Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** Not applicable	
Name of active ingredient: BI 671800 HEA		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 MAR 2012	**Trial No. / U No.:** 1268.15 / U12-1103-01	**Dates of trial:** 04 OCT 2010 – 28 DEC 2010	**Date of revision:** Not applicable

Title of trial:	A randomised, double-blind (within dose groups), parallel group, placebo-controlled phase I study to evaluate the safety, tolerability and pharmacokinetics of single rising doses (50 mg, 200 mg, 400 mg) of BI 671800 HEA in Chinese healthy male volunteers and multiple rising doses (50 mg b.i.d., 200 mg b.i.d., 400 mg b.i.d.) of BI 671800 HEA in Japanese healthy male volunteers
Principal Investigator:	[redacted]
Trial site:	[redacted] Korea
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	The objectives of the trial were to investigate safety, tolerability and pharmacokinetics following single doses of BI 671800 HEA in healthy male Chinese subjects and single and multiple doses of BI 671800 HEA in healthy male Japanese subjects, and to investigate pharmacodynamics in the healthy male Japanese subjects.
Methodology:	This randomized trial with 2 parts, i.e. SRD (single rising dose) part, MRD (multiple rising dose) part, each with 3 dose groups was placebo controlled and double blinded within each dose group.
No. of subjects:	
planned:	entered: 72 subjects (12 subjects in each dose group)

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actual:	entered: 73 subjects (Dose group 1-4 and 6: 12 subjects in each dose group, dose group 5: 13 subjects) Single rising dose (SRD) part: Dose group 1 (50 mg BI 671800 HEA) entered: 12 subjects / treated, analysed (for primary endpoint): 11 subjects Dose group 2 (200 mg BI 671800 HEA) entered: 12 subjects / treated, analysed (for primary endpoint): 12 subjects Dose group 3 (400 mg BI 671800 HEA) entered: 12 subjects / treated, analysed (for primary endpoint): 12 subjects Multiple rising dose (MRD) part: Dose group 4 (50 mg bid BI 671800 HEA) entered: 12 subjects / treated, analysed (for primary endpoint): 12 subjects Dose group 5 (200 mg bid BI 671800 HEA) entered: 13 subjects / treated, analysed (for primary endpoint): 12 subjects Dose group 6 (400 mg bid BI 671800 HEA) entered: 12 subjects / treated, analysed (for primary endpoint): 10 subjects
Diagnosis and main criteria for inclusion:	Healthy male Japanese and Chinese volunteers, age ≥20 years and ≤50 years, BMI ≥18.5 and ≤25 kg/ m^2
Test product:	BI 671800 HEA tablets 50 mg or BI 671800 HEA tablets 200 mg
dose:	SRD part : 50 mg single dose , 200 mg single dose, 400 mg single dose MRD part: 50 mg, 200 mg, 400 mg as single dose or twice daily depending on treatment period
mode of admin.:	Oral administration with 240 mL of water
batch no.:	50 mg tablets: B093000812 200 mg tablets: B093000815
Reference therapy:	Placebo tablet
dose:	Not applicable
mode of admin.:	Oral administration with 240 mL of water
batch no.:	B101002081

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Duration of treatment:	SRD part (Group 1-3): Single dose MRD part (Group 4-6): Single dose on day 1 (visit 2) followed by 6 days of twice daily dosing from day 1 to day 6 (visit 3), and last dose (single dose) on day 7 (visit 3)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The following pharmacokinetic parameters were analysed as secondary endpoints: SRD part: C_{max}, t_{max}, AUC_{t1-t2}, AUC_{0-tz}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F of BI 671800 and its metabolite BI 600957. MRD part : C_{max}, t_{max}, AUC_{t1-t2}, AUC_{0-tz}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{po}, CL/F, V_z/F after first dose and $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $t_{min,ss}$, $C_{pre,ss}$, $AUC_{t1-t2,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, CL/F_{ss}, Vz/F_{ss} after the last dose of BI 671800 and its metabolite BI 600957. In addition, the accumulation ratios $R_{A,AUC,13}$, $R_{A,Cmax,13}$ and linearity index (LI) of BI 671800 HEA was calculated. The following pharmacodynamics parameters were determined from the EOS WBSC assay as secondary endpoints: $AUEC_{0-24,N}$ absolute inhibition of eosinophil shape change, $AUEC_{0-24,N}$ percent inhibition of eosinophil shape change
Safety:	Safety and tolerability were the primary objectives of this trial and were determined based on physical examination, pulse rate, blood pressure, 12-lead ECG, clinical laboratory assessments (clinical chemistry, haematology, and urinalysis) and monitoring of adverse events
Statistical methods:	Descriptive statistics for safety, pharmacokinetic and pharmacodynamic parameters were calculated. Dose proportionality of BI 671800 HEA was analysed using the power model for the relationship between the dose and PK endpoints. Attainment of steady state was explored by using repeated measures ANOVA for trough concentrations.
SUMMARY – CONCLUSIONS:	

