

# An assessment of plasma amprenavir (APV) pharmacokinetics (PK) following administration of two GW433908 (908) and ritonavir (RTV) BID regimens in combination with efavirenz (EFV) in healthy adult subjects (APV10010)

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## Introduction

GW433908 is a phosphate ester prodrug of amprenavir (APV), an HIV protease inhibitor. GW433908 (to be formulated as a 700 mg tablet) will be available as a compact regimen that should enhance patient adherence. Administration of GW433908 1395 mg twice daily (BID) produced an ~2-log reduction in plasma HIV-1 RNA concentrations following 4 weeks of administration to antiretroviral-naïve subjects (1). Ritonavir (RTV) is a potent inhibitor of APV metabolism, even at sub-therapeutic concentrations (2, 3). The safety and efficacy of GW433908 700 mg (equivalent to APV 600 mg) BID + RTV 100 mg BID is being studied in PI-experienced HIV-infected subjects. Efavirenz (EFV) is a non-nucleoside reverse transcriptase inhibitor (NNRTI) that may be used in combination with GW433908 and RTV, especially in subjects with prior PI exposure. EFV is a potent inducer of APV metabolism (4). A National Institutes of Health (NIH)-sponsored study demonstrated that EFV decreased plasma APV  $AUC_{0-24}$ ,  $C_{max,ss}$ , and  $C_{24h}$  by 24%, 33%, and 43%, respectively, in eight HIV-infected subjects who received APV 1200 mg BID with and without EFV 600 mg QD (4). Another NIH-sponsored study demonstrated that a RTV dosage regimen of at least 200 mg BID was sufficient to counteract the CYP3A4 induction effect of EFV such that APV concentrations were not different when APV 1200 mg BID was co-administered with RTV with or without EFV 600 mg QD to HIV-infected subjects (5). Data from two small studies indicated that administration of APV 600 mg BID + RTV 100 mg BID + EFV 600 mg QD resulted in plasma APV concentrations higher than those achieved with the standard APV 1200 mg BID (without RTV) regimen, although it could not be determined whether RTV 100 mg BID was sufficient to completely counteract the CYP3A4 induction effect of EFV (6, 7). When EFV 600 mg QD and RTV 500 mg BID were co-administered, plasma RTV and EFV  $AUC_{0-24}$  values were both increased by ~20% (8). APV10010 was designed to evaluate the ability of RTV 100 mg BID and RTV 200 mg BID to counteract the CYP3A4 induction effect of EFV by examining plasma APV pharmacokinetics (PK); data from this study will aid in the selection of a GW433908 + RTV BID regimen for co-administration with EFV QD.

## Methods

### Study Design

Thirty-two healthy adult subjects were to be randomized to one of the following two arms in order to achieve 24 evaluable subjects.

Table 1 • Study design

Arm	Sample Size	Period 1		Period 2	
		Days 1–14 (morning)	Treatment A	Days 14 (evening) – 28 (morning)	Treatment B
1	16		Treatment A		Treatment B
2	16		Treatment A		Treatment C

Treatment A = GW433908\* 700 mg BID + RTV 100 mg BID  
Treatment B = GW433908\* 700 mg BID + RTV 100 mg BID + EFV 600 mg QD  
Treatment C = GW433908\* 700 mg BID + RTV 200 mg BID + EFV 600 mg QD  
\*GW433908 700 mg = 600 mg APV molar equivalents

Healthy, HIV-seronegative, male and female (females had to be of non-childbearing potential) adults (≥ 18 and ≤ 60 years of age) without clinically significant laboratory or ECG abnormalities and with body mass indexes (BMIs) of 20–32 kg/m<sup>2</sup> were eligible for enrollment. Subjects could not have participated in another research study within 1 month prior to screening, donated ≥ 1 unit (450 mL) of blood within 3 months prior to screening, or taken medications within 2 weeks prior to dosing. The study was approved by each study center's IRB and all subjects gave written informed consent to participate in the study prior to initiation of any study-related procedures.

Subjects who met the protocol entry criteria returned to the study center on Day 1 (following an 8-hour fast) to undergo baseline assessments and to receive the first dose of Period 1 study drug. Subjects then returned to the study center the evening of Day 13 in preparation for the Day 14 assessments. On the morning of Day 14, following a 10-hour fast, subjects received the last dose of Period 1 study drug. Prior to dosing and for 12 hours following dosing, subjects underwent safety assessments and PK sampling. Subjects fasted for an additional 4 hours after dosing. Subjects initiated their second treatment following the 12-hour PK sampling (on the evening of Day 14). Subjects repeated the Days 13–14 assessments on Days 27–28 (Period 2). Subjects returned to the study center for a follow-up visit within 14–21 days after discontinuation of study drug.

