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
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Name of active ingredient: BI 653048 BS H_3PO_4		**Page:** 1 of 8	**Synopsis No.:**
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Report date: 16 MAY 2012	**Trial No. / U No.:** 1262.2 / U12-1218-01	**Dates of trial:** 13 OCT 2009 – 16 MAR 2010	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability, pharmacokinetics and pharmacodynamics (biomarkers) of BI 653048 BS H_3PO_4 capsule formulation administered as multiple doses of 25 mg to 200 mg qd for 10 days. A randomised, double-blind within dose groups, placebo-controlled, multiple rising dose trial with open-label active comparator
Principal Investigator:	[redacted]
Trial site:	[redacted] Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	The objectives of the trial were to assess safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple rising doses of BI 653048 BS H3PO4 (called BI 653048 for short in this clinical trial report) compared with prednisolone.
Methodology:	This randomised, multiple rising dose trial was placebo-controlled and double-blinded within each dose group of the test product. Test product, placebo, or open-label active comparator was given once daily to healthy male subjects for ten days in a single centre.
No. of subjects:	
planned:	entered: 140 total
actual:	entered: 140 total; treated: 139 total 25 mg, 50 mg, and 100 mg BI 653048: entered, treated and analysed (for safety): 25 subjects per dose group (20 on active drug, 5 on placebo) 200 mg BI 653048: entered: 25 subjects, treated and analysed (for safety): 24 subjects (19 on active drug, 5 on placebo) 10 mg and 20 mg prednisolone: entered, treated and analysed (for safety): 20 subjects per dose group (20 on active drug)
Diagnosis and main criteria for inclusion:	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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Test product:	BI 653048, 25 mg and 75 mg capsules
dose:	25, 50, 100, and 200 mg once daily
mode of admin.:	Oral
batch no.:	B093000595 (25 mg capsules) B093000596 (75 mg capsules)
Reference therapy 1:	Placebo, matching the BI 653048 capsules
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B093000543 (placebo matching the 25 mg capsules) B093000544 (placebo matching the 75 mg capsules)
Reference therapy 2:	Prednisolone, 10 mg and 20 mg tablets (Decortin H®)
dose:	10 and 20 mg once daily
mode of admin.:	Oral
batch no.:	75530 01 (10 mg tablets) 75558 21 (20 mg tablets)
Duration of treatment:	Ten days
Criteria for evaluation:	
Clinical pharmacology:	The following pharmacokinetic and pharmacodynamic parameters were analysed as secondary endpoints: Pharmacokinetics The following pharmacokinetic parameters of BI 653048 and prednisolone were determined: C_{max}, t_{max}, AUC_{0-tz}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, Ae_{t1-t2}, CL_R, $C_{max,ss}$, $t_{max,ss}$, $AUC_{0-tz,ss}$, $AUC_{0-\infty,ss}$, $\%AUC_{tz-\infty,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{po,ss}$, CL/F_{ss}, V_z/F_{ss}, $C_{min,ss}$, $C_{max,ss,norm}$, $AUC_{0-\infty,ss,norm}$, ,$Ae_{t1-t2,ss}$, $CL_{R,ss}$, $RA_{AUC\tau}$, RA_{Cmax}, and LI.

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Clinical pharmacology (continued):	Pharmacodynamics/biomarkers • The following parameters were determined for cortisol and osteocalcin in serum: $AUEC_N$, $E_{min,N}$, $AUEC_{below\_base}$, and $E_{pre,N}$. • Concentrations of glucose and insulin in the fasted state were used for the homeostasis model assessment (HOMA). • Concentrations of glucose, insulin and C-peptide obtained during an oral glucose tolerance test were used to calculate the oral glucose insulin sensitivity (OGIS). • Concentrations of adrenocorticotropic hormone (ACTH), aldosterone, dehydroepiandrosterone (DHEAS), parathyroid hormone (PTH), lipids, amino-terminal propeptide of type I collagen (P1NP), carboxy terminal propeptide of type I collagen (P1CP), amino terminal telopeptide of type I collagen (NTX) and white blood cells (WBCs) with differentials were to be measured. • Expression of the glucocorticoid responsive genes *FKBP5*, *IL1R2*, *ZBTB*, *SDPR*, *ITGB3*, and *DDIT4* was analysed.
Safety:	Safety and tolerability were the primary objective of this trial and were determined based on physical examination, vital signs (blood pressure, pulse rate, body temperature, orthostatic test), 12-lead electrocardiogram, clinical laboratory assessments (clinical chemistry, haematology and urinalysis), monitoring of adverse events, and assessment of overall tolerability.
Statistical methods:	Descriptive statistics for safety, pharmacokinetic and pharmacodynamic endpoints were calculated. Dose proportionality of BI 653048 was explored using a linear regression model on log-transformed scale. A 95% confidence interval for the slope was computed. For the attainment of steady state, the trough concentrations of BI 653048 were analysed per dose level by a repeated measures linear model on the logarithmic scale with 'time' as repeated effect. Subsequently, pair-wise comparisons of the differences between all time points were performed using t-tests. 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 'subject' and 'order' as fixed effects. Subsequently, pairwise comparisons of $AUC_{\tau,ss}$ and $AUC_{0-\infty}$ provided the linearity index including a 2-sided 95% confidence interval. The change from baseline for gene expression data was analysed by an ANCOVA including treatment and baseline as covariate.

