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CRITICAL REVIEW – INVITED COMMENTARY

Epilepsia®

Clinical implications of trials investigating drug-drug interactions between cannabidiol and enzyme inducers or inhibitors or common antiseizure drugs

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Abstract

Highly purified cannabidiol (CBD) has demonstrated efficacy with an acceptable safety profile in patients with Lennox-Gastaut syndrome or Dravet syndrome in randomized, double-blind, add-on, controlled phase 3 trials. It is important to consider the possibility of drug-drug interactions (DDIs). Here, we review six trials of CBD (Epidiolex/Epidyolex; 100 mg/mL oral solution) in healthy volunteers or patients with epilepsy, which investigated potential interactions between CBD and enzymes involved in drug metabolism of common antiseizure drugs (ASDs). CBD did not affect CYP3A4 activity. Induction of CYP3A4 and CYP2C19 led to small reductions in exposure to CBD and its major metabolites. Inhibition of CYP3A4 activity did not affect CBD exposure and caused small increases in exposure to CBD metabolites. Inhibition of CYP2C19 activity led to a small increase in exposure to CBD and small decreases in exposure to CBD metabolites. One potentially clinically important DDI was identified: combination of CBD and clobazam (CLB) did not affect CBD or CLB exposure, but increased exposure to major metabolites of both compounds. Reduction of CLB dose may be considered if adverse reactions known to occur with CLB are experienced when it is coadministered with CBD. There was a small increase of exposure to stiripentol (STP) when coadministered with CBD. STP had no effect on CBD exposure but led to minor decreases in exposure to CBD metabolites. Combination of CBD and valproate (VPA) did not cause clinically important changes in the pharmacokinetics of either drug, or 2-propyl-4-pentenoic acid. Concomitant VPA caused small increases in exposure to CBD metabolites. Dose adjustments are not likely to be necessary when CBD is combined with STP or VPA. The safety results from these trials were consistent with the known safety profile of CBD. These trials indicate an overall low potential for DDIs between CBD and other ASDs, except for CLB.

KEYWORDS
clobazam, Dravet syndrome, Lennox-Gastaut syndrome, stiripentol, valproate

1 | INTRODUCTION

Seizures associated with Lennox-Gastaut syndrome (LGS) and Dravet syndrome (DS) severely impact quality of life, cognition, behavior, morbidity, and mortality in patients with these epileptic encephalopathies.[1–5] These seizures are highly treatment resistant,[6,7] and administration of multiple antiseizure drugs (ASDs) is therefore common.[6,8,9] Clinicians should give due consideration to the potential for drug-drug interactions (DDIs) among patients receiving multiple ASDs.

Highly purified cannabidiol (CBD) is approved in the USA as Epidiolex (Greenwich Biosciences, Inc.) for the treatment of seizures associated with LGS, DS, or tuberous sclerosis complex (TSC) in patients ≥1 years of age, and is also approved in the EU as Epidyolex (GW Pharma [International] B.V.) in conjunction with clobazam (CLB) for LGS and DS in patients ≥2 years of age.[10,11] In four randomized, controlled phase 3 trials, CBD has demonstrated efficacy with an acceptable safety profile in patients with LGS or DS.[12–15]

In vitro and in vivo studies of CBD have demonstrated that it is subject to extensive hepatic metabolism by enzymes of the cytochrome P450 (CYP) family, as well as uridine 5′-diphospho-glucuronosyltransferases (UGTs). 7-hydroxy-cannabidiol (7-OH-CBD) is a first-step metabolite of CBD,[16] while 7-carboxy-cannabidiol (7-COOH-CBD) is the most abundant metabolite in human plasma.[17,18] The formation of 7-OH-CBD from CBD is predominantly metabolized by CYP2C19, while CYP3A4 may also catalyze this biotransformation.[16,17] Both CBD and hydroxylated metabolites of CBD also undergo direct conjugation by UGTs.[17]

Induction or inhibition of CYP enzymes is a major mechanism that underlies DDIs.[19] It is important to consider the possibility of DDIs between CBD and other ASDs, as it is anticipated that CBD will be used concomitantly with other ASDs, notwithstanding the requirement of CBD to be used in conjunction with CLB in patients with LGS or DS in the

Key Points

- Six trials of highly purified CBD investigated potential interactions between CBD and common antiseizure drugs
- CBD did not affect CYP3A4 activity; induction or inhibition of CYP3A4 and CYP2C19 activity led to small changes in exposure to CBD and CBD metabolites
- CBD and valproate did not cause clinically important changes in exposure to either drug, while CBD and STP led to a small increase in exposure to STP
- Combination of CBD and clobazam led to a significant increase in exposure to major metabolites of both compounds
- Safety results were consistent with the known safety profile of CBD

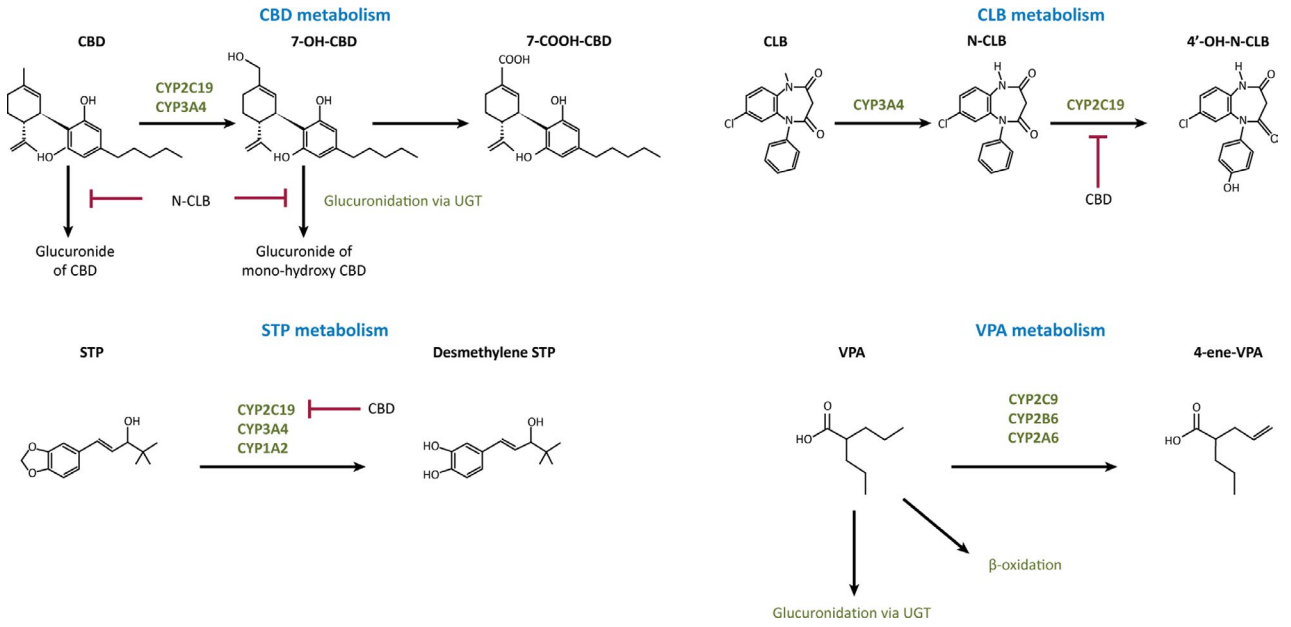

FIGURE 1 Biotransformation of antiseizure drugs and their major CYPs and UGTs, including potential for drug-drug interactions.[16,17,21,23–26,51] 4-ene-VPA, 2-propyl-4-pentenoic acid; 4′-OH-N-CLB, 4′-hydroxy-N-desmethylclobazam; 7-COOH-CBD, 7-carboxy-cannabidiol; 7-OH-CBD, 7-hydroxy-cannabidiol; CBD, cannabidiol; CLB, clobazam; CYP, cytochrome P450; N-CLB, N-desmethylclobazam; STP, stiripentol; UGT, uridine 5′-diphospho-glucoronosyltransferase; VPA, valproate

