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RESEARCH**

APPLICATION NUMBER:

210365Orig1s000

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

**OFFICE OF CLINICAL PHARMACOLOGY
INTEGRATED REVIEW**

NDA Number	210365
Link to EDR	\\cdsesub1\evsprod\NDA210365\0004
Submission Date	6/6/2017 to 10/27/2017
Submission Type	Priority (Rolling Submission)
Brand Name	EPIDIOLEX
Generic Name	Cannabidiol (CBD)
Dosage Form and Strength	Oral Solution 100 mg/mL
Route of Administration	Oral
Proposed Indication	For the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older.
Applicant	GW Therapeutics Inc.
Associated IND	120055
OCP Review Team	Jagan Parepally, Angela Men, Michael Bewernitz, Kevin Krudys, Manuela Grimstein, Xinyuan Zhang
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1. EXECUTIVE SUMMARY

Cannabidiol is a highly purified cannabinoid obtained from Cannabis Sativa plant. Cannabidiol reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 channels and modulation of adenosine-mediated signaling. The applicant is seeking approval for the adjunctive treatment of seizures associated with Dravet Syndrome (DS) or Lennox Gastaut Syndrome (LGS). The proposed dosing regimen includes titration to a therapeutic dose based on individual clinical response and tolerability upto 10 mg/kg twice daily (20 mg/kg/day). The recommended starting dose is 2.5 mg/kg taken twice daily (5 mg/kg/day).

The efficacy and safety of cannabidiol in DS and LGS patients was supported by three pivotal Phase III randomized, double-blind, placebo controlled, multicenter trials. The primary endpoints were percentage change from baseline in convulsive seizure frequency and drop seizure frequency in DS and LGS respectively. There were 10 clinical pharmacology studies in this submission. Cannabidiol increases exposure of clobazam's active metabolite n-clobazam (N-CLB) by 300% on average. Administering CBD oral solution with food increases CBD exposure approximately 4 to 5-fold. Hepatic impairment results in a significant increase in exposure to cannabidiol and its metabolites.

The Applicant reports statistically significant differences in placebo-controlled pivotal trials for convulsive seizure frequency in DS and drop seizure frequency in LGS. The key review questions focus on whether the observed treatment effect is due to cannabidiol or due to increased n-clobazam (NCLB) exposure, acceptability of proposed alternate dosing regimen and appropriateness of dosing recommendations for cannabidiol with regard to food, in specific populations and patients taking concomitant medications.

1.1 Recommendations

The Office of Clinical Pharmacology Divisions of Clinical Pharmacology I and Pharmacometrics, have reviewed the information contained in NDA 210,365. The review team recommends approval of this NDA from a clinical pharmacology perspective. The key review issues with specific recommendations /comments are summarized below:

Review Issues	Recommendations and Comments
Supportive evidence of effectiveness	A single pivotal trial in DS and two pivotal Phase III trials in LGS provide primary evidence of effectiveness.

<p>General dosing instructions</p>	<p>The proposed dosing regimen includes recommended starting dose of 2.5 mg/kg taken twice daily (5 mg/kg/day) for 1 week. After one week’s treatment, each dose to 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) and based on individual clinical response and tolerability up to 10 mg/kg twice daily (20 mg/kg/day) taken consistently with respect to meal, is acceptable from clinical pharmacology perspective.</p> <p>Note: Lower dose (10 mg/kg/day) was not studied in DS pivotal clinical trials. However, 10 mg/kg/day and 20 mg/kg/day were studied in LGS patients. An alternative titration regimen is proposed for patient convenience (see Section 3.3.2 for further details), which is acceptable from OCP and DNP.</p>
<p>Dosing in patient subgroups (intrinsic and extrinsic factors)</p>	<ul style="list-style-type: none"> • A lower starting dose in patients with severe hepatic impairment is recommended with a slow dose titration and a lower maintenance dose may be necessary in patients with moderate and severe hepatic impairment. • Refer to Section 1.2 for PMRs for drug-drug interaction studies based on CYP inhibition, induction.
<p>Bridge between the “to-be-marketed” and clinical trial formulations</p>	<p>Not applicable. To-be-marketed formulation was used in clinical trials.</p>

1.2 Post-Marketing Requirements

Key Issue(s) to be Addressed	Rationale	Key Considerations for Design Features
	(b) (4)	A drug-drug interaction study to evaluate the effects of rifampin on the pharmacokinetics of cannabidiol in healthy volunteers.
Effect of strong CYP3A inhibitors on the pharmacokinetics of cannabidiol	Cannabidiol is primarily metabolized by CY3A4, CYP2C19 and glucuronidation.	A drug-drug interaction study to evaluate the potential effects of strong CYP3A inhibitor on the pharmacokinetics of cannabidiol in healthy volunteers
Effect of strong CYP2C19 inhibitors on the pharmacokinetics of cannabidiol	Cannabidiol is primarily metabolized by CY3A4, CYP2C19 and glucuronidation.	A drug-drug interaction study to evaluate the potential effects of strong CYP2C19 inhibitor on the pharmacokinetics of cannabidiol in healthy volunteers

	(b) (4)	A drug-drug interaction study to evaluate the potential effects of cannabidiol on the pharmacokinetics of caffeine in healthy volunteers
Effect of cannabidiol on the pharmacokinetics of CYP2B6 sensitive substrate	Cannabidiol is an inhibitor and inducer of CYP2B6.	A drug-drug interaction study to evaluate the potential effects of cannabidiol on the pharmacokinetics of CYP2B6 sensitive substrate in healthy volunteers
Effect of cannabidiol on the pharmacokinetics of CYP2C9 sensitive substrates	Cannabidiol is an inhibitor of CYP2C9.	A drug-drug interaction study to evaluate the potential effects of cannabidiol on the pharmacokinetics of a CYP2C9 sensitive substrate in healthy volunteers
(b) (4)		
Effect of cannabidiol on the pharmacokinetics of UGT1A9 sensitive substrate	Cannabidiol is an inhibitor of UGT1A9	A drug-drug interaction study to evaluate the potential effects of cannabidiol on the pharmacokinetics of UGT1A9 sensitive substrate in healthy volunteers
Effect of cannabidiol on the pharmacokinetics of UGT2B7 sensitive substrate	Cannabidiol is an inhibitor of UGT2B7	A drug-drug interaction study to evaluate the potential effects of cannabidiol on the pharmacokinetics of UGTB7 sensitive substrate in healthy volunteers

2. SUMMARY OF CLINICAL PHARMACOLOGY ASSESSMENT

2.1 Pharmacology and Clinical Pharmacokinetics

Mechanism of Action (MOA): Cannabidiol reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 channels and modulation of adenosine-mediated signaling.

Absorption: Cannabidiol exposure exhibits nonlinear increase with dose up to 6000 mg under fasting conditions. The median cannabidiol T_{max} ranged from 2.5 to 5 hours. Absolute bioavailability has not been determined. With a high-fat meal C_{max} and AUC of cannabidiol increased by approximately 5-fold and 4-fold respectively.

Distribution: The estimated volume of distribution in healthy volunteers was 20963 L to 42849 L. High plasma protein binding (i.e., >94 %) was observed for cannabidiol and its metabolites (7-COOH-CBD, 7-OH-CBD and 6-OH-CBD).

Metabolism: Cannabidiol is extensively metabolized in liver and gut, primarily by CYP2C19, CYP3A4 and UGT1A7, UGT1A9, and UGT2B7 enzymes. The major circulating metabolites include, 7-carboxy-cannabidiol (7-COOH-CBD) which was approximately 40 fold higher, 7-hydroxy-cannabidiol (7-OH-CBD) which was approximately 38% based on AUC of cannabidiol and a minor metabolite, 6-hydroxy-cannabidiol (6-OH-CBD (< 10% of CBD)). Cannabidiol and 7-OH-CBD (equipotent) were found to be active and the most abundant metabolite, 7-COOH-CBD was found to be inactive in nonclinical animal models of epilepsy.

Elimination: The mean elimination half-life ranged from 56 to 61 hours following twice-daily dosing for 7 days in healthy volunteers. Following a single oral dose of ¹⁴C-CBD at 5 mg/kg, radioactivity was excreted predominantly via the fecal route (84%), and smaller proportions of administered radioactivity recovered in the urine (8%). The total recovery after 168 hours was 94%.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The applicant recommended starting dose 2.5 mg/kg of Epidiolex taken twice daily (5 mg/kg/day) for 1 week and the dose to 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) is acceptable from clinical pharmacology perspective (see Section 3.3.2). Epidiolex (cannabidiol) is recommended to be dosed consistently with respect to meals.

2.2.2 Therapeutic individualization

CYP2C19 and CYP3A Inhibitors: Dedicated drug-interaction trials evaluating concomitant administrations of CYP2C19 and CYP3A inhibitors were not conducted. Co-administration with moderate or strong inhibitors of CYP3A4 or CYP2C19 is predicted to increase CBD plasma concentrations which may increase the risk CBD toxicities. Reduction of CBD dose should be considered when co-administered with moderate or strong inhibitors of CYP3A4 or CYP2C19.

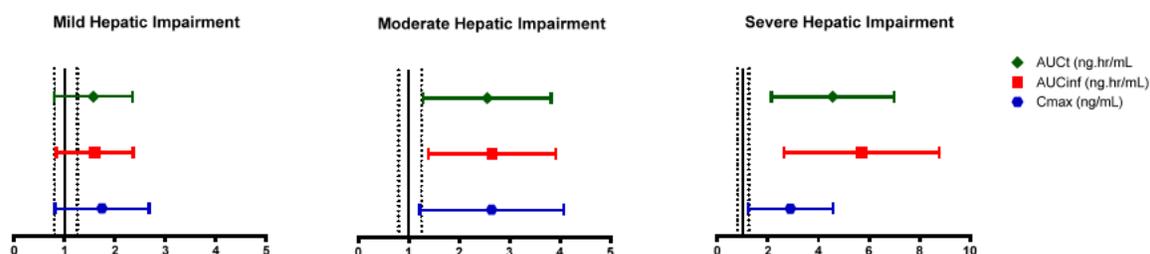
CYP2C19 and CYP3A Inducers: Dedicated drug-interaction trials evaluating concomitant administrations of CYP2C19 and CYP3A inducers were not conducted. An increase in CBD dose should be considered based on efficacy and tolerability when co-administered with a strong CYP3A4 or CYP2C19 inducers.

Hepatic Impairment: Cannabidiol is extensively metabolized. The effect of hepatic impairment on PK of CBD was evaluated in a dedicated study GWEP1539. The geometric mean AUC(0-∞) for total CBD increased by 2.45- and 5.15-fold (90% CI [1.50, 4.01] and [2.94, 9.00] respectively), in moderate and severe hepatic-impaired subjects and about 50% increase in mild hepatic impairment compared with subjects with normal hepatic function as shown in Figure 1 below.

In patients with moderate hepatic impairment a slow dose titration with a 2-fold lower starting dose and 2-fold lower maintenance dose is recommended. The starting dose 1.25 mg/kg of Epidiolex taken twice daily (2.5 mg/kg/day) for 1 week and the dose to be increased weekly by 1.25 mg/kg administered twice daily (2.5 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 1.25 mg/kg administered twice daily (2.5 mg/kg/day) until attainment of a maintenance dose of 5 or 10 mg/kg/day.

In severe hepatic impairment a slow dose titration with a 5-fold lower starting dose and a 5-fold lower maintenance dose is recommended. The starting dose 0.5 mg/kg of Epidiolex taken twice daily (1 mg/kg/day) for 1 week and the dose to be increased weekly by 0.5 mg/kg administered twice daily (1 mg/kg/day) to a therapeutic dose of 2 mg/kg twice daily (2 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 0.5 mg/kg administered twice daily (1 mg/kg/day) until attainment of a maintenance dose of 2 or 4 mg/kg/day.

Figure 1: Effect (GMR and 90% CIs) of Hepatic Impairment on CBD Cmax and AUC



Note: Since five-fold reduction in dose is recommended for patients with severe hepatic impairment the applicant should consider supplying 1 mL oral syringe in addition to planned 5 mL syringe or develop a lower strength formulation.

2.3 Outstanding Issues

We have issued (b) (4) PMR clinical trials: (b) (4) A DDI trial evaluating the effect of strong CYP3A inhibitors on cannabidiol; (b) (4) A DDI trial evaluating the effect of strong CYP2C19 inhibitors on cannabidiol; (b) (4) A DDI trial evaluating the effect of CBD on CYP2C9 substrate; (b) (4) A DDI trial evaluating the effect of cannabidiol on PK of and CYP2B6 sensitive substrates; (b) (4) A DDI trial evaluating the potential effects of cannabidiol on the pharmacokinetics of UGT1A9 sensitive substrates in healthy volunteers; (b) (4) A DDI trial evaluating the potential effects of cannabidiol on the pharmacokinetics of UGT2B7 sensitive substrates in healthy volunteers. Refer to Section 1.2 above for details.

2.4 Summary of Labeling Recommendations

The Office of Clinical Pharmacology recommends the following labeling concepts to be included in the final package insert:

- In section 12.3, Absorption, OCP recommends removing the statement related to (b) (4)
- Applicant's proposed text referring to the (b) (4) should be deleted.
- Removal of the proposed language (b) (4) Cannabidiol should be dosed consistently with respect to meals.
- In moderate hepatic impairment a slow dose titration with a lower starting dose with slow increases and 2-fold lower a maintenance dose is recommended.
- Cannabidiol starting dose should be (b) (4) 1 mg/kg/day and slowly titrated to a maximum maintenance dose of 4 mg/kg/day in patients with severe hepatic impairment.
- Dose reduction of cannabidiol dose should be considered when co-administered with moderate or strong inhibitors of CYP3A4 or CYP2C19.
- Increase in cannabidiol dose should be considered based on (b) (4) tolerability when co-administered with a strong CYP3A4 or CYP2C19 inducers.
- Removal of the (b) (4)
- Clobazam dose reduction maybe necessary when adverse events are experienced.
- Removal of proposed (b) (4) in Section 12.3 of the label is recommended.

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

3.1 Overview of the Product and Regulatory Background

Cannabidiol is planned to be available as 100 mg/mL in sesame oil with (b) (4) with added (b) (4) [sucralose] and strawberry flavoring (b) (4) for oral administration. It is proposed for the adjunctive treatment of seizures associated with Dravet Syndrome (DS) or Lennox Gastaut Syndrome (LGS). There are no approved drugs for DS in the United States. The approvals in LGS were based on drop seizure frequency. Cannabidiol for the adjunctive treatment of seizures associated with DS and LGS was developed under IND 120055. Orphan product designation for cannabidiol was granted for DS indication in November, 2013 and for LGS indication on February 27th. Rare pediatric disease designation request was granted for cannabidiol under both LGS and DS indications on April 20th, 2017.

3.2 General Pharmacological and Pharmacokinetic Characteristics

SUMMARY OF CLINICAL PHARMACOLOGY AND PHARMACOKINETICS

Pharmacology	
Mechanism of Action	Cannabidiol reduces neuronal hyperexcitability and inflammation through modulation of intracellular calcium via GPR55 and TRPV1 channels and modulation of adenosine-mediated signaling. However, the exact mechanisms by which cannabidiol exerts its anticonvulsant effect in humans is unknown. Cannabidiol does not exert its anticonvulsant effects through interaction with cannabinoid receptors.
Active Moieties	Cannabidiol and 7-OH-CBD (approximately ^(b) ₍₄₎ % of CBD) are the active moieties circulating in plasma. 7-OH-CBD demonstrated anticonvulsant activity in a mouse model and was approximately equipotent compared to CBD.
QT Prolongation	The TQT study submitted by the applicant 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 conduct another TQT study with appropriate dosing (e.g., dosing in fed state) to satisfy the requirement for adequate characterization of QTc prolongation risk.
General Information	
Bioanalysis	Validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of CBD and THC and their major metabolites 7-hydroxy-cannabidiol (7-OH-CBD) 7-carboxy-cannabidiol (7-COOH-CBD), 11-hydroxy- Δ 9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol (11-COOH-THC) in human plasma. A summary of the method validation reports is included as an appendix.
Healthy Volunteers vs Patients	The multiple-dose exposures appear higher in patients compared to healthy volunteers (cross study-comparison). This may be due to comparison of fixed dose exposures in healthy subjects to body weight normalized dose exposures in patient trials.
Drug exposure at steady state following the therapeutic dosing regimen	The mean overall CBD exposure at the steady state (AUC _{0-τ}) of cannabidiol at 10 mg/kg/day was 966 ng.hr/mL and at 20 mg/kg/day was 2000 ng.hr/mL in patients 18-55 years old.
Dose Proportionality	The pharmacokinetics of cannabidiol were nonlinear over the dose range of 750 to 6000 mg in healthy subjects and 5 to 20 mg/kg/day in patients.
Accumulation	A mean accumulation ratio observed at steady-state was approximately 1.79 to 2.0.
Variability	Intra-subject variability is not known. Inter-individual variability in ranged from 35.1% to 112.8% for CBD C _{max} , and from 32.3% to 104.1% for CBD AUC, central volume of distribution 28% to 73%, and in peripheral volume of distribution 91%.
ADME	

Absorption	Cannabidiol was administered as an oral solution.		
T_{max}	The median cannabidiol T _{max} ranged from 2.5 to 5 hours.		
Food effect (high-fat)		AUC_{0-∞}	C_{max}
GMR (90% CI)	CBD	3.94 (3.45-4.51)	4.85 (4.01-5.87)
	7-OH-CBD	3.24 (2.72-3.87)	2.91 (2.43-3.48)
Distribution	The estimated volume of distribution in healthy volunteers was 20963 L to 42849 L. High plasma protein binding was observed for cannabidiol and its metabolites (i.e., >94 %).		
Elimination			
Mean Terminal Elimination half-life	56 to 61 hours		
Metabolism			
Primary metabolic pathway(s) [in vitro]	Cannabidiol is extensively metabolized in liver and gut, primarily by CYP2C19 CYP3A4 and UGT1A7, UGT1A9, and UGT2B7 enzymes. The major circulating metabolites include, 7-carboxy-cannabidiol (7-COOH-CBD) which was approximately 40 folds higher, 7-hydroxy-cannabidiol (7-OH-CBD) which was approximately 38% based on AUC of cannabidiol and a minor metabolite, 6-hydroxy-cannabidiol (6-OH-CBD (< 10% of CBD). Cannabidiol and 7-OH-CBD (equipotent) were found to be active and the most abundant metabolite, 7-COOH-CBD was found to be inactive in nonclinical animal models of epilepsy.		
Inhibitor/Inducer (in vitro)	Cannabidiol inhibits (IC ₅₀ <10 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4. CBD is also a time-dependent inhibitor of CYP3A4, CYP1A2 in vitro. Cannabidiol is a strong inhibitor of UGT1A9 and UGT2B7 in human liver microsomes. Cannabidiol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations.		
Transporter Systems (in vitro)	Cannabidiol is not a substrate of MDR1 (P-glycoprotein), OATP1B1, OATP1B3 or BCRP. CBD is not an inhibitor of P-glycoprotein or any investigated renal (OAT1, OAT3, OCT2, MATE1 and MATE2-K) or liver (OATP1B1, OATP1B3, BSEP, OCT1 and MATE1) uptake transporters. The CBD metabolite, 7-OH-CBD was not a substrate of P-gp, BCRP, OATP1B1, OATP1B3 or OCT or an inhibitor of transport mediated via P-gp, BCRP, OATP1B1, MATE1 OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE2-K and BSEP. The CBD metabolite, 7-COOH-CBD was not a substrate of BCRP, OATP1B1, OATP1B3 or OCT or an inhibitor of transport mediated via BCRP, OATP1B1, MATE1 OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE2-K and BSEP. However, 7-COOH-CBD was found to be a substrate of P-gp.		
Excretion	Following a single oral dose of 14C-CBD at 5 mg/kg, radioactivity was excreted predominantly via the fecal route (84%), and smaller proportions of administered radioactivity recovered in the urine (8%). The total recovery after 168 hours was 94%.		

3.3 Clinical Pharmacology Questions

3.3.1 Does the clinical pharmacology information provide supportive evidence of effectiveness?

The Applicant provided results of 3 clinical trials in support of the proposed indications.

Efficacy Trials:

Trials 1414 and 1423 provided information regarding CBD effectiveness in patients with LGS. Trial 1414 is a Phase 3, randomized, double-blind, placebo-controlled trial to assess efficacy of 14 weeks of placebo, 10 mg/kg CBD, or 20 mg/kg CBD in adult and pediatric LGS patients (n=225). Trial 1423 is a Phase 3, randomized, double-blind, placebo-controlled trial to assess efficacy of 14 weeks of placebo or 20 mg/kg CBD in adult and pediatric LGS patients (n=171). The Applicant reported that the trial demonstrated efficacy of 10 mg and 20 mg/kg dose levels for LGS. Please refer to the review of the medical officer for additional details.

Trial 1332 provided information regarding CBD effectiveness in patients with DS. Trial 1332 is a Phase 3, double-blind, placebo-controlled trial that assessed dose-ranging in terms of safety and PK of 5, 10, and 20 mg/kg/day CBD (Part A; n=34) and safety and efficacy of 20 mg/kg/day CBD (Part B; n=120) in DS patients up to 18 years of age. The Applicant reported that the trial demonstrated efficacy of the 20 mg/kg/day dose level. Please refer to the review of the medical officer for additional details.

Exposure-Response Analyses in LGS Patients: The Applicant conducted exposure-response analyses for safety as well as efficacy in LGS patients. However, based on concerns about the food effect magnitude, unrestricted meal access in Phase 3 trials, and lack of documented fasted fed status in Phase 3 trials, it is not clear that the observed PK values used in the E-R analyses can be considered to be representative of the CBD-time profile throughout the duration of the LGS Phase 3 trials. As such the utility of E-R analyses for safety or efficacy is limited. Please refer to section 3.3.2 for details regarding dose selection in LGS trials and Section 4.4.2 for details regarding exposure-response analyses in LGS patients.

Exposure-Response Analyses in DS Patients: In DS patients enrolled in Trial 1332, there was no apparent exposure-response relationship between CBD AUC assessed at Visit 5 and either the time until first seizure or probability of being a seizure responder. As was the case with the LGS trials, Trial 1332 in DS patients permitted morning and evening dosing to occur without regard to meals. In addition, no data was collected regarding meal status with respect to CBD administration. For these reasons, it is not clear that the observed PK values used in the E-R analyses can be considered to be representative of the CBD-time profile throughout the duration of Trial 1332. As such it is not clear that the E-R analyses for safety or efficacy can be used to inform CBD dose selection in DS patients. Please refer to sections 3.3.2 for details regarding dose selection for Trial 1332 in DS patients and 4.4.1 for details regarding exposure-response analyses in DS patients.

Potential Confounding by Active Nor-Clobazam metabolite: CBD is known to inhibit CYP2C19 enzyme which is known to metabolize nor-clobazam (N-CLB), an active metabolite of the concomitant medication clobazam. In Phase 3 trial 1423 in LGS patients, N-CLB exposure was over 300% higher in the CBD arm compared to the PBO arm. The Applicant identified the potential concern that an increase in N-CLB exposure may contribute to the efficacy findings in CBD trials.

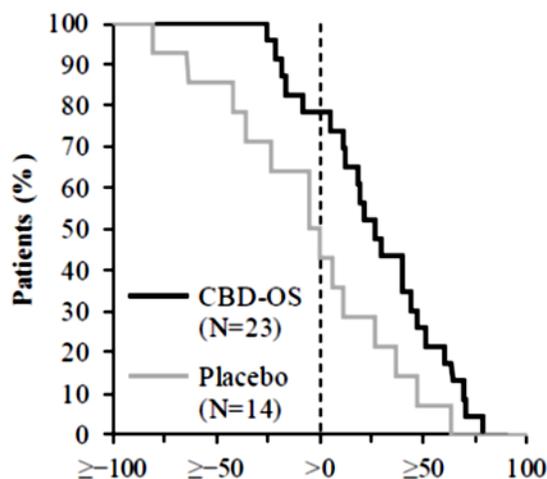
The Applicant provided rationale intended to support effectiveness of CBD independent of N-CLB exposure increase. Sponsor provided rationale from a nonclinical as well as a clinical perspective. From a clinical pharmacology perspective, one key portion of Applicant's rationale was as follows:

“In patients with DS taking STP (a CYP2C19 inhibitor shown to prevent CBD-OS-mediated increases in N-CLB), 20 mg/kg/day CBD-OS was superior to placebo for reducing convulsive seizure frequency both in the absence and presence of CLB.”

Source: summary-clin-efficacy-dravet-syn.pdf, page 112 of 122

Stiripentol (STP) is a concomitant medication that was utilized by a subset of patients in Phase 3 Trial 1332 in DS patients. STP also inhibits CYP2C19. In patients in whom CBD was added to existing background STP therapy and existing CLB therapy, the 20 mg/kg/day CBD arm in trial 1332 in DS patients appeared to provide a better efficacy response compared placebo. In particular, approximately 80% of patients experienced benefit (> 0% reduction in seizure frequency) while on CBD versus 50% experiencing benefit while on placebo in this subset of patients with existing STP and existing CLB (see figure below).

Figure 2: Cumulative Distribution of Seizure Reduction By Treatment Arm in Study 1332 in DS Patients



X-axis values to the right of the vertical dashed line refer to an improvement compared to baseline seizure frequency (a positive reduction in seizure frequency). X-axis values to left of the dashed vertical line refer to a worsening compared to baseline seizure frequency (a negative reduction in seizure frequency [an increase in seizure frequency]). Each vertex on the plot refers to the proportion of patients (y-axis) who achieved a reduction in seizure frequency at or better than the corresponding x-value. For example, the plot indicates that ~80% of patients in the CBD arm demonstrated an improvement (reduction in seizure frequency $> 0\%$) and ~50% of patients in the placebo arm demonstrated an improvement (reduction in seizure frequency $> 0\%$).

Source: *summary-clin-efficacy-dravet-syn.pdf*, page 83 of 122

It is likely that patients receiving concomitant STP experience 2C19 inhibition to such an extent that addition of CBD results in no appreciable augmenting of 2C19 inhibition. Thus, when adding CBD to patients with existing CLB and existing STP, it is likely that the levels of active metabolite N-CLB before adding CBD are comparable to N-CLB levels after adding CBD. This observation supports the Sponsor's claim that CBD has therapeutic benefit independent of an increase in N-CLB.

No patients reported stiripentol use in either trial 1414 or trial 1423 in LGS patients. Thus, the analysis of CBD effectiveness with concomitant STP and CLB could not be conducted in LGS patients.

3.3.2 Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Applicant's Rationale for Selection of Dose Levels to Use in Phase 3 for LGS, DS

The Applicant cites a literature report that CBD doses up to 21.4 mg/kg/day (1500 mg CBD per day, normalized to a 70-kg adult) were tolerated for up to 4 weeks in adults. In their expanded access IND studies, applicant reports that up to 22 mg/kg/day was tolerated in an individual

pediatric patient. The Applicant's data monitoring safety committee recommended a maximum of 20 mg/kg/day with titration increments of 2.5 to 5 mg/kg/day in the Phase 3 Trial 1332 in DS patients. This maximum dose and titration regimen were also selected for use in the Phase 3 trials in LGS patients.

Maintenance Dose: The Phase 3 program demonstrated effectiveness of CBD in the LGS and DS populations at 20 mg/kg/day and in LGS population at 10 mg/kg/day. Please refer to section 3.3.1 for details regarding the clinical trials.

Exposure-response analyses were performed in LGS patients, but based on concerns about food effect, etc. (see section 3.3.1 and 4.4.2 for details) it is not clear that the E-R analyses are reliable in LGS patients. However, the Phase 3 trials demonstrated efficacy for the LGS at the 10 mg/kg/day and 20 mg/kg/day dose levels.

Overall, OCP supports labeling for 10 to 20 mg/kg/day as target maintenance dose range in LGS patients.

There was no relationship between CBD exposure and either time until first seizure or probability of having at least one seizure in patients with DS enrolled in trial 1332. As was the case with the LGS trials, Trial 1332 in DS patients permitted morning and evening dosing to occur without regard to meals. In addition, no data was collected regarding meal status with respect to CBD administration. As such it is not clear that the E-R analyses for safety or efficacy can be used to inform CBD dose selection in DS patients. However, the 20 mg/kg/day dose level demonstrated efficacy in DS patients enrolled in Phase 3 trial 1332.

The Applicant is proposing to label the 10 mg/kg/day dose for the DS indication. However, the 10 mg/kg/day dose level was not assessed in DS patients in trial 1332. Also, there is no clear exposure-efficacy relationship in DS patients. However, there is a desire in the Clinical team to provide identical dosing instructions for both DS and LGS. In an effort to provide flexibility in treatment, the label will recommendation titration to a minimum maintenance dose level of 10 mg/kg/day with subsequent titration based on individual response and tolerability to no more than 20 mg/kg/day. The review team determined that this approach is appropriate as it provides flexibility to physicians to titrate the dose based on individual response to the dose level they deem to be acceptable.

Overall, OCP supports 10 to 20 mg/kg/day as the target maintenance dose range in DS patients.

Alternate titration regimen: Sponsor conducted PK analyses to support an alternate titration regimen compared to the regimen used in the clinical trials. The regimen used in the clinical trials was a 2.5 mg/kg/day initiation dose which increased by 2.5 mg/kg/day every 2 days until 10 mg/kg/day was reached. If patients were titrated to the 20 mg/kg/day target, starting from the 10 mg/kg/day level, the dose increased by 5 mg/kg/day every 2 days until the target was reached. Applicant proposes an alternate titration regimen of 5 mg/kg/day initially with increases of 5 mg/kg/day every week. The PPK model developed for the DS population was used by the Applicant to conduct the PK simulations. The simulated PK profile for the original titration

regimen was compared with the simulated PK profile for the alternate titration regimen. Applicant concludes that the alternate titration regimen has potential reduced toxicity but also potential for delayed efficacy compared to the original regimen due to the more gradual increase in CBD exposure with the alternate regimen. The Applicant proposes implementing the alternate titration regimen

Based on concerns about food effect (see section 3.3.1 for details), the PK models for DS and LGS are not considered reliable. In addition, the Applicant simulated two-weeks of PK data which is not a sufficient duration to reach 20 mg/kg/day.

As such, the reviewer utilized the PPK model for the HV patients to address the acceptability of the new regimen. The reviewer simulated the PK profile for each individual subject in the HV PPK dataset for both the alternate titration regimen as well as the original titration regimen. The PK simulations utilized a time duration that allowed the target dose to be achieved (e.g. 4 weeks for the 20 mg/kg/day maintenance dose level). The results of this titration regimen comparison for targets of 10 mg/kg/day and 20 mg/kg/day for a representative individual receiving CBD administration while in a fed state are presented in the figures below.

Figure 3: Simulated PK Profile for Original Titration Regimen used in Clinical Trials and Proposed Alternate Regimen up to 10 mg/kg/day



This plot represents Subject (b) (6) according to the NONMEM ID numbering and subject (b) (6) according to the Study 1544 ID numbering.

The red series represents the simulated PK profile for the original titration regimen. The vertical red lines connecting the red PK profile to the top of the plot represent times where the total daily dose increases by 2.5 mg/kg/day every 2 days until 10 mg/kg/day is achieved, then increases 5 mg/kg/day every 2 days, in accordance with the original titration regimen. The red text at the top of the plot shows the total daily dose administered during that portion of the original titration regimen.

The green series represents the simulated PK profile for the Applicant's proposed alternate regimen. The vertical green lines connecting the green PK profile to the bottom of the plot represent times where the total daily dose increases by 5 mg/kg/day in accordance with the alternate titration regimen. The green

text at the bottom of the plot shows the total daily dose administered during that portion of the Applicant's proposed titration regimen.

Figure 4: Simulated PK Profile for Original Titration Regimen used in Clinical Trials and Proposed Alternate Regimen up to 20 mg/kg/Day



This plot represents Subject (b) (6) according to the NONMEM ID numbering and subject (b) (6) according to the Study 1544 ID numbering.

The red series represents the simulated PK profile for the original titration regimen. The vertical red lines connecting the red PK profile to the top of the plot represent times where the total daily dose increases by 2.5 mg/kg/day every 2 days until 10 mg/kg/day is achieved, then increases 5 mg/kg/day every 2 days, in accordance with the original titration regimen. The red text at the top of the plot shows the total daily dose administered during that portion of the original titration regimen.

The green series represents the simulated PK profile for the Applicant's proposed alternate regimen. The vertical green lines connecting the green PK profile to the bottom of the plot represent times where the total daily dose increases by 5 mg/kg/day in accordance with the alternate titration regimen. The green text at the bottom of the plot shows the total daily dose administered during that portion of the Applicant's proposed titration regimen.

Overall, the new regimen is expected to result in PK exposures that are greater for the alternate regimen until approximately Day 4. Without reliable exposure-safety information, it is not clear whether the elevated exposures expected for the alternate titration regimen can be expected to result in tolerability issues.

After Day 4, the alternate regimen is expected to result in lower exposures until approximately Day 9 for the 10 mg/kg/day target and until Day 23 for the 20 mg/kg/day target. Without reliable exposure-efficacy information, it is not clear whether the reduced exposures expected for the alternate titration regimen can be expected to result in a clinically-relevant delay of effectiveness. The PK profile for the alternate titration regimen results in exposure differences that are minor and last for a few days in comparison to the clinical trial titration regimen. As such, both regimens appear reasonable from a pharmacokinetic perspective. The alternative regimen may simplify titration logistics, but has potential to increase tolerability issues following the first dose and may delay the attainment of therapeutic exposure.

DNP and OCP agree that the alternate titration regimen is acceptable. The approved labeling will reflect the final titration directions that were agreed upon with the applicant.

3.3.3 Is an alternative dosing regimen and management strategy required for subpopulations based on intrinsic factors?

Yes. Cannabidiol is extensively metabolized and hepatic impairment increases CBD exposure. A study in patients with renal impairment showed that creatinine clearances (CrCl) in the range had no meaningful influence on the clearance of CBD. The population PK analyses for LGS and DS patients are unable to inform dose adjustments for neither intrinsic factors nor extrinsic factors. Refer to the Pharmacometrics review in the Appendix for more details. The assessment of the effects of hepatic and renal impairment and CYP3A4 and CYP2C19 polymorphisms on cannabidiol are further discussed in this section.

Hepatic Impairment: The effect of hepatic impairment on PK of CBD was evaluated in a dedicated study GWEP1539. The PK of a single oral dose of 200 mg CBD in subjects with mild (Child-Pugh Grade A, Score: 5-6), moderate (Child-Pugh Grade B, Score: 7-9), or severe (Child-Pugh Grade C, Score: 10-15) hepatic impairment was compared with subjects with normal hepatic function, with 8 subjects per group. The geometric mean C_{max} for CBD increased by approximately 2.5 folds in both the moderate and in the severe hepatic-impaired subjects, compared with subjects with normal hepatic function. The geometric mean AUC(0-∞) for total CBD increased by 2.45- and 5.15-fold (90% CI [1.50, 4.01] and [2.94, 9.00] respectively), in moderate and severe hepatic-impaired subjects compared with subjects with normal hepatic function as shown in Table below.

Table 1: Effect of Hepatic Impairment on CBD C_{max} and AUC (GWPP1539)

Comparison	GMR (90% CI)		
	C _{max} (ng/mL)	AUC(0-∞) (h*ng/mL)	AUC(0-t) (h*ng/mL)
Total			
Mild/Normal	1.57 (0.90, 2.75)	1.48 (0.90, 2.41)	1.44 (0.86, 2.41)
Moderate/Normal	2.39 (1.37, 4.18)	2.45 (1.50, 4.01)	2.35 (1.41, 3.92)
Severe/Normal	2.57 (1.41, 4.70)	5.15 (2.94, 9.00)	4.13 (2.38, 7.18)

Geometric mean AUC (0-∞) for 6-OH-CBD and 7-OH-CBD also increased by 2.16 to 2.59 folds in the moderate and severe hepatic-impaired subjects. There was no clear trend in change in AUC (0-∞) for the major metabolite 7-COOH-CBD across all groups of hepatic-impaired subjects relative to subjects with normal hepatic function. Starting dose of cannabidiol should be lowered in patients with severe hepatic impairment.

