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: ---				
Name of active ingredient: BILR 355 BS		**Page:**	**Number:**	
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Report date: 04 JUL 2005	**Number:** U05-1840	**Study period (dates):** 03/2003 – 12/2003		

Title of study:	An open study to investigate the effect of different boosting agents 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
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	none
Clinical phase:	I
Objectives:	Assessment of the effect of different boosting agents 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:	
planned:	To be entered: 48 (Eight subjects per dose group, six dose groups)
actual:	entered: 44
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; different boosting agents
dose:	single doses 5 and 12.5 mg BILR 355 BS; different boosting agents
mode of admin.:	p.o.
batch no.:	B030101, B030102, PD-2352, PD-2295, PD-2353, 88056VA, MGA05, MHA07, K030401 = E2451 Roche
Duration of treatment:	One single dose of BILR 355 BS, different boosting agents
Reference therapy:	none
dose:	n.a.
mode of admin.:	n.a.
batch no.:	n.a.
Criteria for evaluation:	
Efficacy:	PK: C_{max}, t_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, $t_{½}$, CL/F, MRT_{tot}, V_z/F
Safety:	General medical examination, blood pressure, pulse rate, ECG, laboratory parameters and adverse events

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Statistical methods: Descriptive statistics

SUMMARY – CONCLUSIONS:

Efficacy results:

At 5 mg level, grapefruit juice was able to boost the absorption of the BILR 355, resulting in an increase of mean C_{max} from 3.64 to 6.9 ng/mL; however, at the 12.5 mg dose level, only a slightly increase of mean C_{max} of BILR 355 was observed after co-administration. The grapefruit juice had no effects on the half-life of BILR 355 at both 5 mg and 12.5 mg dose levels. At 5 mg dose level, after co-administered with NFV, the mean C_{max} and AUC of BILR 355 were increased by 6.4-fold and 20.6-fold, respectively. At the 12.5 mg dose level, the mean C_{max}, AUC, and half-life, were increased 3.7-fold, 7.9-fold, and 1.3-fold, respectively, as compared with those observed in 12.5 mg BILR 355 alone. Compared to the treatment of BILR 355 alone, the mean C_{max}, $AUC_{0\text{-}inf}$, half-life were approximately 5.4-fold, 17.5-fold, and 2.5-fold higher after ATV boosting. The boosting effects of 300 mg ATV + 100 mg of ritonavir on PK of 12.5 mg of BILR 355 were similar to those of 100 mg ritonavir.

Safety results:

Overall 15 AE episodes were reported. Eight of these episodes were assessed as possibly drug related and occurred in 7 of the 44 subjects. Four of these episodes, occurring in three subjects, were reported as headache. One episode of headache was reported on 12.5 mg BILR 355 BS and grapefruit juice, two on atazanavir and ritonavir (before dosing of BILR 355 BS), and one episode on atazanavir, ritonavir and 12.5 mg BILR 355 BS. Two episodes were reported as maculopapulous exanthema, both on nelfinavir and 5 mg BILR 355 BS. The remaining two episodes were reported as diarrhoea, one on nelfinavir and 5 mg BILR 355 BS, and one on nelfinavir alone, before dosing of BILR 355 BS.

All eight possibly drug related AE episodes were of mild intensity. Among the AEs assessed as not drug related there were two episodes of headache of moderate intensity and one urticaria at ECG electrode site of moderate intensity, all other AEs were of mild intensity, no AE was of severe intensity. 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, with the exception of an increase in Bilirubin in the subjects receiving atazanavir. Beside this, no other increases of the parameters ASAT, ALAT,

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	GGT, AP, GLDH and Total, Direct and Indirect Bilirubin above the double of the upper limit of normal were seen except a single, slight and reversible increase in GLDH after dosing of nelfinavir (before BILR 355 BS dosing). Taken together, the laboratory parameters did not reveal any clinically relevant changes except an increase in Bilirubin which can clearly be attributed to atazanavir dosing. Vital signs, physical examination, neurological assessment and faecal occult blood testing did not show any clinically relevant, treatment related changes. Also from the global tolerability assessment no treatment related change could be concluded. There was no evidence that the treatment with BILR 355 BS and the boosting agents used in this study resulted in clinically relevant ECG changes. No relevant changes in morphology (including T waves and U waves), rhythm or conduction were observed. There was no evidence for an impact on QT interval.
Conclusions:	The safety and tolerability of BILR 355 BS in the doses of 5 mg and 12.5 mg in combination with the different boosting agents (grapefruit juice, nelfinavir, atazanavir, and atazanavir plus ritonavir) in healthy male volunteers was established. First data on the pharmacokinetic interactions of BILR 355 BS with the different boosting agents in man were gained. 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 BILR 355 BS in combination with the boosting agents used. No treatment relationship was observed for any of the adverse events. No adverse events were identified as could be expected in further trials with BILR 355 BS. There were also no drug related vital signs or laboratory abnormalities identified, except an increase in Bilirubin which can clearly be attributed to atazanavir dosing. This study showed GFJ was able to slightly increase the plasma levels of BILR 355 but had not effects on the terminal half-life of BILR 355 after co-administered with BILR 355; NFV moderately boosted AUC, C_{max}, and half-life of BILR 355 after co-administration, however, the boosting effects of NFV were somewhat less sustainable than those with ritonavir; The boosting effects of ATV on the C_{max} of BILR 355 was similar to those observed with ritonavir boosting but the effects on AUC and half-life of BILR 355 were not as strong as those of ritonavir. The results of this trial support the continued investigation of BILR 355 BS in combination with different boosting agents at higher concentrations and longer plasma exposure.