Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2010-023462-52	
Name of active ingredient: BI 137882		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 10 APR 2014	**Trial No. / U No.:** 1306.1 / U13-1329-01	**Dates of trial:** 04 MAY 2011 – 16 AUG 2011	**Date of revision:** Not applicable

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Title of trial:	Safety, tolerability and pharmacokinetics of single rising oral doses of BI 137882 in healthy male volunteers (A randomised, single-blind, placebo-controlled Phase I study) This trial was prematurely discontinued.
Principal Investigator:	[redacted]
Trial site:	Boehringer Ingelheim Pharma GmbH & Co. KG Human Pharmacology Centre Binger Strasse 173 Ingelheim, Germany
Publication (reference):	Data of this trial have not been published.
Clinical phase:	I
Objectives:	The primary objective was to investigate the safety and tolerability of BI 137882 after oral administration of single rising doses in healthy male volunteers. The secondary objective was to explore the pharmacokinetics (including dose proportionality) and pharmacodynamics of BI 137882.
Methodology:	This single-rising-dose trial was randomised, placebo-controlled, and single-blind within dose groups. Nine dose groups of BI 137882 or placebo were planned to be administered consecutively in ascending order of dose to healthy male volunteers in a 3:1 ratio. However, a fatal adverse event which was not related to the trial medication was reported in 1 subject in dose group 5; therefore, the trial was put on hold and then prematurely discontinued.

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No. of subjects:	
planned:	To be entered: 72
actual:	Entered: 40 Total BI 137882 (Dose groups 1 to 5): Entered: 30 treated: 30 analysed (for primary endpoint): 30 Dose group 1: BI 137882 0.01 mg: Entered: 6 treated: 5 analysed (for primary endpoint): 5 Dose group 2: BI 137882 0.03 mg: Entered: 6 treated: 6 analysed (for primary endpoint): 6 Dose group 3: BI 137882 0.1 mg: Entered: 6 treated: 6 analysed (for primary endpoint): 6 Dose group 4: BI 137882 0.25 mg: Entered: 6 treated: 6 analysed (for primary endpoint): 6 BI 137882 0.5 mg: Entered: 0 treated: 1 analysed (for primary endpoint): 1 Dose group 5: BI 137882 0.6 mg: Entered: 6 treated: 6 analysed (for primary endpoint): 6 Total Placebo (Dose groups 1 to 5): Entered: 10 treated: 10 analysed (for primary endpoint): 10
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age 21 to 50 years with body mass index 18.5 to 29.9 kg/m^2 were eligible for this trial.
Test product:	BI 137882 as powder for oral solution (reconstituted in 0.7% sodium dodecyl sulphate)
dose:	Nine dose groups were planned (0.01, 0.03, 0.1, 0.25, 0.6, 1.25, 2.5, 5, 10 mg). The first 5 dose groups were administered (0.01, 0.03, 0.1, 0.25, and 0.6 mg). In addition, 1 subject in dose group 1 inadvertently received 0.5 mg BI 137882.
mode of admin.:	Oral
batch no.:	B111000139

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Reference product:	Placebo solution (0.7% sodium dodecyl sulphate aqueous)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B111000140
Duration of treatment:	One day (single dose)
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy was not evaluated in this trial. *Pharmacokinetics* The following pharmacokinetic (PK) parameters were determined for BI 137882: C_{max}, t_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, λ_z, $t_{½}$, MRT_{po}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, and $CL_{R,t1-t2}$. *Biomarkers and pharmacodynamics* Concentrations of the following biomarkers were determined in whole blood stimulated *ex vivo*: • tumour necrosis factor-α (TNF-α) induced by lipopolysaccharide (LPS) and • leukotriene B4 (LTB4) induced by N-formyl-methionine-leucine-phenylalanine (fMLP). The ability of BI 137882 to inhibit production of the above biomarkers was evaluated by determining the pharmacodynamic (PD) parameters AUEC, E_{max}, and E_{min} for each biomarker.
Safety:	Safety and tolerability were evaluated based on adverse events, clinical laboratory tests, vital signs (blood pressure and pulse rate, body temperature, respiratory rate, and orthostasis test), 12-lead electrocardiogram (ECG), physical examination, and assessment of tolerability by the investigator.

