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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2009-017127-26	
Name of active ingredient: BI 653048 BS H_3PO_4		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 02 DEC 2013	**Trial No. / U No.:** 1262.9 / U13-2566-01	**Date of trial:** 19 MAR 2010 – 12 MAY 2010	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability, pharmacodynamics and pharmacokinetics of a BI 653048 BS H_3PO_4 capsule formulation administered as multiple doses of 25 mg to 200 mg once daily (qd) for 3 days assessing pharmacodynamics as endotoxin-induced inflammatory response of a single intravenous bolus administration of 2 ng/kg body weight lipopolysaccharide (LPS). A randomised, double-blind within dose groups, placebo-controlled, multiple rising dose phase I trial with open-label active comparator in healthy male subjects
Principal Investigator:	[redacted]
Trial sites:	[redacted] Germany
Publication (reference):	Data of this study has not been published.
Clinical phase:	I
Objectives:	The general aim of the current study was to investigate the safety and tolerability, and pharmacodynamics (endotoxin-induced inflammatory response of a single intravenous bolus administration of 2 ng/kg body weight Escherichia. coli LPS) of BI 653048 BS H_3PO_4 capsules in healthy male subjects following oral administration of multiple rising doses of 25 mg to 200 mg over three days compared to the active comparator prednisolone and placebo. Pharmacodynamics were assessed by investigating the influence of LPS administration on inflammatory parameters. More specifically, it was evaluated whether and to what extent the symptoms induced by LPS challenge can be attenuated by ascending BI 653048 BS H_3PO_4 doses using prednisolone as positive control and placebo as negative control. A secondary objective was the exploration of pharmacokinetics of BI 653048 BS, the investigation of other pharmacodynamic parameters (biomarker) and of the tolerability of LPS.

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Methodology:	Single centre, randomised, double-blind and placebo controlled (within dose groups) multiple rising dose trial with an open-label active comparator.
No. of subjects:	
planned:	entered: 56 subjects
actual:	entered: 56 subjects Treatment A: 25 mg BI 653048 BS q.d. treated: 8 analysed (for primary endpoint): 8 Treatment B: 50 mg BI 653048 BS q.d. treated: 8 analysed (for primary endpoint): 8 Treatment C: 100 mg BI 653048 BS q.d. treated: 8 analysed (for primary endpoint): 8 Treatment D: 200 mg BI 653048 BS q.d. treated: 8 analysed (for primary endpoint): 8 Treatment E: 10 mg prednisolone q.d. treated: 8 analysed (for primary endpoint): 8 Treatment F: 20 mg prednisolone q.d. treated: 8 analysed (for primary endpoint): 8[#] Treatment: Placebo treated: 8 analysed (for primary endpoint): 8 # The clinical endpoints for LPS responsive biomarkers were not calculated for one subject treated with 20 mg prednisolone because the subject did not perform the LPS challenge due to safety reasons.
Diagnosis and main criteria for inclusion:	Healthy male subjects, age ≥18 and ≤50 years, body mass index range: ≥18.5 and ≤29.9 kg/m^2

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Test product:	BI 653048 BS H_3PO_4, 25 mg and 75 mg capsules
dose:	25 mg, 50 mg, 100 mg, 200 mg q.d.
mode of admin.:	oral
batch no.:	B093000595 (25 mg), B093000596 (75 mg) labelled: PR09/10692
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B093000543 (matching to 25 mg), B093000544 (matching to 75 mg) labelled: PR09/10692
Reference therapy:	Prednisolone (Decortin H®), 10 and 20 mg tablets
dose:	10 mg, 20 mg qd
mode of admin.:	oral
batch no.:	7553001 (10 mg), 7555821 (20 mg) (labelled: PR09/10692)
Other test product	*Escherichia coli* LPS
dose:	2 ng/kg body weight, concentration 200 ng/mL
mode of admin.:	Intravenous bolus injection
batch no.:	Lot 3 labelled: PR09/10692
Duration of treatment:	3 days once daily dosing at each dose level

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Criteria for evaluation:

Efficacy / clinical pharmacology:	Not applicable
Pharmacokinetics:	Secondary endpoints: C_{max}, t_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2,}$ MRT_{po} $C_{max,ss}$, $t_{max,ss}$, $AUC_{0-tz,ss}$, $AUC_{0-\infty,ss}$, $\%AUC_{tz-\infty,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, $CL/F_{,ss}$, $Vz/F_{,ss}$
Pharmacodynamics:	Primary endpoints: E_{max} and AUEC of tumour necrosis factor α (TNF α) and interleukine-6 (IL-6) Secondary endpoints: E_{min}, AUEC and E_t of cortisol, osteocalcin, and c-reactive protein (CRP)
Safety:	Physical examination, vital signs (blood pressure, pulse rate, and body temperature), 12-lead electrocardiogram, laboratory tests (haematology, clinical chemistry, and urinalysis), adverse events, and assessment of tolerability by the investigator
Statistical methods:	Descriptive statistics for safety, pharmacokinetic, and pharmacodynamic endpoints were calculated.

