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			
BI Investigational Product: BI 691751		**Page:** 1 of 6	
Report Date: 19 JAN 2015	**Trial No. / Doc. No.:** 1334.5 / c02736843-01	**Dates of Trial:** 06 Mar 2014 - 17 May 2014	**Date of Revision:** Not applicable

Title of Trial:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 691751 in healthy Asian male volunteers in a randomised, double-blind, placebo-controlled design
Principal Investigator:	[redacted]
Trial Sites:	[redacted] Korea
Publications:	Data of this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objectives:	To investigate safety, tolerability, and pharmacokinetics of BI 691751 in healthy Asian population.
Methodology:	Randomised, placebo-controlled, double-blind, single rising dose (SRD)
No. of Subjects:	
Planned:	Entered: 64
Actual:	Entered: 64
	BI 691751:
	Entered: 48 Treated: 48 Analysed (for primary endpoint): 48
	Placebo:
	Entered: 16 Treated: 16 Analysed (for primary endpoint): 16
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Healthy male volunteers, Chinese or Japanese ethnicity, with body mass index (BMI) $\geq$ 18.5 and $\leq$ 25 kg/m^2, and age within the range of 20 to 45 years.
BI Investigational Product:	BI 691751
Dose:	5, 10, 30, and 60 mg (as tablets of unit strength 0.5, 2, and 10 mg)
Mode of Admin.:	Oral with 240 mL water after an overnight fast of at least 10 h
Batch No.:	B131003652 (0.5 mg), B131003654 (2 mg), and B131003656 (10 mg)

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Comparator Product:	Placebo
Dose:	Not applicable
Mode of Admin.:	Oral with 240 mL water after an overnight fast of at least 10 h
Batch No.:	B131003653 (for 0.5 mg), B131003655 (for 2 mg), and B131003657 (for 10 mg)
Duration of Treatment:	Single dose
Criteria for Evaluation:	
Clinical Pharmacology:	Secondary endpoints: C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, and $t_{1/2}$ in plasma and whole blood.
Safety:	The primary safety endpoint was the frequency of subjects with drug-related adverse events (AEs). Additional safety assessments included safety laboratory tests, 12-lead electrocardiograms (ECG), vital signs (blood pressure, pulse rate) and physical examinations.
Statistical Methods:	Safety and tolerability and pharmacokinetic (PK) parameters were analysed descriptively. Dose proportionality was evaluated using the power model and fit as a linear regression model after transformation. The slope parameter and its two-sided 95% confidence interval were calculated. No interim analysis was performed.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 64 Asian male subjects (mean age 29.0 years, SD 5.52) entered the study, including 2 subgroups. One subgroup included 32 Chinese subjects (mean age 25.6 years, SD 4.33) and the other included 32 Japanese subjects (mean age 32.4 years, SD 4.33). In each subgroup, 8 subjects received placebo, and 6 subjects at each dose level received a single dose of BI 691751 tablets (5, 10, 30, and 60 mg). All except 2 Chinese subjects completed the study (Table 1).

No important protocol violations were identified at the blinded report planning meeting. All subjects fulfilled the inclusion and exclusion criteria. Compliance with trial medication intake was assured by administration of trial medication under supervision of the investigating physician or his authorised designee.

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Table 1 Subject disposition (overall)

	Placebo	5 mg	10 mg	30 mg	60 mg	Total
Subjects entered, N	16	12	12	12	12	64
Subjects treated, N (%)	16 (100)	12 (100)	12 (100)	12 (100)	12 (100)	64 (100)
Planned observation time completed, N (%)	16 (100)	10 (83.3)	12 (100)	12 (100)	12 (100)	62 (96.9)
Planned observation time not completed, N (%)	0	2 (16.7)	0	0	0	2 (3.1)
Consent withdrawn[1], N (%)	0	2 (16.7)	0	0	0	2 (3.1)

[1] Two Chinese subjects withdrew their consents not due to AE.

Clinical Pharmacology Results:

All 48 BI 691751 treated subjects (24 Chinese and 24 Japanese) who had measurable concentrations of BI 691751 were included in the PK analysis. The PK characteristics were similar between the Chinese and Japanese subjects. The PK profile of BI 691751 consisted of a rapid absorption phase (median t_{max} about 20 to 40 min) and multiple elimination phases. The terminal half-life was longer in blood than in plasma. In plasma, C_{max} and AUC_{0-tz} showed the super-proportional increase among the dose range investigated. In blood, dose proportional increases in C_{max} were observed, but sub-proportional increase in $AUC_{0-\infty}$ and AUC_{0-tz} were observed among the dose range investigated (Tables 2 and 3).

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Clinical Pharmacology Results (continued):

