

# The Pharmacokinetic (PK) Interaction Between GW433908 (908) with Lopinavir (LPV)/Ritonavir (RTV) (APV10011 and APV10012)

## Introduction

908 is a convenient (flexible dosing, no food or water restrictions) protease inhibitor approved in the US (as Lexiva) for the treatment of HIV-infection in combination with other antiretroviral agents. 908, the phosphate ester prodrug of amprenavir (APV), is rapidly and extensively converted to APV *in vivo*. 908 700 mg is a molar equivalent dose to APV 600 mg.

Previous data demonstrated that the combination of APV (Agenerase; AGN) and LPV/RTV (Kaletra) resulted in reduced plasma concentrations of LPV relative to LPV/RTV and reduced plasma concentrations of APV relative APV/RTV; although APV concentrations were elevated relative to APV 1200 mg BID.

### AGN 600 mg BID + LPV/RTV 400/100 mg BID vs AGN 600mg BID + RTV 100 mg BID and vs LPV/RTV 400/100 mg BID<sup>1</sup>

- LPV C<sub>max</sub> ↓~35%
- APV C<sub>max</sub> ↓~42%

### AGN 750 mg BID + LPV/RTV 400/100 mg BID vs AGN 1200 mg BID and vs LPV/RTV 400/100 mg BID<sup>2</sup>

- LPV C<sub>max</sub> ↓57%, AUC<sub>0-12</sub> ↓38%, C<sub>max,ss</sub> ↓28%
- APV C<sub>max,ss</sub> ↑5.82-fold, AUC<sub>0-12</sub> ↑72%, C<sub>max,ss</sub> ↑12%

Therefore, two studies (APV10011 and APV10012) were conducted with 908 and LPV/RTV to assess dosing strategies to overcome this interaction.

## Methods

Table 1 • Study Design

Study APV10011			
Arm	Period 1	28-day washout	Period 2
A	908 + RTV		908 + LPV/RTV
B	908 + LPV/RTV		908 + RTV
C	LPV/RTV		908 + LPV/RTV
D	908 + LPV/RTV	LPV/RTV	
Study APV10012			
Arm	Period 1	8-day washout	Period 2
A	908 + RTV		908 + RTV + LPV/RTV
B	908 + RTV + LPV/RTV		908 + RTV
C	LPV/RTV		908 + RTV + LPV/RTV
D	908 + RTV + LPV/RTV	LPV/RTV	

908 + RTV = 908 700 mg BID + RTV 100 mg BID  
LPV/RTV = LPV/RTV 400/100 mg BID  
908 + LPV/RTV = 908 1400 mg BID + LPV/RTV 533/133 mg BID  
908 + RTV + LPV/RTV = 908 700 mg BID + RTV 100 mg BID + LPV/RTV 400/100 mg BID

For each period: Subjects received study drugs at the study center on Day 1 and returned on Day 7 for compliance and safety assessments. Subjects were housed at the study center from the evening of Day 13 until the morning of Day 15. A pre-dose PK sample was collected on the evening of Day 13 and subjects initiated a 10-hour fast. Subjects received a moderate-fat meal on the morning of Day 14; dosing and serial PK sampling were initiated within 15 minutes after meal consumption.

PK samples were assayed for APV and LPV concentrations by separate validated HPLC-MS-MS methods. Noncompartmental PK analysis was performed. Treatment comparisons were conducted by ANOVA considering treatment and period as fixed effects and subject as a random effect. The ratio of GLS means and associated 90% CIs were estimated.

## Results

Table 2 • Demographics

Study	Sex	Race	Age	Weight	Height	BMI
APV10011	M: 64%	W: 94%	16-60 yr	58-98 kg	157-185 cm	20-29 kg/m <sup>2</sup>
	F: 36%	B: 6%				
APV10012	M: 67%	W: 75%	18-57 yr	53-96 kg	151-190 cm	20-29 kg/m <sup>2</sup>
	F: 33%	B: 8%				
		H: 14%				
		A: 3%				

## ADVERSE EVENTS

- A large percentage of subjects prematurely discontinued due to AEs while receiving one of the combination regimens.
- **APV10011:** 13 subjects prematurely discontinued, 11 during combination treatment (908+LPV/RTV). 10 premature discontinuations were due to AEs, including GI disturbances (N = 6), rash (N = 3), and a combination of lightheadedness, tingling lips, racing heart, headache, and dry mouth (N = 1).
- **APV10012:** 16 subjects prematurely discontinued, 12 during combination treatment (908+RTV+LPV/RTV). 13 premature discontinuations were due to AEs, including GI disturbances (N = 7), rash (N = 2), elevated bilirubin (N = 2, 1 also had elevated triglycerides), elevated AST, ALT, and LDH (N = 1), and perioral numbness (N = 1).
- **Both Studies:** AEs reported in both studies by >1 subject were diarrhea/loose stools, nausea, vomiting, colic, headache, oral/perioral numbness/tingling, pruritus, rash, dizziness/lightheadedness and sore throat. Generally, AEs were more frequently reported on the combination treatments, most notably diarrhea, nausea, vomiting, colic, and oral/perioral numbness/tingling.

