 6000mg CBD single dose (median) <ul style="list-style-type: none"> <li>1270 L/h</li> </ul>
Intrinsic Factors	Age	None – no plans for a formal study of this
	Sex	None – no plans for a formal study of this
	Race	None – no plans for a formal study of this. There will be population pharmacokinetics includes in the ongoing phase III clinical programme which will include covariates around age, sex and race.
	Hepatic & Renal Impairment	Effect of hepatic and renal impairment to be determined in formal Hepatic and renal Impairment Phase I studies (GWEP 1539 & GWEP 1540)
Extrinsic Factors	Drug interactions	To be determined in a formal Phase I drug drug interaction study and a Phase II 1 drug-drug interaction study in patients with epilepsy
	Food Effects	To be determined in a formal single dose study (GWEP 1544).
Sativex Repeat dose TQT Clinical Study	GWCP0607 Clinical Study report <ul style="list-style-type: none"> <li>Supra-therapeutic dose of 24-36 sprays of Sativex (THC:CBD; 2.7mg : 2.5mg per spray)</li> <li>60-90mg CBD (given as Sativex) had no effect on cardiac repolarization</li> </ul>	
Expected High Clinical	The variability in plasma concentrations of CBD is relatively high and	

<p>Exposure Scenario for CBD</p>	<p>appears to be of the order of 2-8 fold.</p> <p>For example in the 6000 mg CBD cohort of study GWEP 1544, one subject reported a C<sub>max</sub> and AUC<sub>0-inf</sub> of 223 ng/mL and 1299 ng.h/mL respectively and in the same cohort another subject had a C<sub>max</sub> and AUC<sub>0-inf</sub> of 1760 ng/mL and 9389 ng.h/mL.</p> <p>Given that the therapeutic range in the target population is likely to be between 700- 1500 mg CBD day (350-750 mg b.i.d CBD), we propose a therapeutic single dose of 750mg CBD, close to the higher end of the therapeutic range and a supratherapeutic single dose of 3000 mg CBD, 4- 5 times above the upper limit of therapeutic. We propose to administer this dose single dose of 750 mg CBD (7.5 mL of 100mg/mL CBD solution) and 3000 mg CBD (30 mL of 100mg/mL of a 100mg/mL CBD solution) The rationale for this is discussed at greater length in an attachment to the previously submitted proposed QT study synopsis.</p>
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/s/  
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DHANANJAY D MARATHE  
04/02/2018

FERDOUSE BEGUM  
04/02/2018

DALONG HUANG  
04/02/2018

MOHAMMAD A RAHMAN  
04/02/2018

MICHAEL Y LI  
04/02/2018

CHRISTINE E GARNETT  
04/02/2018

# Memo to File:

## OSIS Evaluation of MHRA Emails related to NDA 210365

**Date:** December 19, 2017

**To:** NDA 210365

**Through:** Charles R. Bonapace, PharmD  
Director  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

**From:** Zhou Chen, MD, PhD  
Lead Pharmacologist  
Division of New Drug Bioequivalence Evaluation  
Office of Study Integrity and Surveillance

**Subject:** Review of findings from MHRA inspection at (b) (4)

On 10/6/2017, OSIS received an email from Mr. Martin Reed, GLP Investigator of MHRA, expressing concerns with bioanalytical reports from 10 GLP toxicity studies (see table below). Mr. Reed stated the

(b) (4)  
(b) (4) MHRA conducted a GLP inspection at (b) (4) during (b) (4) the location where the bioanalysis was performed.

**NDA Number:** 210365  
**Product Name:** (b) (4) (Cannabidiol)  
**Sponsor:** GW Research, Ltd., Cambridge, UK  
**Review Division:** Division of Neurological Products (DNP)  
**Testing Facility:** (b) (4)  
**Test Site for Bioanalysis:** (b) (4)

(b) (4) Study Number	Study Title	(b) (4) Study Number
8302-923	26-Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4-Week Treatment-Free Period	267582QB01*
8328-341	14-Day Intravenous (Infusion) Administration Toxicity Study in the Rat	280819QB01*
8309-535	Oral (Gavage) Study of Embryo-Foetal Development in the Rat	277188QB01*
8302-481	10-Week Subcutaneous and Oral (Gavage) Administration Toxicity Study in the Juvenile Rat Followed by a 6 Week Treatment-free Period	267585QB01*
(b) (4)		
8315-321	13 Week Oral (Gavage) Administration Range-finding Study in the Mouse	277637QB01*

8302-924	39 Week Oral (Gavage) Administration Toxicity Study in the Dog Followed by a 4 Week Treatment-free Period	267583QB01*
(b) (4)		
8305-752	26-Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4 Week Treatment-free Period	270830QB01
		*: Interim report

On 10/19/2017, Ms. Lesley Graham, Lead Senior Inspector of MHRA, sent FDA a second email, summarizing the inspection she conducted at (b) (4) during (b) (4). The email also provided responses to OSIS's concerns shown below.



The MHRA inspection covered 10 (b) (4) bioanalytical studies listed in the table above. In these bioanalytical studies, concentrations of cannabidiol (CBD) and its metabolites, including 7-OH-CBD, 6-OH-CBD, 7-COOH-CBD, THC, 11-OH-THC, 11-COOH-THC, were measured. Except for study (b) (4) 270380QB01 (related to (b) (4) study 8305752), all (b) (4) bioanalytical study reports are interim reports. All bioanalytical studies were conducted in compliance with the MHRA GLP regulations and OECD GLP principles.

In nine of the 10 final (b) (4) study reports, the compliance statement states that (b) (4)

(b) (4)

Therefore, at this time all data, for all seven analytes (the parent drug and its metabolites) presented in the signed interim phase report should be viewed with caution.

In all nine interim and one finalized (and amended) (b) (4) bioanalytical phase reports, the Compliance Statement states (b) (4)

The Compliance Statement of the bioanalytical phase reports also lists different issues (compliance exceptions) such as (b) (4)

(b) (4) It was stated in reports many times that the data “should be treated with caution.” Ms. Lesley Graham summarized these exceptions in an Excel sheet (see attachment). The exceptions are also summarized in the table below.

Exceptions of bioanalytical phase reports

(b) (4)

Many issues were reported in the 10 bioanalytical phase reports and nine of the reports are interim reports. (b) (4)

Lesley Graham mentioned in the email that in the Compliance Statements, the phrase “the results should be treated with caution” was used throughout, which was not clear whether the data were valid and what impact it could generate. (b) (4)

(b) (4)

(b) (4)

. All these were listed in the Compliance Statements and were asked by the PI to be “treated with caution.” The reviewer considers these exceptions the scientific issues, and they should not be considered as the GLP compliance issues.

**Conclusions and Recommendations:** The bioanalytical and TK data are not reliable because of many deficiencies in the bioanalytical studies. These deficiencies were scientific issues and not the GLP compliance issues. The OND reviewer may need complete data for review and evaluation of the bioanalytical and TK data.

#### Attachments

1. Email from Reed Martin dated 10/6/2017
2. Email from Lesley Graham dated 10/19/2017
3. Summary of “exceptions” from the Compliance Statement of (b) (4) bioanalytical phase reports
4. Email from Lesley Graham dated 12/14/2017

cc: via DARRTS  
OSIS/Kassim/Fenty-Stewart/Nkah/Johnson/Miller  
OSIS/DNDBE/Bonapace/ChenZ/Seaton  
DNP/Edward J. Fisher/Pharmacologist (NDA 210365)  
DNP/Stephanie N. Parncutt/Regulatory PM (NDA 210365)

Draft: ZC 11/9/2017, 12/17/2017  
Edits: MS 11/9/2017, CB 12/15/2017, 12/19/2017

**Attachment 1: Email from Martin Reed dated 10/6/2017**

## Chen, Zhou

---

**From:** Chen, Zhou  
**Sent:** Tuesday, December 19, 2017 3:29 PM  
**To:** Chen, Zhou  
**Subject:** FW: Potential GLP impact on NDA submission

**From:** Reed, Martin [<mailto:Martin.Reed@mhra.gov.uk>]  
**Sent:** Friday, October 06, 2017 10:15 AM  
**To:** Bonapace, Charles  
**Subject:** Potential GLP impact on NDA submission

Dear Charles,

Please allow me to introduce myself, my name is Martin Reed, I am a GLP inspector with the UK GLPMA. I want to make you aware of a situation that has been brought to the attention of GLPMA that impacts upon an NDA submission to the FDA. The application number is 210365 with a Product Description of Cannabidiol 100mg/ml Oral Solution. The proposed indication for use is 'adjunctive treatment of seizures associated with Dravet syndrome or Lennox Gastaut syndrome in patients 2 years and older'.

The application was submitted by GW pharma at the end of June 2017. The concerns we have relate to (b) (4) The 10 studies concerned are listed below

8302-923 - 26 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4 Week Treatment-free Period  
8328-341 - 14 day Intravenous (Infusion) Administration Toxicity Study in the Rat  
8309-535 - Oral (Gavage) Study of Embryo-Foetal Development in the Rat  
8302-481 - 10 Week Subcutaneous and Oral (Gavage) Administration Toxicity Study in the Juvenile Rat Followed by a 6 Week Treatment-free Period

(b) (4)

8315-321 - 13 Week Oral (Gavage) Administration Range-finding Study in the Mouse  
8302-924 - 39 Week Oral (Gavage) Administration Toxicity Study in the Dog Followed by a 4 Week Treatment-free Period

(b) (4)

8305-752 - 26 Week Oral (Gavage) Administration Toxicity Study in the Rat Followed by a 4 Week Treatment-free Period

(b) (4)

If you have any questions on the above please do not hesitate to contact me.

Kind regards  
Martin

**Martin Reed**  
GLP Inspector  
Inspections, Enforcement and Standards

MHRA

151 Buckingham Palace Road, London, SW1W 9SZ, UK

Telephone: 020 3080 6304

(b) (6)

Email: [martin.reed@mhra.gov.uk](mailto:martin.reed@mhra.gov.uk)  
[gov.uk/mhra](http://gov.uk/mhra)

Subscribe to the MHRA Inspectorate [blog](#) to stay up to date with our latest news and insights  
MHRA is a centre of the Medicines and Healthcare Products Regulatory Agency

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[DHTermsAndConditions](#)

**Attachment 2: Email from Lesley Graham dated 10/19/2017**

## Chen, Zhou

---

**From:** Bonapace, Charles  
**Sent:** Friday, October 27, 2017 7:56 AM  
**To:** Chen, Zhou  
**Subject:** FW: GW Pharma - Potential GLP impact on NDA submission 210365 Cannabidiol 100mg/ml  
**Attachments:** Summary of GW Pharma Studies conducted at (b) (4) and (b) (4).xlsx; (b) (4) SD statements for GW Pharma studies.pdf; (b) (4) PI statements for GW Pharma studies.pdf

Zhou,

Here is some background of what I would like to discuss today.

