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 BS, ritonavir (Norvir®)		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 30 JUN 2005	**Number:** U05-1809	**Study period (dates):** 11/02-12/03		

Title of study:	An open study to investigate the effect of two times oral 100 mg ritonavir capsules on pharmacokinetics of single doses of BILR 355 BS (dose steps: 5 and 12.5 mg) dissolved in 5 mL PEG 400 after oral administration in healthy male volunteers, and a double blind, placebo controlled study for doses from 25 mg to 100 mg BILR 355 BS
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	no
Clinical phase:	I
Objectives:	Assessment of the effect of two times oral 100 mg ritonavir capsules on pharmacokinetics of a single dose of BILR 355 BS dissolved in PEG 400
Methodology:	Two sequential single oral doses of BILR 355 BS, open label
No. of subjects:	64
planned:	to be entered: 64 (Eight subjects per dose level, eight dose levels)
actual:	entered: 62
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 – 50 years, BMI: 18.5 – 29.9 kg/m^2
Test product:	BILR 355 BS solved in 5 mL PEG 400; ritonavir (Norvir®) 100 mg capsules
dose:	single doses 5 and 12.5 mg BILR 355 BS; two times 100 mg ritonavir
mode of admin.:	p.o.
batch no.:	PD-2141, PD-2142, PD-2143, PD-2144, PD-2148
Duration of treatment:	One single dose of BILR 355 BS, two times 100 mg ritonavir, all within less than 12 hours
Reference therapy:	none
dose:	n.a.
mode of admin.:	n.a.
batch no.:	n.a.

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Criteria for evaluation:

Efficacy: PK: C_{max}, t_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, $t_{½}$, CL/F, MRT_{tot}, V_z/F, CL_R, Ae

Safety: General medical examination, blood pressure, pulse rate, ECG, laboratory parameters and adverse events

Statistical methods: Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results:

Following oral co-administration with two doses of 100 mg ritonavir, BILR 355 was rapidly absorbed, resulted in a mean t_{max} around 3-6 hours for the subjects in lower dose levels (5 mg and 12.5 mg) and 1-2 hours for the subjects in the dose level of 25 mg and above. After reaching the peaks, the plasma BILR 355 concentrations declined at a moderately rate, displayed terminal half-lives around 14-16 hours and 10-12 hours for low dose levels (5 mg and 12.5 mg) and for the other higher dose levels, respectively. Increases in the dose of BILR 355 led to approximate linear increases in AUC_{INF} over the studied dose range of 5 mg to 87.5 mg; the proportional increases in C_{max} with increased doses were observed only in the dose range of 25 mg to 87.5 mg. Across all dose levels, about 5% of the administered dose were excreted as unchanged drug during the time interval of 0-72 h. After co-administered with 2 doses of 100 mg ritonavir, the increases in mean AUC_{INF} of BILR 355 ranged from 15-fold (Doses 50 mg and 75 mg) to 31-fold (12.5 mg and 25 mg) as compared with those without ritonavir boosting; the mean C_{max} values of BILR 355 were increased about 2~3-fold and 5~6-fold for high (50 and 75 mg) and low (12.5 and 25 mg) dose levels, respectively, as compared with those of BILR 355 administered alone. The half-lives were increased from 2~4 hours (without ritonavir boosting) to 11~16 hours (with co-administration with ritonavir). After oral administration of a single dose of BILR 355 with ritonavir, the plasma BILR 402 concentrations achieved peaks after 4-8 hours post dose in most of the subjects, with only a few subjects having t_{max} less than 2 hours. Compared to the values of BILR 355, across studied dose range, the mean C_{max} values of BILR 402 were less than 3% of those of BILR 355, the mean AUC_{INF} values were less than 5% of those of BILR 355 (not including 25 mg). The subjects receiving 50 mg dose cohort also received 50 mg BILR 355 under fed conditions. No clinically relevant food effects on pharmacokinetics of BILR 355 were observed for BILR 355 BS in this formulation (PIB).

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Safety results:

Overall 15 AE episodes were reported. Eight of these episodes were assessed as possibly drug related and occurred in 7 of the 62 subjects. Three of these episodes, occurring in three subjects, were reported as maculopapulous exanthema, treatment at onset was ritonavir and 25 mg, 37.5 mg and 87.5 mg BILR 355 BS, respectively. The subject on 25 mg BILR 355 BS + ritonavir also experienced an oral aphthous ulcer. Diarrhoea was reported in three episodes in three subjects, one with ritonavir only, one with 5 mg BILR 355 BS + ritonavir, and one with 87.5 mg BILR 355 BS + ritonavir. Tiredness was reported once with 50 mg BILR 355 BS + ritonavir fed (Appendix 16.2, Listing 7.2.1 to 7.2.4). All eight possibly drug related AE episodes were of mild intensity, and all of these resolved completely without therapy. Among the AEs assessed as not drug related there was one episode of headache of moderate intensity which resolved without therapy, and one episode of headache of mild intensity which was treated. All other AEs were of mild intensity and did not require any treatment. All AEs were transient in nature and resolved completely. In the majority of cases they resolved without therapy.

Laboratory parameters did not reveal any clinically relevant, drug-related changes. This is also the case for the parameters of special interest concerning liver function (ASAT, ALAT, GGT, AP, GLDH and Total, Direct and Indirect Bilirubin). No increases of these parameters above the double of the upper limit of normal were seen.

Vital signs, physical examination, neurological assessment and faecal occult blood testing did not show any clinically relevant, drug related changes. Also from the global tolerability assessment no dose related change could be concluded.

There was no evidence that the treatment with BILR 355 BS in this study resulted in clinically relevant ECG changes. No changes in morphology (including T waves and U-waves), rhythm or conduction were observed. There was no evidence for an impact on QT-interval.

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Conclusions:

The safety and tolerability of BILR 355 BS in doses up to 87.5 mg in combination with ritonavir in healthy male volunteers was established. The target plasma levels of about 1000 ng/mL were achieved.

The analysis of AEs, laboratory and other safety data did not raise any concerns regarding the safety and tolerability of single oral doses of up to 87.5 mg in combination with ritonavir. There were no dose relationships observed for any type of adverse events. Also for vital signs and laboratory values no such changes could be identified. No impact of the application of BILR 355 BS on ECG parameters, including the QT interval, could be seen.

The results of this trial support the continued investigation of BILR 355 BS in combination with ritonavir at higher concentrations and longer plasma exposure.

The pharmacokinetic profiles of BILR 355 after co-administration of BILR 355 with two doses of ritonavir suggest BILR 355 could be dosed as once daily or twice daily regimen after ritonavir boosting to achieve the target therapeutic concentrations.