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 Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-016369-27	
Name of active ingredient: BI 671800 HEA		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 JUL 2011	**Trial No. / U No.:** 1268.59 / U11-1892-01	**Dates of trial:** 06 OCT 2010 – 09 DEC 2010	**Date of revision:** Not applicable

Title of trial:	Pharmacokinetics, safety and tolerability of BI 671800 HEA given 200 mg b.i.d. or 400 mg b.i.d. over 7 days. A randomised, double blind, placebo controlled within dose groups, phase I study in healthy male and female volunteers
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Department of Translational Medicine/Human Pharmacology Centre, Ingelheim, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	Phase I
Objectives:	The objectives of the trial were to investigate pharmacokinetics, safety and tolerability of 200 mg or 400 mg BI 671800 HEA given as a single dose (single dose segment) or twice daily over 6.5 days (multiple dose segment).
Methodology:	This randomised trial with 2 treatment periods (single dose segment and multiple dose segment) and 2 dose groups (200 mg and 400 mg BI 671800 HEA) was placebo controlled and double-blind within each dose group.
No. of subjects:	
planned:	entered: 24 subjects (12 in each dose group)
actual:	entered: 24 subjects (12 in each dose group) Dose group 1 (200 mg BI 671800 HEA): entered, treated and analysed (for safety): 12 subjects (9 on active drug, 3 on placebo) Dose group 2 (400 mg BI 671800 HEA): entered, treated and analysed (for safety): 12 subjects (9 on active drug, 3 on placebo)
Diagnosis and main criteria for inclusion:	Healthy male and female subjects at the age of 21 to 50 years with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.

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Test product:	BI 671800 HEA, 200 mg tablets
dose:	200 mg and 400 mg, single dose or twice daily (depending on the dose group and the treatment period)
mode of admin.:	Oral administration with 240 mL of water
batch no.:	B093000815
Reference therapy:	Placebo, matching the BI 671800 HEA tablets
dose:	Not applicable
mode of admin.:	Oral administration with 240 mL of water
batch no.:	B101002081
Duration of treatment:	Trial medication was given as 1 single dose in the single dose segment and twice daily for 6.5 days during the multiple dose segment. A washout period of at least 120 h was required between drug administrations in the 2 treatment periods.
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic parameters were analysed as secondary endpoints: C_{max}, t_{max}, $AUC_{0-\infty}$, $AUC_{\tau,1}$, and AUC_{0-tz} of BI 671800 and its metabolite BI 600957 (previously named CD 6384) after first dose and $C_{max,ss}$, $t_{max\ ss}$, $C_{avg,,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,\ ss}$, $t_{½,ss}$, and $MRT_{po,ss}$ of BI 671800 and BI 600957 as well as $MRT_{po,ss}$, CL/F_{ss}, and Vz/F_{ss} of BI 671800 after last dose. In addition, the metabolite-to-parent ratios $RAUC_{\tau,ss,M/P}$ and $RC_{max,ss,M/P}$, the accumulation ratios $R_{A,Cmax}$ and $R_{A,AUC}$ and the peak-trough fluctuation (PTF) of BI 671800 and BI 600957 as well as the linearity index (LI) of BI 671800 were calculated.
Safety:	Safety and tolerability were the primary objective of this trial and were determined based on physical examination, vital signs (pulse rate and blood pressure), 12-lead electrocardiogram, clinical laboratory assessments (clinical chemistry, haematology, and urinalysis), monitoring of adverse events, and assessment of global tolerability.

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Statistical methods: Descriptive statistics for safety and pharmacokinetic parameters were calculated. Dose proportionality of BI 671800 was analysed using the power model for the relationship between the dose and pharmacokinetic endpoints. Attainment of steady state was explored by using repeated measures linear model on the logarithmic scale..

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

In this trial, 24 subjects were treated and 22 subjects completed the planned observation time. The trial population consisted of healthy male and female subjects. The mean age was 42.8 years, ranging from 29 to 50 years, and the mean BMI was 24.79 kg/m^2, ranging from 19.3 to 29.4 kg/m^2. All subjects were White. Overall, the treatment groups were balanced with regard to demographic and other baseline characteristics.

Under steady state conditions, BI 671800 was rapidly absorbed after oral administration, reaching peak concentrations at 1.48 h to 1.73 h. The gMean $C_{max,ss}$ values ranged from 4780 ng/mL to 7600 ng/mL and the gMean $AUC_{\tau,ss}$ values (area under the plasma concentration-time curve at steady state for the complete dosing interval of 12 h) ranged from 19100 ng·h/mL to 32500 ng·h/mL for the 2 dose groups (200 mg and 400 mg BI 671800 HEA given twice daily). The BI 671800 plasma concentration-time profile showed a biphasic decline with a rapid distribution phase and a slower elimination phase. The gMean $t_{1/2,ss}$ values were 9.05 h and 15.2 h, when administering 200 mg and 400 mg BI 671800 HEA twice daily, respectively. The gMean $CL/F_{,ss}$ were 174 mL/min and 205 mL/min and gMean $MRT_{po,ss}$ were 5.39 h and 6.22 h, when administering 200 mg and 400 mg BI 671800 HEA twice daily, respectively. The $Vz/F_{,ss}$ tended to increase with dose, with gMean values being 137 L and 269 L, when administering 200 mg and 400 mg BI 671800 HEA twice daily, respectively. The gMean accumulation ratios $R_{A,AUC}$ and $R_{A,Cmax}$ were ≤ 1.44 for both dose groups, indicating little or no accumulation of BI 671800 after multiple oral doses. The gMean LI ranged from 1.11 to 1.28, implying linearity between single dose and steady state. Statistical analysis showed that steady state was achieved latest on Day 3 for both BI 671800 and BI 600957.