---

**From:** Graham, Lesley [mailto:Lesley.Graham@mhra.gov.uk]  
**Sent:** Thursday, October 19, 2017 10:27 AM  
**To:** Bonapace, Charles  
**Subject:** GW Pharma - Potential GLP impact on NDA submission 210365 Cannabidiol 100mg/ml

Dear Charles,

I hope you are well? The purpose of my email is to update you and hopefully answers your queries below regarding the pre-clinical studies used to support the GW Pharma NDA submission. These studies were run as multi sites, (b) (4) acted as the test facility and is where the Study Director was a located. The bioanalysis and toxicokinetic phases of these studies were performed by a test site called (b) (4). It was the test site that was subject to both a GCP and GLP inspection (b) (4). I have attached the following documents for your reference:

1. An excel spreadsheet that summarises my review of the PI statements and studies in general.
2. Copies of the PI compliance statements for all phases
3. Copies of the SD statements for all studies.

I have also answered you questions, see the red and I have provided more context as to the issues below.

The main issues with these studies are this:

For every study on the list:

(b) (4)

(b) (4)

(b) (4)

(b) (4)

2. As it stands I don't know the impact these exceptions have on the overall study. I have discussed this with the PIs and have asked them as a matter of urgency to do the following:

(b) (4)

If you have any questions or wish to discuss I will be in the office next Tuesday.

Kind Regards  
Lesley

Lesley Graham  
Lead Senior Inspector (GLP/GMP)  
MHRA  
I,E&S/Library  
National Institute for Biological Standards and Control - A Centre of the Medicines and Healthcare Products Regulatory Agency  
Blanche Lane  
South Mimms  
Potters Bar  
Hertfordshire  
EN6 3QG

Tel: +44 (0)20 3080 6064  
Mob: (b) (6)

Fax: +44(0)20 3118 9805

Email: [lesley.graham@mhra.gov.uk](mailto:lesley.graham@mhra.gov.uk)

My work days are Tuesday to Thursdays

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<https://www.gov.uk/good-manufacturing-practice-and-good-distribution-practice>

**Please note MHRA email addresses have changed. From Monday 10 April, all @MHRA email addresses have dropped the .gsi – see signature above.**

**Please update your contacts accordingly. Emails sent to the old addresses will continue to be forwarded until further notice.**

---

**From:** Bonapace, Charles [<mailto:Charles.Bonapace@fda.hhs.gov>]

**Sent:** 08 October 2017 15:04

**To:** Reed, Martin <[Martin.Reed@mhra.gov.uk](mailto:Martin.Reed@mhra.gov.uk)>

**Cc:** Gray, Andrew <[Andrew.Gray@mhra.gov.uk](mailto:Andrew.Gray@mhra.gov.uk)>; Turner-Rinehardt, Sharon <[Sharon.Turner-Rinehardt@fda.hhs.gov](mailto:Sharon.Turner-Rinehardt@fda.hhs.gov)>

**Subject:** RE: Potential GLP impact on NDA submission

Dear Martin,

Thank you for notifying me of the concerns described below with studies supporting an application submitted to FDA. I understand that MHRA will be inspecting the testing facility (b) (4)

(b) (4)

If time permits during the inspection, please investigate the following:

(b) (4)

This is what I have asked the PIs to assess and to communicate the impact with the SD; so the answer to this is not know at this time.

Charles

---

**From:** Reed, Martin [<mailto:Martin.Reed@mhra.gov.uk>]

**Sent:** Friday, October 06, 2017 10:15 AM

9 Pages have been Withheld in Full as b4 (CCI/TS)  
immediately following this page

**Attachment 4: Email from Lesley Graham dated 12/14/2017**

## Chen, Zhou

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**From:** Bonapace, Charles  
**Sent:** Friday, December 15, 2017 10:55 AM  
**To:** Chen, Zhou  
**Subject:** FW: GW Pharma - Potential GLP impact on NDA submission 210365 Cannabidiol 100mg/ml  
**Attachments:** Summary of GW Pharma Studies conducted at (b) (4) and (b) (4).xlsx

[New information.](#)

---

**From:** Graham, Lesley [mailto:Lesley.Graham@mhra.gov.uk]  
**Sent:** Thursday, December 14, 2017 11:44 AM  
**To:** Bonapace, Charles  
**Cc:** Vinter, Stephen; Gray, Andrew; McGuinness, Michael; Walker, Paula; Reed, Martin; Whale, Emma  
**Subject:** RE: GW Pharma - Potential GLP impact on NDA submission 210365 Cannabidiol 100mg/ml

Dear Charles,

We have some update on the situation with the GW Pharma pre-clinical GLP studies submitted that were submitted to the FDA in support of a Clinical Trial. Please see attached spreadsheet as a reminder of the affected studies.

(b) (4)

(b) (4)

(b) (4)

Please feel free to give myself or Andrew a call or email if you wish to discuss further.

Kind regards  
Lesley

Lesley Graham

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/s/  
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ZHOU CHEN  
12/20/2017

CHARLES R BONAPACE  
12/21/2017

**Department of Health and Human Services  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Surveillance and Epidemiology**

**Pharmacovigilance Memo**

**Date:** December 4, 2017

**Reviewers:** David Croteau, MD, FRCPC, Medical Officer  
Division of Pharmacovigilance I (DPV I)

Karen Long, PharmD, Safety Evaluator  
DPV I

Hongliu Ding, MD, PhD, MPH  
Division of Epidemiology I

**Team Leaders:** Corrinne Kulick, PharmD  
DPV I

Cynthia Kornegay, PhD  
Division of Epidemiology II

**Directors:** Cindy Kortepeter, PharmD  
DPV I

Judy Staffa, PhD, RPh  
Associate Director for Public Health Initiatives

**Product Name:** (b) (4) (cannabidiol)

**Subject:** All adverse events and abuse potential

**Application Type/Number:** NDA 210365

**Applicant/Sponsor:** GW Research Ltd

**OSE RCM #:** 2017-2266

## 1 INTRODUCTION

This memorandum responds to the Controlled Substance Staff's (CSS) request for evaluation of all adverse events associated with cannabidiol use in the FDA Adverse Event Reporting System (FAERS) database and adverse events relating to abuse potential in the medical literature, and the National Poison Data System (NPDS) and National Electronic Injury Surveillance System—Cooperative Adverse Drug Event Surveillance (NEISS-CADES) databases. OSE's evaluation will inform CSS's Eight-Factor Analyses of cannabidiol to decide if cannabidiol warrants control under the Controlled Substances Act.

On October 27, 2017, GW Research LTD submitted a new drug application (NDA) for cannabidiol ((b) (4) 100 mg/ml oral solution) as adjunctive treatment of seizures associated with Dravet syndrome and Lennox-Gastaut syndrome. FDA granted cannabidiol oral solution fast track designation for Dravet syndrome.

Cannabidiol is one of the many active moieties of cannabis. As such, its pharmacodynamic effects are thought to be mediated by the endocannabinoid system. Cannabinoid receptor-1 (CB1) appears to play an important role in mediating the psychoactive effects of cannabis.<sup>1</sup> However, cannabidiol has been shown to have a very low affinity for and have some indirect antagonist activity on CB1, likely accounting for its lack of psychoactive effects.<sup>2</sup> The anticonvulsant mechanism of cannabidiol has yet to be elucidated, but appears to be mediated through multiple targets and receptors.<sup>2</sup>

Sativex, cannabidiol in combination with delta-9-tetrahydrocannabinol, was approved in Europe in 2010 as an oral spray for symptomatic treatment of multiple sclerosis including spasticity. Cannabidiol is in clinical development in the U.S. but is also available as an unapproved product sold by marijuana dispensaries among other suppliers.

## 2 METHODS AND MATERIALS

### 2.1 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 1.

<b>Table 1. FAERS Search Strategy*</b>	
Date of search	November 9, 2017
Time period of search	All reports through November 9, 2017
Search type	FBIS Quick Query FBIS Product Manufacturer Reporting Summary
Product terms	Product active ingredient: cannabidiol Active ingredient: cannabidiol
MedDRA search terms (version 20.1)	All PT terms
* See Appendix A for a description of the FAERS database.	

Additionally, we screened all cases for the following abuse-misuse preferred terms<sup>a</sup> to identify cases that may provide general abuse-related information.

- Euphoria-related terms (euphoric mood, elevated mood, feeling abnormal, feeling drunk, feeling of relaxation, dizziness, thinking abnormal, hallucination, inappropriate affect)
- Terms indicative of impaired attention, cognition, and mood (somnolence, sedation, mood disorders and disturbances)
- Dissociative/psychotic terms (psychosis, aggression, confusion, and disorientation)
- Related terms not captured elsewhere (drug tolerance, habituation, drug withdrawal syndrome, substance-related disorders)

### 2.2 LITERATURE SEARCH

DPV searched the medical literature with the strategy described in Table 2.

<b>Table 2. Literature Search Strategy</b>	
Date of search	November 9, 2017
Time period of search	All dates through November 9, 2017
Database	PubMed and Embase
Search terms	Cannabidiol[ti] AND (abuse OR misuse OR overdose OR addiction OR withdrawal OR dependence OR diversion OR "use disorder")
Additional search criteria	Human

---

<sup>a</sup> Guidance for Industry: Assessment of Abuse Potential of Drugs. The Controlled Substance Staff, FDA. Jan 2017.

## 2.3 OTHER DATABASES

The American Association of Poison Control Centers (AAPCC) maintains the National Poison Data System (NPDS), which captures data regarding calls to U.S. Poison Control Centers (PCCs) on a near real-time basis. These PCCs receive calls for exposures to a variety of substances from patients, caregivers, or health care providers and document reported events in the database. The cases documented in NPDS represent the number of exposures.

The Division of Epidemiology (DEPI) searched the AAPCC-NPDS database with the strategy described in Table 3.

<b>Table 3. AAPCC-NPDS Search Strategy*</b>	
Date of search	January 1, 2000 through November 17, 2017
Database	National Poison Data System
Restrictions	Age: $\geq 18$ years Age estimate: No Species: Human Exposure: Closed cases Exposure type: Single substance Product type: Contains at least one
Product codes	Cannabidiol: 7836947 Epidiolex: 8114016 Sativex: 6749042
Generic codes	Cannabidiol: 083000 Sativex: 200618

The National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database collects adverse drug-related events by active surveillance from a nationally representative sample of hospital emergency departments. DEPI searched the NEISS-CADES database with the strategy described in Table 4.

<b>Table 4. NEISS-CADES Search Strategy*</b>	
Date of search	November 30, 2017
Time period of search	2004-2015*
Search type	NEISS-CADES query builder: Drug data
Search terms	Cannabidiol, Epidiolex, Sativex
* Available NEISS-CADES data range is 2004-2015	

### 3 RESULTS

#### 3.1 FAERS CASE SELECTION

Our FAERS search retrieved 106 reports. After accounting for duplicate reports, we included 83 cases in the case series (see Figure 1). Appendix B has a line listing of the 83 cases in this case series.

