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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.:** 2013-003814-42	
BI Investigational Product: BI 691751		**Page:** 1 of 6	
Report Date: 09 Jan 2015	**Trial No. / Doc. No.:** 1334.10 / c02336088-01	**Dates of Trial:** 30 Jan 2014 - 12 May 2014	**Date of Revision:** Not applicable

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Title of Trial:	Relative bioavailability of a single oral dose of BI 691751 when administered alone or in combination with multiple oral doses of itraconazole in healthy male subjects (an open-label, randomised, two-period, two-sequence crossover study)
Principal Investigator:	[redacted]
Trial Site:	Boehringer Ingelheim Pharma GmbH & Co. KG Department of Translational Medicine & Clinical Pharmacology Human Pharmacology Centre Birkendorfer Str. 65, Biberach/Riß, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report.
Clinical Phase:	I
Objectives:	The objective of this trial was to investigate whether and to what extent co-administration of multiple doses of itraconazole affects single dose pharmacokinetics of BI 691751 in healthy male subjects.
Methodology:	This was an open-label, randomised, 2-way crossover trial with 2 treatments (R and T) and 2 treatment sequences (T_R and R_T). The single dose BI 691751 administrations in the reference treatment and in the test treatment were separated by a washout period of at least 7 weeks.
No. of Subjects:	
Planned:	Entered: 20 subjects (10 in each of the 2 treatment sequences)
Actual:	Entered: 20 subjects <u>Treatment T (itraconazole + BI 691751):</u> Treated and analysed (for primary endpoint): 20 <u>Treatment R (BI 691751 alone):</u> Treated and analysed (for primary endpoint): 20
Diagnosis:	Not applicable
Main Criteria for Inclusion:	Only healthy male subjects in the age range of 18 to 50 years and with a body mass index (BMI) of 18.5 to 29.9 kg/m^2 were included.

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Trial product 1:	BI 691751, 10 mg tablet
Dose:	10 mg single dose in each of the 2 treatment periods (treatments T and R)
Mode of Admin.:	Oral administration with 240 mL water after intake of a standarised meal
Batch No.:	B131000766
Trial product 2:	Itraconazole (Sempera®), 100 mg capsules
Dose:	200 mg twice daily on the first day of treatment T (loading dose), followed by 200 mg once daily for the next 9 days of treatment T
Mode of Admin.:	Oral administration with 240 mL water after intake of a standarised meal
Batch No.:	DBL9100 (Janssen-Cilag, EU commercial product)
Duration of Treatment:	Treatment T (BI 691751 + itraconazole): Two capsules of 100 mg itraconazole were given twice daily on Day -3 (loading dose) and once daily on Day -2 to Day 7 (10 days of itraconazole treatment in total). In addition, 1 tablet of 10 mg BI 691751 was given as a single dose on Day 1 (corresponding to the fourth day of the 10-day itraconazole treatment). Treatment R (BI 691751 alone): One tablet of 10 mg BI 691751 was given as a single dose on Day 1. Each subject was to receive both treatments (T and R) in the order of [redacted] assigned treatment sequence (T_R and R_T). The BI 691751 single dose administrations in the 2 treatments were separated by a washout period of at least 7 weeks.
Criteria for Evaluation:	
Clinical Pharmacology:	The following pharmacokinetic parameters were analysed as primary endpoints: AUC_{0-tz} and C_{max} of BI 691751 in plasma and whole blood. The following pharmacokinetic parameter was assessed as secondary endpoint: $AUC_{0-\infty}$ of BI 691751 in plasma and whole blood. Other pharmacokinetic parameters of BI 691751 as well as itraconazole plasma concentrations were calculated as appropriate.

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Safety:	The frequency [number (%)] of subjects with drug-related adverse events was considered an 'other' endpoint and was used to assess safety and tolerability of BI 691751 given alone or in combination with itraconazole. Further criteria of interest were adverse events, safety laboratory tests, vital signs (blood pressure and pulse rate), 12-lead electrocardiogram (ECG), and physical examination.
Statistical Methods:	Relative bioavailability was estimated based on the ratios (test to reference treatment) of the geometric means (gMeans) of the primary and secondary endpoints. Additionally, their 2-sided 90% confidence intervals (CIs) were provided. The statistical model was an analysis of variance (ANOVA) on the logarithmic scale, including effects for 'sequence', 'subjects within sequences', 'period', and 'treatment'. CIs were calculated based on the residual error from ANOVA. Descriptive statistics were calculated for all endpoints.

SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:	A total of 20 subjects were entered into this trial and treated at a single centre (HPC, Biberach/Riß, Germany). All 20 subjects completed the planned trial observation time. The subjects in this trial were healthy white male subjects. The mean age was 36.3 years, ranging from 21 to 49 years, and the mean BMI was 25.2 kg/m^2, ranging from 20.7 to 29.7 kg/m^2. Nineteen of the 20 subjects each received a total dose of 20 mg BI 691751 (corresponding to two 10 mg doses) and of 2200 mg itraconazole (corresponding to eleven 200 mg doses) over the entire course of the trial. Because of elevated ALT/GPT values, one subject was not administered the last 2 itraconazole doses in order to avoid a possible further increase. Therefore, this subject received a total dose of 20 mg BI 691751 (corresponding to two 10 mg doses) and of 1800 mg itraconazole (corresponding to nine 200 mg doses). Safety assessments and pharmacokinetic analyses were based on the data of all 20 treated subjects.
Clinical Pharmacology Results:	Following administration of a single dose of BI 691751 alone (reference treatment) or in the presence of multiple dose itraconazole (test treatment), BI 691751 concentrations increased relatively quickly and then decreased somewhat faster in the presence than in the absence of itraconazole. Pharmacokinetic parameters of BI 691751 in plasma and whole blood are listed in Table 1 for both treatments.