In patients with moderate hepatic impairment a slow dose titration with a 2-fold lower starting dose and 2-fold lower maintenance dose is recommended. The starting dose 1.25 mg/kg of Epidiolex taken twice daily (2.5 mg/kg/day) for 1 week and the dose to be increased weekly by 1.25 mg/kg administered twice daily (2.5 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 1.25 mg/kg administered twice daily (2.5 mg/kg/day) until attainment of a maintenance dose of 5 or 10 mg/kg/day.

In severe hepatic impairment a slow dose titration with a 5-fold lower starting dose and a 5-fold lower maintenance dose is recommended. The starting dose 0.5 mg/kg of Epidiolex taken twice daily (1 mg/kg/day) for 1 week and the dose to be increased weekly by 0.5 mg/kg administered twice daily (1 mg/kg/day) to a therapeutic dose of 2 mg/kg twice daily (2 mg/kg/day). Based on individual clinical response and tolerability, each dose can be further increased in weekly increments of 0.5 mg/kg administered twice daily (1 mg/kg/day) until attainment of a maintenance dose of 2 or 4 mg/kg/day. Since five-fold reduction in dose is recommended for patients with severe hepatic impairment the applicant should consider supplying 1 mL oral syringe in addition to planned 5 mL syringe or develop a lower strength formulation.

Renal Impairment: A dedicated renal impairment trial (GWEP1540) was conducted to evaluate the effect of renal impairment on PK of CBD in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function. There was a minor increase in C_{max} and AUC in patients with mild, moderate and severe impairments (Table below) because of large variability and small sample size. However, there was no particular trend in increase in exposure with changes in renal function. It can be concluded that mild, moderate and severe renal impairment does not affect the exposure of cannabidiol. No dose adjustments are recommended in patients with renal impairment.

Table 2: Geometric Mean Ratios and 90% Confidence Intervals for CBD by Status of Renal Function

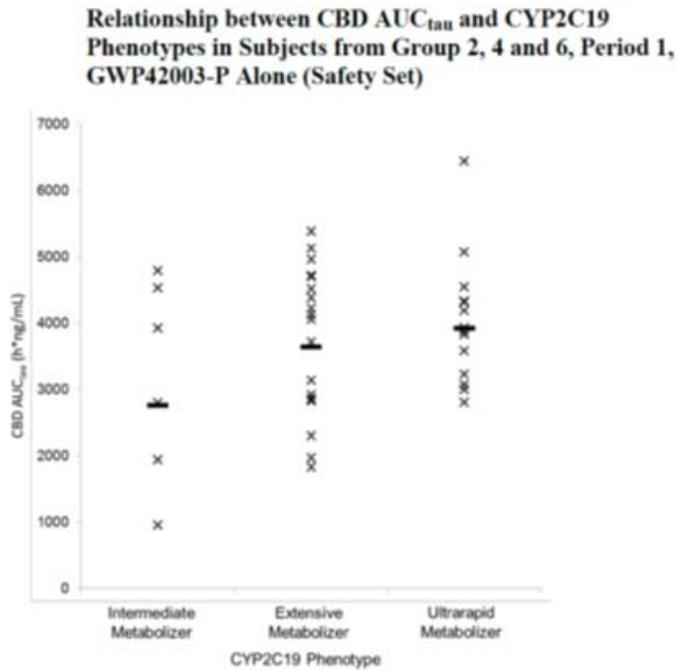
Comparison (Test/Reference)	C _{max} (ng/mL)	AUC(0-∞) (ng·h/mL)	AUC(0-t) (ng·h/mL)	CL/F (L/h)
	Ratio of Geometric Least Squared Means (90% CI)			
CBD				
Mild/Normal	1.31 (0.73, 2.35)	1.20 (0.59, 2.45)	1.44 (0.83, 2.51)	1.31 (0.73, 2.35)
Moderate/Normal	1.12 (0.62, 2.02)	1.05 (0.56, 1.96)	1.14 (0.66, 1.98)	1.12 (0.62, 2.02)
Severe/Normal	1.02 (0.57, 1.83)	1.20 (0.64, 2.25)	1.15 (0.66, 1.99)	1.02 (0.57, 1.83)

Pharmacogenomics: Cannabidiol is extensively metabolized by the liver via CYP450 enzymes and UGT enzymes. The major CYP450 isoforms responsible for the phase I metabolism of cannabidiol are primarily by the polymorphic enzymes CYP2C19 and to lesser extent CYP3A4. The in vitro and clinical drug interaction studies indicated that CBD is metabolized by CYP2C19.

To determine the relationship of CYP2C19 function on CBD exposure, the exposure data (AUC) from the 2 clinical trials was summarized by CYP2C19 function. Analyses showed a trend of increased CBD exposure with increasing CYP2C19 activity (Figures below). The sponsor did not investigate if CYP2C19 genotype had any effect on safety or efficacy of CBD. Firm conclusions regarding any impact of CYP2C19 genomics on CBD exposure are difficult to draw given the small sample size, (b) (4)

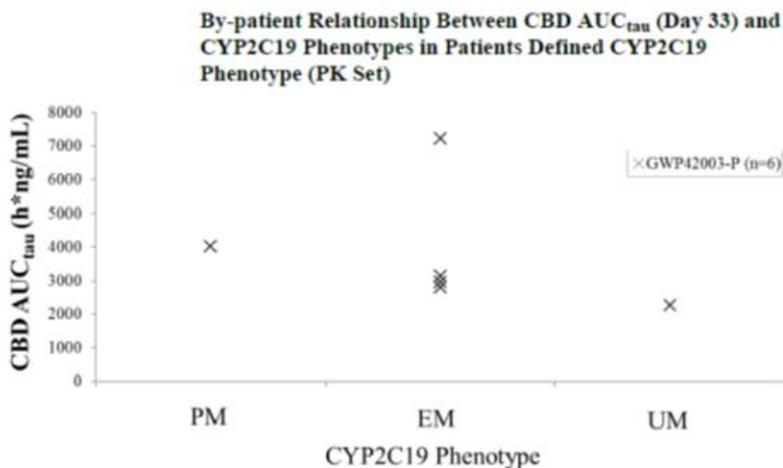
Figure 5: CBD Exposure by CYP2C19 Phenotype in GWEP1543

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Source: GWEP1543 Study Report, Page 156, Figure 8.4.4.2-2 5

Figure 6: CBD Exposure by CYP2C19 Phenotype in GWEP1428



Source: GWEP1428 Study Report, Page 101, Figure 8.4.5.2-2

3.3.4 Are there clinically relevant food-drug or drug-drug interactions and what is the appropriate management strategy?

Cannabidiol metabolism is primarily mediated by CYP2C19 and CYP3A4 with contribution from UGT1A7, UGT1A9, and UGT2B7, based on in vitro studies. A significant food effect was observed with Epidiolex. The effects of extrinsic factors such as herbal products, diet, smoking, and alcohol use on the dose-exposure and/or dose-response for cannabidiol were not assessed in a formal study. The in vitro drug interaction potential, clinical drug-drug interactions between CBD, midazolam, clobazam, valproate, stiripentol and the food effect on cannabidiol are further discussed in this section.

In Vitro DDI Potential

In vitro studies indicate that cannabidiol inhibits (IC₅₀ <10 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C19, CYP2C9 and CYP3A4. CBD is also a time-dependent inhibitor of CYP3A4, and CYP1A2 in vitro. Cannabidiol is a strong inhibitor of UGT1A9 and UGT2B7 in human liver microsomes.

Cannabidiol is not a substrate of MDR1 (P-glycoprotein), OATP1B1, OATP1B3 or BCRP. CBD is not an inhibitor of P-glycoprotein or any investigated renal (OAT1, OAT3, OCT2, MATE1 and MATE2-K) or liver (OATP1B1, OATP1B3, BSEP, OCT1 and MATE1) uptake transporters.

The CBD metabolite, 7-OH-CBD was not a substrate of P-gp, BCRP, OATP1B1, OATP1B3 or OCT or an inhibitor of transport mediated via P-gp, BCRP, OATP1B1, MATE1 OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE2-K and BSEP. The CBD metabolite, 7-COOH-CBD was not a substrate of BCRP, OATP1B1, OATP1B3 or OCT or an inhibitor of transport mediated via BCRP, OATP1B1, MATE1 OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE2-K and BSEP. However, 7-COOH-CBD was a substrate of P-gp.

Note: The CBD metabolite, 7-COOH-CBD was found to be inactive in nonclinical animal models of epilepsy. P-gp inhibitors include drugs such as clarithromycin, erythromycin, ritonavir and verapamil. The effect of increased plasma levels to 7-COOH-CBD, when administered concomitantly with P-gp inhibitors is unknown.



Cannabidiol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations. A PMR will be issued to the applicant to perform and submit DDI interaction studies evaluating CBD (b) (4) CYP2B6.

The applicant relied on PBPK modeling to predict the in vivo interaction potential of cannabidiol as a CYP 2B6, 2C8, 2C9, 3A4 and UGT 1A9 and 2B7 perpetrator in adult and pediatric populations (2 -17 years of age). However, the current PBPK model for cannabidiol did not

include the formation of two major metabolites, 7-OH-CBD and 7-COOH-CBD, and their possible contribution on the interaction potential of CBD oral solution. As noted above, the in vitro DDI potentials of these metabolites are currently under investigation. This model deficiency precluded the acceptance of the current model to predict DDIs of CBD oral solution as a perpetrator. Refer to the PBPK review in the Appendix 4.4 for further details.

Effect of Cannabidiol on Other Drugs

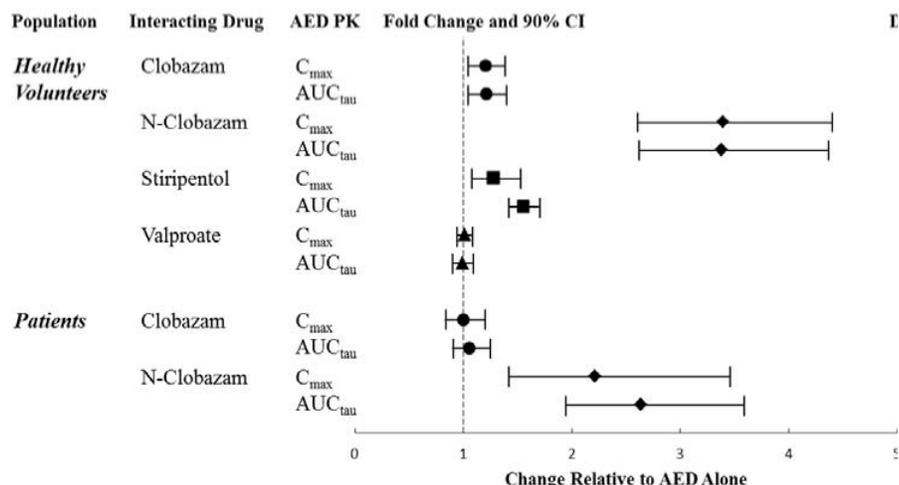
Effect of Cannabidiol on Clobazam (CLB) and Other AEDs

A dedicated drug-drug interaction study (GWEP1543) was conducted to evaluate the effect of multiple dose administration of CBD on steady-state plasma concentrations of CLB (and N-desmethyclobazam [N-CLB]), stiripentol (STP) or valproate (VPA) in healthy male and female subjects. CLB exposure increased slightly (20%) was combined with CLB. However, there was a significant increase in its metabolite (N-CLB) of 3.4-fold. When CBD was combined with STP there was a minor increase (1.28-fold increase in C_{max} and 1.55-fold increase in AUC_{tau}). There was no effect of concomitant CBD administration on VPA exposure as shown in the Figure below.

In a Phase 2 (GWEP1428), drug-drug interaction study between clobazam (CLB) and CBD, the applicant also determined the CBD effects on pharmacokinetic (PK) profile of CLB and its primary metabolite N-desmethyclobazam (N-CLB). Cannabidiol did not alter the C_{max} or AUC of CLB. However, there was a significant DDI between CBD and N-CLB, the mean ratio and 90% CIs of 2.22 [1.42, 3.46] for C_{max} and 2.64 [1.95, 3.58] for AUC_{tau} as shown in the Figure below.

CLB is extensively metabolized in the liver via N-demethylation and hydroxylation, and has 2 major metabolites, N-CLB and 4'-hydroxyclobazam, the former of which is active. N-CLB is estimated to be one-fifth to equally as potent as CLB. The main enzyme that facilitates the process of N-demethylation is CYP3A4, and to a lesser extent CYP2C19 and CYP2B6. N-CLB is metabolized via hydroxylation, primarily by CYP2C19. Reduction of CLB dose may be considered depending on the tolerability when co-administered with cannabidiol.

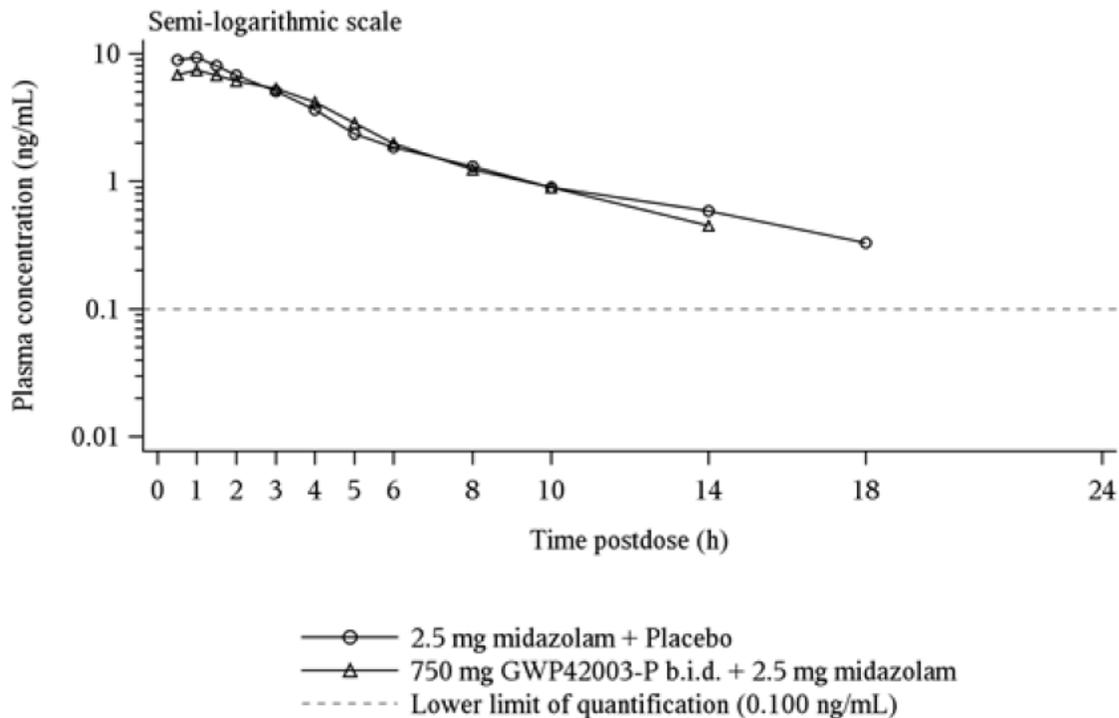
Figure 7: Effect (GMR and 90% CIs) of CBD on AED PK Parameters in Healthy Volunteers and Patients



Effect of Cannabidiol on Midazolam (MZ)

A dedicated drug-drug interaction study (GWEP17028) was conducted to evaluate the effect of cannabidiol treatment following repeated dosing on the pharmacokinetics of a single dose of midazolam in healthy male and female subjects. In vitro metabolism studies suggest that CBD may act as an inhibitor of CYP3A4 in a time-dependent manner. CBD may also induce CYP3A4. Midazolam is considered a sensitive CYP3A4/5 substrate and is commonly used for DDI studies investigating PK interactions affecting CYP3A4/5. Concomitant administration of midazolam following repeated dosing of cannabidiol (at steady-state) resulted in relatively small changes in $AUC_{0-\infty}$ (8% lower), and C_{max} was reduced by 20% when compared to midazolam administered alone as shown in the Figure below. However there was a 2 fold increase in 1'-hydroxymidazolam (active metabolite, 10% when compared to parent MZ) concentrations. The increase exposure to 1'-hydroxymidazolam may be due to inhibition of downstream metabolism of 1'-hydroxymidazolam by CBD probably due to inhibition of glucuronidation by UGT2B7. CBD was an inhibitor of UGT1A9 and 2B7 in both Supersomes™ and HLMs in vitro with nanomolar potency (IC_{50} 19.2 to 317 nM). Relatively small changes in midazolam exposures indicate that cannabidiol has a minor effect on CYP3A4 substrates.

Figure 8: Geometric Mean Plasma Concentrations of Midazolam Following Single Oral Dose Administration of 2.5 mg Midazolam + Placebo (Day -1) or 2.5 mg Midazolam + Steady State 750 mg Cannabidiol b.i.d. (Day 25)



(b) (4) PMRs related to drug-drug interactions studies will be issued to the sponsor (see section 1.2). Examples of the most commonly used concomitant UGT and CYP enzymes substrates include following drugs. Lorazepam and morphine are known to cause respiratory depression at high blood levels. Drugs including phenytoin and propofol are narrow therapeutic index drugs, can cause seizures at high blood concentrations.

UGT1A9: Propofol

UGT2B7: Lorazepam, lamotrigine, morphine

CYP2B6: Bupropion, efavirenz

CYP2C9: Phenytoin, THC, NSAIDs

(b) (4)

Effect of Other Drugs on Cannabidiol

Effect of Moderate or Strong Inhibitors of CYP3A4 or CYP2C19

Coadministration with moderate or strong inhibitors of CYP3A4 or CYP2C19 is predicted to increase CBD plasma concentrations which may increase the risk CBD toxicities. The applicant plans to conduct study (b) (4)

(b) (4) to evaluate the effect of inhibitors of CYP3A4 or CYP2C19. A PMR will be issued to the applicant to perform and submit the results this trial. Reduction of CBD dose should be considered based on tolerability, when coadministered with moderate or strong inhibitors of CYP3A4 or CYP2C19.

Effect of Strong CYP3A4 or CYP2C19 Inducers

Coadministration of CBD with a strong CYP3A4 or CYP2C19 inducers is predicted to decrease cannabidiol plasma concentrations which may lead to decreased CBD efficacy. (b) (4)

An increase in CBD dose should be considered based on efficacy and tolerability, when coadministered with a strong CYP3A4 or CYP2C19 inducers.

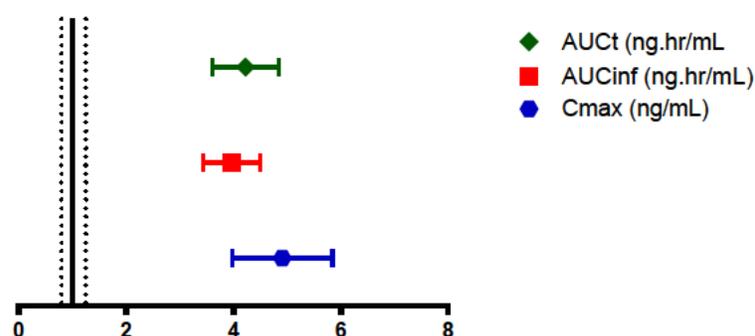
Effect of AEDs (CLB, STP and VPA) on CBD

When AEDs (CLB, STP and VPA) were combined with CBD there was no major effect on CBD plasma exposure (C_{max} and AUC_{tau}), however there was a relatively minor effect of STP on CBD metabolites whereby 7-OH-CBD exposure was reduced by 29% and 7-COOH-CBD exposure reduced by 13%. Following concomitant VPA administration with CBD, 7-COOH-CBD exposure increased by 32%. The clinical relevance of 29% decrease in 7-OH-CBD exposure is unknown. Since the CBD is titrated based on individual clinical response and tolerability no dose adjustment is necessary.

Food Effect

In a sub-study of GWEP1544, a single ascending dose and multiple dose study to evaluate the safety, tolerability and pharmacokinetics of Cannabidiol, a high-fat meal increased cannabidiol exposure approximately 4 to 5-fold compared with cannabidiol administration under fasting conditions (Figure below). Total variability in PK parameters for CBD was relatively lower in the fed group than the fasted group. For C_{max} , the coefficient of variation (CV) % was 81.3% for the fasted group and 51.4% for the fed group. For area under the plasma concentration-time curve (AUC [AUC_{0-t} and $AUC_{0-\infty}$]), the CV% was 48.2% to -53.6% for the fasted group and 33.9% to -34.1% for the fed group.

Figure 9: Food Effect on CBD PK Parameters



Cannabidiol when administered with high-fat meal also resulted in increased exposures to 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD by approximately 2 to 3 fold when compared with cannabidiol administration under fasting conditions (Table below).

Table 3: Summary of Primary PK Parameters of CBD Metabolites

Integrated Food Effect					
Analyte	Parameter	Fed	Fasted	Estimate	90% CI
6-OH-CBD	C _{max}	27.1	9.68	2.80	2.32-3.36
	AUC _{0-t}	250	94.7	2.64	2.14-3.25
	AUC _{0-∞}	274	106	2.59	2.06-3.26
7-COOH-CBD	C _{max}	4585	2205	2.08	1.64-2.64
	AUC _{0-t}	123735	51202	2.42	2.05-2.85
	AUC _{0-∞}	140311	59613	2.35	2.02-2.74
7-OH-CBD	C _{max}	378	130	2.91	2.43-3.48
	AUC _{0-t}	3218	1018	3.16	2.64-3.78
	AUC _{0-∞}	3337	1030	3.24	2.72-3.87

Based on the results from food effect study, to increase exposure and reduce variability, patients were advised to administer with food in Phase 3 clinical trials. In Phase 3 clinical trials patients were not restricted with regards to food intake in Phase 3 clinical trials and no data regarding dosing in relation to meal times were collected. The patients were instructed to take each dose consistently with respect to meals throughout each trial. The treatment emergent adverse events (TEAEs) were of mild or moderate severity (25% vs 67%). There were increased AE with the increased exposure of CBD and metabolites when administered with food. Since food increases bioavailability and which may also result in increased AEs, the OCP recommends that cannabidiol be dosed consistently with respect to meals. In the expanded access programs CBD was dosed above 40 mg/kg daily doses.

3.3.5 Is the to-be-marketed formulation the same as the clinical trial formulation, and if not, are there bioequivalence data to support the to-be-marketed formulation?

The to-be-marketed (TBM) formulation will be a 100 mg/mL oral solution of cannabidiol. In all clinical pharmacology and patient trials, same formulation of CBD was used (the only exception was in trial GWEP1332 Part A, (b) (4))

4. APPENDICES

4.1 Summary of Bioanalytical Method Validation and Performance

4.2 Population PK and/or PD Analyses

4.3 Exposure Response Analyses and Alternative Dosing Regimen Simulations

4.4 Physiologically-based Pharmacokinetic Modeling Review

4.5 Pharmacogenomics Summary

4.6 Individual Study Summaries

Appendix 4.1: Summary of Bioanalytical Method Validation and Performance

4.1.1 How are the active moieties identified and measured in the clinical pharmacology and biopharmaceutics studies?

Validated liquid chromatographic-tandem mass spectrometric (LC/MS/MS) bioanalytical methods were used to quantify plasma concentrations of CBD and THC and their major metabolites 7-hydroxy-cannabidiol (7-OH-CBD) 7-carboxy-cannabidiol (7-COOH-CBD), 11-hydroxy- Δ^9 -tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (11-COOH-THC) in human plasma.

4.1.2 What bioanalytical methods are used to assess cannabidiol concentrations? Briefly describe the methods and summarize the assay performance.

Plasma cannabidiol, its metabolites and THC concentrations were measured by a validated LC/MS/MS. The accuracy, precision, and other relevant parameters for the assay are described in Table below. This is sufficient to meet the requirements of the submitted studies.

Summary of Assay Validation Report

Analytes	CBD 6-OH-CBD 7- OH-CBD 7- COOH-CBD
Analytical matrix	Plasma, heparin lithium
Internal standards (ISTD)	CBD-d3 for CBD 7-OH-CBD-d5 for 6-OH-CBD and 7-OH-CBD 7-COOH-CBD-d5 for 7-COOH-CBD
Validated method	CBD4HPP
Validated ranges	CBD: 10.0-10000 ng/mL 6-OH-CBD: 1.25-1250 ng/mL 7- OH-CBD: 1.25-1250 ng/mL 7- COOH-CBD: 10-20000 ng/mL
Quality control (QC) levels	CBD: 10.0, 30.0, 500, 8000 and 14000 ng/mL 6-OH-CBD: 1.25, 3.75, 62.5, 1000 and 1750 ng/mL 7-OH-CBD: 1.25, 3.75, 62.5, 1000 and 1750 ng/mL

	7-COOH-CBD: 10.0, 30.0, 700, 16000 and 28000 ng/mL
Analytical technique/method of detection	Liquid-liquid extraction followed by liquid chromatography with tandem mass spectrometric detection
Sample volume	50 μ L
Calibration model	Linear
Weighting factor	1/x ²
Precision and accuracy	Requirements fulfilled
Stability of primary standard solutions	CBD: 24 hours at room temperature CBD: 27 days refrigerated 6-OH-CBD: 24 hours at room temperature 6-OH-CBD: 58 days refrigerated 7-OH-CBD: six hours at room temperature 7-OH-CBD: 58 days refrigerated 7-COOH-CBD: 24 hours at room temperature 7-COOH-CBD: 58 days refrigerated
Stability of intermediate solutions (All analytes)	24 hours at room temperature 28 days refrigerated
Processed sample stability (All analytes)	152 hours refrigerated
Sample collection stability (All analytes)	Two hours at room temperature Two hours on wet ice

Freeze/thaw matrix stability	Seven cycles at nominal -20°C Five cycles at nominal -80°C for CBD (seven cycles at nominal -80°C for 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD)
Room temperature matrix stability (All analytes)	Seven days
Long term frozen matrix stability (All analytes)	229 days at nominal -20°C in polypropylene tubes 229 days at nominal -80°C in polypropylene tubes 210 days at nominal -20°C in amber glass vials 210 days at nominal -80°C in amber glass vials
Haemolysis assessment	Acceptable for all Analytes
Hyperlipidemic plasma assessment	Affect quantification of CBD (%Bias values <-15.0% down to -25.3%) Affect quantification of 6-OH-CBD (%Bias values <-15.0% down to -17.6%) 7-OH-CBD: No effect 7-COOH-CBD: No effect
Co-administered drugs:	
- THC*, 11-OH-THC and 11-COOH-THC	No effect on quantification for all Analytes
- 5AEDS (Clobazam, N-Desmethyloclobazam, Levetiracetam, Topiramate and Stiripentol)	No effect on quantification for all Analytes
2 AEDS (Valproic acid and 4-ene VPA)	No effect on quantification for all Analytes
Maximum validated analytical run size	192 injections
Mass Spectrometers validated	API5000 and API5500

4.1.3 What is the range of the standard curve? How does it relate to the requirements for clinical studies?

The range of the standard curve used for clinical sample analysis was from 1 to 2000 ng/mL for CBD, and 0.25 to 250 ng/mL for all the metabolites including 6-hydroxy-cannabidiol (6-OH-CBD), 7-carboxy-cannabidiol (7-COOH-CBD), 7-hydroxy-cannabidiol (7-OH-CBD). The assay

range combined with the validated dilution methods are acceptable based on serum cannabidiol and its metabolite concentrations observed in the studies.

4.1.4 What is the QC sample plan?

Quality Control (QC) samples were freshly prepared on each analysis day by spiking the respective working solutions into human plasma. The run acceptance criteria was $\%CV \leq 20\%$, $\% Bias \pm 20\%$ for 6 ng/mL (LQC), 500 ng/mL (MQC) and 1500 ng/mL (HQC) for CBD and 0.75 ng/mL (LQC), 62.5 ng/mL (MQC) and 187.5 ng/mL (HQC) for 7-COOH-CBD and 7-OH-CBD.

4.3 Population PK and/or PD Analyses

4.3.1 Population PK Model Developed in Healthy Volunteers (Report gwpp16110):

The Applicant developed a population PK model to characterize the pharmacokinetics of CBD and two major circulating metabolites, 7-hydroxy CBD (7-OH CBD, molecular weight 330.46 grams per mole) and 7-carboxy CBD (7-COOH CBD, molecular weight (b) (4) grams per mole) in healthy volunteers. An additional objective was to assess the relationship between CBD concentration with demographics and other covariates.

Summary of PK Data:

There were 3766 measurable observations of CBD, 7-OH CBD, and 7-COOH CBD from n=45 healthy volunteers. In the PK dataset, the dose of CBD was converted to molar units using the molecular weight of 314.46 grams per mole.

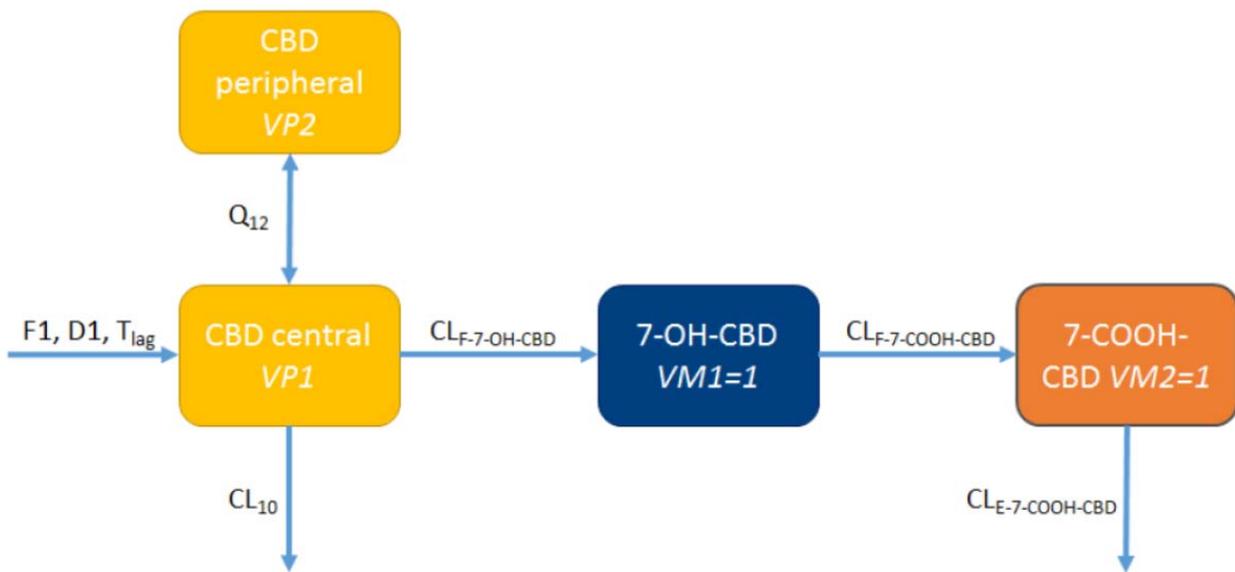
PK Study 1544: Applicant included PK data from Phase 1 study 1544, a randomized, double-blind, placebo controlled single ascending dose and multiple ascending dose study to assess PK as well as food effect on PK. Applicant randomized n=56 healthy adult subjects age 18-45 years. The trial consisted of a SAD phase, a MAD phase, and a food effect phase. Subjects received single administrations of 1500, 3000, 4500, and 6000 mg CBD in the food effect phase and in each period of the SAD phase. Subjects that entered the MAD phase of the trial received either 750 or 1500 mg CBD twice daily for 6 days and a single administration on Day 7.

- *PK Samples during SAD*: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, and 48 hours post-dose.
- *PK samples during Food Effect Assessment*: pre-dose and 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose.
- *PK Samples during MAD*:
 - *Day 1*: pre-morning dose, 0.5, 1, 2, 2.5, 3, 4, 5, 6, 8 and 12 hours post-morning dose and 0.5, 1, 2, 2.5, 3, 4, 5 and 12 hours post-evening dose
 - *Days 3, 4, 5, and 6*: pre-morning dose
 - *Day 7*: pre-dose and 0.5, 1, 2, 2.5, 3, 4, 5, 6, 8, 12, 24, 48, and 72 hours post-dose

Healthy Volunteer Population PK Model:

The base structural model was a 2-compartment model for CBD with 2 compartments for the metabolites (1 compartment for 7-OH CBD, 1 compartment for 7-COOH-CBD), zero-order absorption, and absorption lag time. CBD PK parameters include $CL_{F-7-OH-CBD}$ (apparent formation clearance of 7-OH CBD), CL_{10} (summation of all apparent clearance mechanisms which don't create 7-OH-CBD), $VP1$, $VP2$, and Q_{12} . Metabolite PK parameters include $CL_{F-7-COOH-CBD}$ (apparent formation clearance of 7-COOH CBD) and $CL_{E-7-COOH-CBD}$ (apparent elimination clearance of 7-COOH CBD). The only elimination pathway for 7-OH-CBD in this model is by formation of 7-COOH-CBD (and thus apparent elimination clearance of 7-OH CBD was set equal $CL_{F-7-COOH-CBD}$). $D1$ is duration of absorption duration. T_{lag} is absorption lag time and $F1$ is bioavailability. A schematic representation of the model is shown in the figure below.

Figure 4.3.1-1: Schematic Representation of Final HV Population PK Model



Source: sequence 0004, gwpp16110.pdf, page 25 of 97

Allometric Scaling: CL_{10} , $VP1$, $VP2$, Q_{12} , $CL_{F-7-OH-CBD}$, $CL_{F-7-COOH-CBD}$, and $CL_{E-7-COOH-CBD}$ had allometric scaling applied using body weight normalized to 70 kg. The exponent was 0.75 for all terms except for $VP1$ and $VP2$ which had exponents of 1.

Inter-individual variability: exponential

Residual variability: additive plus proportional error model

Covariates: duration of zero-order absorption increases with dose, bioavailability decreases with dose, and bioavailability is greater in a fed state compared to a fasted state. No other covariates were assessed. The models for absorption covariates are shown below.

Figure 4.3.1-2: Models for Absorption Covariates in HV PPK Model

<p>F1 decreases with dose</p> $F_1 = \left(1 - \frac{Dose}{Dose_{50} + Dose}\right)$	<p>D1 increases with dose</p> $D_1 = D_{10} \left(1 + \frac{Dose}{D1_{50} + Dose}\right)$	<p>F1 increases with food</p> $F_1 = (1 + Food_{effect})$
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Source: sequence 0004, gwpp16110.pdf, page 25 of 97

[Reviewer comment: The $F1$, $Dose_{50}$, D_{10} , and $D1_{50}$ terms in the models above are expressed as $F2$, $D050$, $D2$, and $D250$, respectively, in the NONMEM control stream.]

The final model parameter estimates are shown in the table below.

Table 4.3.1-1: PK Parameter Estimates for Final PPK Model in Healthy Volunteers

Description	Unit	Estimate on normal scale	95%CI
$D1_{50}$	mg	424	28.9 - 6217
$D1_0$	h	2.36	1.58 - 3.53
CL10	L/h	282	206 - 386
VP1	L	4132	2781 - 6139
Q_{12}	L/h	51.5	28.9 - 91.9
VP2	L	4996	1569 - 15906
$Dose_{50}$	mg	2416	855 - 6829
T_{lag}	h	0.13	0.11 - 0.77
Food effect on F1		1.52	1.31 - 1.73
$CL_{F-7-OH-CBD}$	L/h	0.0012	0.0008 - 0.0018
$CL_{F-7-COOH-CBD}$	L/h	8.78	7.12 - 10.8
$CL_{E-7-COOH-CBD}$	L/h	0.14	0.11 - 0.17
RUV_{CBD}	%	50.4	47.6 - 57.2
$RUV_{7-OH-CBD}$	%	15.4	14.3-16.5
$RUV_{7-COOH-CBD}$	%	41.1	39.1-43.1
Common $RUV_{CDB-7-OH-CBD-7-COOH-CBD}$	μM	0.87	0.84 - 0.89

CI: Confidence interval; CL10: Apparent CBD clearance not forming 7-OH CBD; $CL_{E-7-COOH-CBD}$: Apparent elimination clearance of 7-COOH CBD; $CL_{F-7-COOH-CBD}$: Apparent formation clearance of 7-COOH CBD; $CL_{F-7-OH-CBD}$: Apparent formation clearance of 7-OH CBD; Common $RUV_{CDB-7-OH-CBD-7-COOH-CBD}$: Absolute residual unexplained variability common to the 3 analytes; $D1_0$: Minimum absorption duration; $D1_{50}$: Potency parameter of the dose effect on the duration of absorption; $Dose_{50}$: Potency of the dose effect on bioavailability; Food effect on F1: Food-effect on bioavailability (fractional change from nonfed conditions); Q_{12} : Apparent intercompartmental clearance of CBD; $RUV_{7-COOH-CBD}$: Percent residual unexplained variability on 7-COOH CBD; $RUV_{7-OH-CBD}$: Percent residual unexplained variability on 7-OH CBD; RUV_{CBD} : Percent residual unexplained variability on CBD; T_{lag} : Lag time; VP1: Apparent central volume of distribution of CBD; VP2: Apparent peripheral volume of distribution of CBD

Source: sequence 0004, gwpp16110.pdf, page 5 of 97.