**Figure 1. FAERS Case Selection**

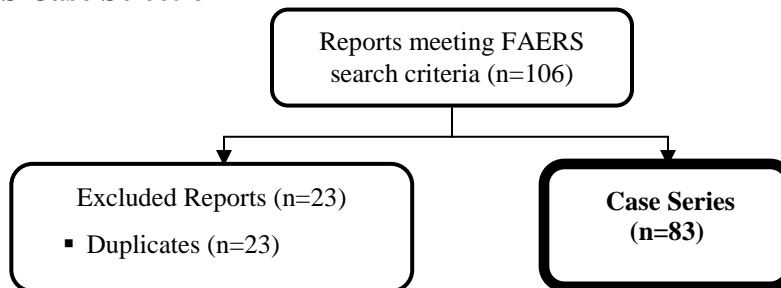


Table 5 presents the descriptive characteristics of the 83 FAERS cases. Most of the reports were domestic and were submitted to FDA in 2017 as periodic reports for co-suspect approved products. The primary reported reason for use of cannabidiol was epilepsy/seizure. The cases where cannabidiol was used for epilepsy/seizure appear to involve younger patients, i.e., mean 12 years old, and were submitted as periodic reports. However, the cases where cannabidiol was used for reasons other than epilepsy/seizure appear to involve older individuals, i.e., mean 49 years old, and were submitted as direct reports (i.e., directly submitted to FDA from consumers or health care professionals).

Table 5. Descriptive Characteristics of FAERS Cases for Cannabidiol Received by FDA Through November 9, 2017 (N=83)						
	All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Age, years	(n=35)		(n=20)		(n=15)	
	Mean	27.3	Mean	11.8	Mean	48.9
	Median	16	Median	8	Median	55
	Range	2-73	Range	2-57	Range	21-73
Sex	Male	20	Male	12	Male	8
	Female	20	Female	9	Female	11
	Unknown	43	Unknown	40	Unknown	3
Country	United States	77	United States	60	United States	17
	Foreign	5	Foreign	1	Foreign	4
	Unknown	1	Unknown	0	Unknown	1
Report type	Expedited	13	Expedited	6	Expedited	7
	Periodic	56	Periodic	53	Periodic	3
	Direct	14	Direct	2	Direct	12
Report year	2014	1	2014	0	2014	1
	2015	26	2015	20	2015	6
	2016	7	2016	4	2016	3
	2017	49	2017	37	2017	12

**Table 5. Descriptive Characteristics of FAERS Cases for Cannabidiol Received by FDA Through November 9, 2017 (N=83)**

	All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Serious outcomes (n=26)*	Death	1	Death	0	Death	1
	Life-threatening	2	Life-threatening	0	Life-threatening	2
	Hospitalization	6	Hospitalization	4	Hospitalization	2
	Disability	2	Disability	0	Disability	2
	Other serious	20	Other serious	6	Other serious	14
Reported reason for use†	Epilepsy/seizure	61	Epilepsy/seizure	61	Pain	6
	Pain	6			Cancer	4
	Cancer	4			Affective disorder	2
	Affective disorder	2			Skin related	2
	Skin related	2			Malaise	1
	Malaise	1			Nausea	1
	Nausea	1			Smoking cessation	1
	Smoking cessation	1			Unknown	5
	Unknown	5				

\* For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention, and other serious important medical events. A report may have one or more outcomes.

† “Pain” includes the following reported reasons for use: analgesic therapy, fibromyalgia, gastritis and pain, migraine/headache and osteopenia, rheumatoid arthritis, sleep disorder and pain. “Cancer” includes the following reported reasons for use: breast cancer, lung cancer, malignant neoplasm. “Affective disorder” includes the following reported reasons for use: affective disorder with anger, depression. “Skin related” includes the following reported reasons for use: rash, dry skin.

Table 6 presents the most frequently reported preferred terms (PTs) in the 83 FAERS cases in decreasing frequency order. PTs relating to drug interaction and potential anticonvulsant neurotoxicity symptoms were predominantly reported for cases where cannabidiol was used for epilepsy/seizure, while more heterogeneous PTs were reported for cases where cannabidiol was used for reasons other than epilepsy/seizure. Appendix C: Table A has a list of all PTs in the 83 FAERS cases.

**Table 6. Most Frequently Reported MedDRA Preferred Terms (PTs) for Cannabidiol FAERS Cases with N≥2, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per PT\***

All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases
Drug interaction	37	Drug interaction	34	Drug interaction	3
Somnolence	25	Somnolence	24	Amnesia	2
Anticonvulsant drug level increased	23	Anticonvulsant drug level increased	22	Depression	2
Sedation	14	Sedation	14	Drug ineffective	2
Sedation complication	7	Sedation complication	7	Headache	2
Seizure	5	Seizure	5	Nausea	2
Amnesia	3	Ataxia	2	Pain	2
Ataxia	2	Drug withdrawal convulsions	2	Palpitations	2
Depression	2	Irritability	2	Product label confusion	2
Drug dependence	2	Petit mal epilepsy	2	Vomiting	2
Drug ineffective	2	Tremor	2		
Drug withdrawal convulsions	2				
Headache	2				

Table 6. Most Frequently Reported MedDRA Preferred Terms (PTs) for Cannabidiol FAERS Cases with N≥2, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per PT*					
All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases
Irritability	2				
Migraine	2				
Nausea	2				
Off label use	2				
Pain	2				
Palpitations	2				
Petit mal epilepsy	2				
Poor quality sleep	2				
Product label confusion	2				
Tremor	2				
Vomiting	2				
*One case may report one or more PTs					

### 3.1.1 Drug interactions

Thirty-seven cases reported the PT “drug interaction,” also the most frequently reported PT. Therefore, we evaluated all cases reporting “drug interaction,” “drug level increased,” and “anticonvulsant drug level increased.” We identified 39 cases reporting any of the above PTs. Thirty-seven of the 39 cases reported a drug interaction with cannabidiol and clobazam. Clobazam is an FDA-approved benzodiazepine for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome, an epilepsy syndrome with heterogeneous and refractory seizures. These drug interaction cases were attributed to cannabidiol inhibition of CYP2C19, typically leading to clobazam clinical neurotoxicity through increased levels of clobazam and its metabolites. Thirty-four of the 37 cases were published in the medical literature.<sup>3-7</sup> These 34 literature cases used Epidiolex (initially proposed trade name for cannabidiol during clinical development by GW Pharmaceuticals). The two remaining cases reported a drug interaction with cannabidiol and sildenafil (n=1) and fosaprepitant dimeglumine (n=1) leading to orthostatic hypotension and serotonin syndrome, respectively.

### 3.1.2 Abuse-Misuse

We reviewed 55 cases identified by specific abuse-misuse PTs for general abuse-related information.

We attributed the following abuse-misuse PTs to an etiology other than cannabidiol:

- “confusional state” (n=1) attributed to an opioid, tapentadol
- “feeling abnormal” (n=1) referred to abnormal somatosensory symptoms and not to a neuropsychiatric phenomenon
- “poisoning” and “mental impairment” (n=1) which could not be clearly attributed to the cannabidiol product due to the inability to ascertain product ingredients. This case is discussed below under “poisoning” (FAERS #13596532)

- “mental status changes” (n=1) attributed to a cannabidiol overdose without evidence of misuse or abuse. This case is discussed below under “mental status changes” (FAERS #13167455)

We attributed the following abuse-misuse PTs to a drug interaction with cannabidiol:

- “dizziness postural” (n=1) attributed to orthostatic hypotension resulting from an interaction between cannabidiol and sildenafil
- “somnolence” (n=25), “sedation” (n=14), and “sedation complication” (n=7) were attributed to clobazam neurotoxicity in all cases except for one that resulted from concurrent use of cannabidiol and sodium oxybate and is discussed below (FAERS #12913917)

### **Drug dependence**

Two cases reported the PT “drug dependence.” The first case (FAERS #13078273) was reported by a physician and involved a 40-year-old male with seropositive rheumatoid arthritis who was taking medical marijuana for pain (presumably arthralgia). The report stated that “without it he says he would not function/marijuana helps the most.” The case was coded and reported as drug dependence. There was no specific reference to cannabidiol in regards to drug dependence even though it was reported that the patient used both medical marijuana and cannabidiol. The second case (FAERS #12943319) was reported by a consumer of unknown age and sex with addiction to many drugs with various qualifiers: “def” to caffeine; “probably” to lacosamide, gabapentin, oxcarbazepine, and clonazepam; “may be on CBD (cannabidiol), fish oil and magnesium (drug dependence), meat and cheese.”

*Reviewer comments – These two cases do not provide support for cannabidiol drug dependence.*

### **Drug withdrawal convulsion**

Two cases reported the PT “drug withdrawal convulsion.” These two cases were also reported in a published case series on a drug-drug interaction between clobazam and cannabidiol in children with refractory epilepsy (Geffrey et al., 2015). The first case (FAERS #11251581) involved a 19-year-old male with refractory epilepsy treated with phenytoin, lacosamide, clobazam, and cannabidiol. After a dose reduction of clobazam (presumably because of the known drug-drug interaction with cannabidiol), the patient experienced an increase in seizure frequency along with urinary retention and ataxia. The second case (FAERS #11252686) involved a 13-year-old male with refractory epilepsy treated with levetiracetam, lacosamide, clobazam, and cannabidiol. After a dose reduction of clobazam (presumably because of the known drug-drug interaction with cannabidiol), the patient experienced an increase in seizure frequency along with drowsiness (coded as “somnolence”).

*Reviewer comments – These two cases of withdrawal seizures are not consistent with cannabidiol withdrawal effect, but are consistent with a dose reduction of clobazam in anticipation of interaction with cannabidiol.*

### **Miscellaneous**

One case reported the PTs “hallucination visual” and “psychotic disorder.” This case (FAERS #13895897) was reported by a male consumer of unknown age. He had a past medical history of schizoaffective disorder treated successfully with lurasidone and lamotrigine without symptoms relapse in 14 years. He reportedly obtained a tincture of 32:1 cannabidiol/tetrahydrocannabinol (THC) in a medical marijuana dispensary. He suspects the product had a much higher THC amount as he experienced psychoactive effects after taking the product. Based on prior personal experience with hemp oil with a 32:1 ratio of cannabidiol/THC, he never experienced psychoactive effects with that type of products. He specifically reports experiencing mild psychosis with visual hallucinations as well as mild depressive symptoms. He returned to the dispensary for a refund but was offered store credit with which he bought another product with the same ingredients as the one initially bought but in “vape form” and he experienced the same psychoactive effects.

*Reviewer comments – While the ingredients in the reported products cannot be ascertained, the underlying schizoaffective disorders may be a contributing factor to the adverse events experienced. In addition, THC is known to have psychoactive effects.*

One case reported the PT “poisoning” and “mental impairment.” This case (FAERS #13596532) was reported by a 32-year-old male consumer. He had a past medical history of asthma and was not on any concomitant medications. He tried Diamond CBD oil for general wellness because it was advertised as all natural and to have no psychological effects. He became seriously impaired including blurred vision, clouded decision making as well as slowed reflexes. He nearly crashed his vehicle. He also stated that he found that there is no “CBD” in this product. After ingesting, he also began having depressed thoughts and at one point even suicidal thoughts, which he had never experienced before. The experience left him very shaken up because he had not called someone to pick him up and he could have done serious harm to himself or others.

