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: 23 October 2006	**Number:** U06-3660-01	**Study period (dates):** 19 January 2006 to 21 July 2006		**Date of Revision:** 08 March 2007

Title of study:	Evaluating the effects of Tipranavir (with ritonavir) capsule and liquid formulation on cytochrome P450 and P-glycoprotein activity using a biomarker cocktail in healthy human volunteers
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	NA
Clinical phase:	I
Objectives:	**Primary:** To quantify the influence of single-dose and steady-state tipranavir/ritonavir 500/200 mg on intestinal and hepatic cytochrome P450 (CYP) and P-glycoprotein (P-gp) biomarkers, as a means of predicting drug interactions. The AUCs for biomarkers caffeine, warfarin, omeprazole, dextromethorphan, midazolam, and digoxin will be assessed.
Methodology:	Open-label, parallel dosing formulation, within-group comparison study in healthy male and female volunteers administered a single-dose cocktail of 200 mg PO caffeine, 10 mg PO warfarin, 10 mg PO vitamin K, 40 mg PO omeprazole, 30 mg PI dextromethorphan, midazolam (2 mg IV and 5 mg PO), and digoxin (0.25 mg IV and 0.25 mg PO). This cocktail was given at baseline, on Day 1 of TPV/r (500 mg/200 mg BID), and on Day 13-15 of TPV/r.
No. of subjects:	
planned:	enrolled: 40
actual:	enrolled: 41 Treatment A: Tipranavir (Oral Capsule) referred to as SEDDS. entered: 21 treated: 20 analysed (for primary endpoint): 16 Treatment B: Tipranavir (Oral Solution) referred to as Solution entered: 12 treated: 11 analysed (for primary endpoint): 7
Diagnosis and main criteria for inclusion:	Healthy male and female subjects age ≥18 to ≤45; weight ≥50 kg; BMI ≤30 kg/m^2; negative HIV ELISA

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: 23 October 2006	**Number:** U06-3660-01	**Study period (dates):** 19 January 2006 to 21 July 2006		**Date of Revision:** 08 March 2007

Test product:	Tipranavir capsules (SEDDS formulation)
dose:	500 mg BID
mode of admin.:	Oral
batch no.:	PD 2534
Duration of treatment:	15 days
Test product:	Tipranavir solution
dose:	500 mg/5 mL BID
mode of admin.:	Oral
batch no.:	PD 2567 A
Duration of treatment:	15 days
Test product:	Ritonavir capsules
dose:	200 mg BID
mode of admin.:	Oral
batch no.: (manufacturing lot nos.)	317072E22; 342702E22; 342682E21; 354572E23; 354582E21; 342692E21; 354592E22; 354632E22; 377722E21; 354602E22; 380102E21
Duration of treatment:	15 days
Reference therapy:	
dose:	Not applicable
mode of admin.:	
batch no.:	
Criteria for evaluation:	
Efficacy:	Not applicable, there were 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: 23 October 2006	**Number:** U06-3660-01	**Study period (dates):** 19 January 2006 to 21 July 2006		**Date of Revision:** 08 March 2007

Pharmacokinetics:

Primary pharmacokinetic endpoints:

- Eight primary comparisons: Comparison of CYP 1A2, 2C9, 2C19, 2D6, 3A4/5 (H+I vs. H), and P-gp (H+I vs. H) activity before and after TPV/r administration at steady-state. Phenotyping probe drug exposure will be used to assess the activity of CYP 1A2, 2C9, 2C19, 2D6, 3A4/5.

Secondary pharmacokinetic endpoints:

- Seven comparisons: Comparison of CYP 1A2, 2C9, 2C19, 2D6, 3A4/5 (H+I vs. H), and P-gp activity after first dose administration of TPV/r versus activity at baseline and steady-state. (baseline vs. first dose) (capsule vs. oral soln)
- Urinary molar ratio of (1X+1U+AFMU)/17U
- Urinary molar ratio of AFMU/(1X+1U+AFMU)
- Urinary molar ratio of 1U/(1X+1U)
- Urinary molar ratio of dextromethorphan/dextrophan
- Tipranavir pharmacokinetic parameters: $AUC_{0\text{-}12h}$, C_{max} and C_{p12h}
- Ritonavir pharmacokinetic parameters: $AUC_{0\text{-}12h}$, C_{max} and C_{p12h}
- Caffeine, warfarin, omeprazole, dextromethorphan, midazolam, digoxin, tipranavir and ritonavir pharmacokinetic parameters: clearance, C_{max}, T_{max} and $t_{1/2}$

For $AUC_{0\text{-}xh}$: X represents 24h for caffeine, omeprazole, dextromethorphan and IV midazolam; 48h for PO midazolam and PO digoxin; 51h for IV digoxin and 72h for warfarin.

Safety:

Physical examination, vital signs (BP, PR, temperature, respiratory rate), laboratory tests, EKG, adverse events, tolerability

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: 23 October 2006	**Number:** U06-3660-01	**Study period (dates):** 19 January 2006 to 21 July 2006		**Date of Revision:** 08 March 2007

Statistical methods:

Safety and tolerability:

Intensity of adverse events was graded using the Boehringer Ingelheim-modified ACTG DAIDS Scale. Data were be summarized by frequency tables and descriptive statistics.

Pharmacokinetics:

The area under the plasma concentration time curve (AUC, trapezoidal rule) for caffeine, warfarin, omeprazole, dextromethorphan, midazolam, digoxin, tipranavir and ritonavir will be derived using noncompartmental analysis.