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SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

In this trial, 140 subjects were entered, 139 subjects were treated, and 136 subjects completed the trial according to the clinical trial protocol. The trial population consisted of healthy male subjects. The mean age was 38.9 years, ranging from 21 to 50 years, and the mean BMI was 25.5 kg/m^2, ranging from 20.8 to 29.8 kg/m^2. The subjects were white, with the exception of 1 black person in the 100 mg BI 653048 group. There were no relevant differences in the demographic and baseline characteristics between the treatment groups.

Pharmacokinetics

After 10 days of once daily dosing, BI 653048 was absorbed rapidly, with a mean t_{max} of 2.5 h. The gMean elimination half-life was 10 to 12 h. The pharmacokinetic profile after multiple dosing was very similar to the pharmacokinetic profile after single dosing. Steady-state of BI 653048 was attained by Day 7, and there was only a small accumulation of 20% to 40% at steady-state. The linearity index indicated that the pharmacokinetic properties of BI 653048 were time-independent. Statistical analysis of C_{max} and $AUC_{0\text{-}tz}$ values after single and multiple dosing showed that the increase in BI 653048 exposure was less than linear for both single and multiple oral doses.

Less than 8% of the BI 653048 dose was excreted unchanged in urine in all 4 BI 653048 dose groups both after single and multiple dose administration. The fraction excreted did not appear to depend on the administered dose. Urinary excretion of unchanged BI 653048 seemed to be incomplete after 24 h, when the sampling interval ended. Renal clearance was relatively low at all dose levels.

The pharmacokinetic parameters of 10 mg and 20 mg prednisolone were very similar to the pharmacokinetic parameters obtained in a previous Boehringer Ingelheim trial with prednisolone [U07-3132-02]. This indicates that prednisolone exposure in the current study was sufficient for studying its pharmacodynamic effects and comparing them to the effects of BI 653048.

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Clinical pharmacology results (continued):

Pharmacodynamics (biomarkers)

Neither BI 653048 nor prednisolone had a large effect on the metabolic biomarkers. There was no consistent effect on insulin, and only a small decrease in glucose, which did not appear to be dose-related. C-peptide concentrations increased to a greater extent in both prednisolone dose groups as well as the 100 mg and 200 mg BI 653048 dose groups than in the placebo group. There were no consistent effects for the derived OGIS, HOMA or Index HOMA parameters, or the lipid profile.

A substantial dose-related effect of both BI 653048 and prednisolone on the concentrations of the endocrine biomarkers cortisol and DHEAS could be seen. For cortisol suppression, 200 mg BI 653048 was approximately equivalent to 10 mg prednisolone. The effect of 200 mg BI 653048 on DHEAS was about the same as that observed for 20 mg prednisolone, while the effect of 100 mg BI 653048 was lower than that seen for 10 mg prednisolone. No significant effect was seen for aldosterone and PTH.

There was also a substantial dose-related decrease in the levels of the bone biomarker osteocalcin both after BI 653048 and prednisolone administration compared with placebo. The AUEC of baseline-adjusted osteocalcin was about the same for 100 mg and 200 mg BI 653048 dose groups, indicating a maximal effect was achieved with 100 mg BI 653048. The effect was approximately equivalent to that seen for 20 mg prednisolone. However, the median baseline adjusted osteocalcin concentrations in the 2 highest BI 653048 dose groups showed a greater decrease in the 12 h to 24 h interval after drug administration than in the 20 mg prednisolone dose group, suggesting that 100 mg to 200 mg BI 653048 suppressed osteocalcin to a greater extent than 20 mg prednisolone.

With respect to the blood biomarkers, single dose and multiple dose administrations of BI 653048 and prednisolone led to a decrease in mean absolute eosinophil and lymphocyte cell counts, and to an increase in mean absolute neutrophil cell counts, compared with placebo. The effects were all dose-related. With respect to lymphocytes, the effect was greater for both prednisolone dose groups than for any of the BI 653048 dose groups. Regarding the decrease of eosinophils, 100 mg and 200 mg BI 653048 were about as potent as 10 mg prednisolone, but less potent than 20 mg prednisolone. With respect to neutrophils, 200 mg BI 653048 gave about the same effect as 20 mg prednisolone. Mean absolute monocyte cell counts were decreased after single dose and multiple dose administrations of prednisolone and to a smaller extent after single dose administration of 100 mg and 200 mg BI 653048, but not after multiple dose administration of BI 653048.