Table 4.3.1-2: Variability of PK Parameters for Final PPK Model in Healthy Volunteers

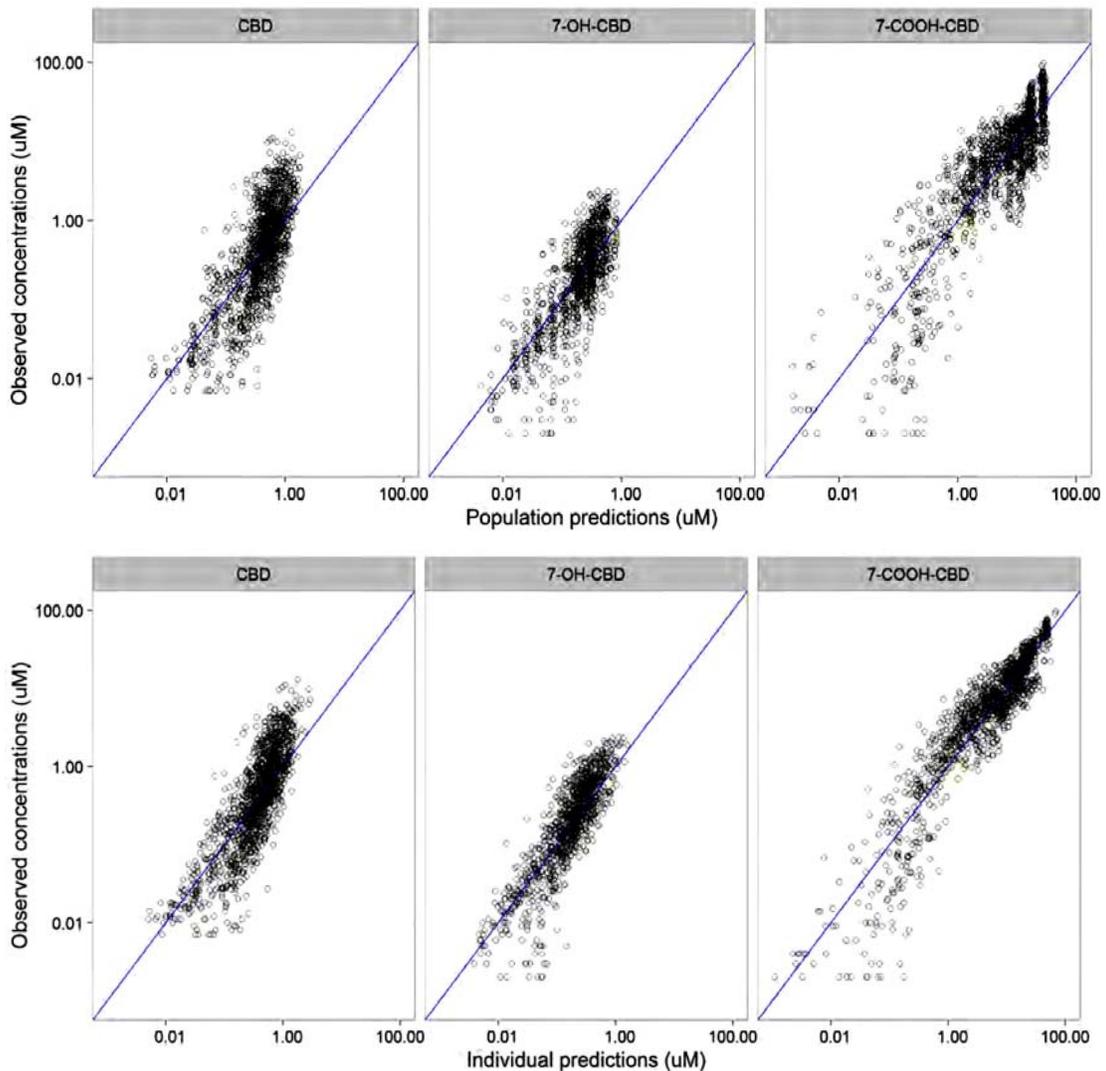
Description	Estimate	SE	RSE (%)	CV%	Shrinkage (%)
IIV D_{10}	0.122	0.0834	68.4	34.9	28.4
IIV VP_1	0.0764	0.0576	75.4	27.6	25.5
IIV VP_2	0.833	1.43	171.7	91.3	61.4
IIV $Dose_{50}$	0.682	0.625	91.6	82.6	18.9
IIV $CL_{F-7-OH-CBD}$	0.285	0.0858	30.1	53.4	3.90
IIV $CL_{F-7-COOH-CBD}$	0.143	0.077	53.8	37.8	3.80
IIV $CL_{E-7-COOH-CBD}$	0.17	0.0767	0.451	41.2	19.0

CV%: IIV expressed as percent coefficient of variation; IIV: interindividual variability; RSE: percent relative standard error; SE: standard error

Source: sequence 0004, gwpp16110.pdf, page 6 of 97.

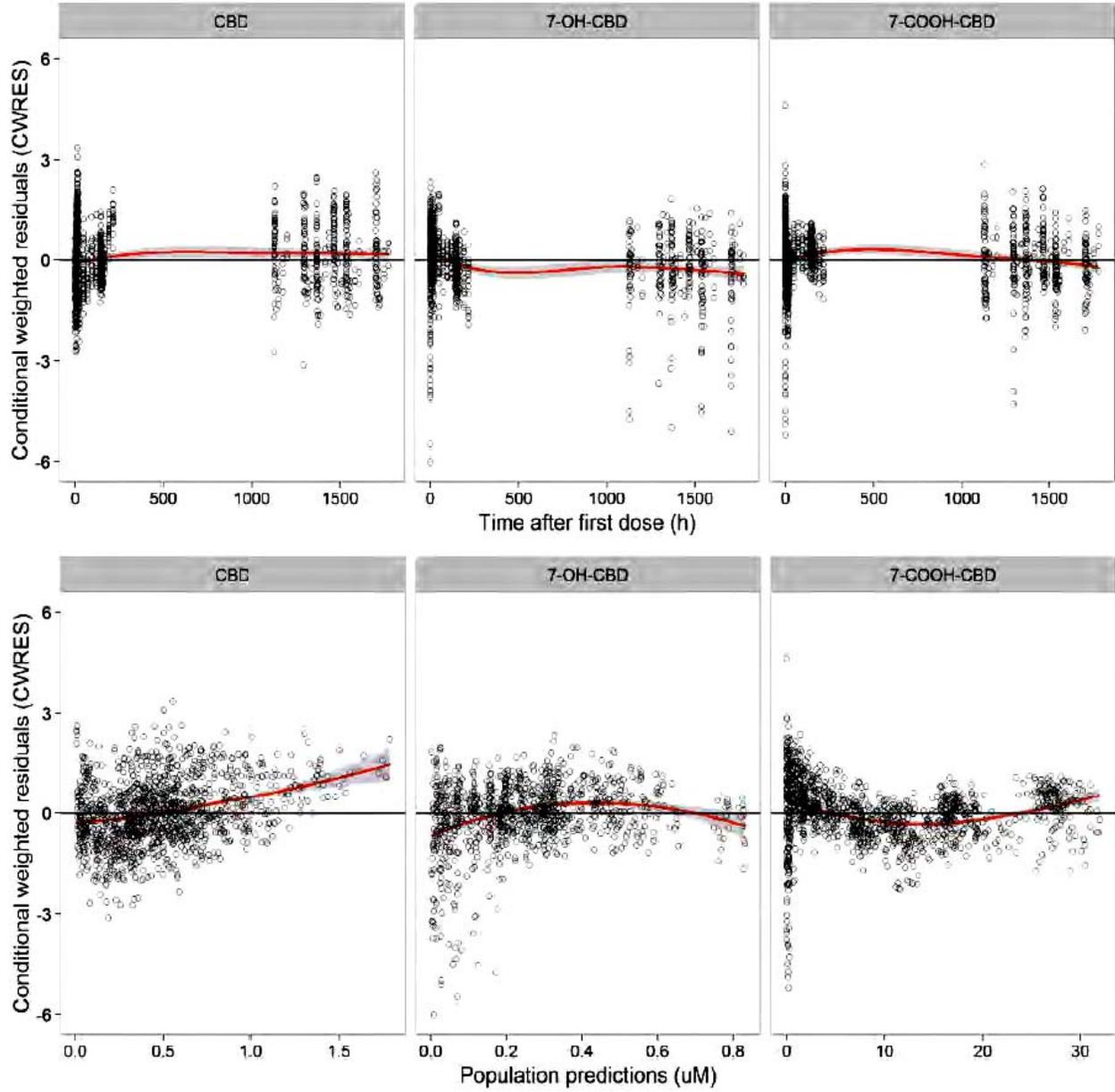
Model diagnostics are presented in the figures below.

Figure 4.3.1-3: Diagnostic Plots for Final PK Model in Healthy Volunteers



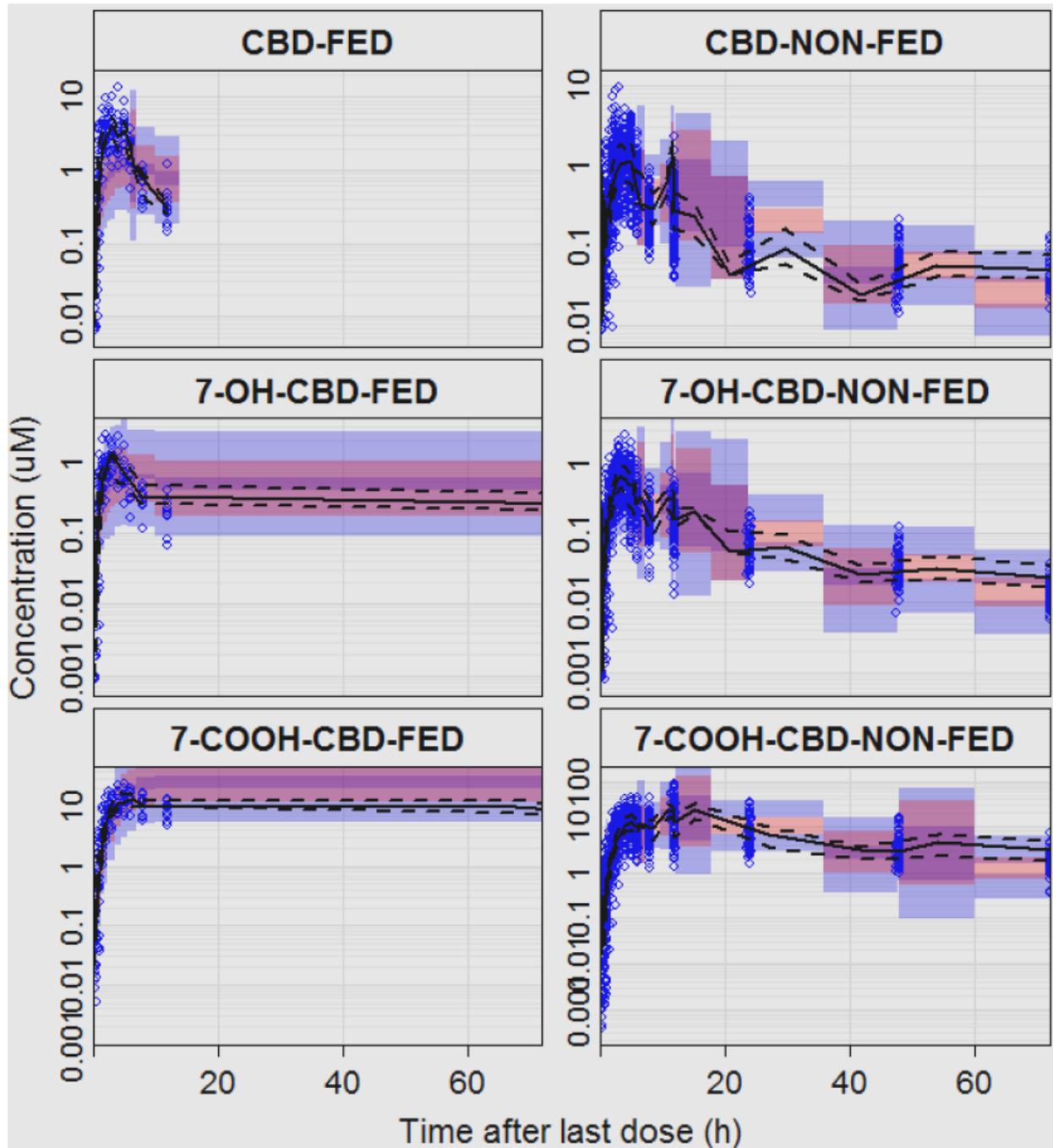
Source: sequence 0004, gwpp16110.pdf, page 30 of 97

Figure 4.3.1-4: Diagnostic Plots for Final PK Model in Healthy Volunteers



Source: sequence 0004, gwpp16110.pdf, page 31 of 97

Figure 4.3.1-5: Prediction-Corrected Visual Predictive Check Plot for Final PK Model in Healthy

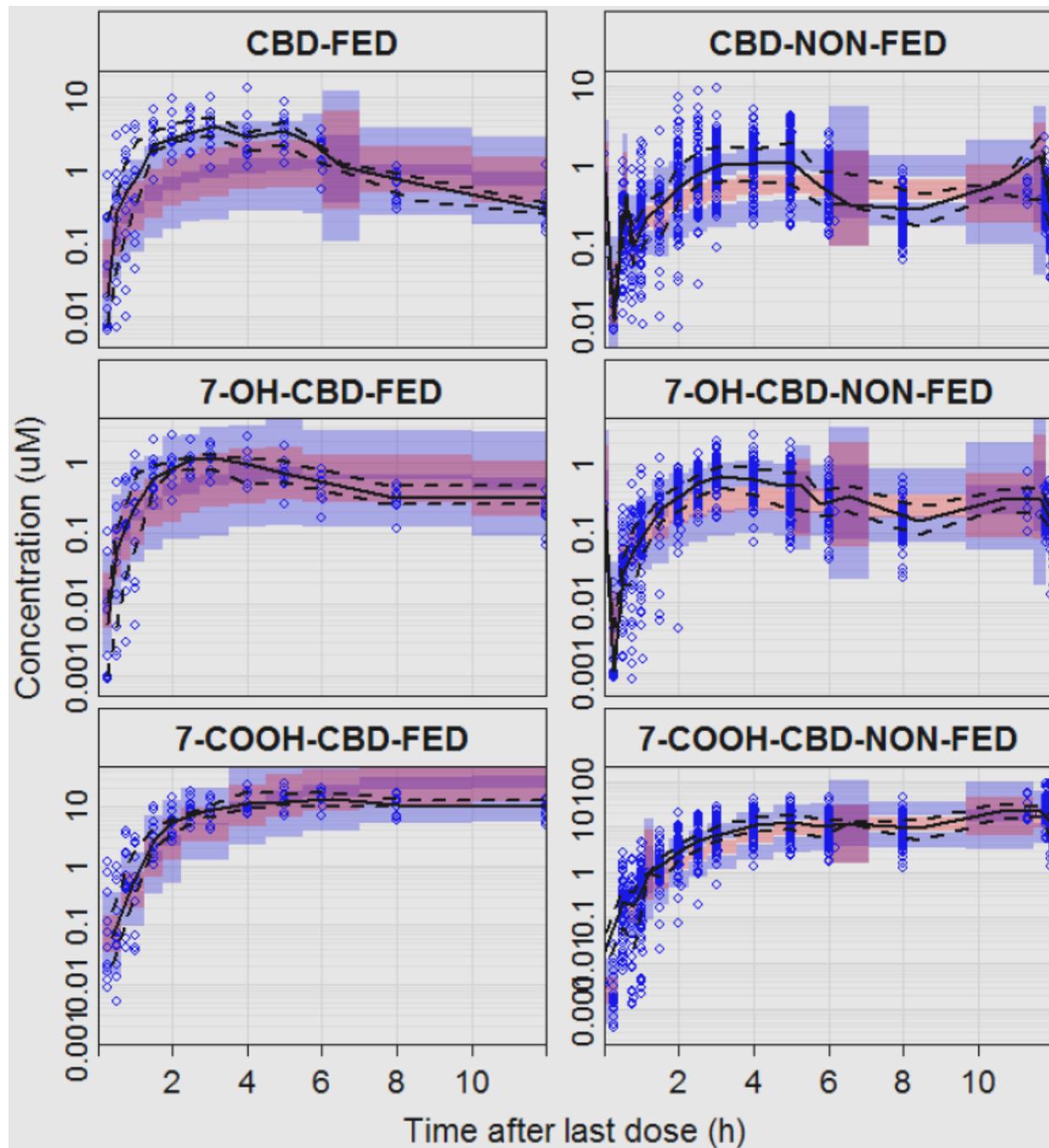


Volunteers up to 70 hours Post Dose

Source: *sequence 0004, gwpp16110.pdf, page 32 of 97*

The blue areas are the 95% predictions intervals of the first and third quartiles. The pink areas are the 95% predictions intervals of the median. The lower and upper dotted lines are the first and third quartiles of observations, respectively. The solid lines are the median observations.

Figure 4.3.1-6: Prediction-Corrected Visual Predictive Check Plot for Final PK Model in Healthy Volunteers up to 12 hours Post Dose



Source: sequence 0004, gwpp16110.pdf, page 54 of 97

The blue areas are the 95% predictions intervals of the first and third quartiles. The pink areas are the 95% predictions intervals of the median. The lower and upper dotted lines are the first and third quartiles of observations, respectively. The solid lines are the median observations.

[Reviewer comment: The plots of CWRES versus concentration indicate that systematic bias manifests at exposures $\geq 1 \mu\text{M}$ CBD.

In addition, according to the VPC, the model appears to under predict CBD exposures in the timeframe near C_{max} (e.g. 0 to 4 hours post-dose) regardless of whether patients are fasted or fed. According to the VPC, in the fed state, the model tends to overpredict CBD exposure at time ≥ 8 hours post administration. The VPC shows that while in the fasted state, the model performs better than in the fed state for the time period ≥ 8 hours. However, it is not clear why the observed CBD PK profile appears to increase starting at about 6 hours post-dose in the fasted state population.

Overall, the HV PPK model is likely to under predict CBD exposure in the vicinity of T_{max} . However, the model appears to be reasonable for use in comparing the original titration regimen with the alternate titration regimen as the interest is in simulating the general shape and time-course of CBD concentrations over the titration duration and not absolute CBD levels within the dosing interval. Due to the large exposure difference between fed and non-fed states, the assessment of the two titration regimens was performed in both the fasted state as well as the fed state. Please refer to section 4.3.5 for details regarding the PK simulations conducted by the Reviewer to compare the original versus alternate titration regimens.]

4.3.2 Population PK Model Developed in Dravet Syndrome Patients (Report 17003):

The Applicant developed a population PK model to characterize the pharmacokinetics of CBD and two major circulating metabolites, 7-hydroxy CBD (7-OH CBD, molecular weight 330.46 grams per mole) and 7-carboxy CBD (7-COOH CBD, molecular weight (b) (4) grams per mole) in DS patients. An additional objective was to assess the relationship between covariates and PK variability.

Summary of PK Data:

There were 335 measurable observations of CBD, 7-OH CBD, and 7-COOH CBD from n=27 patients with Dravet Syndrome enrolled in Phase 3 Trial 1332. PK data were available in patients age 3.9 to 10.9 years. In the PK dataset, the dose of CBD was converted to molar units using the molecular weight of 314.46 grams per mole.

Phase 3 Trial 1332 (Part A): Trial 1332 was a randomized, placebo-controlled, two-part study to investigate the dose-ranging safety and PK, followed by efficacy and safety of CBD in n=34 patients with

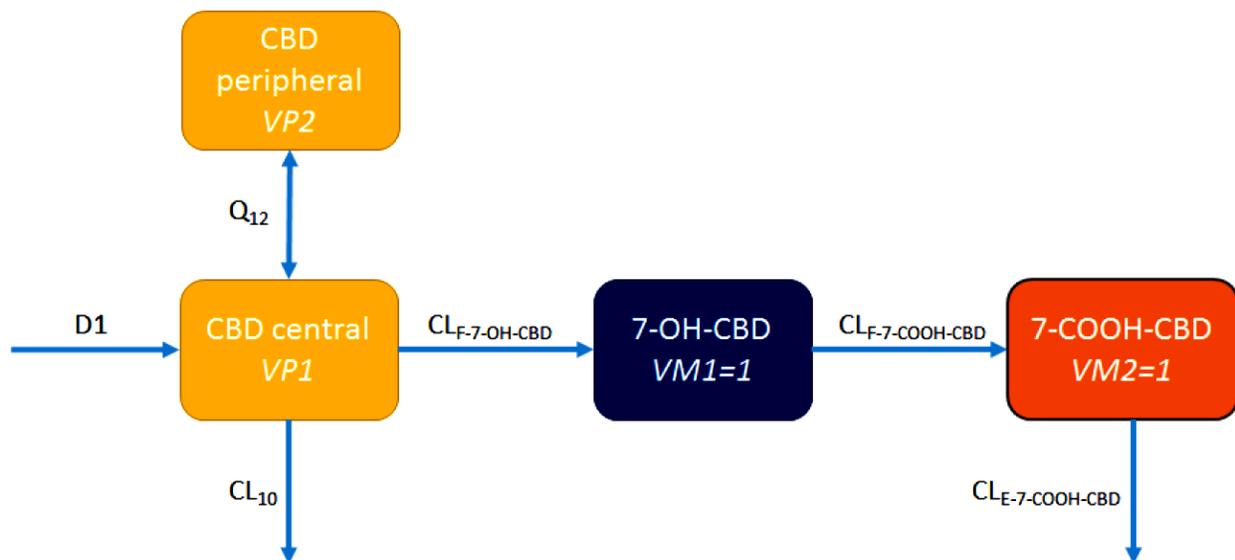
Dravet Syndrome ages 2 to 18 years. All patients initiated dosing at 2.5 mg/kg/day and increased the dose by 2.5 mg/kg/day every 2 days. When titrating to doses higher than 10 mg/kg/day, the dose increased by 5 mg/kg/day every 2 days. Target dose levels in Part A (PK assessments, no efficacy assessments) were 5, 10, and 20 mg/kg/day. Total treatment duration in Part A, including titration, is 21 days. The total daily dose was split evenly with half the total daily dose administered every 12 hours.

PK samples: On Day 1 and Day 21, PK samples were collected at the following times: pre-dose, 2-3 hours post-dose, 4-6 hours post-dose (3 samples total per day).

DS Patient Population PK Model:

The structural model is identical to the HV PPK structural model (see section 4.3.1 for description of the model structure) except the DS model does not estimate bioavailability (no F1 estimate, thus apparent clearance and apparent volumes are estimated) and does not include a T_{lag} parameter. D1 is duration of zero-order absorption. A schematic representation of the model is shown in the figure below.

Figure 4.3.2-1: Schematic Representation of DS Population PK Model



Source: sequence 0004, gwpp17003.pdf, page 29 of 222

Allometric Scaling: Not implemented.

Inter-individual variability: exponential

Residual variability: additive plus proportional error model

Covariates: **None.** Only age and use of valproic acid were statistically significant in univariate forward addition. However, age was not statistically significant after backward deletion. Valproic acid use was significant after backward deletion, but precision was poor on the valproic acid effect (RSE% = 158%) and its inclusion resulted in a large increase in the IIV of CL10 (RSE% = 312%). Thus the Sponsor did not include any covariates in the final model.

The final model parameter estimates are shown in the table below.

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Table 4.3.2-1: PK Parameter Estimates for Final PPK Model in DS Patients

Table 4.1.2-2		Parameter Estimates of the Base Model After Conversion to a Normal Scale	
Description	Unit	Estimate on normal scale	95%CI
D1	h	2.36	
CL ₁₀	L/h	71.5	51.4 – 99.6
VP1	L	1719.9	1108.8 – 2667.8
Q ₁₂	L/h	122.7	56.9 – 264.5
VP2	L	12708.2	3644.6 – 44311.5
CL _{F-7-OH-CBD}	L/h	0.0016	0.00068 – 0.0036
CL _{F-7-COOH-CBD}	L/h	5.47	3.01 – 9.95
CL _{E-7-COOH-CBD}	L/h	0.14	0.073 – 0.26
RUV _{CBD}	%	43.3	0.322-0.544
RUV _{7-OH-CBD}	%	15.4	
RUV _{7-COOH-CBD}	%	40.4	0.287-0.521
Common RUV _{CBD-7-OH-CBD-7-COOH-CBD}	μM	0.57	0.364-0.784

CI: confidence interval; CL₁₀: Apparent CBD clearance not forming 7-OH CBD; CL_{E-7-COOH-CBD}: Apparent elimination clearance of 7-COOH CBD; CL_{F-7-COOH-CBD}: Apparent formation clearance of 7-COOH CBD; CL_{F-7-OH-CBD}: Apparent formation clearance of 7-OH CBD; Common RUV_{CBD-7-OH-CBD-7-COOH-CBD}: Absolute residual unexplained variability common to the 3 analytes; D1: Absorption duration; Q₁₂: Apparent intercompartmental clearance of CBD; RUV_{7-COOH-CBD}: Percent residual unexplained variability on 7-COOH CBD; RUV_{7-OH-CBD}: Percent residual unexplained variability on 7-OH CBD; RUV_{CBD}: Percent residual unexplained variability on CBD; VP1: Apparent central volume of distribution of CBD; VP2: Apparent peripheral volume of distribution of CBD.

Source: sequence 0004, gwpp17003.pdf, page 29 of 222

Table 4.3.2-2: Variability of PK Parameters for Final PPK Model in DS Patients

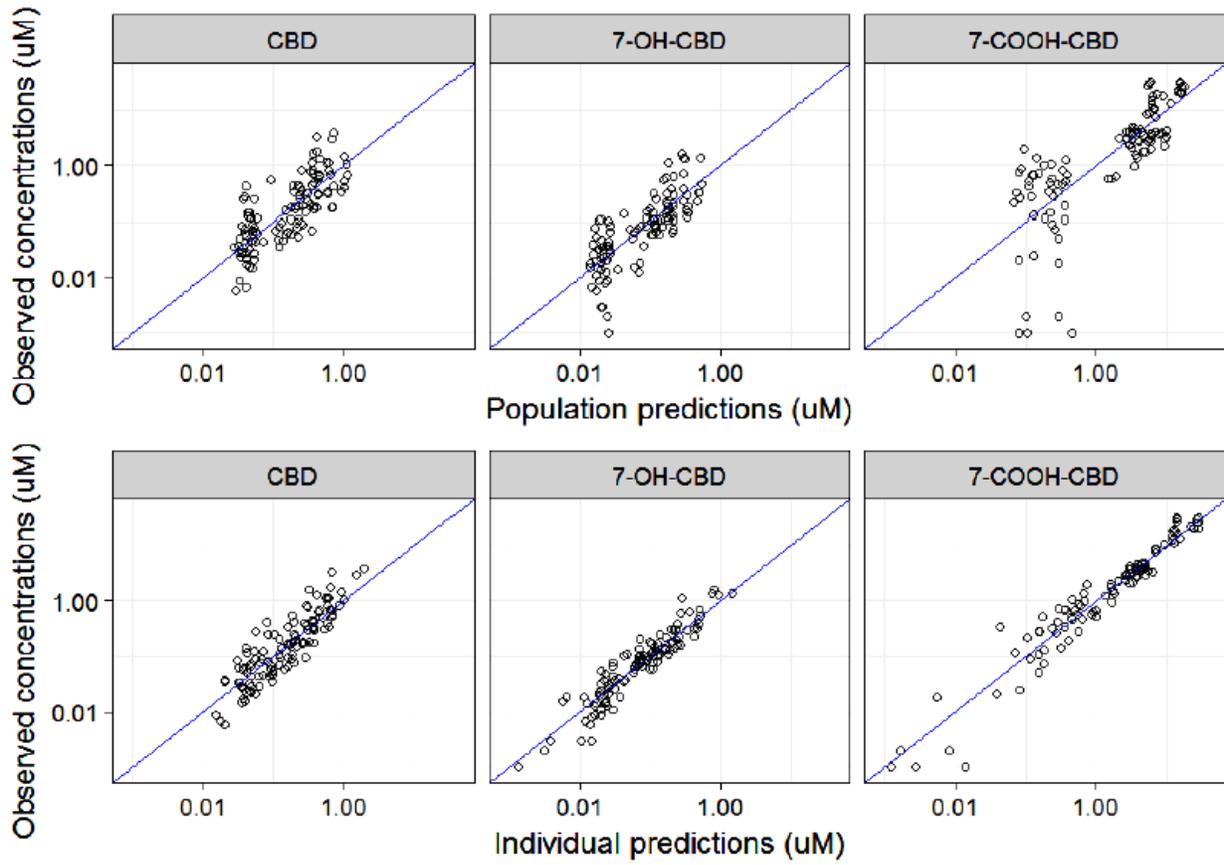
Table 4.1.2-3 InterIndividual Variability in Model Parameters					
Description	Estimate	SE	RSE%	CV%	Shrinkage %
IIV CL ₁₀	0.308	0.131	42.5	55.5	21.5
IIV VP1	0.531	0.34	64	72.9	12.9
Correlation IIV CL ₁₀ -VP1	0.296	0.173	58.4	73.2	
IIV CL _{F-7-OH-CBD}	3.89	1.25	32.1	197.2	4.9
IIV CL _{F-7-COOH-CBD}	2.54	0.899	35.4	159.4	4.8
IIV CL _{E-7-COOH-CBD}	2.75	1.23	44.7	165.8	7.3
Correlation IIV CL _{F-7-OH-CBD} - CL _{F-7-COOH-CBD}	3.01	1.01	33.6	95.8	
Correlation IIV CL _{F-7-COOH-CBD} - CL _{E-7-COOH-CBD}	2.52	1.03	40.9%	95.3	
Correlation IIV CL _{F-7-OH-CBD} - CL _{E-7-COOH-CBD}	3.16	1.13	35.8	96.6	

CV%: IIV expressed as percent coefficient of variation; IIV: interindividual variability; RSE%: percent relative standard error; SE: standard error.

Source: sequence 0004, gwpp17003.pdf, page 30 of 222

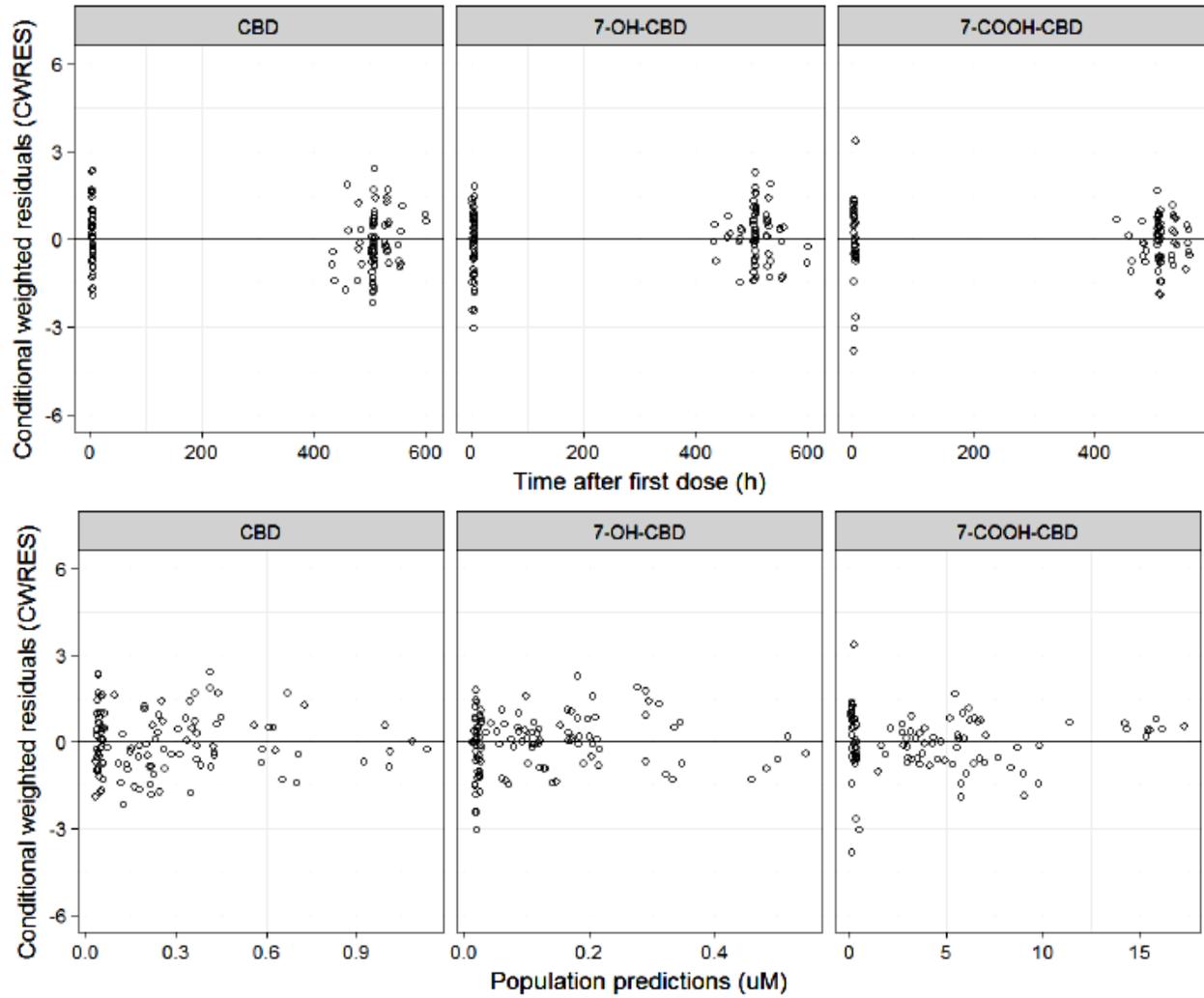
Model diagnostics are presented in the figures below.