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Efficacy / clinical pharmacology results:

In this trial, 69 subjects (SRD part 35 subjects, MRD part 34 subjects) were treated and 67 subjects (SRD part 35 subjects, MRD part 32 subjects) completed the trial according to the clinical trial protocol. The trial population consisted of healthy male Chinese and Japanese subjects. The mean age was 26.3 years (Chinese SRD part: 23.2 years, Japanese MRD part: 29.4 years), ranging from 20 to 40 years (Chinese SRD part: 20 to 32 years, Japanese MRD part: 20 to 40 years) and the mean BMI was 22.13 kg/m^2 (Chinese SRD part: 22.44 kg/m^2, Japanese MRD part: 21.81 kg/m^2), ranging from 18.8 to 24.9 kg/m^2 (Chinese SRD part: 19.1 to 24.9 kg/m^2, Japanese MRD part: 18.8 to 24.4 kg/m^2). All subjects were Asian (Chinese, Japanese). There were only minor differences in the demographic and baseline characteristics between the treatment groups.

SRD part (Chinese subjects)

The plasma concentration of BI 671800 reached a maximum at 1.50 hours to 1.75 hours after drug administration and declined rapidly thereafter. The geometric mean terminal half-life was 7.87 hours to 9.59 hours. The results of visual inspection and statistical analysis indicated that C_{max} and AUC of BI 671800 in Chinese subjects did not apparently deviate from dose proportionality within the dose range investigated.

The plasma concentration of BI 600957 reached a maximum at approximately 4.00 hour after drug administration and then gradually declined. A second hump in the plasma concentration-time profile of most subjects was observed at 8.00 hours to 14.0 hours after drug administration.

The geometric mean terminal half-life at the steady state was 12.2 hours to 14.7 hours. The results of visual inspection and statistical analysis indicated that BI 600957 showed a less than dose proportional increase of C_{max} and AUC within the dose range investigated.

The metabolic ratio based on AUC_{0-12} ($RAUC_{0-12,Met}$) was higher in the 200 mg BI 671800 HEA group (0.828) than in the 50 mg BI 671800 HEA (0.695) and 400 mg BI 671800 HEA groups (0.601).

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Efficacy / clinical pharmacology results (continued):

MRD part (Japanese subjects)

The plasma concentration of BI 671800 reached a maximum at approximately 2.00 hour after drug administration and declined rapidly thereafter. The geometric mean terminal half-life at the steady state was 5.22 hours to 6.46 hours. The accumulation ratios of BI 671800 based on C_{max} and AUC_{0-12} were 1.12 to 1.25 and 1.25 to 1.31, respectively. The results of visual inspection and statistical analysis indicated that C_{max} and AUC of BI 671800 increased dose proportionally within the dose range investigated.

The plasma concentration of BI 600957 reached a maximum at approximately 4.00 hours after drug administration and then gradually declined. A second hump in the plasma concentration-time profile of most subjects was observed at 8.00 hours to 14.0 hours after drug administration. The geometric mean terminal half-life at the steady state was 9.81 hours to 12.0 hours. The accumulation ratios of BI 600957 based on C_{max} and AUC_{0-12} were 3.17 to 3.53 and 3.50 to 3.67, respectively. The results of visual inspection and statistical analysis indicated that BI 600957 showed a less than dose proportional increase of C_{max} and AUC within the dose range investigated.

The metabolic ratio based on $AUC_{\tau,ss}$ ($RAUC_{\tau,ss,Met}$) decreased with increasing dose from 2.85 in the 50 mg bid BI 671800 HEA group to 1.59 in the 400 mg BI 671800 bid HEA group.

BI 671800 and BI 600957 were considered to have reached the steady state at least 3 days after the start of twice-daily administration.

Pharmacodynamics (Japanese subjects only)

The percent of EOS WBSC after PGD2 stimulation reached 48.6%, 30.9%, and 13.0% at 4 hours after the last dose in the 50 mg bid, 200 mg bid, and 400 mg bid BI 671800 HEA groups, respectively. The percent of EOS WBSC after PGD2 stimulation returned to the pre-dose level at 12 hours in the 50 mg bid and 200 mg bid BI 671800 HEA groups and at 24 hours in 400 mg bid BI 671800 HEA group. $AUEC_{0-12}$ and $AUEC_{\tau,13}$ decreased with increasing dose. The value of the pharmacodynamic parameter at steady state ($AUEC_{\tau,13}$) was lower than that after single dose administration ($AUEC_{0-12}$).