*Reviewer comments – This case appears to describe some psychoactive effects although the ingredients in the reported product cannot be ascertained.*

One case reported the PT “mental status changes.” This case (FAERS #13167455) was submitted by a physician. The case involved a 9-year-old boy with past medical history significant for probable structural epilepsy (from hypothalamic hamartoma and right hemispheric stroke/cerebral palsy) including focal seizures with gelastic phenomenology and impairment of awareness/consciousness, diabetes insipidus, hypothyroidism, arachnoid cyst, and gastroesophageal reflux. The patient’s concomitant medications included desmopressin, diazepam (intra-rectal) felbamate, hydrocortisone, ibuprofen, lansoprazole, and pyridoxine. In addition, several supplements were also reported including avocado oil, coconut oil, lavender oil, melatonin, shea butter, and an unspecified vitamin. The patient was inadvertently given an unusually high dose of cannabidiol hemp oil in “MCT” (Palmetto Harmony Hemp Extract) by a new reportedly inexperienced care provider and became unresponsive (coded as “mental status changes”). The patient had two seizures at 3:00 AM and 5:00 AM and was given the entire syringe (5 mL), instead of a “dab (<0.1 mL)” dose, to prevent an additional cluster of seizures.. The patient had experienced prior episodes of prolonged somnolence (up to 24-48 hours) following doses of 0.4 mL, the suggested starting dose of the product. The patient remained unresponsive until the next staff arrived at 3:00 PM. The patient was hospitalized and underwent an endotracheal intubation because of respiratory decline. A mass spectrometry of

urine revealed 123 ng/mL of 11-nor-9-carboxy-delta-tetrahydrocannabinol. The patient was discharged home and additional details on the hospital stay were not provided. A sample of the particular lot/batch of product the patient received was analyzed by the FDA and revealed the following: cannabidiol 15 mg/g, THC 0.53 mg/g, cannabidiolic acid 0.13 mg/g, and cannabinol 0.082 mg/g.

*Reviewer comments – This case appears to be primarily related to an inadvertent overdose of an unapproved cannabidiol product containing other cannabis derivatives. The product was administered for seizures by a care provider without evidence of misuse or abuse. In addition, the epileptic events and concomitant medications (e.g., felbamate, diazepam) may have also contributed to mental status changes and respiratory decline.*

One case reported the PT “death” and “somnolence.” This case (FAERS #12913917) was reported by a consumer or other non-health professional. The case involved a 70-year-old female with metastatic lung cancer who was on cannabidiol for approximately 3 months with an unknown reason for use. Cannabidiol was discontinued due to difficulty waking up attributed to concurrent use of sodium oxybate given for narcolepsy. The patient expired from metastatic lung cancer 3 months later.

*Reviewer comments – This fatal case relates to progressive metastatic disease without any causal role for cannabidiol as it was discontinued 3 months before death.*

Table 7 presents concomitant medications used with cannabidiol in the 83 FAERS cases. The most frequently reported concomitant medications, overall and for cases where cannabidiol was used for epilepsy/seizure, were anticonvulsants, with clobazam being the most frequently reported. The most frequently reported concomitant medications for cases where cannabidiol was used for reasons other than epilepsy/seizure were cannabis products (i.e., cannabis sativa seed oil, hemp oil) reported in seven instances. Appendix D: Table B has a list of all concomitant medications in the 83 FAERS cases.

<b>Table 7. Most Frequently Reported Concomitant Medications for Cannabidiol FAERS Cases with N≥2, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per Concomitant Medication*</b>					
<b>All cases (n=83)</b>		<b>Cases with epilepsy/seizure reported reason for use (n=61)</b>		<b>Cases with other or unknown reported reason for use (n=22)</b>	
<b>Concomitant drug name</b>	<b>Total cases</b>	<b>Concomitant drug name</b>	<b>Total cases</b>	<b>Concomitant drug name</b>	<b>Total cases</b>
Clobazam	57	Clobazam	56	Cannabis sativa seed oil	6
Levetiracetam	7	Levetiracetam	7	Duloxetine	3
Cannabis sativa seed oil	6	Lacosamide	6	Amphetamine/dextroamphetamine	2
Lacosamide	6	Valproic acid	5	Aspirin	2
Lamotrigine	5	Felbamate	3	Calcium	2
Valproic acid	5	Lamotrigine	3	Dexamethasone	2
Vitamin	4	Diazepam	2	Folic acid	2
Duloxetine	3	Lansoprazole	2	Lamotrigine	2
Felbamate	3	Melatonin	2	Omega 3	2
Melatonin	3	Rufinamide	2	Omeprazole	2

Table 7. Most Frequently Reported Concomitant Medications for Cannabidiol FAERS Cases with N≥2, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per Concomitant Medication*					
All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Concomitant drug name	Total cases	Concomitant drug name	Total cases	Concomitant drug name	Total cases
Acetaminophen	2	Vigabatrin	2	Oxycodone	2
Amphetamine/ dextroamphetamine	2	Vitamin	2	Probiotics	2
Aspirin	2			Progesterone	2
Calcium	2			Vitamin	2
Clonazepam	2				
Dexamethasone	2				
Diazepam	2				
Folic acid	2				
Lansoprazole	2				
Magnesium	2				
Omega 3	2				
Omeprazole	2				
Oxycodone	2				
Probiotics	2				
Progesterone	2				
Rufinamide	2				
Vigabatrin	2				
*One case may report one or concomitant medications					

### 3.2 LITERATURE SEARCH RESULTS

DPV's search of the medical literature using the search criteria in Section 2.2, retrieved 41 publications in PubMed and 25 publications in Embase. We identified three publications relevant to abuse potential. These three publications reporting on clinical studies suggest minimal or no abuse potential of cannabidiol used in different populations, including frequent and infrequent marijuana users and multiple sclerosis patients.<sup>8-10</sup> Table 8 presents a summary of these three studies.

<b>Table 8. Summary of Publications on Cannabidiol Abuse Potential</b>						
<b>Publication</b>	<b>Population Studied</b>	<b>Design</b>	<b>Patients and Study Sites N</b>	<b>Intervention</b>	<b>Endpoints</b>	<b>Key Findings</b>
Babalonis et al., 2017	Marijuana frequent users	Within subjects randomized, placebo-controlled, double-blind	31 (14 women, 17 men) from 3 study sites	Oral placebo, CBD 200, 400, and 800 mg with or without smoked marijuana	Physiologic: HR, BP Performance: DSST, CPT Participant-rated: VAS of marijuana effects and 44-item mood inventory	Outcome measures similar between CBD and placebo groups

<b>Table 8. Summary of Publications on Cannabidiol Abuse Potential</b>						
<b>Publication</b>	<b>Population Studied</b>	<b>Design</b>	<b>Patients and Study Sites N</b>	<b>Intervention</b>	<b>Endpoints</b>	<b>Key Findings</b>
Garrido et al., 2013 (meeting abstract only)	Marijuana infrequent users	Double-blind, randomized, controlled, cross-over study	24 men, number of study sites N/R	Sublingual THC 7.5 mg, CBD 7.5 mg, combination, or placebo	VAS of “high,” “any effect,” “bad effects,” “visions,” “auditory effects,” “drug liking,” anxiety, nausea, sleepiness, and dry mouth	Abuse potential and overall subjective effects produced by sublingual THC, CBD, or the combination of both are not clinically relevant
Robson, 2011	Multiple sclerosis; healthy non-dependent regular recreational marijuana users	Review of literature and Sativex integrated safety analysis	1100 patients with multiple sclerosis, 23 healthy marijuana users, multiple study sites	Variable doses of THC/CBD mouth spray (Sativex); dronabinol (Marinol) in healthy marijuana user subset	Multiple endpoints outlined under each study in the publication	Generally low intoxication scores with euphoria reported in 2.2%; some abuse potential in experienced cannabis smokers
BP=blood pressure; CBD=cannabidiol; CPT= continuous performance task; DSST=digit symbol substitution task; HR=heart rate; N/R=not reported; THC=δ-9-tetrahydrocannabinol; VAS=visual analog scales						

In addition, we identified one case report and one case series that describe the effectiveness of cannabidiol in cannabis withdrawal syndrome.<sup>11, 12</sup> Lastly, one publication discusses a potential drug interaction with cannabidiol and commonly used anticonvulsants. This publication reports significant changes in serum levels of clobazam, eslicarbazepine, rufinamide, topiramate, and zonisamide when used concurrently with cannabidiol.<sup>6</sup>

### 3.3 OTHER DATABASES

DEPI’s search of the AAPCC-NPDS database using the search criteria in Section 2.3, retrieved 88 cases. All 88 cases reported exposure to marijuana (dried plant). DEPI did not identify any cases exposed to either Sativex or Epidiolex.

DEPI’s search of the NEISS-CADES database using the search criteria in Section 2.3, did not retrieve any cases.

## 4 REVIEWER’S COMMENTS

DPV identified 83 FAERS cases reporting adverse events with cannabidiol as a suspect drug, most of which were reported in 2017. The source of cannabidiol was reported in 34 of the cases (cannabidiol provided in clinical trials) while for the remaining 49 cases the exact source could not be determined. The most frequently reported reason for use of cannabidiol was

epilepsy/seizure and the most frequently reported concomitant medications were anticonvulsants. The most frequently reported adverse event PT was drug interaction. Clobazam was the most frequently reported concomitant medication and increased levels of clobazam was the most frequent drug-drug interaction. The older individuals and higher proportion of direct reports observed in cases reporting a reason for use other than epilepsy/seizure may suggest use of cannabidiol without medical supervision.

We identified 55 cases reporting specific abuse-misuse PTs with cannabidiol use, but none appear to have convincing evidence of abuse potential. Given the pre-clinical observations of euphoric behavior, it is important to mention that we did not identify any euphoria-related terms in our review, except for one patient with pre-existing schizoaffective disorder who experienced visual hallucinations after using a product reportedly containing a mixture of cannabidiol and THC. One case reporting somnolence with a fatal outcome appears causally unrelated to cannabidiol. The medical literature findings also suggest minimal or low abuse potential with cannabidiol and describes drug interactions between cannabidiol and clobazam and other anticonvulsants, which can alter the serum levels of anticonvulsants.

Adverse event reports for cannabidiol-containing products are entered into the FAERS database when received by the FDA. Importantly, the FAERS database is designed to capture adverse event reports for FDA-approved products. Because cannabidiol is not an FDA-approved product, FAERS reports may be received from manufacturers of approved co-suspect products, or from health professionals or consumers with unapproved cannabidiol as the primary suspect drug. Because cannabidiol is not an FDA-approved product, it is not known if FAERS would capture serious, rare, or new toxicity of cannabidiol. Other general FAERS limitations include the lack of certainty that the reported event was caused by the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain sufficient detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether an event will be reported, such as the time a product has been marketed and publicity about an event.

