

# Phase 1, Open-Label, Fixed-Sequence, Bidirectional, Pharmacokinetic (PK) Drug-Drug Interaction (DDI) Study Between Cannabidiol (CBD) and Cenobamate (CNB) in Healthy Adult Participants

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## Objective

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



## 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
  - 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 dosages or longer durations of dosing

First presented at the American Epilepsy Society Annual Meeting, 2025.

References: 1. Smith MC, et al. *Neurol Ther*. 2022;11(4):1705–1720. 2. US Food and Drug Administration. Epidiolex® Prescribing Information, 2025. Available from: [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2025/210365s023lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/210365s023lbl.pdf). (Accessed 25 September 2025). 3. Bekkiani H, et al. Presented at the International Epilepsy Congress 2025 Annual Meeting, 30 August–3 September 2025; Lisbon, Portugal. Abstract 1525. 4. Vijan A, et al. Presented at the International Epilepsy Congress 2025 Annual Meeting, 30 August–3 September 2025; Lisbon, Portugal. Poster 166.

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**Disclosures:** All authors met ICMJE authorship criteria and had full access to relevant data. Neither honoraria nor payments were made for authorship. AV, HX, PC, SM, and CC are employees of Jazz Pharmaceuticals, Inc., and hold stock and/or stock options in Jazz Pharmaceuticals, Inc.

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.



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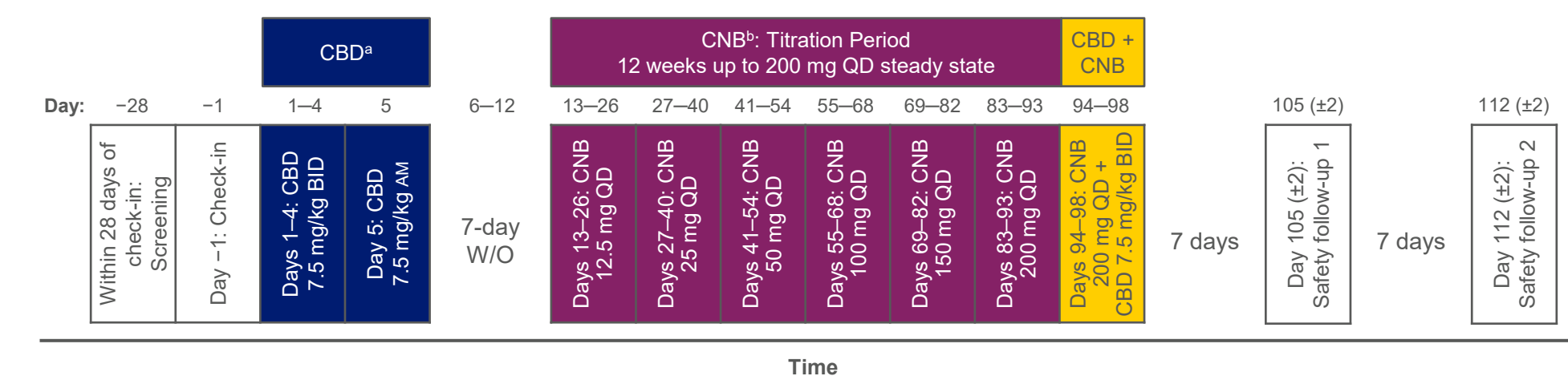
## Introduction

- Antiseizure medications (ASMs) are often used in combination to improve seizure control in people with epilepsy<sup>1</sup>
- 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)<sup>2</sup>
  - 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 a pharmacokinetic (PK) drug-drug interaction (DDI) for the parent molecules of CBD and cenobamate (CNB)<sup>3</sup>
- 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<sup>4</sup>
- CNB is primarily metabolized to CNB-glucuronide, an inactive metabolite, via UGT2B7; CNB is a moderate inhibitor of CYP2C19 and inducer of CYP3A4<sup>1</sup>
- 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<sup>1</sup>; however, there has been no formal investigation of a PK DDI between CBD and CNB to date

