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A Two-Way Pharmacokinetic Interaction Between Efavirenz (EFV) and Carbamazepine (CBZ)

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Abstract

Background: EFV and CBZ are substrates of CYP3A4 and/or CYP2B6. Both drugs are CYP-inducers. The purpose of this study was to assess the multiple-dose pharmacokinetic (PK) interaction between EFV and CBZ.

Methods: An open-label, parallel-arm, 2-period crossover, steady-state PK study was conducted in adult healthy subjects. Arm A (N=18) received: EFV 600 mg QD on Days 1-14; EFV 600 mg QD + CBZ on Days 15-35 (CBZ 200 mg QD on Days 15-17, 200 mg BID on Days 18-20, and 400 mg QD on Days 21-35). Arm B (N=18) received: CBZ 200 mg QD on Days 1-3, 200 mg BID on Days 4-6, and 400 mg QD on Days 7-21; CBZ 400 mg QD + EFV 600 mg QD on Days 22-35. PK samples were collected over 24 h on Days 14, 35 (Arm A), and Days 21, 35 (Arm B). EFV, CBZ, and CBZ epoxide (CBZE) were analyzed by HPLC. PK parameters were calculated by non-compartmental analysis. Safety was monitored throughout the study.

Results: 36 subjects were enrolled (69% male, 67% Caucasian; mean age 30 y and weight 76 kg). There were no serious adverse events. Adverse events and laboratory abnormalities were, in general, typical of those seen with EFV or CBZ administration. Co-administration of EFV + CBZ did not appear to decrease the tolerability of either drug. PK results are summarized below:

Arm	Drug (N)	PK Parameter	Geometric Mean Ratios (90% Confidence Intervals)	
			EFV + CBZ vs. EFV	CBZ + EFV vs. CBZ
A	EFV (N=14)	C _{max}	0.792 (0.740, 0.848)	-
		AUC	0.637 (0.601, 0.676)	-
		C _{min}	0.526 (0.470, 0.590)	-
B	CBZ (N=12)	C _{max}	-	0.804 (0.761, 0.849)
		AUC	-	0.729 (0.668, 0.796)
		C _{min}	-	0.652 (0.560, 0.760)
B	CBZE (N=12)	C _{max}	-	1.050 (0.905, 1.219)
		AUC	-	0.989 (0.854, 1.145)
		C _{min}	-	0.866 (0.703, 1.066)

Conclusions: Co-administration of EFV and CBZ results in a 2-way drug interaction whereby both EFV and CBZ concentrations are decreased.

There are no data for this combination using higher doses of either drug; therefore, no dose recommendation can be made. Use of alternate anticonvulsants may be necessary for optimal antiretroviral/anticonvulsant therapy. The drugs were generally safe and well-tolerated when administered alone or in combination.

Background

During their lifetime, nearly 40% of AIDS patients develop neurological symptoms related either to the primary HIV infection or secondarily to opportunistic infections.¹ Currently the frequency of new-onset seizures in HIV-infected patients has been estimated to be approximately 3%.² There is also a potential that patients on anticonvulsant therapy could become infected with HIV. Thus there is a medical need in certain cases to provide anticonvulsant therapy in addition to the treatment of HIV infection.

Background (continued)

■ Efavirenz (EFV) is a component of leading Highly Active Anti-Retroviral Treatment (HAART) regimens.³ It has the potential for drug interactions due to its involvement with cytochrome P450 enzymes.⁴ EFV is an inducer of CYP3A4 resulting in an induction of its own metabolism as well as an increase in the metabolism of drugs that are substrates for CYP3A4.⁵ EFV is also a substrate for CYP3A4 and/or CYP2B6, and hence drugs that induce CYP3A4/2B6 increase the clearance of efavirenz.⁶

■ Carbamazepine (CBZ) is one of the most commonly prescribed drugs for epilepsy, and is also widely used in the treatment of pain associated with trigeminal neuralgia.⁷ It is predominantly a substrate for CYP3A4 and for CYP2C8 and CYP1A2. CBZ is a potent inducer of several cytochrome P450 enzymes, including CYP3A4, and may increase the clearance of concomitantly administered drugs.⁸

■ Due to the involvement of a common metabolic enzyme (CYP3A4) in the clearance of EFV and CBZ, the potential for pharmacokinetic (PK) drug-drug interaction exists when the two drugs are co-administered. Hence, this study investigated the PK drug interaction between EFV and CBZ.

