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.

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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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2012-005614-19	
Name of active ingredient: BI 1015550		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Disclosure synopsis date: 15 OCT 2015	**Trial No. / Doc No.:** 1305.2 / c02191718-02	**Dates of trial:** 11 APR 2013 - 13 JUN 2013	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability and pharmacokinetics of multiple rising oral doses of BI 1015550 powder for oral solution in healthy male volunteers q.d. or b.i.d. for 14 days (a randomised, double-blind, placebo-controlled within dose groups Phase I trial)
Principal Investigator:	[redacted]
Trial site:	[redacted]
Publication (reference):	Data from this trial have not been published
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, and pharmacokinetics of BI 1015550 after multiple oral dosing
Methodology:	This study of multiple doses over 14 days was randomised, double-blind, and placebo-controlled within dose groups.

No. of subjects:

planned: entered: 48 subjects
BI 1015550: 36 (9 in each dose group)
Placebo: 12 (3 in each dose group)

actual:

Trial medication	Dose	Entered	Treated	Analysed (for primary endpoint[1])
Total	-	24	24	24
BI 1015550	1 mg twice daily	9	9	9
BI 1015550	6 mg twice daily	9	9	9
Placebo (all dose groups)	-	6	6	6

Note: dose escalation was stopped after the second dose group (BI 1015550 6mg twice daily)
[1]Drug related adverse events, as assessed by the investigator.

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 18 to 50 years, body mass index (BMI) 18.5 to 29.9 kg/m^2
Test products:	BI 1015550 as a powder for oral solution
dose:	1 mg, 6 mg, and 12 mg twice daily; 18 mg once daily
mode of admin.:	Oral
batch no.:	B131000019 (BI 1015550 30 mg powder) B101004730 (tartaric acid solvent 0.5%, 80 mL solution) B131000081 (solvent component hydroxy-propyl-β-cyclodextrin 8.60 g powder)
Reference therapy:	Placebo
dose:	Volume matching BI 1015550
mode of admin.:	Oral
batch no.:	B101004730 (tartaric acid solvent 0.5%, 80 mL solution) B131000081 (solvent component hydroxy-propyl-β-cyclodextrin 8.60 g powder)
Duration of treatment:	14 days
Criteria for evaluation:	
Clinical pharmacology:	The primary endpoint in this trial was a safety endpoint and is described in the safety section below. Pharmacokinetic parameters of BI 1015550 were defined as secondary endpoints: C_{max}, $AUC_{\tau,1}$, and $AUC_{0-\infty}$ (after the first dose) and $C_{max,ss}$ and $AUC_{\tau,ss}$ (after the last dose). Other endpoints included the exploratory pharmacodynamic biomarker tumor necrosis factor-α (TNF-α).

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Safety:	There was no primary endpoint in the statistical sense. The assessment of safety and tolerability of BI 1015550 was primarily based on the number (%) of subjects reported with drug related adverse events (AEs), as evaluated by the investigator. Other safety endpoints were analysis of AEs, clinical laboratory assessments (haematology, clinical chemistry, and urinalysis), vital signs (blood pressure, pulse rate, respiratory rate, body temperature, body weight, and orthostasis test), faecal calprotein and occult blood tests, electrocardiograms (ECG), physical examinations, and tolerability assessments. Interim PK analyses were included to avoid dosing above the NOAEL (no observed adverse effect level).
Statistical methods:	Descriptive statistics were calculated for safety, pharmacokinetic, and pharmacodynamic endpoints. Dose proportionality in plasma was explored using a power model with a 95% confidence interval (CI) for the slope. Linearity with respect to multiple administration using $AUC_{0-\infty}$ and $AUC_{\tau,ss}$ was addressed using a linear model on the logarithmic scale with a 2-sided 95% CI. The attainment of steady state was assessed by analysing the trough concentrations of BI 1015550 using a mixed linear model with 'subject' as a random effect and 'time' as a repeated effect.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Disposition and demographics

The trial was planned to include 48 healthy male subjects randomised to 1 of 4 active dose groups or the placebo group. Dose escalation was stopped as per protocol after the second dose group because the interim pharmacokinetic evaluation predicted that exposure in dose group 3 would be above the NOAEL; therefore, 24 subjects were randomised in the trial. Of the 24 subjects who were entered in the trial and treated, 22 subjects (91.7%) completed the planned observation time. Two subjects prematurely discontinued the trial medication (1 each due to an AE and personal reasons). All other subjects received all planned doses of medication.

