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: 12 November 2003	**Number:** U03-3408	**Study period (years):** 15 May 2002 – 25 June 2002		

Title of study:	A single centre, open-label, randomized, parallel group, multiple dose comparison of the effect of Tipranavir 750 mg and Ritonavir 200 mg or Tipranavir 500 mg and Ritonavir 100 mg, administered twice daily, on the pharmacokinetic characteristics of Norethindrone-Ethinyl Estradiol (Ortho®-1/35) administered as a single dose, in healthy female adult volunteers.
Investigator:	[redacted]
Study center(s):	[redacted]
Publication (reference):	Not yet published
Clinical phase:	I
Objectives:	To characterize the effects of two dose combinations of TPV/RTV (TPV 750 mg/RTV 200 mg and TPV 500 mg/RTV 100 mg), administered twice-daily, on the pharmacokinetics of NET/EE 1 mg/ 0.035 mg administered as a single dose.
Methodology:	Open-label, randomized, parallel group, two dose pairs of TPV/RTV, pharmacokinetic study
No. of subjects:	52 adults
	26 (required 20 completed) per treatment arm
planned:	entered: 52
actual:	enrolled: 177
	Treatment TPV/RTV 500/100 mg: 26 entered: 26 treated, 21 included in the primary endpoint analysis, 26 included in the safety analysis: Treatment TPV/RTV 750/200 mg: 26 entered: 26 treated: 13 included in the primary endpoint analysis, 26 included in the safety analysis:
Diagnosis and main criteria for inclusion:	Females of any race, in good health and between the ages of 18 and 50 years inclusive. Negative HIV serology, and negative Hepatitis B and Hepatitis C serology.

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: 12 November 2003	**Number:** U03-3408	**Study period (years):** 15 May 2002 – 25 June 2002		

Test product:	TPV, 250 mg, Soft Elastic Capsules (SECs), Self-Emulsifying Drug Delivery System (SEDDS) formulation
Dose:	TPV 750 mg or 500 mg b.i.d. for 12 consecutive days and q.d for 1 day
mode of admin.:	Oral
batch no.:	PD-2062
Duration of treatment:	13 days
Test product:	RTV (NORVIR-SEC®) Soft Elastic Capsules (100 mg)
dose:	RTV 200 mg or 100 mg b.i.d. for 12 consecutive days and q.d. for 1 day
mode of admin.:	Oral
batch no.:	828592E21
Duration of treatment:	13 days
Test product:	NET/EE (Ortho®-1/35) 1/35 Tablet
dose:	1 mg Norethindrone; 0.035 mg Ethinyl Estradiol
mode of admin.:	Oral
batch no.:	01GS088
Duration of treatment:	Single dose Day 1, and single dose Day 15
Reference therapy:	None
dose:	n/a
mode of admin.:	n/a
batch no.:	n/a
Criteria for evaluation:	
Efficacy:	There are no efficacy endpoints

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: 12 November 2003	**Number:** U03-3408	**Study period (years):** 15 May 2002 – 25 June 2002		

Pharmacokinetics

Primary endpoints:

- Single dose pharmacokinetics of NET/EE (with and without TPV and RTV):
  AUC_{0-24h}
  C_{max}
- Steady state pharmacokinetics of TPV/RTV (with and without NET/EE):
  AUC_{0-12}
  C_{max}
  C_{12h}

Secondary endpoints

- Identification of additional pharmacokinetic parameters including CL/F, t_{max} and $t_{1/2}$ for NET/EE and for TPV/RTV, were analyzed and are presented in sections 11.4 and 14.4 of this report.

Safety:

Primary endpoints: None

Secondary endpoints: Treatment related AEs and laboratory assessment of safety parameters including hematology, chemistry, liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), and lipid parameters (triglycerides, HDL and LDL)

Reference therapy: Not applicable

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 (Cmax), trough plasma concentration (C_{12h}), and concentration at a specified time after dosing (NET/EE, 24 hours; TPV and RTV, 12 hours). The following ratios of specified PK parameters with 90% confidence intervals will be calculated:

1) NET/EE single dose with/without TPV/RTV: AUC_{0-24h} and C_{max};

2) TPV/RTV at steady state with/without NET/EE: AUC_{0-12h}, C_{max} and C_{12h}.

Ratio of 1.00 indicates no effect; comparison days are Day 1 to Day 15 for NET/EE and Day 14 to Day 15 for TPV/RTV

SUMMARY – CONCLUSIONS:

Efficacy results: No efficacy measures were performed

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: 12 November 2003	**Number:** U03-3408	**Study period (years):** 15 May 2002 – 25 June 2002		

Pharmacokinetics

The addition of TPV/RTV at doses of either 500/100 or 750/200 mg bid to NET/EE (1/0035mg) therapy reduced the total EE exposure (AUC_{0-24h}) by 43-48.3%, and the maximal EE concentrations (C_{max}) by approximately 50%. This is clinically relevant.

A 14-27% increase in the exposure to NET (AUC_{0-24h}) after co-administration of TPV/RTV was observed and is not expected to be clinically significant

Safety results:

There were no SAEs in the trial.

Of the 501 AEs reported during the study, 92.6 % were of worst intensity mild, and 7.4% were of worst intensity moderate. No AEs of worst intensity severe were reported. (Appendix 16.1.9.2 TABLE 7.2.2.4)

AEs leading to discontinuation:

In the TPV/RTV low dose group, 7 subjects were discontinued due to AEs

In the TPV/RTV high dose group, 12 subjects were discontinued due to AEs

The percentage of subjects who were withdrawn due to AEs, per MedDRA system organ class were as follows:

(% in low dose group (n=26) / % in high dose group (n=26):

Total: 26.9 / 46.2

Skin and subcutaneous tissue disorders: 15.4/26.9
(variously described as rash, pruritic rash)
General disorders and administrative site conditions: 7.7/7.7
Musculoskeletal and connective tissue disorders: 3.8/7.7
Gastrointestinal disorders: 0/7.7
Infections and infestations (Hepatitis NOS): 3.8/0
Nervous system disorders: 0/3.8
Renal and urinary disorders: 0/3.8

Source data: Appendix 16.1.9.2 TABLE 7.2.7.1

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: 12 November 2003	**Number:** U03-3408	**Study period (years):** 15 May 2002 – 25 June 2002		

Conclusions:	The cutaneous and musculo-skeletal AEs reported were in higher frequency than has been described in other TPV/RTV trials in both healthy volunteer subjects and in HIV-positive patients. The early discontinuation of this trial, prior to administration of the final dose of study medication, was due to the frequency of these AEs, which were considered by the investigator to be related to study drug. A comprehensive investigation of the cause of these unexpected AEs is still ongoing, and current information is summarized in Section 12. No cause for these unexpected AEs has yet been identified, leaving drug reaction as the most likely cause.