GW433908 and RTV could be administered without regard to meals and EFV was to have been administered at least two hours apart from a meal in the evening. Subjects fasted for 10 hours prior to and for an additional 4 hours after receiving GW433908 and RTV on plasma PK sampling days (Days 14 and 28).

### Pharmacokinetic Sampling

On the mornings of Days 14 (Period 1) and 28 (Period 2), pre-dose clinical laboratory samples and a PK blood sample (0 hours) were collected. After administration of study drug, serial 4.5 mL blood samples were collected in sodium citrate-containing tubes at 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 8, 10, and 12 hours post-dose for measurement of APV and GW433908 concentrations.

### Pharmacokinetic Analysis

Plasma samples were analyzed for APV and GW433908 by GlaxoSmithKline using a validated HPLC-MS-MS assay following solid phase extraction. The validated calibration range was 10–10,000 ng/mL, the accuracy (% bias) was ≤ ± 6.35 and the global precision (% CV) was ≤ 7.03. PK analysis of plasma APV

concentration–time data was conducted using non-compartmental methods, with the log-linear trapezoidal option, of the WinNonlin Professional computer software, Version 3.0 (Pharsight Corporation, Mountain View, CA, USA).

### Statistical Analysis of the Pharmacokinetic Data

Plasma APV PK parameters, except  $t_{max,ss}$ , were log<sub>e</sub>-transformed prior to statistical analyses and the comparisons were expressed as ratios on the original scale. No adjustments were made for multiple comparisons for the statistical analyses of the plasma APV PK data. Steady state plasma APV PK parameters were compared within subject as follows:

Arm 1: Treatment B (GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD) to Treatment A (GW433908 700 mg BID + RTV 100 mg BID).

Arm 2: Treatment C (GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD) to Treatment A (GW433908 700 mg BID + RTV 100 mg BID).

Plasma APV PK parameters for each treatment were compared within-subject using SAS Mixed Linear Models procedure. Treatment was considered a fixed effect and subject was considered a random effect. The geometric least squares (GLS) mean ratio and associated 90% confidence interval (CI) were estimated for each plasma APV PK parameter.

### Safety

The following safety data were collected:

- Adverse events (AEs)
- Clinical laboratory assessment (collected under fasting conditions on Days 1, 14, 28 and at follow-up)
- Hematology: hemoglobin, hematocrit, RBC, WBC, WBC with differential, and platelet count
- Chemistry: AST, ALT, alkaline phosphatase, GGT, LDH, glucose, albumin, total protein, total bilirubin, creatinine, uric acid, BUN, serum amylase, calcium, sodium, potassium, chloride, bicarbonate, triglycerides (TG), and cholesterol
- Urinalysis: dipstick for blood and protein
- Vital signs (blood pressure and pulse rate)
- Concurrent medications
- Pregnancy testing

### Statistical Analysis of Clinical Laboratory Data

Day 14, Day 28, and follow-up cholesterol and TG were compared within-subject to Day 1 by ANOVA using SAS Mixed Linear Models procedure. Day was considered a fixed effect and subject was considered a random effect. The least squares (LS) mean change from baseline and associated standard error (SE) were estimated for each treatment and statistical significance was noted (at  $p < 0.05$ ).

## Results

### Subject Accountability

Thirty-one subjects were enrolled, 15 subjects in Arm 1 and 16 subjects in Arm 2. Five subjects, 1 subject from Arm 1 and 4 subjects from Arm 2, prematurely withdrew from the study (3 due to AEs). Two additional subjects, both from Arm 2, were excluded from the PK analysis due to dosing errors or presumed nonadherence.

### Demographics

The demographic characteristics of subjects enrolled in each arm were similar. Overall, more males (81%) than females (19%) and more Whites (77%) than Blacks (23%) were included. Ages ranged from 21–58 years old, body weights ranged from 62–103 kg, heights ranged from 153–187 cm, and BMIs ranged from 20.2–29.8 kg/m<sup>2</sup>.

