

## ABSTRACT

**Background:** Tipranavir (TPV) is a next generation protease inhibitor (PI) with potent activity against multiple PI-resistant HIV-1. This study determined the effects of steady-state TPV/r 500/200 mg bid on the pharmacokinetics (PK) of acyclovir, administered as the prodrug valacyclovir, a commonly used therapy for herpes virus infections.

**Methods:** Open label, one-sequence cross-over PK study in HIV-negative adults administered single oral doses of valacyclovir 500 mg alone and in combination with TPV/r. Plasma drug concentrations were measured by validated LC/MS/MS; PK was determined by non-compartmental methods. The geometric mean ratio and 90% CI [GMR, 90% CI] was used to evaluate the drug interaction.

**Results:** Twenty-six of 29 subjects completed the trial. With steady-state TPV/r, acyclovir C<sub>max</sub> decreased 4.9% [0.95, 0.88–1.02], C<sub>p12h</sub> increased 18.9% [1.19, 1.11–1.27] and AUC<sub>0-12h</sub> increased 6.6% [1.07, 1.04–1.09]. The effect of single-dose valacyclovir on TPV C<sub>max</sub>, C<sub>p12h</sub>, and AUC<sub>0-12h</sub> were minimal (+2.3%, -1.9% and +1.0%, respectively) while RTV C<sub>max</sub>, C<sub>p12h</sub>, and AUC<sub>0-12h</sub> decreased 19.4%, 5.7% and 14.0%, respectively. Study medications were generally well tolerated. The majority of subjects experienced at least one AE, most of which were mild. As expected, the majority of AEs were gastrointestinal disorders. Three subjects discontinued TPV/r treatment as a result of drug-related increases in ALT/AST, including one subject who experienced mild upper abdominal pain. All subjects recovered without sequelae.

**Conclusions:** When administered as a single dose of valacyclovir with steady-state TPV/r, there were no clinically important changes in acyclovir, TPV, or RTV PK. These results indicate that these drugs can be co-administered safely with no dose adjustments.

## INTRODUCTION

Tipranavir (TPV, APTIVUS™) is an approved protease inhibitor (PI) with potent activity against multiple PI resistant HIV-1. To achieve therapeutic plasma TPV concentrations in treatment experienced patients, dosing of 500 mg TPV with 200 mg of ritonavir (TPV/r) twice-daily is required [1].

Valacyclovir hydrochloride (VAL) (Valtrex®) [2] is the salt of the L-valyl ester of the antiviral drug acyclovir (Zovirax®). It is converted to acyclovir (ACV) which has antiviral activity against herpes simplex virus types 1 (HSV-1) and 2 (HSV-2) and varicella-zoster virus (VZV) both *in vitro* and *in vivo*. VAL is rapidly absorbed from the gastrointestinal tract after oral administration, and is converted to ACV and L-valine by first-pass intestinal and/or hepatic metabolism. Unlike ACV, VAL is a substrate for intestinal and renal peptide transporters [3].

Infections with HSV-1 and HSV-2 are common in HIV+ patients and reactivation of herpes zoster occurs in 10 to 20% of HIV infected patients. Both HSV-1 and HSV-2 can be successfully treated with ACV or VAL. Since the concomitant use of VAL with TPV/r is very likely to occur in clinical practice, it is important to establish the drug-drug interaction potential for these medications.

## METHODS

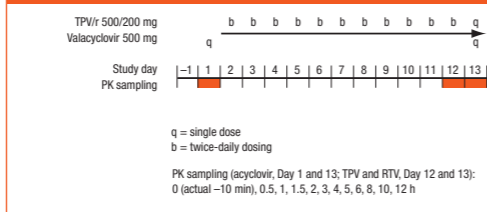
### Study Design

Open-label, single-sequence pharmacokinetic drug-drug interaction study with steady-state TPV/r 500/200 mg and single-dose VAL 500 mg in healthy female and male volunteers. Figure 1 describes the study design. The study was conducted in compliance with the protocol, the Declaration of Helsinki (1996 Version) and the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Written informed consent was obtained from each volunteer prior to participation in the trial and in accordance with the regulatory and legal requirements of Germany.