Objectives

Primary Objective:

■ To evaluate whether the PK of EFV or CBZ are affected by their co-administration.

Secondary Objective:

■ To assess the safety of EFV and CBZ when administered alone or in combination.

Methods

■ Phase I, open-label, parallel-arm, 2-period crossover study in 2 cohorts of healthy subjects (18/cohort).

■ The design of this study (Figure 1) incorporated the sequential introduction of specified drug or drug combinations. Arm A evaluated the effect of CBZ on the steady state PK of EFV and Arm B evaluated the effect of EFV on the steady state PK of CBZ and CBZ epoxide (CBZE).

■ EFV was administered as 600-mg Sustiva® tablets and CBZ was administered as 200-mg Tegretol® conventional tablets. Dosing was under fasted conditions. EFV was administered in the evening prior to bedtime (at approximately 9:00 PM). CBZ was administered in the morning (at approximately 9:00 AM) and in the evening (at approximately 9:00 PM) for BID dosing, and in the evening (at approximately 9:00 PM) for QD dosing.

■ Serial blood samples were collected on Days 14 and 35 (Arm A) and Days 21 and 35 (Arm B) at pre-dose and up to 24 hours post-dose. Blood samples for C_{min} values were collected on even days up to Day 32.

■ Plasma samples were assayed for EFV, CBZ, and/or CBZE by validated HPLC assay methods.

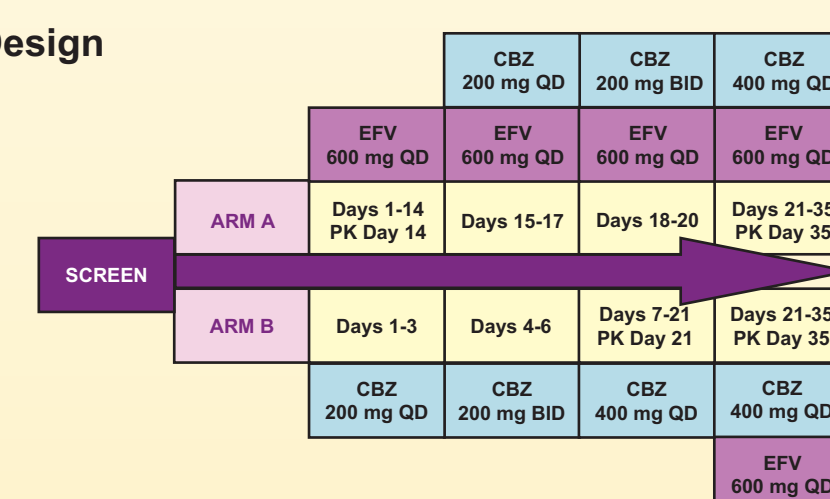
■ PK parameters for EFV, CBZ, and CBZE were derived using a non-compartmental analysis.

■ Absence of drug interaction was concluded if the 90% confidence interval (CI) for the ratio of test to reference geometric means fell within 0.80-1.25 interval for AUC; similar assessments were conducted for C_{max} and C_{min}.

■ Clinical safety evaluations were performed at screening, during the study, and at the time of discharge from the study.

Methods (continued)

Figure 1: Study Design



Results

■ This study enrolled 36 subjects, of which 27 completed the study (15 in Arm A and 12 in Arm B). The 9 discontinuations were due to adverse events (AEs).