EU.[11] Several ASDs, notably CLB, valproate (VPA), and stiripentol (STP), are commonly used in the first- and second-line treatment of LGS and DS.[4,6,7]

CBD, CLB, STP, and VPA all interact with and utilize CYP and UGT enzymes. There is thus potential for DDIs between CBD and these ASDs, and also their major metabolites (Figure 1). CBD potently inhibits CYP3A4 and CYP2C19 in human liver microsomes, and UGT1A9 and UGT2B7 in vitro.[20–22] Preclinical studies therefore demonstrate the potential for an interaction between CBD and CYP enzymes in humans. CLB is metabolized by CYP3A4 and CYP2C19 to form the major active metabolite, N-desmethylclobazam (N-CLB),[23] which is further metabolized by CYP2C19.[23] N-CLB is a weak UGT inhibitor.[24] STP is metabolized by CYP1A2, CYP2C19, and CYP3A4,[25] and is both a substrate for and potent inhibitor of CYP2C19 and CYP3A4.[25] The major routes of VPA metabolism are glucuronidation and β-oxidation. A minor metabolic route involving CYP enzymes forms 2-propyl-4-pentenoic acid (4-ene-VPA) and other metabolites[26]; 4-ene-VPA has been associated with hepatotoxicity independently of VPA.[27–29]

The effect of CBD or other drugs on common enzymes that metabolize drugs can be investigated using standard probes or specific inhibitors/inducers. These include midazolam (MDZ), a probe used to measure CYP3A4 activity[30]; rifampicin (RIF), an inducer of CYP3A4 and CYP2C19 activity[31,32]; and itraconazole (ITC) and fluconazole (FLU), which inhibit CYP3A4 and CYP2C19 activity, respectively.[32]

Here, we review six trials designed to investigate DDIs between CBD and other ASDs (Table 1). Four phase 1 trials were performed in healthy volunteers and investigated the effect of CBD on CYP3A4 activity (trial 17028),[33] the effect of CYP enzyme inhibition or induction on CBD pharmacokinetics (PK; trials 17074 and 17075),[34] and bidirectional DDIs between CBD and commonly used ASDs (trial 1543).[35] In addition, two randomized phase 2 trials in patients with epilepsy were subsequently conducted to confirm the effects of CBD on the PK of CLB, STP, and VPA (trials 1428[36] and 1447[37]).

2 | MATERIALS AND METHODS

2.1 | Trial subjects

The main inclusion/exclusion criteria have been previously published[35–37] or are available in Tables S1-S3. In brief, all phase 1 trials enrolled healthy male or female adults, with no clinically significant findings from medical history or clinical laboratory evaluations (GW Research Ltd. Data on file).

For both phase 2 trials, male or female patients (aged 16-55 years in trial 1447 and 18-65 years in trial 1428) must have experienced at least one countable seizure

TABLE 1 Trial design

Trial number[a]	DDIs investigated	Doses
Phase 1 open-label, fixed-sequence trials in healthy volunteers		
17028[33] (GW Research Ltd. Data on file)	**CBD** → MDZ (sensitive CYP3A4 probe)	CBD: 750 mg BID (20 mg/kg/d for a 75-kg subject); 10-d uptitration; 14-d maintenance MDZ: 2.5 mg on Days −1 and 25
17074[34] (GW Research Ltd. Data on file)	RIF (CYP3A4/2C19 inducer) → **CBD**	CBD: 750 mg on Days 1 and 20 RIF: 600 mg QD on Days 5-24
17075[34] (GW Research Ltd. Data on file)	ITC (CYP3A4 inhibitor)/FLU (CYP2C19 inhibitor) → **CBD**	CBD: 750 mg on Days 1 and 15 ITC: 400 mg on Day 8; 200 mg QD on Days 9-21 FLU: 400 mg on Day 8; 200 mg QD on Days 9-21
1543[35]	**CBD** → CLB/VPA/STP CLB/VPA/STP → **CBD**	CBD: 750 mg BID (20 mg/kg/d for a 75-kg subject); 0- to 10-d uptitration; 6- to 26-d maintenance CLB: 5 mg BID for 23-34 d VPA: 500 mg BID for 7-17 d STP: 750 mg BID for 7-17 d
Phase 2 randomized, double-blind, placebo-controlled trials in patients with epilepsy		
1428[36]	**CBD** → CLB	CBD: 20 mg/kg/d; 10-d uptitration; 21-d maintenance CLB: stable dose of ≤20 mg/d
1447[37]	**CBD** → VPA **CBD** → STP	CBD: 20 mg/kg/d; 10-d uptitration; 14-d maintenance VPA: stable median dose of 1115 mg/d STP: stable median dose of 625 mg/d

Bold indicates the involvement of CBD in the interaction being studied.

Abbreviations: BID, twice daily; CBD, cannabidiol; CLB, clobazam; CYP, cytochrome P450; DDI, drug-drug interaction; FLU, fluconazole; ITC, itraconazole; MDZ, midazolam; QD, once daily; RIF, rifampicin; STP, stiripentol; VPA, valproate.

[a]Trial identifiers. ClinicalTrials.gov identifiers: 1428 (NCT02565108), 1447 (NCT02607891).

of any type within 2 months prior to randomization, and must not have had a clinically significant unstable medical condition or had a clinically significant illness (other than epilepsy) in the 4 weeks prior to screening. Patients were receiving a stable dose of CLB, STP, or VPA for 4 weeks prior to screening and throughout the double-blind period.

2.2 | Trial designs

All phase 1 trials were open-label, fixed-sequence trials (GW Research Ltd. Data on file). Both phase 2 trials were randomized, double-blind, placebo-controlled trials (Table 1). In all trials, subjects received a pharmaceutical formulation of highly purified CBD derived from the *Cannabis sativa* L. plant (100 mg/mL oral solution; Epidiolex in the USA; Epidyolex in the EU); results do not apply to other CBD-containing products. In trial 17028, single doses of MDZ were administered in the presence of placebo or steady-state CBD.[33] In trials 17074 and 17075, CBD was administered in two single doses (750 mg) in the absence and presence of steady-state RIF, ITC, or FLU.[34] In trials 1543, 1428, and 1447, CBD or placebo was administered at steady state in the absence and presence of a second ASD at steady state. To achieve steady state, CBD was administered in two daily doses of 750 mg in healthy volunteers for 6-24 days, and at 20 mg/kg/d for 14-21 days in patients with epilepsy (Table 1). Two daily doses of 750 mg are equivalent to 20 mg/kg/d in a 75-kg patient. The trial designs for trials 17028, 17074, and 17075 are shown in Figure S1.

The protocol and informed consent forms for all trials were approved by local independent ethics committees. Written informed consent was obtained from each patient (or parent/legal representative) before any trial-specific procedures were performed.

