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.:** 2011-004615-23	
BI Investigational Product: BI 1034020		**Page:** 1 of 6	
Report Date: 03 MAR 2015	**Trial No. / Doc. No.:** 1312.1 / c02731051-01	**Dates of Trial:** 18 Oct 2013 - 28 Apr 2014	**Date of Revision:** Not applicable

Title of Trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics of single rising intravenous and subcutaneous doses of BI 1034020 in healthy male volunteers (partially randomised, single-blind, placebo-controlled within dose groups, clinical phase I study) This trial was prematurely discontinued.
Coordinating/Principal Investigators:	[redacted]
Trial Site:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany
Publications:	Data from this trial have not been published at the time of this clinical trial report
Clinical Phase:	I
Objectives:	To investigate safety, tolerability, pharmacokinetics, and pharmacodynamics of BI 1034020
Methodology:	Partially randomised, placebo-controlled within dose groups, single-blind, single rising dose, multiple centres (dose escalation intravenous [iv] bridging to subcutaneous [sc] in parallel). This trial was initiated at 2 centres. As one of the trial centres did not enrol any subjects by the time of premature termination of the trial; the trial was conducted only at one centre.
No. of Subjects:	
Planned:	Entered: 80 (10 dose levels, 8 subjects at each dose level) BI 1034020: 60 (6 at each dose level) Placebo: 20 (2 at each dose level)

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No. of subjects (continued):

Actual: Entered/Randomised: 35

Treated: 32; Completed: 30

Trial medication	Dose	Randomised	Treated	Analysed (for primary endpoint)	Analysed (for secondary endpoints)
BI 1034020	5 mg	6	6	6	6
BI 1034020	10 mg	6	6	6	6
BI 1034020	20 mg	5	5	5	5
BI 1034020	50 mg	7	6[1]	6	5[2]
BI 1034020	100 mg	1	1	1[3]	-
Placebo	–	10	8[1]	8	-

[1] One subject in the 50 mg iv dose group and 2 subjects in the placebo group were not treated with trial medication

[2] One subject in the 50 mg iv dose group did not receive complete dose of trial medication

[3] One subject in the 100 mg iv dose group did not receive complete dose of trial medication

Diagnosis: Not applicable

Main Criteria for Inclusion: Healthy male volunteers, aged 18 to 40 years, with body mass index (BMI) ranging from 18.5 to 29.9 kg/m^2

BI Investigational Product: BI 1034020

Doses: Single dose of 5 mg, 10 mg, 20 mg, 50 mg, 100 mg, 200 mg, 400 mg for iv infusion, and 50 mg, 100 mg, 200 mg for sc injection

Mode of Admin.: iv infusion and sc injection

Batch Nos.: B131002441/314660002

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Reference Product:	Placebo to BI 1034020
Doses:	Not applicable
Mode of Admin.:	iv infusion and sc injection
Batch Nos.:	B131002442/314660001
Duration of Treatment:	Single dose of active trial medication or matching placebo
Criteria for Evaluation:	
Clinical Pharmacology:	The primary endpoint in this trial was a safety endpoint and is described in the safety section below. Secondary endpoints: • Pharmacokinetics based on C_{max}, $AUC_{0-\infty}$ and AUC_{0-tz}
Safety:	Primary endpoint: • Safety and tolerability based on the number of subjects (%) with drug related adverse events. Other safety parameters: • Physical examination • Vital signs (blood pressure (BP), pulse rate (PR), oral body temperature • 12-lead ECG (electrocardiogram) and continuous ECG monitoring • Adverse events • Suicidality assessment • Neurological examination • Assessment of local tolerability by investigator • Clinical laboratory tests (haematology, clinical chemistry and urinalysis)
Statistical Methods:	Descriptive statistics for safety and PK endpoints were to be calculated. Dose proportionality of BI 1034020 was to be explored using a regression model; a 95% confidence interval for the slope was to be computed. The statistical model for the analysis of relative bioavailability of BI 1034020 (sc formulation versus iv formulation) was to be an analysis of variance (ANOVA) on the log scale (inter-individual comparison); a 2-sided 90% confidence interval for the formulation ratio was to be calculated.

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SUMMARY - CONCLUSIONS:

Trial Subjects and Compliance with Trial Protocol:

Trial medication was administered to 32 healthy male volunteers. In total 2 subjects, 1 subject each in the 50 mg and 100 mg BI 1034020 iv dose groups did not receive complete dose of trial medication. All subjects were of white race. The mean age of subjects (±SD) was 31±4.9 years with mean BMI of 25.3 kg/m^2. There were no important protocol violations or inclusion and exclusion criteria violations reported in this trial.

Due to a serious, drug-related AE in the first subject of 100 mg BI 1034020 single iv dose group (post-fulfilment of a trial stopping criteria), the trial was prematurely terminated; refer to Safety results section for details. No further iv dosing or any planned sc administration was performed and no further subjects were recruited in this trial.

