Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

The synopsis - which is part of the clinical study report - had been prepared in accordance with best practice and applicable legal and regulatory requirements at the time of study completion.

The synopsis may include approved and non-approved uses, doses, formulations, treatment regimens and/or age groups; it has not necessarily been submitted to regulatory authorities.

A synopsis is not intended to provide a comprehensive analysis of all data currently available regarding a particular drug. More current information regarding a drug is available in the approved labeling information which may vary from country to country.

Additional information on this study and the drug concerned may be provided upon request based on **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		**(For National Authority Use only)**
Name of finished product: Tipranavir				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 14 August 2003	**Number:** U03-3120	**Study period (years):** 13 November 2001- 04 February 2002		

Title of study:	A Single Center, Open-Label, Randomised, Parallel, Multiple Dose Comparison of the Effect of Tipranavir 500 mg and Ritonavir 100 mg or Tipranavir 750 mg and Ritonavir 200 mg twice a day for 11.5 days on the Pharmacokinetic Characteristics of Zidovudine 300 mg in Healthy Volunteers
Investigator:	[redacted]
Study center(s):	[redacted]
Publication (reference):	None
Clinical phase:	I
Objectives:	The objective of this study was to characterize the effect of two dose combinations of tipranavir/ritonavir (TPV 500 mg/RTV 100 mg and TPV 750 mg/RTV 200 mg) administered twice daily on the pharmacokinetics of zidovudine (ZDV) and zidovudine-glucuronide (GZDV) as well as the effects of zidovudine on the pharmacokinetics of TPV/RTV.
Methodology:	Open label, multiple dose, randomised, parallel group drug-drug interaction (two dose level TPV with RTV) pharmacokinetic study
No. of subjects:	
planned:	entered: 56
actual:	entered: 60 - TPV 500 mg + RTV 100 mg + ZDV 300 mg entered: 30 treated: 30 analyzed (for primary endpoint): 29 -TPV 750 mg + RTV 200 mg + ZDV 300 mg entered: 30 treated: 30 analyzed (for primary endpoint): 25
Diagnosis and main criteria for inclusion:	HIV-negative and non-active Hepatitis B and Hepatitis C healthy male and female volunteers, ages 18 to 60 years old
Test product:	TPV SEDDS capsule (250 mg) + RTV 100 mg soft gel capsules (Norvir®) + ZDV 300 mg tablet (Retrovir®)
dose:	(TPV 500 mg + RTV 100 mg) or (TPV 750 mg + RTV 200 mg) b.i.d + ZDV 300mg
mode of admin.:	Oral
batch no.:	TPV: PD-2062

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Duration of treatment:	ZDV: once daily on trial Days 1 and 13 (two single doses) TPV / RTV: b.i.d. daily on trial Days 2 to 12 then once daily Day 13 (11.5 days)
Reference therapy:	No reference therapy
Criteria for evaluation:	
Efficacy:	There are no efficacy endpoints
Pharmacokinetics:	Primary endpoints: • Single-dose pharmacokinetics of ZDV and GZDV (with and without TPV/RTV): $AUC_{0\text{-}12h}$, Cp_{6h}, C_{max} • Steady-state pharmacokinetics of TPV and RTV (with and without ZDV): $AUC_{0\text{-}12h}$, C_{max}, Cp_{12h} Secondary endpoints: Secondary pharmacokinetic parameters analyzed were determined on an as-needed-basis by the trial pharmacokineticist. These included $t_{½}$, Cl/F, T_{max} and Vz/F for TPV, RTV, ZDV and GZDV, and $C_{max\ ss}$, C_{min} and MRT for TPV and RTV.
Safety:	The study also assessed the safety profile of the two dose combinations of TPV and RTV used in the trial as secondary endpoints. These assessments included vital signs (pulse rate, systolic and diastolic blood pressure), physical examinations, laboratory measurements and adverse event (AE) assessments.
Statistical methods:	The following pharmacokinetic parameters were derived using non-compartmental analysis: area under the plasma concentration time curve (AUC, trapezoidal rule), maximum observed concentration (C_{max}), trough plasma concentration (Cp_{12h}), and concentration at a specified time after dosing (ZDV and GZDV, 6 hours; TPV and RTV, 12 hours). The following ratios of specified PK parameters with 90% confidence intervals were calculated for single-dose zidovudine and TPV/RTV at steady-state: 1) Zidovudine and GZDV with/without TPV/RTV: $AUC_{0\text{-}12h}$, Cp_{6h}, C_{max}; 2) TPV and RTV with and without zidovudine: $AUC_{0\text{-}12h}$, C_{max}, Cp_{12h}. Ratio of 1.00 indicates no effect; comparison days are Day 1 to Day 13 for ZDV and GZDV and Day 12 to Day 13 for TPV and RTV.

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SUMMARY – CONCLUSIONS:

Efficacy results: Not applicable

Pharmacokinetic results: When TPV and RTV were coadministered with ZDV, statistically significant decreases in ZDV exposure occurred at both the TPV 500 mg/RTV 100 mg dose (AUC ↓43%) and the TPV 750 mg/RTV 200 mg dose (AUC ↓33%). However, the clinical importance of this decrease in ZDV exposure is not known. Zidovudine glucuronide exposure, however, was not affected by coadministration of TPV/RTV at either dose as reflected by slight increases in AUC (2% and 9%).

Tipranavir pharmacokinetics exhibited moderate dose-dependent changes. The Cp_{12h}, C_{max} and AUC in the TPV 500 mg/RTV 100 mg group decreased significantly by 23%, 13% and 18%, respectively, while only slight, insignificant increases of 2-7% were seen in those parameters in the TPV 750 mg/RTV 200 mg dose group.

Ritonavir pharmacokinetics were relatively unaffected by coadministration of ZDV. In the TPV/RTV treatment groups, AUC was decreased the most of the three PK parameters and only by an average of 16%.

Safety results: In general, both doses of TPV/RTV were well-tolerated in this trial. Consistent with other TPV trials, GI events were the most frequently observed AEs in this study (80.0%). The percentage of subjects with AEs was higher in the TPV 750 mg/RTV 200 mg group (96.7%) compared with those in the TPV 500 mg/RTV 100 mg group (73.3%). There were no SAEs, only one subject discontinued due to an AE, and the majority of the AEs were mild (Grade 1) in intensity.

Among laboratory tests of interest, clinically significant elevations in LFTs (AST and ALT) were noted only in the TPV 750 mg/RTV 200 mg group.

No unexpected safety issues arose or were identified from this trial. The safety findings in this study are consistent with previous trials in healthy volunteers and HIV-1 positive adults.

Conclusions: Because plasma concentrations of ZDV do not correlate well with antiviral activity, the clinical significance of the observed decrease in AUC is not known. Therefore, no dose adjustment of ZDV is recommended when coadministered with the combination of TPV 500 mg/ RTV 100 mg or TPV 750 mg/ RTV 200 mg.