2.3 | PK assessments

Blood samples were taken at predefined intervals, and plasma concentrations of analytes were determined using specific and validated liquid chromatography with tandem mass spectrometry analytical procedures. The primary PK parameters were maximum observed plasma concentration (C_{max}), area under the concentration-time curve over the dosing interval (AUC_{tau}), and area under the concentration-time curve up to time t, where t is the last point with a concentration above the lower limit of quantification (AUC_{0-t}). In the trials investigating or modulating CYP3A4 activity (17028, 17074, 17075), half-life ($t_{½}$) and plasma analyte clearance were calculated(GW Research Ltd. Data on file).[33] Time to attain maximum observed plasma concentration (t_{max}) was an additional primary PK parameter in trial 17028 (GW Research Ltd. Data on file).

2.4 | Safety

Safety and tolerability assessments across the trials included treatment-emergent adverse events (AEs), clinical laboratory evaluations, vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and the Columbia–Suicide Severity Rating Scale (C-SSRS) questionnaire (GW Research Ltd. Data on file).[37]

2.5 | Statistical analysis

Across all trials, the PK population included all subjects who received at least one dose of CBD or trial medication and provided sufficient bioanalytical assessments to calculate reliable estimates of PK parameters. The safety population included all subjects who received at least one dose of CBD or trial medication. In the trials investigating or modulating CYP3A4 activity (17028, 17074, 17075), healthy volunteers in the safety population were also required to have at least one postdose safety assessment (GW Research Ltd. Data on file).

Because patients with epilepsy were receiving their standard dose of ASD, C_{max} and AUC_{tau} for CLB, N-CLB, STP, VPA, and 4-ene-VPA were dose-normalized by dividing by the ASD dose (expressed in mg/kg).

Potential DDIs were analyzed using a standard 90% confidence interval (CI) approach for the between time point ratios of geometric means of C_{max}, AUC_{tau}, or AUC_{0-t} on a logarithmic scale using a linear mixed effect model with treatment as a fixed effect and subject as a random effect. For trials investigating DDIs between CBD and other ASDs, if the 90% CI described above fell within the interval 0.5-2.0, a lack of meaningful effect was declared. In trial 17028, nonparametric analysis of t_{max} comparisons was performed using a Wilcoxon signed-rank test.

3 | RESULTS

3.1 | Patient disposition

A total of 142 healthy volunteers and 55 patients with epilepsy were enrolled across the six trials (Table 2). Overall, 93% (132/142) of healthy volunteers and 87% (48/55) of patients with epilepsy completed the trials (GW Research Ltd. Data on file).

3.2 | Demographics and baseline characteristics

Overall, the mean age of healthy volunteers was between 26 and 45 years, and 56%-97% were male (Table 3; GW Research Ltd. Data on file). The mean age of patients with epilepsy in the two phase 2 trials was 30 and 37 years; 50%

TABLE 2 Subject disposition (GW Research Ltd. Data on file)

	Trial number					
Subjects, n (%)	**17028**	**17074**	**17075**	**1543**	**1428**	**1447**
Enrolled	16	16	32	78	20	35
Withdrawal prior to treatment	0 (0)	0 (0)	0 (0)	1 (1)	0 (0)	1 (3)
Withdrawal during treatment phase	2 (13)	0 (0)	0 (0)	7 (9)	2 (10)	4 (11)
Completed	14 (88)	16 (100)	32 (100)	70 (90)	18 (90)	30 (86)
Safety population	16 (100)	16 (100)	32 (100)	77 (99)	20 (100)	34 (97)
PK population	16 (100)	16 (100)	32 (100)	77 (99)	13 (65)	29 (83)

Abbreviation: PK, pharmacokinetics.

and 65% were male. The most common (≥20%) baseline seizure types in patients with epilepsy were secondarily generalized tonic-clonic, generalized tonic-clonic, complex partial seizures (focal dyscognitive), absence or atypical absence, myoclonic, and other nonconvulsive seizures; most common (≥20%) baseline ASDs were levetiracetam, carbamazepine, lacosamide, lamotrigine, CLB, and VPA.

3.3 | Effect of CBD on CYP3A4 activity in healthy volunteers

There was no effect of steady-state CBD on exposure to MDZ (Figure 2A).[33] The $t_{½}$, t_{max}, and clearance of MDZ were also unaffected by concomitant CBD administration (Table 4; GW Research Ltd. Data on file).[33] Concomitant CBD led to a minor (C_{max} = 12%, AUC_{tau} = 68%) increase in exposure to the active metabolite 1′-hydroxymidazolam (1′-OH-MDZ). There was a delay to t_{max} (median of differences = 2.25 hours, 90% CI = 1.00-2.52) and a small (35%) increase in the $t_{½}$ of 1′-OH-MDZ (Table 4; GW Research Ltd. Data on file).

3.4 | Effect of CYP3A4 and CYP2C19 induction on the PK of CBD in healthy volunteers

Following a single dose of CBD, concomitant steady-state RIF reduced CBD exposure slightly (C_{max} = 34%, AUC_{tau} = 32%;

TABLE 3 Overall demographics (safety population; GW Research Ltd. Data on file)

	Trial number					
	17028, N = 16	**17074, N = 16**	**17075, N = 32**	**1543, N = 77**	**1428, N = 20**	**1447, N = 34**
Age, y						
Mean (SD)	36 (11.6)	45 (11.2)	32 (12.8)	Range across groups = 26-35	37 (8.7)	30 (10.5)
Sex, n (%)						
Male	9 (56)	13 (81)	31 (97)	50 (65)	10 (50)	22 (65)
Female	7 (44)	3 (19)	1 (3)	27 (35)	10 (50)	12 (35)
Race, n (%)						
White	13 (81)	16 (100)	22 (69)	62 (81)	19 (95)	34 (100)
Black or African American	3 (19)	0 (0)	4 (13)	7 (9)	0 (0)	0 (0)
American Indian or Alaska Native	0 (0)	0 (0)	2 (6)	0 (0)	0 (0)	0 (0)
Asian	0 (0)	0 (0)	3 (9)	3 (4)	1 (5)	0 (0)
Multiple	0 (0)	0 (0)	1 (3)	5 (6)	0 (0)	0 (0)
Body mass index, kg/m^2						
Mean (SD)	25.4 (2.7)	26.1 (2.4)	24.3 (3.1)	Range across groups = 23.2-25.7	27.8 (5.3)	26.8 (5.3)

Abbreviation: SD, standard deviation.