Clinical Pharmacology Results:

Pharmacokinetic Results

Maximum plasma concentrations were reached at the end of the infusion interval (median t_{max} values ranging between 1.5 h and 1.78 h) and increased in proportion with the dose from 1.5 to 17.2 µg/mL. After reaching maximum plasma levels, BI 1034020 declined rapidly in plasma in an at least biphasic manner. The first elimination phase is described by the initial half-life, which increased with increasing dose from ~4 h to ~8 h. In consequence to that AUC_{0-tz} increased more than dose-proportional (Table 1). The second elimination phase is described by the terminal half-life, which could only be evaluated for the 50 mg dose group ($t_{1/2}$ = ~90 h). The clearance and volume of distribution, both calculated based on the terminal half-life, were both low.

No BI 1304020 was detectable in urine.

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Clinical Pharmacology Results (Continued):

Table 1 PK parameters of total BI 1034020 after single intravenous infusion over 90 min of 5 mg to 50 mg BI 1034020 - Pharmacokinetic set (PKS)

Parameter	Unit	5 mg N=6	10 mg N=6	20 mg N=5	50 mg N=5
		gMean (gCV%)			
C_{max}	µg/mL	1.50 (8.69)	3.30 (17.6)	6.90 (15.7)	17.2 (11.5)
AUC_{0-tz}	µg·h/mL	7.30 (9.60)	20.1 (28.5)	83.7 (94.4)	242 (15.4)
$AUC_{0-\infty}$ [1]	µg·h/mL	---	---	---	314 (7.66)[2]

[1] $AUC_{0-\infty}$ could be assessed only in 50 mg iv dose group as terminal phase was below BLQ for other dose groups

[2] N=4

Analysis of dose proportionality:

Dose proportionality for $AUC_{0-\infty}$ could not be performed in this trial. The C_{max} increased in proportion with the dose, while AUC_{0-tz} did increase more than dose proportional (Table 2).

Table 2 Dose proportionality evaluation of BI 1034020 after single iv dose of 5 mg to 50 mg BI 1034020 - PKS

Parameter [Unit]	N	Slope ß	95% CI for slope ß	
			Lower	Upper
C_{max} [µg/mL]	22	1.0604	0.9901	1.1308
AUC_{0-tz} [µg·h/mL]	22	1.5629	1.3426	1.7833

Safety Results:

Adverse events:

Treatment-emergent AEs were reported in 22 of 32 subjects (66.8%) who received trial medication. Of the 32 treated subjects, drug-related AEs were reported by the investigator in 11 subjects (34.4%; 8 subjects treated with BI 1034020 and 3 subjects treated with placebo). The most frequently

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Safety Results (Continued):	reported AE by preferred term was headache reported in 11 subjects, of which 8 were considered to be drug-related by the investigator. Two subjects (one in the 50 mg iv dose group and one in the 100 mg iv dose group) experienced drug-related AEs leading to drug discontinuation which were reported respectively by the investigator as allergic reaction non-serious of moderate intensity for one subject and anaphylactoid reaction serious of severe intensity for the other subject. This last AE (anaphylactoid reaction) fulfilled protocol stopping rule criteria and led to the premature trial termination. All subjects recovered from the AEs by the end of the trial *Other safety measurements:* No clinically relevant changes were noted in the clinical laboratory assessments or vital signs (systolic BP, diastolic BP, pulse rate, and body temperature). There were 2 subjects who experienced ECG changes reported as AEs by the investigator during the trial: palpitations reported in 1 subject from the placebo iv dose group and sinus tachycardia reported in the first subject in the BI 1034020 100 mg iv dose group. There were no clinically relevant findings related to local tolerability and suicidal ideation as per the assessments performed by the investigator.
Conclusions:	*Overall Conclusions* Fifty percent (11 of 22 subjects with treatment-emergent AEs) of the subjects with treatment-emergent AEs experienced drug-related AEs by the investigator. Single iv doses from 5 mg to 50 mg BI 1034020 were generally well tolerated in the healthy volunteers. Due to a serious, drug-related AE (first subject of 100 mg BI 1034020 iv dose group) that fulfilled stopping rule criterion for trial termination, the trial was prematurely terminated. The safety profile of higher iv doses or sc administration of BI 1034020 could not be studied further. After single iv infusion of BI 1034020 up to 50 mg, maximum plasma levels were detected at the end of infusion interval and declined afterwards rapidly in an at least biphasic manner. Increases in exposure based on AUC_{0-tz} were more than proportional with dose whereas C_{max} increased dose-proportional. The terminal half-life could only be evaluated for the 50 mg BI 1034020 iv dose group ($t_{1/2}$ = ~90 h). The clearance and volume of distribution were low; both calculated based on the terminal half-life.