Boehringer Ingelheim

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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-003813-17	
BI Investigational Product: BI 691751		**Page:** 1 of 4	
Report Date: 30 Apr 2015	**Trial No. / Doc. No.:** 1334.2/c02736728-01	**Dates of Trial:** 26 May 2014 – 20 Aug 2014	**Date of Revision:** Not applicable

Title of Trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of multiple rising oral doses of BI 691751 in healthy male subjects This trial was prematurely discontinued due to termination of the clinical development of BI 691751
Principal Investigator:	[redacted]
Trial Sites:	[redacted] Germany
Publications:	Data from this trial have not been published at the time of this clinical report.
Clinical Phase:	I
Objectives:	The primary objective of this trial was to investigate the safety and tolerability of BI 691751 in healthy male subjects following oral administration of multiple rising doses of 0.5 mg, 3 mg, 10 mg, 30 mg, 60 mg, and 90 mg once daily over 14 days. Secondary objectives were the exploration of the pharmacokinetics (PK), including dose proportionality, and pharmacodynamics (PD) of BI 691751 after multiple dosing, and the assessment of the PK/PD relationship.
Methodology:	Randomised, placebo-controlled within dose groups, and double-blinded, multiple dose trial.
No. of Subjects:	
Planned:	Entered:60 healthy male subjects (10 per dose group; 8 on active drug, 2 on placebo); planned doses were 0.5 mg, 3 mg, 10 mg, 30 mg, 60 mg, and 90 mg BI 691751
Actual:	Entered: 18 healthy male subjects; no subjects were dosed with any dose above 3 mg BI 691751 0.5 mg once daily: Entered: 8 Treated: 8 Analysed (for primary endpoint): 8 3 mg once daily: Entered: 7 Treated: 7 Analysed (for primary endpoint): 7 Placebo once daily: Entered: 3 Treated: 3 Analysed (for primary endpoint): 3

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Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male subjects at the age of 18 to 50 years (inclusive) with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 (inclusive)
BI Investigational Product:	BI 691751 tablets of 0.5 mg, 2 mg, and 10 mg
Dose:	Dose group 1 = 0.5 mg once daily, given as 1 tablet of 0.5 mg BI 691751 Dose group 2 = 3 mg once daily, given as 1 tablet of 2 mg BI 691751 and 2 tablets of 0.5 mg BI 691751 Dose group 3 = 10 mg once daily, given as 1 tablet of 10 mg BI 691751 (not used) Dose group 4 = 30 mg once daily given as 3 tablets of 10 mg BI 691751 (not used) Dose group 5 = 60 mg once daily given as 6 tablets of 10 mg BI 691751 (not used) Dose group 6 = 90 mg once daily, given as 9 tablets of 10 mg BI 691751 (not used)
Mode of Admin.:	Oral with 240 mL of water
Batch No.:	B131002842 (0.5 mg tablets), B131002843 (2 mg tablets), B131000766 (10 mg tablets; not used)
Comparator Product:	Matching placebo tablets
Dose:	Not applicable
Mode of Admin.:	Oral with 240 ml of water
Batch No.:	B131003277 (placebo to 2 mg tablets), B131003279 (placebo to 0.5 mg tablets and 10 mg tablets)
Duration of Treatment:	14 days with once daily dosing at each dose level
Criteria for Evaluation:	
Clinical Pharmacology:	The primary endpoint of this study was a safety endpoint and is described below. Pharmacokinetics: The following parameters of BI 691751 were planned to be determined as secondary endpoints in plasma and whole blood: $AUC_{\tau,1}$ and C_{max} after the first dose and $AUC_{\tau,ss}$ and $C_{max,ss}$ after the last dose. Further