– Arm A: 1 hematuria (EFV alone); 1 neutropenia and 1 increased ALT (EFV+CBZ)

– Arm B: 2 thrombocytopenia, 1 increased ALT/AST, 1 decreased platelet count, and 1 maculopapular rash (CBZ alone); and 1 neutropenia (CBZ+EFV)

■ There were no deaths or other serious adverse events.

■ AEs occurring in more than 20% of the subjects for any treatment were: headache, dizziness, somnolence, abdominal pain, flushing, insomnia, intoxicated feeling, nausea, musculoskeletal pain, elevated mood, euphoric mood, throat irritation, and pruritis. Headache, the most frequently reported AE, was similar between the 2 arms:

– Arm A: EFV alone (33.3%), EFV+CBZ (29.4%)

– Arm B: CBZ alone (38.9%), CBZ+EFV (30.8%)

■ Most laboratory abnormalities were Grade 1 or 2, of which neutropenia was most common (22-29% in CBZ containing treatments).

■ There were three Grade 3 laboratory abnormalities (Arm A: 1 decrease in neutrophils; Arm B: 1 increase in ALT and 1 decrease in platelets), all of which lead to discontinuations.

■ All AEs resolved by discharge or during follow-up.

Table 1: Demographic Characteristics

Characteristic	Arm A	Arm B
Mean Age, years (Range)	30 (20-43)	30 (21-45)
Sex, N (%)		
Male	11 (61)	14 (78)
Female	7 (39)	4 (22)
Race, N (%)		
White	12 (67)	12 (67)
Black	4 (22)	3 (17)
Native American	2 (11)	2 (11)
Other	0 (0)	1 (6)
Mean Weight, kg (Range)	78.8 (54.4-91.7)	74.2 (55.7-91.8)
Mean Height, cm (Range)	169.9 (156.0-182.0)	171.6 (150.0-188.5)
Mean BMI, kg/m ² (Range)	26.5 (22.0-29.9)	25.2 (22.0-30.0)

PHARMACOKINETICS OF EFAVIRENZ

Figure 2: Mean (+SD) Plasma Concentration-Time Profiles for EFV Following Administration of EFV Alone and EFV+CBZ

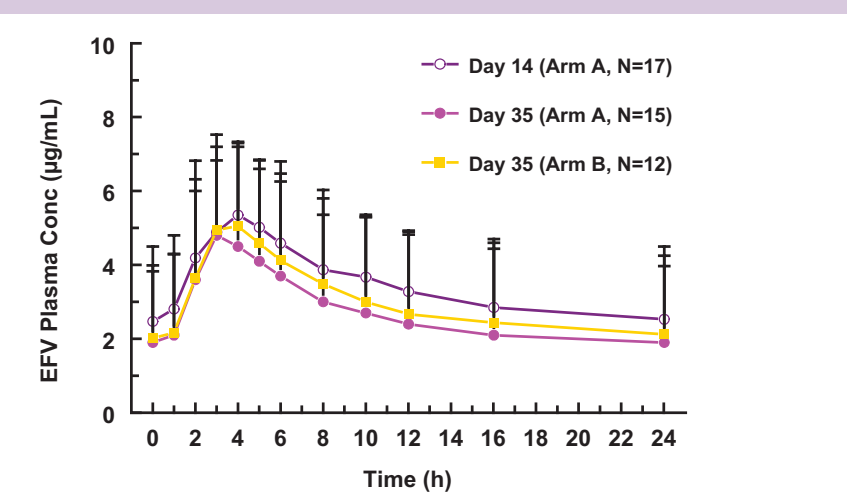


Table 2: Geometric Means and Point Estimates (90% CI) for AUC, C_{max} and C_{min} for EFV: Arm A (N=14)