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Clinical pharmacology results (continued):

Under steady state conditions, the metabolite BI 600957 reached peak concentrations at 1.98 h to 2.97 h after oral administration. The gMean $C_{max,ss}$ values ranged from 5390 ng/mL to 7490 ng/mL and gMean $AUC_{\tau,ss}$ values of 43200 ng·h/mL and 62500 ng·h/mL for 2 dose groups (200 mg and 400 mg BI 671800 HEA given twice daily). The BI 600957 plasma concentration-time profile also showed a biphasic decline. The gMean $t_{1/2,ss}$ values were 12.4 h and 14.4 h, when administering 200 mg and 400 mg BI 671800 HEA twice daily, respectively. The gMean accumulation ratios $R_{A,AUC}$ and $R_{A,Cmax}$ ranged from 3.54 to 4.44, implying a relatively large accumulation of BI 600957 after multiple oral doses. The gMean LI ranged from 1.09 to 1.22, implying linearity also existed between single dose and steady state for BI 600957.

The results of the log-transformed linear regression model indicated that dose proportionality did not exist for either BI 671800 or BI 600957. Exposure of both BI 671800 and BI 600957 increased to a much smaller extent than the corresponding dose increase from 200 mg to 400 mg.

Safety results:

The 24 entered subjects were allocated to 1 of the 2 dose groups and randomly assigned to placebo or active treatment within those dose groups. Depending on the allocated treatment, mean total exposure to trial medication varied from 0 to 5600 mg BI 671800 HEA over the entire course of the trial.

A total of 9 subjects (37.5%) reported at least 1 adverse event in at least 1 of the treatment periods (single dose and multiple dose segment). The frequency of subjects with adverse events was highest in the 200 mg BI 671800 HEA group (55.6%), followed by the 400 mg BI 671800 HEA group (33.3%) and the placebo group (16.7%). The most frequently reported adverse events overall at the SOC level were nervous system disorders (headache and dysgeusia), which were reported by a total of 3 subjects (12.5%). Gastrointestinal disorders (upper abdominal pain, dry mouth, and vomiting), infections and infestations (nasophyringitis in both cases) as well as investigations (increased body temperature and increase in blood creatine kinase, see also below) were reported by 2 subjects (8.3%) each. The most frequent adverse event by preferred term was headache (3 subjects, 12.5%), followed by nasopharyngitis (2 subject, 8.3%). All other adverse events were reported by 1 subject (4.2%) each. No clustering of any specific adverse event in any treatment group was apparent.

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Safety results (continued):

One adverse event (biliary colic), which was reported in the 200 mg BI 671800 HEA group, was classified as severe and serious. It required code break, hospitalisation, and discontinuation of the subject from the trial. The investigator rated this adverse event as not related to the trial medication and the subject recovered from the adverse event after a cholecystectomy. All other adverse events were of mild or moderate intensity. Over the course of the trial, the investigator rated 3 adverse events (1 mild case each of dysgeusia, upper abdominal pain, and vomiting) as related to the trial medication.

The creatine kinase activity of 1 subject was approximately 3-fold above the upper limit of normal on Day 8 of Visit 3. This elevation was assessed as clinically relevant and reported as an adverse event. The creatine kinase activity had returned to a normal level at the end-of-trial examination 8 days later. No other clinically relevant finding was reported with respect to the clinical laboratory evaluation, vital signs and ECG recordings.

The investigator rated the overall tolerability in the single dose segment (Visit 2) as 'good' for all 23 subjects, who participated in this segment of the trial. Of the 24 subjects participating in the multiple dose segment (Visit 3), the overall tolerability was rated as 'good' for 22 subjects and as 'satisfactory' for the remaining 2 subjects.

Conclusions:

Overall, administration of a single dose as well as multiple twice daily doses of 200 mg or 400 mg BI 671800 HEA was well tolerated by the healthy male and female subjects in this trial. No clustering of any specific adverse event in any treatment group was apparent and no dose dependent increase in adverse events was observed for BI 671800 HEA.

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Conclusions (continued):	The plasma concentration-time profiles of both BI 671800 and BI 600957 showed a biphasic decline with a rapid distribution phase and a slower elimination phase. The gMean accumulation ratios suggested little or no accumulation of the parent compound BI 671800 and a relatively large accumulation of the metabolite BI 600957 after multiple oral doses of 200 mg or 400 mg BI 671800 HEA. Consequently, BI 600957 exposure is higher than BI 671800 exposure at steady state. The results of the log-transformed linear regression model revealed no dose proportionality in this trial, with the exposure of both BI 671800 and BI 600957 increasing in a less than proportional fashion in the tested dose range. Steady state was achieved latest on Day 3 for both BI 671800 and BI 600957.