Figure 4.3.2-2: Diagnostic Plots for Final PK Model in DS Patients



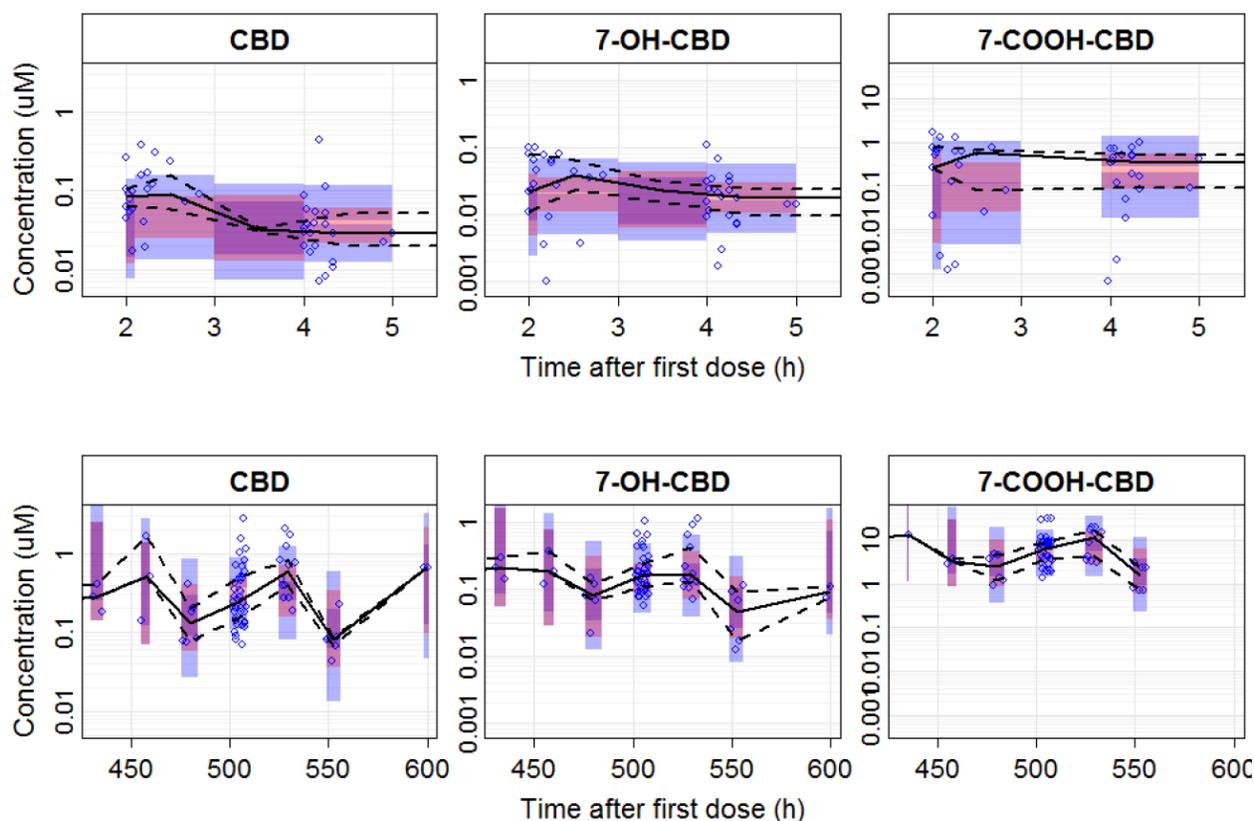
Source: sequence 0004, gwpp17003.pdf, page 57 of 222

Figure 4.3.2-3: Diagnostic Plots for Final PK Model in DS Patients



Source: sequence 0004, gwpp17003.pdf, page 63, 65 of 222

Figure 4.3.2-4: VPC Plots for Final PK Model in DS Patients



Source: sequence 0004, gwpp17003.pdf, page 32 of 222

[Reviewer comment The Applicant reports: “.. that when estimated, the allometric exponents converge toward zero, suggesting no need for an allometric correction in this dataset”. However, in light of the weight range of 17.0 to 47.2 kg (age range of 3.9 to 10.9 years) of patients with PK data in Phase 3 Trial 1332, it is expected that weight would be considered a covariate on CBD PK.

Also, based on the forward addition procedure, the only potential candidate for a PPK covariate was the effect of valproate on CBD CL_{10} . However, the applicant rejected this covariate for the DS PPK model due to poor precision in the estimate of valproate covariate effect on CBD CL_{10} (158% RSE) and the poor precision of CL_{10} IIV (312% RSE) when the valproate covariate is included.

There are significant concerns regarding the reliability of the PPK analyses due to the conduct of the Phase 3 Trial 1332 in DS patients. The effect of food, as shown in study 1544, can result in an exposure increase up to 5-fold. In addition, study 1544 has demonstrated a prandial effect such that a C_{max} difference of > 3-fold can occur between consecutive administrations spaced 12 hours apart (e.g. administering in the morning after a 10-hour fast versus administering in the evening after a 2-hour fast with 1 hour fast post-dose). However, the Phase 3 Trial 1332 report indicates that CBD was administered twice daily without regard to meals. Though Applicant states that patients were instructed to take each

dose consistently with respect to meals throughout the trial, no data were collected regarding meal intake during Trial 1332. As a result, it is not clear to what extent the effect of food and overall prandial effect is contributing to observed PK data utilized in the PPK analyses. **Overall, it is not clear that the DS PPK model can be considered reliable due to the magnitude of the food effect, the lack of meal restriction during Phase 3 trial 1332, lack of meal data collection during Phase 3 trial 1332.** (b) (4)

Due to the concerns regarding the DS PPK model the Reviewer utilized the HV PPK model to assess the alternate titration regimen (please see section 4.3.5 for details.)

4.3.3 Population PK Model Developed in Lennox-Gastaut Syndrome Patients (Report 17004):

The Applicant developed a population PK model to characterize the pharmacokinetics of CBD and two major circulating metabolites, 7-hydroxy CBD (7-OH CBD, molecular weight 330.46 grams per mole) and 7-carboxy CBD (7-COOH CBD, molecular weight (b) (4) grams per mole) in LGS patients. An additional objective was to assess the relationship between covariates and PK variability.

Summary of PK Data:

There were 3144 measurable observations of CBD, 7-OH-CBD, and 7-COOH-BD in n=216 subjects with Lennox Gastaut syndrome. In the PK dataset, the dose of CBD was converted to molar units using the molecular weight of 314.46 grams per mole. The PK data came from Phase 3 trial 1414 and Phase 3 trial 1423.

Phase 3 Trial 1414: A randomized, double-blind, placebo-controlled trial to investigate the efficacy and safety of 10 mg/kg/day or 20 mg/kg/day CBD in n=225 patients with LGS ages 2 to 55 years. Target dose levels were 10 mg/kg/day and 20 mg/kg/day. All patients initiated dosing at 2.5 mg/kg/day and increased the dose by 2.5 mg/kg/day every 2 days. For titration beyond 10 mg/kg/day, the dose was increased by 5 mg/kg/day every 2 days. Treatment duration was 14 weeks (up to 2 weeks titration, at least 12 weeks maintenance). The total daily dose was split evenly with half the total daily dose administered every 12 hours.

PK samples: On Day 1 and Day 99, PK samples were collected at the following times: pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose.

Phase 3 Trial 1423: A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of 20 mg/kg/day CBD in n=171 patients with LGS ages 2 to 55 years. Initiation and titration was same as in Trial 1414 except the only target dose was 20 mg/kg/day. Treatment duration was 14 weeks (2 weeks

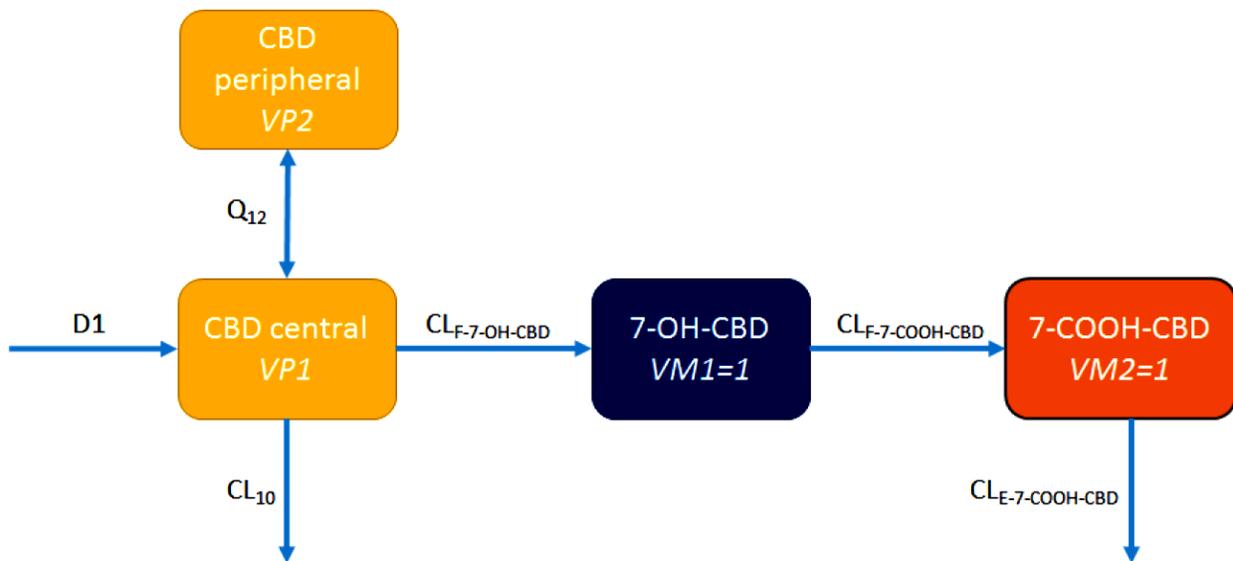
titration, 12 weeks maintenance). The total daily dose was split evenly with half the total daily dose administered every 12 hours.

PK samples: Same as for Trial 1414.

LGS Patient Population PK Model:

The structural model is identical to the DS PPK structural model (see section 4.3.2 for description of the model structure) except that F1 (bioavailability of administration into central compartment) is included in the model. A schematic representation of the model is shown in the figure below.

Figure 4.3.3 -1: Schematic Representation of Final Population PK Model in LGS Patients



Source: sequence 0004, gwpp17004.pdf, page 32 of 152

Allometric Scaling: Not implemented.

Inter-individual variability: exponential

Residual variability: additive plus proportional error model

Covariates: A decrease in bioavailability with increasing dose is the only covariate included in the final model. This covariate was carried over from the HV model. The model for this absorption covariate is shown below.

Figure 4.3.3-2: Model for Absorption Covariate in LGS PPK Model

$$F_1 \text{ decreases with dose}$$

$$F_1 = \left(1 - \frac{Dose}{Dose_{50} + Dose} \right)$$

In regards to other potential covariates (e.g. weight or age), Applicant states:

“However, the full model was not able to converge successfully and to estimate the variance-covariance matrix for parameter estimate precision. Therefore, none of these covariate effects were included in the final population PK model” (gwpp17004.pdf, page 34 of 152).

Thus, the Applicant did not include any other covariates to the final model aside from dose effect on bioavailability.

The final model parameter estimates are shown in the table below.

Table 4.3.3-1: PK Parameter Estimates for Final PPK Model in LGS Patients

Table 4.1.2.4-1 Parameter Estimates of the Base Model After Conversion to a Normal Scale			
Description	Unit	Estimate on normal scale	95%CI
D1	h	2.25	1.94-2.61
CL ₁₀	L/h	35.52	23.0– 54.8
VP1	L	6836	4505 -10373
Q ₁₂	L/h	159.2	17.4 -1458
VP2	L	4629	0.08 – 281319052
CL _{F-7-OH-CBD}	L/h	0.0009	0.0006 – 0.001
CL _{F-7-COOH-CBD}	L/h	15.03	13.5 - 16.7
CL _{E-7-COOH-CBD}	L/h	0.194	0.174 -0.216
Dose ₅₀	mg	134.3	75.9 - 237
RUV _{CBD}	%	0.444	0.424 – 0.464
RUV _{7-OH-CBD}	%	0.154 FIX	
RUV _{7-COOH-CBD}	%	0.496	0.473 – 0.519
Common RUV _{CBD-7-OH-CBD-7-COOH-CBD}	μM	0.738	0.703 – 0.773

CI: Confidence interval; CL₁₀: Apparent CBD clearance not forming 7-OH-CBD; CL_{E-7-COOH-CBD}: Apparent elimination clearance of 7-COOH-CBD; CL_{F-7-COOH-CBD}: Apparent formation clearance of 7-COOH-CBD; CL_{F-7-OH-CBD}: Apparent formation clearance of 7-OH-CBD; Common RUV_{7-OH-CBD-7-COOH-CBD}: Absolute residual unexplained variability common to the 3 analytes; D1: Minimum absorption duration; Dose₅₀: Potency of the dose effect on bioavailability; Food effect on F1: Food-effect on bioavailability (fractional change from nonfed conditions); Q₁₂: Apparent intercompartmental clearance of CBD; RUV_{7-COOH-CBD}: Percent residual unexplained variability on 7-COOH-CBD; RUV_{7-OH-CBD}: Percent residual unexplained variability on 7-OH-CBD; RUV_{CBD}: Percent residual unexplained variability on CBD; VP1: Apparent central volume of distribution of CBD; VP2: Apparent peripheral volume of distribution of CBD.

Source: sequence 0004, gwpp17004.pdf, page 33 of 152

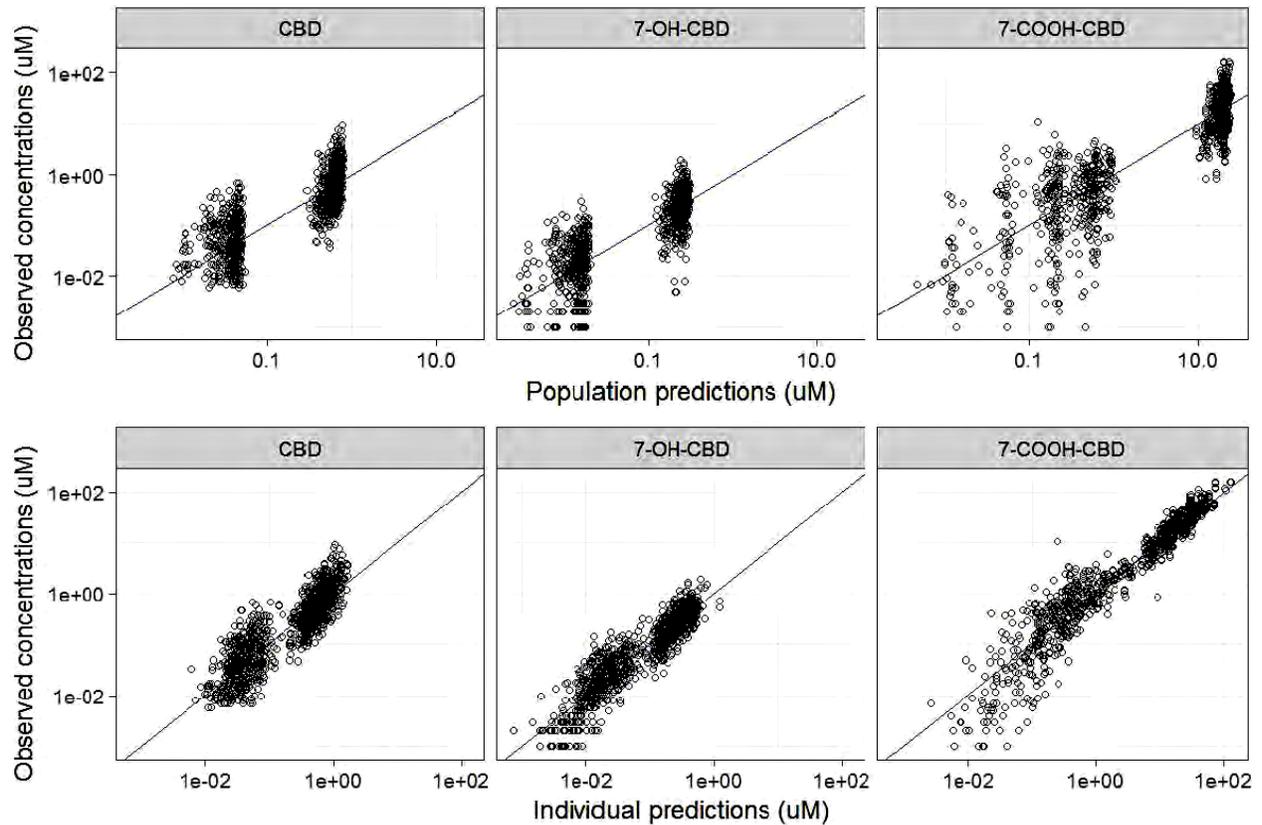
Table 4.3.3-2: Variability of PK Parameters for Final PPK Model in LGS Patients

Table 4.1.2.4-2 Interindividual Variability in Model Parameters					
Description	Estimate	SE	RSE (%)	CV%	Shrinkage (%)
IIV VP1	0.236	0.0533	22.6	48.6	35.5
IIV CLF-7-OH-CBD	0.598	0.0877	14.7	77.3	16.7
IIV CLF-7-COOH-CBD	0.203	0.0290	14.3	45.1	20.3
IIV CLE-7-COOH-CBD	0.153	0.0406	26.5	39.1	41.8
IIV Dose ₅₀	0.481	0.0944	19.6	69.3	27.5

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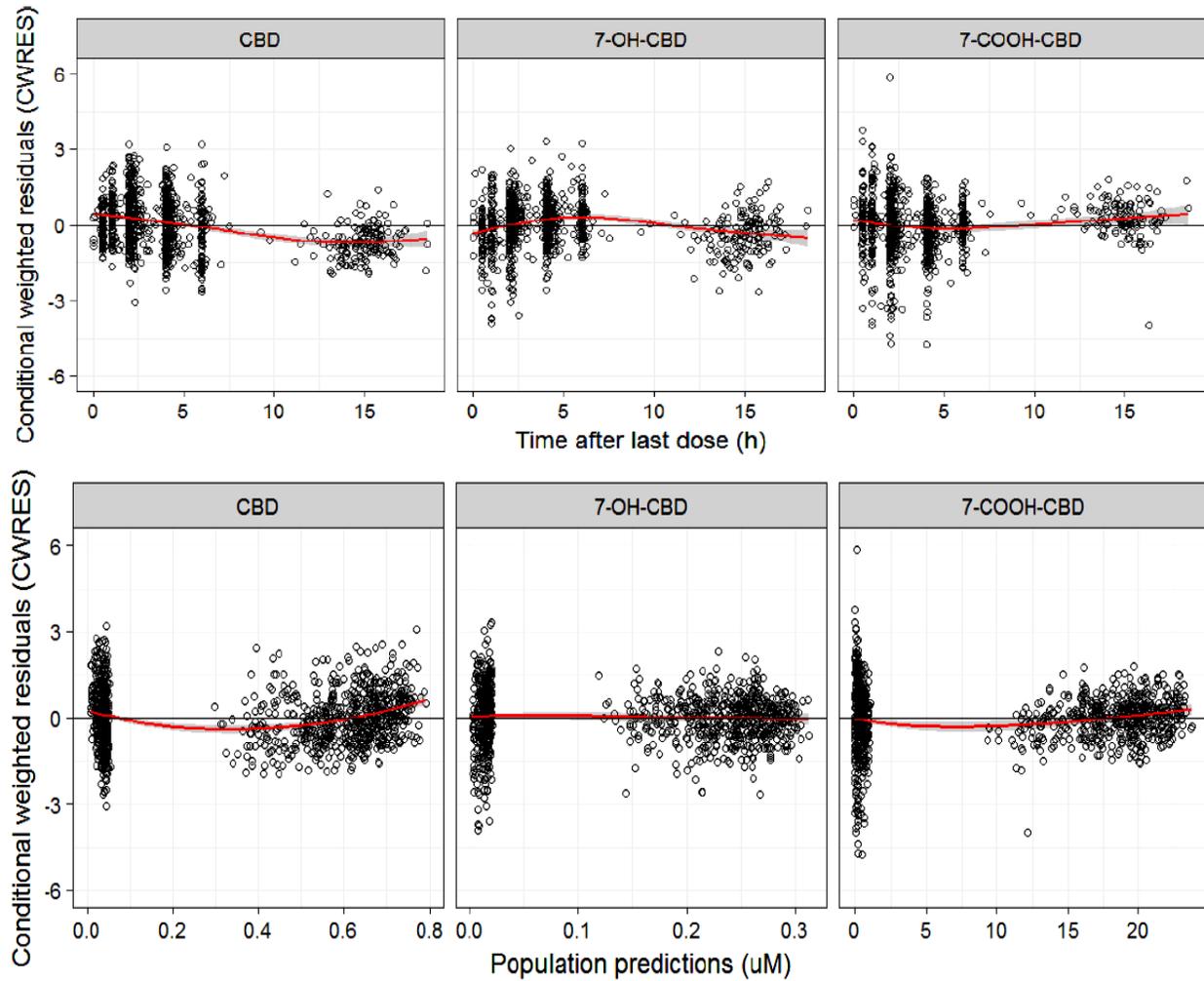
Model diagnostics are presented in the figures below.

Figure 4.3.3-3: Diagnostic Plots for Final PK Model in LGS Patients



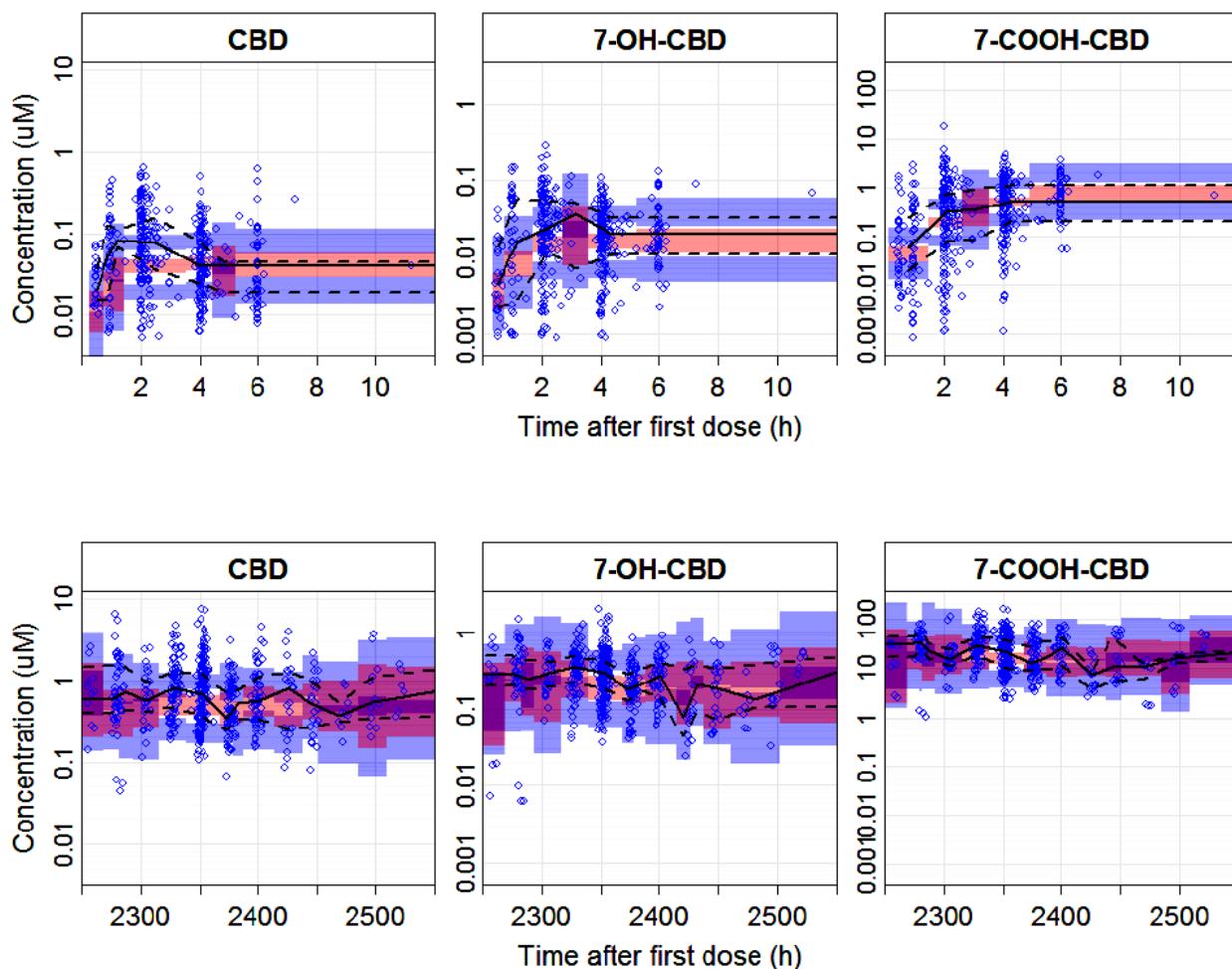
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Figure 4.3.3-4: Diagnostic Plots for Final PK Model in LGS Patients



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Figure 4.3.3-5: VPC Plots for Final PK Model in LGS Patients



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[Reviewer comment: There are significant concerns regarding the reliability of the PPK analyses due to the conduct of the Phase 3 Trials 1414 and 1423. The same concerns as were expressed regarding the conduct of Phase 3 Trial 1332 (see section 4.3.2 for details) are present with Phase 3 trials 1414 and 1423.

There was no restriction on food intake relative to dosing time in Trial 1414 or in trial 1423. Though Applicant states that patients were instructed to take each dose consistently with respect to meals throughout the trial, no data were collected regarding meal intake during Trials 1414 or 1423. As a result, it is not clear to what extent the effect of food and overall prandial effect is contributing to observed PK data utilized in the PPK analyses. In addition, the LGS PPK analysis report indicates that the model was not able to converge for any covariates other than dose. Also, as was the case for the DS PPK model (see section 4.3.2), body weight is expected to be a covariate in the final model considering the weight range (10.8 to 83.2 kg) observed across the age range (2.61 to 17.9 years) of pediatric LGS

patients with available PK data in Trials 1414 and 1423. **Overall, it is not clear that the LGS PPK model can be considered reliable due to the magnitude of the food effect, the lack of meal restrictions, lack of meal data collection during Phase 3 trials 1414 and 1423, lack of convergence for the majority of covariates, and poor model performance as indicated in the diagnostic plots.**

(b) (4)

These concerns also contributed to the reviewer's decision to select the HV PPK model for conducting PK simulations to assess the alternate titration regimen (please see section 4.3.5 for details).

4.3.4 PK Simulations by Applicant to Compare Original versus Alternate Titration Regimens Using the Dravet Syndrome Population PK Model (Report 17045):

The Applicant conducted PK simulations to assess an alternate titration regimen that differs from the original titration regimen applied in the Phase 3 trials. In the Phase 3 trials, for both LGS and DS patients the starting dose was 2.5 mg/kg/day which was increased by 2.5 mg/kg/day every 2 days. For dose increases above 10 mg/kg/day, the dose increased by 5 mg/kg/day every 2 days. The Applicant is proposing an alternate titration regimen where the starting dose is 5 mg/kg/day and dosing is increased by 5 mg/kg/day every week until the target dose is achieved. All dosing in the Phase 3 trials as well as the PK simulations were administered such that the total daily dose was split in half and half the dose was administered every 12 hours.

The Applicant utilized the DS PPK model to conduct the PK simulations. Using the individual PK parameters from patients in the DS trial 1332, the Applicant conducted PK simulations to generate individual simulated PK profiles using the original and alternate titration regimen with 10 and 20 mg/kg/day as target dose levels. The following plots show the results of the Applicant's PK simulations with 10 mg/kg/day and 20 mg/kg/day as the target doses.

Figure 4.3.4-1: Simulated CBD PK Profiles for Individual DS Patients following the Original and Alternative Titration Schedules with a Target of 10 mg/kg/day

(b) (6)



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Figure 4.3.4-2: Simulated CBD PK Profiles for Individual DS Patients Following the Original and Alternative Titration Schedules with a Target of 20 mg/kg/day

(b) (6)



The Applicant concludes that in comparison the original titration regimen, the alternate regimen:

- while at 5 mg/kg/day, produces a superimposable PK profile (during days 0-4)
- while at 10 mg/kg/day, produces comparable PK profile after Day 8
- while approaching 20 mg/kg/day, demonstrates lower CBD exposure for all 4 weeks.

Applicant suggests that the reduced exposures in the alternate regimen while titration approaches the 20 mg/kg/day target dose may result in decreased and/or delayed efficacy but also reduced toxicity.

[Reviewer comment: Based on the concerns regarding the population PK model developed for the DS population (see section 4.3.2 for details), it is not clear that the PK simulations generated from this model can be considered reliable. Similar concerns exist for the PPK model developed in the LGS population (see section 4.3.3 for details). In addition, the Applicant simulated two-weeks of PK data which is not a sufficient duration for titration to reach 20 mg/kg/day.

As the HV PPK model appears to be more reliable than the DS model or the LGS model, the reviewer conducted PK simulations using the HV PPK model to assess the proposed alternate titration regimen. The PK simulations utilized a time duration that allowed the maximum target dose to be achieved (e.g. 4 weeks for the 20 mg/kg/day maintenance dose level). Please refer to section 4.3.1 for details regarding the HV PPK model and section 4.3.5 for details regarding the reviewers assessment of the alternate titration regimen.]

4.3.5 PK Simulations by Reviewer to Compare Original Versus Alternate Titration Regimens Using the Healthy Volunteer Population PK Model

The reviewer conducted PK simulations using the HV PPK model to assess the alternate titration regimen proposed by the Applicant. The original titration regimen is to initiate treatment at 2.5 mg/kg/day and increase the dose by 2.5 mg/kg/day every 2 days. For dose increases beyond 10 mg/kg/day, the dose increase 5 mg/kg/day every 2 days. The applicant's proposed alternate titration regimen is to initiate treatment at 5 mg/kg/day and increase the dose by 5 mg/kg/day every 7 days.

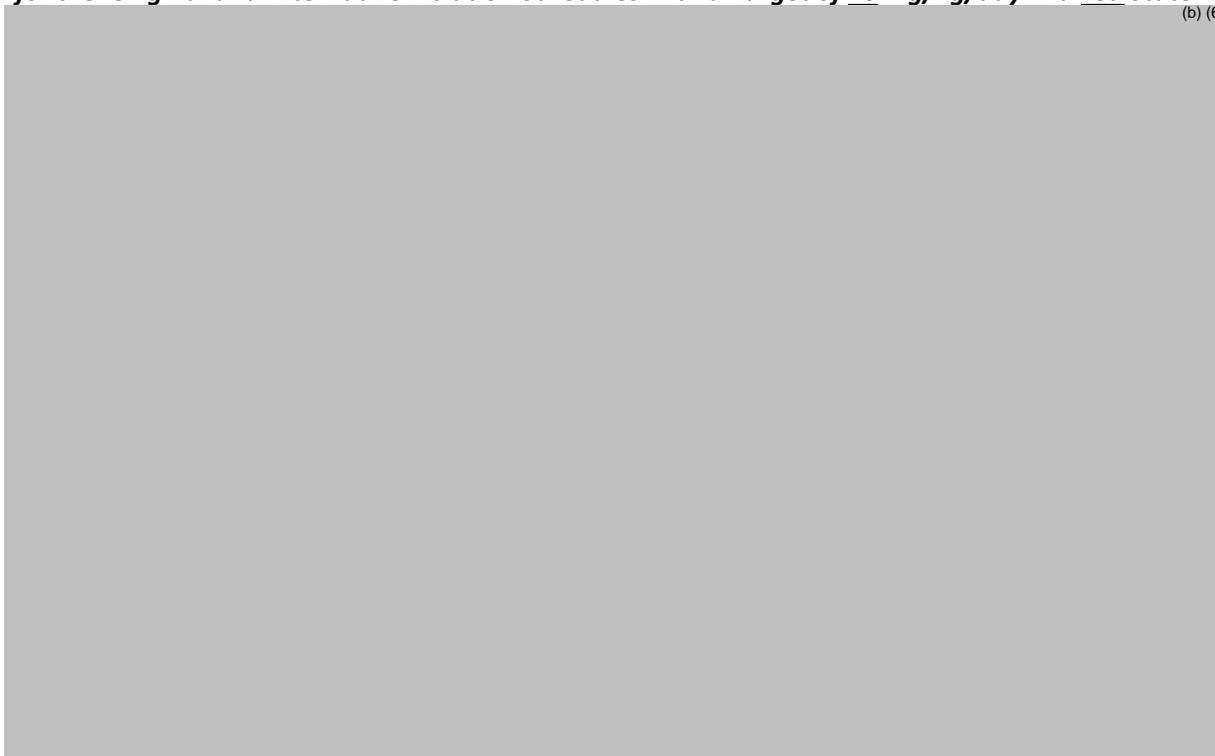
The HV PPK model (see section 4.3.1 for details) was deemed to be the appropriate model for this task based on concerns with the PPK model developed for the DS population (see section 4.3.2) as well concerns with the PPK model developed for the LGS population (see section 4.3.3).

The reviewer utilized the individual PK parameter estimates from each subject in the HV PPK dataset to simulate individual PK profiles for the original titration regimen as well as the Applicant's proposed alternate titration regimen. Target dose levels of 10 mg/kg/day as well as 20 mg/kg/day were assessed.

In all simulations, the total daily dose was split evenly such that half of the total daily dose was administered every 12 hours.

The following plot shows the comparison of the simulated PK profile for original and alternate titration regimens with a 10 mg/kg/day target for a representative subject receiving administrations while in a fed state.

Figure 4.3.5-1: Simulated CBD PK Profiles for an Individual Subject from the HV PPK Dataset for the Original and Alternative Titration Schedules with a Target of 10 mg/kg/day in a Fed State



This plot represents Subject (b) (6) according to the NONMEM ID numbering and subject (b) (6) according to the Study 1544 ID numbering.

The red series represents the simulated PK profile for the original titration regimen. The vertical red lines connecting the red PK profile to the top of the plot represent times where the total daily dose increases by 2.5 mg/kg/day every 2 days until 10 mg/kg/day is achieved, then increases 5 mg/kg/day every 2 days, in accordance with the original titration regimen. The red text at the top of the plot shows the total daily dose administered during that portion of the original titration regimen.

The green series represents the simulated PK profile for the Applicant's proposed alternate regimen. The vertical green lines connecting the green PK profile to the bottom of the plot represent times where the total daily dose increases by 5 mg/kg/day in accordance with the alternate titration regimen. The green text at the bottom of the plot shows the total daily dose administered during that portion of the Applicant's proposed titration regimen.

The following plot shows the comparison of the simulated PK profile for original and alternate titration regimens with a 10 mg/kg/day target for a representative subject receiving administrations while in a fasted state .

Figure 4.3.5-2: Simulated CBD PK Profiles for an Individual Subject from the HV PPK Dataset for the Original and Alternative Titration Schedules with a Target of 10 mg/kg/day in a Fasted State (b) (6)



This plot represents Subject (b) (6) according to the NONMEM ID numbering and subject (b) (6) according to the Study 1544 ID numbering.

The red series represents the simulated PK profile for the original titration regimen. The vertical red lines connecting the red PK profile to the top of the plot represent times where the total daily dose increases by 2.5 mg/kg/day every 2 days until 10 mg/kg/day is achieved, then increases 5 mg/kg/day every 2 days, in accordance with the original titration regimen. The red text at the top of the plot shows the total daily dose administered during that portion of the original titration regimen.

The green series represents the simulated PK profile for the Applicant's proposed alternate regimen. The vertical green lines connecting the green PK profile to the bottom of the plot represent times where the total daily dose increases by 5 mg/kg/day in accordance with the alternate titration regimen. The green text at the bottom of the plot shows the total daily dose administered during that portion of the Applicant's proposed titration regimen.

The following plot shows the comparison of the simulated PK profile for original and alternate titration regimens with a 20 mg/kg/day target for a representative subject while in a fed state.

Figure 4.3.5-3: Simulated CBD PK Profiles for an Individual Subject from the HV PPK Dataset for the Original and Alternative Titration Schedules with a Target of 20 mg/kg/day in a Fed State



This plot represents Subject (b) (6) according to the NONMEM ID numbering and subject (b) (6) according to the Study 1544 ID numbering.

The red series represents the simulated PK profile for the original titration regimen. The vertical red lines connecting the red PK profile to the top of the plot represent times where the total daily dose increases by 2.5 mg/kg/day every 2 days until 10 mg/kg/day is achieved, then increases 5 mg/kg/day every 2 days, in accordance with the original titration regimen. The red text at the top of the plot shows the total daily dose administered during that portion of the original titration regimen.

The green series represents the simulated PK profile for the Applicant's proposed alternate regimen. The vertical green lines connecting the green PK profile to the bottom of the plot represent times where the total daily dose increases by 5 mg/kg/day in accordance with the alternate titration regimen. The green text at the bottom of the plot shows the total daily dose administered during that portion of the Applicant's proposed titration regimen.

The following plot shows the comparison of the simulated PK profile for original and alternate titration regimens with a 20 mg/kg/day target for a representative subject while in a fasted state.

Figure 4.3.6-4: Simulated CBD PK Profiles for an Individual Subject from the HV PPK Dataset for the Original and Alternative Titration Schedules with a Target of 20 mg/kg/day in a Fasted State (b) (6)



This plot represents Subject (b) (6) according to the NONMEM ID numbering and subject (b) (6) according to the Study 1544 ID numbering.

The red series represents the simulated PK profile for the original titration regimen. The vertical red lines connecting the red PK profile to the top of the plot represent times where the total daily dose increases by 2.5 mg/kg/day every 2 days until 10 mg/kg/day is achieved, then increases 5 mg/kg/day every 2 days, in accordance with the original titration regimen. The red text at the top of the plot shows the total daily dose administered during that portion of the original titration regimen.