PK Parameter	Treatment	Adjusted Geometric Mean	Point Estimate (90% CI)
AUC (µg·h/mL)	600 mg EFV QD	71.52	-
	600 mg EFV QD + 400 mg CBZ QD	45.59	0.637 (0.601, 0.676)
C _{max} (µg/mL)	600 mg EFV QD	5.65	-
	600 mg EFV QD + 400 mg CBZ QD	4.48	0.792 (0.740, 0.848)
C _{min} (µg/mL)	600 mg EFV QD	2.01	-
	600 mg EFV QD + 400 mg CBZ QD	1.06	0.526 (0.470, 0.590)

Results (continued)

PHARMACOKINETICS OF CARBAMAZEPINE

Figure 3: Mean (+SD) Plasma Concentration-Time Profiles for CBZ Following Administration of CBZ Alone and CBZ+EFV

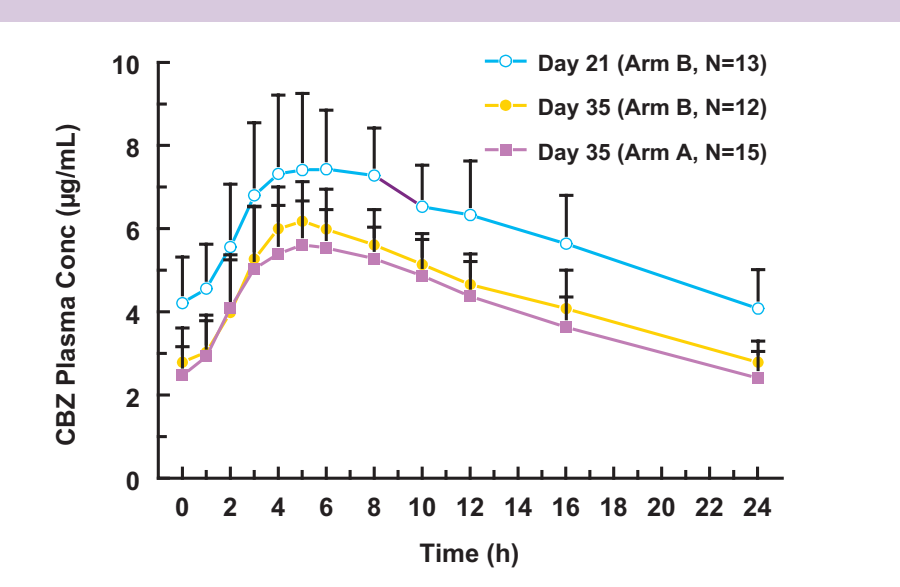


Table 3: Geometric Means and Point Estimates (90% CI) for AUC, C_{max}, and C_{min} for CBZ: Arm B (N=12)

PK Parameter	Treatment	Adjusted Geometric Mean	Point Estimate (90% CI)
AUC (µg·h/mL)	400 mg CBZ QD	138.89	-
	400 mg CBZ QD + 600 mg EFV QD	101.31	0.729 (0.668, 0.796)
C _{max} (µg/mL)	400 mg CBZ QD	7.89	-
	400 mg CBZ QD + 600 mg EFV QD	6.34	0.804 (0.761, 0.849)
C _{min} (µg/mL)	400 mg CBZ QD	4.06	-
	400 mg CBZ QD + 600 mg EFV QD	2.65	0.652 (0.560, 0.760)

PHARMACOKINETICS OF CARBAMAZEPINE EPOXIDE

Figure 4: Mean (+SD) Plasma Concentration-Time Profiles for CBZE Following Administration of CBZ Alone and CBZ+EFV

