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 Trial Report**		Boehringer Ingelheim
Name of finished product: BILR 355		**EudraCT No.:**		
Name of active ingredient: BILR 355, Ritonavir (Norvir)		**Page:**	**Number:**	**Synopsis No.:**
Ref. to Documentation:	**Module:**	**Volume:**		
Report date: 10 Oct 2007	**Trial No. / U No.:** 1188.33 / U07-3432	**Date of trial:** 30 Oct 2006 – 20 Dec 2006		**Date of revision** (if applicable)**:** Not applicable

Title of trial:	An open-label, randomized, crossover relative BA study of pharmacokinetics and safety of new SDS-containing tablet and capsule formulations of BILR 355 compared to the current formulation (50 mg tablet), after single dose oral administration of BILR 355 plus low dose ritonavir in healthy male volunteers
Principal/ Coordinating Investigator:	[redacted]
Trial sites:	[redacted]
Publication (reference):	Data from this study have not been published
Clinical phase:	I
Objectives:	To determine the single dose, relative BA of new SDS-containing formulations of BILR 355 (150 mg and 200 mg capsules and 150 mg tablet), compared to the current SDS tablet formulation (50 mg tablet)

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Methodology: This study was an open-label, randomized, crossover study in healthy HIV-negative adult male volunteers. There were two study groups. Group 1 had three crossovers and Group 2 had two crossovers. The five dose forms and abbreviations are listed below.
150 mg dose
Current formulation 50 mg x 3 (HM150T – tablet)
New formulation 150 mg x 1 (SDS150T – tablet)
New formulation 150 mg x 1 (SDS 150C – capsule)
200 mg dose
Current formulation 50 mg x 4 (HM200T – tablet)
New formulation 200 mg x 1 (SDS200C – capsule)
All study subjects were randomized to one of five treatment sequences. Groups ran in parallel with 24 subjects in Group 1 and 16 subjects in Group 2.

Dose Group	Sequence	Treatment	First Dosing Period	Second Dosing Period	Third Dosing Period
1	1	ABC	50 mg tabsx3**	150 mg tab x1*	150 mg cap x1*
	2	CAB	150 mg cap x1*	50 mg tabsx3**	150 mg tab x1*
	3	BCA	150 mg tab x1*	150 mg cap x1*	50 mg tabsx3**
2	1	DE	50 mg tabsx4**	200 mg cap x1*	N/A
	2	ED	200 mg cap x1*	50 mg tabsx4**	N/A

* new SDS-containing formulations for tablet (tab) or dry-fill capsule (cap)
** current SDS-containing formulation

Ritonavir, (RTV) 100 mg will be administered with each dose of BILR 355, the evening before each dose, and on Days 2, 3, 4, and 5 after each dose of BILR 355.

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 (-15 minutes) safety labs and PK sampling, subjects were administered BILR 355 SDS and RTV100 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 SDS dose. An additional ritonavir, 100 mg tablet was administered at each of 24, 48, 72, and 96 hours post BILR 355 SDS dose. Each dose of BILR 355 was separated by an inter dose period of 12 days. End of trial testing was performed within 12 days after the last dose of BILR 355 SDS.

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No. of subjects:	
planned:	entered: 40
actual:	enrolled: 40
	Treatment 1: entered: 24 treated: 24 analysed (for primary endpoint): 24 Treatment 1: entered: 16 treated: 16 analysed (for primary endpoint): 16
Diagnosis and main criteria for inclusion:	Healthy HIV-negative male volunteers, age ≥ 18 and ≤ 50 years, BMI: 18.5 – 29.9 kg/m2
Test product:	BILR 355 (SDS)
dose:	150 mg tablet, 150 mg capsule, 200 mg capsule
mode of admin.:	p.o.
batch no.:	B063000352 and B063000353
Reference therapy:	BILR 355 (SDS)
dose:	50 mg tablet x 3 (150 mg)
mode of admin.:	p.o.
batch no.:	B053000174
Duration of treatment:	The study was a single dose 2 or 3 way crossover trial within two study groups up to 36 days for Group 1 and 24 days for Group 2 for study treatment participation, not including screening period.
Criteria for evaluation:	

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Efficacy / clinical pharmacology:	Efficacy was not studied. BILR 355 (SDS) pharmacokinetic parameters ($AUC_{0\text{-}inf}$, and C_{max}) were compared among treatments to determine relative bioavailability. AUC0-tz, CI/F, Tmax, and T1/2 p.o. were also examined for BILR 355. All pharmacokinetic parameters estimated for BILR 355 were estimated for BILR 516.
Safety:	Adverse events, laboratory tests, vital signs, and physical examinations.
Statistical methods:	Geometric mean ratios and corresponding 90% confidence intervals were calculated for all pharmacokinetic parameters in pairwise comparisons of test and reference treatment.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: The Table below shows the geometric mean ratios (GMR) and 90% CI for AUC(0-inf) and Cmax for the BILR 355 formulation and dose treatment pairs after single oral co-administration with 100 mg ritonavir.

Comparison	GMR (%)	gSE (Est.)	Lower limit	Upper limit
AUC(0-inf)				
SDS150T-HM150T	84.77	1.10	71.99	99.83
SDS150C-HM150T	87.04	1.10	73.91	102.49
SDS150C-SDS150T	102.67	1.10	87.19	120.90
SDS200C-HM200T	122.48	1.13	100.26	149.63
Cmax				
SDS150T-HM150T	80.20	1.14	64.59	99.60
SDS150C-HM150T	88.03	1.14	70.89	109.31
SDS150C-SDS150T	109.75	1.14	88.38	136.29
SDS200C-HM200T	124.17	1.17	95.24	161.88

Source: Tables 15.5.1: 7 – 15.5.1: 10, 15.5.2:3 – 15.5.2: 4.

At the 150 mg dose level, the new capsule (SDS150C) had comparable exposures to the new tablet (SDS150T), and the new tablet had lower exposures compared to the current tablet (HM150T). At the 200 mg dose level, the new capsule (SDS200C) had higher systemic exposure compared to the current tablet (HM200T).

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Safety results:

The overall incidence of adverse events among subjects was comparable for the BILR 355 dose and formulations. Gastrointestinal (n=4) and neurological (n=4) disorders were the most frequently observed adverse events and were generally mild in this trial. Neither gastrointestinal nor neurological adverse events appeared to be related to formulation or dose.

Laboratory abnormalities observed in this study were generally mild and without pattern to BILR 355 dose or formulation. Minor changes in the urine analysis such as proteinuria and hematuria were found during the study post BILR 355/r treatment and are of unknown significance among unique subjects. These urine findings were neither formulation nor dose related.

Overall, BILR 355 doses and formulations were 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.

Conclusions:

In this trial, the results indicate that at the BILR 355 150 mg dose level, the new capsule has comparable exposures to the new tablet but that the new tablet has lower exposures to the current tablet (50 mg x 3). At the BILR 355 200 mg dose level the new capsule was shown to have greater systemic exposure compared to the current 50 mg tablet x 4. No clinically significant AEs, changes in laboratory measurements or vital sign measurements were identified in this study in any of the dose or formulations of BILR 355/r. Collectively, these results suggest that BILR 355, in a SDS containing capsule, has a favourable human pharmacokinetic and safety profile which may be used in Phase IIa clinical trials.