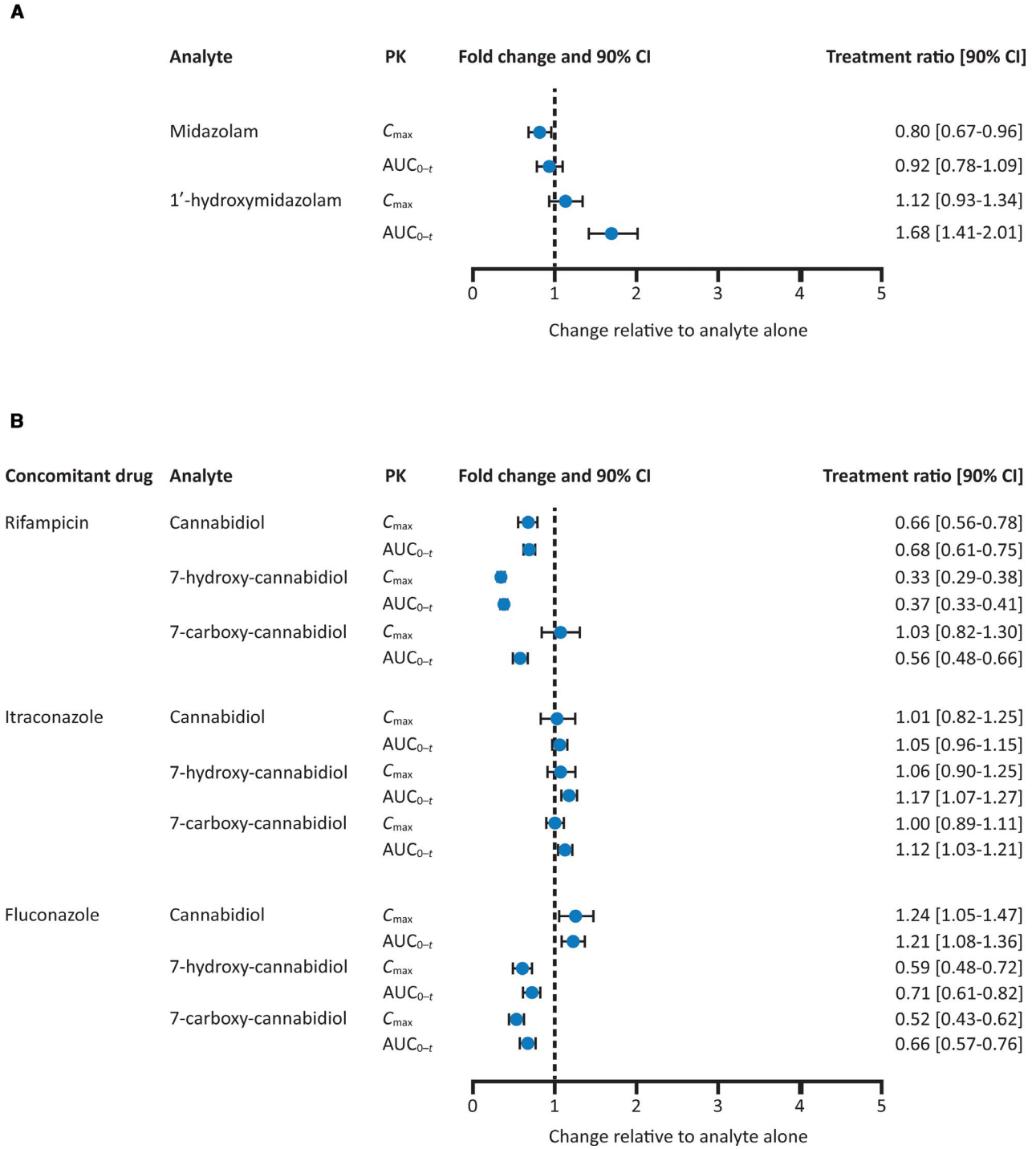

FIGURE 2 Treatment ratios with 90% confidence intervals (CIs) for the effect of (A) cannabidiol (CBD) on exposure to midazolam and 1′-hydroxymidazolam in healthy volunteers and (B) rifampicin, itraconazole, or fluconazole on exposure to CBD, 7-hydroxy-cannabidiol, and 7-carboxy-cannabidiol in healthy volunteers (PK population; GW Research Ltd. Data on file). AUC_{0-t}, area under the concentration-time curve up to time t, where t is the last point with a concentration above the lower limit of quantification; C_{max}, maximum observed plasma concentration; PK, pharmacokinetics

Figure 2B). Clearance of CBD increased 1.5-fold (46%), while $t_{½}$ was unaffected (Table 5). RIF also caused small decreases in exposure to 7-OH-CBD (C_{max} = 67%, AUC_{tau} = 63%) and 7-COOH-CBD (C_{max} = 3% [increase], AUC_{tau} = 44%; Figure 2B). The $t_{½}$ of both metabolites was reduced by 29% and 40% (Table 5; GW Research Ltd. Data on file).

3.5 | Effect of CYP3A4 inhibition on the PK of CBD in healthy volunteers

Concomitant steady-state ITC did not affect CBD exposure following a single dose of CBD. ITC caused small increases in exposure

TABLE 4 Pharmacokinetic parameters of MDZ and 1'-OH-MDZ in trial 17028 investigating the effect of CBD on CYP3A4 enzyme activity (GW Research Ltd. Data on file)

	$t_{½}$, h[a]	t_{max}, h[b]	CL/*F*, L/h[c]
MDZ [placebo, n = 16; CBD, n = 14]			
MDZ + placebo	4.99 (13.1)	0.50 (0.48-2.00)	57.8 (33.8)
MDZ + CBD	4.53 (14.5)	1.00 (0.5-3.00)	61.6 (35.8)
1'-OH-MDZ			
MDZ + placebo	6.11 (39.0)	0.50 (0.48-1.55)[d]	NC
MDZ + CBD	8.23 (64.9)	3.00 (0.50-5.02)[e]	NC

Abbreviations: 1′-OH-MDZ, 1′-hydroxymidazolam; CBD, cannabidiol; CL/*F*, apparent clearance of drug from plasma; CV, coefficient of variation; MDZ, midazolam; NC, not calculated; $t_{½}$, half-life; t_{max}, time to attain maximum observed plasma concentration.

[a] Arithmetic mean (CV%).

[b] Median (min-max).

[c] Geometric mean (CV%).

[d] n = 15.

[e] n = 7.

TABLE 5 PK parameters of CBD and metabolites in trials investigating the effect of CYP enzyme induction or inhibition on the PK of CBD (PK population; GW Research Ltd. Data on file)

Trial 17074: CYP3A4 and CYP2C19 induction [RIF]			Trial 17075: CYP3A4 inhibition [ITC]			Trial 17075: CYP2C19 inhibition [FLU]		
	$t_{½}$, h[a]	CL/*F*, L/h[b]		$t_{½}$, h[a]	CL/*F*, L/h[b]		$t_{½}$, h[a]	CL/*F*, L/h[b]
CBD [both groups n = 16]								
CBD alone	32.5 (26.0)	181 (28.3)	CBD alone	56.8 (20.1)	160 (34.7)	CBD alone	51.2 (14.0)	166 (33.3)
CBD + RIF	35.5 (23.3)	264 (20.7)	CBD + ITC	68.4 (21.6)	149 (36.4)	CBD + FLU	54.5 (16.3)	137 (29.0)
7-OH-CBD								
CBD alone	16.5 (13.2)	NC	CBD alone	19.4 (30.2)	NC	CBD alone	18.8 (21.0)	NC
CBD + RIF	11.7 (13.0)[c]	NC	CBD + ITC	22.5 (34.8)	NC	CBD + FLU	19.3 (28.1)	NC
7-COOH-CBD								
CBD alone	26.8 (23.4)	NC	CBD alone	24.6 (14.1)	NC	CBD alone	24.7 (9.4)	NC
CBD + RIF	16 (10.6)	NC	CBD + ITC	26.4 (15.1)	NC	CBD + FLU	27.1 (14.7)	NC

Abbreviations: 7-COOH-CBD, 7-carboxy-cannabidiol; 7-OH-CBD, 7-hydroxy-cannabidiol; CBD, cannabidiol; CL/*F*, apparent clearance of drug from plasma; CV, coefficient of variation; CYP, cytochrome P450; FLU, fluconazole; ITC, itraconazole; NC, not calculated; PK, pharmacokinetics; RIF, rifampicin; $t_{½}$, half-life.

[a] Arithmetic mean (CV%).

