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Poster A-1607

Comparison of GW433908 (908) Single Dose and Steady-state Pharmacokinetics (PK): Induction Potential and AAG Changes (APV10013)

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Introduction

908 is a convenient (flexible dosing, no food or water restrictions) investigational protease inhibitor (PI) with demonstrated antiviral efficacy, durability, and tolerability in antiretroviral (ART)-naïve and PI-experienced subjects. 908, the phosphate ester prodrug of amprenavir (APV), is rapidly converted to APV *in vivo*.

Time-variant plasma APV PK, characterized by reductions in plasma APV AUC values between Day 1 and Day 28, has been observed following 908 administration to HIV-infected subjects. In a Phase II 908 study, APV20001, the Day 28/Day 1 APV AUC ratios (90% CIs) for the 908 regimens were: 0.73 (0.61-0.87) for 908 1395 mg BID and 0.55 (0.47-0.66) for 908 1860 mg BID.[1]

Time-variance in plasma APV PK has been correlated with reductions in plasma α-1-acid glycoprotein (AAG) concentrations, an APV binding protein, as patients receive effective antiretroviral therapy.[2] However, in the Phase II 908 study, plasma APV AUC values declined despite statistical adjustment for AAG reductions, suggesting that a mechanism other than, or in addition to, reductions in AAG is responsible for the time-variance. Mechanisms other than changes in AAG that could theoretically contribute to reduced APV exposure with multiple dosing include limitation of absorption and increased elimination through metabolic induction (CYP3A4).

As part of a PK interaction study with atorvastatin (ATO), time-variance in plasma APV PK, and potential mechanisms, were further evaluated in healthy subjects.

Methods

39 healthy adults were enrolled and 26 subjects completed the study as described in Table 1. This poster presents data for the 12 subjects who received 908 1400 mg BID alone (ie, Arm 1 in Period 2) as described in Table 2. The 908-ATO PK interaction data are presented elsewhere.[3]

Table 1 • Study Design

Period 1			Period 2	Period 3
Arm 1 21 enrolled 12 completed	ATO 10 mg QD x 4 days	Washout x 7-10 days	908 1400 mg BID x 14 days	ATO 10 mg QD + 908 1400 mg BID x 4 days
Arm 2 18 enrolled 14 completed	ATO 10 mg QD x 4 days	Washout x 7-10 days	908 700 mg BI + RTV 100 mg BID x 14 days	ATO 10 mg QD + 908 700 mg BID + RTV 100 mg BID x 4 days

Table 2 • Study Design: Arm 1, Period 2 Details

Day -1	Day 1	Days 2-13	Day 14
	908 single dose	908 BID dosing	908 AM dosing
	24-hour serial PK sampling	Predose PK sampling Days 3, 6, 9, 12, 13	12-hour serial PK sampling
	AAG concentration		AAG concentration
24-hour 6β-HC/C			24-hour 6β-HC/C

Serial plasma PK samples were collected on Days 1 and 14 as follows: 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, and 12 hours on both days, plus at 16 and 24 hours on Day 1. Plasma PK samples were analyzed for APV by a validated HPLC-MS-MS method.

The achievement of steady state by Day 14 was assessed by calculating the 90% CI of the slope from linear regression analysis of the Day 12, 13, and 14 predose plasma APV concentrations. Day 1 and Day 14 PK parameters were estimated by noncompartmental methods and compared by ANOVA, with and without correction for AAG.

Urine samples were analyzed for 6β-hydroxycortisol (6β-HC) and cortisol (C) by an HPLC-MS-MS method. The amount of each compound excreted in the urine over 24 hours (AE_{0-24}) was calculated and the ratio of these amounts (6β-HC/C ratio) was compared between Day 14 and Day 1 by ANOVA to assess potential metabolic (CYP3A4) induction by 908.

Plasma AAG concentrations were compared by ANOVA.

Results

Twelve (12, 100%) males and equal numbers of whites and blacks (6/12, 50%) were included in the analysis. Ages ranged from 18 to 54 years, body weights ranged from 56.3-86.9 kg, heights ranged from 165-196 cm, and BMIs ranged from 20.6 to 28.4 kg/m^2.

The safety results are presented elsewhere.[3]

Steady-state was achieved by Day 14 because the 90% CI from the linear regression of log-transformed plasma APV trough concentrations collected on Days 12, 13, and 14 included zero and the slope estimate was close to zero: -0.1051 (-0.3036 to 0.0933).

Median Day 1 and Day 14 plasma APV concentration-time profiles are displayed in Figure 1. PK parameter estimates are presented in Table 3 and PK comparisons are presented in Table 4. The geometric mean steady-state plasma APV PK parameter values predicted from the single dose PK values assuming that PK is not time-variant were: $AUC_{\tau,ss}$: 19.5 h*µg/mL, $C_{max,ss}$: 4.80 µg/mL, and $C_{\tau,ss}$: 0.44 µg/mL. There was an unexpected 14% decrease in plasma AAG concentrations between Days 1 and 14 (Table 5). Inclusion of AAG as a covariate in the ANOVA model accounted for the lower than predicted AUC value but did not account for the lower than predicted $C_{\tau,ss}$ value. The $C_{max,ss}$ value was similar to the predicted value.

