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: 14 May 2004	**Number:** U04-3216	**Study period (dates):** 7 July 03 – 11 October 03		

Title of study:	A Two-way Pharmacokinetic Interaction Study of Single-Dose Atorvastatin (LIPITOR®) with Tipranavir/Ritonavir (500mg/200mg) at Steady-State and the Effect of Antacid (Maalox®) on the Pharmacokinetics of Single-Dose Tipranavir/Ritonavir (500mg/200mg) in Healthy Volunteers
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	
Clinical phase:	I
Objectives:	To determine the effects of combined tipranavir and ritonavir treatment (at steady-state) on the single-dose pharmacokinetics of atorvastatin, the effects of single-dose atorvastatin on the steady-state pharmacokinetics of tipranavir, and the effects of antacid on the pharmacokinetics of tipranavir.
Methodology:	Open label study in healthy volunteers receiving single doses of atorvastatin (ATV) in the absence and presence of steady-state Tipranavir/Ritonavir (TPV/r) and a single dose of antacid co-administered with TPV/r.
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 36 Treatment A: TPV/r + Atorvastatin entered: 23 treated: 23 analysed (for primary endpoint): 23 Treatment B: TPV/r + antacid (Maalox) entered: 23 treated: 23 analysed (for primary endpoint): 23
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, 250mg, Soft Elastic Capsules (SEC), Self-Emulsifying Drug Delivery System (SEDDS) formulation
dose:	500mg BID
mode of admin.:	Oral
batch no.:	1004251
Duration of treatment:	8 days
Test Product	RTV (NORVIR-SEC®) Soft Gel Capsules (100mg)

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dose:	RTV 200mg
mode of admin.:	Oral
lot no.:	908432E21
Duration of treatment:	8 days
Test Product	Atorvastatin (Lipitor™)
dose:	40mg and 10mg
mode of admin.:	Oral
lot no.:	lot no. for 40mg tablets: 302-37031; lot no. for 10mg tablets: 302-37081
Duration of treatment:	2 days
Test product:	Maalox Extra Strength Suspension, 350mL liquid bottle
dose:	20mL
mode of admin.:	Oral
batch no.:	319606
Duration of treatment	1 day
Reference therapy:	None
dose:	
mode of admin.:	
batch no.:	
Criteria for evaluation:	
Efficacy:	No efficacy parameters were assessed in this study

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Pharmacokinetics:	**PRIMARY ENDPOINTs** • Effect of steady-state TPV/r on single-dose pharmacokinetics of ATV, Ortho-hydroxy-ATV (O-OH-ATV), and Para-hydroxy-ATV (P-OH-ATV): o $AUC_{0-\infty}$ o C_{max} o C_{p12h} • Effect of single-dose ATV on steady-state pharmacokinetics of TPV: o AUC_{0-12h} o C_{max} o C_{p12h} • The single-dose pharmacokinetics of TPV with and without co-administration of a single-dose of antacid: o $AUC_{0-\infty}$ o C_{max} o C_{p12h} **SECONDARY ENDPOINTS** • Identification of additional pharmacokinetic parameters (eg., CL/F, V, t_{max}, $t_{1/2}$, and MRT) for atorvastatin and metabolites, and TPV as required. • Determination of the effect of single-dose TPV/r on hepatic CYP3A4 activity using the Erythromycin Breath Test. • Safety assessment.
Safety:	In addition to adverse events monitoring, subject safety was evaluated by assessment of laboratory safety parameters including hematology, chemistry, liver function tests (AST, ALT, alkaline phosphatase, total bilirubin), lipid parameters (triglycerides, HDL and LDL) at screening visit and various days throughout the study.