## 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 titration of CNB according to its USPI, starting at 12.5 mg once daily (QD), followed by 25 mg QD, 50 mg QD, and then increased by 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 ( $AUC_{0-12h}$  for CBD, 7-OH-CBD, and 7-COOH-CBD;  $AUC_{0-24h}$  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 versus 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

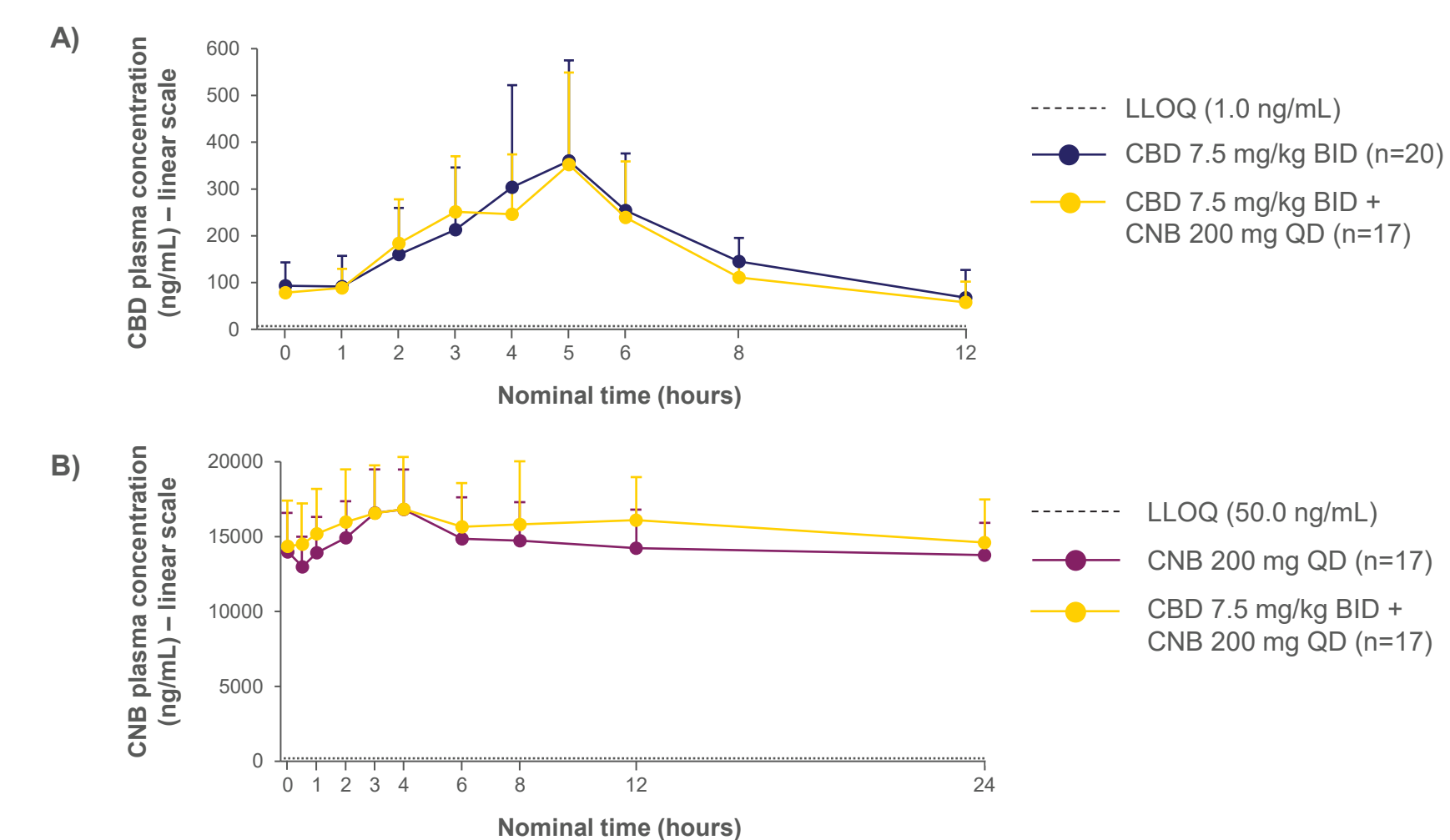
Table 1. Demographics

| Overall (N=20) | Age, years<br>Mean (SD) | Sex, n (%) |          | Weight, kg<br>Mean (SD) | BMI, kg/m <sup>2</sup><br>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