We did not identify any additional cases of abuse with cannabidiol in the AAPCC-NPDS or NEISS-CADES databases. NPDS case records are self-reported mainly from the public (68.9% from a residence vs 23.2% from a Health Care Professional).<sup>13</sup> Although Poison Control Centers perform follow-up calls, they are not able to verify the accuracy of every report made to AAPCC member centers.<sup>14</sup> Therefore, while the 88 cases identified from this database were all documented as marijuana (dried plant)-related, the exposure to cannabidiol itself (unapproved product) cannot be excluded due to the potential misclassification resulting from patient self-reporting.

The limitation of NEISS-CADES data available from 2004-2015 is it does not include cases with intentional drug injuries resulting from alcohol, tobacco, and illicit substances.<sup>15</sup> Because the NEISS-CADES database started to collect information about drug abuse in 2016, it is likely the reason we did not capture any cases of cannabidiol abuse during this study period (through 2015). The data relating to emergency department visits from drug abuse are not yet available in NEISS-CADES.

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## **6 APPENDICES**

### **6.1 APPENDIX A. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)**

#### **FDA Adverse Event Reporting System (FAERS)**

FAERS is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary.

## 6.2 APPENDIX B. FAERS LINE LISTING OF CANNABIDIOL CASE SERIES

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
1	7/10/2017 10/13/2017 7/7/2017	13736878 14092001 13726399	1 1 1		Direct	2	M	USA	HO
2	5/18/2016	12383229	1	US-LUNDBECK-DKLU2013871	Expedited	3.0	M	USA	OT
3	6/29/2016	12510269	1	US-LUNDBECK-DKLU2014739	Non- Expedited	3	M	USA	
4	7/30/2015	11323715	2	US-LUNDBECK-DKLU2001652	Non- Expedited	4	F	USA	
5	5/26/2016	12408707	2	US-LUNDBECK-DKLU2014301	Expedited	4.6	F	USA	HO
6	7/30/2015	11323740	2	US-LUNDBECK-DKLU2001650	Non- Expedited	5	M	USA	
7	7/6/2017 7/11/2017	13720537 13742610	1 1	FR-UCBSA-2017026106 FR-ABBVIE-17P-056-2034331-00	Expedited	5	M	FRA	HO
8	7/30/2015	11323739	2	US-LUNDBECK-DKLU2001649	Non- Expedited	6	F	USA	
9	7/30/2015	11323717	2	US-LUNDBECK-DKLU2001653	Non- Expedited	7	F	USA	
10	7/30/2015	11323703	2	US-LUNDBECK-DKLU2001655	Non- Expedited	8	F	USA	
11	7/30/2015	11323736	2	US-LUNDBECK-DKLU2001647	Non- Expedited	8	F	USA	
12	1/27/2017 2/15/2017	13167455 13238111	1 1		Direct	9	M	USA	HO
13	7/30/2015	11323722	2	US-LUNDBECK-DKLU2001651	Non- Expedited	12	F	USA	
14	7/30/2015	11323707	2	US-LUNDBECK-DKLU2001654	Non- Expedited	12	M	USA	
15	7/8/2015	11252686	1	US-LUNDBECK-DKLU2001395	Non- Expedited	13	M	USA	OT
16	7/30/2015	11323737	1	US-LUNDBECK-DKLU2001646	Non- Expedited	14	M	USA	
17	7/30/2015	11323741	2	US-LUNDBECK-DKLU2001645	Non- Expedited	16	M	USA	
18	7/30/2015	11323738	2	US-LUNDBECK-DKLU2001648	Non- Expedited	16	M	USA	
19	7/8/2015	11251581	1	US-LUNDBECK-DKLU2001209	Non- Expedited	19	M	USA	OT
20	8/17/2015	11393943	1		Direct	21	F	USA	OT
21	6/6/2017	13619417	1		Direct	26	F	USA	
22	3/26/2017	13373054	1		Direct	28	M	USA	DS,OT
23	5/23/2017	13596532	1		Direct	28.2	M	USA	OT
24	1/2/2017 12/23/2016 1/17/2017 11/6/2017 11/8/2017	13078273 13058820 13121184 14162821 14170084	3 2 2 1 1	CA-AMGEN-CANSL2016079069 CA-APOTEX-2016AP015802 CA-SA-2017SA006087 CA-AMGEN-CANSP2017165151 CA-PFIZER INC-2017480210	Expedited	40	M	CAN	OT

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
	1/18/2017	13128603	2	CA-CONCORDIA PHARMACEUTICALS INC.- GSH201701-000467					
25	10/4/2016	12806365	2	GXBR2016US002623	Non- Expedited	44	F	USA	
26	10/18/2016	12856924	3	US-PFIZER INC-2016380232	Non- Expedited	46	F	USA	
27	9/30/2015 9/29/2015	11582805 11576206	1 1		Direct	55	F	USA	OT
28	5/27/2017	13596798	1		Direct	57	M	USA	OT
29	6/27/2017	13694089	3	US-JNJFOC-20170620141	Expedited	57.4	F	USA	OT
30	5/24/2017	13596653	1		Direct	58	F	USA	OT
31	8/27/2015	11422350	1	US-PFIZER INC-2015281877	Non- Expedited	60	M	USA	
32	10/24/2017	14121775	1	US-009507513-1710USA011668	Expedited	60.8	F	USA	LT,OT
33	8/30/2017	13919249	1	CA-AMGEN-CANSL2017102053	Expedited	65	M	CAN	OT
34	11/4/2016 12/15/2016	12913917 13032728	5 2	US-JAZZ-2016-US-021533 US-BAUSCH-BL-2016-027201	Expedited	70.4	F	USA	DE,HO,OT
35	9/30/2015	11578634	1	IT-DEP_08229_2015	Expedited	73.5	F	ITA	HO
36	6/29/2017	13703332	1	PHHY2017AU093588	Expedited		F	AUS	OT
37	9/15/2017	13976115	1	US-UCBSA-2017036826	Expedited		F	USA	OT
38	6/9/2017	13636386	1		Direct		F	USA	
39	10/8/2015	11615752	1		Direct		M	NULL	OT
40	8/21/2017	13895897	1		Direct		M	USA	OT
41	5/28/2015	11146696	1	US-LUNDBECK-DKLU1112067	Non- Expedited		NULL	USA	
42	6/21/2017	13675616	1	US-LUNDBECK-DKLU2032793	Non- Expedited		NULL	USA	
43	9/12/2017 4/8/2016	13960015 12249472	1 1	US-LUNDBECK-DKLU2035996 US-LUNDBECK-DKLU2012125	Non- Expedited		NULL	USA	
44	6/21/2017	13675682	1	US-LUNDBECK-DKLU2033149	Non- Expedited		NULL	USA	
45	9/15/2017 4/29/2016	13974206 12319484	1 1	US-LUNDBECK-DKLU2037053 US-LUNDBECK-DKLU2012844	Non- Expedited		NULL	USA	
46	6/21/2017	13675618	1	US-LUNDBECK-DKLU2033150	Non- Expedited		NULL	USA	
47	9/15/2017 4/29/2016	13974227 12319494	1 1	US-LUNDBECK-DKLU2037054 US-LUNDBECK-DKLU2012845	Non- Expedited		NULL	USA	
48	6/21/2017	13675686	1	US-LUNDBECK-DKLU2033151	Non- Expedited		NULL	USA	
49	9/15/2017	13974244	1	US-LUNDBECK-DKLU2037055	Non- Expedited		NULL	USA	
50	6/21/2017	13675675	1	US-LUNDBECK-DKLU2033152	Non- Expedited		NULL	USA	

	Initial FDA Received Date	FAERS Case #	Version #	Manufacturer Control #	Case Type	Age (years)	Sex	Country Derived	Serious Outcome(s)*
51	9/15/2017	13974237	1	US-LUNDBECK-DKLU2037056	Non- Expedited		NULL	USA	
52	6/21/2017	13675673	1	US-LUNDBECK-DKLU2033153	Non- Expedited		NULL	USA	
53	9/15/2017	13974257	1	US-LUNDBECK-DKLU2037057	Non- Expedited		NULL	USA	
54	6/21/2017	13675688	1	US-LUNDBECK-DKLU2033154	Non- Expedited		NULL	USA	
55	6/21/2017	13675694	1	US-LUNDBECK-DKLU2033155	Non- Expedited		NULL	USA	
56	6/21/2017	13675693	1	US-LUNDBECK-DKLU2033156	Non- Expedited		NULL	USA	
57	6/21/2017	13675690	1	US-LUNDBECK-DKLU2033157	Non- Expedited		NULL	USA	
58	5/28/2015	11146708	1	US-LUNDBECK-DKLU1113100	Non- Expedited		NULL	USA	
59	6/21/2017	13675612	1	US-LUNDBECK-DKLU2033141	Non- Expedited		NULL	USA	
60	9/15/2017	13974021	1	US-LUNDBECK-DKLU2037045	Non- Expedited		NULL	USA	
	4/29/2016	12319307	1	US-LUNDBECK-DKLU2012836					
61	5/28/2015	11146676	1	US-LUNDBECK-DKLU1113101	Non- Expedited		NULL	USA	
62	6/21/2017	13675648	1	US-LUNDBECK-DKLU2033142	Non- Expedited		NULL	USA	
63	9/15/2017	13974028	1	US-LUNDBECK-DKLU2037046	Non- Expedited		NULL	USA	
	4/29/2016	12319338	1	US-LUNDBECK-DKLU2012837					
64	5/28/2015	11146769	1	US-LUNDBECK-DKLU1113102	Non- Expedited		NULL	USA	
65	6/21/2017	13675657	1	US-LUNDBECK-DKLU2033143	Non- Expedited		NULL	USA	
66	9/15/2017	13974042	1	US-LUNDBECK-DKLU2037047	Non- Expedited		NULL	USA	
	4/29/2016	12319384	1	US-LUNDBECK-DKLU2012838					
67	5/28/2015	11146794	1	US-LUNDBECK-DKLU1113103	Non- Expedited		NULL	USA	
68	6/21/2017	13675656	1	US-LUNDBECK-DKLU2033144	Non- Expedited		NULL	USA	
69	9/15/2017	13974103	1	US-LUNDBECK-DKLU2037048	Non- Expedited		NULL	USA	
	4/29/2016	12319430	1	US-LUNDBECK-DKLU2012839					
70	5/28/2015	11146881	1	US-LUNDBECK-DKLU1113104	Non- Expedited		NULL	USA	
71	6/21/2017	13675661	1	US-LUNDBECK-DKLU2033145	Non- Expedited		NULL	USA	
72	9/15/2017	13974105	1	US-LUNDBECK-DKLU2037049	Non- Expedited		NULL	USA	
	4/29/2016	12319445	1	US-LUNDBECK-DKLU2012840					
73	5/28/2015	11146892	1	US-LUNDBECK-DKLU1113105	Non- Expedited		NULL	USA	
74	6/21/2017	13675671	1	US-LUNDBECK-DKLU2033146	Non- Expedited		NULL	USA	
75	9/15/2017	13974169	1	US-LUNDBECK-DKLU2037050	Non- Expedited		NULL	USA	
	4/29/2016	12319460	1	US-LUNDBECK-DKLU2012841					
76	6/21/2017	13675681	1	US-LUNDBECK-DKLU2033147	Non- Expedited		NULL	USA	
77	9/15/2017	13974197	1	US-LUNDBECK-DKLU2037051	Non- Expedited		NULL	USA	
	4/29/2016	12319470	1	US-LUNDBECK-DKLU2012842					