## CLINICAL LABORATORY CHANGES

- There were no significant changes in clinical labs with the exception of fasting total cholesterol and triglycerides.

Table 3 • Changes in Fasting Total Cholesterol and Triglycerides: Day 14 – Day 1 (Least Squares Mean Increase)

Dose (mg)	Total Cholesterol (mg/dL)		Triglycerides (mg/dL)	
	908	LPV/RTV	RTV	LPV/RTV
700	0	100	+21.2	+14.7
0	400/100	0	+27.9	+21.0
1400	533/133	0	+34.7	NA
700	400/100	100	NA	+41.5

## PHARMACOKINETICS

### Amprenavir

Plasma APV concentrations were significantly reduced for both combination regimens relative to 908 + RTV as demonstrated in Figure 1 and Table 4. When compared across studies, the 908 1400 mg BID + LPV/RTV 533/133 mg BID regimen appeared to deliver higher plasma APV concentrations than the 908 700 mg BID + RTV 100 mg + LPV/RTV 400/100 mg BID regimen.

Figure 1 • Median Plasma APV Concentration–Time Profiles

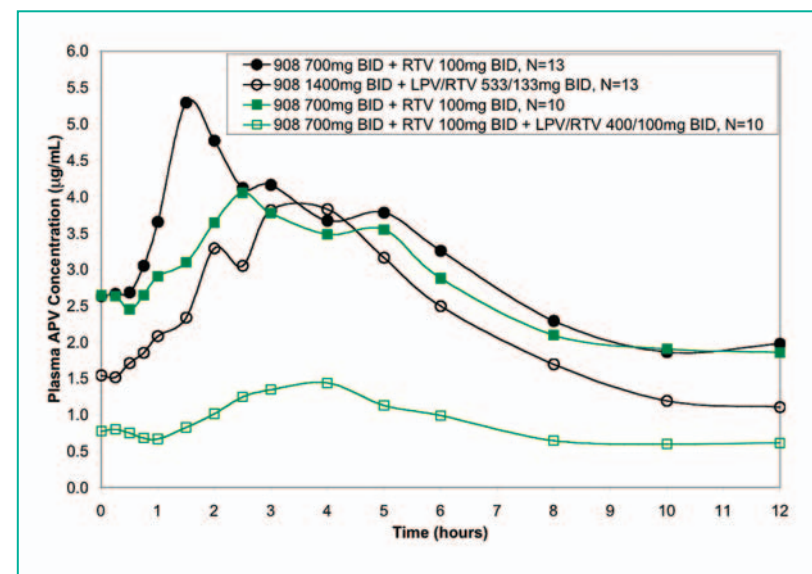


Table 4 • Plasma APV PK Summary (Geometric Mean [95% CI]) and Treatment Comparisons (Geometric Least Squares Mean Ratio [90% CI])

Plasma APV PK Parameter	Study APV10011 N = 13			Study APV10012 N = 10		
	908+LPV/RTV	908+RTV	908+LPV/RTV vs 908+RTV	908+RTV LPV/RTV	908+RTV	908+RTV LPV/RTV vs 908+RTV
C <sub>max,ss</sub> (µg/mL)	4.99 (3.94-6.33)	5.72 (5.13-6.39)	0.87 (0.74-1.02)	1.88 (1.24-2.84)	4.61 (3.57-5.96)	0.42 (0.30-0.58)
AUC <sub>0-12</sub> (h*µg/mL)	27.2 (21.6-34.2)	36.5 (32.0-41.7)	0.74 (0.65-0.85)	11.3 (8.14-15.7)	31.2 (24.6-39.6)	0.37 (0.28-0.49)
C <sub>min</sub> (µg/mL)	1.35 (1.01-1.81)	2.35 (2.02-2.74)	0.58 (0.48-0.70)	0.72 (0.52-1.00)	2.10 (1.64-2.67)	0.35 (0.27-0.46)

908 + RTV = 908 700 mg BID + RTV 100 mg BID  
908 + LPV/RTV = 908 1400 mg BID + LPV/RTV 533/133 mg BID  
908 + RTV + LPV/RTV = 908 700 mg BID + RTV 100 mg BID + LPV/RTV 400/100 mg BID

### Lopinavir

Increasing the dose of LPV/RTV or administering additional RTV when combined with 908 either maintained or increased Plasma LPV concentrations (variability was increased) as demonstrated in Figure 2 and Table 5.