[b]Geometric mean (CV%).

[c]n = 15.

to 7-OH-CBD (C_{max} = 6%, AUC_{tau} = 17%) and 7-COOH-CBD (C_{max} = 0%, AUC_{tau} = 12%; Figure 2B). Clearance of CBD, and $t_{½}$ of CBD and both metabolites, were unaffected by concomitant ITC (Table 5; GW Research Ltd. Data on file).

3.6 | Effect of CYP2C19 inhibition on the PK of CBD in healthy volunteers

Concomitant steady-state FLU led to a small increase in exposure to a single dose of CBD (C_{max} = 24%, AUC_{tau} = 21%). FLU caused small decreases in exposure to 7-OH-CBD (C_{max} = 41%, AUC_{tau} = 29%) and 7-COOH-CBD (C_{max} = 48%, AUC_{tau} = 34%; Figure 2B). Clearance of CBD and $t_{½}$ of CBD were not affected by concomitant FLU (Table 5; GW Research Ltd. Data on file).

3.7 | Clobazam

3.7.1 | The effect of CBD on the PK of CLB in healthy volunteers and patients with epilepsy

In healthy volunteers, concomitant administration of CBD led to a small increase in exposure to steady-state CLB (C_{max} = 20%, AUC_{tau} = 21%), and a notable increase in exposure to

N-CLB (C_{max} = 3.4-fold [239%], AUC_{tau} = 3.4-fold [238%]; Figure 3). In patients with epilepsy on a stable dose of CLB, concomitant administration of CBD had no effect on exposure to CLB. However, there was again an increase in exposure to N-CLB (C_{max} = 2.2-fold [122%], AUC_{tau} = 2.6-fold [164%]; Figure 3).

3.7.2 | The effect of CLB on the PK of CBD in healthy volunteers

Concomitant administration of CLB led to small increases in exposure to steady-state CBD (C_{max} = 1.3-fold [34%], AUC_{tau} = 1.3-fold [30%]), 7-OH-CBD (C_{max} = 1.7-fold [73%], AUC_{tau} = 1.5-fold [47%]), and 7-COOH-CBD (C_{max} = 1.4-fold [35%], AUC_{tau} = 1.3-fold [31%]; Figure 4).

3.8 | Stiripentol

3.8.1 | The effect of CBD on the PK of STP in healthy volunteers and patients with epilepsy

Concomitant administration of CBD led to a small increase in exposure to steady-state STP in both healthy volunteers (C_{max} = 28%, AUC_{tau} = 55%) and patients with epilepsy (C_{max} = 17%, AUC_{tau} = 30%; Figure 3).

3.8.2 | The effect of STP on the PK of CBD in healthy volunteers

Concomitant administration of STP had no effect on exposure to steady-state CBD. However, minor decreases in exposure to 7-OH-CBD (C_{max} = 29%, AUC_{tau} = 28%) and 7-COOH-CBD (C_{max} = 13%, AUC_{tau} = 13%) were reported (Figure 4).

3.9 | Valproate

3.9.1 | The effect of CBD on the PK of VPA in healthy volunteers and patients with epilepsy

In healthy volunteers, there was no effect of concomitant administration of CBD on exposure to steady-state VPA (Figure 3). All plasma concentrations for 4-ene-VPA were below the limit of quantification, probably reflecting the lack of sensitivity of the assay (data not shown). In patients with epilepsy on a stable dose of VPA, concomitant CBD did not show a marked effect on exposure to VPA (C_{max} = 13% [decrease], AUC_{tau} = 17% [decrease]) or 4-ene-VPA (C_{max} = 23% [decrease], AUC_{tau} = 30% [decrease]; Figure 3).

3.9.2 | The effect of VPA on the PK of CBD in healthy volunteers

Concomitant administration of VPA did not affect exposure to steady-state CBD but led to a small increase in exposure to 7-OH-CBD (C_{max} = 3% [decrease], AUC_{tau} = 22%) and 7-COOH-CBD (C_{max} = 25%, AUC_{tau} = 32%; Figure 4).

3.10 | Safety and tolerability

The most commonly reported AEs across all trials are summarized in Tables 6 and 7. Safety and tolerability data have been published[33,35–37] or are provided in the supporting information for trials 17074 (Table S4) and 17075 (Tables S5 and S6).

3.10.1 | Healthy volunteers: CBD as two single doses (trials 17074 and 17075)

AEs were reported by 16 of 16 (100%; trial 17074) and 20 of 32 (63%; trial 17075) healthy volunteers. Most AEs were mild. There were no withdrawals due to AEs and no reports of serious AEs (SAEs; GW Research Ltd. Data on file).[34]

In trial 17074, AEs were reported in seven of 16 (44%) healthy volunteers after receiving CBD alone, 13 of 16 (81%) during RIF treatment, and six of 16 (38%) after receiving CBD and RIF. There were no reports of elevations in transaminase levels as AEs or laboratory evaluations (GW Research Ltd. Data on file).

In the ITC arm of trial 17075, AEs were reported in 13 of 16 (81%) healthy volunteers, seven of 16 (44%) after receiving CBD alone, four of 16 (25%) during ITC treatment, and eight of 16 (50%) after receiving CBD and ITC. In the FLU arm of trial 17075, AEs were reported in seven of 16 (44%) healthy volunteers, three of 16 (19%) after receiving CBD alone, three of 16 (19%) during FLU treatment, and six of 16 (38%) after receiving CBD and FLU. Although not reported as AEs, increases in creatine kinase and aspartate aminotransferase (AST) were observed in two healthy volunteers and were considered to be of musculoskeletal origin (GW Research Ltd. Data on file).

3.10.2 | Healthy volunteers: CBD as multiple doses (trials 17028 and 1543)

In trial 17028, AEs were reported by 15 of 16 (94%) healthy volunteers; most AEs were mild. Two healthy volunteers withdrew due to AEs (rash erythematous and hepatic enzyme increased). No SAEs were reported. Elevations in transaminase levels were reported as AEs in