### Bioanalytical

A bioanalytical method was established at NOTOX B.V. (Hambakenwetering 7, 5231 DD 's-Hertogenbosch, The Netherlands) to measure the concentrations of TPV, RTV and ACV in heparinized human plasma samples. The method was based on HPLC with tandem mass spectrometric detection. For TPV and RTV, the standard curve concentration ranges were 25 to 2500 ng/mL and 1,000 to 100,000 ng/mL; for ACV, the standard curve concentration range was 5.00 to 1000 ng/mL.

Figure 1: TPV/r – valacyclovir drug-drug interaction study design



**Pharmacokinetics**  
Plasma drug concentration–time profiles on Days 1, 12 and 13 were analyzed with WinNonlin Professional version 5.0 (Pharsight Corporation, Mountain View, California, USA) and non-compartmental pharmacokinetics were determined. The geometric mean ratio (GMR) and the associated 90% confidence interval (CI) were derived and evaluated for each primary pharmacokinetic parameter (AUC, C<sub>max</sub> and C<sub>p12h</sub>) using SAS Release 8.2 (SAS Institute, Cary, North Carolina, USA).

## RESULTS

### Study population

Table 1 summarizes the basic demographics of the study population. Twenty-nine subjects were randomized and treated. A total of 26 subjects completed the trial as planned. Three subjects discontinued treatment as a result of adverse events.

Table 1: Demographics and baseline characteristics of the study population

Number of subjects	29
Gender N (%)	
Male	25 (86.2%)
Female	4 (13.8%)
Race N (%)	
White	29 (100%)
Age (years)	43.1 ± 8.6 (28 – 58)
Height (cm)	177.7 ± 8.4 (156 – 196)
Weight (kg)	78.4 ± 10.9 (60 – 111)
Body mass index (kg/m <sup>2</sup> )	24.82 ± 2.76 (19.8 – 29.7)

Note: Arithmetic mean ± SD (minimum – maximum)

### Pharmacokinetics

#### Effect of TPV/r on ACV

The pharmacokinetics of ACV alone and co-administered with steady-state TPV/r 500/200 mg bid are summarized in Table 2. Steady-state TPV/r had no effect on acyclovir C<sub>max</sub> or AUC (less than a 10% change relative to valacyclovir alone) but was associated with a 19% increase in the concentration of acyclovir measured 12 h after valacyclovir dosing (C<sub>p12h</sub>) (GMR [90% CI]: 1.19 [1.11, 1.27]).

The plasma ACV concentration–time profile for VAL alone and when co-administered with TPV/r is shown in Figure 2. The interaction of TPV/r with ACV is shown in Figure 3.

For a 500 mg single dose of valacyclovir, C<sub>max</sub>, AUC and t<sub>1/2</sub> for acyclovir in this clinical study were comparable to the values reported in the VALTRESX® product label [2] (mean ± SD C<sub>max</sub>, 3.28 ± 0.83 μg/mL; AUC, 11.59 ± 1.79 h•μg/mL; typical average range for t<sub>1/2</sub>, 2.5 – 3.3 h).

#### Effect of VAL on TPV and RTV

The pharmacokinetics for TPV and RTV alone and when co-administered with VAL 500 mg are summarized in Tables 3 and 4, respectively. A single dose of valacyclovir had no effect on steady-state TPV C<sub>max</sub>, C<sub>p12h</sub> or AUC<sub>0-12h</sub> (less than a 10% change relative to TPV/r alone). A single dose of VAL had no effect on steady-state RTV C<sub>p12h</sub> (less than a 10% change relative to TPV/r alone) but was associated with a 19% decrease in C<sub>max</sub> and a 14% decrease in AUC<sub>0-12h</sub>.