	<b>Initial FDA Received Date</b>	<b>FAERS Case #</b>	<b>Version #</b>	<b>Manufacturer Control #</b>	<b>Case Type</b>	<b>Age (years)</b>	<b>Sex</b>	<b>Country Derived</b>	<b>Serious Outcome(s)*</b>
78	6/21/2017	13675672	1	US-LUNDBECK-DKLU2033148	Non- Expedited		NULL	USA	
79	9/15/2017 4/29/2016	13974209 12319478	1 1	US-LUNDBECK-DKLU2037052 US-LUNDBECK-DKLU2012843	Non- Expedited		NULL	USA	
80	11/15/2016	12943319	1	US-UCBSA-2016042816	Expedited		NULL	USA	OT
81	2/18/2014	9907219	1	US-LUNDBECK-DKLU1097435	Expedited		NULL	USA	OT
82	12/29/2015	11878269	1		Direct		NULL	USA	DS,LT
83	6/6/2017	13620135	1		Direct		NULL	USA	
<p>*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, and other serious important medical events. This outcome should not be confused with the clinical outcome of the reported adverse drug experience. Those which are blank were not marked as serious (per the previous definition) by the reporter, and are coded as non-serious. A report may have more than one serious outcome.</p> <p>Abbreviations: DE=Death, HO=Hospitalization, LT= Life-threatening, DS= Disability, OT=Other medically significant</p>									

### 6.3 APPENDIX C. MOST FREQUENTLY REPORTED PTs

<b>Table A. Most Frequently Reported MedDRA Preferred Terms (PTs) for all Cannabidiol FAERS Cases, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per PT*</b>					
<b>All cases (n=83)</b>		<b>Cases with epilepsy/seizure reported reason for use (n=61)</b>		<b>Cases with other or unknown reported reason for use (n=22)</b>	
<b>Preferred Term (PT)</b>	<b>Total cases</b>	<b>Preferred Term (PT)</b>	<b>Total cases</b>	<b>Preferred Term (PT)</b>	<b>Total cases</b>
Drug interaction	37	Drug interaction	34	Drug interaction	3
Somnolence	25	Somnolence	24	Amnesia	2
Anticonvulsant drug level increased	23	Anticonvulsant drug level increased	22	Depression	2
Sedation	14	Sedation	14	Drug ineffective	2
Sedation complication	7	Sedation complication	7	Headache	2
Seizure	5	Seizure	5	Nausea	2
Amnesia	3	Ataxia	2	Pain	2
Ataxia	2	Drug withdrawal convulsions	2	Palpitations	2
Depression	2	Irritability	2	Product label confusion	2
Drug dependence	2	Petit mal epilepsy	2	Vomiting	2
Drug ineffective	2	Tremor	2	Abulia	1
Drug withdrawal convulsions	2	Amnesia	1	Accidental exposure to product	1
Headache	2	Aphasia	1	Alanine aminotransferase increased	1
Irritability	2	Aspiration	1	Angina pectoris	1
Migraine	2	Atelectasis	1	Anticonvulsant drug level increased	1
Nausea	2	Decreased appetite	1	Arthralgia	1
Off label use	2	Drug dependence	1	Bradykinesia	1
Pain	2	Drug level increased	1	Bradyphrenia	1
Palpitations	2	Dyskinesia	1	Brain cancer metastatic	1
Petit mal epilepsy	2	Feeling abnormal	1	C-reactive protein increased	1
Poor quality sleep	2	Generalised tonic-clonic seizure	1	Chills	1
Product label confusion	2	Hyperammonaemia	1	Confusional state	1
Tremor	2	Incorrect dose administered	1	Constipation	1
Vomiting	2	Mental status changes	1	Cough	1
Abulia	1	Metabolic acidosis	1	Death	1
Accidental exposure to product	1	Migraine	1	Dermatitis psoriasiform	1
Alanine aminotransferase increased	1	Neoplasm malignant	1	Disease progression	1
Angina pectoris	1	Off label use	1	Dizziness postural	1
Aphasia	1	Partial seizures	1	Drug dependence	1
Arthralgia	1	Pneumonia	1	Drug dispensing error	1
Aspiration	1	Poor quality sleep	1	Drug dose omission	1
Atelectasis	1	Respiratory disorder	1	Dry skin	1
Bradykinesia	1	Salivary hypersecretion	1	Dyspnoea	1
Bradyphrenia	1	Status epilepticus	1	Encephalopathy	1
Brain cancer metastatic	1	Urinary retention	1	Erythema	1
Chills	1	Urine output decreased	1	Fall	1
Confusional state	1			Fatigue	1

**Table A. Most Frequently Reported MedDRA Preferred Terms (PTs) for all Cannabidiol FAERS Cases, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per PT\***

All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases
Constipation	1			Fear	1
Cough	1			Fibromyalgia	1
C-reactive protein increased	1			Gastrointestinal disorder	1
Death	1			Gingival pain	1
Decreased appetite	1			Gingival swelling	1
Dermatitis psoriasiform	1			Hallucination, visual	1
Disease progression	1			Hypertension	1
Dizziness postural	1			Hypoacusis	1
Drug dispensing error	1			Hyporeflexia	1
Drug dose omission	1			Incontinence	1
Drug level increased	1			Injection site mass	1
Dry skin	1			Injection site pain	1
Dyskinesia	1			Injury associated with device	1
Dyspnoea	1			Jaw disorder	1
Encephalopathy	1			Joint contracture	1
Erythema	1			Joint swelling	1
Fall	1			Liver function test increased	1
Fatigue	1			Loss of consciousness	1
Fear	1			Lung neoplasm malignant	1
Feeling abnormal	1			Malignant neoplasm progression	1
Fibromyalgia	1			Mental impairment	1
Gastrointestinal disorder	1			Migraine	1
Generalised tonic-clonic seizure	1				
Gingival pain	1			Mobility decreased	1
Gingival swelling	1			Muscle twitching	1
Hallucination, visual	1			Nasopharyngitis	1
Hyperammonaemia	1			Nervousness	1
Hypertension	1			Off label use	1
Hypoacusis	1			Orthostatic hypotension	1
Hyporeflexia	1			Poisoning	1
Incontinence	1			Poor quality sleep	1
Incorrect dose administered	1			Product advertising issue	1
Injection site mass	1			Product formulation issue	1
Injection site pain	1			Product label issue	1
Injury associated with device	1			Product quality issue	1
Jaw disorder	1			Product tampering	1
Joint contracture	1			Product taste abnormal	1
Joint swelling	1			Product use in unapproved indication	1
Liver function test increased	1			Pruritus	1
Loss of consciousness	1			Psychotic disorder	1
Lung neoplasm malignant	1			Serotonin syndrome	1
Malignant neoplasm progression	1			Somnolence	1
Mental impairment	1				
				Stomatitis	1
				Stress	1

**Table A. Most Frequently Reported MedDRA Preferred Terms (PTs) for all Cannabidiol FAERS Cases, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per PT\***

All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases	Preferred Term (PT)	Total cases
Mental status changes	1			Suicidal ideation	1
Metabolic acidosis	1			Tinnitus	1
Mobility decreased	1			Tooth fracture	1
Muscle twitching	1			Unevaluable event	1
Nasopharyngitis	1			Urticaria	1
Neoplasm malignant	1			Vision blurred	1
Nervousness	1			Visual impairment	1
Orthostatic hypotension	1			Wrong technique in product usage process	1
Partial seizures	1				
Pneumonia	1				
Poisoning	1				
Product advertising issue	1				
Product formulation issue	1				
Product label issue	1				
Product quality issue	1				
Product tampering	1				
Product taste abnormal	1				
Product use in unapproved indication	1				
Pruritus	1				
Psychotic disorder	1				
Respiratory disorder	1				
Salivary hypersecretion	1				
Serotonin syndrome	1				
Status epilepticus	1				
Stomatitis	1				
Stress	1				
Suicidal ideation	1				
Tinnitus	1				
Tooth fracture	1				
Unevaluable event	1				
Urinary retention	1				
Urine output decreased	1				
Urticaria	1				
Vision blurred	1				
Visual impairment	1				
Wrong technique in product usage process	1				
*One case may report one or more PTs					

## 6.4 APPENDIX D. MOST FREQUENTLY REPORTED CONCOMITANT MEDICATIONS

<b>Table B. Most Frequently Reported Concomitant Medications for all Cannabidiol FAERS Cases, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per Concomitant Medication*</b>					
<b>All cases (n=83)</b>		<b>Cases with epilepsy/seizure reported reason for use (n=61)</b>		<b>Cases with other or unknown reported reason for use (n=22)</b>	
<b>Concomitant drug name</b>	<b>Total cases</b>	<b>Concomitant drug name</b>	<b>Total cases</b>	<b>Concomitant drug name</b>	<b>Total cases</b>
Clobazam	57	Clobazam	56	Cannabis sativa seed oil	6
Levetiracetam	7	Levetiracetam	7	Duloxetine	3
Cannabis sativa seed oil	6	Lacosamide	6	Amphetamine/ dextroamphetamine	2
Lacosamide	6	Valproic acid	5	Aspirin	2
Lamotrigine	5	Felbamate	3	Calcium	2
Valproic acid	5	Lamotrigine	3	Dexamethasone	2
Vitamin	4	Diazepam	2	Folic acid	2
Duloxetine	3	Lansoprazole	2	Lamotrigine	2
Felbamate	3	Melatonin	2	Omega 3	2
Melatonin	3	Rufinamide	2	Omeprazole	2
Acetaminophen	2	Vigabatrin	2	Oxycodone	2
Amphetamine/ dextroamphetamine	2	Vitamin	2	Probiotics	2
Aspirin	2	Acetaminophen	1	Progesterone	2
Calcium	2	Avocado oil	1	Vitamin	2
Clonazepam	2	Brivaracetam	1	Acetaminophen	1
Dexamethasone	2	Caffeine	1	Anastrozole	1
Diazepam	2	Cetirizine	1	Aprepitant	1
Folic acid	2	Citalopram	1	Armodafinil	1
Lansoprazole	2	Clonazepam	1	Bismuth subsalicylate	1
Magnesium	2	Clonidine	1	Bupropion	1
Omega 3	2	Coconut oil	1	Capecitabine	1
Omeprazole	2	Desmopressin	1	Clobazam	1
Oxycodone	2	Erythromycin	1	Clonazepam	1
Probiotics	2	Esomeprazole	1	Co Q 10	1
Progesterone	2	Fish oil	1	Curcumin	1
Rufinamide	2	Fluticasone	1	Cyanocobalamin	1
Vigabatrin	2	Fluticasone-salmeterol	1	Cyclophosphamide	1
Anastrozole	1	Gabapentin	1	Denosumab	1
Aprepitant	1	Glycopyrrolate	1	Docetaxel	1
Armodafinil	1	Hydrocortisone	1	Enoxaparin	1
Avocado oil	1	Ibuprofen	1	Estradiol	1
Bismuth subsalicylate	1	Ketamine	1	Etanercept	1
Brivaracetam	1	Lavender oil	1	Evolocumab	1
Bupropion	1	Levalbuterol	1	Exemestane	1
Caffeine	1	Lorazepam	1	Famotidine	1
Capecitabine	1	Magnesium	1	Fulvestrant	1
Cetirizine	1	Midazolam	1	Gemcitabine	1
Citalopram	1	Oxcarbazepine	1	Glatiramer acetate	1
Clonidine	1	Phenytoin	1	Guaifenesin	1
Co Q 10	1	Polyethylene glycol	1	Hemp oil	1
Coconut oil	1	Probiotic	1	Hydromorphone	1
Curcumin	1	Pyridoxine	1	Hydroxychloroquine	1
Cyanocobalamin	1	Rivaroxaban	1	Indapamide	1
Cyclophosphamide	1	Shea butter	1	Krill oil	1