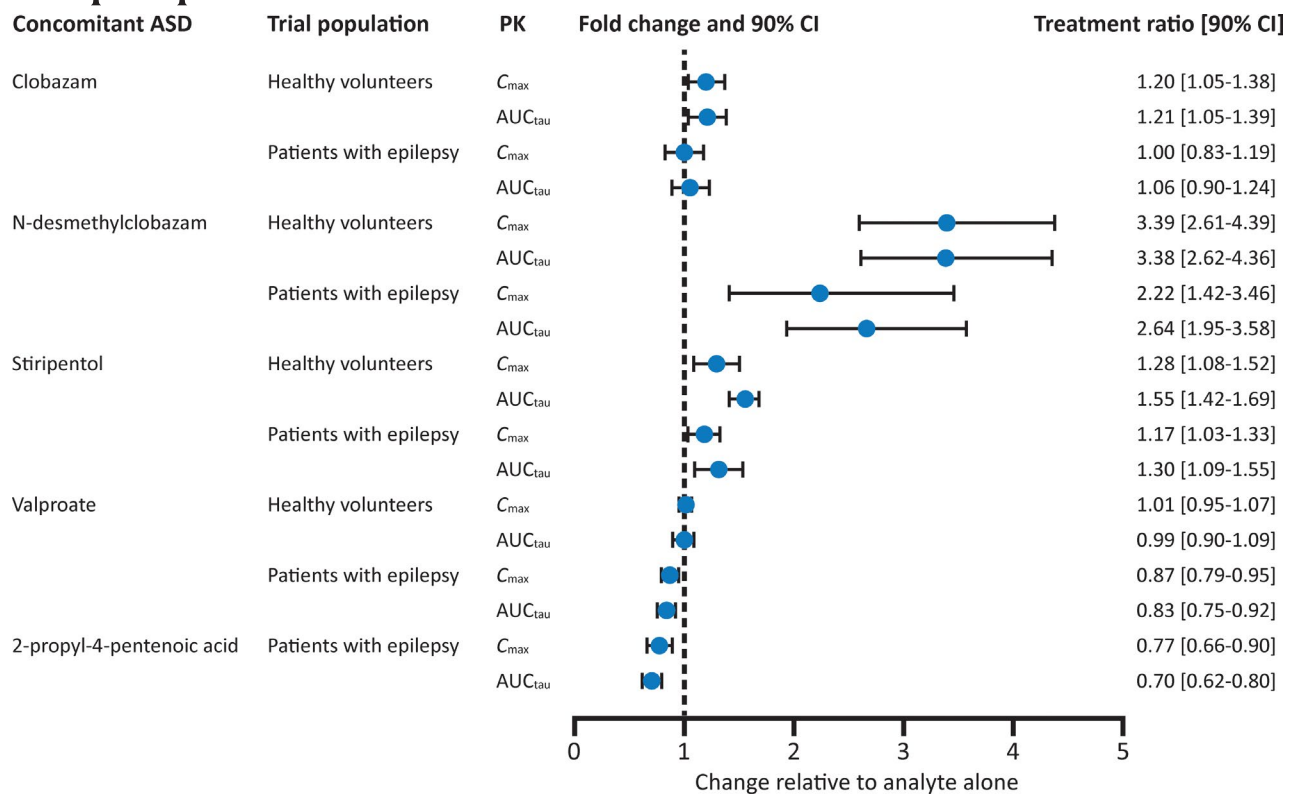

FIGURE 3 Treatment ratios with 90% confidence intervals (CIs) for the effect of CBD on exposure to clobazam, N-desmethylclobazam, stiripentol, valproate, and 2-propyl-4-pentenoic acid (4-ene-VPA) in healthy volunteers and patients with epilepsy (PK population). Plasma concentrations of 4-ene-VPA were below the limit of quantification in healthy volunteers owing to inadequate assay sensitivity. ASD, antiseizure drug; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum plasma concentration; PK, pharmacokinetics

four of 16 (25%) healthy volunteers. Elevations in alanine aminotransferase levels were observed in three healthy volunteers, and elevation in AST levels were observed in four healthy volunteers (GW Research Ltd. Data on file).[33]

In trial 1543, 72 of 77 (94%) healthy volunteers experienced an AE; most were mild or moderate. Early in the trial, nine of 77 (12%) subjects experienced an AE of rash; all but one case was considered to be treatment related. Six healthy volunteers discontinued CBD due to AEs (five due to rashes/rash-related AEs and one due to atrioventricular block, first-degree). There were no SAEs. There were no reports of elevations in transaminase levels as AEs or laboratory evaluations.

3.10.3 | Patients with epilepsy: CBD as multiple doses (trials 1428 and 1447)

AEs were reported by 15 of 20 (75%; trial 1428) and 23 of 34 (68%; trial 1447) patients with epilepsy. Most AEs were mild or moderate. In total, three patients with epilepsy withdrew due to AEs. One patient in trial 1428 withdrew due to seizure cluster, and two patients in trial 1447 withdrew (one due to a rash; one due to hypertransaminasemia). These AEs were also classified as SAEs. A third patient in trial 1447 withdrew consent to participate in the trial after experiencing diarrhea and nausea. Elevations in transaminase levels were reported as AEs in two patients in trial 1428 and three patients in trial 1447. Two further incidences of elevated transaminase levels were observed in trial 1447 but were not reported as AEs.

3.10.4 | Other safety parameters for all trials

There were no significant findings for physical examinations, vital signs, laboratory evaluations, or ECGs, apart from those described above. There were no instances that met Hy's law criteria for potential drug-induced liver injury. No suicidal ideation or behavior was identified by completion of the C-SSRS (GW Research Ltd. Data on file).

Overall, the incidence of serious or severe AEs was low. The most common AEs across all trials were diarrhea, somnolence, headache, hepatic enzyme increased, fatigue, abdominal pain, nausea, chromaturia, and flatulence (GW Research Ltd. Data on file). See Tables 6 and 7 for a summary of AEs across all trials.

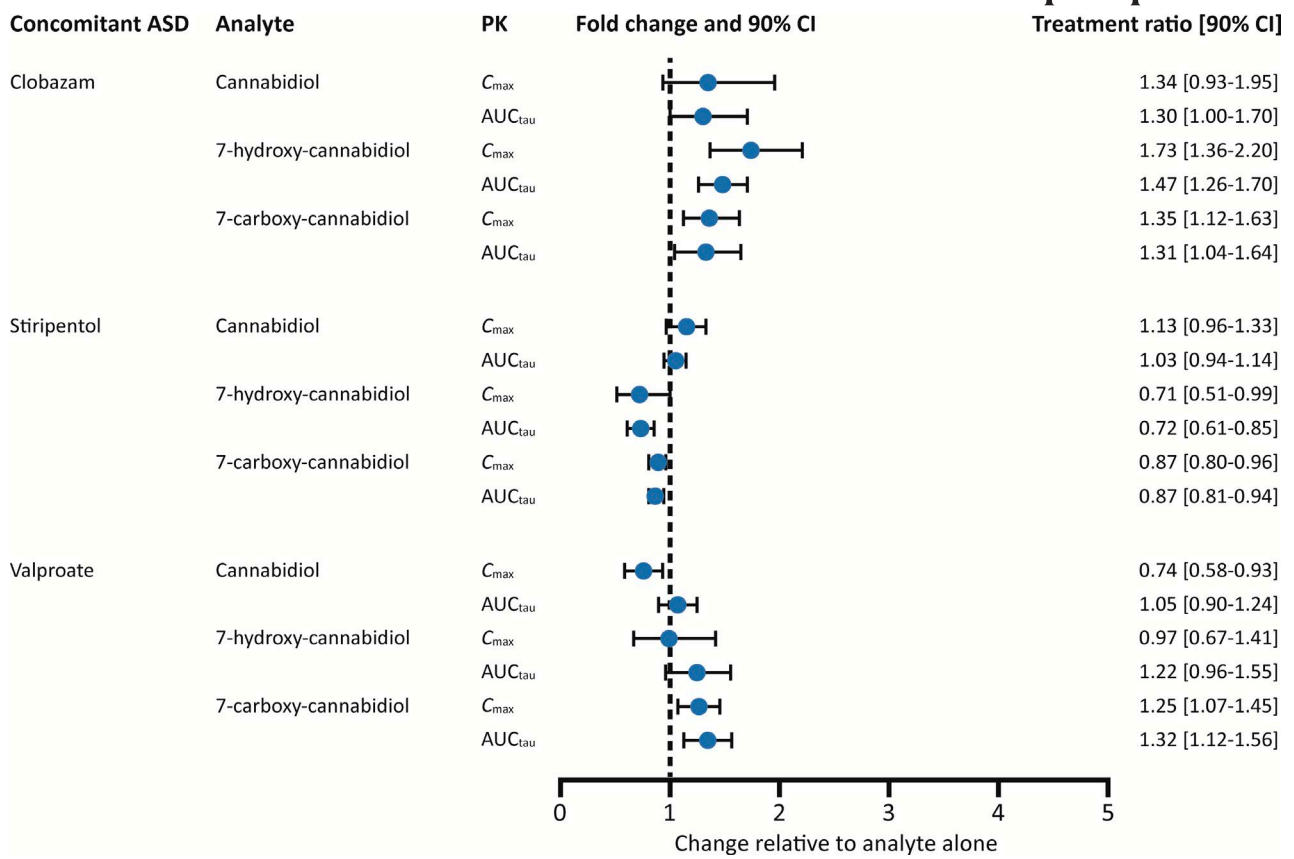

FIGURE 4 Treatment ratios with 90% confidence intervals (CIs) for the effect of clobazam, stiripentol, or valproate on exposure to cannabidiol, 7-hydroxy-cannabidiol, and 7-carboxy-cannabidiol in healthy volunteers (PK population). ASD, antiseizure drug; AUC_{tau}, area under the concentration-time curve over the dosing interval; C_{max}, maximum plasma concentration; PK, pharmacokinetics

