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:				
Name of active ingredient: BILR 355 (SDS), ritonavir (Norvir®)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 6 March 2007	**Number:** U07-3058	**Study period (dates):** 30 May 2006 to 28 August 2006		

Title of study:	Phase I sequential dose escalation study of pharmacokinetics, safety and tolerability after single dose (225 mg-450 mg) oral administration of BILR 355 (SDS) plus low-dose ritonavir in healthy volunteers
Investigator:	[redacted]
Study center:	[redacted]
Publication (reference):	n/a
Clinical phase:	I
Objectives:	1-To explore the relative bioavailability of increasing doses of BILR 355, as an SDS-containing formulation (SDS) in combination with ritonavir 100 mg, and the dose-concentration proportionality of increasing doses 2-To explore the effect of food on the pharmacokinetics of BILR 355 (SDS)
Methodology:	This was sequential dose escalation study of healthy adult male and female volunteers. Subjects were recruited from a single site and were assigned sequentially to four treatment dose groups (225, 300, 375 and 450 mg single dose regimens). Twelve subjects were assigned to each dose group. The male:female ratio for each dose group was 6:6 (± 1 for each gender). All subjects received one 100 mg capsule of ritonavir at the following times: 10 hours before treatment with BILR 355 (SDS), on Day 1 at the same time with a single BILR 355 (SDS) dose while fasting, and 24, 48, and 72 hours post BILR 355 (SDS) dose. Each dosed group completed treatment and follow-up evaluation, before the dosing of the next dose group. The Trial Team evaluated adverse events and safety laboratory findings for the current dose group, before dosing the next higher dose group. For dose groups above 225 mg, BILR 355 and BILR 516 C_{max} and AUC and safety data were examined before initiation of the next higher dose group for evidence of increasing plasma concentration with increasing dose. The 225 mg dose group participated in a food effect study. After a wash out period of 14 days, these subjects were dosed again with a single BILR 355 (SDS) 225 mg dose, 30 minutes following a high fat breakfast.
No. of subjects: **planned:** **actual:**	48 entered: 48 enrolled: 48 Twelve subjects per dose level (225, 300, 375 and 450 mg)

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Diagnosis and main criteria for inclusion:	Healthy volunteers, age >=18 and <=50 years, BMI: 18.5 – 29.9 kg/m^2
Test product:	BILR 355 (SDS); ritonavir (Norvir®) 100 mg capsules
dose:	Single doses 225, 300, 375 and 450 mg BILR 355 SDS; 100 mg ritonavir
mode of admin.:	p.o.
batch no.:	
Duration of treatment:	Single dose
Reference therapy:	None
dose:	n.a.
mode of admin.:	n.a.
batch no.:	n.a.
Criteria for evaluation:	
Pharmacokinetic:	BILR 355 (SDS) and BILR 516 pharmacokinetic parameters ($AUC_{0\text{-}inf}$, and C_{max}) were compared among the increasing dose groups to determine relative bioavailability and dose proportionality. $AUC_{0\text{-}tz}$, CI/F, t_{max}, and $t_{1/2}$ were also examined.
Safety:	General medical examination, blood pressure, pulse rate, ECG, laboratory parameters and adverse events
Statistical methods:	Descriptive statistics for PK endpoints and safety were calculated. Dose proportionality was explored using a linear regression model. Two-sided 95% confidence intervals for the slope parameter β_1 were computed to assess the dose proportionality. Relative bioavailability analyses for BILR with and without food comparison were performed to evaluate the food effect.

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SUMMARY – CONCLUSIONS:

Pharmacokinetic results: Over the studied single dose range of BILR 355 SDS 225 mg to 450 mg, the exposures ($AUC_{0\text{-}inf}$, and C_{max} in log scale) to BILR 355 appeared to be approximately linear to the administered doses in log scale. Following a single dose of BILR 355 SDS 225 mg tablet, the $AUC_{0\text{-}inf}$ and C_{max} were 21700 h.ng/ml and 1830 h.ng/ml, respectively. Following a single dose of BILR 355 SDS 300 mg tablet, the $AUC_{0\text{-}inf}$ and C_{max} were 27400 h.ng/ml and 2220 h.ng/ml, respectively. Following a single dose of BILR 355 SDS 375 mg tablet, the mean $AUC_{0\text{-}inf}$ and mean C_{max} were 44800 h.ng/ml and 3020 h.ng/ml, respectively. Following a single dose of BILR 355 SDS 450 mg tablet, the mean $AUC_{0\text{-}inf}$ and mean C_{max} were 53400 h.ng/ml and 3940 h.ng/ml, respectively. The $AUC_{0\text{-}inf}$ and C_{max} were 30200 h.ng/ml and 2150 h.ng/ml, respectively, following a single dose of BILR 355 SDS 225 mg tablet taken with a high fat breakfast. Co-administration of a high fat breakfast with BILR 355/r resulted in a 51% increase and a 29% increase in the geometric mean of $AUC_{0\text{-}inf}$ and C_{max}, respectively.

Safety results: There were no significant safety issues that arose during the trial. A total of 10 AEs were identified among the 48 subjects entered in this trial. Gastrointestinal (n=5) and neurological (n=5) disorders were the most frequently observed adverse events in this trial. The three most common AEs were headache (N=4), diarrhea (N=2) and nausea (N=2). No subjects discontinued due to AEs. Hematuria occurred in eleven female patients who had menses at the time a urine sample was provided. Hematuria did not appear to be dose related. Aside from the hematuria, the overall effect of BILR 355 SDS on laboratory parameters appeared to be minimal. There were no serious adverse events or deaths in this trial.

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Conclusions:

Over the studied dose range of 225 mg to 450 mg for SDS containing BILR 355 tablets, the exposures ($AUC0_{-inf}$ and C_{max} in log scale) to BILR 355 appeared to be approximately linear to the administered doses in log scale. Co-administration of a high fat breakfast with BILR 355/r in this formulation resulted in an approximate 1.5 hour delay in reaching C_{max} along with a 51% and a 29% increase in AUC_{0-inf} and C_{max} values, respectively. Future confirmatory studies are warranted to examine a final formulation of BILR 355 to determine the effects of food on the BILR 355 pharmacokinetics observed in this exploratory study.

Compared to the values of BILR 355, the mean C_{max} values of BILR 516 were 26 -34% of those of BILR 355, and the mean AUC_{0-inf} values of BILR 516 were 2.3 – 2.6 fold of those of BILR 355.

BILR 355 was well tolerated, and no severe adverse events were identified. The most common AEs were gastrointestinal and neurological disorders. Asymptomatic hematuria occurred among eleven females during menses. Aside from the hematuria, the overall effect of BILR 355 SDS on laboratory parameters appeared to be minimal. No clinically significant changes in vital sign measurements or ECG were identified in this study.

Collectively, these results suggest that BILR 355, in SDS tablet formulation, has favourable human pharmacokinetic and safety profile which may be used in Phase IIa clinical trials.