In order to reach the primary goal of the study a paired t-test (two sided, α=0.05) will be performed. Moreover, calculation of two sided 90% confidence interval as a measure of uncertainty of the study results will be provided. The 90% confidence intervals (CI) will be constructed for the ratio of geometric means.

SUMMARY – CONCLUSIONS:

Efficacy results: NA

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: 23 October 2006	**Number:** U06-3660-01	**Study period (dates):** 19 January 2006 to 21 July 2006		**Date of Revision:** 08 March 2007

Safety results:

Safety results:

Twenty-nine of the 31 subjects (93.5%) [SEDDS 18/20 (90.0%):SOLN 11/11 (100.0%)] treated with TPV/r reported at least one AE during the study. The most frequently reported AEs during the TPV/r were assigned to the gastrointestinal (GI) system organ class followed by those assigned to the general disorder class and nervous system organ class.

Consistent with previous TPV trials in healthy subjects (U03-3217, U04-3216, U04-1257, U04-3198), the most frequently observed AEs during the study were GI-related. The data presented in this report show that the SEDDS capsule formulation of TPV was better tolerated than the TPV oral solution (SOLN). Higher frequencies of gastrointestinal (18% vs. 5%) and skin and subcutaneous tissue (18% vs. 0%) events leading to treatment discontinuation were observed in subjects that were randomized to the oral solution formulation of TPV compared to the TPV SEDDS capsule group. Two subjects in the SOLN arm developed urticaria and needed to be removed from the study; one of them was classified as a SAE as the subject was hospitalized for observation. All subjects were followed up until complete resolution of the events. No deaths were reported in this study. No new TPV/r safety concerns arose from these study subjects. During the conduct of this study, BI issued a Dear Healthcare professional letter and revised labelling, including important new safety information and a boxed warning for intracranial haemorrhage. This letter was based on a comprehensive search of data on TPV/r treated HIV+ patients which revealed a series of 14 cases of intracranial hemorrhage in 13 HIV-infected patients receiving TPV/r. Although none of the normal healthy subjects in this study were found to have clinically significant changes in PT, aPTT or INR, despite receiving warfarin (+vitamin K), in the opinion of the investigators the report of these cases caused the risk:benefit ratio to change unfavourably in this healthy volunteer population, resulting in premature discontinuation of the study.

The most frequent GI events in this study were nausea (SEDDS 50.0%: SOLN 36.4%) and diarrhea (SEDDS 40.0%:SOLN 18.2%). Vomiting occurred in 20.0% of the SEDDS group and 18.2% of the oral solution group. 9 (45.0%) and 3 (27.3%) of subjects reported general disorders and administration site conditions-associated AEs in the SEDDS capsule arm and oral solution treatment arm, respectively, with fatigue (SEDDS 15.0%:SOLN 18.2%) and pain at IV site (SEDDS 15.0%:SOLN 18.2%) being the most common events.

Overall, the majority of treatment related AEs in the study were mild, self-limiting, and rarely required treatment intervention.

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: 23 October 2006	**Number:** U06-3660-01	**Study period (dates):** 19 January 2006 to 21 July 2006		**Date of Revision:** 08 March 2007

Pharnmacokinetic Conclusions:

Overall, there do not appear to be clinically significant differences between capsule and liquid formulations on the influence of CYP isozyme or P-glycoprotein activity.

Over the first few doses of TPV/r modest inhibition of CYP1A2, CYP2C9, and CYP2C19 occurs, moderate inhibition of p-glycoprotein occurs, and potent inhibition of CYP2D6 and hepatic and intestinal CYP3A occurs. Intestinal P-glycoprotein and CYP3A activity are more profoundly affected than hepatic P-glycoprotein and CYP3A activity.

Prolonged TPV/r exposure induces the activity of CYP1A2, CYP2C9, CYP2C19, hepatic and intestinal P-glycoprotein, and hepatic and intestinal CYP3A, whereas prolonged exposure further inhibits CYP2D6 activity.

At steady-state, modest net induction of CYP1A2, CYP2C9 and CYP2C19 occurs, and potent inhibition of CYP2D6 and hepatic and intestinal CYP3A occurs. The net effect on P-glycoprotein, as measured by digoxin, is activity similar to baseline conditions.

Overall Conclusions:

A phenotypic cocktail study was conducted with normal volunteers to quantify the influence of 10 days of TPV/r administration on the activity of hepatic CYP1A2 (caffeine), 2C9 (warfarin), 2C19 (omeprazole), 2D6 (dextromethorphan) and the activity of intestinal and hepatic CYP3A4/5 (midazolam) and P-gp (digoxin). This study determined the first-dose and steady-state effects of 500 mg of TPV capsules and oral solution administered with 200 mg of RTV capsules administered twice-daily.

Overall, there do not appear to be clinically significant differences between capsule and liquid formulations on the influence of CYP isozyme or P-gp activity. There was no net effect on CYP2C9 or hepatic P-gp at first dose or steady state. CYP2C19 exhibited modest inhibition with the first dose and modest induction at steady state. There was no net effect after first dose on CYP1A2, but there was moderate induction at steady state. Potent inhibition of CYP2D6 and both hepatic and intestinal CYP3A4/5 activities were observed after first dose and steady state. Intestinal P-gp activity was inhibited after first dose but there was no net effect at steady state.

TPV/r was well tolerated by all subjects in this study.