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Statistical methods: The following pharmacokinetic parameters were derived for atorvastatin, atorvastatin metabolites (ortho-hydroxy-atorvastatin and para-hydroxy-atorvastatin), and tipranavir using non-compartmental analysis: area under the plasma concentration time curve (AUC, trapezoidal rule), maximum observed plasma concentration (C_{max}) and plasma concentration at a specified time after dosing ($C_{p_{12h}}$). Comparison of geometric means of primary pharmacokinetics parameters, including associated 90% confidence intervals, for atorvastatin (as well as metabolites) and tipranavir were made as follows: Day 1 and 19 to Day 20 for atorvastatin-tipranavir interaction; Day 8 to Day 13 for antacid-tipranavir interaction. A ratio of 1 indicated lack of effect.

SUMMARY – CONCLUSIONS:

Efficacy results: Not applicable.

Pharmacokinetics results:

- Results from the Erythromycin Breath Test (ERMBT) showed near complete inhibition of hepatic Cytochrome P450 3A4 (CYP3A4) activity (reduced by 96% relative to base line) after a single-dose of TPV/r 500mg/200mg. Hepatic CYP3A4 activity returned to baseline by 48 hours after administration of single-dose TPV/r.
- Simultaneous ingestion of antacid and TPV/r reduced the plasma TPV concentrations by about 25-29%.
- No clinically relevant effects of single-dose ATV on the steady-state pharmacokinetics of TPV/r were observed in this study.
- Co-administration of steady-state TPV/r increased the dose-normalized [values multiplied by factor of 4 to adjust for the ATV dose differences between day 1 (40mg) and day 20 (10mg)] ATV $AUC_{0-\infty}$ by approximately 9-fold and reduced the $AUC_{0-\infty}$ of Ortho-OH-ATV and Para-OH-ATV by 89% and 82%, respectively.

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Safety results:

Consistent with previous TPV trials the most frequently observed AEs were GI-related on TPV/r treatment (95.7% of the subjects). Of these, diarrhea and nausea were the most frequent during all treatment phases. During the TPV/r treatment phase 82.6% of subjects reported diarrhea, 56.5% of subjects reported nausea, and 56.5% of the subjects reported AEs coded to the nervous system organ class. There were no discontinuations, deaths, or other significant adverse events in this study. One serious adverse event unrelated to study medications (sprained ankle/torn ligaments due to exercise) occurred during the study.

There were no clinically relevant changes in the results of laboratory test of project-specific special interest except for 1 report of an asymptomatic DAIDS Grade 3 elevation in ALT. Overall, only median maximum post-baseline triglycerides and ALT levels increased by 1.7-fold and 3.1-fold, respectively, relative to baseline. Vital sign measurements (blood pressure and pulse rate) did not significantly deviate from baseline during this study.

Conclusions:

This rapid reconstitution of CYP3A4 activity following TPV/r treatment discontinuation may be important to patients co-administering TPV/r with drugs that are affected by CYP3A4 activity and especially those drugs which may require a dosage adjustment when co-administered with TPV/r. Therefore, these patients should be closely monitored and the dose of such co-administered drugs should be re-evaluated upon discontinuation of TPV/r in case dose adjustments were made to counterbalance interactions during combination with TPV/r.

Co-administration of steady-state TPV/r with single-dose (10mg) ATV had no clinically relevant effect on the PK parameters of TPV. The $AUC_{0-\infty}$ of dose-adjusted ATV (assuming linear pharmacokinetics for ATV), however, increased by 9-fold. This increase in the exposure to ATV is considered clinically relevant, and it is therefore recommended that other HMG-CoA reductase inhibitors that are less sensitive to changes in CYP3A4 activity (such as pravastatin, fluvastatin or rosuvastatin) be considered for use with TPV/r. When co-administration of ATV with TPV/r is required, it is recommended to start patients on lowest dose of ATV that is expected to achieve the desired clinical benefit with monitoring. Increases in the ATV dose may be carried out under close clinical monitoring. Due to the effect ingestion of Maalox had on the TPV plasma concentrations, it is recommended that antacid administration should be separated from TPV/r administration. From a safety perspective, co-administrations of steady-state TPV/r with single-dose (10mg) ATV as well as single-dose TPV/r with single-dose antacid were well-tolerated in this study population with the majority of AEs being mild gastrointestinal event.