The green series represents the simulated PK profile for the Applicant's proposed alternate regimen. The vertical green lines connecting the green PK profile to the bottom of the plot represent times where the total daily dose increases by 5 mg/kg/day in accordance with the alternate titration regimen. The green text at the bottom of the plot shows the total daily dose administered during that portion of the Applicant's proposed titration regimen.

The relationship between the PK profile in the original titration regimen and the PK profile of the alternate titration regimen is similar whether assessed in a fasted state or a fed state.

For both the 10 mg/kg/day target as well as the 20 mg/kg/day target, the alternate titration regimen is expected to result in greater exposures initially and until approximately Day 4. However, without reliable exposure-safety information, it is not clear whether the elevated exposures expected for the alternate titration regimen can be expected to result in tolerability issues.

After Day 4, the alternate regimen is expected to result in lower exposures until approximately Day 9 for the 10 mg/kg/day target and until Day 23 for the 20 mg/kg/day target. However, without reliable exposure-efficacy information, it is not clear whether the reduced exposures expected for the alternate titration regimen can be expected to result in a clinically-relevant delay of effectiveness.

Overall, the PK profile for the alternate titration regimen results in exposure differences that are minor and last for a few days in comparison to the clinical trial titration regimen. As such, both regimens appear reasonable from a pharmacokinetic perspective. The alternative regimen may simplify titration logistics, but has potential to increase tolerability issues following the first dose and may delay the attainment of therapeutic exposure.

DNP and OCP agree that the alternate titration regimen is acceptable. The approved labeling will reflect the final titration directions that were agreed upon with the applicant.

4.4 Exposure-Response Analyses

4.4.1 Exposure-Response Analyses for Efficacy for DS Patients (Trial 1332)

Applicant conducted exploratory exposure-response analyses using data collected from n=34 DS patients (27 patients who received CBD, 7 patients who received placebo) enrolled in Part A of Trial 1332. Patients received 3 weeks of treatment (including up to 11 days of titration). The following table summarizes the patients assigned to each arm.

Table 4.4.1-1: Sample Size in the Exposure-Response Analysis Set for DS Patients in Trial 1332

Sample Size in the Exposure-Response Analysis Set		
Dose level	N under active treatment	N under placebo
5 mg/kg/day	10	3
10 mg/kg/day	8	2
20 mg/kg/day	9	2
Total	27	7

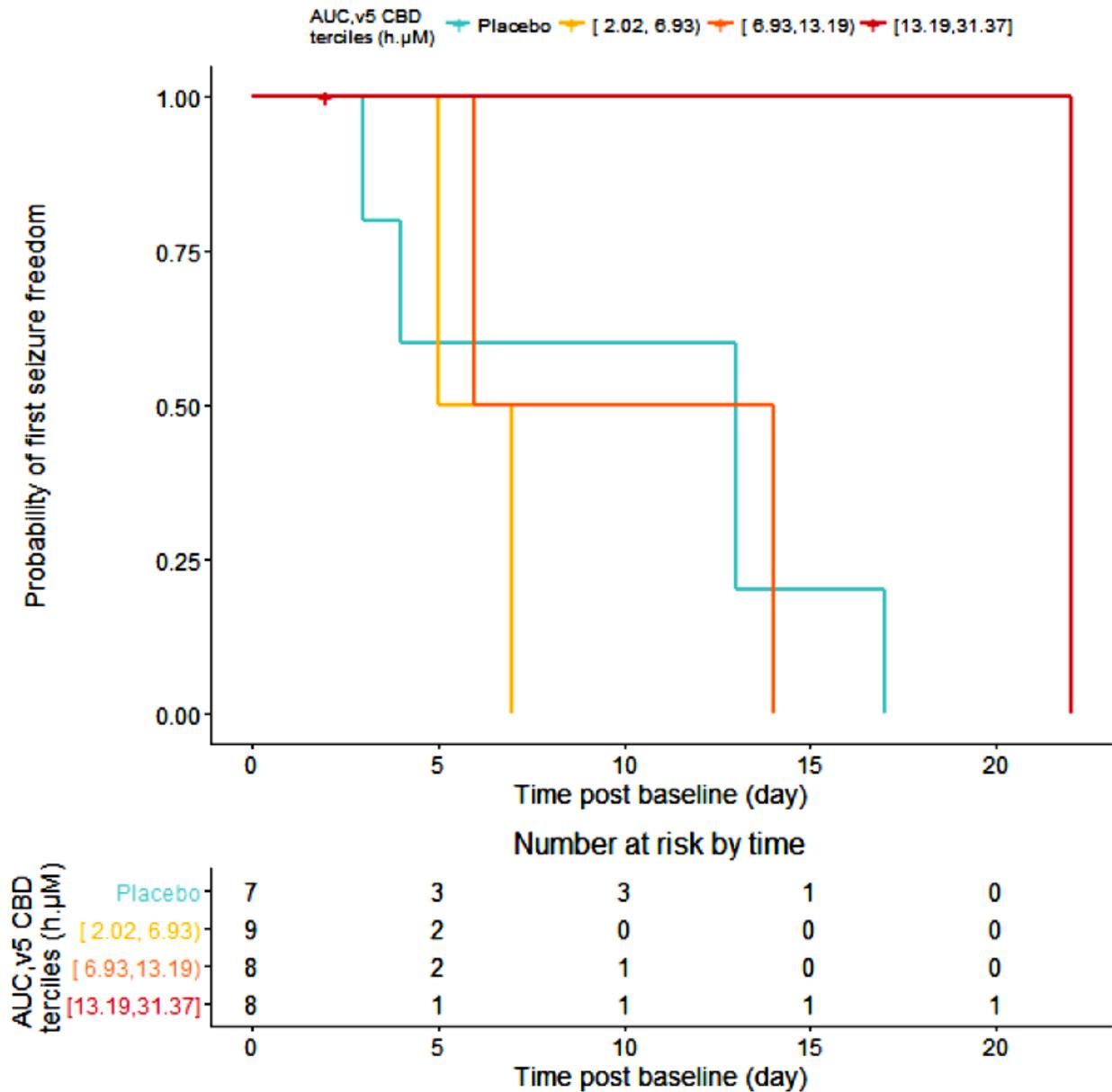
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In Part A of Trial 1332, PK samples were acquired on the day of the first dose and at 3 weeks. During each of these two PK sampling periods, 3 PK samples were collected: pre-dose, at 2-3 hours post-dose, and at 4-6 hours post dose.

The Applicant used the AUC computed from the 6-hour PK sampling period scheduled at 3-weeks after initiation (Visit A5) for exposure-response analyses. The relationship of CBD exposure and metabolite exposure with daily seizure frequency as well as time until first seizure in patients was explored.

The following Kaplan-Meier plot describes the data for time until first seizure stratified by exposure (CBD AUC tertile at visit 5).

Figure 4.4.1-1: Kaplan-Meier Plot of Time Until First Seizure Stratified by Tertile of CBD AUC at Visit 5 vs Placebo

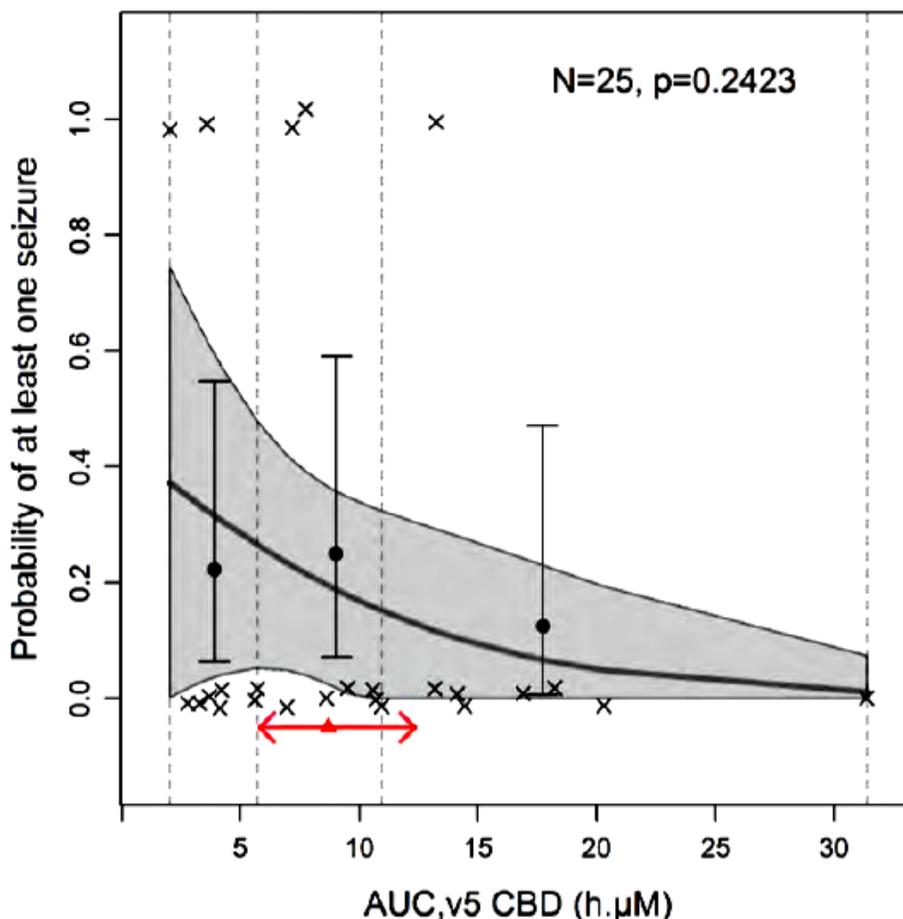


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The Applicant concludes that the Kaplan-Meier plot did not present any clear-cut difference between the placebo group and the 3rd (and highest) tertile of exposure. A similar observation was reported when using the 7-COOH-CBD metabolite instead of CBD.

The Applicant assessed the relationship between the AUC of CBD and metabolites and the probability of experiencing at least one seizure during the trial period using logistic regression. The model predictions and observed data are presented in the figure below for CBD.

Figure 4.4.1-2: Logistic Regression for the Probability of Experiencing ≥ 1 Seizure During Trial Period As a Function of CBD AUC at Visit 5 in DS Patients in Trial 1332



AUC_{v5}: 24-hour area under the curve at visit A5; N: number of patients; p: p value of Wald test in logistic regression of at least one seizure vs. exposure). The grey solid line and shaded area represent the logistic regression slope model and 95% prediction interval. The filled circles and error bar represent rate of seizure in exposure tertiles and 95% CI. The vertical lines are the limits of the exposure tertiles. The crosses are the patient response events (0:No, 1:Yes). The triangle and two-headed arrow (in red) represent the mean exposure and exposure interval between the 10th and the 90th percentile for patients receiving 10 mg/kg CBD, respectively.

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The Applicant notes that while there appears to be a trend of a decreasing seizure probability with increasing AUC CBD at Visit 5, the relationship was not statistically significant (see table below).

Table 4.4.1-2: Parameter Estimates of the Logistic Regressions for the Probability of Experiencing at least one Seizure in the Trial Period as a Function of Analytes' AUC at Visit A5 in DS Patients in Trial 1332

AUC _{vs} (h.µM)	N	p value	Sign
CBD	25	0.2423	-
7-OH CBD	25	0.6999	-
7-COOH CBD	25	0.6228	+

AUC_{vs}: 24-hour area under the curve at visit A5; N: number of patients; p value of exposure metrics parameter estimate using Wald test; Sign: Sign of exposure metrics parameter estimate in logistic regression, negative sign: probability of response tends to decrease with exposure, positive sign: response probability of response tends to increase with exposure.

[Reviewer comment: Though the sample size is limited, the available analyses do not support an exposure—response relationship between the visit A5 CBD AUC and either time until first seizure nor probability of having ≥ 1 seizure during the treatment period.

As was the case with the LGS trials, Trial 1332 in DS patients permitted morning and evening dosing to occur without regard to meals. In addition, no data was collected regarding meal status with respect to CBD administration. As such it is not clear that the E-R analyses for safety or efficacy can be used to inform CBD dose selection in DS patients.]

4.4.2 Exposure-Response Analyses for Efficacy for LGS Patients (Trials 1414 and 1423)

Applicant conducted exploratory exposure-response analyses using data collected from n=360 LGS patients enrolled in trials 1414 and 1423. The following table shows the number of LGS patients for which data are utilized in the exposure-response analyses.

**Table 4.4.2-1: Sample Sizes in the Exposure-Response Analysis
Dataset for LGS Patients in Trials 1414 and 1423**

Table 4.2-1		Trial Arms, Number of Subjects, and Observations used in the Exposure-response Analysis	
Studies	Arm	Subjects	Observations
1414, 1423	Placebo	161	16741
1414	10 mg/kg GWP42003-P	62	6567
1414, 1423	20 mg/kg GWP42003-P	137	14269

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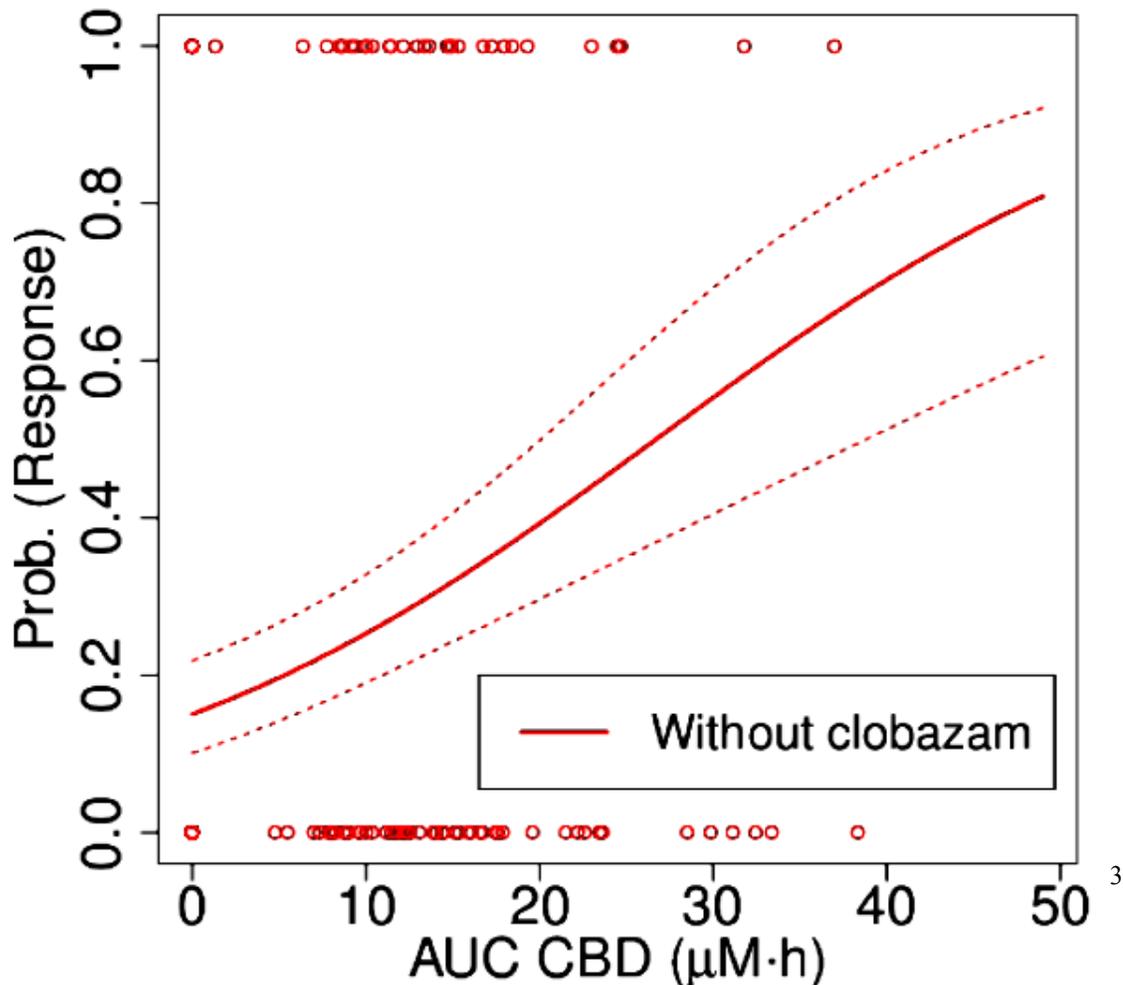
In both Trial 1414 and Trial 1423, PK was sampled on Day 1 and Day 99 at the following times; pre-dose, 0.5, 1, 2, 4, and 6 hours post-dose.

A logistic regression model was used to characterize the relationship between AUC of CBD and metabolites and the probability of being a drop seizure responder. The Applicant computed AUC from the PK data acquired on Day 99 (Visit 8) for CBD and metabolites. A drop seizure responder is defined as person who achieved an average change from baseline drop seizure rate of $\leq -50\%$.

Clobazam use was assessed as a potential covariate on intercept, on slope, as well as on both intercept and slope. Some patients exhibited “responder” status on Day 1 of the study which the Applicant states is the result of a shifting baseline. The “Day 1 response” (BSLRESP) was tested as a covariate on intercept. The final model included BSLRESP as a covariate on intercept and concomitant clobazam use as a covariate on intercept.

In order to illustrate the Applicant’s view that AUC has a meaningful relationship with the probability of being a responder, the Applicant conducted a simulation using the final exposure-response model where clobazam was not used and where patients did not exhibit a Day 1 response (see figure below).

Figure 4.4.2-1: Simulated Response Probability as a Function of CBD AUC ($\mu\text{M} \cdot \text{h}$) For the Scenario of No “Day 1 Response” and No Concomitant Clobazam Use



Plot of the probability of being a drop seizure responder vs. AUC for the final model for the case off Clobazam (CLOBAZ = 0) and with Day 1 response (BSLRESP = 0). The raw data is shown in the top and bottom of each figure. The dotted curves represent the 95% confidence interval.

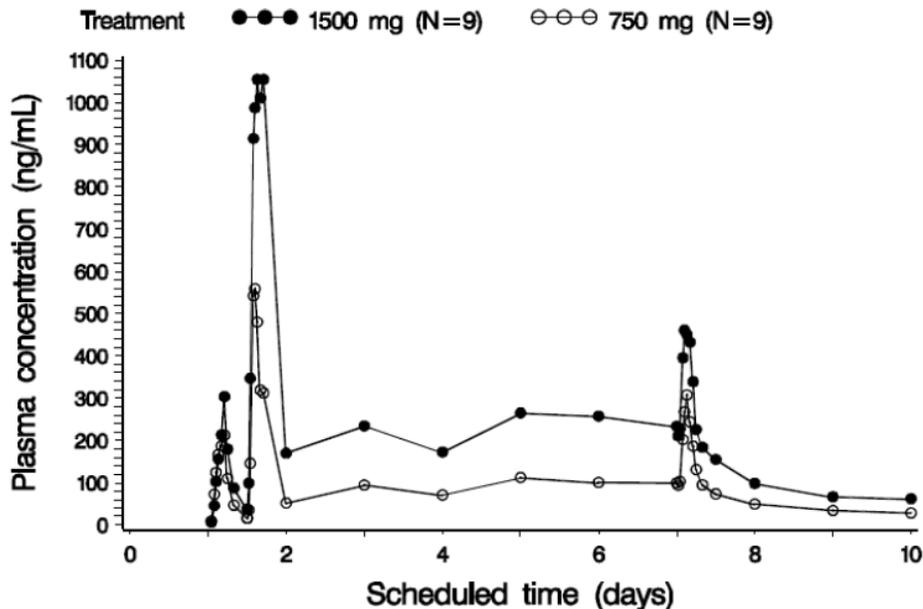
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A similar trend was demonstrated using 7-OH-CBD and 7-COOH-CBD. The Applicant concludes that there is a significant positive relationship between the probability of a subject being a drop seizure responder and AUC of each analyte.

[Reviewer comment: There is concern regarding the stability of the patients' PK profiles throughout the course of the Phase 3 LGS trials (e.g. throughout the time period between Day 1 and Day 99).

This concern can be illustrated most clearly with the PK data collected in Study 1544. CBD accumulation is expected to be modest over a 12-hour period (one dosing interval). However, in Study 1544, a 3-fold difference in the mean CBD maximum concentration was observed between morning administration and the subsequent evening administration on Day 1. This 3-fold increase in mean CBD maximum concentration is likely due to a prandial effect (e.g. 10-hour overnight fast before morning dose versus the 2-hour fast before the subsequent dose in the evening; see the figure below for 1500 mg arm).

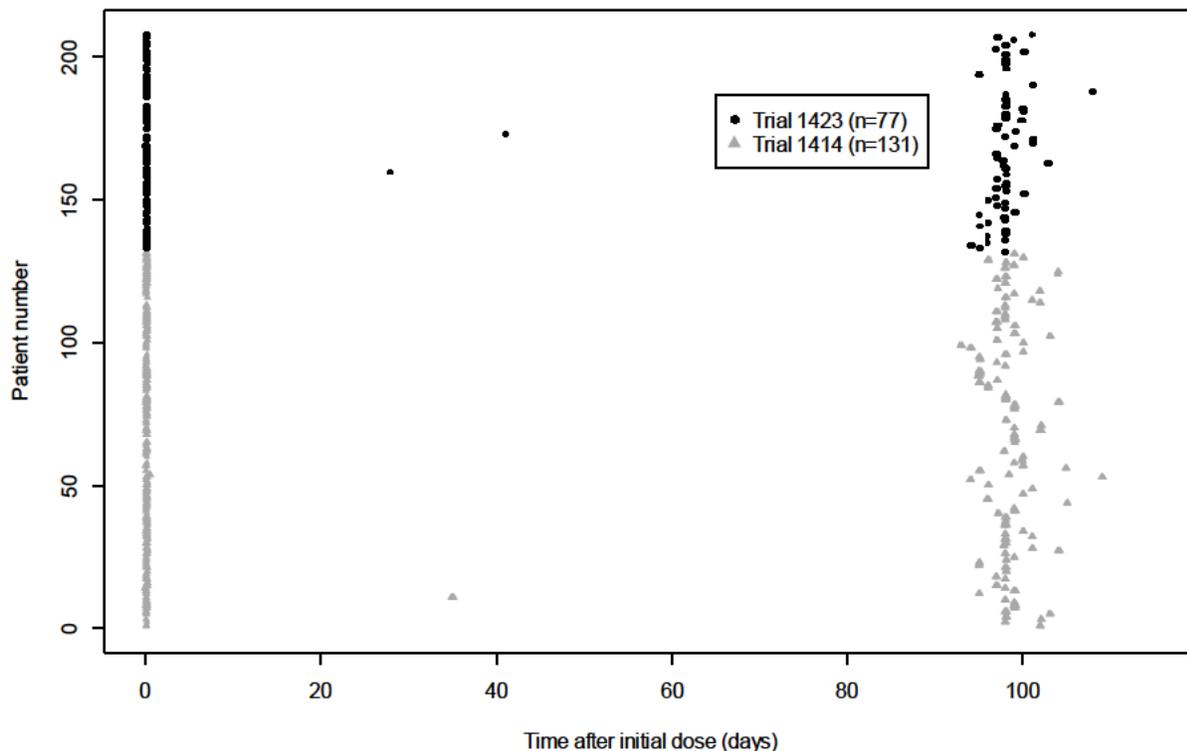
Figure 4.4.2-2: Mean CBD Plasma Concentration Time Profile in MAD Study 1544



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The figure above suggests that differences in the prandial state may cause CBD PK profile to vary widely from one administration to the next. Unfortunately, none of the available PK data from any of the Phase 3 trials are able to provide insight into the extent of unrestricted diet on inter-occasion PK variability as is demonstrated on Day 1 in Study 1544. For example, in trials 1414 and 1423, PK was sampled for a 6-hour duration on Day 1 (± 3 days) and for a 6-hour duration on Day 99 (± 3 days). However, the 6-hour PK sampling periods each span one-half of a dosing interval and thus do not provide insight into intra-subject variability in the time period from Day 1 through Day 99 (see the figure below for an illustration of the PK sampling times with respect to the timeline for Trials 1414 and 1423).

Figure 4.4.2-3: PK Sampling Times for Each Subject in LGS Trials 1414 and 1423 Across full Duration of Study (~100 days)



Each row represents a unique patient and each point represents a time when a PK sample was drawn. The black circles represent patients in trial 1423 and grey triangles represent patients in trial 1414.

As such, it is not clear whether the PK samples acquired on Day 99 are representative of the PK profile between Days 1 and Day 99. Thus, the interpretability of the exposure-response model based on this PK data is questionable.

Overall, in consideration of the magnitude of the food effect observed in study 1544 (high-fat, high-calorie meal resulted in a 5-fold C_{max} increase and a 4-fold AUC increase), the apparent aforementioned prandial effect in study 1544 (3-fold C_{max} difference between morning and evening doses on Day 1), the lack of meal restrictions during all Phase 3 trials, the lack of documentation of meal intake during phase 3 trials, it is not clear that the observed PK values used in the E-R analyses can be considered to be representative of the CBD-time profile throughout the duration of the study. As such it is the E-R analyses for safety or

efficacy cannot be used to inform CBD dose selection in LGS patients. Please refer to section 3.3.2 for details regarding LGS dose selection.]

4.4 Physiologically-based Pharmacokinetic Modeling Review

Physiologically-based Pharmacokinetic Modeling Review

Division of Pharmacometrics, Office of Clinical Pharmacology

Application Number	210365
Drug Name	Cannabidiol
Proposed Indication	As adjunctive treatment of seizures associated with Lennox–Gastaut syndrome (LGS) and Dravet syndrome (DS) in treatment-resistant patients aged 2 years and older [REDACTED] (b) (4) [REDACTED]
Clinical Division	DNP
PBPK Consult request	Jagan M. Parepally, Ph.D.
Primary PBPK Reviewer	Manuela L. T. Grimstein, M.Sc., Ph.D.
Secondary PBPK Reviewer	Xinyuan Zhang, Ph.D.
Applicant	GW Therapeutics Inc.

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OBJECTIVES

The main objective of this review is to evaluate the adequacy of applicant's conclusions regarding the ability of a physiologically-based pharmacokinetic (PBPK) model to predict the drug-drug interaction (DDI) potential of cannabidiol (CBD) oral solution as a CYP2B6, CYP2C8, CYP2C9, CYP3A4 and UGT1A9 and UGT2B7 perpetrator in adult and pediatric populations (aged 2 years and older).

To support its conclusions the applicant provided the following PBPK modeling and simulation reports and updates:

- Quantitative Prediction of the Pharmacokinetics of Cannabidiol (CBD) in Paediatric Subjects Aged 1 to 24 Months and of the Drug-Drug Interaction Potential of CBD as a Perpetrator of CYP 2B6, 2C8, 2C9, and 3A4, and UGT 1A9, and 2B7 in Healthy Adults and Paediatric Patients Aged 2 to 17 Years [1]
- GW Research Response (16 February 2018) to FDA Information Request (08 February 2018) [2]

The applicant also proposed using PBPK model to predict PK in pediatric subjects aged 1 to 24 months (b) (4)

CBD is not proposed to be indicated for pediatric patients aged 1 to 24 months. (b) (4)

This review does not evaluate the adequacy of PBPK modeling and simulation (b) (4) of PK prediction in pediatric subjects aged 1 to 24 months.

BACKGROUND

Cannabidiol is currently under development as an oral liquid formulation (CBD-OS) for the treatment of rare childhood-onset epilepsy disorders, namely Dravet and Lennox-Gastaut syndromes [5].

The pharmacokinetics of CBD (as CBD-OS) have been determined in healthy adult volunteers (study GWEP1544). CBD-OS had a low bioavailability (<10%) and high apparent oral clearance (CL/F= 1111 - 1909 L/h). CBD-OS displays dose and time-dependent PK. Following multiple dose (MD), the accumulation ratios for day 7 compared to day 1 were 1.80 and 2.6 for the 750 mg and 1500mg BID dosing, respectively. Administration of CBD-OS following a high-fat meal increased C_{max} and AUC_{inf} to CBD by approximately 5-fold and 4-fold, respectively. Plasma

levels of CBD (as CBD-OS) have also been determined to pediatric patients with Dravet (study GWEP1332) and Lennox-Gastaut (studies GWEP1414 and GWEP1423) syndromes [5]. In humans, hepatic clearance is a major route of CBD metabolism. The oxidative biotransformation of CBD was investigated using human liver microsomes (HLM; studies GWOR1227, GWPP1347A), human hepatocytes (HHEP; study GWPP1404A) and human recombinant cytochrome P450 enzymes (rCYP; study GWPP1347A). In vitro data indicated that CYPs 3A4 and 2C19 are likely the main enzymes responsible for phase I metabolism of CBD. CYP2C19 is likely to be the major enzyme in vitro responsible for the hydroxylation of CBD to 7-OH-CBD; while CYP3A4 is likely the enzyme responsible for the further oxidation of 7-OH-CBD to 7-COOH-CBD, and for the formation of 6-hydroxy-cannabidiol. The phase II metabolism of CBD to form the O-glucuronide was studied in HLM (study GWPP1347B), HHEP (study GWPP1404A) and recombinant UDP glucuronosyltransferase enzymes (rUGT; study GWPP1347B). The direct conjugation of CBD to form CBD-O-glucuronide was approximately 30% of the rate of oxidative metabolism, likely mediated by UGT1A7, UGT1A9 and UGT2B7 [5].

In healthy volunteers and patients, the major circulating analyte in plasma was the 7-COOH-CBD metabolite followed by parent drug CBD, and then 7-OH-CBD and 6-OH-CBD. Following MD administration (750 mg and 1500 mg bid), exposure (based on AUC_{tau}) to 7-OH-CBD (an active metabolite) was approximately $\frac{(b)}{(4)}\%$ of the parent drug. Exposure (based on AUC_{tau}) to 7-COOH-CBD was approximately 40-fold that of CBD; and exposure (based on C_{max} and AUC) to 6-OH-CBD was consistently < 10% that of CBD (study GWEP1544) [3].

Clinically, concomitant dosing of CBD (as Sativex formulation, oromucosal spray) with ketoconazole (a strong CYP3A4 inhibitor) resulted increases in CBD C_{max} and AUC approximately 2-fold and 2.7-fold, respectively, confirming CBD as a substrate for CYP3A4 [5].

In vitro studies in MDCK cells indicated that CBD was unlikely a substrate of P-gp and BCRP; likewise, CBD was not a substrate for, or an inhibitor of, human renal and hepatic uptake transporters (namely, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, OCT1, MATE1, MATE2-K, and BSEP) (study GWPP1313) [5].

In vitro DDI studies indicated that CBD was a reversible competitive inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4 (IC₅₀ < 10 μM) (studies GWPP1346A and GWOR0989), and UGT1A9 and UGT2B7 (IC₅₀ < 0.5 μM) (study GWPP1346B). CBD was also a time-dependent inhibitor (TDI) of CYP3A4 (kinact = 0.140 min⁻¹ and K_i = 1.5 μM). CBD showed a positive inductive effect on CYP1A2, CYP2B6, and CYP3A4 based on mRNA expression in HHEP assays (study GWPP1345) [5].

(b) (4)

Clinically, concomitant dosing of CBD-OS (20 mg/kg/day, 21 days; or 750 mg bid, 7-14 days) with clobazam, a substrate for CYP3A4 (minor CYP2C19 and CYP2B6), had no effect on clobazam exposure in epilepsy patients and healthy volunteers. However, plasma exposure (AUC) to the active metabolite N-desmethyloclobazam (N-CLB, a CYP2C19 substrate) were increased approximately 3-fold in healthy volunteers, and around 2.5-fold in patients (study GWEP1428 and GWEP1543). In healthy volunteers, data suggested that the interaction with clobazam was bi-directional with 1.5- and 1.7- fold increase in C_{max} and AUC of CBD, respectively (study GWEP1543) [3]. Onfi® (clobazam oral tablets) is a weak CYP3A4 inducer and a CYP2D6 inhibitor, based on clinical studies. (b) (4)

The applicant is also planning the following clinical DDI studies to evaluate the effects of strong modulators of CYP2C19 and CYP3A4 on exposure to CBD-OS [7]:

In the current submission, PBPK modeling was used to predict the effect of cannabidiol oral solution, on the PK of drug substrates for CYP2B6, CYP2C8, CYP2C9, CYP3A4 and UGT1A9 and UGT2B7 [1]. Based on the simulation results, the applicant proposed (b) (4)

On February 08 2018, an Information Request was sent to the applicant (see Supplemental Material 6.2). The Response to FDA Request was received on February 16, 2018 [2].

At the end of the review cycle, the applicant submitted the CSR of the clinical DDI study between CBD-OS and midazolam, an index CYP3A substrate (study GWEP17028). While there was no effect on midazolam exposure; there was a 2-fold increase in the metabolite 1'-hydroxy-midazolam. The applicant suggested that increased exposure to the metabolite may be due to CBD inhibition of UGT2B7 mediated-metabolism of 1'-hydroxymidazolam [8].

This review evaluated the adequacy of applicant's PBPK analyses to predict the DDI potential of cannabidiol as a perpetrator towards CYP2B6, CYP2C8, CYP2C9, CYP3A4, UGT1A9 and UGT2B7, in adult and pediatric populations (aged 2 years and older).

METHODS

Simulations were performed using Simcyp Simulator software (Version 15.1, Simcyp, Sheffield, UK). Supplemental Table 1 summarizes CBD parameters used in the PBPK model. Predictions of plasma drug concentration-time profiles and drug-drug interactions were conducted using Simcyp's built-in virtual North European Caucasian population. The 'Simcyp Paediatric Simulator' was used for prediction in subjects 2 - 17 years of age.

PBPK Model Development

PBPK model of CBD was developed based on its physicochemical properties, in vitro determinations and clinical PK data. Briefly, the first order model was used to describe the absorption phase of CBD oral formulation. A combination of the in vitro CL_{int} data (HML data), and ketoconazole inhibition was initially used to obtain the fraction metabolized by CYP3A4 (fmCYP3A). This approach was unable to recover clinical PK data for CBD. The fmCYP3A was then further refined based on clinical data following multiple-dosing. The model also incorporated auto-inhibition and auto-induction of CYP3A using in vitro kinetic data for CYP3A induction and TDI. In vitro parameters for competitive inhibition of CYP2B6, CYP2C8, CYP2C9 and CYP3A4 were also included. The contribution of CYP2C19, and UGT1A9 and UGT2B7 to CBD overall metabolism were not incorporated in the model [1].

Model Application

The applicant used PBPK model to predict the inhibitory potential of CBD (as CBD-OS) towards CYPs 2B6, 2C8, 2C9, 3A4, and UGTs 1A9 and 2B7. PBPK simulations were conducted with index substrates for these enzymes using the Simcyp's library compounds, except where noted. The substrates used were bupropion (fmCYP2B6 = 0.58), rosiglitazone (fmCYP2C8 = 0.46),

repaglinide (fmCYP2C8 = 0.6), S-warfarin (fmCYP2C9 = 0.98), tolbutamide (fmCYP2C9 = 0.99), midazolam (fmCYP3A4 = 0.86), simvastatin (fmCYP3A4 = 0.89), propofol (new compound model, fmUGT1A9 = 0.6), lorazepam (fmUGT2B7 = 0.93) and zidovudine (fmUGT2B7 = 0.67).

For all interactions (except CYP3A4 mediated), sensitivity analysis of the inhibition constant (Ki), considering values up to 10-fold lower than the in vitro experimental results, was also performed.

Simulations were performed in adults (750 mg BID), adolescents (12-17 years; 10 mg/kg BID) and children (2-11 years; 10 mg/kg BID), under fasting conditions.

RESULTS

The current PBPK model for cannabidiol did not include the formation of two major metabolites, 7-OH-CBD and 7-COOH-CBD. (b) (4)

the formation of these metabolites should be incorporated in the CBD model to allow predictions of the interaction potential of CBD oral solution. The absence of metabolite prediction and their contribution on the interaction potential of CBD in the current PBPK model was considered a major issue precluding the acceptance of the model to predict drug-drug interactions of CBD as a perpetrator.

The applicant replied that, if there is any inhibitory potential for the metabolites, these analytes will be incorporated into the CBD PBPK model [2].

