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: Not applicable		**EudraCT No.:** 2009-016368-35	
Name of active ingredient: BI 671800 HEA		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:**	
Report date: 09 AUG 2010	**Trial No. / U No.:** 1268.60/ U10-2275-01	**Dates of trial:** 06 JAN 2010 – 08 MAR 2010	**Date of revision:** Not applicable

Title of trial:	Relative bioavailability of single doses of 200 mg BI 671800 HEA administered orally as a delayed release (enteric coated) tablet; or via the Enterion™ capsule as solution to the jejunum, ascending colon or descending colon; or via the Enterion™ capsule as particulate to the ascending colon. An open-label, five periods, fixed sequence phase I study in healthy male volunteers
Principal Investigator:	[redacted]
Trial site:	[redacted] UK
Publication (reference):	Data of this study have not been published
Clinical phase:	I
Objectives:	The goal of the study was to determine the bioavailability of a single dose of 200 mg BI 671800 HEA (choline) administered as a delayed-release, enteric-coated tablet, relative to single 200 mg doses administered as solution to the jejunum, ascending or descending colon, and relative to a single 200 mg dose administered as a particulate to the ascending colon.
Methodology:	This study was a non-randomised, open-label, five-period, fixed-sequence crossover study in healthy male volunteers. The last two treatment periods (Treatment D, solution administered to the descending colon, and Treatment E, particulate administered to the ascending colon) were not performed, per the decision criteria specified in the clinical trial protocol.

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No. of subjects:	
planned:	entered: 10
actual:	entered: 10 Treatment A: 200 mg BI 671800 HEA, delayed-release, enteric-coated tablet: treated: 10 analysed (for primary endpoint): 10 Treatment B: 200 mg BI 671800 HEA as solution, delivered in the Enterion™ capsule to the jejunum: treated: 9 analysed (for primary endpoint): 9 Treatment C: 200 mg BI 671800 HEA as solution, delivered in the Enterion™ capsule to the ascending colon: treated: 10 analysed (for primary endpoint): 10
Diagnosis and main criteria for inclusion:	Included in the study were healthy male volunteers, age ≥21 and ≤65 years, with a BMI ≥18.5 and ≤29.9 kg/m^2.
Test product:	Treatment A: BI 671800 HEA delayed-release, enteric-coated tablet (reference treatment)
dose:	200 mg single dose
mode of admin.:	Oral, with 240 mL water
batch no.:	B0930000857
Test product:	Treatments B and C: BI 671800 HEA solution in the Enterion™ capsule, radiolabelled with up to 1 MBq ^{111}In (test treatments) Test treatments D (BI 671800 HEA solution to descending colon) and E (BI 671800 HEA particulate to ascending colon) were not administered
dose:	200 mg single dose
mode of admin.:	Oral, with 210 mL water, followed by 30 mL of water containing up to 4 MBq ^{99m}Tc-DTPA
batch no.:	BI 671800 HEA: B093000581 (used to prepare the solution within the Enterion capsules) Enterion capsule: 1338/C/02 (Treatment B) and 1338/C/04 (Treatment C)

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Duration of treatment:	Single doses separated by a washout period of at least 3 days
Criteria for evaluation:	
Clinical pharmacology:	For all treatments, the primary endpoint was determination of the $AUC_{0-\infty}$ of BI 671800. Secondary endpoints were determination of AUC_{0-tz}, t_{max}, C_{max}, λ_z, $t_{½}$, MRT_{po}, CL/F, V_z/F, and t_{lag}.
Safety:	Safety was monitored by physical examination, vital signs including blood pressure and pulse rate, 12-lead electrocardiogram, clinical laboratory tests (haematology, clinical chemistry and urinalysis), and recording of adverse events (AEs).
Statistical methods:	The statistical model used for the analysis of $AUC_{0-\infty}$ of BI 671800 HEA was an ANOVA (analysis of variance) model on the logarithmic scale, including effects for 'subject' and 'treatment'. The relative bioavailability of BI 671800 HEA was investigated by applying the average bioequivalence method to the $AUC_{0-\infty}$ ratio between Treatment A (BI 671800 HEA oral enteric-coated tablet; reference treatment) and Treatments B and C (BI 671800 HEA solution administered to jejunum and ascending colon; test treatments). Point estimators of the median intra-subject ratios and their 90% onfidence intervals (CI) were computed, then back-transformed to the original scale to give the geometric mean (gMean) and interval estimates for the median test/reference ratio. Descriptive statistics were employed in the evaluation of safety.
SUMMARY – CONCLUSIONS:	
Clinical pharmacology results:	Ten subjects were entered in the trial. All 10 subjects received Treatments A and C, and 9 of 10 subjects received Treatment B. The data from all treated subjects were analysed for the primary endpoint. All 10 subjects were white men; median age was 45 years. No subject reported concomitant therapy.