The treated set comprised 23 White (95.8%) and 1 Black (4.2%) male subjects. The mean age was 42.0 years (SD 8.8) and mean BMI was 25.4 kg/m^2 (SD 2.4). There were no relevant differences in the demographic and baseline characteristics between the treatment groups.

Pharmacokinetics

The shapes of the geometric mean (gMean) plasma concentration-time profiles were similar for both doses and for single dose and multiple dose administration. Plasma concentrations reached their maximum within approximately 1 h and quickly declined thereafter in a biphasic manner. Secondary endpoints after single dose and at steady state are summarised in the table below.

Parameter	1 mg (N = 9[1])		6 mg (N = 9[1])	
	gMean	gCV%	gMean	gCV%
Single dose				
$AUC_{0-\infty}$ [nmol·h/L]	131	18.6	958	20.9
$AUC_{\tau,1}$ [nmol·h/L]	94.9	10.3	622	20.7
C_{max} [nmol/L]	24	25.1	133	14.9
Steady state				
$AUC_{\tau,ss}$ [nmol·h/L]	148	10.7	1090	19.6
$C_{max,ss}$ [nmol/L]	28.6	15.3	199	14.5

[1] N = 8 for steady state parameters

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Clinical pharmacology results (cont.):

Steady state was attained by Day 9. AUC and C_{max} values were up to 1.69-fold higher at steady state compared with single dose administration, indicating some accumulation of BI 1015550 at steady state (gMean $R_{A,\ AUC}$: 1.60 and 1.69; gMean $R_{A,Cmax}$; 1.19 and 1.45). The terminal half-life was comparable between doses (24.3 and 25.2 h). After multiple doses of BI 1015550, oral clearance and the apparent volume of distribution were lower in the 6 mg dose group than in the 1 mg dose group (gMean $CL/F_{,ss}$ [mL/min]: 204 vs. 251; gMean $V_z/F_{,ss}$ [L]: 444 vs 528). BI 1015550 exposure was nearly proportional to dose at steady-state from 1 to 6 mg BI 1015550 twice daily. However, the 95% CIs for $C_{max,ss}$ and $AUC_{\tau,ss}$ extended to 1.17 and 1.21, respectively, and did not include unity for $AUC_{\tau,ss}$, suggesting a trend toward over proportionality.

Pharmacodynamics

BI 1015550 dosed at 6 mg twice daily inhibited TNF-α release with a maximum mean inhibitory effect size between 35% vs. predose (Day 1 after single dose) and 56% vs. predose (Day 12 at steady state). A clear discrimination to placebo was observed throughout most of the dosing interval of 6 mg BI 1015550. No relevant inhibition was seen with 1 mg BI 1015550 twice daily. No plasma concentration-effect relationship was established from this trial, due to the limited data and high variability observed in the biomarker data set.

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Safety results:	After administration of BI 1015550 1 to 6 mg twice daily or matching placebo to 24 healthy volunteers over 14 days, 6 subjects (25.0%) reported AEs. The frequency of subjects with treatment-emergent AEs was highest in the 1 mg treatment group (4 subjects, 44.4%), followed by placebo (1 subject, 16.7%) and the 6 mg treatment group (1 subject, 11.1%). Subjects with investigator defined drug related AEs were reported with the same frequencies per treatment group. Subjects most frequently reported headache and abdominal pain (2 out of 24 subjects [8.3%] each). One subject was reported with an 'other significant AE' (according to ICH E3), which the investigator assessed as drug related (elevated C-reactive protein) and which led to the discontinuation of the trial medication. All AEs had resolved by the end-of-study examination. No subject was reported with severe AEs or significant AEs (pre-specified events). There were no deaths or other serious AEs. There were no findings of clinical significance in the clinical laboratory evaluation, 12-lead ECG, or vital signs, except for an increase in C-reactive protein in 1 subject (part of a series of drug related AEs) and a positive test for occult blood in the faeces of 2 subjects; these subjects were on active treatment. A transient elevation in faecal calprotectin was measured in 7 subjects.
Conclusions:	The study was prematurely completed as per protocol after 2 of the originally planned 4 dose groups because of higher than expected drug exposure. Linear pharmacokinetics with a nearly dose-proportional increase in plasma exposure but a trend toward over proportionality were observed for the 2 doses tested (1 and 6 mg BI 1015550). Steady state was reached by Day 9, with slight accumulation after multiple twice daily administration. Inhibition of TNF-α release, an exploratory target engagement biomarker, was observed for the 6 mg dose group. Multiple oral doses of BI 1015550 1 and 6 mg twice daily were safe and well tolerated.