Other issues in the current CBD PBPK model were also identified and communicated to the applicant:

- CYP2C19, which was considered as one of the major metabolic enzymes of CBD based on in vitro data, was not incorporated in CBD PBPK model. CYP3A4 was assigned as the primary enzyme. Based on in vitro data, CYP3A4 catalyzes the conversion of 7-OH CBD to 7-COOH CBD, and the formation of minor metabolites. Inclusion of the metabolites in the model may provide insight on defining fmCYPs, which is vital for developing the pediatric population model.
- CBD PBPK model was not verified using the available DDI studies conducted in the program, such as the DDI study GWEP1543: a phase 1, open-label, pharmacokinetic trial to investigate possible drug-drug interactions between clobazam, stiripentol or valproate

and cannabidiol (GWP42003-P) in healthy subjects. Bi-directional interaction was observed between CBD and clobazam. Model verification against this dataset may provide insight on the effect of CBD on clobazam (a CYP3A4 substrate), and its active metabolite, N-desmethyloclobazam (a CYP2C19 substrate).

- The model could not predict the effect of CBD on the PK of midazolam, a CYP3A4 substrate. The current CBD PBPK model, incorporating induction, TDI and competitive inhibition of CYP3A4, predicted a strong interaction (>5-fold increase in C_{max} or AUC) with a CYP3A4 substrate (for both midazolam and simvastatin); while clinical data indicated a lack of interaction between CBD-OS and the CYP3A4 substrate midazolam, [8]. Similarly, CBD-OS had no effect on the exposure of the CYP3A4 substrate clobazam (a CYP3A4 substrate). The applicant was advised to use data from all clinical DDI studies conducted with CBD to refine key parameters of CBD PBPK model such as fmCYPs and interaction kinetics

The applicant replied that fmCYP2C19 data were found to be more qualitative than quantitative during initial model development, and a high fmCYP3A4 was required to predict the oral bioavailability of CBD. Because additional clinical DDI studies are currently being conducted/planned, the applicant proposed to reassess the relative assignment of CYP3A4 and CYP2C19 to the metabolism of CBD once clinical data is available [2].

- In the development of the pediatric model (2-17 years of age), ontogeny of renal function and CYP3A4 was incorporated. All non-hepatic CL was assigned as renal clearance. This approach may not be able to capture ontogeny of other enzymes such as CYP2C19.

The applicant replied that once clinical data from the additional DDI studies become available, the contribution of CYP2C19 can be reassessed. Ontogenies including CYP2C19 can be incorporated in the pediatric model [2].

CONCLUSIONS

In the absence of incorporating the major circulating metabolite(s), the current PBPK model cannot be used to predict the DDI potential after oral administration of cannabidiol as a perpetrator towards CYP2B6, CYP2C8, CYP2C9, and CYP3A4; and UGT1A9 and UGT2B7 in adult and pediatric populations (2-17 years of age). Additional flaws were identified as stated in the review. We recommended removing ^{(b) (4)} in the proposed draft labeling.

SUPPLEMENTAL MATERIAL

Abbreviations

AUC, area under the concentration-time curve; b.i.d., twice daily dosing; B/P, blood to plasma concentration ratio;; C_{max}, maximal concentration in plasma; CL, systemic clearance; CL/F – apparent oral clearance; Cl_{int}, intrinsic metabolic clearance; CL_r, renal clearance; DDI, drug-drug interaction; IC₅₀, inhibitory concentration causing one-half of maximum effect; CYP – cytochrome P450; F, bioavailability; f_a, fraction absorbed; f_m – fraction metabolized; f_u, unbound fraction in plasma; f_{ugut}; free fraction of drug within the enterocyte f_{uinc}, fraction unbound in in vitro incubations; k_a, first order absorption rate constant; HLM, human liver microsomes; IC₅₀, concentration of inhibitor producing half maximal inhibition; K_p, tissue-to-plasma partition coefficient; K_i, reversible inhibition constant; K_m, Michaelis constant; LogP, log of the octanol/water partition coefficient; PBPK, Physiological-based Pharmacokinetic; P-gp, P-glycoprotein; Q_{gut}, nominal blood flow; V_{max}, maximal velocity; V_{ss}, volume of distribution at steady-state.

Information Request

02/08/2018 IR

Please refer to your New Drug Application (NDA) 210365 for (b) (4) (Cannabidiol). We also reference the report GWPP17025 (submitted on 09/26/2017)

We are reviewing your submission and have the following requests for information.

1. The current PBPK model for cannabidiol (CBD) does not include the formation of two major metabolites, 7-OH-CBD and 7-COOH-CBD. It was communicated to the Division (Response to FDA request dated 01/18/2017) (b) (4) [REDACTED], the formation of these metabolites should be incorporated in the CBD model to allow predictions of the interaction potential of CBD towards CYP and UGT substrates.
Please refer to FDA Guidance for Industry: “In Vitro Metabolism- and Transporter-Mediated Drug-Drug Interaction Studies” Draft 2017”. (Available at <https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM581965.pdf>) for guidance on evaluating drug metabolites as perpetrators of drug interactions.
2. CYP2C19, which is considered as one of the major metabolic enzymes of CBD based on in vitro data, is not incorporated in CBD model. It seems that CYP3A4 plays the role to convert 7-OH CBD to 7-COOH CBD and CYP3A4 was assigned as the primary enzyme. Current model does not include metabolite(s) prediction. We wonder if the inclusion of the metabolites in the model may provide insight on defining fmCYPs, which is vital for developing the pediatric population model. leverage. If possible, consider using data from in-vivo DDI studies conducted with CBD to refine CBD PBPK model key parameters = such as fmCYPs and interaction kinetics.
3. For development of the pediatric model (>2-17 years of age), all non-hepatic CL was assigned as CL_r, ontogeny of renal function and CYP3A4 was incorporated. We wonder if this approach would capture ontogeny contributed by other enzymes such as CYP2C19.
4. Perform parameter sensitivity analysis to identify the parameters that may affect the unbound concentrations of CBD (and metabolites(s), if needed) in the liver and portal vein, which are used as the driving force for inhibition of metabolism in the liver and gut, respectively.
5. As part of the verification of CBD PBPK model, provide predicted CBD exposure at steady-state in adult population following 10 mg/kg BID dosing and compare with data from studies GWE1423/GWE1414/GWEP 1332.

6. Simulations performed to predict drug-drug interaction liability towards CYPs and UGTs should be performed using the proposed highest therapeutic dose using dose in mg/kg unit in adult population. Certify that the predicted CBD exposure is comparable to observed and expected CBD exposure under the proposed dosage and administration [REDACTED] ^{(b) (4)}
[REDACTED]

Supplemental Tables and Figures

Supplemental Table 1. PBPK Model Input Parameters for Cannabidiol (Simcyp, v15.1)

(b) (4)

A large grey rectangular area representing a redacted table. The table content is completely obscured by a solid grey fill.

REFERENCES

1. GW Therapeutics. Quantitative Prediction of the Pharmacokinetics of Cannabidiol (CBD) in Pediatric Subjects Aged 1 to 24 Months and of the Drug-Drug Interaction Potential of CBD as a Perpetrator of CYP 2B6, 2C8, 2C9, 3A4 And UGT 1A9, 2B7 in Healthy Adults and Pediatric Patients Aged 2 to 17 Years. GW Project Code: GWPP17025 (26 September 2017)
2. GW Therapeutics. NDA 210365: Response to FDA Information Request (16 February 2018)
3. FDA. NDA 210365: Filing Communication (20 December 2017)
4. GW Therapeutics. NDA 210365: Draft Labeling (08 January 2018)
5. GW Therapeutics. Summary of Clinical Pharmacology Studies- Cannabidiol Oral Solution (26 October 2017)
6. Stott CG, White L, Wright S, Wilbraham D, Guy GW. A Phase I, open-label, randomized, crossover study in three parallel groups to evaluate the effect of Rifampicin, Ketoconazole, and Omeprazole on the pharmacokinetics of THC/CBD oromucosal spray in healthy volunteers. Springer Plus 2013b; 2:236
7. GW Therapeutics. NDA 210365: Response to FDA Filing Communication and Filing Review Issues Identified (18 January 2018).

SUMMARY OF PHARMACOGENOMICS OF CANNABADIOL

(Prepared by Dr. Jeffrey Kraft)

Background

The current submission is for cannabidiol (CBD), which is to be used as an adjunctive therapy to [REDACTED] (b) (4) for the treatment of Dravet Syndrome or Lennox Gastaut Syndrome. The metabolism of CBD is thought to be primarily mediated by CYP2C19 and CYP3A4 with contribution from UGT1A7, UGT1A9, and UGT2B7. The sponsor investigated the effects of CYP2C19 pharmacogenomics in 2 studies, GWEP1543 in healthy subjects and GWEP1428 in patients with partial onset seizure (POS) disorders. CBD exposure showed a trend towards an increase with increased CYP2C19 activity (IM<EM<UM), although firm conclusions regarding any impact of CYP2C19 genomics on CBD exposure are difficult to draw given the small sample size. The sponsor has submitted summary data of exposure (AUC) by CYP2C19 phenotype. The purpose of this review is to determine if CYP2C19 variation and its resulting effects on function have a clinically relevant impact on CBD exposure.

Contents

The sponsor submitted summary level data for CYP2C19 genotyping performed in subjects from 2 clinical trials to investigate the effect of CYP2C19 variation on CBD exposure. [REDACTED] (b) (4)

Methods

The sponsor included 79 unique subjects (6 from GWEP1428; 73 from GWEP1543) who were genotyped for variants in CYP2C19 and were utilized for the statistical analyses. DNA from blood samples was extracted using the QIAasymphony SP instrument in conjunction with the QIAasymphony DSP DNA Midi Kit (96). DNA concentration was measured using a Nanodrop 8000 Spectrophotometer and DNA stored in 2D barcoded tubes at +4°C until sequenced. DNA samples were analyzed for genetic variants in the CYP2C19 gene via Sanger sequencing for the entire coding sequence of CYP2C19 using an ABI 3700 analyzer. Sequencing files were analyzed using Mutation Surveyor software by 2 analysts, and any changes affecting enzyme activity confirmed by a second sequencing reaction. All pharmacogenomic (PGx) analysis were performed at [REDACTED] (b) (4)

Classification of genotypes into functional phenotype categories were interpreted and reported per the Human Cytochrome P450 Allele Nomenclature Committee as stated on their website; phenotype categories were verified by the reviewer to be accurate.

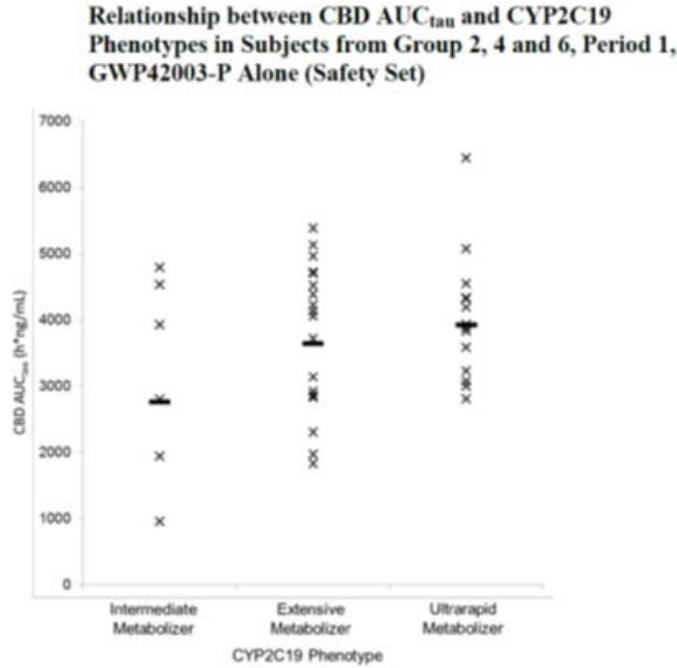
Summary of Findings

The in vitro and clinical drug interaction studies indicated that CBD is metabolized by CYP2C19. To determine the relationship of CYP2C19 function on CBD exposure, the exposure

data (AUC) from the 2 clinical trials was summarized by CYP2C19 function. Analyses showed a trend of increased CBD exposure with increasing CYP2C19 activity (Figures 1/2). The sponsor did not investigate if CYP2C19 genotype had any effect on safety or efficacy of CBD. Firm conclusions regarding any impact of CYP2C19 genomics on CBD exposure are difficult to draw given the small sample size, (b) (4)

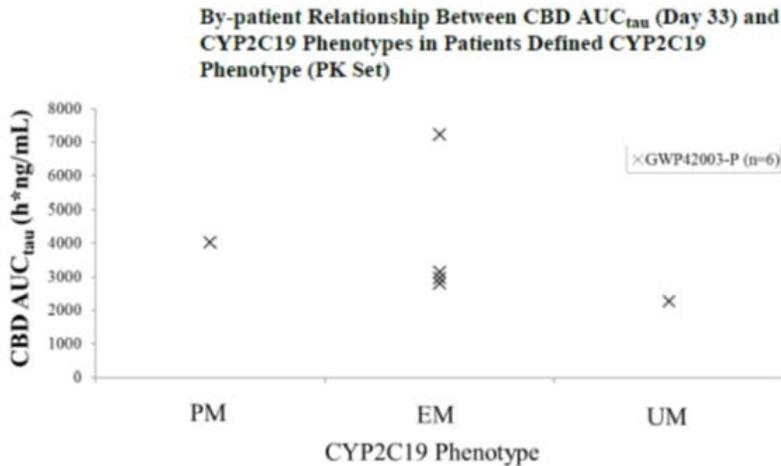
Figure 1: CBD Exposure by CYP2C19 Phenotype in GWEP1543

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Source: GWEP1543 Study Report, Page 156, Figure 8.4.4.2-2 5

Figure 2: CBD Exposure by CYP2C19 Phenotype in GWEP1428



Source: GWEP1428 Study Report, Page 101, Figure 8.4.5.2-2

4.6 Individual Study Summaries

Study GWEP1544: A randomized, double-blind, placebo-controlled, single ascending dose and multiple dose study to evaluate the safety, tolerability and pharmacokinetics of Cannabidiol (CBD, GWP42003-P) oral liquid formulation with an open-label two-period cross-over part to study food effects in healthy subjects

Objectives:

The primary objective was to evaluate the safety and tolerability of single ascending doses (SADs) and multiple doses (MDs) of cannabidiol in healthy male and female subjects compared with placebo with respect to incidence, type, and severity of adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), clinical laboratory parameters, and physical examinations.

The secondary objectives were to assess the following:

- Pharmacokinetics (PK) of SADs and MDs of CBD in healthy male and female subjects.
- Effect of food on the PK of CBD following a single dose of CBD in healthy male and female subjects.

Study Design	This study was a randomized, double-blind, placebo-controlled, single ascending dose and multiple dose study
Study Population	Healthy Subjects (males and females) Age: 18-45 years BMI: 18 to 28 kg/m ² . 56 enrolled (32 in the SAD and 24 in MD part)
Methodology	This trial consisted of a SAD part with integrated food effect (FE) group, and an MD group to assess the safety, tolerability, and PK of ascending single and multiple oral doses of cannabidiol. Subjects in the double-blind, randomized, placebo-controlled SAD part of the trial (Groups 1-3: Period 1), comprising 8 healthy subjects (6 receiving investigational medicinal product [IMP] and 2 receiving placebo), received a single oral dose of CBD or placebo under fasted conditions. Group 4 could be enrolled to receive a higher single dose if the maximum tolerated dose had not been reached in Groups 1-3.
Treatments	Group 1: Period 1: A single oral dose of 1500 mg CBD (n=6) or matching placebo (n=2). • Group 2: Period 1: A single oral dose of 3000 mg CBD (n=6) or matching placebo (n=2). • Group 3: Period 1: A single oral dose of 4500 mg CBD (n=6) or matching placebo (n=2). • Group 4: Period 1: A single oral dose of 6000 mg CBD (n=6) or matching placebo (n=2). Group 5: Multiple oral doses of 750 mg CBD (n=9) or matching placebo (n=3) b.i.d. for 6 consecutive days (Days 1-6), with a single 750 mg dose administered in the morning of Day 7. • Group 6: Multiple oral doses of 1500 mg CBD (n=9) or matching placebo

	<p>(n=3) b.i.d. for 6 consecutive days (Days 1-6), with a single 1500 mg dose administered in the morning of Day 7.</p> <p>The following treatments were administered to each subject in 1 of 2 possible sequences: Period 2: A single oral dose of 1500 mg CBD (n=12) under fasted or fed conditions. Period 3: A single oral dose of 1500 mg CBD (n=12) under fed or fasted conditions. The washout period between IMP administration in the SAD part and the integrated FE part of the trial was ≥ 7 days. The washout period between IMP administration in both periods of the integrated FE part of the trial was ≥ 7 days.</p>
Pharmacokinetic Assessments	The pharmacokinetic parameters were calculated, using noncompartmental analysis from the plasma concentration-time data for CBD, $\Delta 9$ -tetrahydrocannabinol (THC), and their major metabolites after SADs and MDs of CBD: C _{max} , T _{max} , t _{lag} , K _{el} , t _{1/2} , CL/F, V _z /F, AUC _{0-t} , AUC _{0-inf} and F _{rel} .
Safety Assessments	Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms, physical examination, sleep disruption 0-10 NRS score, ESS (0-3 NRS score), CWS (0-10 NRS score), and C-SSRS (MD part of the trial only).
Statistical Methods	<p>All statistical testing was 2-sided and used the 5% significance level in accordance with standard practice. Continuous variables were summarized with descriptive statistics and categorical data were summarized with frequencies and percentages.</p> <p>Descriptive statistics were used to summarize the plasma concentrations by part of trial and treatment at each scheduled time point. Linear and semi logarithmic plots of the geometric mean and combined individual plasma concentration by scheduled and actual sampling time, respectively, were provided by part of trial and treatment.</p> <p>Descriptive statistics were used to summarize the calculated PK parameters by part of trial and treatment. Noncompartmental methods estimated PK parameters for all analytes with sufficient data above LLOQ from the concentration–time profiles for all PK set subjects. During the SAD part of the trial (Groups 1-4, Period 1), an interim PK analysis was conducted on blinded PK data to calculate the exposure.</p> <p>A regression power model, relating log-transformed C_{max} and area under the curve parameters to log-transformed dose, was used to investigate dose proportionality. Individual and geometric mean dose-normalized C_{max}, AUC_{0-t} and AUC_{0-∞} were plotted against dose level.</p> <p>To analyze the FE, an analysis of variance, with a model including fixed effects for treatment, period, and sequence, and a random effect for subject within sequence, was performed on natural log-transformed C_{max}, AUC_{0-t}, and AUC_{0-∞} data. The back-transformed least-squares means for each treatment and the ratio of least-squares geometric means between the test</p>

	treatment and the reference was calculated (fed over fasted). The presence or absence of a statistically significant FE depended on whether the corresponding 90% confidence interval (CI) did not or did contain 1.
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Bioanalytical: 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- Δ^9 -tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (11-COOH-THC) in human plasma.

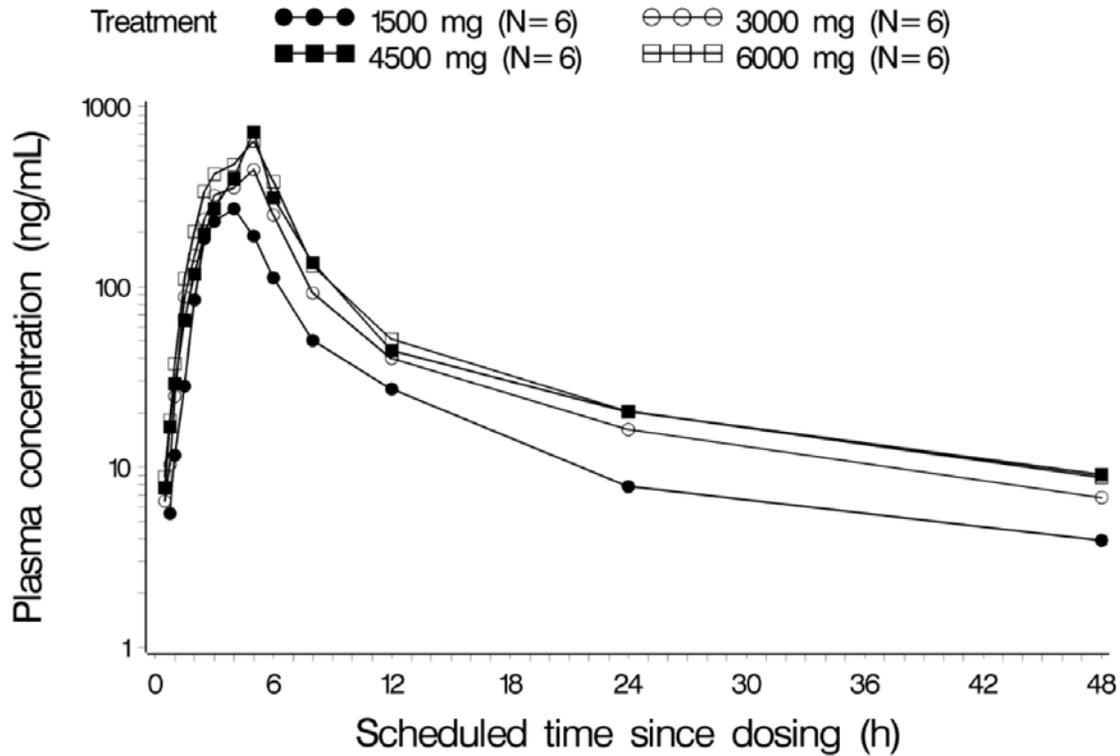
Summary of control results for CBD and its metabolites are presented in the table below.

Analyte	CBD	7-OH-CBD	7-COOH-CBD
Internal standard	d3-CBD	d5-7-OH-CBD	d5-7-COOH-CBD
Lower limit of quantitation	2.000 ng/mL	0.2500 ng/mL	0.2500 ng/mL
Calibration Standards range	2.000 – 2000 ng/mL (lower) 90.00 – 10000 ng/mL (higher)	0.2500 – 250.0 ng/mL (lower A) 0.2408 – 240.8 ng/mL (lower B) 11.25 – 1250 ng/mL (higher)	0.2500 – 250.0 ng/mL (lower) 180.0 – 20000 ng/mL (higher)
Between Batch Precision (%CV)	1.8 to 7.6	3.4 to 8.3	3.0 to 7.2
Between Batch Accuracy (%RE/Bias%)	-1.0 to 1.4	-2.6 to 2.7	-3.7 to 3.2
Quality Control (QC) levels	Low QC 6.000 ng/mL (lower) Med QC 500.0 ng/mL (lower) High QC 1500 ng/mL (lower) Low QC 270.0 ng/mL (higher) Med QC 1800 ng/mL (higher) High QC 7500 ng/mL (higher)	Low QC 0.7500 ng/mL (lower A) Low QC 0.7224 ng/mL (lower B) Med QC 62.50 ng/mL (lower A) Med QC 60.20 ng/mL (lower B) High QC 187.5 ng/mL (lower A) High QC 180.6 ng/mL (lower B) Low QC 33.75 ng/mL (higher) Med QC 225.0 ng/mL (higher) High QC 937.5 ng/mL (higher)	Low QC 0.7500 ng/mL (lower) Med QC 62.50 ng/mL (lower) High QC 187.5 ng/mL (lower) Low QC 540.0 ng/mL (higher) Med QC 3600 ng/mL (higher) High QC 15000 ng/mL (higher)
Between Batch Precision (%CV)	0.8 to 7.6	3.0 to 19.0	3.1 to 10.7
Between Batch Accuracy (%RE/Bias%)	0.6 to 6.8	0.3 to 10.0	4.8 to 13.4

RESULTS:

Cannabidiol and Metabolites

SAD: Plasma CBD Concentration versus Time, by Treatment Single Ascending Dose



SAD: Dose Proportionality PK Parameters for CBD and Metabolites

Analyte	Parameter	Slope ^a	Standard Error	90% CI	p-value
CBD	C_{max}	0.73	0.23	0.35, 1.12	0.0038
	AUC_{0-t}	0.64	0.22	0.27, 1.01	0.0068
	$AUC_{0-\infty}$	0.64	0.21	0.28, 1.00	0.0061
6-OH-CBD	C_{max}	0.49	0.19	0.16, 0.81	0.0169
	AUC_{0-t}	0.38	0.21	0.02, 0.74	0.0867
	$AUC_{0-\infty}$	0.29	0.22	-0.09, 0.67	0.2073
7-COOH-CBD	C_{max}	0.35	0.16	0.08, 0.62	0.0345
	AUC_{0-t}	0.46	0.21	0.09, 0.83	0.0419
	$AUC_{0-\infty}$	0.50	0.25	0.07, 0.93	0.0608
7-OH-CBD	C_{max}	0.54	0.18	0.23, 0.85	0.0066
	AUC_{0-t}	0.53	0.19	0.20, 0.85	0.0111
	$AUC_{0-\infty}$	0.49	0.19	0.16, 0.81	0.0169

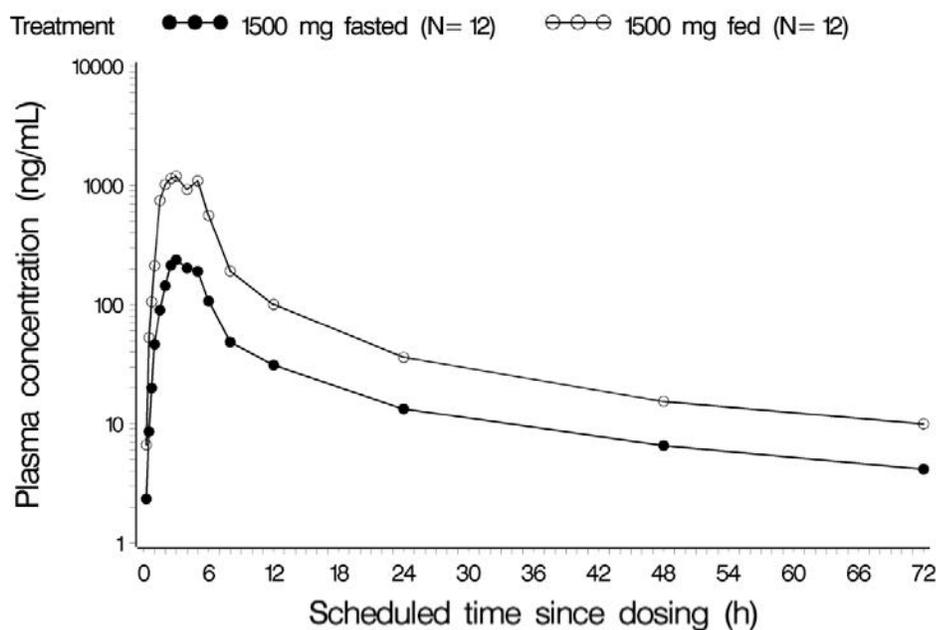
^a A slope close to 1 suggests dose proportionality.

SAD: Summary of Primary PK Parameters of CBD and Metabolites

SAD: PK Parameters of CBD and Metabolites								
Analyte & Dose of GWP42003- P (mg)	C_{max} ng/mL n=6	t_{max} hb n=6	AUC_{0-t} ng h/mL n=6	AUC_{0-∞} ng.h/mL	%AUC_{extra}	CL/f L/h n=6	V_z/f L n=6	t_{1/2} h
CBD								
1500	292.4 (87.9)	4.00 (3.00-5.00)	1517 (78.2)	1618 (74.6) (n=6)	6.20 (51.7) (n=6)	1111 (67.2)	20963 (55.3)	14.43 (36.1) (n=6)
3000	533.0 (35.1)	5.00 (3.00-5.00)	2669 (36.4)	2802 (35.5) (n=6)	4.74 (27.0) (n=6)	1121 (30.5)	23357 (32.9)	14.39 (14.9) (n=6)
4500	722.1 (52.3)	5.00 (5.00-5.00)	3215 (50.3)	3426 (48.3) (n=6)	6.15 (28.5) (n=6)	1445 (52.6)	36575 (66.8)	16.61 (18.7) (n=6)
6000	782 (83.0)	5.00 (3.00-5.02)	3696 (79.9)	3900 (79.3) (n=6)	5.16 (66.0) (n=6)	1909 (77.3)	42849 (75.5)	15.42 (29.0) (n=6)
6-OH-CBD								
1500	10.7 (65.7)	4.00 (2.50-4.00)	91.23 (66.7)	132.5 (93.7) (n=4)	20.97 (28.1) (n=4)	-	-	40.75 (73.6) (n=6)
3000	14.4 (28.6)	4.50 (2.50-5.00)	121.1 (14.7)	126.0 (18.2) (n=3)	5.35 (33.4) (n=3)	-	-	22.78 (81.9) (n=4)
4500	14.5 (36.5)	5.00 (4.00-5.00)	127.1 (53.1)	127.1 (50.3) (n=3)	14.56 (76.1) (n=3)	-	-	33.92 (55.9) (n=6)
6000	23.5 (68.6)	5.00 (3.00-5.02)	160.7 (91.4)	215.0 (92.0) (n=5)	11.29 (49.2) (n=5)	-	-	28.67 (104.5) (n=6)
7-COOH-CBD								
1500	3060 (62.4)	4.00 (4.00-5.00)	60467 (85.4)	75869 (95.1) (n=3)	21.64 (11.4) (n=3)	-	-	25.98 (26.5) (n=6)
3000	3557 (34.7)	5.00 (4.00-5.00)	74660 (40.2)	90818 (47.5) (n=4)	17.74 (41.3) (n=4)	-	-	23.88 (40.5) (n=6)
4500	5120 (19.7)	5.00 (4.00-8.00)	111025 (39.7)	132731 (51.1) (n=4)	22.75 (23.7) (n=4)	-	-	25.18 (25.3) (n=6)
6000	4591 (44.3)	5.01 (4.00-8.00)	107022 (74.1)	113026 (42.3) (n=3)	17.89 (44.2) (n=3)	-	-	30.24 (52.7) (n=6)
7-OH-CBD								
1500	238.7 (84.0)	3.50 (2.50-4.00)	1616 (76.9)	1826 (74.6)	11.46 (32.1) (n=6)	-	-	18.70 (11.4)

				(n=6)				(n=6)
3000	332.2 (30.2)	4.50 (3.00-5.00)	1959 (24.1)	2143 (23.2) (n=6)	8.41 (74.0) (n=6)	-	-	15.42 (32.5) (n=6)
4500	404.8 (37.3)	5.00 (4.00-5.00)	2810 (40.3)	3039 (42.2) (n=6)	7.49 (41.2) (n=6)	-	-	14.89 (22.4) (n=6)
6000	515.8 (42.3)	5.00 (3.00-5.02)	3299 (63.5)	3531 (63.1) (n=6)	6.51 (55.1) (n=6)	-	-	14.46 (23.1) (n=6)

Integrated FE: Plasma CBD Concentration versus Time, by Fed and Fasted State



Integrated Food Effect					
Analyte	Parameter	Fed	Fasted	Estimate	90% CI
CBD	C _{max}	1588	327	4.85	4.01-5.87
	AUC _{0-t}	8337	1985	4.20	3.63-4.85
	AUC _{0-∞}	8670	2198	3.94	3.45-4.51
6-OH-CBD	C _{max}	27.1	9.68	2.80	2.32-3.36
	AUC _{0-t}	250	94.7	2.64	2.14-3.25
	AUC _{0-∞}	274	106	2.59	2.06-3.26
7-COOH-CBD	C _{max}	4585	2205	2.08	1.64-2.64
	AUC _{0-t}	123735	51202	2.42	2.05-2.85
	AUC _{0-∞}	140311	59613	2.35	2.02-2.74
7-OH-CBD	C _{max}	378	130	2.91	2.43-3.48
	AUC _{0-t}	3218	1018	3.16	2.64-3.78

	AUC _{0-∞}	3337	1030	3.24	2.72-3.87
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Total variability in PK parameters for CBD was relatively lower in the fed group than the fasted group.

- For C_{max}, the coefficient of variation (CV)% was 81.3% for the fasted group and 51.4% for the fed group.
- For area under the plasma concentration-time curve (AUC [AUC_{0-t} and AUC_{0-∞}]), the CV% was 48.2% to -53.6% for the fasted group and 33.9% to -34.1% for the fed group.

MD: Summary of Primary PK Parameters of CBD and Metabolites (PK Set)							
GWP42003-P							
		750 mg			1500 mg		
		Day 1 (morning) (n = 9)	Day 1 (evening) (n = 9)	Day 7 (morning) (n = 9)	Day 1 (morning) (n = 9)	Day 1 (evening) (n = 9)	Day 7 (morning) (n = 9)
CBD							
C _{max} ng/mL	Geo Mean	290.8	732.4	330.3	361.8	1385	541.2
t _{max} h	Median	5.00	2.50	3.00	5.00	4.00	3.00
AUC _{0-tau} ng h/mL	Geo Mean	1070 (n=9)	2683 (n=8)	1745 (n=9)	1444 (n=9)	9819 (n=2)	3236 (n=9)
t _{1/2} h	Mean	-	-	56.41 (n=9)	-	-	60.54 (n=9)
6-OH-CBD							
C _{max} ng/mL	Geo Mean	8.2	15.3	12.8	9.0	21.4	16.3
t _{max} h	Median	5.00	2.50	2.50	4.03	3.00	3.00
AUC _{0-tau} ng h/mL	Geo Mean	47.60 (n=4)	71.90 (n=7)	93.35 (n=8)	30.50 (n=5)	96.41 (n=2)	104.3 (n=9)
t _{1/2} h	Mean	-	-	21.54 (n=8)	-	-	82.21 (n=9)
7-COOH-CBD							
C _{max} ng/mL	Geo Mean	2785	5307	9824	2748	9776	16,306
t _{max} h	Median	5.00	4.00	4.00	5.00	12.00	3.00
AUC _{0-tau} ng h/mL	Geo Mean	20807 (n=9)	41,656 (n=4)	86,179 (n=8)	20,526 (n=9)	86,076 (n=6)	151,336 (n=9)
t _{1/2} h	Mean	-	-	21.32 (n=9)	-	-	22.00 (n=9)
7-OH-CBD							
C _{max} ng/mL	Geo Mean	123.0	197.2	152.6	139.5	305.2	187.9
t _{max} h	Median	4.00	2.50	2.50	4.03	4.00	3.00
AUC _{0-tau} ng h/mL	Geo Mean	699.0 (n=4)	958.7 (n=7)	976.3 (n=9)	457.4 (n=5)	- (n=0)	1246 (n=9)
t _{1/2} h	Mean	-	-	24.73 (n=9)	-	-	31.70 (n=9)

Δ9-Tetrahydrocannabinol and Metabolites

- THC and its metabolites were detected only at low levels, and generally only around t_{max}, and concentrations were below the LLOQ for most subjects at most time points.
- The C_{max} for THC ranged from 0.1 to 0.9 ng/mL in the SAD part of the trial. The C_{max} was 0.2 ng/mL in the fasted state and 0.8 ng/mL in the fed state, indicating a food effect in the integrated FE part of the trial consistent with that seen with CBD. The C_{max} was 0.2 ng/mL after 750 mg CBD (approximately 1650 times less than the concentration of CBD at this dose) and 0.4 ng/mL after 1500 mg CBD at steady state in the MD part of the trial.

CONCLUSIONS:

Single Ascending Dose

- The increase in exposure (C_{max} and AUC_{0-t}) for CBD and metabolites with was less than dose proportional.
- The CL/f of CBD was high with a large V_z/f, suggesting extensive biotransformation of CBD and a wide distribution in the body.
- The most abundant CBD metabolite was 7-COOH-CBD (b) (4) followed by 7-OH-CBD (b) (4) with 6-OH-CBD having the smallest exposure.
- THC and its metabolites were detected only at low levels, and generally only around t_{max} and concentrations were below the LLOQ for most subjects at most time points (C_{max} ranged from 0.1-0.9 ng/mL).

Food Effect

- There was a marked increase in C_{max} for CBD by approximately 5-fold and 4-fold for AUC_{0-t}. The extent of the food effect by approximately 2 to 3 fold was also seen in CBD metabolite exposure. The exposure increase coincided with a higher incidence of TEAEs in the fed group.
- PK parameter variability for CBD was generally lower in the fed group than the fasted group.
- The time to reach maximum concentration, t_{max} was slightly lower under fed conditions (3.5 hours fasting and 3.0 hours fed). The half-life, t_{1/2} was lower under fed conditions (24 hours fed and 30 hours fasted) for CBD and the metabolites.

