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.

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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: BILR 355 BS				
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Report date: 23 May 2006	**Number:** U06-3313	**Study period (dates):** 01 June 2005 to 26 September 2005		

Title of study:	Randomized Single Dose Multiple Crossover Relative Bioavailability Trial of New Tablet Formulations and Suspension Formulation Compared to Current (1B) Formulation of BILR 355 BS in Healthy Male Volunteer Subjects
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	N/A
Clinical phase:	I
Objectives:	**1**. To investigate the relative bioavailability (BA) of improved tablet formulation candidates in comparison to the current formulation known as 1B, to determine which formulation will be developed for use in late Phase II and Phase III clinical trials. **2.** To investigate the relative BA of the pediatric suspension, compared to the current 1B formulation. **3.** To investigate the bioequivalence (BE) of BILR 355 BS in 2 tablet strengths; 3 25 mg tablets vs. one 75 mg tablet, current 1B formulation.
Methodology:	This study was an open-label, single dose, randomized, crossover study in healthy HIV-negative adult male volunteers. There were 4 study Groups, A, B, C and D. All groups had three crossovers with the exception of Group A which had two crossovers. All study subjects were randomized to one of two or three crossover sequences within their group. Groups A and D were conducted in parallel. Fourteen subjects were randomized to Group A in order to meet a total of twelve evaluable subjects. Twenty-one subjects were randomized to Group D in order to meet a total of eighteen evaluable subjects. Subsequently, Groups B and C were conducted in parallel. Twenty-seven subjects were to be randomized to each Group B and C for a total of at least 24 evaluable in each group, however 26 subjects were randomized to Group B.

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Methodology (continued):	The subjects were admitted the evening prior to the BILR 355 dose administration, where each subject received the first RTV 100 mg dose. At approximately 8:00 AM, immediately after pre-dose safety labs and PK sampling, subjects were administered BILR 355 BS and RTV 100 mg, followed by a 24-hour period of intensive PK sampling. Additional PK samples were taken at 48, 72 and 96 hours after the single BILR 355 BS dose. An additional ritonavir, 100 mg tablet was administered at each of 24, 48 and 72 hours post the BILR 355 BS dose. Each dose of BILR 355 was separated by a washout period of 10-14 days. Every subject received either two or three formulations/doses, separated by the washout period. End of study testing was performed 7 to 14 days after last BILR dose.
No. of subjects:	
planned:	entered: 297 enrolled: 89
actual:	entered: 292 enrolled: 88
Diagnosis and main criteria for inclusion:	Healthy, HIV negative adult male volunteers
Test product:	BILR 355 BS
dose:	75, 100, 150, or 200 mg BILR 355 BS in combination with ritonavir capsules (100 mg)
mode of admin.:	po
batch no.:	25 mg - PD-2421, HM-PD-2570, JM- PD-2571, 75 mg - PD-2568, 25 mg/ml-PD 2576.
Duration of treatment:	Up to 43 days study treatment participation, not including screening
Reference therapy:	N/A
dose:	
mode of admin.:	
batch no.:	25 mg - PD-2421, HM-PD-2570, JM- PD-2571, 75 mg- PD-2568, 25 mg/ml-PD-2576.

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Criteria for evaluation:

Pharmacokinetics:

The primary endpoint for comparison are $AUC_{0-\infty}$ C_{max}

Secondary endpoints are T_{max}, AUC_{0-tz}, λ_z, MRT_{po}, T1/2, CL/F, and V_z/F.

The primary comparisons are:

- Group A: within group comparisons of three 25 mg 1B formulation tablets versus one 75 mg 1B formulation tablet, all which did not contain SDS.
- Group B: within group comparisons of the micronized SDS formulation (JM + SDS), the non-micronized SDS formulation (HM + SDS), and the current 1B formulation at doses of 100 mg.
- Group D: within group comparison of three 25 mg 1B tablet formulation compared to 75 mg in 3 ml of suspension.

The secondary comparisons are:

- Group D: within group comparison of the 75 mg vs. 150 mg suspension to establish dose proportionality.
- Group B and C: cross group comparisons of JM + SDS for the dose groups of 100 mg (Group B) versus 150 mg (Group C) and versus 200 mg (Group C) to test dose proportionality of JM + SDS.
- Cross group comparisons of HM + SDS for the dose groups of 100 mg (Group B) versus 200 mg (Group C) to test dose proportionality of HM + SDS.

