Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of Company: Boehringer Ingelheim		**Synopsis**	Boehringer Ingelheim
BI Proprietary Name: Not applicable		**EudraCT No.:** 2012-005721-67	
BI Investigational Product: BI 691751		**Page:** 1 of 10	
Report Date: 15 SEP 2014	**Trial No. / Doc. No.:** 1334.1 / c02248490-02	**Dates of Trial:** 30 Apr 2013 - 27 Nov 2013	**Date of Revision:** Not applicable

Title of Trial:	Safety, tolerability, pharmacokinetics, and pharmacodynamics of single rising oral doses of BI 691751 in healthy male volunteers in a randomised, single-blind, placebo-controlled design (part I) and investigation of relative bioavailability of BI 691751 given as tablet and oral solution to healthy male subjects in an open, randomised, single-dose, single period parallel group design (part II)
Principal Investigator:	[redacted]
Trial Site:	Boehringer Ingelheim Pharma GmbH & Co. KG, Human Pharmacology Centre, Birkendorfer Straße 65, Biberach/Riß, Germany
Publications:	Trial data were not published at the time of clinical trial report preparation
Clinical Phase:	I
Objectives:	To investigate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of single rising doses (SRD) of BI 691751 in healthy male subjects (Part I); and, based on CYP2D6 genotype, to investigate the relative bioavailability (BA) of 10 mg BI 691751 administered as tablet compared with oral solution (Part II).
Methodology:	Part I: randomised, placebo-controlled, single-blind, single rising dose Part II: randomised, open, parallel group, single dose
No. of Subjects:	
Planned:	Entered: 86
Actual:	Entered: 81
	Part I:
	Entered: 52 Treated: 52 Analysed (for primary endpoint): 52
	Part II:
	Entered: 29 Treated: 29 Analysed (for primary endpoint): 24
Diagnosis:	Not applicable

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Main Criteria for Inclusion:	Healthy male volunteers, with body mass index (BMI) ≥18.5 and ≤29.9 kg/m^2. For Part I, subjects were to be ≥18 and ≤45 years of age, and those with poor CYP2D6 metabolism were to be excluded. For Part II, subjects were to be ≥18 and ≤55 years of age, and both those with poor and extensive CYP2D6 metabolism were to be included.
BI Investigational Product:	BI 691751
Dose:	Part I: 0.5, 1.5, 5, 15, 30, 60 or 90 mg powder for oral solution (single dose) Part II: 10 mg tablet or 10 mg powder for oral solution (single dose)
Mode of Admin.:	Oral with 240 mL water after an overnight fast of at least 10 h
Batch No.:	Part I: B131000117 (0.5, 1.5, 5 mg dose groups); B131000118 (15, 30, 60, 90 mg dose groups) Part II: B131000118 (powder); BI 131000766 (tablet)
Comparator Product:	Part I: placebo
Dose:	Not applicable
Mode of Admin.:	Oral with 240 mL water after an overnight fast of at least 10 h
Batch No.:	B131000119
Duration of Treatment:	Part I: single dose Part II: single dose
Criteria for Evaluation:	
Clinical Pharmacology:	Part I: Secondary endpoints: $AUC_{0-\infty}$, AUC_{0-tz}, $t_{1/2}$, C_{max}, and t_{max} in plasma Part II: Primary endpoints: AUC_{0-72h} and C_{max} in plasma; secondary endpoint: AUC_{0-tz} in plasma Pharmacodynamics: An exploratory analysis was performed correlating PK exposure to BI 691751 with inhibition of leukotriene A4 hydrolase (LTA_4H) and calcimycin-stimulated leukotriene B4 (LTB_4) production in whole blood, as well as urinary excretion of leukotriene E4 (LTE_4; measured in Part I only).

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Criteria for Evaluation (continued): **Safety:**	In Part I, the primary endpoint was the frequency of subjects with drug-related adverse events (AEs). In addition, in Parts I and II, safety assessment included monitoring for AEs, safety laboratory tests, 12-lead electrocardiogram (ECG), continuous ECG monitoring (Part I only), vital signs (blood pressure, pulse rate), and physical examination.
Statistical Methods:	Part I: Primary and secondary endpoints: descriptive statistics were calculated for safety, PK, and PD parameters. Dose proportionality in plasma and whole blood was explored using a regression model; a 95% confidence interval for the slope was computed. Part II: Primary and secondary endpoints: relative bioavailability was estimated by the ratios of the geometric means (test/reference). In addition, their two-sided 90% confidence intervals (CIs) were provided. The statistical model was an ANOVA on the logarithmic scale including the effect for 'treatment' (formulation comparison) or 'phenotype' (comparison of metabolisers). CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints. No inferential statistical interim analysis was performed.

