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**		
Name of finished product: Tipranavir				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 13 August 2003	**Number:** U03-3217-01	**Study period (dates):** 06 December 2001- 16 March 2002		**Date of Revision:** 14 May 2004

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, Administered Daily on 3 Non-Consecutive Days and Twice Daily for 7 Days, on the Pharmacokinetic Characteristics of Efavirenz (Sustiva®) 600 mg a Day in Healthy Adult Volunteers
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	None
Clinical phase:	I
Objectives:	The objective of this study was to characterize the effects of two dose combinations of tipranavir/ritonavir (TPV 500 mg/RTV 100 mg and TPV 750 mg/RTV 200 mg), administered daily and BID, on the pharmacokinetics of efavirenz (EFV), 600 mg daily.
Methodology:	Open label, multiple dose, randomised, parallel group drug-drug interaction (two dose level TPV with RTV) pharmacokinetic study
No. of subjects:	
planned:	enrolled: 56
actual:	enrolled: 68 - TPV 500 mg + RTV 100 mg + EFV 600 mg entered: 34 treated: 34 - TPV 750 mg + RTV 200 mg + EFV 600 mg entered: 34 treated: 32
Diagnosis and main criteria for inclusion:	HIV-negative and negative or 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®) + EFV 200 mg capsules (Sustiva®)
dose:	(TPV 500 mg + RTV 100 mg) or (TPV 750 mg + RTV 200 mg) b.i.d + EFV 600 mg
mode of admin.:	Oral
batch no.:	TPV: PD-2062

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Tipranavir		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 13 August 2003	**Number:** U03-3217-01	**Study period (dates):** 06 December 2001- 16 March 2002		**Date of Revision:** 14 May 2004

Duration of treatment:	EFV: Trial Days 1, 5 and 7-21 (17 days) TPV / RTV: b.i.d. Trial Days 15-21 and once daily Trial Days 3, 5 and 14 (10 days)
Reference therapy:	No reference therapy
Criteria for evaluation:	
Efficacy:	There are no efficacy endpoints
Pharmacokinetics:	Primary endpoints: Tipranavir with Ritonavir (with and without Efavirenz) • AUC_{0-12} • Cp_{12h} • C_{max} Efavirenz (with and without Tipranavir and Ritonavir) • AUC_{0-24} • Cp_{24h} • C_{max} Secondary endpoints: Secondary pharmacokinetic parameters analyzed were determined on an as-needed-basis by the trial pharmacokineticist. These included CL/F, V, T_{max} and $t_{1/2}$ for EFV, 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.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Tipranavir		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 13 August 2003	**Number:** U03-3217-01	**Study period (dates):** 06 December 2001- 16 March 2002		**Date of Revision:** 14 May 2004

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}) and concentration at a specified time after dosing (efavirenz, 24 hours; tipranavir and ritonavir, 12 hours). Ratio (with and without TPV/RTV) of EFV pharmacokinetic parameters (90% Confidence Intervals) for AUC_{0-24h}, C_{max}, and C_{24h} where no effect = 1.00; comparison days are Day 1 to Day 5 and Day 13 to Day 21. Ratio (with and without EFV) of TPV/RTV pharmacokinetic parameters (90% Confidence Intervals) for AUC_{0-12h}, C_{max}, and C_{12h} where no effect = 1.00; comparison days are Day 3 to Day 5 and Days 3 and 14 to Day 21.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Not applicable
Pharmacokinetic results:	When EFV and TPV/RTV were coadministered as single-doses (Day 1 vs. Day 5) or when coadministered at steady-state (Day 13 vs. Day 21), no substantial changes in the AUC, C_{max}, or C_{24h} for EFV were observed. The AUC, C_{max}, and C_{12h} for TPV were not substantially affected by co-administration with EFV (and RTV) after single doses of drug (Day 3 vs. Day 5). The slight decrease observed in these parameters may be the result of CYP3A4 induction on Day 1 by the single dose of EFV, a CYP3A4 inducer with a long single-dose terminal half-life (52 h to 76 h). When coadministered with EFV at steady-state (Day 14 vs. Day 21), substantial increases in the AUC (500/100, 94% [n=18]; 750/200, 78% [n=19]), C_{max} (500/100, 117% [n=18], 750/200, 114% [n=19]) and C_{12h} (500/100, 71% [n=18]; 750/200, 92% [n=19]) for TPV were observed, which is consistent with establishing TPV steady-state in the presence of the CYP3A4 inhibitor RTV and the CYP3A4 inducer EFV. The AUC, C_{max}, and C_{12h} for single-dose RTV were slightly decreased when TPV was coadministered (Day 3) and when TPV and EFV were coadministered (Day 5), with the decrease being less pronounced in the TPV 750 mg/RTV 200 mg dose group. When coadministered with steady-state EFV (Day 14 vs. Day 21), substantial increases in AUC (500/100, 53% [n=7]; 750/200, 84% [n=20]), C_{max} (500/100, 49% [n=7]; 750/200, 123% [n=20]) and C_{12h} (500/100, 415% [n=7]; 750/200, -8% [n=20]) of RTV generally were observed; these increases are attributed to establishing steady state.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Tipranavir		**SUPPLEMENTARY SHEET**		
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 13 August 2003	**Number:** U03-3217-01	**Study period (dates):** 06 December 2001- 16 March 2002		**Date of Revision:** 14 May 2004

Safety results:

In general, both doses of TPV/RTV were moderately well-tolerated in this trial. Consistent with other TPV trials, GI events were the most frequently observed AEs in this study (86.4%). The percentage of subjects with AEs was not significantly (p=0.6139) different in the TPV 750 mg/RTV 200 mg group (96.9%) compared with those in the TPV 500 mg/RTV 100 mg group (91.2%). There was one non-study drug related SAE (pyelonephritis) in a subject in the TPV 500 mg/RTV 100 mg group. Fourteen subjects (21.2% of 66 total subjects) were discontinued due to an AE after they received at least one dose of TPV/RTV following the initial administration of EFV. Of these, 6 (17.6%) were in the TPV 500 mg/RTV 100 mg and 8 (25.0%) subjects were in the TPV 750 mg/RTV 200 mg. The majority of the AEs were mild or moderate (Grades 1 and 2, respectively) in intensity.

Among laboratory tests, clinically significant elevations (Grade 3 or 4) in LFTs (AST and ALT) were noted only in the TPV 750 mg/RTV 200 mg group.

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

Conclusions:

Based on data from this study, no dose adjustment in EFV is required when coadministered in combination of doses of either TPV 500 mg/RTV 100 mg or TPV 750 mg/RTV 200 mg. No dose adjustment in TPV/RTV is required when coadministered with EFV in the presence of 750 mg TPV and 200 mg RTV. If TPV 500 mg b.i.d. is used in combination with EFV 600 mg once daily, the dose of RTV should be 200 mg b.i.d., as 100 mg of RTV appears inadequate to boost TPV levels to plasma concentrations required for antiviral efficacy in treatment-experienced HIV-1 positive adult patients.