Safety:

Adverse events, laboratory tests, vital signs, and physical examinations.

Statistical methods:

$AUC_{0-\infty}$ and C_{max} were log transformed prior to fitting an ANOVA model. Confidence intervals for the differences of the logs were computed, then back-transformed to the original scale to give the geometric mean and interval estimates for the median ratio (test / reference).

For Groups A and D, the test and reference were to be declared pharmacokinetically equivalent if the 90% confidence intervals of the median ratios of $AUC_{0-\infty}$ and C_{max} are within 80%-125%.

For Group B, the test formulation were to be considered superior to the reference if the 95% confidence intervals of the median ratios of $AUC_{0-\infty}$ and C_{max} are greater than 1.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results: Following oral single administration of BILR 355/r, the $AUC_{0\text{-}inf}$ and C_{max} mean values of BILR 355 for 3x25 mg 1B tablet were 10100 h.ng/mL and 483 ng/mL, respectively; for 1x75 mg 1B tablet, the values were 12100 h.ng/mL and 605, respectively. The geometric mean treatment ratios of 1x75 mg 1B vs. 3x25 mg 1B and the associated 90% confidence interval (CI) were 121.9% (105.5, 140.8) and 126.8% (108.5, 148.3), respectively, for $AUC_{0\text{-}inf}$ and C_{max}. As the 90% CI for the exposures parameters fell outside the upper boundary of the bioequivalent region it is concluded that 1x75 mg 1B tablet is not bioequivalent to 3x25 mg 1B tablet, but tended to result in higher BIILR 355 concentrations than the 3x25 mg dose.

Following oral single administration of BILR 355/r, the $AUC_{0\text{-}inf}$ mean values of BILR 355 for 100 mg 1B tablet, 100 mg JM + SDS tablet, and 100 mg HM + SDS tablet were 10900, 19500, and 15800 h.ng/mL, respectively. The C_{max} mean values of BILR 355 for 100 mg 1B tablet, 100 mg JM + SDS tablet, and 100 mg HM + SDS tablet were 527, 1110, and 895 ng/mL, respectively. The geometric mean treatment ratios of 100 mg JM + SDS tablet vs. 100 mg 1B tablet and the associated 90% confidence interval (CI) were 177.7% (161.9, 194.9) and 212.9% (185.7, 244.2), respectively. As the low limit of 90% CI for the exposures parameters exceeded one, it was concluded that at 100 mg dose level, JM + SDS formulation results in greater exposures than the100 mg 1B tablet. The geometric mean treatment ratios of 100 mg HM + SDS tablet vs. 100 mg 1B tablet and the associated 90% confidence interval (CI) were 144.1% (131.6, 157.7) and 170.2% (149.9, 193.3), respectively. As the low limit of 90% CI for the exposures parameters exceeded one, it was concluded that at 100 mg dose level, HM + SDS formulation resulted in greater exposure than the 100 mg 1B tablet. The geometric mean treatment ratios of 100 mg JM + SDS tablet vs. 100 mg HM + SDS tablet and the associated 90% confidence interval (CI) were 124.3% (114.5, 134.9) and 126.1% (112.9, 140.8), respectively. As the low limit of 90% CI for the exposures parameters exceed one, it was concluded that at 100 mg dose level, JM + SDS formulation tended to have greater relative bioavailability than the HM 100 mg tablet.

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Pharmacokinetic results (continued):

Following oral single administration of BILR 355/r, the AUC $_{0\text{-inf}}$ mean values of BILR 355 for 150 mg JM + SDS tablet, 200 mg JM + SDS tablet, and 200 mg HM + SDS tablet were 23800, 29000, and 26300 h.ng/mL, respectively. The C_{max} mean values of BILR 355 for 150 mg JM + SDS tablet, 200 mg JM + SDS tablet, and 200 mg HM + SDS tablet were 1500, 1890, and 1750 ng/mL, respectively. The geometric mean treatment ratios of 200 mg JM + SDS tablet vs. 200 mg HM + SDS tablet and the associated 90% confidence interval (CI) were 109.8% (100.3, 120.2) and 109.5% (99.3, 120.7), respectively. As the geometric mean ratios of 200 mg JM + SDS vs. 200 mg HM + SDS and the associated 90% CI for both AUC $_{0\text{-inf}}$ and C_{max} were contained in the pre-defined the bioequivalent region of 80-125%, it was concluded that the HM + SDS tablet was bioequivalent to JM + SDS tablet at 200 mg dose level.

