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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Title of study:	Study of Pharmacokinetic Interaction between Combivir® (ZDV+3TC) and BILR 355 BS plus ritonavir
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	N/A
Clinical phase:	I
Objectives:	To determine the effect of BILR 355/r on Combivir® pharmacokinetics and the effect of Combivir® on BILR 355 BS pharmacokinetics.
Methodology:	Collection of PK blood samples
No. of subjects:	
planned:	Enrolled:80
	Entered: 34
actual:	Enrolled: 88
	Entered: 51
	Treatment A: entered: 39 treated: 39 analysed (for primary endpoint): 36 Treatment B: entered: 12 treated: 12 analysed (for primary endpoint): 11
Diagnosis and main criteria for inclusion:	Healthy males and females, not pregnant or nursing, subjects between ages 18 to 60 with BMI between 18.5 and 29.9 kg/m^2
Test product:	BILR 355 BS
dose:	150 mg BID
mode of admin.:	PO
batch no.:	PD 2421 and PD 2511
Duration of treatment:	10 - 17 days

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Reference therapy:	Combivir®
dose:	150 mg lamivudine/300 mg zidovudine BID
mode of admin.:	PO
batch no.:	4ZP6753, 5ZP3216 and 5ZP6096
Criteria for evaluation:	
Pharmacokinetic:	Primary Endpoints: Steady-state AUC_{0-12h} and C_{max} for both ZDV and 3TC when administered as Combivir® both with and without BILR 355/r; steady-state AUC_{0-12h} and C_{max} for BILR 355 administered with and without Combivir®, and plasma concentration at 24 hours post final dose, for BILR 355 BS (and ritonavir). Data from the BILR 355/r group will be combined with data from Trials 1188.7, 1188.8 and 1188.10 in a separate pharmacokinetic report.
Safety:	Adverse events, laboratory tests, vital signs and physical examinations
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). ZDV administered in combination with BILR 355/r will be declared bioequivalent to ZDV given without BILR 355/r 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). Similarly, 3TC administered in combination with BILR 355/r will be declared pharmacokinetically equivalent to 3TC given without BILR 355/r if the confidence intervals for both AUC_{0-12} and C_{max} are within (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 Combivir®.
SUMMARY – CONCLUSIONS:	
Pharmacokinetic results:	The co-administration of BILR 355/r with CBV was associated with increased plasma concentrations of 3TC, compared to those observed with CBV administration alone. $C_{max,ss}$ for ZDV concentrations were marginally decreased, but the lower 90% CI for the ratio of CBV+BILR 355/r versus CBV alone fell just below 80%. ZDV ratios for $AUC_{0-12,ss}$ and $C_{p12h,SS}$ values were within the 80% to 125% range.

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Pharmacokinetic results continued:

Thus the $AUC_{0\text{-}12,ss}$ was in the "no effect" region, and the $C_{max,ss}$ 90 % CI reached to just below the limit of "no effect". This variance however is not clinically important.

Following oral multiple administration, the $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $C_{p12,ss}$ mean values of 3TC for CBV+BILR 355/r treatment were 9620 h.ng/mL, 1960 ng/mL, and 255 ng/mL respectively.

For CBV treatment alone, the values were 6590 h.ng/mL, 1580 ng/mL, and 131 ng/mL, respectively. The geometric treatment ratios of 3TC (CBV+BILR 355/r vs. CBV alone) and the associated 90% confidence interval (CI) were 145.08% (139.51, 150.86), 123.85% (118.57, 129.36), and 192.78% (180.76, 205.59), for $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $C_{p12h,ss}$, respectively. As the 90% CI for all exposures parameters fell outside the upper boundary of the no effect region it is concluded that co-administration of BILR 355/r with CBV increased the exposures to 3TC. However, because the antiviral efficacy of 3TC, a nucleoside reverse transcriptase inhibitor (NRTI), is related to the intracellular concentration, not the plasma concentration of 3TC, the increase in the plasma level of 3TC may not result in clinically relevant changes in the antiretroviral effectiveness of 3TC (P99-00581).