Figure 1 • Median Plasma APV Concentration-time Profiles

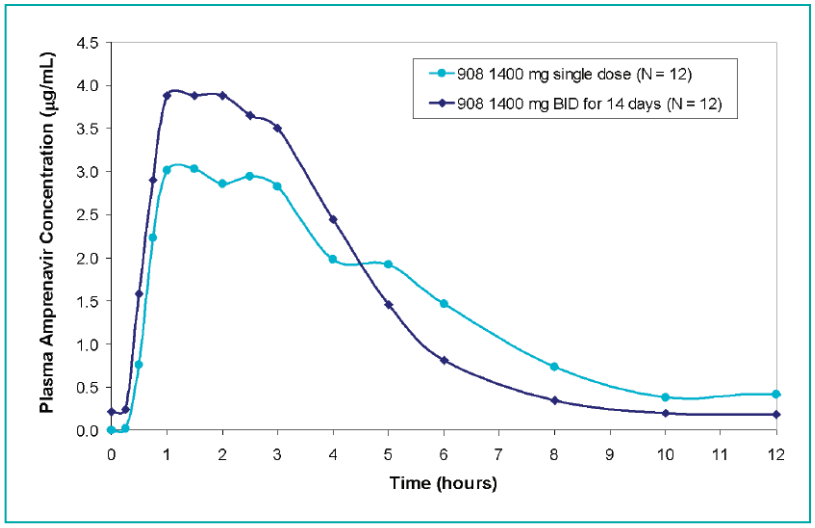

Table 3 • Plasma APV PK Parameter Estimates (Geometric Mean [95% CI])

Plasma APV PK Parameter	Day 1	Day 14[b]
AUC (h*µg/mL)[a]	19.5 (15.0-25.4)	17.0 (13.3-21.9)
C_{max} (µg/mL)	4.00 3.11-5.14)	4.52 (3.41-6.00)
C_{12} (µg/mL)	0.369 (0.254-0.536)	0.23 (0.17-0.30)

[a]AUC_{∞} for Day 1 and $AUC_{\tau,ss}$ for Day 14
[b]Predicted geometric mean Day 14 $AUC_{\tau,ss}$ = 19.5 h*µg/mL, $C_{max,ss}$ = 4.80 µg/mL, and $C_{\tau,ss}$ = 0.44 µg/mL

Table 4 • Plasma APV PK Comparisons (Day 14/Day 1) (GLS Mean Ratio [90% CI])

Plasma APV PK Comparison	Without AAG Covariate[a]	With AAG Covariate
$AUC_{\tau,ss}/AUC_{\infty}$	0.87 (0.70-1.10)	0.98 (0.75-1.29)
$C_{max,ss}/C_{max}$	1.13 (0.92-1.38)	1.29 (1.00-1.68)
$C_{\tau,ss}/C_{12}$	0.62 (0.53-0.72)	0.62 (0.50-0.77)

[a]Predicted GLS mean ratio = 1.20 for $C_{max,ss}$ and $C_{\tau,ss}$

Table 5 • Plasma AAG Concentration Summary (Geometric Mean [95% CI]) and GLS Mean Difference (Day 14–Day 1), 95% CI

Day 1	Day 14	Day 14–Day 1
75.8 (65.3-88.0)	65.6 (59.2-72.7)	-11.23 (-20.8-1.69)

AAG concentration unit = mg/dL

Table 6 • Urine 6β-HC/C Ratio Comparison (Day 14/Day 1) (GLS Mean Ratio [90% CI])

Day -1	Day 14	Day 14/Day -1
6.90	5.90	0.86 (0.72-1.02)

Discussion

- The ability to evaluate the metabolic induction potential of APV in HIV-infected subjects is confounded by reductions in plasma AAG concentrations which occur as patients are effectively treated. Thus, this study was designed to evaluate single-dose and steady-state plasma APV PK in healthy adult subjects in order to gain a better understanding of the mechanism(s) resulting in time-variant plasma APV PK.
- There was a small, approximately 13%, decrease in plasma APV AUC over 14 days of 908 1400 mg BID dosing. There may be multiple mechanisms causing this reduction, including induction of CYP3A4, induction of P-glycoprotein, limitation of absorption, and plasma AAG changes.
- Despite the initial decrease in plasma APV C_{12} values, plasma APV $C_{\tau,SS}$ values were stabilized between Days 12 and 14 (ie, steady-state was achieved).
- It is apparent that 908 administered at a dose of 1400 mg BID is not a potent CYP3A4 inducer based on the average 14% decrease in the 24-hour urinary 6β-HC/C ratio observed in this study, rather than an increase in this ratio which would indicate induction.

Conclusions

- ◆ There was a small, approximately 13%, decrease in plasma APV AUC over 14 days of 908 1400 mg BID dosing in healthy subjects.
- ◆ GW433908 is not a potent CYP3A4 inducer based on the urinary 6β-HC/C ratio.
- ◆ Given the inconsistent changes in the plasma APV PK parameters, the lack of evidence of CYP3A4 induction, and the inability for AAG to fully account for the plasma APV PK changes, the mechanisms responsible for time-variant plasma APV PK are likely multifactorial.

References

1. Wood R, et al. Manuscript submitted to *Antimicrob Agents Chemother*.
2. Sadler BM, et al. *Antimicrob Agents Chemother*. 2001;45(3):852-856.
3. Wire MB, et al. *43rd ICAAC*. 2003. Abstract A-1622.