Following oral single administration of BILR 355/r, the $AUC_{0\text{-inf}}$ mean values of BILR 355 for 75 mg 1B tablet, 75 mg dose of suspension, and 150 mg dose of suspension were 9420, 10700, and 14500 h.ng/mL, respectively. The C_{max} mean values of BILR 355 for 75 mg 1B tablet, 75 mg suspension, and 150 mg suspension were 466, 515, and 795 ng/mL, respectively. The geometric mean treatment ratios of 75 mg suspension vs. 75 mg 1B tablet and the associated 90% confidence interval (CI) were 114.1% (99.8, 130.4) and 109.9% (94.0, 128.5), respectively, for $AUC_{0\text{-inf}}$ and C_{max}. As the 90% CI for the exposures parameters fell outside the upper boundary of the no effect region it is concluded that 75 mg suspension was not bioequivalent to 75 mg 1B tablet, although the suspension tended to produce higher concentrations at this dose.

Analyses of dose proportionality showed in the studied dose range of 100 mg to 200 mg, for JM + SDS tablet, the increase in dose did not lead to proportional increase in exposures. For HM + SDS tablet, the exposures were slightly less proportional to doses. For suspension formulation, in the studied dose range of 75 mg to 150 mg, the increase in dose led to less proportional increase in exposures.

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Safety results:

Although 50 subjects were exposed to at least one dose of the HM + SDS, and 52 subjects were exposed to at least one dose of the JM + SDS, the protocol design resulted in a greater exposure to the JM + SDS formulations than to the HM + SDS formulation. There were 50 total exposures to HM + SDS compared to 77 total exposures to JM + SDS.

Although the overall proportion of subjects with AEs tended to be higher in subjects receiving the JM + SDS formulation (32.7%) as compared to the HM + SDS formulation (24.0%), when the number of doses is taken into consideration, the overall rates are similar. The overall proportion of subjects with AEs tended to be higher among those subjects receiving SDS-containing formulations than the 1B formulation (18.0%), and the suspension (9.5%), and there was no clear pattern of specific AE's to suggest an increased risk. There were no apparent dose-related trends of adverse events within any of the formulations.

When comparing the current 1B formulation to the new formulations consisting of SDS (HM + SDS, and JM + SDS), the frequency of upper and lower GI adverse events are too few to indicate an increased risk of GI complaints with exposure to the SDS formulations.

There were no significant mean differences for all vital parameters between treatments as well as dose related differences within treatments.

The overall effect of BILR 355 BS on laboratory parameters appeared to be minimal. Apart from the mild decreases seen in hematology parameters which may be due to repeated phlebotomy, the degree of change in laboratory parameters may be due to normal subject variability.

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Conclusions:

There were no significant safety findings including any indication of significant changes in laboratory parameters or vital signs associated with BILR 355 BS administration however the safety of BILR 355 BS needs to be evaluated in longer term trials in HIV-1 infected adults.

Following oral single administration of BILR 355/r, it was found that based on the statistical analysis 1x75 mg 1B tablet had higher exposure as compared to 3x25 mg 1B tablet. It was also concluded that at 100 mg dose level, both JM and HM + SDS tablet were superior to 1B tablet in terms of exposures to BILR 355. However, at 200 mg dose level, it was demonstrated that JM + SDS containing tablet was statistically bioequivalent to HM + SDS tablet. It was shown by statistical analysis that at 75 mg dose level, suspension was not bioequivalent to 75 mg 1B tablet with respective to AUC $_{0\text{-inf}}$ and C_{max} and to yield 9% to 14% greater exposure than the 1B tablet.

Analyses of dose proportionality showed in the studied dose range of 100 mg to 200 mg, for JM + SDS tablet, the increase in dose lead to increase in concentrations which were less than proportional to increases in dose. For HM + SDS tablet, the exposures were slightly less than proportional to increases in doses. For suspension formulation, in the studied dose range of 75 mg to 150 mg, the increase in dose led to less than proportional increase in exposures.