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SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

A total of 81 male subjects was entered in the trial. For the entire trial, all but one subject completed the planned observation time; Subject No. 125 (15 mg BI 691751) withdrew from the trial for personal reasons. Eighty subjects (98.8%) were White and 1 subject (1.2%) was Black. Mean age of the treated subjects was 31.8 years (SD 8.3). Demographic characteristics were similar between treatment groups in both Parts I and II.

In Part I of the trial, 52 subjects were included; 39 subjects in seven dose groups were administered BI 691751 and 13 subjects were administered placebo (Table 1).

Table 1 Number of subjects administered BI 691751 or placebo in Part I

Dose group	0.5 mg	1.5 mg	5 mg	15 mg	30 mg	60 mg	90 mg	Total
Subjects (N)	8	7	7	8	8	7	7	52
Placebo (N)	2	2	1	2	2	2	2	13
BI 691751 (N)	6	5	6	6	6	5	5	39

In Part II, 29 subjects were to be administered 10 mg BI 691751 either as a tablet (17 subjects) or as an oral solution (12 subjects). However, 5 subjects in the oral solution group had plasma and whole blood concentrations of BI 691751 below the lower limit of quantification. An analysis of residual solution in the administration devices indicated that there was no trial medication in the devices (by mistake pure solvent was administered instead of reconstituted drug solution). These 5 subjects were therefore excluded from the PK analysis.

No other important protocol violations were identified at the database lock 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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Clinical Pharmacology:

Phamacokinetics: All 63 treated subjects in Parts I and II who had measurable concentrations of BI 691751 were included in the PK analysis. Plasma concentration time profiles indicated that the drug was rapidly absorbed, with median t_{max} values of approximately 40 min for all dose groups (Table 2). In plasma, overproportional behaviour in C_{max} and AUC parameters was evident at doses of 10 mg or less, whereas linear dose proportionality was observed for doses of 15 mg or greater. Geometric mean (gMean) plasma C_{max} ranged from 3.45 nmol/L for the 0.5 mg dose group to 4180 nmol/L for the 90 mg dose group. Geometric mean values of $AUC_{0\text{-}tz}$ ranged from 29.5 nmol·h/L for the 1.5 mg dose group to 40500 nmol·h/L for the 90 mg dose group, and values of $AUC_{0-\infty}$ ranged from 1140 nmol·h/L for the 5 mg dose group to 41000 nmol·h/L for the 90 mg dose group. The gMean values of $t_{1/2}$ were independent of the administered dose and ranged from 57.2 to 97.4 h.

Table 2 Plasma PK parameters for SRD of BI 691751

Dose group	0.5 mg (N=4)	1.5 mg (N=5)	5 mg (N=6)	10 mg (N=7)	15 mg (N=6)	30 mg (N=6)	60 mg (N=5)	90 mg (N=5)
t_{max}[1] [h]	0.667 (0.333, 0.667)	0.667 (0.350, 0.667)	0.842 (0.333, 2.02)	0.667 (0.333, 1.50)	0.500 (0.333, 0.667)	0.350 (0.333, 0.667)	0.667 (0.333, 1.50)	0.667 (0.333, 1.02)
C_{max} [nmol/L]	3.45 (15.5)	18.3 (39.3)	88.9 (59.1)	220 (14.4)	729 (21.5)	1320 (31.5)	3320 (46.7)	4180 (22.2)
AUC_{0-tz} [nmol·h/L]	NC	29.5 (18.4)	791 (45.4)	3300 (28.5)	6 130 (15.4)	11400 (28.3)	24100 (21.1)	40500 (27.2)
$AUC_{0-\infty}$ [nmol·h/L]	NC	NC	1140 (34.5)	3630 (28.5)	7250 (15.9)	11900 (27.2)	24500 (20.0)	41000 (26.9)
$t_{½}$ [h]	NC	NC	65.4 (37.8)	59.4 (57.1)	97.4 (63.3)	74.9 (49.2)	57.2 (34.3)	78.3 (16.9)

NC = not calculated
All parameters except for t_{max} are presented as gMean with gCV(%).
[1] Results for t_{max} are presented as median (minimum, maximum)

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Clinical Pharmacology (continued):

PK parameter assessment in whole blood demonstrated that at the lowest doses of BI 691751, exposure parameters were much higher than those in plasma. Underproportional increases in exposure with increasing dose were evident for AUC parameters over the entire dose range and for C_{max} for doses of 10 mg or less. In combination with the overproportional increases in plasma exposure parameters, this result suggests preferential partitioning of BI 691751 into the cellular fraction of blood at low doses.