SUMMARY – CONCLUSIONS:

Pharmacokinetic results:	Pharmacokinetic data from this study show that after 3 days of dosing, BI 653048 was absorbed rapidly, with mean t_{max} values of 2.0-2.1 hours. After absorption, the geometric mean elimination half-life was 11-14 hours. The pharmacokinetic profile after multiple dosing was very similar to the pharmacokinetics after single dosing, and similar to those observed after multiple oral doses of BI 653048 in study 1262.2. However, overall exposure was somewhat lower after three days of dosing in this study compared to 10 days of dosing in study 1262.2. This could be due to the fact that BI 653048 pharmacokinetics are not at steady state after only three days of dosing.

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Pharmacodynamic results:

After LPS challenge, both the TNFα and IL-6 plasma concentrations showed a lower increase in the subjects treated with either BI 653048 or prednisolone compared to placebo (except for TNFα after the 25 mg qd dose of BI 653048). There was a stronger effect on IL-6 concentrations than TNFα concentrations, but the pattern of inhibition of biomarker production by the treatments in the study was the same for each biomarker. There were only minimal changes in the biomarker concentrations for the 25 mg qd dose of BI 653048 H_3PO_4. The 50 mg qd and 100 mg qd doses of BI 653048 H_3PO_4 and the 10 mg prednisolone dose showed approximately a 40% decrease of TNFα concentrations and 60% decrease of IL-6 concentrations from concentrations after placebo dosing. There were decreases of approximately 60% of the TNFα concentrations and 75% of the IL-6 concentrations from placebo for the 200 mg qd BI 653048 H_3PO_4 dose and the 20 mg prednisolone dose.

For the exploratory biomarkers, inhibition of osteocalcin and cortisol production generally increases with increasing dose for both BI 653048 and prednisolone (except for the 100 mg qd dose of BI 653048). For both osteocalcin and cortisol, the greatest effect was seen with 20 mg prednisolone qd. For osteocalcin, the response following 200 mg qd dosing of BI 653048 was between the response for 10 mg qd prednisolone and 20 mg qd prednisolone. For cortisol, dosing with 200 mg BI 653048 qd gave a response essentially equivalent to 10 mg prednisolone qd.

Twenty-one hours after LPS challenge, c-reactive protein serum concentrations following each treatment are noticeably lower than after placebo dosing. The largest decrease was after either 10 mg or 20 mg prednisolone dosing. The c-reactive protein serum concentration was somewhat higher after BI 653048 dosing, and did not appear to be dose related.

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Safety results:

No serious, pre-specified significant or other significant adverse events (according to the definitions of the ICH E3 guideline) occurred and none of the subjects discontinued the trial due to an adverse event.

No adverse events were reported prior to drug administration.

After drug administration, 6 of the 56 treated subjects reported adverse events prior to LPS challenge and 51 of the 55 treated and challenged subjects reported adverse events after LPS challenge. All events were of mild or moderate intensity. Two episodes of mild headache reported by two subjects of the 100 mg BI 6503048 BS H_3PO_4 dose group prior to LPS challenge were assessed as drug-related. After LPS challenge, most of the subjects reported adverse events considered to be related to LPS challenge (headache, back pain, chills, tachycardia, myalgia, feeling cold, and pyrexia). None of these adverse events was assessed as drug-related. The number of subjects reporting any adverse event after LPS challenge was similar for all treatment groups, ranging between 6 subjects in the 100 mg and 8 subjects in the 25 mg, 50 mg and 200 mg BI 653048 BS H_3PO_4 groups and 7 subjects in the placebo and prednisolone groups.

No adverse events were reported 93 hours after LPS challenge.

Forty-four subjects received concomitant medications for the treatment of adverse events. All adverse events had resolved by the end of the trial.

None of the subjects had an adverse event associated with safety laboratory.

Tachycardia was reported for 15 subjects, for 1 subject after administration of prednisolone and prior to LPS challenge and for 14 subjects after LPS challenge (1 subject after administration of placebo, 11 subjects after administration of BI 653048 BS H_3PO_4 and 2 subjects after administration of prednisolone).

Pyrexia was reported for 5 subjects after LPS challenge, one subject in the placebo group, one subject in the 20 mg prednisolone group and one subject each in the 25 mg, 50 mg and 100 mg BI 653048 BS H_3PO_4 group.

The global tolerability was rated as good for 14 subjects (25.0%) and as satisfactory for 42 subjects (75%).

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Conclusions:

Overall, following LPS challenge, with respect to anti-inflammatory biomarkers, the 50 or 100 mg qd dose of BI 653048 H_3PO_4 is about as potent as 10 mg qd prednisolone, and the 200 mg qd BI 653048 H_3PO_4 is about as potent as the 20 mg qd prednisolone dose.

For the exploratory biomarkers, the inhibition of both osteocalcin and cortisol production was greatest for 20 mg qd prednisolone. The effect on osteocalcin of 200 mg qd BI 653048 was somewhat lower than 20 mg qd prednisolone, but higher than 10 mg qd prednisolone. The effect on cortisol of 200 mg qd BI 653048 was about the same as 10 mg qd prednisolone.

The strongest inhibition of c-reactive protein production was with either 10 mg qd or 20 mg qd prednisolone. Responses following all BI 653048 treatments were somewhat weaker, and did not appear to be dose-related.

No relevant safety issues were identified in this trial with LPS administration.