Table 2: Effect of steady-state TPV/r 500/200 mg bid on the single-dose pharmacokinetics of acyclovir (N=26 subjects)

Pharmacokinetic parameter	Treatment	Mean	SD	Median	Geometric mean	Geometric mean ratio (90% CI)
T <sub>max</sub> (h)	VAL	1.6	0.5	1.5	1.5	–
	VAL + TPV/r	2.0	0.5	2.0	2.0	–
C <sub>max</sub> (μg/mL)	VAL	3.81	0.88	3.64	3.72	0.95 (0.88, 1.02)
	VAL + TPV/r	3.64	0.85	3.55	3.54	–
C <sub>p12h</sub> (μg/mL)	VAL	0.13	0.04	0.12	0.12	1.19 (1.11, 1.27)
	VAL + TPV/r	0.15	0.05	0.14	0.15	–
AUC <sub>0-12h</sub> (h•μg/mL)	VAL	11.17	2.25	10.86	10.97	1.06 (1.04, 1.09)
	VAL + TPV/r	11.88	2.45	11.91	11.64	–
AUC <sub>0-∞</sub> (h•μg/mL)	VAL	11.69	2.35	11.30	11.48	1.07 (1.04, 1.09)
	VAL + TPV/r	12.48	2.54	12.44	12.24	–
CL/F (L/h)	VAL	44.3	8.3	44.3	43.6	–
	VAL + TPV/r	41.7	8.6	40.2	40.9	–
Vz/F (L)	VAL	175.2	44.3	175.0	169.8	–
	VAL + TPV/r	163.3	41.3	163.5	158.1	–
t <sub>1/2</sub> (h)	VAL	2.73	0.39	2.63	2.70	–
	VAL + TPV/r	2.70	0.34	2.65	2.68	–

Figure 2: Plasma acyclovir concentration–time profile after a single dose of valacyclovir 500 mg alone and co-administered with steady-state TPV/r 500/200 mg bid

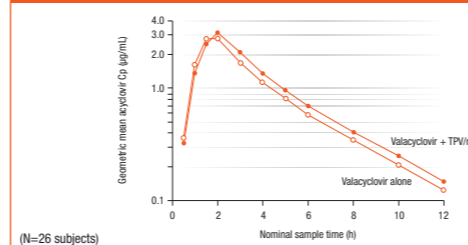


Figure 3: Effect of steady-state TPV/r on single-dose plasma acyclovir C<sub>max</sub>, C<sub>p12h</sub> and AUC<sub>0-12h</sub>

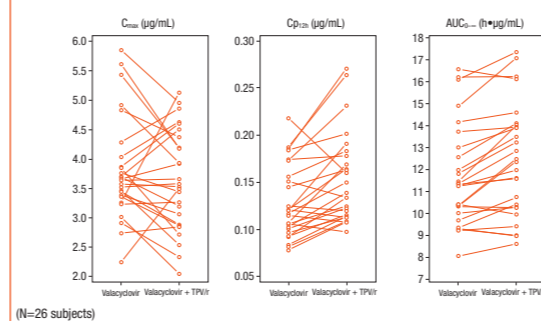


Table 3: Effect of single-dose VAL 500 mg on the steady-state pharmacokinetics of TPV 500 mg (co-administered with RTV 200 mg) (N=26 subjects)

Pharmacokinetic parameter	Treatment	Mean	SD	Median	Geometric mean	Geometric mean ratio (90% CI)
T <sub>max</sub> (h)	TPV/r	2.9	0.7	3.0	2.8	–
	TPV/r + VAL	2.6	0.7	3.0	2.5	–
C <sub>max</sub> (μM)	TPV/r	129.5	38.3	130.5	124.4	1.02 (0.95, 1.10)
	TPV/r + VAL	133.4	42.2	128.7	127.3	–
C <sub>p12h</sub> (μM)	TPV/r	32.13	18.85	25.84	28.20	0.98 (0.93, 1.04)
	TPV/r + VAL	31.63	18.03	26.12	27.65	–
AUC <sub>0-12h</sub> (h•μM)	TPV/r	881.9	312.9	862.8	833.4	1.01 (0.96, 1.06)
	TPV/r + VAL	889.7	307.5	830.1	841.5	–
CL/F (L/h)	TPV/r	1.05	0.36	0.96	1.00	–
	TPV/r + VAL	1.04	0.36	1.00	0.99	–
Vz/F (L)	TPV/r	6.33	1.71	6.11	6.12	–
	TPV/r + VAL	6.97	3.46	5.72	6.42	–
t <sub>1/2</sub> (h)	TPV/r	4.4	1.4	4.1	4.3	–
	TPV/r + VAL	5.0	3.2	3.9	4.5	–