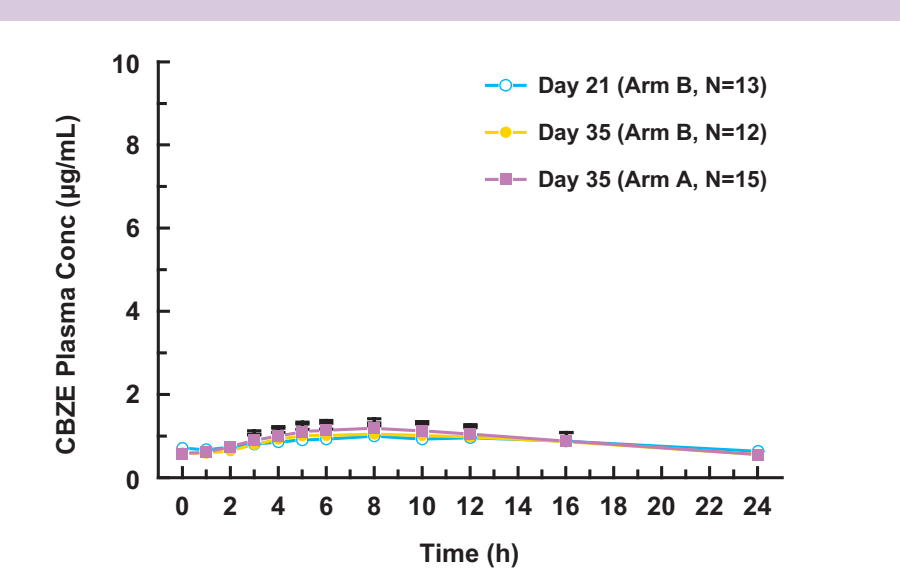


Table 4: Geometric Means and Point Estimates (90% CI) for AUC, C_{max} and C_{min} for CBZE: Arm B (N=12)

PK Parameter	Treatment	Adjusted Geometric Mean	Point Estimate (90% CI)
AUC (µg·h/mL)	400 mg CBZ QD	19.35	-
	400 mg CBZ QD + 600 mg EFV QD	19.13	0.989 (0.854, 1.145)
C _{max} (µg/mL)	400 mg CBZ QD	1.00	-
	400 mg CBZ QD + 600 mg EFV QD	1.05	1.050 (0.905, 1.219)
C _{min} (µg/mL)	400 mg CBZ QD	0.66	-
	400 mg CBZ QD + 600 mg EFV QD	0.57	0.866 (0.703, 1.066)

Discussion

■ Co-administration of EFV (600 mg orally QD) with CBZ (400 mg QD) in healthy subjects decreased the steady-state AUC, C_{max} and C_{min} of EFV by 36%, 21%, and 47%, respectively, while the steady-state AUC, C_{max} and C_{min} of CBZ decreased by 27%, 20% and 35%, respectively. The steady-state AUC, C_{max} and C_{min} of the active CBZE metabolite remained unchanged.

■ Although the decreased exposure of EFV and CBZ could potentially be overcome by dose increases, there are no data with co-administration of higher doses of either medicinal product; therefore, no dose recommendation can be made, and alternate anticonvulsant treatment should be considered in those patients managed on EFV-based regimens.

■ No data are available on the potential interactions of EFV with other anticonvulsants that are substrates of CYP450 isozymes. When EFV is administered concomitantly with these agents, there is a potential for reduction or increase in the plasma concentrations of each agent; therefore, periodic monitoring of plasma levels should be conducted. Specific interaction studies have not been performed with EFV and vigabatrin or gabapentin. Clinically significant interactions would not be expected since vigabatrin and gabapentin are exclusively eliminated unchanged in the urine⁹ and would be unlikely to compete for the same metabolic enzymes and elimination pathways as EFV.

■ There were no serious adverse events. Adverse events and laboratory abnormalities were, in general, typical of those seen with EFV or CBZ administration.

Conclusions

■ Co-administration of EFV and CBZ results in a 2-way drug interaction whereby both EFV and CBZ concentrations are decreased.

■ There are no data for this combination using higher doses of either drug; therefore, no dose recommendation can be made.

■ Use of alternate anticonvulsants may be necessary for optimal antiretroviral/anticonvulsant therapy.

■ The study medications were generally safe and well-tolerated when administered alone or in combination. The concomitant administration of EFV with CBZ did not adversely impact the safety profile of either medicinal product.

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