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Clinical pharmacology results (continued):

For oral administration of an enteric-coated tablet of BI 671800 HEA (Treatment A; oral tablet), the gMean overall extent of exposure ($AUC_{0-\infty}$) was 21500 h*ng/mL and gMean maximum plasma concentration (C_{max}) was 5590 ng/mL. For administration of BI 671800 HEA solution to the jejunum (Treatment B; jejunal solution), both gMean $AUC_{0-\infty}$ and C_{max} were substantially increased relative to the oral tablet, at 29600 ng*h/mL and 9830 ng/mL, indicating a 1.4-fold higher exposure in terms of $AUC_{0-\infty}$ and 1.8-fold higher exposure in terms of C_{max}. Administration of BI 671800 HEA solution to the ascending colon (Treatment C; colonic solution) resulted in a gMean $AUC_{0-\infty}$ of 2210 ng*h/mL and C_{max} of 193 ng/mL. Therefore, gMean values of $AUC_{0-\infty}$ were 13-fold less than for the jejunal solution and 10-fold less than for the oral tablet. Similarly, gMean C_{max} values were 51-fold lower than for the jejunal solution and 29-fold lower than for the oral tablet.

Median values of time to maximum plasma concentration (t_{max}) were 3.0 h for the oral tablet, 1.0 h for the jejunal solution, and 1.3 h for the colonic solution. Geometric mean values of the terminal half-life ($t_{1/2}$) also varied, with the oral tablet displaying the shortest $t_{1/2}$ of 4.93 h, the jejunal solution displaying a $t_{1/2}$ value of 6.67 h, and the colonic solution displaying a much longer $t_{1/2}$ value of 12.7 h.

Statistical comparison of gMean exposure indices showed that for jejunal solution, $AUC_{0-\infty}$ and C_{max} values were 141% (90% CI 102%, 194%) and 183% (90% CI 121%, 277%) of the oral tablet, respectively, indicating enhanced absorption of BI 671800 from the jejunum. In contrast, BI 671800 exposure from colonic solution was considerably lower than from the oral tablet. The $AUC_{0-\infty}$ and C_{max} values for colonic solution were 10.3% (90% CI 7.55%, 14.1%) and 3.45% (90% CI 2.31%, 5.14%) of the oral tablet values, respectively, demonstrating that absorption of BI 671800 from the ascending colon was very poor.

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Safety results:	Of the 10 subjects entered in the study, 9 received a total of 600 mg of BI 671800 (3x200 mg single dose) and 1 subject received a total of 400 mg (2x200 mg single dose). No deaths or other serious AEs were reported. During the trial, 3 of 10 subjects (30%) reported AEs. During Treatments B and C (jejunal solution and colonic solution administration), Subject [redacted] reported a skin reaction as a result of the ECG electrode adhesive. During the post-treatment phase after Treatment C, Subject [redacted] reported a viral upper respiratory tract infection and Subject [redacted] reported a skin reaction as a result of the ECG electrode adhesive. All AEs were of mild intensity, all resolved, and no concomitant therapy was required for any AE. There were no clinically relevant findings in the assessment of laboratory values, vital signs, and ECGs.
Conclusions:	Absorption of 200 mg of BI 671800 solution administered to the jejunum was very rapid and exposure was higher than for oral administration of a 200 mg enteric-coated tablet. However, absorption of 200 mg of BI 671800 solution administered to the ascending colon was much lower than for oral administration of a 200 mg enteric-coated tablet. An extended release formulation that relies on delivery to the colon is therefore not a practicable method for improving the PK profile of BI 671800. The results of the safety assessment do not indicate safety concerns for administration of single doses of 200 mg BI 671800 HEA to healthy male volunteers.