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

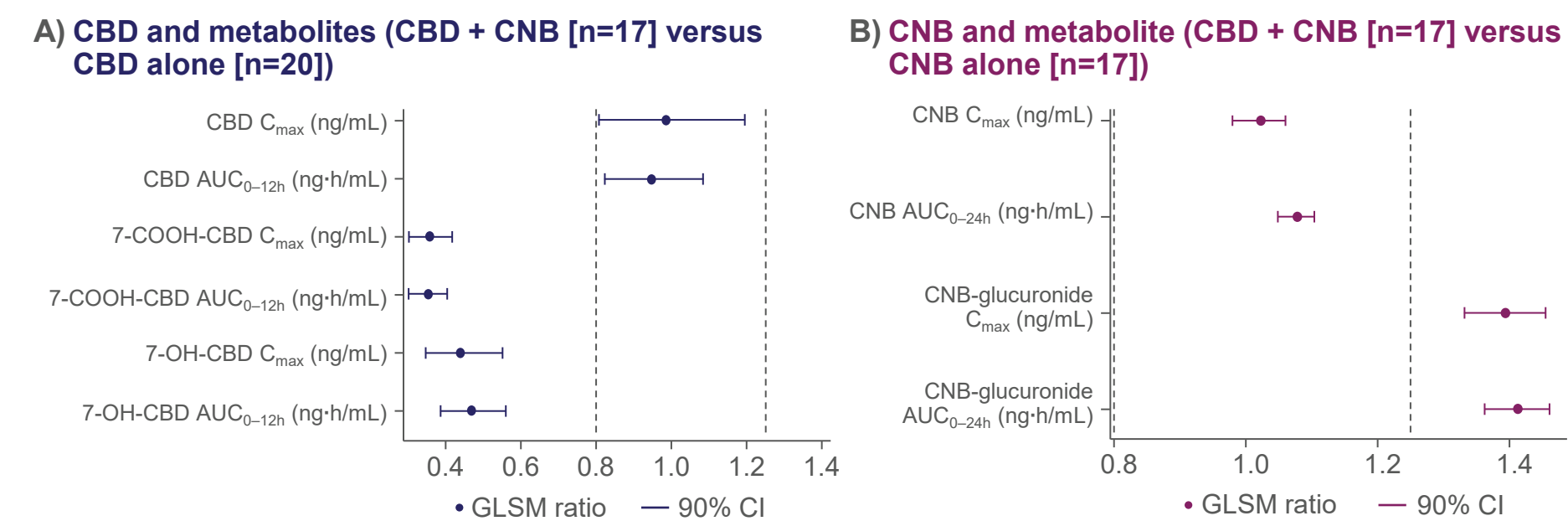
- Similar concentration–time profiles of the CBD parent molecule were observed when CBD was given alone as compared to when concomitantly administered with CNB (**Figure 2A**)
- Similar concentration–time profiles of the CNB parent molecule were observed when CNB was given alone as compared to when concomitantly 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 when either was administered alone; please refer to QR code below for **Figure 3**

