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		**Page:**	**Number:**	
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Report date: 19 December 2003	**Number:** U03-1926	**Study period (dates):** 22 May 02 - 13 Feb 03		

Title of study:	A double-blind (at each dose level), randomised, placebo-controlled single increasing dose safety, tolerability and preliminary pharmacokinetics study in healthy male volunteers after oral administration of BILR 355 BS solved in PEG 400 (dosage: 1 – 200 mg)
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	Data of the trial have not been published
Clinical phase:	I
Objectives:	Assessment of safety, tolerability and preliminary pharmacokinetics in healthy male volunteers after oral administration of BILR 355 BS
Methodology:	Single oral rising doses of BILR 355 BS, double-blind (at each dose level), randomised, placebo-controlled
No. of subjects:	
planned:	To be entered: 72 (Eight subjects (six on active substance, two on placebo) per dose level, nine dose levels)
actual:	Entered: 54 Eight subjects (six on active substance, two on placebo) per dose level, seven dose levels (up to 100 mg), two drop-outs not replaced
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 dissolved in 5 mL PEG 400
dose:	single doses 1, 5, 12.5, 25, 50, 75, 100 mg
mode of admin.:	p.o.
batch no.:	See section 9.4.2
Duration of treatment:	Single doses (one day per subject)

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Reference therapy:	Placebo (5 mL PEG 400)
dose:	5 mL PEG 400
mode of admin.:	p.o.
batch no.:	See section 9.4.2
Criteria for evaluation:	PK: a thorough evaluation of the PK parameters over the studied doses, and comparison of these PK parameters over the doses.
Efficacy:	PK: C_{max}, t_{max}, AUC_{0-tz}, AUC_{0-INF}, $t_{½}$, CL/F, MRT_{tot}, V_z/F, CL_R, Ae
Safety:	General medical examination, vital signs, ECG, laboratory parameters and adverse events, skin inspection, faecal occult blood testing, neurological assessment, assessment of global tolerability
Statistical methods:	Descriptive statistics for all other parameters.

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:

Following oral administration, BILR 355 displayed a short half-life around 2 hours; the t_{maxs} were around 0.5 to 1 hour. The mean C_{max} of BILR 355 ranged from BLQ to 937.23 (ng/mL); and the mean $AUC_{(0-INF)}$ ranged from BLQ to 1308.36 (hr*ng/mL) at the studies doses. At the investigated dose range (1-100 mg), the C_{max} increased more than proportional to the increasing administered doses, so did AUC, but in a less pronounced manner. Overall, it appeared that the first-pass enzymes were saturated; however, systemically, the enzymes (mainly CYP3A4) responsible for metabolizing BILR 355 have not been saturated. As a result, the absorption portion of the pharmacokinetics showed signs of nonlinearity; the elimination portion of the kinetics was still linear over the studied doses. Less than 1% of the doses were excreted as unchanged drug in urine. For the four active metabolites, except for M7, the half-lives were short as 2 to 5 hours; M7 had a half-life around 10 hours. The C_{maxs} and AUC_s of M7, M3, and M7A increased more than proportional to the administered doses of BILR 355, but much less pronounced than those of BILR 355 itself. At 100 mg dose, the mean C_{max} of M7, M3, M7A, and M2A were about 29%, 5%, 38%, and 4%, respectively, of that of BILR 355; the mean $AUC_{(0-INF)}$ of M7, M3, M7A, and M2A were about 139%, 17%, 49%, and 5%, respectively, of that of BILR 355. The renal eliminated metabolites (as % of administered doses) were about 2.5%, 0.1%, 0.1%, and 2.0% for M7, M3, M7A, and M2A, respectively. The total dose eliminated from urine (all metabolites + unchanged drugs) were less than 5%.

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Safety results:

Overall 21 AEs were reported. AEs occurred in 15 of the 54 subjects. Two AEs in two subjects occurred prior to drug administration. Three AEs in two subjects occurred more than 48 hours after drug administration. Sixteen AEs in 11 subjects occurred during the treatment phase defined from drug administration until 48 hours after drug administration. These were almost evenly distributed over all treatment groups including placebo, with a slightly higher rate of six AEs in four subjects in the 75 mg group, the second highest dose group.

All adverse events in all subjects resolved completely, in most cases after less than one day and without intervention. There were no deaths, no SAEs, and no AEs leading to treatment discontinuation. Almost all AEs were mild, with the exception of a moderate episode of vomiting and a moderate episode of migraine, both occurring in the placebo group. No AE was of severe intensity.

The pattern of more frequent AEs (fatigue, gastrointestinal disorders and headache or migraine) is typical for this kind of Phase I studies with healthy volunteers and reflect the thorough documentation of AEs in this setting. There were only single episodes of AEs concerning other system organ classes. Overall, the AEs observed do not suggest any kind of AE which seems to be related to BILR 355 BS.

From the toxicological profile of BILR 355 BS and from the experiences with other drugs of the NNRTI class liver enzyme elevations and skin alterations like rash were monitored especially thoroughly. There was only one episode of ALAT increase beyond the double of the upper limit of normal six days after treatment with 5 mg BILR 355 BS, with a low probability of being caused by the treatment, and one episode of mild rash occurring about 28 hours after administration of 25 mg BILR 355 BS. From these mild and single episodes occurring in lower dose groups, no relationship to drug or dose can be concluded.

Also the other laboratory parameters tested did not reveal any clinically relevant, drug-related changes.

Vital signs, physical examination, skin inspection, 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 100 mg 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 100 mg BILR 355 BS. No kind of adverse event with any dose relationship was observed. No kind of adverse event could be identified that can be expected in further trials with BILR 355 BS. 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.

Following oral administration, BILR 355 displayed a short half-life around 2 hours; the t_{maxs} were around 0.5 to 1 hour. The mean C_{max} of BILR 355 ranged from BLQ to 937.23 (ng/mL); and the mean $AUC_{(0\text{-}INF)}$ ranged from BLQ to 1308.36 (hr*ng/mL) at the studies doses. At the investigated dose range (1-100 mg), the C_{max} increased more than proportional to the increasing administered doses, so did AUC, but in a less pronounced manner.

The results of this trial do not preclude to investigate higher doses of BILR 355 BS, if necessary.