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.

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: Not applicable		**EudraCT No.:** 2009-013280-19	
Name of active ingredient: BI 671800		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 19 APR 2012	**Trial No. / U No.:** 1268.56 / U12-1397-01	**Date of trial:** 17 FEB 2010 – 01 JUL 2010	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of different salt forms and formulations of single doses either 50 or 200 mg BI 671800 in the fasted or fed state. An open-label, randomised, Phase I study with a 3-period crossover followed by two treatment periods in fixed sequence in healthy male and female volunteers
Principal Investigator:	[redacted]
Trial sites:	Boehringer Ingelheim Pharma GmbH & Co. KG Department of Clinical Research, Human Pharmacology Centre Binger Str. 173 55216 Ingelheim/Rhein, Germany Phone: [redacted] Fax: [redacted]
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	To compare the oral bioavailability and rate of absorption of two different formulations of BI 671800 HEA (choline salt) tablets 200 mg, one with enteric coating (EC) and one without EC, versus 2 x 100 mg BI 671800 ED (ethylenediamine salt) capsules. Both BI 671800 HEA formulations were further investigated concerning food effect and one of the two BI 671800 HEA formulations identified by interim pharmacokinetic analysis was further investigated concerning dose proportionality with 50 mg (according to Amendment No. 1).
Methodology:	The study was an open-label, single-dose, randomised, Phase I study in healthy male and female volunteers in a 3-way crossover (reference treatment, test product 1 and 2) followed by a 2-way crossover (test product 3 and 4) for investigation of food effect and one period in fixed sequence (test product 5) for the investigation of dose proportionality (according to Amendment No. 1).

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No. of subjects:

planned: entered: 24

actual: enrolled: 24

Treatment A: two 100 mg BI 671800 ED capsules in fasted state (Reference)
treated: 24 analysed (for primary endpoint): 24

Treatment B: one 200 mg BI 671800 HEA tablet in fasted state (Test 1)
treated: 24 analysed (for primary endpoint): 24

Treatment C: one 200 mg BI 671800 HEA EC tablet in fasted state (Test 2)
treated: 24 analysed (for primary endpoint): 24

Treatment D: one 200 mg BI 671800 HEA tablet in fed state (Test 3)
treated: 24 analysed (for primary endpoint): 24

Treatment E: one 200 mg BI 671800 HEA EC tablet in fed state (Test 4)
treated: 23 analysed (for primary endpoint): 23

Treatment F: one 50 mg BI 671800 HEA tablet in fasted state (Test 5)
treated: 24 analysed (for primary endpoint): 24

Diagnosis and main criteria for inclusion: Healthy male and female volunteers, age ≥21 and ≤50 years, body mass index ≥18.5 and ≤29.9 kg/m^2

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Test products:	BI 671800 HEA, 200 mg tablets (Treatment B, D) BI 671800 HEA EC, 200 mg tablets (Treatment C, E) BI 671800 HEA, 50 mg tablets (Treatment F)
dose:	200 mg (one tablet of 200 mg) (Treatment A, B, C, D, E) 50 mg (one tablet of 50 mg) (Treatment F)
mode of admin.:	oral administration with 240 mL water
batch no.:	B091005237 (Treatment B, D), B091005241 (Treatment C, E), B091005239 (Treatment F)
Reference therapy:	BI 671800 ED, 100 mg capsules (Treatment A)
dose:	200 mg (two capsules of 100 mg)
mode of admin.:	Oral administration with 240 mL of water
batch no.:	B091005223
Duration of treatment:	Single dose administration in each period separated by a wash-out period of at least 5 days between drug administrations
Criteria for evaluation:	
Pharmacokinetics:	Primary endpoints: C_{max}, $AUC_{0-\infty}$ Secondary endpoints: t_{max}, AUC_{0-tz}, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F
Safety:	Physical examination, pulse rate, blood pressure, 12-lead electrocardiogram, laboratory parameters, adverse events and assessment of global tolerability.
Statistical methods:	Confidence intervals, analysis of variance, descriptive statistics.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

For the first part of the study, assessing relative bioavailability of the HEA tablets relative to 1x200 mg BI 671800 capsules, the test/reference $AUC_{0-\infty}$ and C_{max} of BI 671800 from both formulations (EC and uncoated) were equal to or greater than 200%. The data showed that BI 671800 exposure from either uncoated or EC HEA tablets was greater than the exposure from the ED capsule reference formulation. The rate of absorption for the uncoated HEA tablet was essentially the same as the reference ED capsule, but was slower for the EC tablet, as judged by relative t_{max} values.