### Pharmacokinetics

Table 2 • Steady-state plasma APV PK parameter estimates (Geometric mean [95% CI])

Plasma APV PK parameter	Treatment A	Treatment B	Treatment C
	Arms 1 Et 2 Day 14 N = 24	Arm 1 Day 28 N = 14	Arm 2 Day 28 N = 10
$AUC_{0-24}$ (µg·h/mL)	39.6 (34.5–45.3)	37.0 (31.4–43.7)	5.49 (29.1–44.9)
$C_{max,ss}$ (µg/mL)	6.08 (5.38–6.86)	6.11 (5.18–7.21)	4.81 (4.81–6.26)
$C_{24h}$ (µg/mL)	2.12 (1.77–2.54)	1.96 (1.62–2.38)	1.93 (1.45–2.57)
$t_{max,ss}$ (h) <sup>a</sup>	1.50 (0.75–5.00)	1.50 (0.73–2.50)	1.99 (0.75–5.07)

<sup>a</sup>  $t_{max,ss}$  data presented as median (range)

Treatment A = GW433908 700 mg BID + RTV 100 mg BID for 14 days

Treatment B = GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD for 14 days

Treatment C = GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD for 14 days

Figure 1 • Median plasma concentration–time profiles

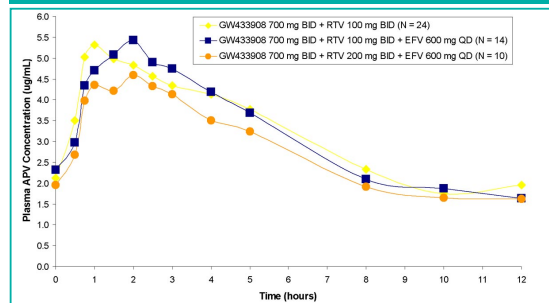


Table 3 • Steady-state plasma APV PK treatment comparisons (GLS mean ratio [90% CI])

Plasma APV PK parameter	Arm 1 Treatment B/Treatment A N = 14	Arm 2 Treatment C/Treatment A N = 10
	$AUC_{0-24}$ (µg·h/mL)	0.91 (0.80–1.03)
$C_{max,ss}$ (µg/mL)	0.98 (0.87–1.11)	0.93 (0.82–1.06)
$C_{24h}$ (µg/mL)	0.83 (0.71–0.96)	1.07 (0.96–1.19)
$t_{max,ss}$ (h) <sup>a</sup>	0.79 (0.48–1.10)	1.08 (0.64–1.52)

<sup>a</sup>  $t_{max,ss}$  data presented as LS mean ratio (90% CI)

Treatment A = GW433908 700 mg BID + RTV 100 mg BID for 14 days

Treatment B = GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD for 14 days

Treatment C = GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD for 14 days

### Safety

#### Adverse Events

All 31 subjects enrolled in the study received GW433908 and RTV. Twenty-seven of the 31 subjects also received EFV. Three subjects prematurely withdrew from the study due to AEs while receiving Treatment A in Period 1; 2 subjects withdrew due to rash and 1 subject withdrew due to diarrhea, fatigue, throat irritation, and pruritus.

Table 4 • Most commonly reported adverse events (> 15%)

Adverse event	Treatment							
	A		B		C		Total	
	No.	n (%)	No.	n (%)	No.	n (%)	No.	n (%)
Any event	51	21 (68)	18	9 (60)	19	9 (56)	88	27 (87)
Loose stools	7	7 (23)	2	2 (13)	0	0	9	8 (26)
Diarrhea	6	6 (19)	0	0	1	1 (6)	7	7 (23)
Fatigue	4	4 (13)	3	3 (20)	1	1 (6)	8	8 (26)
Headache	6	4 (13)	2	2 (13)	3	3 (19)	11	7 (23)
Dizziness/Lightheadedness	2	2 (6)	4	4 (27)	0	0	6	6 (19)
Rash	5	5 (16)	0	0	0	0	5	5 (16)
Nausea	3	3 (10)	2	2 (13)	0	0	5	5 (16)
	Arm 1 N = 31		Arm 2 N = 15		Total N = 31			
Any event	32	13 (87)	56	14 (88)	88	27 (87)		
Loose stools	4	3 (20)	5	5 (31)	9	8 (26)		
Diarrhea	3	3 (20)	4	4 (25)	7	7 (23)		
Fatigue	4	4 (27)	4	4 (25)	8	8 (26)		
Headache	2	2 (13)	9	5 (31)	11	7 (23)		
Dizziness/Lightheadedness	4	4 (27)	2	2 (13)	6	6 (19)		
Rash	0	0	5	5 (31)	5	5 (16)		
Nausea	4	4 (27)	1	1 (6)	5	5 (16)		