Assessment of urinary PK parameters indicated that fractional excretion of BI 691751 was low (less than 6% in all dose groups over 144 h), indicating that the majority of the drug is metabolised and/or eliminated by non-renal mechanisms.

For the analysis of relative bioavailability in Part II, 17 subjects (12 extensive CYP2D6 metabolisers and 5 poor CYP2D6 metabolisers) were administered a 10 mg tablet of BI 691751 and 12 subjects (all extensive CYP2D6 metabolisers) were to be administered 10 mg BI 691751 as oral solution; however, 5 subjects in the latter group were excluded from the PK analysis because they did not receive BI 691751 in the oral solution (see above).

For extensive CYP2D6 metabolisers (12 in the tablet group and 7 in the solution group), the relative bioavailability of 10 mg BI 691751 administered as oral solution (reference) and as tablet (test) was investigated. For AUC_{0-72h}, the adjusted gMean ratio (test/reference) was 97.88% (90% CI: 79.96%, 119.81%); for C_{max}, 101.31% (90% CI: 80.59%, 127.35%); and for AUC_{0-tz}, 95.48% (90% CI: 74.41%, 122.51%), indicating similar exposures between subjects administered oral solution and tablet.

The relative bioavailability of 10 mg BI 691751 administered as tablet to 5 poor CYP2D6 metabolisers (test) and 12 extensive CYP2D6 metabolisers (reference) was also investigated. The adjusted gMean ratio (test/reference) for AUC_{0-72h} was 111.20% (90% CI: 88.60%, 139.58%); for AUC_{0-tz}, 109.8% (90% CI: 84.38%, 142.89%), and for C_{max} 92.69% (90% CI: 68.66%, 125.12%). Therefore, poor and extensive metabolisers appeared to have similar exposures.

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Clinical Pharmacology (continued):

Pharmacodynamics: The extent of LTA_4H inhibition in whole blood at 24 h after treatment with BI 691751 was not dependent on baseline-stimulated LTB_4 levels. Administration of 60 mg or 90 mg BI 691751 to healthy subjects achieved ≥90% inhibition of LTA_4H activity at least up to 24 h after treatment.

For the determination of urinary LTE_4 excretion after LTA_4H inhibition by BI 691751, urine collection for 24 h was more appropriate than spot urine. After dosing with BI 691751, for the 3 highest dose groups (30, 60, and 90 mg), an approximately 70% increase in LTE_4 excretion was detected in both the 0 to 24 h urine collection and in the 24 to 48 h urine collection.

Safety Results:

Investigator-defined drug-related AEs (primary safety endpoint) were reported for 3 subjects (3.7%), all of whom were entered in Part I. Two of the subjects received BI 691751 (1.5 mg or 90 mg) and 1 subject received placebo. Moderate headache was reported for the subject treated with 1.5 mg BI 691751, and mild tachycardia, mild hot flush, and mild upper abdominal pain were reported for the subject treated with 90 mg BI 691751. Mild flatulence was reported for the subject treated with placebo.

Of 81 subjects administered trial medication, AEs were reported for 28 (34.6%). Of the 68 subjects administered BI 691751, AEs were reported for 23 (33.8%); of the 13 subjects administered placebo, AEs were reported for 5 (38.5%). The most frequently reported system organ class (SOC) in BI 691751-treated subjects was infections and infestations (6 of 68 subjects, 8.8%); the second most frequent were nervous system disorders, gastrointestinal (GI) disorders, and injury, poisoning, and procedural complications (each reported for 5 of 68 subjects, 7.4%). The most frequently reported preferred terms (PTs) were nasopharyngitis and headache (each in 5 of 68 subjects, 7.4%). The most frequent SOCs for placebo-treated subjects were infections and infestations, and GI disorders (each in 2 of 13 subjects, 15.4%); nasopharyngitis was the most common PT (in 2 of 13 subjects, 15.4%). All AEs were mild or moderate in severity, except for 1 subject who had two drug-unrelated AEs of severe intensity (road traffic accident with resultant contusion). The subject required hospitalisation for the contusion, which was therefore also classified as a serious AE.

No deaths, protocol-specified significant AEs, AEs leading to treatment discontinuation, or significant AEs according to ICH E3 (other significant AEs) were reported in this trial. An overall summary of AEs is provided in Table 3.