Multiple Dose

- The steady state C_{max} of CBD and its metabolites occurred at approximately 3 hours.
- Plasma concentrations declined for CBD on Day 7 with a t_{1/2} of 56 hours for 750 mg CBD and 61 hours for 1500 mg CBD.
- At steady state, there was a close to doubling in exposure for a 2-fold increase in dose (750 - 1500 mg b.i.d.). C_{max} increased by 1.6-fold and AUC_{0-tau} increased by 1.9-fold. There was moderate accumulation after 7 days of multiple b.i.d. dosing (Rac 1.8-fold after 750 mg and 2.6-fold after 1500 mg). The extent of accumulation was similar for CBD metabolites except for 7-COOH-CBD.
- There was a higher exposure to CBD on Day 1 after the evening dose than after the morning dose (Rac 2.9-fold after 750 mg and 6.3-fold after 1500 mg). This within-day effect was also

observed for CBD metabolites and likely reflects both accumulation and the differences in prandial state between morning, following overnight fasting, and evening administration.

GWEP1540: A Phase 1, Open-label, Parallel Group, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Cannabidiol (GWP42003-P) in Subjects with Varying Degrees of Renal Function

Objectives:

- The primary objective was to evaluate the pharmacokinetic (PK) parameters of a single oral dose of CBD in subjects with mild, moderate, and severe renal impairment compared with subjects with normal renal function.
- The secondary objective was to evaluate the safety and tolerability of a single oral dose of CBD in all the subjects

Study Design	This study was a multisite, open-label, PK and safety trial of a single oral dose of 200 mg CBD in male and female subjects with mild renal impairment, moderate renal impairment, severe renal impairment, and normal renal function
Study Population	Male and female subjects aged 18-75 years, inclusive, with a BMI of 18.0-35.0 kg/m ² . Thirty-two subjects enrolled and completed the trial, which included 3 groups of subjects with renal impairment (with 8 subjects in each of the mild, moderate and severe renal impairment groups) and 8 matching healthy subjects. All 32 subjects completed the trial and were analyzed as planned.
PK Sampling	Pre-dose serial blood samples (within 30 minutes prior to dosing) and after the administration of CBD at 15, 30, and 45 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours post-dose. Pre-dose urine samples for analysis of excretion of CBD, Δ9-tetrahydrocannabinol (THC) and their major metabolites at 0-4, 4-8, 8-12, 12-24, and 24-48 hours post-dose.
Pharmacokinetic Assessments	The pharmacokinetic parameters analyzed for CBD and its major metabolites 6-hydroxy-cannabidiol (6-OH-CBD), 7-carboxy-cannabidiol (7-COOH-CBD), and 7-hydroxy-cannabidiol (7-OH-CBD) in plasma and urine: C _{max} , T _{max} , t _{lag} , K _e , AUC _{0-t} , AUC _{0-inf} , CL/F, V _z /F, A _{elast} , f _e .
Safety Assessments	Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.
Statistical Methods	Analysis of variance (ANOVA) was used to compare primary PK parameters (C _{max} , CL/F, CLR, AUC(0-t) and AUC(0-∞)) between the control group of healthy subjects and each of the groups with renal impairment. Prior to the analysis, the PK values were log transformed. Covariates included sex, age, and BMI, if significant. Geometric least-squares means were used to calculate the ratios of primary PK parameters in each renal impairment group to those in the control group, together with 90% confidence intervals (CIs). The Wilcoxon rank-sum test was used for comparison of the t _{max} values between the control group and each renal

	disease group, and estimates of the median differences between groups were determined, together with 90% CIs. The relationship between log-transformed primary PK parameters (AUC(0-∞), AUC(0-t), C _{max} , CL/F, and CLR) and estimated CL _{cr} (at screening) was analyzed by a linear regression approach that included sex, age, and BMI, if significant. Secondary PK parameters were analyzed descriptively.
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Bioanalytical: 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-Δ⁹-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-Δ⁹-tetrahydrocannabinol (11-COOH-THC) in human plasma.

Summary of control results for CBD and its metabolites are presented in the table below.

Analyte	CBD	7-OH-CBD	7-COOH-CBD
Internal standard	d3-CBD	d5-7-OH-CBD	d5-7-COOH-CBD
Lower limit of quantitation	1.000 ng/mL	0.2500 ng/mL	0.2500 ng/mL
Calibration Standards range	1.000 – 1000 ng/mL	0.125 – 125.0 ng/mL	0.125 – 125.0 ng/mL
Between Batch Precision (%CV)	2.0 to 6.8	3.3 to 7.7	4.6 to 7.2
Between Batch Accuracy (%RE/Bias%)	-1.3 to 1.8	-5.5 to 3.8	-2.2 to 1.4
Linearity	Weighted linear equation (1/X ²), mean r= 0.9991	Weighted linear equation (1/X ²), mean r= 0.9958	Weighted linear equation (1/X ²), mean r= 0.9958
Quality Control (QC) levels	Low QC 6.000 ng/mL Med QC 500.0 ng/mL High QC 1500 ng/mL	Low QC 0.7500 ng/mL Med QC 62.50 ng/mL High QC 187.5 ng/mL	Low QC 0.7500 ng/mL Med QC 62.50 ng/mL High QC 187.5 ng/mL
Between Batch Precision (%CV)	4.1 to 6.4	4.6 to 9.7	5.4 to 11.7
Between Batch Accuracy (%RE/Bias%)	0.9 to 3.9	-0.9 to 4.8	4.8 to 8.1

RESULTS:

Summary of PK Parameters of CBD and Metabolites

PK Parameter	Group 1 Mild Renal Impairment (n=8)	Group 2 Moderate Renal Impairment (n=8)	Group 3 Severe Renal Impairment (n=8)	Group 4 Normal Renal Function (n=8)
	Geometric Mean (CV%)			
CBD				
C _{max} ng/mL	199.669 (42.69)	171.653 (85.29)	155.372 (40.62)	152.832 (74.70)
AUC(0-∞) ng•h/mL	600.165 ^a (49.99)	522.483 ^b (63.56)	601.135 ^b (35.89)	499.457 (76.58)
AUC(0-t) ng•h/mL	670.588 (40.88)	529.623 ^b (74.42)	531.958 (32.73)	464.291 (77.62)
CL/F (L/h)	364.502 ^a (52.27)	433.809 ^b (82.42)	350.711 ^b (37.31)	509.664 (87.58)
6-OH-CBD				
C _{max} ng/mL	4.108 ^b (58.98)	5.171 ^b (32.07)	3.978 ^b (31.75)	3.86 ^d (18.19)
AUC(0-∞) ng•h/mL	61.198 ^c (3.26)	74.945 ^c (2.07)	55.92 ^a (52.60)	34.26 ^c (54.76)
AUC(0-t) ng•h/mL	30.541 ^b (63.10)	35.456 ^b (78.54)	39.237 ^b (48.76)	22.597 ^d (51.68)
7-OH-CBD				
C _{max} ng/mL	44.578 (77.00)	70.542 (30.04)	61.858 ^c (37.61)	52.257 (34.83)
AUC(0-∞) ng•h/mL	381.666 (59.64)	457.641 (24.98)	520.784 ^e (16.96)	335.12 (20.75)
AUC(0-t) ng•h/mL	327.344 (60.18)	399.915 (23.65)	448.06 ^e (15.51)	302.33 (22.58)
7-COOH-CBD				
C _{max} ng/mL	648.329 ^d (109.46)	578.363 ^a (32.90)	571.9 (51.23)	842.49 ^a (49.78)
AUC(0-∞) ng•h/mL	NC	NC	NC	NC
AUC(0-t) ng•h/mL	15676.65 ^d (69.21)	14628.97 ^a (29.25)	15420.08 (37.52)	16301.56 (33.09)

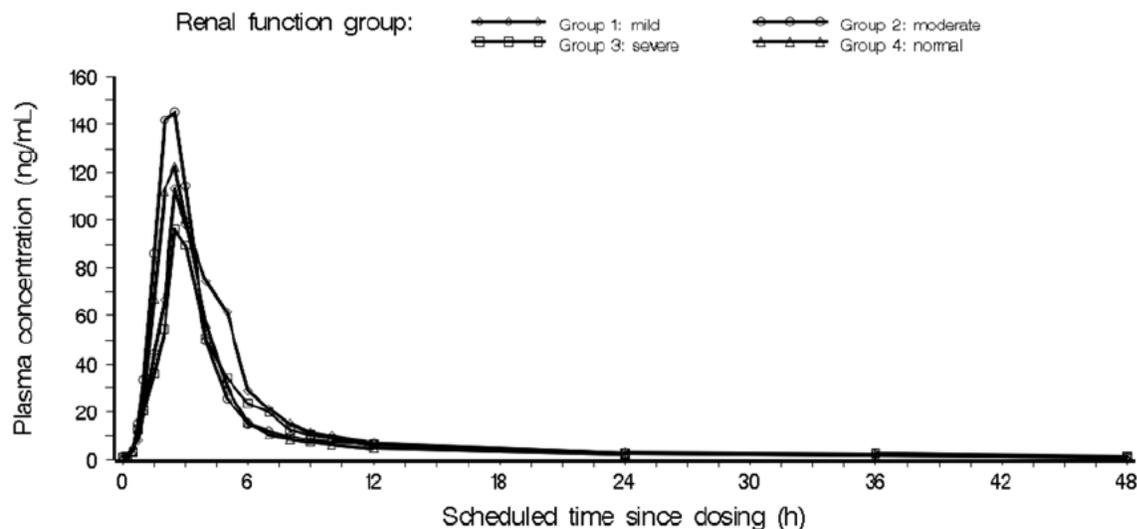
Following table summarizes the C_{max}, AUC(0-t) and AUC(0-∞) geometric mean ratios for subjects with normal renal function and those with renal impairment for CBD and its major metabolites.

Geometric Mean Ratios and 90% Confidence Intervals for CBD and Metabolites

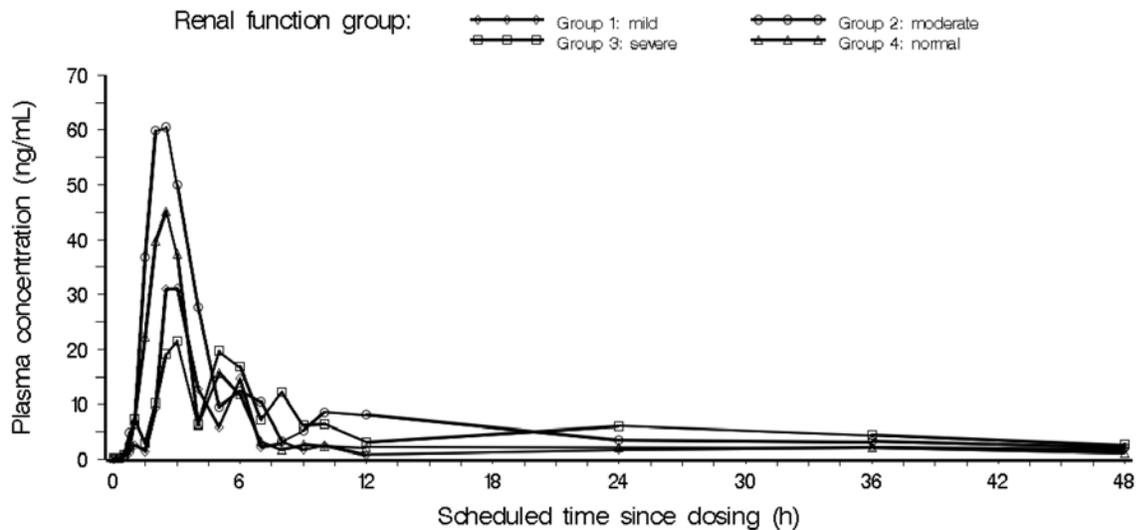
Geometric Mean Ratios and 90% Confidence Intervals for CBD and Metabolites (PK Set)				
Comparison (Test/Reference)	C _{max} (ng/mL)	AUC(0-∞) (ng•h/mL)	AUC(0-t) (ng•h/mL)	CL/F (L/h)
	Ratio of Geometric Least Squared Means (90% CI)			
CBD				
Mild/Normal	1.31 (0.73, 2.35)	1.20 (0.59, 2.45)	1.44 (0.83, 2.51)	1.31 (0.73, 2.35)

Moderate/Normal	1.12 (0.62, 2.02)	1.05 (0.56, 1.96)	1.14 (0.66, 1.98)	1.12 (0.62, 2.02)
Severe/Normal	1.02 (0.57, 1.83)	1.20 (0.64, 2.25)	1.15 (0.66, 1.99)	1.02 (0.57, 1.83)
6-OH-CBD				
Mild/Normal	0.94 (0.66, 1.35)	1.58 (0.98, 2.55)	1.38 (0.83, 2.31)	NR
Moderate/Normal	1.14 (0.80, 1.63)	2.01 (1.25, 3.25)	1.49 (0.90, 2.49)	NR
Severe/Normal	1.01 (0.71, 1.43)	1.65 (1.07, 2.54)	1.74 (1.04, 2.90)	NR
7-OH-CBD				
Mild/Normal	0.85 (0.54, 1.36)	1.14 (0.81, 1.59)	1.08 (0.77, 1.53)	NR
Moderate/Normal	1.35 (0.85, 2.15)	1.37 (0.98, 1.91)	1.32 (0.94, 1.86)	NR
Severe/Normal	1.10 (0.69, 1.75)	1.56 (1.12, 2.19)	1.42 (1.01, 2.00)	NR
7-COOH-CBD				
Mild/Normal	0.88 (0.50, 1.54)	NC	1.04 (0.69, 1.55)	NR
Moderate/Normal	0.89 (0.50, 1.56)	NC	1.07 (0.72, 1.60)	NR
Severe/Normal	0.68 (0.39, 1.19)	NC	0.95 (0.63, 1.41)	NR
NC, not calculable; NR, not reported.				

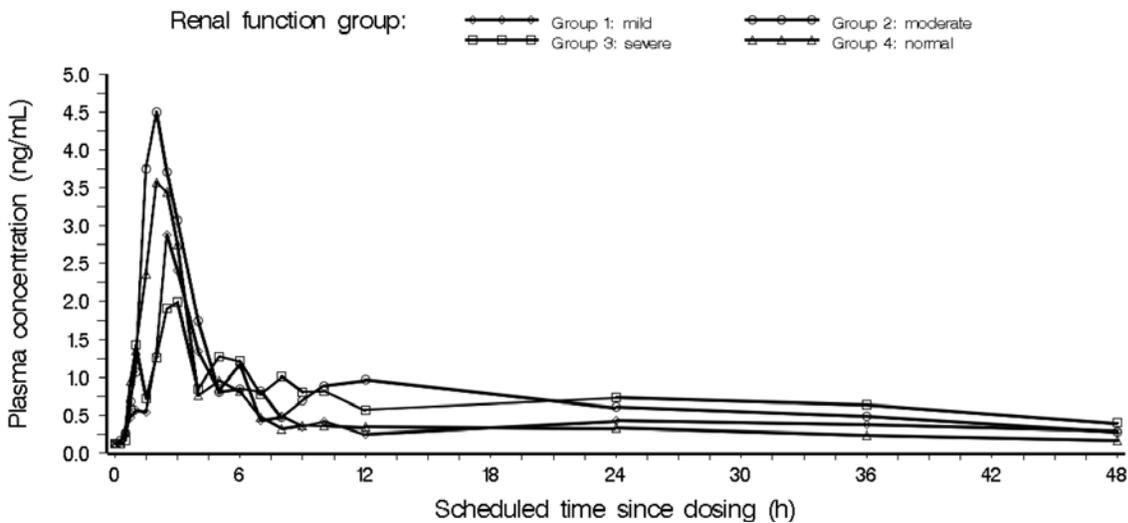
Geometric Mean Plasma CBD Concentration versus Time for all Renal Function Groups



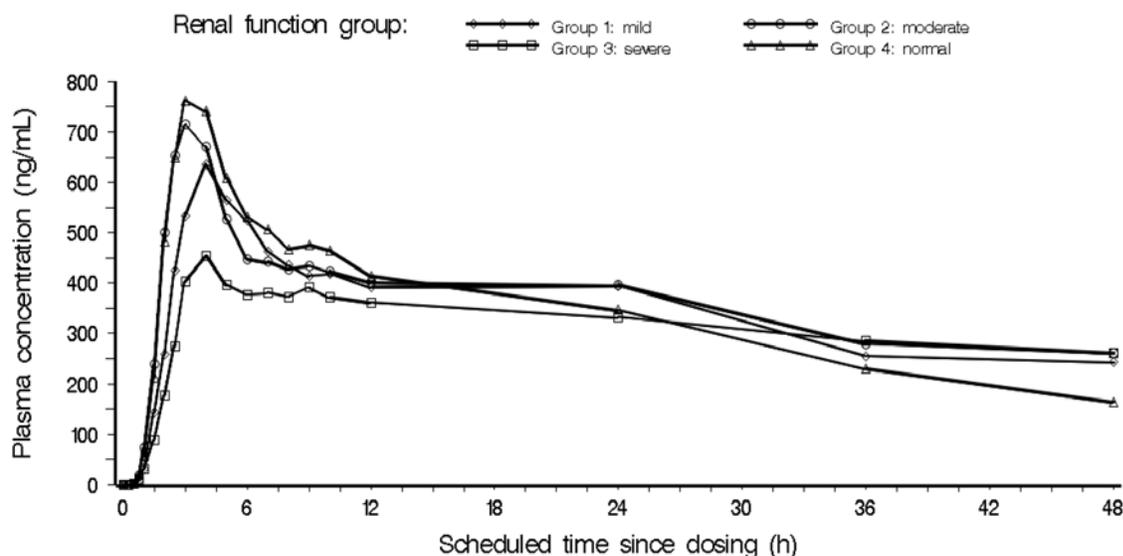
Geometric Mean Plasma 7-OH-CBD Concentration versus Time for all Renal Function Groups



Geometric Mean Plasma 6-OH-CBD Concentration versus Time for all Renal Function Groups



Plasma 7-COOH-CBD Concentration versus Time for all Renal Function Groups



CONCLUSIONS:

- Following a single 200 mg oral dose of CBD, C_{max} of CBD was about 30% higher in patients with mild RI when compared to subjects with normal renal function. However, this increase was not seen in overall exposure AUC.
- There was an increase of ~35% in C_{max} and AUC for 7-OH-CBD in moderate RI group when compared to subjects with normal renal function. In severe RI subjects AUC increase by ~50% with 10% increase in C_{max}.
- No differences were observed with respect to 7-COOH-CBD for any groups.
- CBD, 6-OH-CBD, 7-OH-CBD and 7-COOH-CBD were all highly protein bound (>90%), and this binding was similar in subjects with mild, moderate or severe renal impairment compared with subjects with normal renal function.
- Urinary concentrations of CBD, 6-OH-CBD, 7-OH-CBD or 7-COOH-CBD were undetected in both subjects with mild, moderate or severe renal impairment and subjects with normal renal function.

GWEP1539: A Phase 1, Open-label, Parallel Group, Single-dose Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of CBD (GWP42003-P) in Subjects with Varying Degrees of Hepatic Function.

Objectives:

The primary objective was to evaluate the pharmacokinetic (PK) parameters of a single oral dose of GWP42003-P in subjects with mild, moderate, and severe hepatic impairment compared with subjects with normal hepatic function. The secondary objective was to evaluate the safety and tolerability of a single oral dose of GWP42003-P in subjects with mild, moderate, and severe hepatic impairment and in subjects with normal hepatic function.

Study Design	This study was a multisite, open-label, PK and safety trial of a single oral dose of 200 mg GWP42003-P in male and female subjects with mild
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	hepatic impairment (n=8), moderate hepatic impairment (n=8), severe hepatic impairment (n=6), and normal hepatic function (n=8) based on the Child–Pugh classification for the assessment of hepatic impairment at screening.
Study Population	Male and female subjects aged 18-75 years, inclusive, with a BMI of 18.0-35.0 kg/m ² . Thirty-two subjects were planned (8 per group) and 30 subjects enrolled in the trial: 22 subjects with hepatic impairment (8 subjects in the mild and moderate, and 6 in the severe hepatic impairment groups), and 8 matching subjects with normal hepatic function. All 30 subjects completed the trial and were analyzed as planned.
Treatment Groups	Group 1: mild hepatic impairment (Child–Pugh score 5-6 points). Group 2: moderate hepatic impairment (Child–Pugh score 7-9 points). Group 3: severe hepatic impairment (Child–Pugh score 10-15 points). Group 4: normal hepatic function.
PK Sampling	Predose serial blood samples (within 30 minutes prior to dosing) and after the administration of the investigational medicinal product (IMP) at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 24, 36, and 48 hours postdose.
Pharmacokinetic Assessments	The pharmacokinetic parameters analyzed for CBD and its major metabolites 6-hydroxy-cannabidiol (6-OH-CBD), 7-carboxy-cannabidiol (7-COOH-CBD), and 7-hydroxy-cannabidiol (7-OH-CBD) in plasma and urine: C _{max} , T _{max} , t _{lag} , K _e , AUC _{0-t} , AUC _{0-inf} , CL/F, V _z /F, A _{elast} , f _e .
Safety Assessments	Adverse events (AEs), standard laboratory assessments, vital signs, electrocardiograms and physical examination.
Statistical Methods	Analyses of variance (ANOVA) were used to compare primary PK parameters (C _{max} , AUC(0-∞), AUC(0-t), t _{1/2} and t _{max}) between the control group of subjects with normal hepatic function and each of the groups with hepatic impairment. Prior to the analysis, the PK values were log-transformed. Covariates included sex, age, and BMI, if statistically significant. Geometric least-squares means were used to calculate the ratio of primary PK parameters in each hepatic impairment group to those in the control group, together with 90% confidence intervals (CIs). The Wilcoxon rank–sum test was used for comparison of the t _{max} values between the control group and each hepatic disease group, and estimates of the median differences between groups determined, together with 90% CIs. The relationship between log-transformed PK parameters (C _{max} , AUC(0-∞), AUC(0-t), t _{1/2} , and t _{max}) and continuous variables contributing to the Child–Pugh score (baseline values for serum albumin and bilirubin concentrations and prothrombin time) were explored by a linear regression approach. Safety data were analyzed descriptively; summaries and listings were generated for the safety population set, and were presented by hepatic impairment status.

Bioanalytical: 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- Δ 9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy- Δ 9-tetrahydrocannabinol (11-COOH-THC) in human plasma.

Summary of control results for CBD and its metabolites are presented in the table below.

Analyte	CBD	7-OH-CBD	7-COOH-CBD
Internal standard	d3-CBD	d5-7-OH-CBD	d5-7-COOH-CBD
Lower limit of quantitation	1.000 ng/mL	0.2500 ng/mL	0.2500 ng/mL
Calibration Standards range	2.000 – 2000 ng/mL	0.125 – 125.0 ng/mL	0.125 – 125.0 ng/mL
Between Batch Precision (%CV)	1.6 to 6.3	3.4 to 11.3	3.3 to 7.6
Between Batch Accuracy (%RE/Bias%)	-1.7 to 2.5	-5.5 to 3.8	-2.9 to 3.7
Linearity	Weighted linear equation ($1/X^2$), mean $r= 0.9992$	Weighted linear equation ($1/X^2$), mean $r= 0.9958$	Weighted linear equation ($1/X^2$), mean $r= 0.9946$
Quality Control (QC) levels	Low QC 6.000 ng/mL Med QC 500.0 ng/mL High QC 1500 ng/mL	Low QC 0.7500 ng/mL Med QC 62.50 ng/mL High QC 187.5 ng/mL	Low QC 0.7500 ng/mL Med QC 62.50 ng/mL High QC 187.5 ng/mL
Between Batch Precision (%CV)	4.6 to 5.5	4.3 to 9.7	5.7 to 11.7
Between Batch Accuracy (%RE/Bias%)	1.4 to 4.4	0.6 to 5.8	3.0 to 6.8

RESULTS:

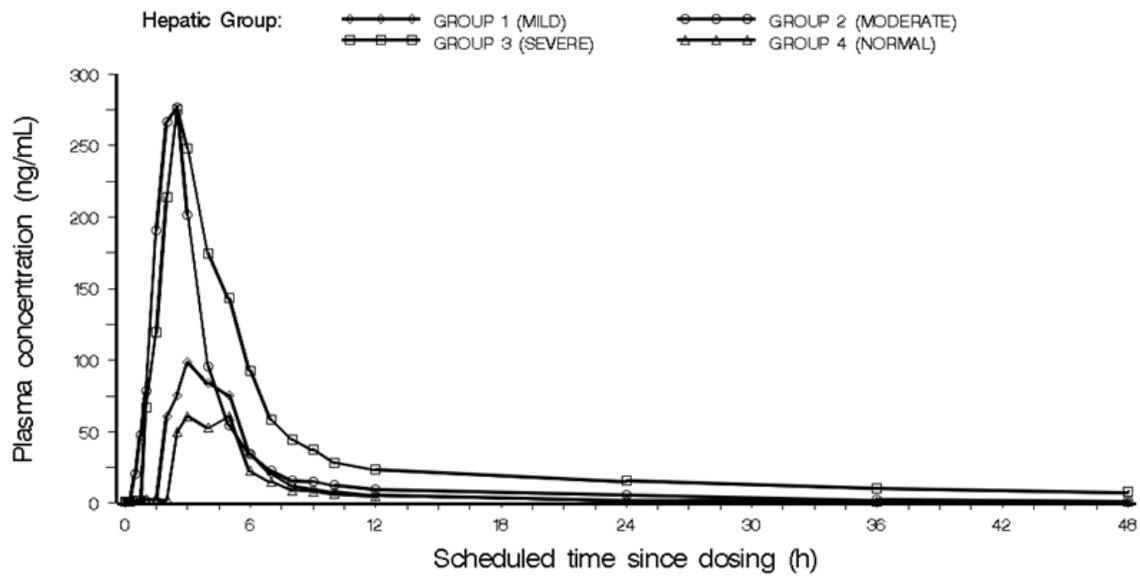
Summary of PK Parameters of Total CBD and Metabolites (PK Set)				
PK Parameter	Mild Hepatic Impairment (n=8)	Moderate Hepatic Impairment (n=8)	Severe Hepatic Impairment (n=6)	Normal Hepatic Function (n=8)
	Geometric Mean (CV%)			
CBD				
C _{max} ng/mL	233.08 (70.51)	354.15 (42.33)	380.94 (52.22)	148.00 (64.97)
AUC(0-∞) ng*h/mL	699.48 (44.18)	1162.70 (39.88)	2438.53 (29.54)	473.68 (73.83)

AUC(0-t) ng*h/mL	648.09 (44.24)	1054.15 (38.90)	1855.10 (51.99)	449.08 (73.50)
CL/F (L/h)	285.93 (44.18)	172.01 (39.88)	82.02 (29.54) ^a	422.23 (73.83)
6-OH-CBD				
C _{max} ng/mL	5.78 (70.67)	7.56 (37.49)	5.35 (50.46)	3.19 (63.56)
AUC(0-∞) ng*h/mL	59.57 (14.72)	67.64 (16.23)	65.75 (39.10)	24.81 (71.51)
AUC(0-t) ng*h/mL	29.35 (89.46)	52.31 (35.05)	51.21 (51.92)	15.40 (115.86)
7-OH-CBD				
C _{max} ng/mL	54.85 (121.29)	76.45 (58.09)	45.46 (45.48)	41.84 (60.17)
AUC(0-∞) ng*h/mL	331.46 (95.66)	611.65 (42.05)	694.18 (47.55) ^a	300.64 (43.80)
AUC(0-t) ng*h/mL	305.44 (93.03)	525.03 (35.19)	531.74 (46.22)	277.18 (40.67)
7-COOH-CBD				
C _{max} ng/mL	706.04 (113.25)	804.14 (70.59)	220.53 (51.05)	823.32 (45.55)
AUC(0-∞) ng*h/mL	14075.20 (114.22)	28273.09 (6.795) ^e	nc	16238.70 (46.38)
AUC(0-t) ng*h/mL	14105.49 (102.17)	18789.42 (63.65)	7226.38 (45.64)	14910.07 (45.82)

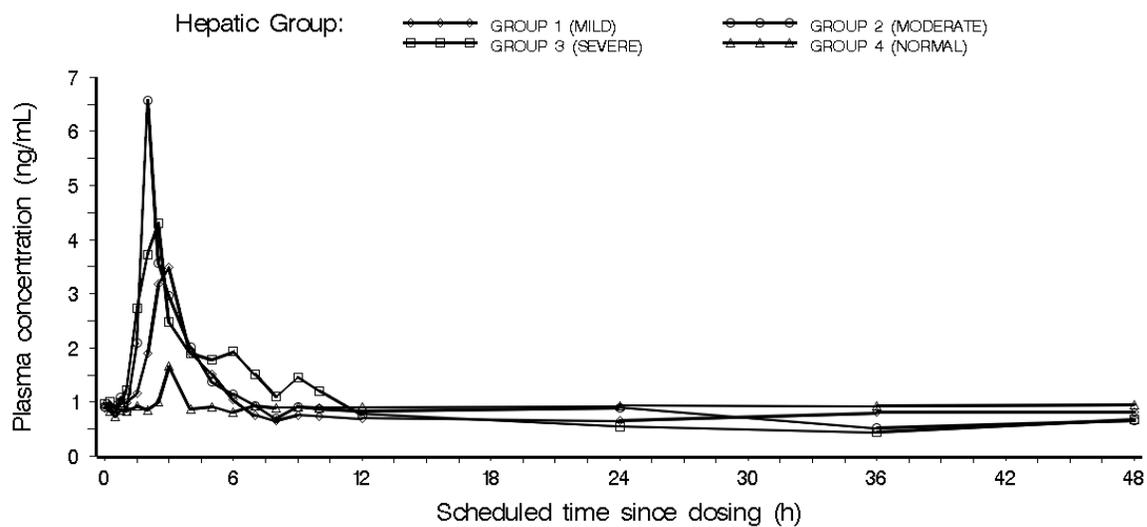
Geometric Mean Ratios and 90% Confidence Intervals for Total CBD and Metabolites (PK Set)				
Comparison (Test/Reference)	C _{max} (ng/mL)	AUC(0-∞) (ng*h/mL)	AUC(0-t) (ng*h/mL)	CL/F (L/h)
	Ratio of Geometric Least Squares Means (90% CI)			
CBD				
Mild/Normal	1.57 (0.90, 2.75)	1.48 (0.90, 2.41)	1.44 (0.86, 2.41)	0.68
Moderate/Normal	2.39 (1.37, 4.18)	2.45 (1.50, 4.01)	2.35 (1.41, 3.92)	0.41
Severe/Normal	2.57 (1.41, 4.70)	5.15 (2.94, 9.00)	4.13 (2.38, 7.18)	0.19
6-OH-CBD				
Mild/Normal	1.81 (1.05, 3.12)	1.50 (0.78, 2.88)	1.91 (0.95, 3.84)	NR
Moderate/Normal	2.37 (1.38, 4.08)	2.59 (1.40, 4.82)	3.40 (1.69, 6.84)	NR
Severe/Normal	1.68 (0.93, 3.02)	2.16 (1.16, 4.01)	3.32 (1.56, 7.08)	NR
7-OH-CBD				
Mild/Normal	1.31 (0.66, 2.59)	1.10 (0.63, 1.92)	1.10 (0.64, 1.89)	NR
Moderate/Normal	1.83 (0.92, 3.62)	2.12 (1.22, 3.69)	1.89 (1.10, 3.26)	NR
Severe/Normal	1.09 (0.52, 2.27)	2.28 (1.26, 4.14)	1.92 (1.07, 3.44)	NR
7-COOH-CBD				
Mild/Normal	0.86 (0.44, 1.68)	1.02 (0.51, 2.03)	0.95 (0.51, 1.77)	NR

Moderate/Normal	0.98 (0.50, 1.91)	1.60 (0.78, 3.27)	1.26 (0.67, 2.36)	NR
Severe/Normal	0.27 (0.13, 0.55)	0.84 (0.33, 2.14)	0.48 (0.25, 0.95)	NR
NR, not reported.				

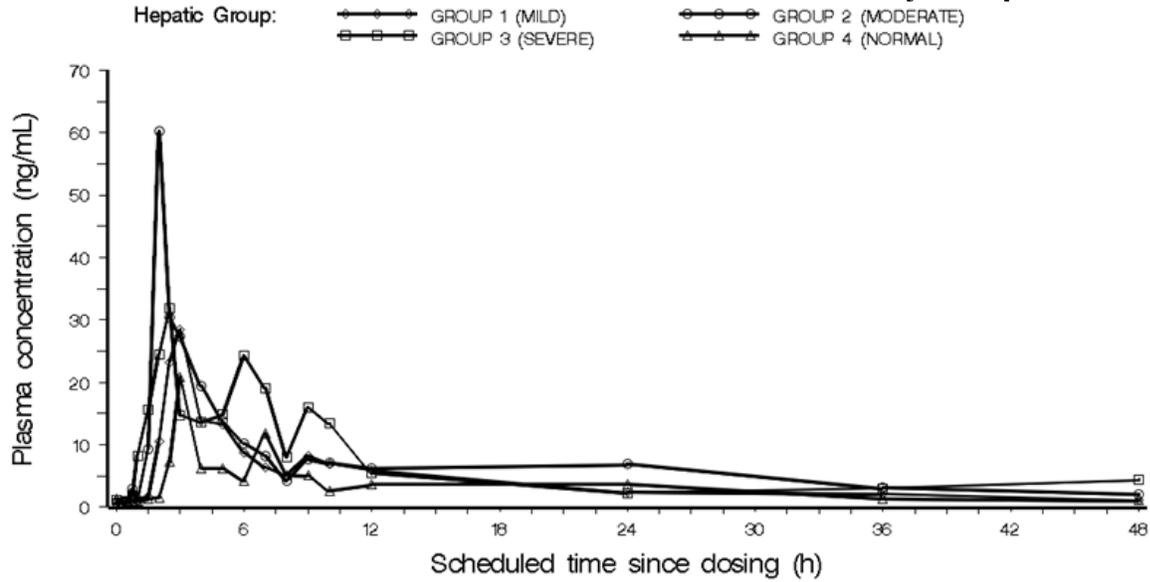
Geometric Mean Plasma CBD Concentration versus Time by Group



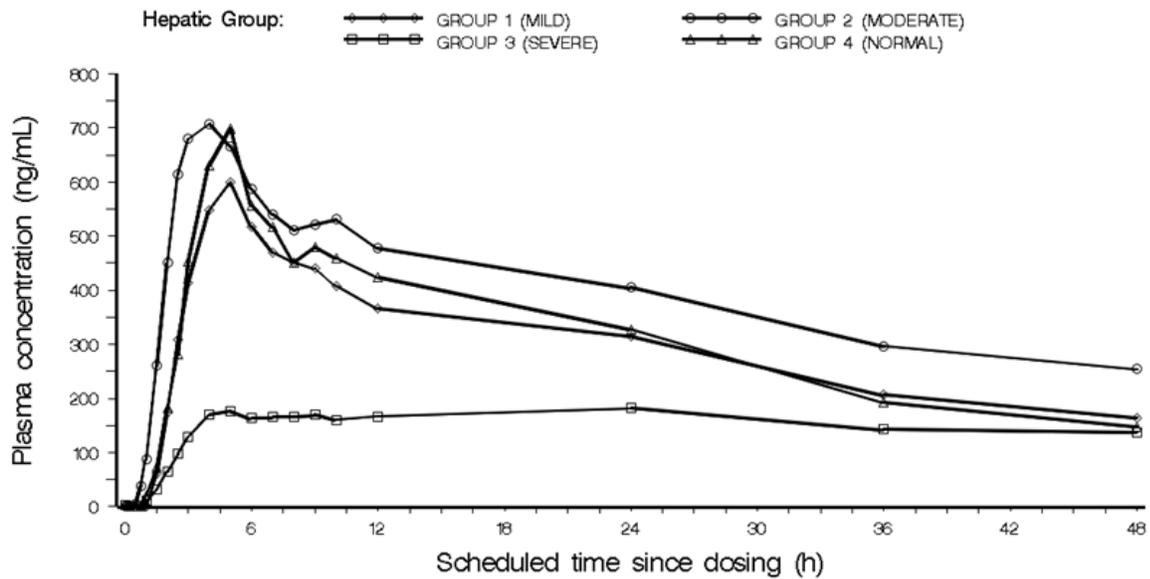
Geometric Mean Plasma 6-OH-CBD Concentration versus Time by Group



Geometric Mean Plasma 7-OH-CBD Concentration versus Time by Group



Plasma 7-COOH-CBD Concentration versus Time by Group



CONCLUSIONS:

- There was a trend to an increase in the unbound fraction of CBD by severity of hepatic impairment (4.88%, 9.42%, 11.69% of CBD was unbound in the mild, moderate and

severe hepatic impairment groups respectively, and 6.98% in the normal hepatic function group), and to a lesser extent the metabolites.