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Clinical pharmacology results (continued):	There was a dose-dependent increase in gene expression for all 6 investigated genes. This trend was observed both for BI 653048 and prednisolone. When comparing all treatment groups of all target genes, the maximum change and therefore the largest up-regulation of gene expression was usually observed in the 20 mg prednisolone group. For *DDIT4*, *FKBP5*, and *ZBTB16*, the increases in gene expression seen in the 200 mg BI 653048 group were comparable with those observed for the 20 mg prednisolone group. These results indicate that genetic biomarkers were generally influenced to a similar or slightly smaller extent by 200 mg BI 653048 than by 20 mg prednisolone.
Safety results:	The 140 entered subjects were allocated to 1 of the 6 dose groups and randomly assigned to placebo or active treatment within dose groups 1 to 4. Depending on the allocated treatment, mean exposure to trial medication in the BI 653048 dose groups varied from 0 mg to 2000 mg and in the prednisolone groups from 100 mg to 200 mg over a period of 10 days. During the treatment period of this trial, a total of 53 subjects (38.1%) reported at least 1 adverse event. The frequency of subjects with adverse events in the 100 mg and 200 mg BI 653048 groups (50.0% and 68.4%) was higher than in the 25 mg and 50 mg BI 653048 groups (40.0% and 30.0%, respectively) and the placebo group (35.0%), suggesting a possible dose-dependent increase of adverse events for BI 653048. In comparison, the occurrence of adverse events in the 10 mg and 20 mg prednisolone groups was 15% and 30%, respectively. The most frequently reported on-treatment adverse events at the SOC level were infections and infestations, followed by nervous system disorders and gastrointestinal disorders. The most frequent adverse event by preferred term was nasopharyngitis, followed by headache, dizziness, upper abdominal pain, nausea, and oropharyngeal pain. Nasopharyngitis was reported by 10 subjects each in the 100 mg and the 200 mg BI 653048 groups, but only by 3 or fewer subjects in each of the other treatment groups. This explains the relatively large number of subjects with any adverse events in the 100 mg and 200 mg BI 653048 groups. Apart from nasopharyngitis, there was no apparent clustering of specific adverse events in any treatment group.

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Safety results (continued):	All adverse events were of mild or moderate intensities. No serious adverse events and no 'other significant' adverse events leading to discontinuation of trial medication were reported during the treatment period of this trial. None of the adverse events were defined as drug-related by the investigator. Twelve subjects received some type of concomitant medication because of their adverse events and all subjects recovered from their adverse events. No clinically relevant finding in respect to laboratory parameters, ECG recordings, or vital sign measurements was reported as an adverse event. Mean WBC, neutrophil, and monocyte counts on Day 12 were elevated from baseline in a dose-related fashion. The increases were largest in the highest dose groups of BI 653048 (200 mg) and prednisolone (20 mg) compared with no changes in the placebo group and small or no changes in the lower dose groups of BI 653048 and prednisolone. No other obvious dose-related changes in any lab parameters were observed. The ECG data for the placebo group and each of BI 653048 dose groups did not reveal any consistent clinically relevant, treatment-induced reaction following dosing with BI 653048. The mean placebo-corrected increases from baseline of the mean and maximum QT, QTcF, and QTcB intervals did not exceed 6 ms when compared with the values of the placebo group. The investigator rated the global tolerability as 'good' for 138 of the 139 treated subjects. Tolerability of multiple dosing could not be assessed for the remaining subject, who had received only a single dose before discontinuing the trial.
Conclusions:	Overall, multiple daily doses of 25 mg to 200 mg BI 653048 were safe and well tolerated by the 139 healthy male subjects in this trial. None of the safety data presented a safety issue for further clinical trials. The pharmacokinetics of BI 653048 showed a moderate clearance of the compound with a plasma half-life of 10 to 12 h. Pharmacokinetic parameters were slightly less than dose proportional. Steady-state concentrations were predictable from single dose pharmacokinetic parameters, and accumulation was minimal after 10 once daily doses.

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Conclusions (continued):	In general, 200 mg BI 653048 seemed to be similar to or slightly less potent than 20 mg prednisolone with respect to most endocrine, blood, and genomic biomarkers, but somewhat less potent with respect to the bone biomarker osteocalcin. As expected for glucocorticoid treatment, dose-related increases in mean absolute neutrophil counts and dose-related decreases in mean absolute eosinophil, lymphocyte, and monocyte cell counts as well as in mean osteocalcin and cortisol concentrations were observed. Neither BI 653048 nor prednisolone had a substantial effect on the metabolic biomarkers.