Following oral multiple administration, the mean $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $C_{p12,ss}$ values of ZDV for CBV+BILR 355/r treatment were 1920 h.ng/mL, 1160 ng/mL, and 7.69 ng/mL respectively. For CBV treatment alone, the mean values were 2000 h.ng/mL, 1400 ng/mL, and 7.50 ng/mL, respectively. The geometric treatment ratios (CBV+BILR 355/r vs. CBV alone) and the associated 90% confidence interval (CI) were 95.57% (90.42, 101.00), 85.28% (74.02, 98.22), and 102.34% (93.84, 111.61), for $AUC_{0\text{-}12,ss}$, $C_{max,ss}$, and $Cp_{12h,ss}$, respectively. Except for the lower boundary of 90 % CI for $C_{max,ss}$, the point estimates as well as 90% CI for all exposures parameters of ZDV fell well inside the predefined no effect region of 80% -125%. Although an effect of BILR 355/r cannot be ruled out statistically, the 14.7% decrease in $C_{max,ss}$ is unlikely to be clinically important. Furthermore, $AUC_{0\text{-}12,ss}$ and $Cp_{12h,ss}$ values were very similar between the concentrations with and without BILR 355/r co-administration. Finally, the antiviral activity of nucleoside reverse transcriptase inhibitors like ZDV is directly related to the intracellular concentrations, not the plasma concentrations. Since plasma concentrations may not reflect intracellular concentrations, it is unlikely that the slightly decrease of $C_{max,ss}$ would be of clinical importance (R05-1623).

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Safety results:

The overall incidence of adverse events was comparable between the CBV group (59.0%) and the CBV+BILR 355/r group (44.7%), as compared to the BILR only group (16.7%).

Consistent with other BILR trials, GI disorders were the most frequently observed adverse events with a higher incidence seen in the CBV group (51.3%), as compared to the CBV+BILR 355/r group (26.3%) and the BILR group (0.0%). Among the GI disorders, nausea was the most common event with a higher incidence in the CBV group (38.5%), as compared to the CBV+BILR 355/r group (13.2%), and the BILR group (0.0%).

All adverse events in this trial were considered to be of mild intensity with the exception of one moderate intensity event. The event that was considered to be of moderate intensity was the event of sinus headache which was reported by the subject while receiving CBV.

One subject in the CBV+BILR 355/r group discontinued study medication on Day 15 due to an adverse event of bilateral ankle joint discomfort secondary to a drug induced rash. Further ritonavir dosing was withheld and the subject completed all remaining study procedures. There were no deaths or serious adverse events reported during this study.

Apart from mild decreases in hemoglobin and other hematology parameters to be expected with repeated phlebotomy, laboratory abnormalities observed in this study were mild. The overall effect of BILR 355 BS on laboratory parameters appeared to be minimal in this trial and no subject discontinued do to an abnormal laboratory parameter.

All ECG and vital findings were considered to be not clinically significant by the investigator and all subjects were asymptomatic. There were no apparent trends or consistency of abnormalities of ECG and vital findings between treatment groups, and no subjects had their treatment changed or discontinued due to ECG or vital findings.

Overall BILR 355 BS was well tolerated in this study. There were no safety findings in this study that would preclude the implementation and conduct of future trials with BILR 355 BS.

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Conclusions:	There was no indication of any significant changes in laboratory parameters, ECG's or vital signs associated with BILR 355/r administration, however exposure to BILR 355/r was limited to seven days. The safety evaluation of BILR 355/r should be investigated in longer term trials. Based on the evaluations of geometric mean ratios for 3TC with and without BILR 355/r, we clearly cannot conclude that BILR 355/r had no effect on the pharmacokinetics of 3TC, and most probably results in higher plasma concentrations. The effects on ZDV were less pronounced, but the lower CI of 74% also does not allow the conclusion that there is no effect on ZDV concentrations. No dose adjustment is needed for CBV when CBV is co-administered with BILR 355/r, and the safety of BILR 355/r in combination with CBV needs to be evaluated in longer term trials in HIV-1 infected adults.