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

|                        | PK parameters          | Geomean (Geo CV%)                                   |   | GLSM ratio test vs reference (%)<br>(90% CI for ratio [%]) |
|------------------------|------------------------|---|---|--|
|                        |                        | Test (n=17)   | Reference (n)                           |  |
| CBD                    | $AUC_{0-12}$ (ng·h/mL) | CNB 200 mg QD + CBD 7.5 mg/kg BID<br>1847 (31.8)    | CBD 7.5 mg/kg BID (n=20)<br>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               | $AUC_{0-12}$ (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             | $AUC_{0-12}$ (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)  |
| Cenobamate             | $AUC_{0-24}$ (ng·h/mL) | CNB 200 mg QD + CBD 7.5 mg/kg BID<br>368,346 (19.0) | CNB 200 mg QD (n=17)<br>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 | $AUC_{0-24}$ (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)                                       |

$AUC_{0-12}$ , area under the concentration–time curve from time zero to 12 hours postdose;  $AUC_{0-24}$ , area under the concentration–time curve from time zero to 24 hours postdose; BID, twice daily; CBD, cannabidiol;  $C_{max}$ , maximum observed plasma concentration; 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 versus each alone



$AUC_{0-12}$ , area under the concentration–time curve from time zero to 12 hours postdose;  $AUC_{0-24}$ , area under the concentration–time curve from time zero to 24 hours postdose; CBD, cannabidiol;  $C_{max}$ , maximum observed plasma concentration; 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  $AUC_{0-12}$  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  $AUC_{0-12}$  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  $AUC_{0-24}$  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  $AUC_{0-24}$  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  $AUC_{0-12h}$  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  $AUC_{0-24h}$  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)

| Number of participants                           | CBD (n=20)<br>n (%) | CNB (n=19)<br>n (%) | CBD + CNB (n=17)<br>n (%) | Overall (N=20)<br>n (%) |
|--|---------------------|---------------------|---------------------------|-------------------------|
| Reporting ≥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)                |
| 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)               |
| Reporting TEAEs leading to study discontinuation | 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 with CBD alone and 1 with CNB alone, and somnolence in 1 participant in the CNB-alone group
- Two participants discontinued due to dermatology-related AEs of rash (moderate; 1 with CBD alone) and dermatitis (mild; 1 with CNB alone)
- No serious AEs, severe AEs, or deaths were reported (**Table 3**)

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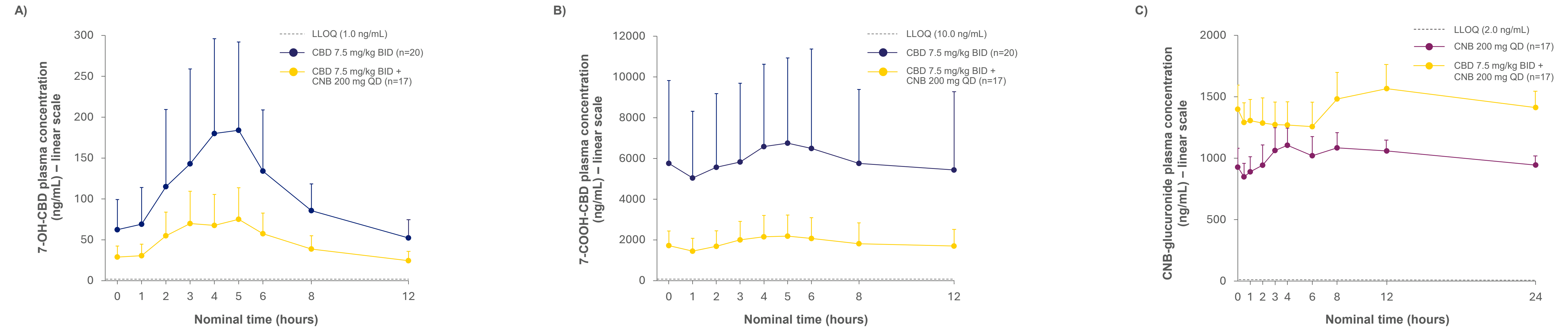
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### Supplementary Material

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



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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