1.545 Phase 1, Open-Label, Fixed-Sequence, Bidirectional, Pharmacokinetic Drug-Drug Interaction Study Between Cannabidiol and Cenobamate in Healthy Adult Participants

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Introduction

- Antiseizure medications (ASMs) are often used in combination to improve seizure control in people with epilepsy[1]
- Plant-derived, highly purified cannabidiol (CBD; Epidiolex®/Epidyolex®, 100 mg/mL oral solution) is approved for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS), Dravet syndrome (DS), and tuberous sclerosis complex (TSC)[2]
  - Maximum approved dose is 20 mg/kg/day for LGS and DS; 25 mg/kg/day for TSC
- Recent therapeutic drug monitoring data showed absence of pharmacokinetic (PK) drug-drug interaction (DDI) for the parent molecules of CBD and cenobamate (CNB)[3]
- CBD is primarily metabolized to 7-OH-CBD and 7-COOH-CBD via CYP2C19 and CYP3A4; CBD and its metabolites are reversible inhibitors of UGT2B7 in vitro but do not affect UGT2B7-mediated metabolism in vivo[4]
- CNB is primarily metabolized to CNB-glucuronide, an inactive metabolite, via UGT2B7; CNB is a moderate inhibitor of CYP2C19 and inducer of CYP3A4[1]
- It has been speculated that a PK DDI between CBD and CNB may result in dose-related central nervous system adverse events (AEs) when administered concomitantly[1]; however, there has been no formal investigation of PK DDI between CBD and CNB to date

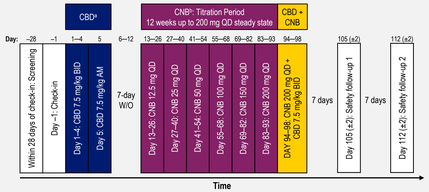
Objective

- A phase 1, open-label, interventional study to evaluate bidirectional PK DDIs between CBD and CNB when concomitantly administered at clinically relevant doses in healthy adults

Methods

- Healthy adults (aged 18–55 years) received CBD 7.5 mg/kg twice daily (BID) on Day (D) 1–D4 followed by a morning dose only on D5. After a 7-day washout period of CBD, participants underwent a 12-week CNB titration according to its USPI, starting at 12.5 mg once daily (QD), followed by 25 mg QD, 50 mg QD, and then increased to 50 mg every 2 weeks until 200 mg QD on D83–D93. Participants received both CBD 7.5 mg/kg BID and CNB 200 mg QD for 5 days (**Figure 1**)
- Blood samples for PK assessments were collected on D5 (CBD alone as reference), D93 (CNB alone as reference), and D98 (CBD + CNB as test)
- Area under the concentration–time curve ($AUC_{0\text{-}12h}$ for CBD, 7-OH-CBD, and 7-COOH-CBD; $AUC_{0\text{-}24h}$ for CNB and CNB-glucuronide) and maximum observed plasma concentration (C_{max}) were obtained and assessed with geometric least-squares mean (GLSM) ratios and associated 90% CIs for CBD + CNB vs each ASM alone
- Safety information was collected from the start of intervention until the follow-up visit and included incidence and severity of treatment-emergent AEs (TEAEs)
- DNA samples were collected for pharmacogenomic analysis of SNP variants related to CYP and UGT metabolism
- This study was conducted with Epidiolex®, and the results do not apply to other CBD-containing products

Figure 1. Study schema



*CBD was dosed 30 minutes after starting a standard-calorie meal. †CNB was dosed in the morning, 30 minutes after starting a standard-calorie meal (when participant was in clinic), or with or without food (when participant dosed at home).
Participants attended an in-clinic screening visit and stayed from check-in (Day –1) to Day 6 for CBD dosing. After washout, participants returned on Day 12 for CNB titrations, with 4-day stays for each titration for the first 5 titrations and a final stay from Day 82 through Day 99, followed by 2 visits.
BID, twice daily; CBD, cannabidiol; CNB, cenobamate; QD, once daily; W/O, washout.