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Statistical methods:

Safety parameters were analysed using descriptive statistics and frequency tabulations.

PK and PD parameters were analysed using descriptive statistics.

Dose proportionality was explored using a regression model. The slope β and its 95% confidence interval were calculated.

ECG endpoints were analysed using descriptive statistics and an analysis of covariance (ANCOVA).

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Subject demographics and disposition

Forty healthy male volunteers were entered and treated in this trial. The mean (range) age, height, weight, and body mass index were 36.8 (23 to 49) years, 180.7 (168 to 195) cm, 83.3 (66 to 105) kg, and 25.6 (20.8 to 29.7) kg/m^2.

Two important protocol violations were reported. One subject in dose group 1 inadvertently received 50 mL placebo solution instead of 1 mL placebo solution and one subject in dose group 1 inadvertently received 0.5 mg BI 137882 instead of 0.01 mg BI 137882; data from the latter subject were analysed in a separate dose group according to the actual dose received instead of the planned dose.

Thirty-nine subjects completed the trial as planned. One subject in dose group 5 did not complete the trial due to a fatal non-drug-related adverse event which occurred 8 days after dosing with BI 137882.

Pharmacokinetics

Plasma concentrations of BI 137882 were almost all undetectable in the 0.01 and 0.03 mg dose groups; therefore, the PK analysis focussed on the 0.1 to 0.6 mg dose groups. The results indicated rapid absorption of BI 137882. The increase in exposure was approximately proportional to dose in the dose range 0.25 to 0.6 mg. The terminal half-life of BI 137882 was relatively long, 34 and 37 h at the 0.25 and 0.6 mg doses, respectively. The half-life was lower at the 0.1 mg dose, likely due to undetectable concentrations in much of the terminal phase.

Urinary PK analysis (0 to 48 h) showed no renal excretion of BI 137882.

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Efficacy / clinical pharmacology results (continued):	Two oxidative metabolites of BI 137882 were found. Plasma concentrations of these metabolites in humans are likely to be much lower than their concentrations in rat plasma at the no adverse effect level (NOAEL) dose. Pharmacokinetic parameters calculated for one subject, who suffered a fatal adverse event, showed that the exposure of BI 137882 in this subject was close to the mean exposure for the dose group. *Pharmacodynamics* The percent inhibition data of LPS-induced TNF-α release and fMLP-induced LTB4 production showed very high intersubject variability at each collection timepoint. There was no demonstrated effect of BI 137882 on LPS-induced TNF-α release of fMLP-induced LTB4 production.
Safety results:	Thirty subjects received single doses of 0.01 to 0.6 mg BI 137882 oral solution and 10 subjects received single doses of matching placebo. Adverse events were reported in 28 subjects during the trial. During the on-treatment period (120 h), adverse events were reported in 18/30 subjects (60.0%) treated with BI 137882 and 7/10 subjects (70.0%) treated with placebo. The numbers of subjects with adverse events in the 0.01, 0.03, 0.1, 0.25, 0.5, and 0.6 mg dose groups were 1/5, 5/6, 5/6, 5/6, 1/1, and 1/6, respectively. The most frequently reported adverse events were oropharyngeal pain (50.0% of subjects treated with BI 137882 vs 40.0% with placebo) and headache (26.7% vs 30.0%). Adverse events which the investigator considered related to the trial medication were reported in 24 subjects during the trial. In the on-treatment period, drug-related adverse events were reported in 17/30 subjects (56.7%) treated with BI 137882 and 6/10 subjects (60.0%) treated with placebo. The most frequently reported drug-related adverse events were oropharyngeal pain (46.7% vs 40.0%) and headache (23.3% vs 10.0%). Most adverse events were mild in intensity (22 subjects overall). The most frequently reported mild adverse events were oropharyngeal pain (50.0% vs 40.0% with placebo) and headache (20.0% vs 30.0%). Adverse events of moderate intensity were reported in 5 subjects in this trial, most frequently headache (6.7% vs 0%).