- There was approximately 50% increase in C_{max} and AUC in mild hepatic impairment when compared with subjects with normal hepatic function.
- The geometric mean C_{max} for CBD increased by approximately 2.5 fold in both the moderate and in the severe hepatic-impaired subjects, compared with subjects with normal hepatic function.
- The geometric mean AUC(0-∞) for total CBD increased by 2.45- and 5.15-fold (90% CI [1.50, 4.01] and [2.94, 9.00] respectively), and for unbound CBD increased by 2.82- and 8.43-fold (90% CI [1.31, 6.07] and [3.53, 20.16] respectively) in moderate and severe hepatic-impaired subjects compared with subjects with normal hepatic function.
- Geometric mean AUC(0-∞) for 6-OH-CBD and 7-OH-CBD also increased by 2.16 to 2.59 fold in the moderate and severe hepatic-impaired subjects. There was 10 to 80% increase in mild hepatic impairment on C_{max} for 6-OH-CBD or 7-OH-CBD.
- There was no clear trend in change in AUC(0-∞) for the major metabolite 7-COOH-CBD across all groups of hepatic-impaired subjects relative to subjects with normal hepatic function. C_{max} (both total and unbound) for 7-COOH-CBD was reduced (both 90%CI < 1) in the severe hepatic impairment group with a 16% reduction in AUC(0-∞).
- Arithmetic mean t_{1/2} was increased by 1.83-, 2.39- and 2.57-fold in the mild, moderate and severe hepatic impairment groups, respectively, compared with the normal hepatic function group.
- THC was below the limit of quantification at all time points for the majority of subjects in all groups. 11-COOH-THC was detectable in most subjects in all groups until 12 hours postdose.

Study GWEP1543: A Phase 1, Open-label, Pharmacokinetic Trial to Investigate Possible Drug-drug Interactions Between Clobazam, Stiripentol or Valproate and Cannabidiol (GWP42003-P) in Healthy Subjects

Objectives:

Primary

- To assess the effect of multiple dose administration of CBD on steady-state plasma concentrations of clobazam (CLB) (and N-desmethyloclobazam [N-CLB]), stiripentol (STP) or valproate (VPA) (and 2-propyl-4-pentonic acid [4-ene-VPA]) in healthy male and female subjects.
- To assess the effect of multiple dose administration of CLB, STP or VPA on steady-state plasma concentrations of CBD in healthy male and female subjects.

Secondary

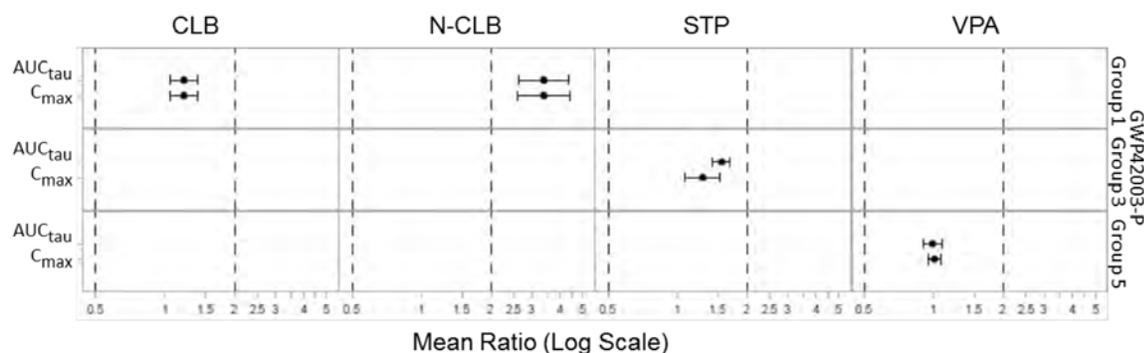
To evaluate the safety and tolerability of CBD when given concurrently with the antiepileptic drugs (AEDs) CLB, STP or VPA.

Study Design	This study was an open-label, fixed-sequence, drug-drug interaction (DDI)
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	trial.
Study Population	<p>Healthy Subjects (males and females) Age: 18-55 years BMI: 18 to 32 kg/m². A total of 72 subjects were planned to be included in the trial, with 12 subjects per group. Seventy-eight subjects were enrolled; 12 in Group 1, 3, 4 and 5, 16 in Group 2 (although 1 withdrew consent before taking any investigational medicinal product [IMP]) and 14 in Group 6. The safety and PK analysis sets included 77 subjects.</p>
Methodology	<p>This was a drug-drug interaction (DDI) trial to assess the effect of multiple dose administration of CBD on steady-state plasma concentrations of CLB (and N-CLB), STP or VPA (and 4-ene-VPA) (in Arm 1 of each drug combination). Secondly, the effect of multiple dose administration of CLB, STP or VPA on steady-state plasma concentrations of CBD was assessed (in Arm 2 of each drug combination). The trial was performed in 6 parallel groups of healthy subjects as follows:</p> <p>DDI CLB Arm 1, Group 1 (n = 12): effect of CBD on steady-state CLB and N-CLB. Arm 2, Group 2 (n = 16): effect of CLB and N-CLB on steady-state CBD.</p> <p>DDI STP Arm 1, Group 3 (n = 12): effect of CBD on steady-state STP. Arm 2, Group 4 (n = 12): effect of STP on steady-state CBD.</p> <p>DDI VPA Arm 1, Group 5 (n = 12): effect of CBD on steady-state VPA. Arm 2, Group 6 (n = 14): effect of VPA on steady-state CBD. In addition, the safety and tolerability of CBD when given concurrently with CLB, STP or VPA was assessed.</p>
Treatments	<p>In the DDI CLB part of the trial (groups 1 and 2) the total treatment duration in Arm 1 was 39 days (32 days if dosed under Protocol v2.0 or 3.0), and in Arm 2 was 38 days (31 days if dosed under Protocol v2.0 or 3.0). In the DDI STP part of the trial (groups 3 and 4) the total treatment duration in Arm 1 was 22 days (15 days if dosed under Protocol v2.0 or 3.0), and in Arm 2 was 15 days (for all versions of the protocol). In the DDI VPA part of the trial (groups 5 and 6) the total treatment duration in Arm 1 was 26 days (19 days if dosed under Protocol v2.0 or 3.0), and in Arm 2 was 27 days (20 days if dosed under Protocol v2.0 or 3.0).</p>
Analysis	<p>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-Δ9-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-Δ9-tetrahydrocannabinol (11-COOH-THC) in human plasma.</p>

Pharmacokinetic Assessments	The pharmacokinetic parameters were calculated, using noncompartmental analysis from the plasma concentration–time data for CBD, Δ9-tetrahydrocannabinol (THC), and their major metabolites after SADs and MDs of CBD.: Cmax, Tmax, tlag, Kel, t1/2, CLss/F, Vz/F, AUC0-t, AUC0-inf and Frel.
Safety Assessments	Safety and tolerability assessments consisted of: AEs, clinical laboratory tests (biochemistry, hematology and urinalysis), vital signs, 12-lead ECG, physical examination and Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire. These assessments were performed in accordance with the schedules of assessments.
Statistical Methods	PK parameters for CBD, THC and their major metabolites, and CLB (and N-CLB), STP and VPA (and 4-ene-VPA) with sufficient data above LLOQ were estimated using noncompartmental methods. Descriptive statistics (n, mean, geometric mean, standard deviation (SD), geometric coefficients of variation (CV), median, min and max) were used to summarize the calculated PK concentrations and parameters by group, ‘victim’/‘perpetrator’, drug name, analyte. Parameters based on adjusted r2 <0.80 were flagged but not excluded from descriptive statistics. In addition a linear mixed-effects model appropriate for this fixed-sequence design was used to compare the victim drug PK (Cmax and AUCTau) after multiple dosing alone with the victim drug PK combined with multiple dosing with the perpetrator drug, using treatment (alone or combined) as a fixed factor and subject as a random factor. Point estimates and 90% confidence intervals (CIs) for the ratios of the treatment means were provided as follows: <ul style="list-style-type: none"> • CLB with CBD/CLB alone (Group 1, Arm 1) (similar for its metabolite N-CLB). • STP with CBD/STP alone (Group 3, Arm 1). • VPA with CBD/VPA alone (Group 5, Arm 1) (similar for its metabolite 4-ene-VPA). • CBD with CLB/CBD alone (Group 2, Arm 2). • CBD with STP/CBD alone (Group 4, Arm 2). • CBD with VPA/CBD alone (Group 6, Arm 2). No statistical comparisons were made between groups.

RESULTS:



Note: Dashed lines at 0.5 and 2 in each figure represent a halving or doubling in exposure.

Effect of CBD on Concomitant AEDs (CLB, STP and VPA)

In Group 1, following repeated concomitant dosing of CBD (750 mg b.i.d.) with CLB (5 mg b.i.d.) for 7 and 14 days, there was an approximately 20% increase in the exposure of CLB C_{max} treatment ratio (TR) 1.20 [90% CI: 1.05, 1.38] and AUC_{tau} TR 1.21 [90% CI: 1.05, 1.39]. There was a significant increase in the exposure of N-CLB C_{max} 3.39-fold [90% CI: 2.61, 4.39] and AUC_{tau} of 3.38-fold [90% CI: 2.62, 4.36].

In Group 3, following repeated concomitant dosing of CBD (750 mg b.i.d.) with STP (750 mg b.i.d.) for 7 and 14 days, there was a 28 and 55% increase in the exposure for STP C_{max} and AUC_{tau} TR 1.28 [90% CI: 1.08, 1.52] and TR 1.55 [90% CI: 1.42, 1.69], respectively.

In Group 5, there was no effect of 7 or 14 days concomitant administration of 750 mg CBD with 500 mg b.i.d. VPA on the exposure of VPA C_{max} and AUC_{tau} TR were 1.01 [90% CI: 0.95, 1.07] and 0.99 [90% CI: 0.90, 1.09], respectively. For the 4-ene-VPA metabolite, all plasma concentrations were below the limit of quantification, probably reflecting the lack of sensitivity of the assay.

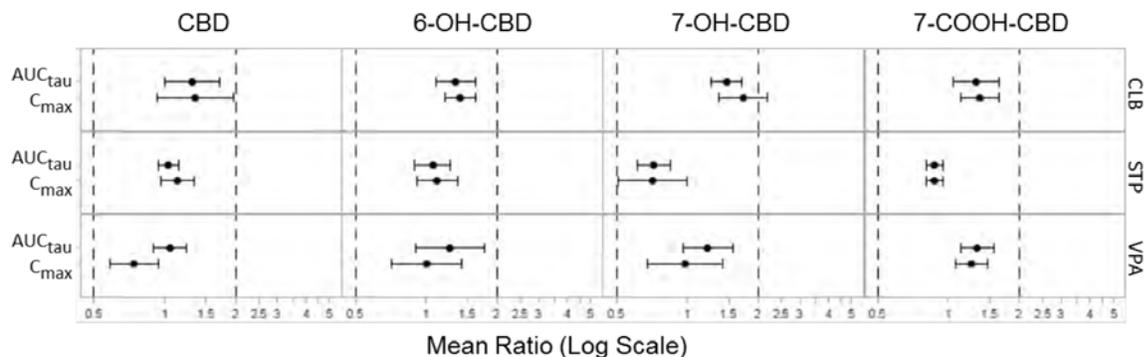
Effect of AEDs (CLB, STP and VPA) on CBD

In Group 2, following 21 days of concomitant administration of 5 mg b.i.d. CLB with 750 mg b.i.d. CBD, there was 30 to 34% increase in CBD exposure (TR for CBD C_{max} and AUC_{tau} 1.34; [90% CI: 0.93, 1.95] and 1.30; [90% CI: 1.00, 1.70] respectively).

There was 40 and 34% increase in exposure for 6-OH-CBD, (C_{max} TR 1.40 [90% CI: 1.20, 1.62] and AUC_{tau} TR 1.34 [90% CI: 1.10, 1.63]) or 7-COOH-CBD (C_{max} TR 1.35 [90% CI: 1.12, 1.63] and AUC_{tau} TR 1.31 [90% CI: 1.04, 1.64]). The C_{max} of the 7-OH-CBD metabolite increased by 1.73-fold [90% CI: 1.36, 2.20]

In Group 4, 4 days concomitant administration of 750 mg STP b.i.d. with 750 mg CBD b.i.d. had no notable effect on the exposure of CBD (C_{max} TR 1.13 [90% CI: 0.96, 1.33] and AUC_{tau} TR 1.03 [90% CI: 0.94, 1.14]) or 6-OH-CBD (C_{max} TR 1.11 [90% CI: 0.91, 1.35] and AUC_{tau} TR 1.07 [90% CI: 0.89, 1.28]). There was about 30% decrease in the exposure of 7-OH-CBD (C_{max} TR 0.71 [90% CI: 0.51, 0.99] and AUC_{tau} TR 0.72 [90% CI: 0.61, 0.85]) and no change in 7-COOH-CBD (C_{max} TR 0.87 [90% CI: 0.80, 0.96] AUC_{tau} TR 0.87 [90% CI: 0.81, 0.94]).

In Group 6, following up to 9 days concomitant administration of 500 mg b.i.d. VPA and 750 mg CBD b.i.d., there was a 26% decrease in CBD C_{max} TR 0.74 [90% CI: 0.58, 0.93] and a slight increase in AUC_{tau} TR 1.05 [90% CI: 0.90, 1.78]. There were relatively small differences in the exposure of any of the metabolites (6-OH-CBD C_{max} TR: 1.01 [90% CI: 0.71, 1.42] and AUC_{tau} TR 1.27 [90% CI: 0.90, 1.78]; 7-OH-CBD C_{max} TR 0.97 [90% CI: 0.67, 1.41] and AUC_{tau} TR 1.22 [90% CI: 0.96, 1.55]; 7-COOH-CBD C_{max} TR 1.25-fold [90% CI: 1.07, 1.45] and AUC_{tau} TR 1.22 [90% CI: 0.96, 1.55]).



Note: Dashed lines at 0.5 and 2 in each figure represent a halving or doubling in exposure.

Effect of AEDs (CLB, STP and VPA) on THC

The steady-state geometric mean THC exposure (C_{max}) in each group was 0.430 (Group 2-CBD alone), 0.487 (Group 4-CBD alone) and 0.334 ng/mL (Group 6-CBD alone) and 0.460 (Group 2-CBD + CLB), 0.569 (Group 4-CBD + STP) and 0.261 ng/mL (Group 6-CBD + VPA).

Pharmacogenomic:

The majority of subjects (73/77) were cytochrome P450 (CYP) 3A4 extensive metabolizers (EMs); the remaining 4 subjects were CYP3A4 intermediate metabolizers (IM). The frequency of the CYP2C19 phenotypes were ranked as EM (34/77) > ultrarapid metabolizer (UM) (27/77) > IM (11/77) > poor metabolizer (PM) (1/77).

In Group 1, in the 1 subject with a CYP2C19 IM phenotype, steady-state exposure to N-CLB was consistent with their phenotype (highest C_{max} and AUC_{tau} values in Group 1). Apart from 1 CYP2C19 UM subject with very low steady-state N-CLB exposure in the absence of CBD and the highest TR of all subjects, there were no other notable differences between N-CLB exposures in EMs vs. UMs. Across Groups 2, 4 and 6, exposure to steady-state CBD tended to be higher in subjects with a CYP2C19 UM phenotype and lowest in subjects with CYP2C19 IM phenotype and therefore overall, given the spread of the individual subject data, there was no obvious trend for a relationship between CYP2C19 phenotype and plasma exposure to CBD. Overall, subject numbers with genetic polymorphisms (particularly PM) were too low to draw conclusions on a pharmacogenomic (PGx) effect on CBD or CLB.

CONCLUSIONS:

Effect of CBD on AEDs (CLB, STP and VPA)

- CLB exposure increased slightly (20%) was combined with CLB. However there was a significant increase in its metabolite (N-CLB) of 3.4-fold.
- When CBD was combined with STP there was a minor increase (1.28-fold increase in Cmax and 1.55-fold increase in AUCtau).
- There was no effect of concomitant CBD administration on VPA exposure.

Effect of AEDs (CLB, STP and VPA) on CBD

When AEDs (CLB, STP and VPA) were combined with CBD there was no major effect on CBD plasma exposure (Cmax and AUCtau), however there was a minor effect of STP on CBD metabolites whereby 7-OH-CBD exposure was reduced by 29% and 7-COOH-CBD exposure reduced by 13%. Following concomitant VPA administration with CBD, 7-COOH-CBD exposure increased by 32%.

Pharmacogenomics

- Since there were insufficient numbers of PMs (CYP2C19 and CYP3A4) it was not possible to draw conclusions on PGx effects.

Study GWEP1428: A Phase 2, Double-blind, Randomized, Placebo-controlled Study to Investigate Possible Drug-drug Interactions Between Clobazam and Cannabidiol (CBD).

Objectives:

Primary Objective: To determine whether CBD affects the pharmacokinetic (PK) profile of clobazam (CLB) and its primary metabolite N-desmethylclobazam (N-CLB).

Secondary Objective: To assess the safety and tolerability of CBD in the presence of CLB.

Study Design	This study was a phase 2, double-blind trial in which 20 patients on stable CLB treatment
Study Population	Patients (male or female) Age: 18-65 years BMI: 18 to 32 kg/m ² . A total of 20 patients were randomized to receive 20 mg/kg/day of CBD or placebo on a 4:1 basis.
Methodology	This was a phase 2, double-blind trial in which 20 patients on stable CLB treatment were randomized (4:1; active: placebo) to receive 20 mg/kg/day CBD or placebo from Days 2-33 (comprising an initial 10 day titration period followed by a 21 day maintenance period). CBD/placebo was taken twice daily (b.i.d.); immediately after the patients' CLB dose. Following the end of the treatment period (Visit 4, Day 34), patients were given the option of continuing into an open label extension (OLE) period (maximum 1 year) if the investigator and patient both agreed that it was in their best interests.

PK Sampling	Blood samples were taken by either direct venipuncture or an indwelling cannula inserted into a forearm vein at the following times: Predose, 15 and 30 minutes, then 1, 1.5, 2, 4, 6, 12 and 24 hours postdose. The timing of each PK sample was relative to the morning dose of CLB. The predose blood sample was taken within 30 minutes prior to dosing. The allowable window for postdose blood sample collection was ± 2 minutes up to and including 1 hour postdose, ± 5 minutes from 1.5 hours up to and including 6 hours post-dose and ± 1 hour at 12 hours and 24 hours postdose.
Pharmacokinetic Assessments	Plasma concentrations of CLB, N-CLB, and other concomitant AEDs were measured prior to the first CBD/placebo dose (Visit 2, Day 1), then again at the end of the maintenance period after multiple doses of CBD/placebo (Visit 4, Day 33). Plasma concentrations of CLB, N-CLB, other concomitant AEDs, CBD and its major metabolites, and $\Delta 9$ -tetrahydrocannabinol (THC) and its major metabolites were measured at the end of the maintenance period after multiple doses of GWP42003-P/placebo (Visit 4, Day 33): Cmax, Tmax, tlag, Kel, t1/2, CLss/F, Vz/F, AUC0-t, AUC0-inf and Frel.
Safety Assessments	Safety and tolerability assessments consisted of: AEs, clinical laboratory tests (biochemistry, hematology and urinalysis), vital signs, 12-lead ECG, physical examination and Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire, seizure frequency, abuse liability and cytochrome P450 (CYP) 2C19 and CYP3A4 patient genotype analysis.
Statistical Methods	For statistical analysis of a drug-drug interaction between CBD and CLB, a standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of Cmax, AUC(0-t), and AUC(0- ∞) was carried out on logarithmic scale using a linear mixed effect model. The no-effect boundary was set between 0.5 and 2.0 and if the 90% CI for the ratio of the geometric means of a PK variable fell within the interval [0.5, 2.0], a lack of meaningful effect was declared. Estimates were back transformed to provide summaries on the original scale. The model included a fixed effect term for PK assessment period. An unstructured covariance matrix was used. Kenward and Roger's method was used to calculate the denominator degrees of freedom for the fixed effects.

CLB is extensively metabolized in the liver via N-demethylation and hydroxylation, and has 2 major metabolites, N-CLB and 4'-hydroxyclobazam, the former of which is active. N-CLB is estimated to be one-fifth to equally as potent as CLB. The main enzyme that facilitates the process of N-demethylation is CYP3A4, and to a lesser extent CYP2C19 and CYP2B6. N-CLB is metabolized via hydroxylation, primarily by CYP2C19

Bioanalytical: 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.

Summary of control results for CBD and its metabolites are presented in the table below.

Analyte	CBD	7-OH-CBD	7-COOH-CBD
Internal standard	d3-CBD	d5-7-OH-CBD	d5-7-COOH-CBD
Lower limit of quantitation	1.000 ng/mL	0.2500 ng/mL	0.2500 ng/mL
Calibration Standards range	2.000 – 2000 ng/mL	0.25 – 250.0 ng/mL	0.25 – 250.0 ng/mL
Between Batch Precision (%CV)	2.2 to 9.6	4.2 to 7.0	3.1 to 9.0
Between Batch Accuracy (%RE/Bias%)	-2.1 to 1.6	-4.0 to 2.0	-4.4 to 2.3
Linearity	Weighted linear equation ($1/X^2$), mean $r= 0.9992$	Weighted linear equation ($1/X^2$), mean $r= 0.9958$	Weighted linear equation ($1/X^2$), mean $r= 0.9953$
Quality Control (QC) levels	Low QC 6.000 ng/mL Med QC 500.0 ng/mL High QC 1500 ng/mL	Low QC 0.7500 ng/mL Med QC 62.50 ng/mL High QC 187.5 ng/mL	Low QC 0.7500 ng/mL Med QC 62.50 ng/mL High QC 187.5 ng/mL
Between Batch Precision (%CV)	4.6 to 5.5	4.3 to 9.7	5.7 to 11.7
Between Batch Accuracy (%RE/Bias%)	1.4 to 4.4	0.6 to 5.8	3.0 to 6.8

RESULTS:

- When CBD was administered concomitantly with CLB for a duration of 31 days (10-day titration, 21 days at maintenance dose of 20 mg/kg/day), there was no evidence of a drug-drug interaction (DDI) between CBD and CLB; the Day 33:Day 1 ratio was 0.997 [0.834, 1.19] for C_{max} and 1.06 [0.898, 1.24] for AUC_{tau}.
- There was a significant DDI between CBD and N-CLB (the major CLB metabolite); the Day 33:Day 1 ratio was 2.22 [1.42, 3.46] for C_{max} and 2.64 [1.95, 3.58] for AUC_{tau}.

Geometric Mean Ratios of CLB and N-CLB PK Parameters on Day 33 Compared with Day 1 (PK Set)		
Parameter	Placebo (n=3)	GWP42003-P (n=10)
	Day 33:Day 1 Ratio [90% CI]	
CLB		
C_{max}	1.05 [0.401, 2.74]	0.997 [0.834, 1.19]
AUC_{tau}	0.996 [0.652, 1.52]	1.06 [0.898, 1.24]
N-CLB		
C_{max}	1.17 [0.628, 2.17]	2.22 [1.42, 3.46]
AUC_{tau}	1.00 [0.795, 1.27]	2.64 [1.95, 3.58]

- There was no effect of placebo on plasma concentrations of CLB, its major metabolite N-CLB, or any of the other AEDs.
- There was no effect of CBD on the PK of LEV (the most common other AED) and there were insufficient data to reach definite conclusions on any DDI between CBD and the PK of VPA (the only other analyzed AED taken concomitantly).
- There were no mutations or polymorphisms in CYP3A4 in any of the patients, and all were therefore classified as extensive metabolizers (EMs) for CYP3A4. Just over half (5/9) of patients tested did not have mutations or polymorphisms in CYP2C19 and were therefore classified as EMs. Exposure (C_{max} and AUC_{tau}) to both CBD and N-CLB in CYP2C19 ultrarapid metabolizers (UMs) and poor metabolizers (PMs) appeared to be generally consistent with their phenotype, although numbers were too low to draw conclusions on pharmacogenetics.

CONCLUSIONS:

- Cannabidiol did not alter the C_{max} or AUC of CLB. However there was a significant DDI between CBD and N-CLB (the major CLB metabolite); 2.22 [1.42, 3.46] for C_{max} and 2.64 [1.95, 3.58] for AUC_{tau}.
- There was no effect on the PK parameters of LEV when combined with CBD. It was not possible to conclude on the potential for a DDI with VPA, STP or TPM because of limited data.

Study GWEP17028: A Phase 1, Open-label, Fixed Sequence Crossover Trial to Investigate the Effect of Cannabidiol (GWP42003-P; CBD) on the CYP3A4 Probe Midazolam in Healthy Subjects

Objectives:

Primary Objective: To investigate the effect of CBD treatment following repeated dosing on the pharmacokinetics (PK) of a single dose of midazolam in healthy male and female subjects.

Secondary Objective: To evaluate the safety and tolerability of GWP42003-P when given with a single dose of midazolam in healthy male and female subjects.

Study Design	This study was a phase 1, open-label, single site, fixed sequence crossover
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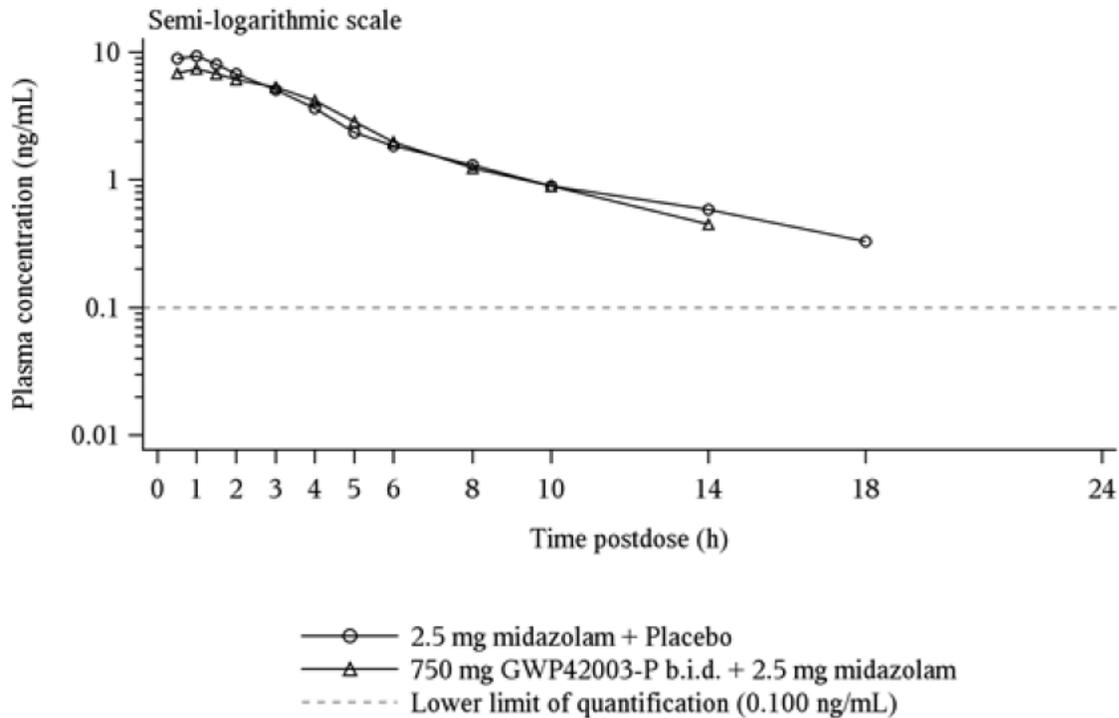
	trial
Study Population	Healthy subjects (male or female) Age: 18-60 years BMI: 18.5 to 30 kg/m ² . A total of 16 subjects were planned and enrolled.
Methodology	All subjects received a concurrent single oral dose of CBD-matched placebo and 2.5 mg midazolam on Day -1. Subjects self-administered escalating doses of CBD with food from Day 1 (250 mg once daily) to Day 11 (750 mg twice daily), followed by 14 days of 750 mg CBD b.i.d. (Days 12-25). On Day 25, subjects received a 2.5 mg oral dose of midazolam concurrently with the morning dose of CBD
PK Sampling	Blood samples were collected for analysis of midazolam and its metabolites Predose, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 14, 18 and 24 hours postdose and on Day 25. The timing of each PK sample was relative to the morning dose of CLB. For analysis CBD concentration blood samples were collected predose on Day 22, 24 and 25. At specified times approximately 6 mL of blood was collected by venipuncture or cannulation for the determination of plasma concentrations of CBD, midazolam and 1'-hydroxymidazolam. Validated liquid chromatographic-tandem mass spectrometric bioanalytical methods were used to quantify plasma concentrations of the above analytes.
Pharmacokinetic Assessments	Blood samples were collected for the analysis of midazolam and its major metabolite 1'-hydroxymidazolam in plasma. Blood samples were also taken for analysis of cannabidiol (CBD) concentrations in plasma at steady-state. The following primary PK parameters were determined for midazolam: area under the concentration-time curve (AUC) from time zero to infinity (AUC(0-∞)); AUC from time zero to the last observable concentration at time t (tlast, AUC(0-t)); maximum observable plasma concentration (Cmax) and time to maximum plasma concentration (tmax). The secondary endpoints were other PK parameters for midazolam (such as apparent plasma terminal [elimination] half-life [t1/2]), predose concentrations (Ctrough) of CBD on Days 22, 24 and 25, all PK parameters for 1'-hydroxymidazolam, and metabolic ratio (MR) based on AUC (MRAUC) and Cmax (MRCmax).
Safety Assessments	Safety endpoints for this trial include adverse events (AEs), vital sign measurements, 12-lead electrocardiograms (ECG), clinical laboratory evaluations, physical examinations, pulse oximetry measurements and Columbia-Suicide Severity Rating Scale (C-SSRS) assessment.
Statistical Methods	PK parameter estimates were evaluated to assess the change in PK parameters of midazolam alone (Reference) and midazolam following multiple dosing of GWP42003-P (Test). Log transformed Cmax, AUC(0-∞), and AUC(0-t) parameters for midazolam and 1'-hydroxymidazolam were analyzed using a linear mixed-effects model with a fixed effect for treatment and a random effect for subject. The treatment differences were back-transformed to present the ratios of geometric means and the

corresponding 90% confidence intervals (CIs). For tmax, a nonparametric analysis of the same comparisons was performed using a Wilcoxon signed-rank test. Medians and median differences between the treatments were presented along with the approximate 90% CI for the median difference. Geometric mean ratios and 90% CIs were used to estimate the magnitude of any interaction and were interpreted based on clinical relevance

RESULTS:

Following figure represents PK profile of midazolam following single oral dose administration of 2.5 mg Midazolam on day 1 and following concomitant administration at steady state CBD.

Geometric Mean Plasma Concentrations of Midazolam Following Single Oral Dose Administration of 2.5 mg Midazolam + Placebo (Day -1) or 2.5 mg Midazolam + Steady State 750 mg Cannabidiol b.i.d. (Day 25)



The PK parameters of midazolam (2.5 mg midazolam with and without steady state 750 mg GWP42003-P b.i.d. treatment) are presented in Table below.

Parameter	2.5 mg Midazolam + Placebo (N=16)	2.5 mg Midazolam + 750 mg GWP42003-P b.i.d. (N=14) ^a
Midazolam Pharmacokinetic Parameters		

AUC(0-t) (ng·h/mL)	41.9 (33.6)	39.4 (36.1)
AUC(0-∞) (ng·h/mL)	43.2 (33.8)	40.6 (35.8)
C _{max} (ng/mL)	10.2 (35.2)	8.34 (39.9)
t _{max} ^b (h)	0.50 (0.48-2.00)	1.00 (0.5-3.00)
t _{last} ^b (h)	23.83 (17.98-23.93)	24.00 (14.00-24.05)
t _{1/2} ^c (h)	4.99 (13.1)	4.53 (14.5)
CL/F (L/h)	57.8 (33.8)	61.6 (35.8)
1-hydroxy-midazolam Pharmacokinetic Parameters		
AUC(0-t) (ng·h/mL)	14.1 (24.9)	23.5 (43.5)
AUC(0-∞) (ng·h/mL)	15.2 (23.7) ^d	32.2 (38.9) ^e
C _{max} (ng/mL)	3.69 (34.4)	4.10 (40.3)
t _{max} ^b (h)	0.50 (0.48-1.55)	3.00 (0.50-5.02)
t _{last} ^b (h)	16.00 (13.98-23.87)	24.00 (14.00-24.05)
t _{1/2} ^c (h)	6.11 (39.0) ^d	8.23 (64.9) ^e
MR AUC(0-t)	0.338 (34.5)	0.597 (20.3)
MR AUC(0-∞)	0.349 (34.6) ^d	0.619 (20.5) ^e
MR C _{max}	0.362 (36.8)	0.492 (21.4)
Geometric mean (geometric mean CV%) data are presented unless otherwise stated.		
a Two subjects were withdrawn from the trial due to TEAEs (see Safety Results).		

Systemic exposure to midazolam was relatively unaffected by concomitant administration of CBD.

The treatment ratios based on AUC(0-t) and AUC(0-∞) were 0.922 (90% CI: 0.778, 1.09) and 0.921 (90% CI: 0.776, 1.09), respectively, and C_{max} was reduced by 20% (ratio [point estimate] of 0.799 [90% CI: 0.667, 0.956]).

1'-hydroxymidazolam AUC was increased by CBD (treatment ratios: AUC(0-t), 1.68 [90% CI: 1.41, 2.01]; AUC(0-∞), 2.11 [90% CI: 1.65, 2.71]), accompanied by a delay to t_{max} (median of differences of 2.25 hours [90% CI: 1.00, 2.52]) and a small increase in t_{1/2}, although C_{max} was unaffected (treatment ratio: 1.12 [90% CI: 0.929, 1.34]).

This effect could not be attributed to a CYP3A4-mediated interaction as midazolam was unaffected.

Reviewer's Comment: The increase exposure to 1'-hydroxymidazolam may be due to inhibition of downstream metabolism of 1'-hydroxymidazolam by CBD probably due to inhibition of glucuronidation by UGT2B7. CBD was an inhibitor of UGT1A9 and 2B7 in both Supersomes™ and HLMs in vitro with nanomolar potency (IC₅₀ 19.2 to 317 nM).

Pharmacogenetic:

CYP2C19, CYP2D6 and CYP3A4 phenotypes were ranked as follows:

- CYP2C19: Other (15/16) > poor metabolizer (PM) (1/16).
- CYP2D6: extensive metabolizer (EM) (11/16) > Other (3/16) > PM (2/16).
- CYP3A4/5: intermediate metabolizer (11/16) > EM (4/16) > PM (1/16).

In this limited subject group there were no notable differences in trough CBD plasma concentrations based on CYP2C19, CYP2D6 or CYP3A4/5 phenotypes. The 1 CYP3A4/5 PM had higher midazolam exposures than the 4 EMs. There was overlap in 1'-hydroxymidazolam exposures between the different CYP3A4/5 phenotypes.

CONCLUSIONS:

- At cannabidiol steady state concentrations, systemic exposure (C_{max} and AUC) to midazolam and its $t_{1/2}$ were relatively unaffected by concomitant administration of midazolam. Midazolam is a sensitive/probe CYP3A substrate. This indicates that cannabidiol does not have inhibitory or induction potential mediated through CYP3A.
- The increase exposure to 1'-hydroxymidazolam by approximately 2 fold may be due to inhibition of downstream metabolism of 1'-hydroxymidazolam by CBD probably due to inhibition of glucuronidation by UGT2B7. CBD was shown to be an inhibitor of UGT1A9 and 2B7 in vitro with nanomolar potency.

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