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Safety results:

The 73 entered subjects were allocated to 1 of the 6 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.

SRD part (Chinese subjects)

A total of 9 subjects (25.7%) reported at least one adverse event. The frequency of subjects with adverse events was highest in the 200 mg BI 671800 HEA group (44.4%), followed by the placebo group (33.3%), 50 mg BI 671800 HEA group (25.0%) and the 400 mg BI 671800 HEA group (0.0%). The most frequently reported adverse events overall at the SOC level were 'nervous system disorders' (4 subjects, 11.4%). 'Respiratory, thoracic and mediastinal disorders' were reported by 2 subjects (5.7%). 'Musculoskeletal and connective tissue disorders', 'general disorders and administration site conditions' and 'injury, poisoning and procedural complications' were reported by 1 subject (2.9%) each. The most frequently reported event by preferred term was somnolence (3 subjects, 8.8%). All other adverse events were reported by 1 subject (2.9%) each.

MRD part (Japanese subjects)

A total of 6 subjects (17.6%) reported at least one adverse event in at least one of the treatment periods (single dose and multiple dose segments). The frequency of subjects with adverse events was highest in the 50 mg bid BI671800 HEA group (22.2%) and placebo group (22.2%), followed by the 400 mg bid BI 671800 HEA group (14.3%) and the 200 mg bid BI 671800 HEA group (11.1%). The most frequently reported adverse events overall at the SOC level were 'nervous system disorders', 'respiratory, thoracic and mediastinal disorders', and 'gastrointestinal disorders', which were experienced by 3 subjects (8.8%) each. 'Musculoskeletal and connective tissue disorders', 'general disorders and administration site conditions' were reported by 2 subjects (5.9%) each. 'Infections and infestations', 'eye disorders', and 'investigations' were reported by 1 subject (2.9%) each.

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Safety results (continued):

The most frequently reported event by preferred term was epistaxis (3 subjects, 8.8%). Headache, paraesthesia and feeling cold were reported by 2 subjects (5.9%) each. All other adverse events were reported by 1 subject (2.9%) each.

No clustering of any specific adverse event in any treatment group was apparent.

One adverse event (blood creatine phosphokinase increase), which was reported in the 200 mg bid BI 671800 HEA group in the MRD part, was classified as serious. All adverse events were of mild or moderate intensity. Over the course of the trial, the investigator rated 12 (7 SRD part, 5 MRD part) adverse events as related to the trial medications.

As mentioned above there was one case of elevated creatine phosphokinase activity on day 3 of visit 3 in the MRD part of this trial and the creatine phosphokinase activity returned to normal approximately 8 days later. The investigator assessed the elevation of creatine phosphokinase as related to the trial medication. No other clinically relevant finding was reported with respect to the clinical laboratory evaluation, vital signs, and ECG recordings.

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Conclusions:

Overall, single doses of 50 mg, 200 mg or 400 mg BI 671800 HEA and multiple twice daily doses of 50 mg, 200 mg or 400 mg BI 671800 HEA were well tolerated by the healthy male Chinese and Japanese subjects respectively in this trial. There was no clustering of adverse events in any treatment group and no dose dependent increase in adverse events was observed for BI 671800 HEA.

In Chinese subjects, the plasma concentration of BI 671800 reached a maximum at 1.50 hours to 1.75 hours after drug administration and declined rapidly thereafter. The terminal half-life was 7.87 hours to 9.59 hours. C_{max} and AUC of BI 671800 did not deviate from dose proportionality within the dose range investigated. The metabolic ratio based on AUC_{0-12} value was higher in the 200 mg BI 671800 HEA group (0.828) than in the 50 mg BI 671800 HEA (0.695) and 400 mg BI 671800 HEA (0.601) groups.

In Japanese subjects, the plasma concentration of BI 671800 reached a maximum at 2.00 hour after drug administration and declined rapidly thereafter. The terminal half-life at the steady state was 5.22 hours to 6.46 hours. The accumulation ratios of BI 671800 based on C_{max} and AUC_{0-12} were 1.12 to 1.25 and 1.25 to 1.31, respectively. C_{max} and AUC of BI 671800 increased dose-proportionally within the dose range investigated. The metabolic ratio of BI 600957 based on $AUC_{\tau,ss}$ decreased with increasing dose from 2.85 in the 50 mg bid BI 671800 HEA group to 1.59 in the 400 mg bid BI 671800 HEA group.

No apparent difference was observed between Japanese and Chinese subjects since the pharmacokinetic parameters were generally comparable between Japanese and Chinese subjects.

The $AUEC_{0-12}$ and $AUEC_{\tau,13}$ of eosinophil whole blood shape change decreased with increasing dose in Japanese subjects.