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Safety results (continued):	An adverse event which was both severe in intensity and serious (fatal) was reported in 1 subject, a male who had never smoked. The medical examiner and the sponsor did not consider this fatal adverse event related to administration of the trial medication. No clinically relevant findings of clinical laboratory parameters, vital signs, or ECG parameters were reported.
Conclusions:	After administration of single doses of 0.01 to 0.6 mg BI 137882 oral solution to healthy male volunteers, the frequency of subjects with adverse events (60.0%) was similar to placebo (70.0%). Most adverse events were mild in intensity. The most frequently reported adverse event, oropharyngeal pain, was considered related to the pharmaceutical vehicle. Sudden death due to natural causes (myocarditis with an additional finding of Hashimoto's thyroiditis) was reported in one subject 8 days after he had received a single dose of 0.6 mg BI 137882. Exposure of BI 137882 in this subject was close to the mean exposure for that dose group. Pharmacokinetic analysis indicated that BI 137882 was rapidly absorbed after oral administration and eliminated with a half-life of approximately 36 h by a route that did not include renal excretion of unchanged drug. Exposure was approximately dose-proportional in the dose range 0.25 to 0.6 mg. Two oxidative metabolites of BI 137882 were found. Plasma concentrations of these metabolites in humans are likely to be much lower than their concentrations in rat plasma at the NOAEL dose, so that these metabolites would not be disproportionate human metabolites. BI 137882 had no effect on LPS-induced TNF-α release or fMLP-induced LTB4 production. After the fatal serious adverse event, the trial was put on hold and then prematurely discontinued.

Trial Synopsis - Appendix

The appended table on the following pages supplement the trial results presented in the Trial Synopsis. They complement the results for secondary endpoints of the trial.

Results for	presented in
Comparison of PK parameters by treatment	Table 15.6.3: 1

Table 15.6.3: 1 Comparison of pharmacokinetic parameters of BI 137882 in plasma after single oral administration of BI 137882 powder for solution by treatment

	0.01 mg BI 137882 powder for solution				0.03 mg BI 137882 powder for solution				0.1 mg BI 137882 powder for solution			
	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]
$AUC_{0-\infty,norm}$ [nmol*h/L/mg]	---	---	---	---	---	---	---	---	---	---	6	364	19.6	370	20.1
$AUC_{0-tz,norm}$ [nmol*h/L/mg]	---	---	---	---	---	---	---	---	---	---	6	146	35.9	154	34.7
$C_{max,norm}$ [nmol/L/mg]	---	---	---	---	---	---	---	---	---	---	6	13.7	20.0	13.9	21.1

--- no descriptive statistics calculated

Source data: Section 15.6, Table 2.1: 1, 2.1: 2, 2.1: 3, 2.1: 4, 2.1: 5, 2.1: 6

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Table 15.6.3: 1 Comparison of pharmacokinetic parameters of BI 137882 in plasma after single oral administration of BI 137882 powder for solution by treatment

	0.25 mg BI 137882 powder for solution				0.5 mg BI 137882 powder for solution				0.6 mg BI 137882 powder for solution			
	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]	N	gMean	gCV [%]	Mean	CV [%]
$AUC_{0-\infty,norm}$ [nmol*h/L/mg]	6	613	27.3	631	25.7	---	---	---	---	---	6	654	25.2	671	24.5
$AUC_{0-tz,norm}$ [nmol*h/L/mg]	6	445	27.5	459	26.1	---	---	---	---	---	6	580	24.9	595	24.4
$C_{max,norm}$ [nmol/L/mg]	6	19.1	25.6	19.7	28.1	---	---	---	---	---	6	18.7	21.7	19.1	20.3

--- no descriptive statistics calculated

Source data: Section 15.6, Table 2.1: 1, 2.1: 2, 2.1: 3, 2.1: 4, 2.1: 5, 2.1: 6

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