Results

Table 1. Demographics

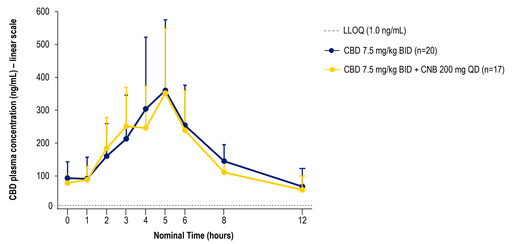
Overall (N=20)	Age, years, mean (SD)	Sex, n (%)		Weight, kg Mean (SD)	BMI, kg/m² Mean (SD)
		Male	Female		
	33.8 (10.3)	17 (85.0)	3 (15.0)	80.1 (11.3)	26.2 (2.6)

BMI, body mass index.

- Twenty healthy participants were included: mean (SD) age was 33.8 (10.3) years, 17 (85%) were male, and mean (SD) weight was 80.1 kg (11.3) (**Table 1**)
- Seventeen participants received concomitant CBD and CNB; 1 participant discontinued due to an AE during CBD treatment alone and 2 participants discontinued (1 due to an AE; 1 due to study exclusion criteria) during CNB treatment alone

Figure 2. Mean (SD) plasma concentration–time profiles of (A) CBD and (B) CNB

A.



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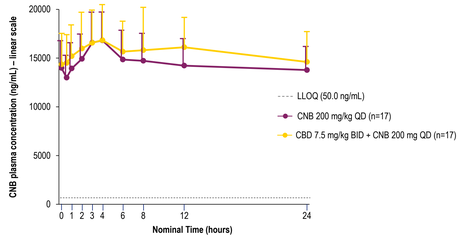


BID, twice daily; CBD, cannabidiol; CNB, cenobamate; LLOQ, lower limit of quantification; QD, once daily.

- Similar concentration-time profiles of the CBD parent molecule are observed when CBD is given alone as compared to when concomitantly administered with CNB (**Figure 2A**)
- Similar concentration-time profiles of the CNB parent molecule are observed when CNB is given alone as compared to when concomitantly administered with CBD (**Figure 2B**)
- Mean plasma concentration-time profiles were decreased for CBD metabolites (7-OH-CBD and 7-COOH-CBD) and increased for the CNB metabolite (CNB-glucuronide) when CBD and CNB were concomitantly administered compared to either administered alone; presented in **Figure S1**

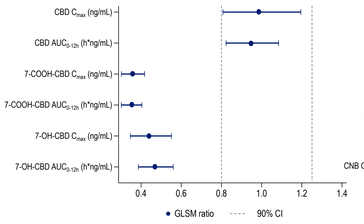
Table 2. Pharmacokinetic parameters and GLSM ratio (%) (90% CI) for CNB plus CBD vs each alone

PK parameters		Geomean (Geo CV%[a])		GLSM ratio test vs reference (%) (90% CI for ratio [%])
		Test (n=17)	Reference (n)	
		CNB 200 mg QD + CBD 7.5 mg/kg BID	CBD 7.5 mg/kg BID (n=20)	
CBD	$AUC_{0\text{-}12}$ (ng·h/mL)	1847 (31.8)	1975 (32.2)	94.3 (82.1, 108.3)
	C_{max} (ng/mL)	382 (42.0)	394 (40.7)	98.1 (80.5, 119.5)
7-OH-CBD	$AUC_{0\text{-}12}$ (ng·h/mL)	514 (40.9)	1121 (52.4)	46.4 (38.4, 55.9)
	C_{max} (ng/mL)	82.1 (38.6)	190 (53.4)	43.6 (34.5, 55.0)
7-COOH-CBD	$AUC_{0\text{-}12}$ (ng·h/mL)	20,477 (41.1)	60,317 (60.5)	34.8 (30.1, 40.2)
	C_{max} (ng/mL)	2169 (41.3)	6248 (59.3)	35.4 (30.1, 41.6)
		CNB 200 mg QD + CBD 7.5 mg/kg BID	CNB 200 mg QD (n=17)	
Cenobamate	$AUC_{0\text{-}24}$ (ng·h/mL)	368,346 (19.0)	342,342 (17.3)	107.6 (104.9, 110.4)
	C_{max} (ng/mL)	17,318 (20.3)	16,976 (16.5)	102.0 (98.2, 106.0)
Cenobamate Glucuronide	$AUC_{0\text{-}24}$ (ng·h/mL)	34,099 (13.0)	24,175 (13.7)	141.1 (136.2, 146.0)
	C_{max} (ng/mL)	1582 (12.9)	1137 (13.2)	139.1 (133.1, 145.4)