**Table B. Most Frequently Reported Concomitant Medications for all Cannabidiol FAERS Cases, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per Concomitant Medication\***

All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Concomitant drug name	Total cases	Concomitant drug name	Total cases	Concomitant drug name	Total cases
Denosumab	1	Sotalol	1	Lapatinib	1
Desmopressin	1	Topiramate	1	Leflunomide	1
Docetaxel	1	Zonisamide	1	Letrozole	1
Enoxaparin	1			Levothyroxine	1
Erythromycin	1			Lidocaine	1
Esomeprazole	1			Liothyronine	1
Estradiol	1			Lisinopril	1
Etanercept	1			Lithium	1
Evolocumab	1			Lurasidone	1
Exemestane	1			Magnesium	1
Famotidine	1			Marijuana	1
Fish oil	1			Melatonin	1
Fluticasone	1			Meloxicam	1
Fluticasone-salmeterol	1			Methotrexate	1
Fulvestrant	1			Metoprolol	1
Gabapentin	1			Nicotine	1
Gemcitabine	1			Nortriptyline	1
Glatiramer acetate	1			Oxazepam	1
Glycopyrrolate	1			Oxycodine and aspirin	1
Guaifenesin	1			Paclitaxel	1
Hemp oil	1			Palbociclib	1
Hydrocortisone	1			Pertuzumab	1
Hydromorphone	1			Phentermine	1
Hydroxychloroquine	1			Potassium	1
Ibuprofen	1			Prasugrel	1
Indapamide	1			Pregabalin	1
Ketamine	1			Pycnogenol	1
Krill oil	1			Sildenafil	1
Lapatinib	1			Sinus rinse	1
Lavender oil	1			Sodium oxybate	1
Leflunomide	1			Somatropin	1
Letrozole	1			Spironolactone	1
Levalbuterol	1			Sulfasalazine	1
Levothyroxine	1			Tapentadol	1
Lidocaine	1			Tramadol	1
Liothyronine	1			Trastuzumab	1
Lisinopril	1			Venlafaxine	1
Lithium	1			Vinorelbine	1
Lorazepam	1			Vitamin D	1
Lurasidone	1			Vitamin B	1
Marijuana	1			Ziprasidone	1
Meloxicam	1			Zoledronic acid	1
Methotrexate	1				
Metoprolol	1				
Midazolam	1				
Nicotine	1				
Nortriptyline	1				
Oxazepam	1				

**Table B. Most Frequently Reported Concomitant Medications for all Cannabidiol FAERS Cases, all Reports Received by FDA Through November 9, 2017, Sorted by Decreasing FAERS Reports per Concomitant Medication\***

All cases (n=83)		Cases with epilepsy/seizure reported reason for use (n=61)		Cases with other or unknown reported reason for use (n=22)	
Concomitant drug name	Total cases	Concomitant drug name	Total cases	Concomitant drug name	Total cases
Oxcarbazepine	1				
Oxycodine and aspirin	1				
Paclitaxel	1				
Palbociclib	1				
Pertuzumab	1				
Phentermine	1				
Phenytoin	1				
Polyethylene glycol	1				
Potassium	1				
Prasugrel	1				
Pregabalin	1				
Pycnogenol	1				
Pyridoxine	1				
Rivaroxaban	1				
Shea butter	1				
Sildenafil	1				
Sinus rinse	1				
Sodium oxybate	1				
Somatropin	1				
Sotalol	1				
Spironolactone	1				
Sulfasalazine	1				
Tapentadol	1				
Topiramate	1				
Tramadol	1				
Trastuzumab	1				
Venlafaxine	1				
Vinorelbine	1				
Vitamin D	1				
Vitamin B	1				
Ziprasidone	1				
Zoledronic acid	1				
Zonisamide	1				
*One case may report one or concomitant medications					

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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DAVID J CROTEAU  
12/04/2017

KAREN M LONG  
12/04/2017

HONGLIU DING  
12/04/2017

CORRINNE KULICK  
12/04/2017

CYNTHIA J KORNEGAY  
12/04/2017

JUDY A STAFFA  
12/04/2017

CINDY M KORTEPETER  
12/04/2017

# MEMORANDUM

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## OSI/DCCE CONSULT: CLINICAL INSPECTIONS REQUEST

*CDER's Clinical Investigator Site Selection Tool Generated*

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**Date:** 11/30/2017

**To:** Ni Khin, M.D., Division Director, DCCE  
Kassa Ayalew, M.D., Branch Chief, GCPAB  
Phillip Kronstein, M.D., Team Leader, GCPAB

Cara Alfaro, Pharm.D  
Division of Clinical Compliance Evaluation  
Office of Scientific Investigations  
Office of Compliance/CDER

**Through:** Natalie Getzoff, M.D., Medical Officer, DNP  
Teresa Buracchio, M.D., Medical Team Leader, DNP

**From:** Stephanie Parncutt, PM, DNP

**Subject:** Request for Clinical Site Inspections

### **I. General Information**

Application#: NDA 210365  
IND#:120055  
Applicant: GW Research LTD  
Phone: 44 (o) 1223 266800  
Email:  
Regulatory Point of Contact: Catherine Maher  
Regulatory Point of Contact Phone: 919-749-0328  
Regulatory Point of Contact Email: cmaher@greenwichbiosciences.com

Drug Proprietary Name: (b) (4) (Proposed)  
Generic Drug Name: cannabidiol  
NME or Original BLA (Yes/No): Yes  
Review Priority (Standard or Priority): Priority

Study Population includes < 17 years of age (Yes/No): Yes

OSI/DCCE/GCPAB Consult  
version: 11/28/2016

Is this for Pediatric Exclusivity (Yes/No): Yes

Proposed New Indication(s): Adjunctive treatment of seizures associated with Dravet syndrome or Lennox Gastaut syndrome in patients 2 years and older

Submission Date: 10/27/17

PDUFA: 6/27/18

Action Goal Date: 6/27/18

Inspection Summary Goal Date: 27Apr2018

**II. Protocol/Site Identification**

<b>(Name, Address, Phone number, email, fax#)</b>	<b>Site #</b>	<b>Protocol ID</b>	<b>Number of Subjects</b>	<b>Study Title</b>
Barron, Todd 228 St. Charles Way, Suite 200 York, PA 17402 USA United States phone:717-741-8121 fax:717-741-2518 email:tbarron@wellspan.org	1191	GWEP1414	13	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003 P; CBD) as adjunctive treatment for seizures associated with Lennox Gastaut
Devinsky, Orin 223 E 34th Street New York, NY 10016 USA United States phone:646-558-0843 fax:646-385-7165 email:od4@nyu.edu	1078	GWEP1332B	7	A double-blind, placebo-controlled, two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P) in children and young
Flamini, Robert 5887 Glenridge, Suite 140 Atlanta, GA 30328 USA United States phone:678-705-7341 fax:678-720-8840 email:rflamini@pandaneuro.com	1087	GWEP1423	11	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003 P; CBD) as adjunctive treatment for seizures associated with Lennox Gastaut
Frost, Michael 225 Smith Avenue North St. Paul, MN 55102 USA United States phone:651-241-5075 fax: email:mfrost@mnepliepsy.net	1147	GWEP1423	14	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003 P; CBD) as adjunctive treatment for seizures associated with Lennox Gastaut
Laux, Linda 225 E. Chicago Avenue, Box 29 Chicago, IL 60611 USA United States phone:312-227-4517 fax:312-227-9644 email:llaux@luriechildrens.org	1083	GWEP1332B	13	A double-blind, placebo-controlled, two-part study to investigate the dose-ranging safety and pharmacokinetics, followed by the efficacy and safety of cannabidiol (GWP42003-P) in children and young
Patel, Anup 700 Children's Drive Columbus, OH 43205 USA United States phone:614-722-4625 fax:614-722-2663 email:anup.patel@nationwidechildrens.org	1090	GWEP1414	20	A randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of cannabidiol (GWP42003 P; CBD) as adjunctive treatment for seizures associated with Lennox Gastaut

(Name, Address, Phone number, email, fax#)	Site #	Protocol ID	Number of Subjects	Study Title
GW Research Ltd. Sovereign House, Vision Park, Chivers Way, Histon Cambridge, Cambridgeshire United Kingdom CB24 9BZ Contact: Catherine Maher, U.S. Agent Contact Phone: 919-749-0328 Fax: 919-800-3820 Email: <a href="mailto:cmaher@greenwichbiosciences.com">cmaher@greenwichbiosciences.com</a>	NA	GWEP1332B GWEP1414 GWEP1423		See above

### III. Site Selection/Rationale

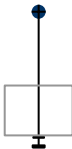
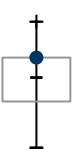
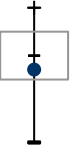
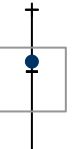
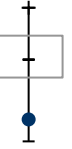

#### Site Information






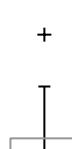

<b>STUDY:</b>	GWEP1332B	<b>SITEID:</b>	1083
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<b>NAME</b>	Laux, Linda
<b>LOCATION</b>	225 E. Chicago Avenue, Box 29 Chicago, IL, USA 60611
<b>PHONE/FAX</b>	312-227-4517 / 312-227-9644
<b>EMAIL</b>	llaux@luriechildrens.org

<b>RANK</b>	1	<b>FINLISC</b>	0	<b>COMPLAINT</b>	1
<b>SITE RISK</b>	18.6	<b>OAI</b>	0	<b>TSLI</b>	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	13	20.87	37.17	62.62	151.52	1.00
Study Rate	5	-23.50	-32.64	-128.19	-110.75	1.00
Min	2	-81.41	-159.13	-385.92	-636.54	1.00
Site	13	-7.60	-52.07	-98.76	-416.54	1.00
						

	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.14	1.80	.00	.33	14.00	2.00	28
Study Rate	3.87	0.36	.00	.10	5.04	0.00	0
Min	0.00	0.00	.00	.00	0.25	0.00	0
Site	4.46	0.85	.00	.00	0.62	0.18	11
							