TABLE 6 Summary of safety results in healthy volunteers and patients with epilepsy who received CBD in drug-drug interaction trials (safety population[a]; GW Research Ltd. Data on file)

	Healthy volunteers				Patients with epilepsy	
	17028, N = 16	17074, N = 16	17075, N = 32	1543, N = 77[b]	1428, N = 20	1447, N = 34
Patient with at least 1 AE, n (%)	15 (94)	16 (100)	20 (63)	72 (94)	15 (75)	23 (68)
AEs leading to withdrawal, n (%)	2 (13)	0 (0)	0 (0)	6 (8)	1 (5)	2 (6)
Serious AEs, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	2 (6)
Severe AEs, n (%)	0 (0)	0 (0)	0 (0)	2 (3)	1 (5)	1 (3)
Death, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

Abbreviations: AE, treatment-emergent adverse event; CBD, cannabidiol.

[a]Placebo groups have not been included for clarity.

[b]The safety population for trial 1543 included all subjects who received at least one dose of CBD, stiripentol, valproate, or clobazam; seven subjects withdrew during period 2 of the trial and so may not have received CBD.

4 | DISCUSSION

The trials summarized in this review collectively investigated potential PK DDIs between CBD and other commonly coadministered ASDs. First, the impact of CBD on CYP3A4 activity and the effect of CYP inhibition or induction on PK of CBD were determined in healthy volunteers. Second, DDIs between CBD and commonly used ASDs (CLB, STP, and VPA) were investigated in both healthy volunteers and patients with epilepsy. The tested dose of CBD at steady state

TABLE 7 Most commonly reported AEs in healthy volunteers and patients with epilepsy who received CBD in DDI trials (safety population[a]; GW Research Ltd. Data on file)

	Healthy volunteers						Patients with epilepsy	
				1543, N = 77				
Subgroup[b]	17028, N = 16	17074, N = 16	17075, N = 32	1 + 2, n = 27	3 + 4, n = 24	5 + 6, n = 26	1428, N = 16	1447, N = 28
AEs reported in ≥20% of subjects in ≥1 trial								
Diarrhea	6 (38)	3 (19)	3 (9)	7 (26)	13 (54)	15 (58)	6 (38)	16 (57)
Somnolence	5 (31)	4 (25)	3 (9)	5 (19)	8 (33)	7 (27)	2 (13)	1 (4)
Headache	4 (25)	2 (13)	6 (19)	13 (48)	9 (38)	8 (31)	1 (6)	0 (0)
Hepatic enzyme increased	4 (25)	0 (0)	0 (0)[c]	0 (0)	0 (0)	0 (0)	0 (0)[d]	0 (0)[e]
Fatigue	3 (19)	0 (0)	2 (6)	14 (52)	8 (33)	14 (54)	1 (6)	3 (11)
Abdominal pain	2 (13)	0 (0)	2 (6)	7 (26)	7 (29)	7 (27)	1 (6)	0 (0)
Nausea	2 (13)	4 (25)	2 (6)	8 (30)	6 (25)	8 (31)	3 (19)	4 (14)
Chromaturia[f]	0 (0)	13 (81)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Flatulence	0 (0)	0 (0)	0 (0)	0 (0)	6 (25)	1 (4)	0 (0)	0 (0)

Abbreviations: AE, treatment-emergent adverse event; CBD, cannabidiol; CLB, clobazam; DDI, drug-drug interaction; N-CLB, N-desmethylclobazam; STP, stiripentol; VPA, valproate.

[a]Placebo groups have not been included for clarity.

[b]Trial 1543 was performed in six parallel groups of healthy subjects. DDI CLB: Group 1, effect of CBD on steady-state CLB and N-CLB; Group 2, effect of CLB and N-CLB on steady-state CBD. DDI STP: Group 3, effect of CBD on steady-state STP; Group 4, effect of STP on steady-state CBD. DDI VPA: Group 5, effect of CBD on steady-state VPA; Group 6, effect of VPA on steady-state CBD.

[c]Two patients (6%) with liver enzyme elevations >3 × upper limit of normal are not reported as AEs.

[d]One patient (6%) with liver function test abnormal, one patient (6%) with hypertransaminasemia.

[e]Three patients (11%) with alanine aminotransferase increased; two patients (7%) with aspartate aminotransferase increased; one patient (4%) with hypertransaminasemia.

[f]All cases of chromaturia were reported in a single trial where rifampicin was coadministered (17074). Chromaturia is a known adverse drug reaction following administration of rifampicin.

was equivalent to the highest maintenance dose used in recent phase 3 trials in DS and LGS.[12–15] These results may therefore inform treatment decisions when concomitant treatment of CBD with enzyme inducers or inhibitors or other ASDs is considered.

In vitro data suggest CBD is a potent inhibitor of CYP3A4.[20,39] However, a trial in healthy volunteers using MDZ as a CYP3A4 probe demonstrated no notable effects of concomitant CBD (750 mg twice daily for 14 days) on exposure, clearance, or $t_{½}$ of MDZ, thus illustrating the need for caution when extrapolating in vitro data to predict DDIs in humans (GW Research Ltd. Data on file).[33] These findings are consistent with results from separate trials in healthy volunteers, showing no interaction when CBD and the CYP3A4 substrate fentanyl were combined,[40] and little effect of concomitant CBD on the PK of CYP3A4 substrate CLB.[23,35] CBD is therefore unlikely to cause clinically relevant DDIs with other medicines metabolized by CYP3A4. MDZ is a benzodiazepine that is a commonly used treatment for status epilepticus.[41] The active metabolite of MDZ, 1'-OH-MDZ, is further metabolized primarily by the UGT isozymes UGT2B4, UGT2B7, and UGT1A4.[42] The observed increase in exposure to the active metabolite 1′-OH-MDZ may therefore be due to CBD-mediated inhibition of UGTs, in particular UGT2B7.[22] The increase in exposure to 1′-OH-MDZ with concomitant CBD could potentially increase the effects of MDZ in cases of impaired drug metabolism or when MDZ is administered at high doses.[43] The clinical relevance of the increase in exposure to 1′-OH-MDZ when MDZ is administered with CBD is unknown.

