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:				
Name of active ingredient: Tipranavir		**Page:**	**Number:**	
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Report date: 16 APR 2004	**Number:** U04-1257-01	**Study period (dates):** 01 AUG 03-06 SEP 03		**Date of Revision:** 08 JUL 2004

Title of study:	A single-centre open-label study in healthy adult volunteers to determine the effects of single-dose and steady-state TPV/r (500 mg/200 mg) on the steady-state pharmacokinetics of Clarithromycin (BIAXIN®) 500 mg bid and a preliminary assessment of the effects of a standard high-fat test meal on the steady-state pharmacokinetics of Tipranavir
Investigator:	[redacted]
Study center(s):	[redacted] Canada.
Publication (reference):	None
Clinical phase:	I
Objectives:	To determine the effects of single-dose and steady-state Tipranavir/Ritonavir (TPV/r; 500 mg/200 mg bid) on the steady-state pharmacokinetics of clarithromycin and to determine the effects of a standard high-fat test meal on the steady-state pharmacokinetics of tipranavir.
Methodology:	Open label study in healthy male and female volunteers receiving commercial clarithromycin administered to steady-state in the absence and presence tipranavir and ritonavir and receiving a standard high-fat test meal with co-administered clarithromycin and TPV/r.
No. of subjects:	
planned:	entered: 24
actual:	enrolled: 158 Treatment A: TPV/r + Clarithromycin + High-fat test meal entered: 24 treated: 24 analysed (for primary endpoint): 24
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, 250 mg, Soft Elastic Capsules (SECs), Self-Emulsifying Drug Delivery System (SEDDS) formulation
dose:	TPV 500 mg bid
mode of admin.:	Oral
batch no.:	1004251
Duration of treatment:	8 days

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Test product:	Ritonavir (NORVIR-SEC®) Soft Gel Capsules (100 mg)
dose:	RTV 200 mg bid
mode of admin.:	Oral
Lot no.:	943332E21
Duration of treatment:	8 days
Test product:	Clarithromycin (BIAXIN®)
dose:	500 mg bid
mode of admin.:	Oral
Lot no.:	05-005NB1
Duration of treatment:	13 days
Reference therapy:	None
Criteria for evaluation:	
Efficacy:	There were no efficacy endpoints in this study.
Pharmacokinetics:	Primary Endpoints: The effect of single dose and steady-state TPV/r on the steady-state pharmacokinetics of clarithromycin and its major metabolite (14-hydroxy-clarithromycin, 14-OH-CLR) was assessed by comparing the AUC_{0-12h}, C_{max} and Cp_{12h} following treatment with all drugs to the same parameters when clarithromycin was taken alone. The effect of a high-fat test meal on the steady-state pharmacokinetics of TPV was assessed by comparing the AUC_{0-12h}, C_{max} and Cp_{12h} of TPV following co-administration with RTV, clarithromycin and the test meal for the same parameters when TPV was taken with RTV, clarithromycin and a light snack. Secondary Endpoints: Identification of additional pharmacokinetic parameters (e.g., Cl/F, V, $t_{1/2}$, t_{max}, and MRT) for TPV and clarithromycin and its metabolite was determined on an as needed basis.

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Safety:	In addition to adverse event monitoring through out the study, subject safety was monitored by assessment of laboratory safety parameters (including blood haematology and chemistry, liver function test, lipid profile tests, urinalysis) carried out at various days during the study. Safety was also monitored by comparing vital sign values (pulse rate and blood pressure) obtained at each visit to baseline values obtained prior to dosing.
Statistical methods:	The following pharmacokinetic parameters were derived for clarithromycin, 14-hydroxy-clarithromycin and tipranavir using non-compartmental analysis: area under the plasma concentration time curve over the dosing interval (AUC_{0-12h}, trapezoidal rule), maximum observed plasma concentration (C_{max}) and plasma concentration at a specified time after dosing (Cp_{12h}). Comparison for pharmacokinetic parameters AUC_{0-12h}, C_{max}, and Cp_{12h} (90% Confidence Intervals; where no effect = 1.00) of clarithromycin, 14-hydroxy-clarithromycin and tipranavir were carried out. Comparison days were: • Day 5 (clarithromycin at steady-state) to Day 6 (clarithromycin - TPV/r single-dose interaction) • Day 5 (clarithromycin at steady-state) to Day 13 (clarithromycin - TPV/r steady-state interaction) • Day 10 (TPV/r at steady-state with high-fat test meal) to Day 13 (TPV/r at steady-state with light snack)
SUMMARY – CONCLUSIONS:	
Efficacy results:	Not applicable

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Pharmacokinetics results:

Co-administration of single-dose TPV/r did not influence the steady-state AUC $_{0\text{-}12h}$ of CLR, but decreased the C_{max} by 12% and increased the Cp_{12h} by 50%. It also decreased AUC $_{0\text{-}12h}$ of 14-OH-CLR by 46%. Co-administration of CLR and steady-state TPV/r resulted in increasing the CLR AUC $_{0\text{-}12h}$ and Cp_{12h} parameters by 19% and 68%, respectively, with no substantial change in the C_{max} (-5%). The formation of 14-OH-CLR, however, was nearly completely inhibited during co-administration of steady-state TPV/r, as evidenced by a more than 95% reduction of the 14-OH-CLR AUC $_{0\text{-}12h}$, C_{max}, and Cp_{12h} PK parameters.