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Safety Results (continued):

Table 3 Overall summary of AEs

	Placebo N (%)	BI 691751 N (%)	Overall[1] N (%)
Number of subjects	13 (100)	68 (100)	81 (100)
Subjects with AEs	5 (38.5)	23 (33.8)	28 (34.6)
Severe AEs	0	1 (1.5)	1 (1.2)
Drug-related AEs[2]	1 (7.7)	2 (2.9)	3 (3.7)
SAEs	0	1 (1.5)	1 (1.2)
Required hospitalisation	0	1 (1.5)	1 (1.2)

[1] Including placebo
[2] As defined by the investigator

No laboratory assessment for any subject was considered to be clinically relevant by the investigator or was reported as an AE.

For Part I, assessment of vital signs and ECG data indicated changes possibly related to treatment with BI 691751. A *post hoc* analysis of covariance (ANCOVA) was performed on blood pressure, heart rate, and ECG interval data. For each dose group, baseline data were subtracted and results were compared with the data for placebo-treated subjects. If the 90% CI did not include the gMean for placebo-treated subjects, the difference is indicated as 'statistically significant' below. However, this does not mean that the results were confirmatory or that the trial was powered to ascertain differences.

For vital signs, there were no mean on-treatment changes in systolic blood pressure relative to baseline for any dose group in Part I. For diastolic blood pressure, both increases and decreases were evident in some dose groups. Statistically significant decreases were observed at one time point at least for the 0.5, 5, 15, and 60 mg dose groups, and statistically significant increases were observed at two time points for the 30 mg dose group and at one time point for the 60 mg dose group. No overall relationship was observed between diastolic blood pressure and dose or time of intake of trial medication.

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Safety Results (continued):

Trial data suggest that BI 691751 may cause an increase in heart rate (HR) at higher doses. In order to allow continuous ECG monitoring, subjects lay down for 4 h after intake of trial medication. This caused a HR decrease in the placebo and 0.5, 1.5, and 5 mg dose groups. However, this decrease was diminished or absent in the higher dose groups (15 to 90 mg). Between 0 and 4 h post dosing, when baseline values were subtracted and the mean values from treated groups were compared with the placebo group, a statistically significant increase in HR of 4 to 7 beats per minute (bpm) was observed for at least one measurement time in the 30, 60, and 90 mg dose groups. For 1 subject in the 90 mg dose group at 96 h after dosing, a notable change was observed (HR of 102 bpm, an increase of 27 bpm from baseline). As no other cause was evident, this was reported as a drug-related AE by the investigator.

It is also possible that BI 691751 may increase the length of the QT interval and QRS complex. QT intervals were corrected for HR according to Fridericia's formula (QTcF). Compared with the mean for placebo-treated subjects, in the initial 4 h time window, statistically significant mean changes in QTcF were observed at one time point at least for the 0.5, 5, 15, 60, and 90 mg dose groups. Prolongations ranged between 7 and 13 ms compared with placebo. No relevant changes were observed for the 1.5 or 30 mg dose groups. For the QRS complex, increases of 2 to 4 ms were observed in the 0.5, 5, 60 and 90 mg dose groups. These increases reached statistical significance. In the 15 and 30 mg dose groups, both statistically significant increases and decreases in QRS were observed.

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Conclusions:

In Part I of the trial (SRD), for $AUC_{0\text{-}tz}$, $AUC_{0\text{-}\infty}$, and C_{max}, linear dose proportionality was observed for doses of 15 mg BI 691751 or higher. In Part II of the trial (relative BA), 10 mg of BI 691751 administered as either tablet or powder in solution resulted in similar exposure for extensive CYP2D6 metabolisers. For the tablet formulation, exposure was similar between poor CYP2D6 metabolisers and extensive CYP2D6 metabolisers. PD analysis indicated at least 90% inhibition of LTA_4H activity for at least 24 h after treatment at doses of 60 mg BI 691751 or higher.

In some dose groups and at some measurement times, safety assessment indicated possible effects of BI 691751 on heart rate (mean increase of up to 7 bpm), QTcF (up to 13 ms), and QRS complex (up to 4 ms) relative to placebo. Although these findings do not indicate a safety risk to healthy subjects, further investigation is warranted. The administration of BI 691751 as oral solution (from 0.5 to 90 mg) or as tablet (10 mg) to healthy male subjects was well tolerated, with trial medication-related AEs reported for only 2 of 63 subjects administered BI 691751.