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Clinical Pharmacology Results (continued):

Table 1 Plasma and whole blood pharmacokinetic parameters of BI 691751 after single oral administration of 10 mg BI 691751 alone or in combination with multiple dose itraconazole

Matrix / Pharmacokinetic parameter	BI 691751 alone (reference)		BI 691751 + itraconazole (test)	
	gMean[1]	gCV [%]	gMean[1]	gCV [%]
Plasma				
C_{max} [nmol/L]	157	24.4	150	34.1
AUC_{0-tz} [nmol·h/L]	2830	34.6	2090	43.2
$AUC_{0-\infty}$ [nmol·h/L]	3160	34.8	2360	43.3
Whole blood				
C_{max} [nmol/L]	217	16.0	203	21.4
AUC_{0-tz} [nmol·h/L]	25 000	25.8	21 600	25.8
$AUC_{0-\infty}$ [nmol·h/L]	27 000	29.6	24 600	29.6

[1] For the calculation of the gMean pharmacokinetic parameters, the data of 20 subjects were used, with the exception of $AUC_{0-\infty}$ in whole blood after treatment with BI 691751 alone, where the data of 19 subjects were used.

The inferential analysis indicates that itraconazole leads to a small decrease in the bioavailability of BI 691751 in plasma and in whole blood compared with administration of BI 691751 alone. No effect of itraconazole on C_{max} of BI 691751 was observed. The gMean ratios of test to reference treatment and the corresponding 90% CIs are shown in Table 2.

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Clinical Pharmacology Results (continued):

Table 2 Inferential analysis of relative bioavailability of plasma and whole blood BI 691751 after single oral administration of BI 691751 alone or in combination with multiple dose itraconazole

Matrix Pharmacokinetic parameter	gMean ratio of test to reference treatment [%][1]	90% CI of gMean ratio		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
Plasma				
C_{max}	95.6	84.2	108.5	23.5
AUC_{0-tz}	74.1	62.4	88.0	32.1
$AUC_{0-\infty}$	74.9	63.0	89.0	32.4
Whole blood				
C_{max}	93.5	86.1	101.6	15.1
AUC_{0-tz}	86.4	78.0	95.6	18.6
$AUC_{0-\infty}$	88.2	78.6	99.0	20.7

[1] For the calculation of the gMean ratios, the data of 20 subjects were used, with the exception of $AUC_{0-\infty}$ in whole blood after treatment with BI 691751 alone, where the data of 19 subjects were used.

The measured plasma trough concentrations of itraconazole on Days 1, 3 and 7 indicated that sufficient exposure of itraconazole was achieved at the time of BI 691751 administration of the test treatment.

Safety Results:

A total of 11 treated subjects (55.0%) reported at least 1 adverse event on-treatment. The most frequently reported on-treatment adverse events at the SOC level were musculoskeletal and connective tissue disorders (4 subjects, 20.0%), followed by infections/infestations, nervous system disorders, and gastrointestinal disorders (3 subjects, 15.0%, each). On the preferred term level, all adverse events were reported by only 1 subject (5.0%) each.

One subject (subject No. [redacted]) did not receive the last 2 doses of the itraconazole treatment during [redacted] first treatment period (BI 691751 + itraconazole) because of slightly elevated ALT/GPT values (in order to avoid a further and potentially critical increase), but participated in the second treatment period (BI 691751 alone) as planned.

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Safety Results (continued):

The corresponding adverse event ('alanine aminotransferase increased') was listed as an adverse event leading to discontinuation of trial medication and was judged by the investigator as related to itraconazole intake. No other drug-related adverse events and no other adverse events leading to discontinuation of trial medication were reported in this trial. Three subjects (15.0%) experienced a severe adverse event. This comprised 'respiratory tract infection' of Subject No. [redacted], 'musculoskeletal pain' of Subject No. [redacted], and 'back pain' of Subject No. [redacted], which all occurred during treatment with BI 691751 alone. All other reported adverse events were of mild or moderate intensity. No death, no serious adverse events, and no protocol-specified adverse events of special interest were reported in this trial.

No clinically relevant findings regarding safety laboratory measurements, ECG recordings, physical examinations, and vital sign measurements were reported in this trial.

Conclusions:

The C_{max} values of BI 691751 were comparable following BI 691751 single dose administration in the presence and absence of multiple dose itraconazole. Co-administration with itraconazole led to a small decrease in the bioavailability (in terms of AUC_{0-tz} and $AUC_{0-\infty}$) of BI 691751. The data of this trial indicate no clinically relevant effect of the CYP3A4 inhibitor itraconazole on the disposition of BI 691751. Inhibition of CYP3A4 by co-administered drugs is therefore not expected to cause significant drug-drug interactions with BI 691751.

Overall, administration of a single dose of 10 mg BI 691751 alone or on the fourth day of a 10-day itraconazole treatment was safe and well tolerated by the subjects in this trial.