



# Bidirectional Pharmacokinetic Interaction between Posaconazole and Fosamprenavir

N-104

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## 1. Introduction

Infections with fungi and yeasts frequently occur in patients infected with the human immunodeficiency virus (HIV). Azole antifungal drugs are first line therapy in the prophylaxis and treatment of invasive fungal infections. Posaconazole is a second generation triazole with a broad antifungal spectrum against yeasts and moulds. It has proven to be effective in the prevention and treatment of invasive fungal infections in high-risk patients, including those who are immunosuppressed. The combination of antiretroviral drugs (either non-nucleoside reverse transcriptase inhibitors (NNRTIs) or protease inhibitors) with azole antifungal drugs is not without risk. Combining fosamprenavir/ritonavir with posaconazole may lead to a bidirectional drug-drug interaction.

To manage the interaction between fosamprenavir/ritonavir and posaconazole, we hypothesized that ritonavir can be replaced by posaconazole as an alternative booster of fosamprenavir with no significant influence on posaconazole pharmacokinetics.

## 2. Method

This open-label, 3-period, cross-over, single-centre, phase-I, multiple-dose trial was conducted from March to May 2009. This trial was conducted in healthy male and female volunteers, aged 18-55 years with a body mass index of 18 to 30 kg/m<sup>2</sup>. All subjects received the following three treatments for 10 days, separated by washout periods of 17 days: posaconazole 400 mg BID; fosamprenavir/ritonavir 700/100 mg BID; posaconazole 400 mg BID with fosamprenavir 700 mg BID.

## 3. Results

Twenty-four healthy volunteers (10 females and 14 males) were included in this trial. The mean (range) age, body weight and body mass index were 36 (18-54) years, 73 (44-104) kg and 23 (18-29) kg/m<sup>2</sup>, respectively. 21 Participants were Caucasian, three participants were from Hispanic ethnicity.

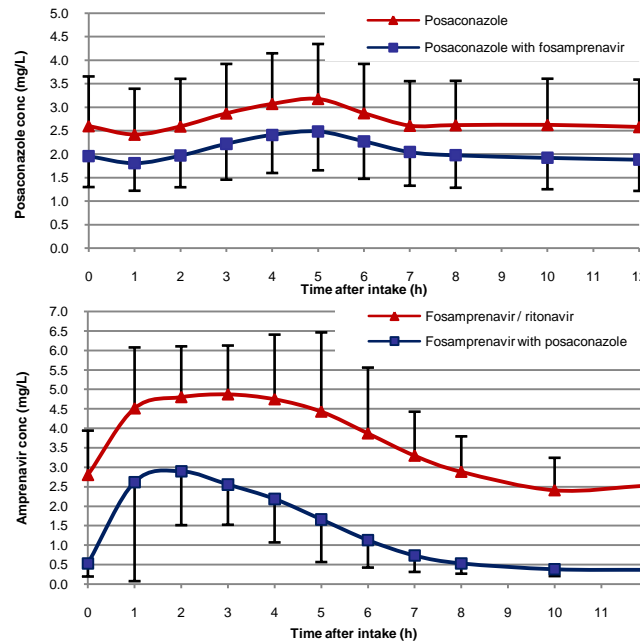
20 subjects (9 female and 11 male) completed the trial. Geometric mean ratios (GMR; +90% CI) of posaconazole AUC and C<sub>max</sub> when taken with fosamprenavir vs. posaconazole alone were 0.77 (0.68-0.87) and 0.79 (0.71-0.89), respectively. The GMRs of amprenavir AUC and C<sub>max</sub> when taken as fosamprenavir and posaconazole vs. fosamprenavir/ritonavir were 0.35 (0.32-0.39) and 0.64 (0.55-0.76), respectively.

No serious adverse events were reported during the trial.

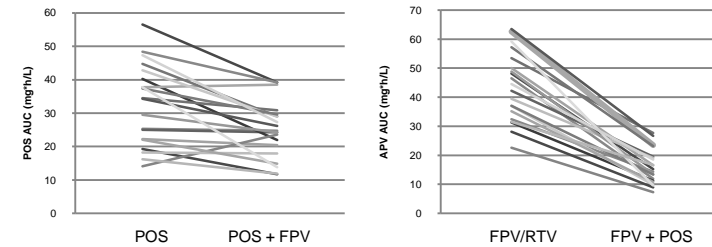
**Table 1: Pharmacokinetic Parameter Estimates and Treatment Comparison of Posaconazole and Fosamprenavir**

Parameter	Steady-State Plasma Pharmacokinetic Parameter Estimates, Geometric Mean (95% CI)		Treatment Comparisons, Geometric Mean Ratio (90% CI)	
	Posaconazole	Amprenavir	POS + FPV vs POS alone	FPV + POS vs FPV / RTV
AUC (mg•h/L)	30.4 (25.2-36.7)	42.0 (36.7-47.9)	0.77 (0.68 - 0.87)	0.35 (0.32 - 0.39)
C <sub>max</sub> (mg/L)	3.0 (2.5-3.6)	3.7 (3.0-4.5)	0.79 (0.71 - 0.89)	0.64 (0.55 - 0.76)
T <sub>max</sub> (h)	5 (4-5)	2 (1-3)	-	-
C <sub>min</sub> (mg/L)	2.2 (1.8-2.7)	0.3 (0.2-0.4)	-	-
CL/F (L/h)	13.2 (10.9-15.9)	47.2 (39.5-56.4)	-	-
V/F (L)	609 (489-759)	241 (171-341)	-	-
T1/2 (h)	32.1 (26.0-39.7)	3.5 (2.7-4.7)	-	-

**Figure 1: Steady State Pharmacokinetic profiles of POS and FPV alone or in combined use**



**Figure 2: Individual changes in Area under the Concentration Time Curve**



**Table 3: Number of subjects experiencing adverse events during the different periods of the trial (possibly, probably and definitely related to treatment)**

System organ class	POS (N=22)	FPV / RTV (N=21)	POS + FPV (N=23)
Gastrointestinal disorders			
abdominal discomfort	3	1	1
flatulence	1		1
less appetite		1	
nausea	2	3	3
loose stool	2	9	4
Nervous System disorders			
depression			1
fatigue	2	1	3
headache	1	4	1
Skin and subcutaneous tissue disorders			
bloating		1	
flushing	1		
petechia	1		
pimples	1	1	1
pruritis	1		1
rash		1	3
Hepatobiliary disorders			
ALAT increased		1	
ASAT increased	1	1	
Other / Unclassified		1	1

## 4. Conclusions

- ✓ Our study demonstrates the complexity of combined use of antiretroviral and antifungal drugs
- ✓ Combined use of fosamprenavir with posaconazole results in subtherapeutic amprenavir concentrations
- ✓ Fosamprenavir can not be used unboosted with posaconazole
- ✓ Posaconazole concentrations must be monitored by means of therapeutic drug monitoring to assure adequate exposure
- ✓ Future studies must reveal whether ritonavir boosted fosamprenavir can be safely combined with posaconazole