Table 2 Plasma and Blood PK parameters for SRD of BI 691751 in Chinese subjects

Chinese	**5 mg**		**10 mg**		**30 mg**		**60 mg**	
PK Parameter	**N**	**gMean gCV(%)**	**N**	**gMean gCV(%)**	**N**	**gMean gCV(%)**	**N**	**gMean gCV(%)**
Plasma								
C_{max} [nmol/L]	6	175 (45.7)	6	477 (25.5)	6	1450 (19.4)	6	3690 (20.5)
t_{max}[1)] [h]	6	0.333 (0.333 - 0.667)	6	0.667 (0.333 - 2.00)	6	0.667 (0.333 - 1.00)	6	0.667 (0.333 - 0.667)
AUC_{0-tz} [nmol·h/L]	4	1320 (22.1)	6	4720 (17.8)	6	17 500 (23.1)	6	37 000 (24.2)
$AUC_{0-\infty}$ [nmol·h/L]	-	NC (NC)	5	5280 (17.3)	6	18000 (22.3)	6	37 400 (23.9)
$t_{1/2}$ [h]	-	NC (NC)	5	94.6 (29.8)	6	102 (34.3)	6	73.5 (40.4)
Blood								
C_{max} [nmol/L]	6	247 (21.5)	6	523 (19.7)	6	1490 (22.1)	6	3470 (16.4)
t_{max}[1)] [h]	6	0.333 (0.333 - 2.00)	6	0.667 (0.333 - 2.00)	6	0.667 (0.333 - 1.00)	6	0.667 (0.333 - 0.667)
AUC_{0-tz} [nmol·h/L]	4	19 200 (11.9)	6	27 900 (9.92)	6	41 000 (14.6)	6	66 600 (14.2)
$AUC_{0-\infty}$ [nmol·h/L]	5	31 600 (23.3)	6	51 800 (22.4)	6	75 600 (13.5)	6	118 000 (10.3)
$t_{1/2}$ [h]	5	243 (40.6)	6	333 (30.6)	6	393 (23.1)	6	417 (23.7)

NC: Not calculated
All parameters except for t_{max} are presented as geometric mean (gMean) with geometric coefficient of variation gCV(%)

[1)] Results for t_{max} are presented as median (Min - Max)

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Clinical Pharmacology Results (continued):

Table 3 Plasma and Blood PK parameters for SRD of BI 691751 in Japanese subjects

Japaese	**5 mg**		**10 mg**		**30 mg**		**60 mg**	
PK Parameter	**N**	**gMean gCV(%)**	**N**	**gMean gCV(%)**	**N**	**gMean gCV(%)**	**N**	**gMean gCV(%)**
Plasma								
C_{max} [nmol/L]	6	129 (33.2)	6	421 (53.4)	6	1520 (18.1)	6	4270 (9.35)
t_{max}[1)] [h]	6	0.667 (0.333 - 0.667)	6	0.500 (0.333 - 0.667)	6	0.667 (0.333 - 0.667)	6	0.667 (0.333 - 0.683)
AUC_{0-tz} [nmol·h/L]	6	1310 (27.3)	6	5060 (38.7)	6	21 600 (28.6)	6	41 100 (13.8)
$AUC_{0-\infty}$ [nmol·h/L]	-	NC (NC)	-	NC (NC)	6	22 400 (28.0)	6	42 000 (14.1)
$t_{1/2}$ [h]	-	NC (NC)	-	NC (NC)	6	95.0 (64.7)	6	89.9 (26.2)
Blood								
C_{max} [nmol/L]	6	213 (17.9)	6	509 (35.4)	6	1530 (22.4)	6	3600 (12.4)
t_{max}[1)] [h]	6	0.500 (0.333 - 4.00)	6	0.333 (0.333 - 0.667)	6	0.667 (0.333 – 1.00)	6	0.667 (0.333- 0.683)
AUC_{0-tz} [nmol·h/L]	6	19 500 (22.2)	6	29 600 (11.1)	6	48 300 (16.2)	6	66 800 (9.51)
$AUC_{0-\infty}$ [nmol·h/L]	6	35 600 (65.5)	6	48 700 (19.6)	6	91 800 (38.6)	6	105 000 (11.4)
$t_{1/2}$ [h]	6	290 (62.8)	6	265 (26.2)	6	403 (48.9)	6	340 (26.0)

NC: Not calculated
All parameters except for t_{max} are presented as gMean with gCV(%)
[1)] Results for t_{max} are presented as median (Min-Max)

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Safety Results:

In the Chinese ethnic group, AEs were reported in 37.5% (3 of 8) subjects in the placebo group, and 50.0% (12 of 24) subjects in the BI total group. There was no notable difference between placebo and BI 691751 total groups, and no notable dose dependency across different dosages in BI 691751 groups. The most common AE was 'respiratory, thoracic and mediastinal disorders' (2 of 8 [25.0%] subjects in the placebo group, and 7 of 24 [29.2%] subjects in BI total group) for system organ class (SOC), and 'rhinorrhoea' (2 of 8 [25.0%] subjects in the placebo group, and 5 of 24 [20.8%] subjects in BI total group) for preferred term (PT).

In the Japanese ethnic group, AEs were reported in 37.5% (3 of 8) subjects in the placebo group, and 33.3% (8 of 24) subjects in the BI total group. There was no notable difference between placebo and BI total groups, and no notable dose dependency across different dosages in BI 691751 groups. The most common AE was 'respiratory, thoracic and mediastinal disorders' (3 of 8 [37.5%] subjects in the placebo group, and 8 of 24 [33.3%] subjects in BI total group) for SOC, and 'oropharyngeal pain' (none in the placebo group, and 6 of 24 [25.0%] subjects in BI total group) for PT.

There were no subjects with severe AEs, investigator defined drug-related AEs, AEs of special interest, other significant AEs according to ICH E3, serious AEs, or death in either ethnic group. There was one Japanese subject had clinically notable HR decreases in the 60 mg dose group.

In general, no clinically relevant findings regarding clinical laboratory values, vital signs, and ECGs were observed.

Conclusions:

The exposure to BI 691751 increased more than dose proportionality in plasma and less than dose proportionality in blood among the dose range investigated. No apparent difference in plasma and blood exposure to BI 691751 was observed between Chinese and Japanese subjects.

The results indicate that, similar to findings in study 1334.1 in healthy Caucasian male subjects, single oral doses of 5 to 60 mg of BI 691751 were safe and well-tolerated in healthy Asian (Chinese and Japanese) male subjects included in this trial. The results do not indicate any safety concerns for future clinical trials of BI 691751.