The steady-state AUC $_{0\text{-}12h}$, C_{max} and Cp_{12h} of TPV (used as TPV/r 500/200 mg twice-daily) were substantially increased (by 59%, 43% and 112%, respectively) during co-administration of steady-state CLR, compared to the historical data (BI study 1182.5 in which healthy volunteers received 1 of 8 TPV/r dose combinations, including TPV/r 500mg/200 mg, for 21 consecutive days with PK profiles collected every 7 days). Furthermore, ingestion of TPV/r 500/200 mg with a high fat test meal resulted in a significantly increased TPV AUC 0-12h (+31%), Cmax (+16%) and Cp12h (+75%) on day 10 relative to day 13. Recently available data from the 1182.24 trial indicates that at least 7 days of BID dosing with TPV/r (500/200 mg) are required to achieve steady-state TPV levels. Therefore, the finding of the high fat test meal component of the study where steady state had not yet been achieved (day 10) does not provide conclusive evidence of the effect of a high fat meal on plasma concentrations of TPV/r.

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Safety results:

A total of 70.8% of the subjects entered into this study reported at least one AE. Consistent with previous TPV trials, the most frequently observed (in 50% of subjects) AEs were GI related. In general, both treatments (CLR alone and TPV/RTV in combination with CLR) were well-tolerated with the majority of AE's being mild in intensity. No unexpected safety issues arose in this study nor were there any discontinuations. There were no deaths, or serious adverse events in this study.

One subject had an asymptomatic DAIDS Grade 3 elevation in ALT during the TPV/r/CLR treatment period and one subject had a DAIDS Grade 3 elevation in lipase during the CLR treatment period. There were no other clinically relevant changes in laboratory test of project-specific special interest. Moreover, there were no relevant changes from baseline in vital sign measurements (blood pressure and pulse rate) in this study.

Overall, the TPV/r/CLR combination treatment was well-tolerated in the healthy subject population used in this study. There were no unexpected safety issues identified in this study.

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Conclusions:

Co-administration of single-dose TPV/r with steady-state CLR led to non-relevant changes in the CLR and 14-OH-CLR levels. The presence of steady-state levels of TPV during CLR dosing, however, resulted in increasing the CLR $AUC_{0\text{-}12h}$ and Cp_{12h} while virtually eliminating the formation of 14-OH-CLR. Given the wide therapeutic range of CLR, the changes in CLR PK profile are not considered clinically significant in patients with normal renal function. For patients with renal impairment, a creatinine clearance-based CLR dosage adjustment may be required. The near complete inhibition of the formation of 14-OH-CLR should be considered for the treatment of certain bacterial pathogens against which this metabolite is highly active.

The steady-state $AUC_{0\text{-}12h}$, C_{max} and Cp_{12h} of TPV were significantly increased during co-administration of steady-state CLR, compared to the historical data (BI study 1182.5). Although concentration-related adverse events have not been observed in studies, the clinical relevance of the increased exposure to TPV during co-administration of CLR is not yet known. Thus, patients using clarithromycin at doses higher than 500mg BID should be carefully monitored for signs of toxicity.

The TPV pharmacokinetic parameters $AUC_{0\text{-}12h}$, C_{max} and Cp_{12h} on day 10, following co-ingestion of TPV/r with a high-fat test meal, increased relative to day 13. The study was designed to compare the pharmacokinetics of TPV/r co-ingested with the test meal after just 4 days of dosing to that of TPV/r co-ingested with light snack after 7 days of dosing. However, data became available during the conduct of this study indicating that at least 7 days of BID dosing with TPV/r (500/200 mg) are required to achieve steady-state TPV levels. As a result, the finding that the high fat test meal increases TPV levels is inconclusive because it was based on a comparison of TPV steady-state PK parameters (day 13) to those obtained before steady-state TPV levels were reached (day 10).

From a drug safety perspective, co-administration of TPV/r with CLR was well-tolerated in the subject population used in this study with the majority of reported AEs being mild GI events. There were no deaths, other serious adverse events or discontinuations due to AEs in this study.