No. = number of events

n (%) = number (percentage) of subjects reporting event

Treatment A = GW433908 700 mg BID + RTV 100 mg BID

Treatment B = GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD

Treatment C = GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD

Arm 1 = Treatment A x 14 days immediately followed by Treatment B x 14 days

Arm 2 = Treatment A x 14 days immediately followed by Treatment C x 14 days

### Clinical Laboratory Tests

Clinical laboratory tests remained within the reference range for most parameters. Fasting triglyceride (TG) concentrations increased to above the reference range in 7 of 14 subjects (50%; N = 6 Grade 1 and N = 1 Grade 2) in Arm 1 and 8 of 12 subjects (67%; N = 4 Grade 1 and N = 4 Grade 2) in Arm 2. Fasting total cholesterol concentrations increased to above the reference range on treatment in 1 of 14 subjects (7%; Grade 1) in Arm 1 and 4 of 12 subjects (33%; all Grade 1) in Arm 2. Overall, median values were stable for chemistry and hematology parameters, with the exception of fasting cholesterol and TG, which tended to increase as described in the following table.

Table 5 • Changes in fasting cholesterol and triglycerides

Treatment	Day	N	Cholesterol (mg/dL) <sup>a</sup>	Change from baseline in cholesterol (mg/dL) <sup>a</sup>	TG (mg/dL) <sup>b</sup>	Change from baseline in TG (mg/dL) <sup>b</sup>
A	1 (Baseline)	28	194 (26.7)	NA	114 (59.5)	NA
A	14	28	223 (38.2)	28.5 (6.48)*	190 (71.9)	73.6 (12.4)*
B	28	14	236 (41.3)	48.7 (8.58)*	224 (124)	111 (25.8)*
C	28	12	245 (59.4)	43.3 (12.9)*	321 (173)	201 (41.6)*

\*Significantly different from baseline,  $p < 0.05$

<sup>a</sup> Data presented as mean (standard deviation)

<sup>b</sup> Data presented as LS mean (standard error)

Treatment A = GW433908 700 mg BID + RTV 100 mg BID

Treatment B = GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD

Treatment C = GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD

## Discussion

- Coadministration of EFV 600 mg QD with GW433908 700 mg BID + RTV 100 mg BID resulted in plasma APV  $AUC_{0-24}$  and  $C_{max,ss}$  values equivalent to those obtained for GW433908 700 mg BID + RTV 100 mg BID (without EFV). Coadministration of EFV 600 mg QD with GW433908 700 mg BID + RTV 100 mg BID resulted in a 17% decrease in plasma APV  $C_{24h}$  values; this 17% decrease is unlikely to be of clinical concern.

- AEs reported in this study were similar to those previously reported for APV, RTV, and EFV. There were no obvious differences in the type or number of AEs reported by subjects receiving Treatment B (GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD) or Treatment C (GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD) in Period 2. Treatments B and C were preceded by 2 weeks of Treatment A (GW433908 700 mg BID + RTV 100 mg BID), which may have allowed time for subjects who experienced AEs to either discontinue or become tolerant to the study drugs.

- Statistically significant elevations in fasting cholesterol and TG concentrations were apparent after 2 weeks of GW433908 + RTV dosing. Further increases were noted after an additional 2 weeks of GW433908 + RTV + EFV dosing. There appeared to be an increased incidence of elevations in fasting total cholesterol concentrations as well as larger increases in fasting TG concentrations in subjects receiving Treatment C (GW433908 700 mg BID + RTV 200 mg BID + EFV 600 mg QD) as compared to Treatment B (GW433908 700 mg BID + RTV 100 mg BID + EFV 600 mg QD) in Period 2.

## Conclusions

- Plasma APV concentrations were maintained when RTV 100 mg BID was coadministered with GW433908 700 mg BID + EFV 600 mg QD. The addition of an extra 100 mg of RTV (i.e. RTV 200 mg BID) did not provide significant additional enhancement of plasma APV concentrations.
- AEs reported in this study were similar to those previously reported for APV, RTV, and EFV. The most common AEs were loose stools, diarrhea, fatigue, headache, dizziness/lightheadedness, rash, and nausea. The addition of an extra 100 mg of RTV (i.e. RTV 200 mg BID) to GW433908 and EFV did not increase the incidence of AEs. With the exception of fasting cholesterol and TG concentrations, there were no significant changes in clinical laboratory tests.
- Statistically significant elevations in fasting cholesterol and TG concentrations were apparent following 14 and 28 days of GW433908 + RTV (+/- EFV) coadministration. The addition of an extra 100 mg of RTV (i.e. RTV 200 mg BID) to GW433908 and EFV appeared to be associated with an increased incidence of elevations in fasting total cholesterol concentrations as well as larger increases in TG concentrations.

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