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: February 07, 2003	**Number:** U03-1070	**Study period (years):** Sept 2001 - March 2002		

Title of study:	An open label, randomised, parallel group study of the drug-drug pharmacokinetic interaction of steady state tipranavir (SEDDS SEC) 500 mg and ritonavir (soft gelatin capsules) 100 mg or tipranavir 750 mg and ritonavir 200 mg, both bid for 13.5 days with single dose didanosine 400 mg (delayed release capsule EC beadlets) in healthy volunteers
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre Boehringer Ingelheim Pharma KG 88397 Biberach an der Riss, Germany
Publication (reference):	not yet published
Clinical phase:	I
Objectives:	To characterise the effects of concurrent tipranavir (TPV) and ritonavir (RTV) administration on the single dose pharmacokinetics of didanosine (ddI), to characterise the effects of single-dose ddI on the pharmacokinetics of TPV and RTV and to assess the short-term safety of this combination.
Methodology:	Open label, multiple dose, randomised, parallel group drug-drug interaction (two dose level TPV with RTV) pharmacokinetic study
No. of subjects:	
planned:	entered: 48
actual:	enrolled: 50 Treatment A: TPV 500 mg + RTV 100 mg + ddI 400 mg entered: 11 treated: 11 analysed (for primary endpoint): 5 Treatment B: TPV 750 mg + RTV 200 mg + ddI 400 mg entered: 12 treated: 12 analysed (for primary endpoint): 0
Diagnosis and main criteria for inclusion:	healthy, 18 to 60 year old male or female (post menopausal / surgically sterile females only) subjects
Test product:	TPV SEC SEDDS (250 mg) + RTV100 mg soft gel capsules (Norvir®) + ddI 400 mg delayed release capsules enteric coated beads (Videx EC®)
dose:	(TPV 500mg + RTV 100mg) or (TPV 750mg + RTV 200mg) bid + ddI 400mg
mode of admin.:	*per os*
batch no.:	TPV: PD-2062 RTV: 739062E2 ddI: MCM01
Duration of treatment:	ddI: once daily days 1 and 15 (two single doses) TPV / RTV: bid daily days 2 to 14 then once day 15 (13.5 days)

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Reference therapy:	no reference therapy
Criteria for evaluation:	
Efficacy:	There are no efficacy endpoints
Pharmacokinetics	Primary endpoints: Concentration-time values (C_{nh}) for ddI, TPV, and RTV. ddI pharmacokinetic parameters ($AUC_{0\text{-}12h}$, C_{max} and C_{6h}; with/without TPV and RTV) and TPV and RTV pharmacokinetic parameters ($AUC_{0\text{-}12h}$, C_{max} and C_{12h}; with/without ddI).
	Secondary endpoints: $C_{max,ss}$ and MRT for TPV and RTV, T_{max}, CL/F, V_z/F, $t_{1/2}$
Safety:	Primary endpoints: none
	Secondary endpoints: vital signs, physical examination, laboratory values, electrocardiogram, adverse events, tolerability
Statistical methods:	The following pharmacokinetic parameters were derived by noncompartmental analysis: AUC (trapezoidal rule), C_{max} and concentration at a specified time after dosing (ddI 6 hours; TPV and RTV 12 hours).
	Ratio (with/without TPV/RTV) of ddI pharmacokinetic parameters (90% Confidence Intervals) for $AUC_{0\text{-}12h}$, C_{max}, and C_{6h} where no effect = 1.00. Comparison days are Day 1 to Day 15. Ratio (with/without ddI) of TPV and RTV pharmacokinetic parameters (90% Confidence Intervals) for $AUC_{0\text{-}12h}$, C_{max}, and C_{12h} where no effect = 1.00. Comparison days are Day 14 to Day 15.
	Descriptive statistics for safety endpoints.
SUMMARY – CONCLUSIONS:	
Efficacy results:	not applicable
Pharmacokinetic results	The interaction of ddI with co-administered TPV and RTV could not be evaluated for the group of subjects that received TPV 750 mg/RTV 200 mg because early discontinuations provided only a single subject on Study Day 15 (ddI + TPV/RTV).
	For the group of subjects that received ddI in the presence of TPV 500 mg/RTV 100mg (n = 5), ddI AUC, C_{max} and C_{6h} were not significantly changed. While TPV AUC was not changed when co-administered with ddI, C_{max} did increase significantly while the decrease in C_{12h} was not significant. RTV AUC and C_{max} also were not significantly changed; C_{12h} could not be evaluated, as concentrations were BLQ for all subjects on Study Days 14 and 15.

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Safety results:

TPV with RTV was not satisfactorily tolerated in 21 of 23 volunteers. Eight of 23 subjects were discontinued early for AEs and 9 subjects discontinued early because of study termination. The study was changed from ambulatory to stationary after the first 11 subjects because 3 subjects from this group had difficulty concentrating. The study was terminated early because subject discontinuations for AEs resulted in loss of power for the primary pharmacokinetic endpoint.

Twenty-two of 23 subjects had AEs as follows: 51 AEs low dose TPV/RTV, 63 AEs high dose TPV/RTV, 2 ddI and 1 with ddI + low dose TPV/RTV. Eight subjects were discontinued for AEs, 4 biochemical (3 elevated ALT, 1 elevated triglyceride) and 4 clinical (cluster headache, poor concentration, chest pain with palpitations and dyspnoea, and diarrhoea). Only the cluster headache was from the low dose group. Most AEs were mild (grade I). The most frequent AEs were diarrhoea (73.9%), nausea (65.2%), flatulence (43.5%), abdominal pain (30.4%), headache (30.4%), dizziness (21.7%), fatigue (17.4%), ALT increase (13%), and concentration impairment (13%). Five subjects had 7 severe intensity AEs ($\geq$ grade III), 3 from the low and 2 from the high dose group. These included dizziness with ataxia, nausea, and cluster headache (low dose); diarrhoea, and elevation in AST and ALT (high dose).

The three elevations in transaminases corresponded to two grade II elevations in ALT and one grade III to IV elevation in ALT and AST. The triglyceride elevation was grade II. Overall, 36% in the low and 77% in the high dose group had elevations in ALT. Elevations in AST were similar, but elevations in GGT less frequent with a later onset and longer resolution. Triglycerides were elevated in 6 and total cholesterol in 20 of 23 volunteers. The LDL fraction accounted for the increased cholesterol. The cholesterol changes persisted for weeks to months. The increase in transaminases, triglyceride and cholesterol was seen in the stationary and ambulatory group. There was a small increase in urea within the normal ranges with no concomitant change in creatinine, potassium or urine sediment.

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Conclusions:

Based on limited data, no dosage adjustment would be needed when ddI is co-administered with TPV 500 mg/RTV 100 mg.

Because of the discontinuations due to AEs, the study was discontinued early. Without replacement of subjects, an adequate power for the analysis of the primary endpoint would not have been achieved. The discontinuation rate for TPV/RTV related AEs in this study was higher than in previously reported studies with TPV alone or with concomitant treatments in healthy volunteers or patients with HIV. As in previous studies, the incidence of AEs was high, especially for those involving the gastro-intestinal tract. The frequency of subjects with TPV/RTV related increase in hepatic transaminases or increases in LDL cholesterol, and discontinuations because of increase in ALT are also greater than previously reported. Three subjects reported difficulties in concentration temporally associated with drug administration. Study site specific reasons for these findings can not be excluded.