Figure 2 • Median Plasma LPV Concentration–Time Profiles

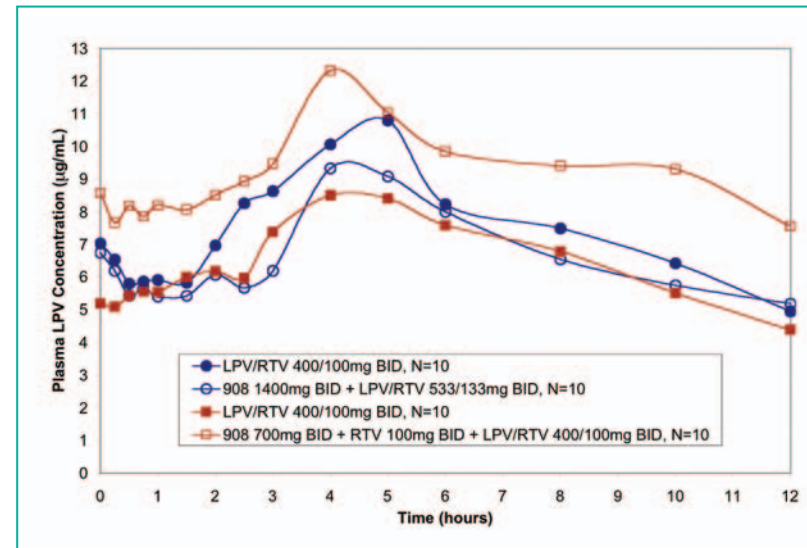


Table 5 • Plasma LPV PK Summary (Geometric Mean [95% CI]) and Treatment Comparisons (Geometric Least Squares Mean Ratio [90% CI])

Plasma LPV PK Parameter	Study APV10011 N = 10			Study APV10012 N = 10		
	908+LPV/RTV	908+RTV	908+LPV/RTV vs 908+RTV	908+RTV LPV/RTV	908+RTV	908+RTV LPV/RTV vs 908+RTV
C <sub>max,ss</sub> (µg/mL)	10.3 (7.43-14.4)	11.3 (9.32-13.6)	0.95 (0.66-1.35)	12.7 (10.0-16.1)	9.80 (8.30-11.6)	1.30 (1.15-1.47)
AUC <sub>0-12</sub> (h*µg/mL)	83.9 (60.6-116)	92.6 (78.8-109)	0.95 (0.67-1.33)	112 (88.6-142)	81.9 (66.1-101.6)	1.37 (1.20-1.55)
C <sub>min</sub> (µg/mL)	6.07 (4.29-8.61)	6.05 (5.13-7.14)	1.01 (0.74-1.39)	8.14 (6.00-11.0)	5.34 (4.05-7.05)	1.52 (1.28-1.82)

LPV/RTV = LPV/RTV 400/100 mg BID  
908 + LPV/RTV = 908 1400 mg BID + LPV/RTV 533/133 mg BID  
908 + RTV + LPV/RTV = 908 700 mg BID + RTV 100 mg BID + LPV/RTV 400/100 mg BID

## Discussion

Similar to the combination of APV (Agenerase; AGN) + LPV/RTV (Kaletra), plasma APV concentrations were significantly reduced when 908 was combined with LPV/RTV relative to 908/RTV; although plasma APV concentrations were elevated relative to historical data for 908 1400 mg BID.<sup>3</sup>

Plasma APV PK values for 908 1400 mg BID + LPV/RTV 533/133 mg BID appear similar or higher than for AGN 750 mg BID + LPV/RTV 400/100 mg BID.

### 908 1400 mg BID + LPV/RTV 533/133 mg BID

C<sub>max,ss</sub> 1.35 µg/mL, AUC<sub>0-12</sub> 27.2h\*µg/mL, C<sub>max,ss</sub> 4.99 µg/mL

### AGN 750 mg BID + LPV/RTV 400/100 mg BID<sup>2</sup>

C<sub>max,ss</sub> 1.38 µg/mL, AUC<sub>0-12</sub> 19.4h\*µg/mL, C<sub>max,ss</sub> 3.37 µg/mL

- The mechanism(s) of the interaction between 908 and LPV/RTV likely involves a complex balance between induction and inhibition of metabolic and, potentially, transport processes
- Another study demonstrated that separation of 908 and LPV/RTV dose administration times does not overcome the negative impact of LPV/RTV on APV PK<sup>4</sup>
- *In vitro* testing completed to elucidate the mechanism of the interaction demonstrated: a) No change in 908 dissolution when LPV/RTV was present in the media, b) LPV and RTV do not inhibit alkaline phosphatase (enzyme converting 908 to APV), c) LPV is a moderate activator and RTV and APV are high activators of PXR, a marker of CYP3A4 and P-gp induction<sup>5</sup>
- Both 908 and LPV/RTV are CYP3A4 inhibitors<sup>3,6</sup>
- LPV, RTV, and APV are P-gp substrates
- 908, LPV, and RTV have demonstrated P-gp induction<sup>7,8,9</sup> and RTV has also demonstrated P-gp inhibition<sup>10</sup>
- Despite the complex PK interaction between APV and LPV/RTV, immunological and virological benefit have been reported for salvage regimens containing APV and LPV/RTV<sup>11,12</sup>

## Conclusions

- ◆ Although co-administration of increased doses of 908 and LPV/RTV appeared to deliver higher plasma APV concentrations than adding extra RTV to the combination, plasma APV concentrations were significantly reduced for both combination regimens
- ◆ Co-administration of increased doses of 908 and LPV/RTV maintained LPV concentrations and adding RTV to the combination increased plasma LPV concentrations; variability was increased
- ◆ The 908 and LPV/RTV combinations were poorly tolerated in healthy adult subjects, especially GI intolerance
- ◆ No dosing recommendation can be given for the combination of 908 and LPV/RTV

## References

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