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: xxx to xxxx**		**Addendum No.:**
Report date: 08 March 2004	**Number:** U04-3100	**Study period (dates):** 26 Jun 03 – 17 Jul 03		

Title of study:	A single centre, open-label study, in healthy adult volunteers, to determine the effects of single-dose and steady-state TPV/RTV 500/200 mg on the steady-state pharmacokinetics of fluconazole 100 mg qd (200 mg loading dose)
Investigator:	[redacted]
Study center:	[redacted] Canada.
Publication (reference):	
Clinical phase:	I
Objectives:	To determine the effects of single-dose and steady-state TPV/RTV 500/200 mg on the steady-state pharmacokinetics of fluconazole
Methodology:	Open-label, single group TPV/RTV, pharmacokinetic study
No. of subjects:	20 healthy adults
planned:	enrolled: 31
	entered: 20
actual:	enrolled: 77
	entered: 20
	Treatment A: TPV + RTV + Fluconazole. entered: 20, treated: 20, analyzed: 20
Diagnosis and main criteria for inclusion:	Healthy male and female volunteers of any race between the age of 18 and 60 years that were HIV, Hepatitis B, and Hepatitis C negative.
Test product:	TPV, 250 mg, Soft Elastic Capsules (SECs), Self-Emulsifying Drug Delivery System (SEDDS) formulation
dose:	TPV 500 mg bid
mode of admin.:	Oral
batch no.:	1004252 (Lot# PD-2149)
Duration of treatment:	7 days
Test product:	RTV (NORVIR-SEC®) Soft Elastic Capsules (100 mg),

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:** **to**		**Addendum No.:**
Report date: 08 March 2004	**Number:** U04-3100	**Study period (dates):** 26 Jun 03 – 17 Jul 03		

dose:	RTV 200 mg bid
mode of admin.:	Oral
batch no.:	908432E21
Duration of treatment:	7 days
Test product:	Fluconazole tablet
dose:	200 mg loading dose on Day 1, followed by 100 mg qd
mode of admin.:	Oral
batch no.:	202-07001
Duration of treatment:	13 days
Reference therapy:	None
Criteria for evaluation:	
Efficacy:	There were no efficacy endpoints in this study.

Pharmacokinetics:	PRIMARY ENDPOINTS:
	• Effect of single-dose and steady-state TPV/RTV on steady-state pharmacokinetics of FCZ:
	  • AUC_{0-24h}
	  • C_{max}
	  • C_{p24h}
	
	SECONDARY ENDPOINTS:
	• Effect of steady-state FCZ on steady-state TPV (co-administered with RTV) PK:
	  • AUC_{0-12h}
	  • C_{max}
	  • C_{p12h}
	• Identification of additional pharmacokinetic parameters (CL/F, t_{max} and $t_{1/2}$) for FCZ and TPV.

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:** to		**Addendum No.:**
Report date: 08 March 2004	**Number:** U04-3100	**Study period (dates):** 26 Jun 03 – 17 Jul 03		

Safety:	Subject safety was monitored by assessment of treatment related adverse events at each visit, in addition to laboratory assessment of safety parameters including hematology, chemistry, liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), lipid parameters (triglycerides, cholesterol) at screening and various days throughout the study.
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 (C_{12h}), and concentration at a specified time after dosing (FCZ, 24 hours; TPV 12 hours). The following ratios of specified PK parameters with 90% confidence intervals were calculated: • FCZ with/without single-dose and steady-state TPV/RTV: AUC_{0-24h}, C_{max}, C_{p24h} • Ratio of 1.00 indicated no effect; comparison days were Day 6 to Day 7 for the effect of single-dose TPV/RTV on steady-state PK of FCZ, and Day 6 to 13 for the effect of steady-state TPV/RTV on steady-state PK of FCZ.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Not applicable.
Pharmacokinetics results:	Co-administration of two doses of TPV/RTV 500/200 mg did not substantially influence the steady-state pharmacokinetics of FCZ (observed changes in the AUC_{0-24h}, C_{max}, and Cp_{24h} were less than or equal to 3%). The 90% confidence intervals for the geometric mean ratios for the AUC_{0-24h}, C_{max} and C_{p24h} of FCZ (FCZ/FCZ + TPV/RTV) all fell completely within the specified bounds of 0.80 to 1.25, indicating the absence of a clinically relevant interaction between FCZ and TPV/RTV. Co-administration of TPV/RTV 500/200 mg twice-daily for 7 days caused small, but statistically significant decreases in the FCZ AUC_{0-24h} (-8%), C_{max} (-6%), and Cp_{24h} (-11%). However, these minor changes are not considered to be clinically relevant. The steady-state AUC_{0-12h}, C_{max} and Cp_{12h} of TPV (co-administered with RTV twice-daily) were substantially increased (≥46%) during co-administration of FCZ, compared to the results from a previous study of TPV/RTV 500/200 mg twice-daily alone (BI protocol 1182.5 [U01-3295]). In addition, steady-state levels of FCZ caused a decrease in the Cl/F (-36%) of TPV relative to historical values.

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:** **to**		**Addendum No.:**
Report date: 08 March 2004	**Number:** U04-3100	**Study period (dates):** 26 Jun 03 – 17 Jul 03		

Safety results:	Consistent with previous TPV trials the most frequently observed AEs were gastrointestinal (GI)-related (35% loose stool, 20% nausea and 15% lower abdominal pain). In general, both treatments (FCZ alone and TPV/RTV in combination with FCZ) were well-tolerated with the majority of AEs being mild in intensity and rarely requiring treatment intervention. No unexpected safety issues arose in this study nor were there any discontinuations due to AEs (or any other reason). There were no deaths, other serious adverse events and other significant adverse events in this study. There were no clinically relevant variations from baseline in the results of laboratory tests of project-specific special interest nor were there any significant changes from baseline in vital sign measurements (blood pressure and pulse rate) in this study.
Conclusions:	Neither single-dose nor steady-state levels of TPV/RTV had any clinically significant effect on the pharmacokinetics of FCZ. In contrast, steady-state levels of FCZ appeared to increase the steady-state $AUC_{0\text{-}12h}$, C_{max}, and C_{p12h} of TPV by 46%, 56% and 104%, respectively, compared to historical values. The clinical relevance of this increase is yet to be determined. From a safety perspective, FCZ and TPV/RTV combination treatment was well-tolerated in the healthy subject population used in this study with the majority of AEs being mild GI events that did not require treatment intervention. There were no deaths, other serious adverse events or other significant adverse events in this study.