The food effect portion of the study showed that the effect of a high-fat meal was different between the two HEA tablets. The uncoated tablet had a small positive food effect, which appeared to be clinically insignificant. The high-fat meal slowed the absorption of BI 671800 from the uncoated HEA tablet, as the t_{max} was lengthened by about an hour.However, the exposure from the EC tablet was much lower after a high-fat meal than fasted, as geometric mean ratios of exposure were less than 60% for the EC tablet taken after a high-fat meal. Because of this large negative food effect, it was decided not to test the dose proportionality of the BI 671800 HEA EC tablet in this study.

Comparison of the descriptive statistics of pharmacokinetic parameters from the 50 mg uncoated tablet and the 200 mg uncoated tablet showed that the pharmacokinetic parameters of BI 671800 HEA are dose proportional between 50 mg and 200 mg single doses.

Finally, the pharmacokinetics of a disproportionate human metabolite, BI 600957 were also assessed. BI 600957 was formed slowly from BI 671800, having a t_{max} ranging from 5 to 8 hours after dosing. The relative large range of t_{max} values also indicated that there is a high degree of inter-subject variability in its formation. As BI 600957 had a relatively slow formation and longer half-life than the parent compound, the sampling timepoints from this study were inappropriate for determining $AUC_{0-\infty}$ and half-life.

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	However, additional samples were obtained from six subjects who received a 200 mg BI 671800 HEA uncoated tablet after food. In these subjects, the half-life is 2 to 3 times greater than that of the parent compound, approximately 12 hours..
Safety results:	Of the 24 subjects, 23 received a single dose of each treatment (5 x 200 mg and 1 x 50 mg, total dose of 1050 mg BI 671800) and one subject received only five of the six treatments (4 x 200 mg and 1 x 50 mg, total dose of 850 mg BI 671800). Altogether 13 of the 24 subjects (54.2%) reported 26 adverse events in this trial. All events were of mild or moderate intensity and had recovered at the end of the trial. The most frequently reported adverse event was headache. Three subjects each reported adverse events under Treatment B and C, i.e. within 72 hours after administration of 200 mg BI 671800 HEA in fasted state and two subjects each reported adverse events under Treatment D and E, i.e. within 72 hours after administration of 200 mg BI 671800 HEA in fed state. Two events were assessed by the investigator as drug-related: one episode of mild headache and one episode of mild fatigue. Both events were reported within 72 hours after administration of 200 mg BI 671800 HEA in fed state (Treatment E). None of the subjects had clinically relevant findings with regard to safety laboratory parameters, vital sign parameters or electrocardiogram parameters and no relevant changes were observed for any of the assessed safety parameter. The global tolerability was rated as good for all subjects at all visits.

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Conclusions:

In fasted subjects, BI 671800 exposure following administration of uncoated or EC BI 671800 HEA 200 mg tablets was about double the exposure of 2 x 100 mg BI 671800 ED capsules. The exposure was slightly higher from the EC tablets. After a high-fat meal, there was a slight positive food effect on exposure from uncoated tablets that was clinically insignificant. However, there was a strong negative food effect on the EC tablet, so that exposure was only about 60% of exposure in fasted individuals.

In fasted subjects, exposure after a 50 mg uncoated tablet was dose proportional to the exposure from the 200 mg uncoated tablet. Thus, the pharmacokinetics are linear between the 50 and 200 mg doses of uncoated tablets.

A disproportionate human metabolite, BI 600957, was formed slowly from BI 671800 with high inter-subject variability. The metabolite had a t_{max} ranging from 5 to 8 hours after dosing. In six subjects receiving 200 mg uncoated tablets, the half-life of the metabolite was estimated to be 12 hours using additional time measurement points for the analysis. These pharmacokinetic characteristics suggest that on bid or qd dosing, BI 600957 is likely to accumulate to a greater extent than BI 671800.

Overall, single oral doses of 200 mg BI 671800 HEA were well tolerated by male and female subjects administered as tablet formulation with or without coating and in fasted or in fed state. No relevant safety issues were identified in this trial. From the adverse events observed in this trial, there is no concern for further investigation of BI 671800 in the doses tested in male and female subjects.