Table 4: Effect of single-dose VAL 500 mg on the steady-state pharmacokinetics of RTV 200 mg (coadministered with TPV 500 mg) (N=26 subjects)

Pharmacokinetic parameter	Treatment	Mean	SD	Median	Geometric mean	Geometric mean ratio (90% CI)
T <sub>max</sub> (h)	TPV/r	4.0	0.7	4.0	3.9	–
	TPV/r + VAL	4.2	0.6	4.0	4.1	–
C <sub>max</sub> (μg/mL)	TPV/r	2.13	0.90	1.91	1.95	0.81 (0.71, 0.91)
	TPV/r + VAL	1.77	0.86	1.62	1.57	–
C <sub>p12h</sub> (μg/mL)	TPV/r	0.081	0.057	0.063	0.070	0.94 (0.83, 1.07)
	TPV/r + VAL	0.077	0.051	0.059	0.066	–
AUC <sub>0-12h</sub> (h•μg/mL)	TPV/r	7.50	2.55	7.16	7.08	0.86 (0.79, 0.94)
	TPV/r + VAL	6.56	2.44	6.45	6.09	–
CL/F (L/h)	TPV/r	30.1	11.4	27.9	28.3	–
	TPV/r + VAL	35.8	16.5	31.0	32.8	–
Vz/F (L)	TPV/r	73.0	25.3	65.1	69.5	–
	TPV/r + VAL	108.2	101.5	80.1	87.6	–
t <sub>1/2</sub> (h)	TPV/r	1.7	0.2	1.7	1.7	–
	TPV/r + VAL	2.0	1.3	1.7	1.8	–

## SAFETY

Twenty-four of 29 subjects experienced an AE during the trial, most of which were mild. The pattern of AEs observed in this study was consistent with that seen in previous Phase I studies with TPV/r or VAL. Table 5 summarizes the adverse events by classification and treatment periods.

Table 5: Overall safety summary on number and frequency of subjects with AEs

	VAL		TPV/r		TPV/r + VAL		Total	
	N	%	N	%	N	%	N	%
Subjects treated	29	100.0	29	100.0	26	100.0	29	100.0
Subjects with any AE	7	24.1	23	79.3	4	15.4	24	82.8
Subjects with drug-related AEs	5	17.2	23	79.3	3	11.5	24	82.8
Subjects with AEs leading to discontinuation of trial drugs	0	0.0	3	10.3	0	0.0	3	10.3
Subjects with SAEs	0	0.0	2	6.9	0	0.0	2	6.9

Amongst study participants, the majority of the AEs reported (13/29 subjects) were gastrointestinal in nature. The second most frequently reported AEs belonged to the "nervous system disorders" system organ class (9/29 subjects), with the most prominent AE "headache". Three subjects discontinued TPV/r treatment as a result of DAIDS grade 3–4 increases in ALT/AST, including one subject who experienced mild upper abdominal pain. All subjects who experienced an AE during the study recovered without sequelae.

## CONCLUSIONS

Co-administration of steady-state TPV/r 500/200 mg bid with single-dose valacyclovir 500 mg did not affect acyclovir C<sub>max</sub> or AUC. The slight decrease in acyclovir concentration measured 12 h after dosing is not considered to be of clinical relevance.

A single dose of valacyclovir had no effect on the steady-state pharmacokinetics of TPV. The slight decrease in steady-state RTV C<sub>max</sub> and AUC<sub>0-12h</sub> in the presence of VAL do not appear to have pharmacokinetic importance as TPV pharmacokinetics, which are dependent upon RTV, were not affected.

Overall, these results indicate that VAL can be safely co-administered with TPV/r 500/200 mg bid without dose adjustments.

## REFERENCES

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