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: -		**EudraCT No.:** 2006-004723-11		
Name of active ingredient: BI 44847		**Page:**	**Number:**	**Synopsis No.:**
Ref. to Documentation:	**Module:**	**Volume:**		
Report date: 15 February 2008	**Trial No. / U No.:** 1224.2 / U07-2459	**Date of trial:** 18 JAN 2007 – 16 MAR 2007		**Date of revision** (if applicable)**:**

Title of trial:	Relative oral bioavailability of 400 mg BI 44847 as suspension compared to 400 mg BI 44847 as tablet and the influence of food (standardised high fat breakfast) on the tablet in a single dose, open-label, randomised three-way crossover trial and relative oral bioavailability of 40 mg BI 44847 as solution compared to 40 mg BI 44847 as tablet in healthy male volunteers in a single dose, open-label, randomised two-way crossover trial.
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
Publication (reference):	-
Clinical phase:	I
Objectives:	To investigate the relative oral bioavailability of 400 mg BI 44847 as suspension vs. 400 mg BI 44847 as tablet, to investigate a food effect on the 400 mg tablet PK and to investigate relative oral bioavailability of 40 mg BI 44847 as solution vs. 40 mg BI 44847 as tablet.
Methodology:	Open-label, randomised, three-way crossover design for the 400 mg part of the study and open-label, randomised, two-way crossover design for the 40 mg part of the study.
No. of subjects:	25
planned:	entered: 26
actual:	enrolled: 25
	Treatment 400 mg: entered: 18 treated: 18 analysed (for primary endpoint) Treatment 40 mg: entered: 7 treated: 7 analysed (for primary endpoint)

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2
Test product:	BI 44847 tablet (fasted versus fed)
dose:	40 mg and 400 mg
mode of admin.:	oral administration with ~240 mL water (fasted versus fed)
batch no.:	PR06/10242
Reference therapy:	BI 44847 PIB reconstituted with 0.2% natrosol solution
dose:	40 mg and 400 mg
mode of admin.:	oral administration after an overnight fast with ~240 mL water
batch no.:	PR06/10242
Duration of treatment:	One day (single dose po) for each treatment, 3 days (400 mg part) or 2 days (40 mg part) total
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Pharmacokinetic parameters: C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Safety:	Tolerability, adverse events, physical examination, vital signs (BP, HR), 12-lead ECG (vital signs and ECG after 5 min. in supine position) and laboratory tests
Statistical methods:	Point estimators (geometric means) of the median intra-subject ratios of $AUC_{0-\infty}$ and C_{max} and their two-sided 90% CIs were calculated. In each trial part, the statistical model was ANOVA on log transformed parameters including effects for "sequence", "subject nested within sequence", "period" and "treatment". CIs were based on the residual error from ANOVA. Descriptive statistics for all other parameters were calculated.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The exposure to BI 44847 after intake of a 400 mg tablet was unaltered compared to the exposure after oral intake of 400 mg BI 44847 as suspension, both assessed in fasted state; the relative oral bioavailability was 101% for C_{max} and 102% for $AUC_{0\text{-}inf}$. The 90% confidence interval was 85.1 to 119.5% for C_{max} and 91.4 to 113.6% for $AUC_{0\text{-}inf}$. Although bioequivalence was not a trial aim, the bioequivalence criteria were fulfilled.

The high-fat breakfast reduced the C_{max} after a 400 mg tablet considerably. The relative bioavailability was 35.2% for C_{max}. However, $AUC_{0\text{-}inf}$ was only slightly reduced and showed a relative oral bioavailability of 87.1%. The 90% confidence interval was 25.5 to 48.5% for C_{max} and 80.7 to 94% for $AUC_{0\text{-}inf}$. Therefore, bioequivalence criteria were fulfilled for $AUC_{0\text{-}inf,}$ but not for C_{max}.

Supralinearity was found when comparing the 400 mg tablet (fasted) to the 40 mg tablet. The geometric mean ratio of dose corrected C_{max} and $AUC_{0\text{-}inf}$ were 1.78 and 1.74, respectively. The reason for the supralinearity is not clear. A possible explanation may be that the 40 mg and 400 mg tablets did not come from a homologous row. However, this finding is considered to be of minor relevance since the 40 mg dose is not considered to be therapeutic. Supralinearity was also observed when comparing the 400 mg suspension (fasted) to the 40 mg solution. The geometric mean ratio of dose corrected C_{max} and $AUC_{0\text{-}inf}$ were 2.84 and 2.36, respectively. The reason for this supralinearity is unclear as it was not observed in the SRD trial 1224.1. However, no direct comparison exists between solution and suspension at one dose level.

Exposure to BI 44847 after intake of a 40 mg tablet (fasted) was increased compared with that after oral intake of 40 mg as solution (fasted). The relative oral bioavailability was 157% for C_{max} and 137% for $AUC_{0\text{-}inf}$. The 90% confidence interval was 120.7 to 203.2% for C_{max} and 95.6% to 197.4% for $AUC_{0\text{-}inf}$.

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Efficacy / clinical pharmacology results cont.:	Intra-individual variability was low to moderate: 20-25% for both fasted treatments of 400 mg, 25-35% for both fasted treatments of 40 mg, 10-15% for $AUC_{0\text{-}inf}$ of the tablet, and 50% for Cmax of the tablet. It is currently not known whether the AUC or Cmax of BI 44847 drive the pharmacodynamics. Hence, it is not possible to gauge the impact of this food effect. The clinical relevance of this study will be better appreciated once the threshold BI 44847 plasma concentrations that are necessary to provide efficacy are defined.
Safety results	The drug was well tolerated by all participating subjects and within the treatment groups. There were no deaths, no serious adverse events and no discontinuations due to adverse events. Only four subjects experienced adverse events (five adverse events in total), all assigned to the 400 mg treatment. Four of the five adverse events were headache (in three subjects), and judged as non drug related and fatigue (in one subject) which was judged as possibly drug related by the. The adverse events were of mild intensity and subjects recovered within a few hours. 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 or heart 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 25 subjects and for all crossover periods.

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Conclusions:

Based on the observations made in this study, and consistent with results of a previous trial, administration of 400 mg during the three-way crossover trial and 40 mg during the two-way crossover trial was safe and well tolerated. The adverse event profile was consistent with that seen in the previous trial of BI 44847 in healthy volunteers.

The aspects of relative oral bioavailability observed in this study can be summarized as follows:

1. No formulation effect was seen for the 400 mg dose group
2. Administration of the 400 mg tablet in the presence of food resulted in a considerable three-fold reduction of C_{max} but not of AUC.
3. The 40 mg tablet was found to be moderately more bioavailable than the 40 mg solution formulation.
4. The intra-individual variability of the exposure parameters was low.