Boehringer Ingelheim

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		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2013-003560-31	
BI Investigational Product: BI 416970		**Page:** 1 of 4	
Report Date: 15 Apr 2015	**Trial No. / Doc. No.:** 1345.1/c02214030-02	**Dates of Trial:** 07 Apr 2014 - 30 Jun 2014	**Date of Revision:** Not applicable

Title of Trial:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 416970 in healthy male volunteers in a partially randomised, single-blind, placebo-controlled trial
Principal Investigator:	[redacted]
Trial Site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach/Riss, Germany
Publications:	Data from this trial have not been published at the time of writing this clinical trial report.
Clinical Phase:	I
Objectives:	The objective of this trial was to investigate the safety, tolerability, and pharmacokinetics (PK) including dose proportionality of BI 416970.
Methodology:	Single rising doses, partially randomised, placebo-controlled, single-blind, parallel group design of approximately 3 months duration
No. of Subjects:	
Planned:	Entered: 56[1] (6 subjects on active treatment and 2 subjects on placebo at each of the 7 dose levels) [1]Additional subjects could be entered to allow testing of additional intermediate doses within the planned dose range on the basis of experience gained during trial conduct (e.g. preliminary PK data), i.e. the actual number of subjects entered could possibly differ from 56)
Actual:	Entered: 60 Dose group 1: 10 mg Entered: 6 Treated: 6 Analysed (for primary endpoint): 6 Dose group 2: 25 mg* Entered:10 Treated: 10 Analysed (for primary endpoint): 10 Dose group 3: 50 mg* Entered: 6 Treated: 6 Analysed (for primary endpoint): 6 Dose group 4: 100 mg Entered: 6 Treated: 6 Analysed (for primary endpoint): 6 Dose group 5: 200 mg Entered: 6 Treated: 6 Analysed (for primary endpoint): 6 Dose group 6: 400 mg

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No. of Subjects:	Entered: 5 Treated: 5 Analysed (for primary endpoint): 5
Actual (continued):	Dose group 7: 600 mg Entered: 6 Treated: 6 Analysed (for primary endpoint): 6 Placebo (dose groups 1-7): Entered: 15 Treated: 15 Analysed (for primary endpoint): 15 *Subjects [redacted], and [redacted] were dosed with 50 mg on 05 May 2014. Subjects [redacted], and [redacted] were dosed by mistake with 25 mg instead of 50 mg on 07 May 2014. Subject [redacted] received placebo matching 25 mg. On 12 May 2014, the reserve medication for Subjects [redacted] to [redacted] was used according to the randomisation plan to complete the 50 mg dose group
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male volunteers, age 18 to 50 years, body mass index (BMI) 18.5 to 29.9 kg/m^2
BI Investigational Product:	BI 416970 film-coated tablets
Dose:	1 x 10, 1 x 25, 2 x 25, 1 x 100, 2 x 100, 4 x 100 or 6 x 100 mg
Mode of Admin.:	Oral, with 240 mL water after an overnight fast of at least 10 h
Batch Nos.:	B131003641 (10 mg), B131003642 (25 mg), B131003643 (100 mg)
Comparator Product:	Placebo
Dose:	Not applicable (matching placebo for tablets)
Mode of Admin.:	Oral, with 240 mL water after an overnight fast of at least 10 h
Batch Nos.:	B131003772 (10 mg), B131003773 (25 mg), B131003774 (100 mg)
Duration of Treatment:	Single dose
Criteria for Evaluation:	
Clinical Pharmacology :	Secondary endpoints: $AUC_{0-\infty}$, C_{max}
Safety:	Primary endpoint: Number (%) of subjects with drug-related adverse events (AEs) Further assessments: AEs, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring, vital signs (blood pressure [BP], pulse rate [PR]) and physical examination

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Statistical Methods: Descriptive statistics were calculated for the primary endpoint (safety) and the secondary endpoints (PK parameters $AUC_{0-\infty}$, C_{max}). Dose proportionality was explored using a regression model; a 90% confidence interval (CI) for the slope was computed. Interim analyses were performed to assess safety and early PK parameters before dose progression.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol: Sixty healthy male subjects were entered, treated and completed the planned observation time. Of those, 15 subjects received placebo, 10 subjects received 25 mg, 5 subjects received 400 mg, and 6 subjects each received 10, 50, 100, 200, or 600 mg BI 416970, respectively. All subjects were White. The mean (SD) age was 34.5 (9.1) years and the mean BMI (SD) was 24.95 (2.63) kg/m^2.

Clinical Pharmacology Results: BI 416970 showed dose proportional increases in C_{max} and $AUC_{0-\infty}$ across the 50 to 600 mg dose range. Somewhat lower dose-normalised C_{max} and $AUC_{0-\infty}$ values were observed for the 10 and 25 mg dose levels as compared with the 50 to 600 mg dose range. The inter-subject variability (gCV) for $AUC_{0-\infty}$ and C_{max} was generally moderate to high, particularly for C_{max}.

Secondary endpoints of BI 416970 are summarised by dose group in the Table below; other PK parameters and their results are presented in the main body of the report.

Comparison of secondary endpoints of BI 416970 after single oral administration of 10 to 600 mg

Secondary endpoints[1]	BI 416970 10 mg (N=6)	BI 416970 25 mg (N=10)	BI 416970 50 mg (N=6)	BI 416970 100 mg (N=6)
$AUC_{0-\infty}$ [nmol·h/L]	72.8 (41.5)	195 (49.8)	566 (54.0)	992 (36.1)
C_{max} [nmol/L]	15.2 (66.3)	44.0 (80.5)	154 (69.6)	250 (37.2)

Secondary endpoints[1]	BI 416970 200 mg (N=6)	BI 416970 400 mg (N=5)	BI 416970 600 mg (N=5)
$AUC_{0-\infty}$ [nmol·h/L]	1770 (34.6)	3970 (61.3)	6150 (23.2)
C_{max} [nmol/L]	482 (40.3)	1060 (70.4)	1610 (50.2)

[1] gMean (gCV [%]) is presented for both endpoints

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Safety Results:	Out of the 60 treated subjects, 11 subjects (18.3%) reported AEs on treatment: 1 subject (6.7%) in the placebo group, 1 subject each (16.7%) of the 10, 50, and 600 mg BI 416970 dose groups, 3 subjects (30.0%) in the 25 mg dose group, 2 subjects (33.3%) in the 200 mg dose group, and 2 subjects (40.0%) in the 400 mg dose group. Investigator-defined drug-related AEs occurred in 2 subjects (3.3%) overall. The most frequent AE was headache, which occurred in 4 subjects (1 subject each of the 25, 50, 200 and 400 mg dose groups). The second most frequent AEs were nasopharyngitis (1 subject each in 10 and 25 mg) and vomiting (1 subject each in 200 and 600 mg). All other on-treatment AEs were reported for individual subjects. The majority of the AEs were of mild or moderate intensity, 1 AE (nausea) was of severe intensity. All subjects recovered from their AEs by the end-of-study examination. No AEs led to premature discontinuation of the trial. No serious AEs and no clinically relevant findings in laboratory evaluation (except for 1 subject), physical examination, vital signs, or ECG measurements were reported.
Conclusions:	Good safety and tolerability was observed in this trial after administration of 10, 25, 50, 100, 200, 400, or 600 mg BI 416970. BI 416970 showed dose-proportional increases in C_{max} and $AUC_{0-\infty}$ across the 50 to 600 mg dose range. Somewhat lower dose-normalised C_{max} and $AUC_{0-\infty}$ values were observed for the 10 and 25 mg dose levels as compared with the 50 to 600 mg dose range.