Clinical Study Synopsis for Public Disclosure

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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***.

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Name of finished product: Tipranavir				
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Report date: 20 May 2004	**Number:** U04-3198	**Study period (dates):** 28 August 2003 - 11 October 2003		

Title of study:	A single-centre open-label study in healthy adult volunteers to determine the effects of steady-state TPV/r (500 mg/200 mg) on the single-dose pharmacokinetics of rifabutin (MYCOBUTIN®) 150 mg, and the effects of single-dose rifabutin (150 mg) on the steady-state pharmacokinetics of TPV 500 mg (co-administered with RTV 200 mg).
Investigator:	[redacted]
Study center(s):	[redacted]
Publication (reference):	
Clinical phase:	I
Objectives:	To determine the effects of steady-state TPV/r (500mg/200mg bid) on the single-dose pharmacokinetics of RFB and to determine the effects of single-dose RFB on the steady-state pharmacokinetics of TPV 500mg (co-administered with RTV 200mg)
Methodology:	Open label study in healthy male and female volunteers administered a single dose of commercial RFB in the absence and presence of steady-state TPV and RTV
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 110 Treatment A: RFB entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment B: TPV/r entered: 24 treated: 24 analysed (for primary endpoint): 20 Treatment C: TPV/r + RFB entered: 24 treated: 21 analysed (for primary endpoint): 20
Diagnosis and main criteria for inclusion:	Males and females of any race, in good health and between the ages of 18 and 60 years, inclusive. Negative HIV, Hepatitis B and Hepatitis C serology.
Test product:	Tipranavir (TPV), Soft elastic capsule, Self Emulsifying Drug Delivery System (SEDDS)
dose:	1000mg (500mg bid)

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mode of admin.:	Oral
batch no.:	1004251
Duration of treatment:	13 days
Test product:	Ritonavir (RTV; Norvir-SEC®) , Soft elastic capsules
dose:	400mg (200mg bid)
mode of admin.:	Oral
Lot no.:	943332E21
Duration of treatment:	13 days
Test product:	Rifabutin (RFB; Mycobutin®), Capsules
dose:	150mg on study days 1 and 15
mode of admin.:	Oral
batch no.:	2GPG0C
Duration of treatment:	2 days
Reference therapy:	Not applicable
Criteria for evaluation:	
Efficacy:	There were no efficacy end points in this study
Pharmacokinetics:	**Primary endpoints:** o Effect of steady-state TPV/r on pharmacokinetics of single-dose RFB as measured by $AUC_{0-\infty}$, C_{max} and Cp_{12h} for RFB and its metabolite 25-O-desacetyl-RFB. o Effect of single-dose RFB on pharmacokinetics of steady-state TPV (co-administration of RTV) as measured by AUC_{0-12}, C_{max} and Cp_{12h}. **Secondary endpoints:** o Determination of additional pharmacokinetic parameters including T_{max}, CL/F, V, and $t_{1/2}$. **Safety monitoring.**

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Safety:	Subject safety was monitored by assessment of AEs at each visit. In addition evaluation of laboratory safety parameters including haematology, chemistry, total cholesterol, and standard urinalysis were carried out during the screening visit and on study days 1, 8, 14, 21. Serum pregnancy tests and urine toxicology profiles were carried out during the screening visit and on study days 0, 7, and 21. All tests were conducted for subjects that prematurely discontinued the study.
Statistical methods:	The following pharmacokinetic parameters were derived for RFB, 25-O-desacetyl-RFB and TPV using non-compartmental analyses: (i) area under the plasma concentration time curve (AUC, trapezoidal rule) from 0 h to infinity for RFB and metabolite ($AUC_{0-\infty}$) and over the 12 h dosing interval for TPV (AUC_{0-12h}); (ii) maximum observed plasma concentration (C_{max}); (iii) plasma concentration at a specified time after dosing (Cp_{12h}). Comparison of primary pharmacokinetic parameter geometric mean ratios, and associated 90% confidence intervals, for RFB, 25-O-desacetyl-RFB and TPV (where ratio of 1 indicates no effect) were carried out as follows: o Day 15 (single-dose RFB + steady-state TPV) to Day 1 (single-dose RFB) o Day 15 (steady-state TPV + single-dose RFB) to Day 14 (steady-state TPV)
SUMMARY – CONCLUSIONS:	
Efficacy results:	Not applicable

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Pharmacokinetics results:	The effect of a single 150mg dose of RFB on the steady-state pharmacokinetics of TPV (co-administered with RTV) was a 16% increase in Cp_{12h} (90% CI, 7% - 27%) with no apparent change in AUC_{0-12h} or C_{max}. Steady-state TPV increased the $AUC_{0-\infty}$, C_{max} and Cp_{12h} RFB primary pharmacokinetic parameters by 2.90-fold, 1.70-fold and 2.14-fold, respectively. The RFB secondary pharmacokinetic parameters $t_{1/2}$ and Cl/F also changed with median $t_{1/2}$ increasing by 19.4 h (from 51.8 h to 71.2 h) and median Cl/F decreasing by 65% (from 69.6 L/h to 24.2 L/h). A larger effect of steady-state TPV on 25-O-desacetyl-RFB was observed with the primary pharmacokinetic parameters $AUC_{0-\infty}$, C_{max} and Cp_{12h} increasing 20.71-fold, 3.20-fold and 7.83-fold, respectively. The increase in the combined parent plus metabolite $AUC_{0-\infty}$, C_{max} and Cp_{12h} parameters was calculated to be 4.33-fold, 1.86-fold and 2.76-fold.
Safety results:	A total of 20 (83.3 %) out of the 24 subjects entered into this study reported at least one AE. Consistent with previous TPV trials, GI-related AEs were the most frequently reported AEs in the current study. The majority of reported AEs were mild (83.3 % of subjects) or moderate (12.2 % of subjects) in intensity. No unexpected safety issues arose in this study. Three subjects developed asymptomatic grades 3 and 4 levels of ALT and AST which led to their early discontinuation from the study. A fourth subject was discontinued due to the appearance of generalized rash. All the AEs that led to discontinuations occurred while subjects were receiving TPV/r. There were no deaths or serious adverse events reported in this study. In addition, there were 2 other subjects with clinically relevant laboratory test findings. One subject had a Grade 3 lipase elevation and the other had a Grade 4 PTT elevation. All elevations returned to normal on follow up visits subsequent to end of treatment. There were no clinically relevant changes in vital sign and ECG parameters in the current study.

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Conclusions:	No clinically relevant changes in the steady-state pharmacokinetic parameters of TPV were observed when a single-dose of RFB was co-administered with steady-state TPV/r. In contrast, co-administration of a single dose of RFB with the steady-state TPV/r led to clinically relevant increases in the primary pharmacokinetic parameters for both RFB and 25-O-desacetyl-RFB. As a result, it is recommended that a reduced RFB dosing regimen (150mg two or three times per week) be used in combination with TPV/r. Moreover, patients receiving RFB with TPV/r should be clinically monitored for emergence of adverse events. The data presented in this report show that both treatments (RFB alone and TPV/r in combination with RFB) were moderately tolerated with the majority of AEs being mild in intensity. No deaths, serious adverse events, or unexpected safety issues occurred during this study.