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: BI 14332 CL		**Page:**	**Number:**	
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Report date: 12 June 2007	**Number:** U07-1442	**Study period (dates):** 14 Sept 2006 to 08 Nov 2006		

Title of study:	Influence of a standardised high fat breakfast on the bioavailability of 10 mg BI 14332 CL taken as two tablets of 5 mg q.d. in healthy male volunteers (an open-label, randomised, single-dose, two-way crossover trial).
Investigator:	[redacted]
Study centre:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	To investigate the relative bioavailability of 10 mg BI 14332 CL as tablets vs. 10 mg BI 14332 CL as tablets after intake of a standardised high fat breakfast
Methodology:	Open-label, randomised, two-way crossover design
No. of subjects:	
planned:	entered: 12
actual:	enrolled: 20 Treatment A: BI 14332 CL tablets after intake of food entered: 12 treated: 11 analysed (for primary endpoint): 11 Treatment B: BI 14332 CL tablets entered: 12 treated: 11 analysed (for primary endpoint): 11
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ‡21 to £65 years, BMI range: ≥18.5 to £29.9 kg/m^2
Test product:	BI 14332 CL tablets after intake of food (T)
dose:	10 mg (2 x 5 mg)
mode of admin.:	Oral
batch no.:	B061001460
Duration of treatment:	One day (single dose po) for each treatment; 2 days total
Reference therapy:	BI 14332 CL tablets (R)
dose:	10 mg (2 x 5 mg)
mode of admin.:	Oral
batch no.:	B061001460

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Criteria for evaluation:

Efficacy: Pharmacokinetic parameters:
primary endpoints: $AUC_{0-¥}$ and C_{max}
secondary endpoints: AUC_{0-tz}, t_{max}, l_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F

Safety: Adverse events, physical examination, vital signs (blood pressure, pulse rate), 12-lead ECG, laboratory tests and tolerability

Statistical methods: Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-¥}$ and C_{max} and their two-sided 90% confidence intervals (CIs) were calculated. The statistical model was ANOVA on log transformed parameters including effects for "sequence", "subjects nested within sequences", "period" and "treatment". CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated.

SUMMARY – CONCLUSIONS:

Efficacy results: All of the 11 subjects participating in the study were healthy male volunteers with a mean age of 41.2 years, ranging from 31 to 54 years, and a mean BMI of 24.69 kg/m².

Overall, plasma concentration-time profiles of BI 14332 BS were comparable between both treatments (10 mg BI 14332 CL as tablets in the presence or absence of food). The intake of a high-fat breakfast led to a slight reduction in the maximum plasma concentration C_{max} (10.5 nmol/L in the fasted state vs. 9.85 nmol/L in the fed state). The overall reduction observed for C_{max} was mainly driven by one subject ([redacted]), whose peak concentrations decreased by more than 50% from 16.6 nmol/L to 7.52 nmol/L when BI 14332 CL was given in the presence of food. All other pharmacokinetic parameters evaluated were comparable between the fasted and the fed state: $AUC_{0-\infty}$ (750 nmol·h/L vs. 713 nmol·h/L), AUC_{0-24} (176 nmol·h/L vs. 172 nmol·h/L), t_{max} (3.00 h vs. 2.98 h), $t_{1/2}$ (85.2 h vs. 76.6 h), MRT_{po} (104 h vs.96.7 h), CL/F (514 mL/min vs. 541 mL/min), V_z/F (3790 L vs. 3590 L). All values given are geometric mean values.

In summary, food did not significantly influence the extent of absorption of the drug with a geometric mean ratio of $AUC_{0-\infty}$ of 95.4%, with the 90% CI ranging from 89.9% to 101.2%. The intraindividual variability was low with 7.5%. A 6.8% reduction in C_{max} was observed in the fed state, with the 90% CI ranging from 77.5% to 112.0%. Since the extent of absorption $AUC_{0-\infty}$, median t_{max}, and half-life $t_{1/2}$ were comparable between the fasted and the fed state, no clinically relevant food effect is expected.

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Safety results:

The drug was very well tolerated by all participating subjects and within both treatment groups (test treatment: 10 mg BI 14332 CL after ingestion of a high fat breakfast; reference treatment: 10 mg BI 14332 CL in fasted state). There were no serious or other significant adverse events, no discontinuations due to adverse events and no deaths.

Only 2 subjects experienced an adverse event: one subject assigned to the test treatment suffered from tonsillitis and one subject assigned to the reference treatment suffered from back pain. The adverse events were of mild intensity and not judged drug-related. Both subjects recovered within a few days.

The descriptive analysis of laboratory parameters revealed no discernable trends. There was no adverse event due to clinically relevant deviations in any of the laboratory parameters evaluated. Regarding vital signs, no clinically relevant changes in blood pressure and pulse rate were noted. The 12-lead ECG interpretation did not reveal any clinically relevant findings. In addition, global tolerability was rated as good for each one of the 11 subjects and for both crossover periods.

Conclusions:

The intake of a high fat breakfast did not significantly influence the extent of absorption ($AUC_{0-\infty}$) of BI 14332 CL. As C_{max} was only slightly reduced by 6.8% in the fed state and all other pharmacokinetic parameters were comparable between treatment groups, no clinically relevant food effect is expected. In addition, the good tolerability of the drug reported in a previous single rising dose study could be confirmed.