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***.

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Name of finished product: BILR 355 BS				
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Report date: 16 February 2006	**Number:** U06-3095-01	**Study period (dates):** 24 Feb 2005-31 May 2005		**Date of Revision:** 28 August 2007

Title of study:	Study of pharmacokinetic interaction between tipranavir and BILR 355 BS plus ritonavir
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	Data from this study have not been published
Clinical phase:	I
Objectives:	To determine the effect of BILR 355/r on tipranavir/r pharmacokinetics and the effect of tipranavir/r on BILR 355 BS pharmacokinetics.
Methodology:	Open-label, single center, outpatient PK trial
No. of subjects:	
planned:	entered: 34
actual:	enrolled: 65 Treatment A: 26 entered: 26 treated: 26 analysed (for primary endpoint): 25 Treatment B: 8 entered: 8 treated: 8 analysed (for primary endpoint): 8
Diagnosis and main criteria for inclusion:	Healthy males and females, not pregnant or nursing, subjects between ages 19 to 60 with BMI between 18.5 and 29.9 kg/m^2
Test product:	BILR 355 BS + ritonavir
dose:	150 mg BILR 355 BS BID + 100 mg ritonavir BID (BILR 355/r alone group) 150 mg BILR 355 BS BID (BILR 355 BS + tipranavir/r group)
mode of admin.:	Oral
batch no.:	BILR 355 BS: PD-2421; PD-2511
Duration of treatment:	10-17 days

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Reference therapy:	Tipranavir
dose:	500 mg BID + 200 mg ritonavir BID
mode of admin.:	Oral
batch no.:	Tipranavir: PD-2350B Ritonavir: Lot #109142E21; 109702E22; 166902E21
Criteria for evaluation:	
Efficacy:	N/A
Safety:	Safety was assessed by reporting of adverse events, physical examinations, vital signs, ECG and laboratory assessments.
Statistical methods:	AUC and C_{max} will be log transformed prior to fitting an ANOVA model. 90% confidence intervals will be computed, then back-transformed to the original scale to give the geometric mean and interval estimates for the median ratio (test / reference). Tipranavir with ritonavir administered in combination with BILR 355 BS will be declared bioequivalent to tipranavir given without BILR 355 BS if the 90% confidence intervals of the geometric means of both ratios AUC_{0-12} and C_{max} are contained in the pre-defined acceptance range (0.80, 1.25). Data from three other interaction trials will be pooled with that of the current trial to perform a similar test of pharmacokinetic equivalence for BILR 355/r when administer with or without tipranavir.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Following oral multiple co-administration of TPV/r with BILR 355 BS, the $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $C_{p12,ss}$ values of TPV for BILR 355 BS + TPV/r treatment were 635000 h.ng/mL, 84400 ng/mL, and 26300 ng/mL respectively; for TPV/r treatment alone, the values were 563000 h.ng/mL, 80000 ng/mL, and 22700 ng/mL, respectively. The $t_{max,ss}$ (median = 2.5) were very similar for both treatments. The geometric mean treatment ratios of TPV (combination vs. TPV/r alone) and the associated 90% confidence interval [CI] were 96.55% [89.05, 104.68], 99.65% [92.64, 107.18], and 101.97% [88.55, 117.42], for $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $C_{p12,ss}$, respectively. The $t_{max,ss}$ (median = 2.5) were very similar for both treatments. The mean half-life of 17.8 hours for TPV after co-administration of TPV/r with BILR 355 BS was much longer than 5.1 hours of TPV/r alone group. This difference was, however, related to the longer sampling time (96 hour) after co-administration of TPV/r with BILR 355 BS and the continued dosing of RTV. As the 90% CI for all exposures parameters fell within no effect region of 80% -125%, it is therefore concluded that co-administration of BILR 355 BS with TPV/r has no effects on the pharmacokinetics of TPV.

In the presence of BILR 355 the mean $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $C_{p12,ss}$ values of RTV were 5920 h.ng/mL, 1320 ng/mL, and 74.6 ng/mL, respectively; for TPV/r treatment alone, the values were 6030 h.ng/mL, 1300 ng/mL, and 74.6 ng/mL, respectively. The exposure parameters were very similar for both treatments. The mean half-life of 1.81 hours for RTV after co-administration of TPV/r with BILR 355 BS was comparable to 1.68 hours of TPV/r alone group, indicating co-administration did not alter the elimination of RTV. The $t_{max,ss}$ (median = 4 hour) were very similar for both treatments.

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Safety results:

Overall, fifteen (57.7%) subjects experienced adverse events while receiving TPV alone with all 15 having events being defined as drug related. Thirteen (52.0%) subjects experienced adverse events with 12 (48.0%) having events being defined as drug related while receiving TPV/BILR/r. Five (62.5%) subjects experienced adverse events with all having events being defined as drug related while receiving BILR/r only.

No single event was reported in more than three subjects in any treatment group. However, various types of rash were reported in six subjects in the TPV/r and TPV/BILR/r groups, all of whom discontinued the trial due to the rash, making rash the most common adverse event overall. Gastrointestinal complaints, including diarrhea, nausea and dyspepsia were the second most common type of event reported across all treatment groups and the most common type of event reported in the TPV/r and BILR/r treatment groups. No event of rash was reported in the BILR/r group, and the rash events are most likely due to TPV due to the timing of the onset of the rashes (6-12 days after the onset of TPV treatment).

Six subjects discontinued the trial due to adverse events, two (7.7%) in the TPV/r group and five (20.0%) in the TPV/BILR/r group. One subject [redacted] experienced events leading to discontinuation in while on treatment with TPV/r alone and after BILR was added, and appears in both groups. All but one of the discontinuations were due to a rash-type event, the other was due to ALT/AST increase.

The only severe AE reported was the increase in ALT/AST in Subject [redacted] while receiving TPV/r. There were no serious adverse events or deaths in this trial.

The only notable change in laboratory parameters during the trial were increases in ALT and AST in 21 of 26 subjects receiving TPV/r. An increase in median AST (+22 U/L) and ALT (+57 U/L) was seen from beginning to end of treatment with TPV/r. One TPV/r subject [redacted] was discontinued due to the increase in LFTs during the trial. An additional subject [redacted] had a notable increase in LFTs after discontinuing trial medication, after completion of treatment with TPV/BILR/r. Most LFT abnormalities except for Subject [redacted] occurred prior to administration of BILR 355 BS, eliminating BILR 355 BS as a cause for the increases. Elevations in LFTs are a known effect of tipranavir, however the overall rate seen in this trial (21 out of 26 subjects) was higher than that seen in most other TPV/r trials in healthy volunteers (U00-3106). This high rate of LFT increases may have been due to the lack of induction of metabolism which is present in patients already taking HIV regimens.

There were no changes in vital signs or ECG parameters during the trial which would indicate a risk with any of the treatments used in this trial.

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Conclusions: The current study showed that co-administration of TPV/r with BILR 355 BS did not alter the pharmacokinetics of TPV. RTV pharmacokinetic measurements were similar with or without co-administration of BILR 355 BS. Therefore, no dose adjustment is needed for TPV when TPV/r is co-administered with BILR 355 BS. Overall, the rate of abnormalities in the BILR 355/r group was acceptably low. Rash and liver abnormalities seen in TPV/r and TPV/BILR/r groups seemed to be higher than observed in most prior healthy volunteer trials of TPV/r. The timing of these events suggests a relationship to TPV/r but a BILR/r contribution cannot be eliminated. Appropriate monitoring for these events is warranted in other healthy volunteer trials of TPV/r and in trials of TPV/r plus BILR 355 BS.