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Clinical Pharmacology (cont'd):	PK parameters of interest planned to be determined after the first dose were $AUC_{0\text{-}tz}$, t_{max}, λ_z, $Ae_{t1\text{-}t2}$, $fe_{t1\text{-}t2}$, $CL_{R,\,t1\text{-}t2}$, and further PK parameters of interest planned to be measured after the last dose were $C_{min,ss}$, $t_{max,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $V_z/F_{,ss}$, PTF, $Ae_{t1\text{-}t2,ss}$, $fe_{t1\text{-}t2,ss,}$ $CL_{R,t1\text{-}t2,ss,}$ $AUC_{0\text{-}tz}$ $AUC_{0\text{-}\infty}$, and the accumulation ratios $R_{A,AUC}$ and $R_{A,Cmax}$. Pharmacodynamics: As exploratory biomarker, the inhibition of calcimycin stimulated leukotriene B4 production in human whole blood was planned to be measured. Pharmacokinetic and PD parameters were not determined, because the sponsor decided to discontinue the clinical development of BI 691751.
Safety:	The primary endpoint to assess safety and tolerability of BI 691751 was the frequency [N (%)] of subjects with drug-related adverse events (AEs). Further criteria of interest were AEs, safety laboratory tests, 12-lead electrocardiograms (ECGs) and Holter-ECG, exercise ergometry, physical examination, and vital signs (blood pressure and pulse rate).
Statistical Methods:	It was planned to calculate descriptive statistics for all safety and pharmacology endpoints. For Holter ECGs and 12-lead ECGs repeated measures analyses were performed and for heart rate values during exercise ergometry analyses of covariance were performed. Due to premature discontinuation, no PK and PD endpoints were evaluated. No interim analyses were conducted.
SUMMARY - CONCLUSIONS:	
Trial Subjects and Compliance with Trial Protocol:	A total of 18 subjects were entered into the trial, 8 subjects received 0.5 mg BI 691751, 7 subjects received 3 mg BI 691751, and 3 subjects received placebo. All subjects completed the trial according to the clinical trial protocol. None of the subjects discontinued the trial prematurely. All 18 healthy volunteers participating in this trial were male and White. Overall, the mean age (standard deviation [SD]) of the subjects was 32.0 years (4.6). The mean BMI (SD) was 23.64 kg/m^2 (2.59). There were no relevant differences in age and BMI between the placebo group, the 0.5 mg dose group, and the 3.0 mg dose group.
Clinical Pharmacology Results:	Because the sponsor decided to discontinue the clinical development of BI 691751, the analytical determination of BI 691751 concentrations in blood and urine samples for PK evaluation was not performed for any dose group

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	and therefore no secondary and further endpoints were evaluated.
Clinical Pharmacology Results (cont'd):	Due to premature discontinuation of the trial, the inhibition of calcimycin stimulated LTB_4 production in human whole blood by BI 691751 was not performed.
Safety Results:	In total, 6 out of 18 subjects (33.3%) had any AE during the treatment periods of this trial. There were 2 subjects (11.1%) with AEs that the investigator assessed as drug-related (the primary endpoint of this trial). All AEs were of mild intensity. There were no deaths and no serious AEs. There were no AEs that led to discontinuation of the trial drug, no AEs of special interest, and no other significant AEs (according to ICH E3). All AEs were resolved by the end of the trial. The most frequently reported AEs overall were headache (3 subjects, 16.7%), nasopharyngitis (2 subjects, 11.1%), diarrhoea (2 subjects, 11.1%), and flatulence (2 subjects, 11.1%). All other AEs were not reported by more than 1 subject. Drug-related AEs (diarrhoea and flatulence) were only reported in the 3 mg dose group. The frequency of subjects with AEs in the pooled BI 691751 group (5 out of 15 subjects, 33.3%) was equal to the frequency of subjects with AEs in the placebo group (1 out of 3 subjects, 33.3%). The frequency of subjects with drug-related AEs in the pooled BI 691751 group (2 subjects, 13.3%) was higher than the frequency of subjects with drug-related AEs in the placebo group (0 subjects). Since the trial was discontinued prematurely, not all dose groups were administered study drug. Therefore, no firm conclusions can be drawn regarding a possible dose-relationship, although the current results suggest that the number of subjects with at least 1 drug-related AE may increase with the dose. These data and the data from this trial in general should be interpreted with caution as there were only 3 subjects in the placebo group. There were no clinically relevant findings with respect to safety laboratory parameters, ECG recordings (both 12-lead ECGs and Holter ECGs), exercise ergometry, physical examination, and vital signs.
Conclusions:	Multiple doses of up to 3 mg BI 691751 were safe and well tolerated by the healthy male subjects who participated in this trial. Due to premature discontinuation of the trial, dose groups 3 to 6 have not been performed. Because the sponsor decided to discontinue the clinical development of BI 691751, PK and PD parameters have not been determined.