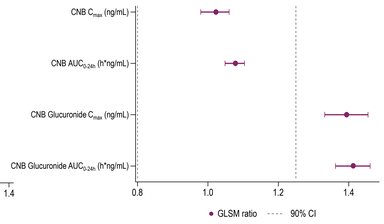
$AUC_{0\text{-}\tau}$, area under the concentration–time curve from time zero to time postdose; BID, twice daily; C_{max}, maximum observed plasma concentration; CBD, cannabidiol; CNB, cenobamate; CV%, percent coefficient of variation; GLSM, geometric least-squares mean; PK, pharmacokinetic; QD, once daily.

Figure 3. GLSM ratios of pharmacokinetic parameters following doses of CNB plus CBD vs each alone

A. CBD and metabolites (CBD + CNB [n=17) vs CBD alone [n=20])



B. CNB and metabolite (CBD + CNB [n=17) vs CNB alone [n=17])



$AUC_{0\text{-}\tau}$, area under the plasma concentration–time curve from time zero to the last observable concentration at time t; BID, twice daily; C_{max}, maximum observed plasma concentration; CBD, cannabidiol; CNB, cenobamate; GLSM, geometric least-squares mean.

Effect of CNB on CBD pharmacokinetics (**Table 2 and Figure 3A**)

- Coadministration of CBD with CNB did not result in changes in C_{max} and $AUC_{0\text{-}12}$ of CBD compared with CBD administration alone
  - GLSM ratio and 90% CI for CBD were within the 80–125% bioequivalence criteria
- Coadministration of CBD with CNB resulted in a decrease in C_{max} and $AUC_{0\text{-}12}$ of ~55% for 7-OH-CBD and ~65% for 7-COOH-CBD compared with CBD administration alone

Effect of CBD on CNB pharmacokinetics (**Table 2 and Figure 3B**)

- Coadministration of CBD with CNB did not result in changes in C_{max} and $AUC_{0\text{-}24}$ of CNB compared with CNB administration alone
  - GLSM ratio and 90% CI for CNB were within the 80-125% bioequivalence criteria
- Coadministration of CBD with CNB resulted in a ~40% increase in C_{max} and $AUC_{0\text{-}24}$ for CNB-glucuronide compared with CNB administration alone

Effect of CYP2C19 phenotype on CBD and its metabolites

- Across all observed CYP2C19 metabolizer phenotypes (normal, intermediate, and rapid), the $AUC_{0\text{-}12h}$ and C_{max} of CBD and its metabolites were similar for CBD alone and when concomitantly administered with CNB

Effect of UGT2B7 phenotype on CNB and its metabolite

- Across all observed UGT2B7 phenotypes (normal and decreased activity), the $AUC_{0\text{-}24h}$ and C_{max} of CNB and its metabolite were similar for CNB alone and in combination with CBD

Table 3. Summary of treatment-emergent adverse events (safety analysis set)

	CBD (n=20) n (%)	CNB (n=19) n (%)	CBD + CNB (n=17) n (%)	Overall (n=20) n (%)
Number of participants reporting at least 1 TEAE	**10 (50.0)**	**12 (63.2)**	**4 (23.5)**	**15 (75.0)**
Mild	7 (35.0)	8 (42.1)	4 (23.5)	9 (45.0)
Moderate	3 (15.0)	4 (21.1)	0	6 (30.0)
Number of participants reporting related TEAEs				
TEAEs related to CBD	6 (30.0)	2 (10.5)	4 (23.5)	8 (40.0)
TEAEs related to CNB	0	10 (52.6)	4 (23.5)	12 (60.0)
Number of participants reporting TEAEs leading to discontinuation from study	**1 (5.0)**	**1 (5.3)**	**0**	**2 (10.0)**

CBD, cannabidiol; CNB, cenobamate; TEAEs, treatment-emergent adverse events.