RIF led to a small decrease in exposure to CBD (by approximately 30% for both C_{max} and AUC_{tau}). RIF is a potent inducer of many CYPs, including CYP2C19 and CYP3A4.[31,32] While plasma levels of CBD were lower when coadministered with RIF, $t_{½}$ was unaffected. Plasma levels of both CBD metabolites were reduced, and their $t_{½}$ were also reduced. These data add to existing preclinical evidence that 7-hydroxylation of CBD is catalyzed by CYP2C19.[16] Coadministration of CBD with a strong CYP3A4 or CYP2C19 inducer may decrease systemic exposure to CBD and the active metabolite 7-OH-CBD,[17] which could potentially lower the efficacy of CBD. An increase in the dose of CBD should be considered

when coadministered with a strong CYP3A4 or CYP2C19 inducer.[10, 11]

Potent CYP3A4 or CYP2C19 inhibition with ITC and FLU did not markedly impact CBD exposure in a clinically important manner. Coadministration of ITC with CBD led to small increases in exposure to CBD metabolites, while coadministration of FLU with CBD led to small decreases in exposure to CBD metabolites. These data suggest that various metabolic pathways other than via CYP2C19 and CYP3A4 are involved in the metabolism of CBD, including other CYP-mediated pathways and conjugations via UGT enzymes.[16,17] Coadministration of CBD with moderate or strong inhibitors of CYP3A4 or CYP2C19 may cause small increases in CBD plasma concentrations, as CBD is metabolized by both enzymes.[16,17] The clinical relevance of these small increases is unknown; however, they are unlikely to be clinically relevant.

Of all DDIs investigated, a single and potentially clinically important DDI was identified when CLB and CBD were combined. This resulted in a bidirectional DDI that increased levels of active metabolites of both compounds. Combination of CBD and CLB led to a small increase in exposure to 7-OH-CBD (C_{max} = 1.7-fold, AUC_{tau} = 1.5-fold) and 7-COOH-CBD (C_{max} = 1.4-fold, AUC_{tau} = 1.3-fold) in healthy volunteers. However, there was a relatively large increase in exposure to N-CLB in both healthy volunteers (C_{max} = 3.4-fold, AUC_{tau} = 3.4-fold) and patients with epilepsy (C_{max} = 2.2-fold, AUC_{tau} = 2.6-fold), which constituted a meaningful DDI (90% CI outside the interval 0.5-2.0).[35,36] These results are consistent with a separate trial in children with refractory epilepsy, in which an increase in N-CLB exposure with concomitant CBD administration was observed.[44] The mechanism behind the increase in exposure to N-CLB is probably related to CYP2C19 inhibition by CBD.[21,23] The increase in exposure to N-CLB and 7-OH-CBD may contribute to treatment efficacy, as both are active metabolites.[17,23] However, the increase in exposure to these active substances may also increase the risk of AEs. Concomitant exposure to CBD and CLB increases the incidence of somnolence and sedation compared to placebo.[11] Reduction in the dose of CLB may therefore be considered if adverse reactions known to occur with CLB are experienced when coadministered with CBD.[10,11,35]

Coadministration of CBD with STP led to a small increase in exposure to STP in healthy volunteers and patients with epilepsy.[35,37] As with CLB, the underlying mechanism leading to the small increase in STP levels is likely a result of inhibition of CYP2C19.[21] The increase in STP exposure is of unknown clinical relevance. Patients receiving CBD and STP should be monitored for adverse drug reactions, as responses of individual patients may vary.

There were no clinically important DDIs between CBD and VPA or its metabolite, 4-ene-VPA, in healthy volunteers or patients with epilepsy.[35,37] Dose-related elevations in transaminase levels with CBD are more common in patients who receive concomitant VPA[11–15,45]; as 4-ene-VPA has been associated with hepatotoxicity,[27–29] it is important to measure plasma levels of both compounds. If such elevations occur, discontinuation or reduction of CBD and/or concomitant VPA should be considered for patients receiving both drugs.[10] If clinically relevant elevations in transaminases occur in patients receiving concomitant VPA and CBD, dose adjustment or discontinuation of VPA should be considered.[11] Dose adjustment of CLB should be considered in this case if patients are also receiving concomitant CLB.[11] While the mechanism behind the elevations in transaminase levels is unknown, it does not appear to be due to concomitant CBD exposure or an increase in VPA exposure.[37] [Correction added on October 6, 2020, after first online publication: in the above paragraph the words 'EPIDIOLEX' and 'valproate' were changed to 'CBD' and 'VPA'.]

The findings of these trials collectively support those of a separate trial in children with DS, which found concomitant CBD increased N-CLB concentrations and had no effect on plasma concentrations of VPA or STP.[46] Of note, N-CLB plasma concentration increased independently of CBD dose but did not increase in the patients on concomitant STP.[46] STP is a potent inhibitor of CYP2C19; thus, this effect is likely to be explained by saturation of CYP2C19 inhibition.[25] Consequently, based on PK alone, increased exposure to N-CLB may not occur if CLB is also coadministered with STP or other CYP2C19 inhibitors.

Plasma protein binding (PPB) displacement interactions are important for highly bound drugs, as they can alter the PK of a drug and thus its therapeutic effect.[47] VPA has the potential to displace the PPB of other ASDs; this mechanism of DDIs has been well documented with phenytoin.[48,49] PPB is extensive for VPA (73.9%-92.7%) and STP (96.1%),[49] and >94% for CBD and its metabolites.[11] Therefore, there is the potential for PPB interactions to occur between these compounds. The ability for CBD to affect the PPB of STP has not been investigated, and an effect of CBD to displace STP PPB cannot be ruled out. However, the combination of CBD and STP is generally well tolerated and leads to a small increase in STP exposure.[37] The PPB of VPA and CBD is not affected when combined in vitro, again suggesting that there is no significant effect of CBD to displace VPA PPB.[37]

The safety results from trials in which CBD was administered in single doses did not identify any additional safety concerns above the known safety profile of CBD.[12–14] Findings from the trials in which CBD was administered in multiple doses at steady state are consistent with the known safety profile of CBD at 20 mg/kg/d, except for the higher incidence of rash in trial 1543. No new cases of rash were reported in this trial following protocol amendments to extend the titration period and change the process for syringe filling and use.[35]

Trials investigating DDIs with CBD have not been conducted formally in pediatric populations for practical and

ethical reasons. However, there is significant clinical experience and safety information in pediatric populations (≥2 years of age) when CBD is given in combination with multiple ASDs.[12–15] From 1 year of age, CYP450 activity and expression are considered to be close to adult levels for the majority of major CYP450 isoforms.[50] It is therefore expected that patients older than 1 year are adequately exposed to administered drugs, are not compromised in their capacity to metabolize CBD or other concomitant medications, and would not require dose modification different from that of adults in the case of CYP-mediated DDIs. The risk of DDIs is further mitigated in pediatric populations, as CBD is titrated according to effect on top of standard-of-care medication and is administered by weight. Together, these approaches can limit the total exposure burden in pediatric populations.

In conclusion, these trials suggest that CBD is not likely to interact with CYP3A4 in a manner that will produce a meaningful DDI, an increase in the dose of CBD should be considered when coadministered with a strong CYP3A4 or CYP2C19 inducer, and the bidirectional DDI between CBD and CLB should be considered when these drugs are administered concomitantly. Based on PK alone, dose adjustments are not likely to be necessary when CBD is given concomitantly with STP or VPA, although an independent effect of increased dose-related elevations in transaminase levels should be considered when CBD and VPA are combined, and patients on concomitant STP should be monitored for AEs.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The sponsor adheres to current requirements of the USA and the EU so will not make individual deidentified participant data available; however, the protocol and statistical analysis plan will be made available upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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