Site Memo

SITEEFFE, highest enrolling site, complaint related to this submission, no prior inspections

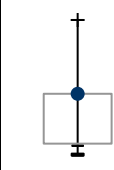
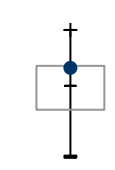
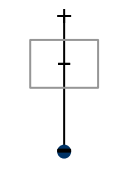
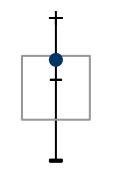
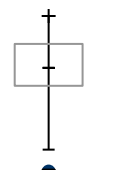

Site Information

STUDY:	GWEP1332B	SITEID:	1078
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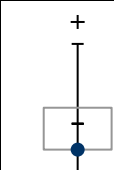
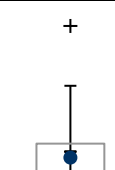

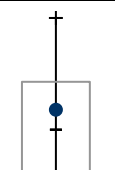
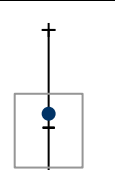
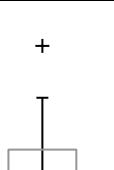
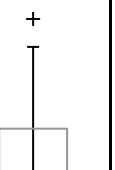
NAME	Devinsky, Orin
LOCATION	223 E 34th Street New York, NY, USA 10016
PHONE/FAX	646-558-0843 / 646-385-7165
EMAIL	od4@nyu.edu

RANK	3	FINLISC	0	COMPLAINT	1
SITE RISK	14.3	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	13	20.87	37.17	62.62	151.52	1.00
Study Rate	5	-23.50	-32.64	-128.19	-110.75	1.00
Min	2	-81.41	-159.13	-385.92	-636.54	1.00
Site	7	-9.35	-159.13	-65.48	-636.54	1.00
						

	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	11.14	1.80	.00	.33	14.00	2.00	28
Study Rate	3.87	0.36	.00	.10	5.04	0.00	0
Min	0.00	0.00	.00	.00	0.25	0.00	0
Site	2.00	0.29	.00	.14	6.29	0.00	0
							

Site Memo

SITEEFFE, complaint related to this submission, no prior inspections

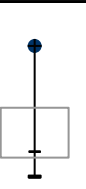
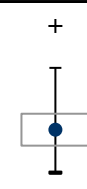
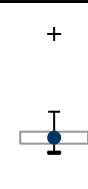
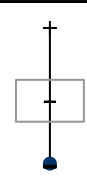
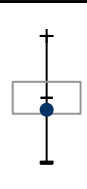

Site Information

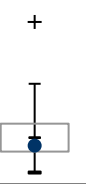


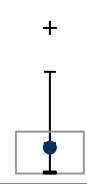
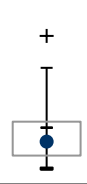
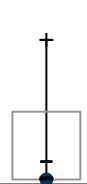
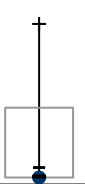
STUDY:	GWEP1414	SITEID:	1090
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NAME	Patel, Anup
LOCATION	700 Children's Drive Columbus, OH, USA 43205
PHONE/FAX	614-722-4625 / 614-722-2663
EMAIL	anup.patel@nationwidechildrens.org

RANK	4	FINLISC	0	COMPLAINT	0
SITE RISK	20.5	OAI	0	TSLI	3

Site Values vs. Overall Study Results

		ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Study Rate	Max	20	31.56	411.04	206.71	411.04	1.00
		8	-27.92	-6.31	-216.64	-89.60	1.00
	Min	1	-54.02	-78.87	-594.18	-608.47	1.00
	Site	20	-28.27	-14.05	-565.36	-182.70	1.00
							

		NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Study Rate	Max	16.00	2.00	.00	.30	20.18	2.00	35
		3.66	0.48	.00	.06	7.00	0.23	2
	Min	0.00	0.00	.00	.00	1.00	0.00	0
	Site	2.90	0.35	.00	.05	5.15	0.00	0
								

Site Memo

Highest enrolling site, no prior inspections

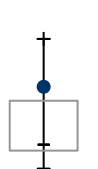
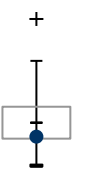
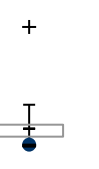
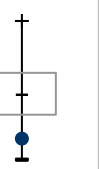
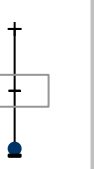

**Site Information**

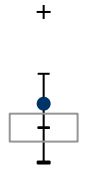

<b>STUDY:</b>	GWEP1414	<b>SITEID:</b>	1191
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<b>NAME</b>	Barron, Todd
<b>LOCATION</b>	228 St. Charles Way, Suite 200 York, PA, USA 17402
<b>PHONE/FAX</b>	717-741-8121 / 717-741-2518
<b>EMAIL</b>	tbarron@wellspan.org

<b>RANK</b>	6	<b>FINLISC</b>	0	<b>COMPLAINT</b>	0
<b>SITE RISK</b>	18.7	<b>OAI</b>	0	<b>TSLI</b>	3

**Site Values vs. Overall Study Results**

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
<b>Max</b>	20	31.56	411.04	206.71	411.04	1.00
<b>Study Rate</b>	8	-27.92	-6.31	-216.64	-89.60	1.00
<b>Min</b>	1	-54.02	-78.87	-594.18	-608.47	1.00
<b>Site</b>	13	-36.30	-67.51	-471.87	-540.08	1.00
						

	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
<b>Max</b>	16.00	2.00	.00	.30	20.18	2.00	35
<b>Study Rate</b>	3.66	0.48	.00	.06	7.00	0.23	2
<b>Min</b>	0.00	0.00	.00	.00	1.00	0.00	0
<b>Site</b>	6.31	0.23	.00	.08	4.62	0.23	13
							

**Site Memo**

SITEEFFE, overperforming IP and underperforming placebo, no prior inspections

Site Information

STUDY:	GWEP1423	SITEID:	1087
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NAME	Flamini, Robert
LOCATION	5887 Glenridge, Suite 140 Atlanta, GA, USA 30328
PHONE/FAX	678-705-7341 / 678-720-8840
EMAIL	rflamini@pandaneuro.com

RANK	3	FINLISC	0	COMPLAINT	0
SITE RISK	18.1	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	15	15.55	91.15	31.10	286.17	1.00
Study Rate	7	-29.53	-13.09	-210.40	-38.51	1.00
Min	2	-67.55	-110.95	-633.58	-334.43	1.00
Site	11	-45.78	-32.96	-503.63	-263.66	1.00

	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	8.00	3.67	.33	.50	14.18	1.90	31
Study Rate	3.06	0.39	.01	.09	5.68	0.25	6
Min	0.00	0.00	.00	.00	1.00	0.00	0
Site	3.73	0.36	.00	.09	14.18	0.00	0

Site Memo

Enrollment, efficacy, complaint related to this submission, no prior inspections

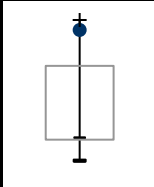
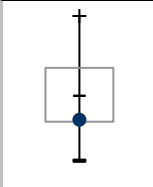
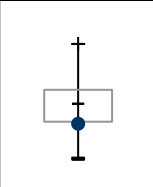
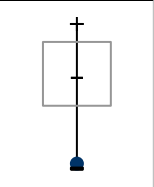
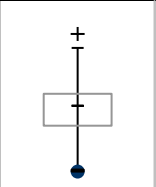
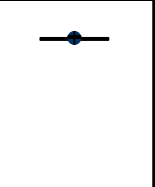
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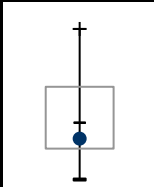
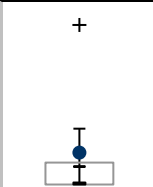
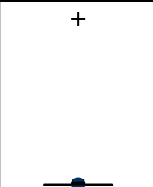
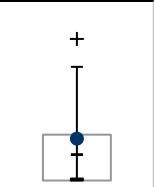
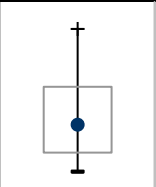
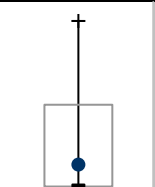
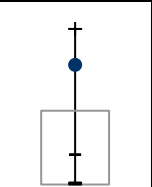
STUDY:	GWEP1423	SITEID:	1147
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NAME	Frost, Michael
LOCATION	225 Smith Avenue North St. Paul, MN, USA 55102
PHONE/FAX	651-241-5075 /
EMAIL	mfrost@mnepliepsy.net

RANK	4	FINLISC	0	COMPLAINT	0
SITE RISK	15.4	OAI	0	TSLI	3

Site Values vs. Overall Study Results

	ENROLL	TRTEFFR	SITEEFFE	EW_TRTEFFR	EW_SITEEFFE	SCREEN
Max	15	15.55	91.15	31.10	286.17	1.00
Study Rate	7	-29.53	-13.09	-210.40	-38.51	1.00
Min	2	-67.55	-110.95	-633.58	-334.43	1.00
Site	14	-43.39	-47.78	-607.49	-334.43	1.00
						

	NSAE	SAE	DEATH	DISCONT	PROTVIOL	INDS	EXPERIENCE
Max	8.00	3.67	.33	.50	14.18	1.90	31
Study Rate	3.06	0.39	.01	.09	5.68	0.25	6
Min	0.00	0.00	.00	.00	1.00	0.00	0
Site	2.21	0.71	.00	.14	5.36	0.25	24
							

Site Memo

Highest enrollment with efficacy, SITEEFFE, no prior inspections

**Domestic Inspections:**

Reasons for inspections (please check all that apply):

- ☒ Enrollment of large numbers of study subjects
- ☒ High treatment responders (specify): Refer to graphs
- ☒ Significant primary efficacy results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, significant human subject protection violations or adverse event profiles.
- ☒ Other (specify): Follow-up on complaints related to this submission

**International Inspections:**

Reasons for inspections (please check all that apply):

- ☐ There are insufficient domestic data
- ☐ Only foreign data are submitted to support an application
- ☐ Domestic and foreign data show conflicting results pertinent to decision-making
- ☐ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.
- ☐ Other (specify) (Examples include: Enrollment of large numbers of study subjects and site specific protocol violations. This would be the first approval of this new drug and most of the limited experience with this drug has been at foreign sites, it would be desirable to include one foreign site in the OSI inspections to verify the quality of conduct of the study).

**Five or More Inspection Sites:**

We have requested 6 domestic sites for inspection because of the following reasons:

High priority application, high profile application, vulnerable population, and a number of complaints received by OSI for some clinical investigator sites chosen for inspection.

Should you require any additional information, please contact *Teresa Buracchio, M.D.* at 301-796-240-402-4274 or *Natalie Getzoff, M.D.* at 301-796-6495.

Concurrence: (as needed)

Teresa Buracchio, M.D. Medical Team Leader  
Natalie Getzoff, M.D. Medical Reviewer

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STEPHANIE N PARNCUTT  
11/30/2017

NATALIE B GETZOFF  
11/30/2017

TERESA J BURACCHIO  
12/04/2017