- The most commonly reported AEs overall (occurring in ≥25% of participants) were headache (25%) and diarrhea (40%)
- Dizziness was reported in 1 participant in CBD alone and CNB alone, and somnolence in 1 participant in the CNB alone group
- Two participants discontinued due to dermatology-related AEs of rash (moderate; 1 CBD alone) and dermatitis (mild; 1 CNB alone)
- No serious AEs, severe AEs, or deaths were reported (**Table 3**)

Limitations

- PK and safety conclusions were based on 5 days of concomitant CBD and CNB administration in healthy volunteers at the specified doses (7.5 mg/kg BID for CBD and 200 mg QD for CNB), which may differ with higher dosage or longer durations of dosing

Conclusions

- No PK interactions were observed for CBD and CNB parent molecules when the two were administered concomitantly at clinically relevant dosages. The clinical significance of reduced CBD metabolite exposures is unknown
- There were no clear trends between CYP2C19 phenotype status and exposure of CBD and its metabolites, or between UGT2B7 activity phenotype status and exposure of CNB and its metabolite
- Coadministration of CBD 7.5 mg/kg BID and CNB 200 mg QD for 5 days showed no evidence of increased or worsening AEs compared with either dosed alone
- These PK DDI results do not support a reduction in CBD dosage when CNB and CBD are concomitantly administered

References: **1.** Smith MC, et al. *Neurol Ther.* 2022;11(4):1705-1720. **2.** Epidiolex® (cannabidiol) oral solution. Prescribing information. Jazz Pharmaceuticals; 2025. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210365s023lbl.pdf. (Accessed September 25, 2025.) **3.** Belikilani H, et al. Clinically relevant pharmacokinetic interactions with cenobamate. IEC; 2025. Abstract 1525. **4.** Vijan A, et al. Investigating the effect of steady state cannabidiol on the single dose pharmacokinetics of CYP2B6, CYP2C9, UGT2B7, and UGT1A9 substrates. IEC; 2025. P166.
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Epidiolex® is approved in the US for the treatment of seizures associated with Lennox-Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex in patients ≥1 year of age.

Poster presented at American Epilepsy Society Annual Meeting, December 5–9, 2025; Atlanta, GA, USA

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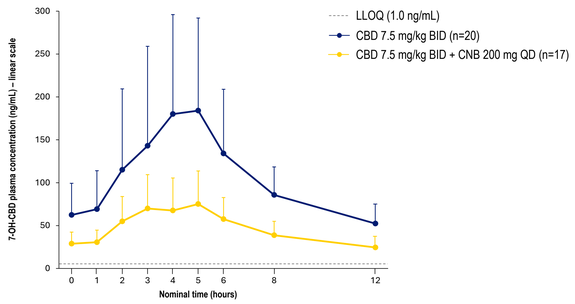
Supplementary Material

Figure S1. Mean (SD) plasma concentration–time profiles of (A) 7-OH-CBD, (B) 7-COOH-CBD, and (C) CNB-glucuronide

A.



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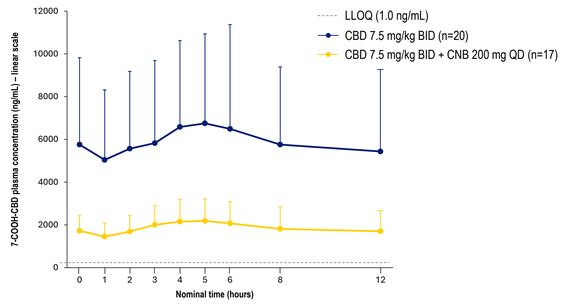

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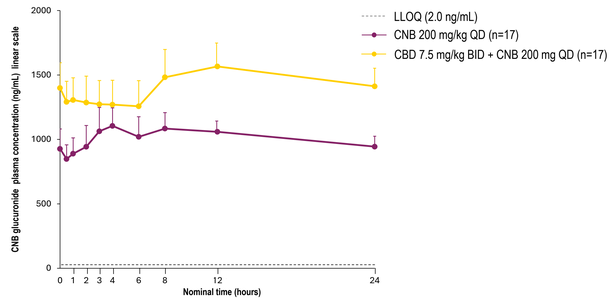

Note: Cenobamate glucuronide is a highly hydrophilic molecule, which is rapidly eliminated.
BID, twice daily; CBD, cannabidiol; CNB, cenobamate; LLOQ, lower limit of quantification; QD, once daily.

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