Clinical Study Synopsis for Public Disclosure

This clinical study synopsis is provided in line with **Boehringer Ingelheim's *Policy on Transparency and Publication of Clinical Study Data***.

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.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Title of trial:	Safety, tolerability and pharmacokinetics of BI 653048 H3PO4 oral drinking solution in healthy male volunteers (dose range: 0.1 mg – 1500 mg). A single-blind (within dose groups), randomised, placebo-controlled within dose groups, single rising dose Phase I study
Principal Investigator:	[redacted]
Trial sites:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany
Publication (reference):	Data of this study have not been published.
Clinical phase:	I
Objectives:	• Investigation of safety and tolerability of BI 653048 H3PO4 following the administration of single rising doses of an aqueous solution in healthy male subjects (primary objective) • PK and PD characteristics of BI 653048, including the investigation of dose proportionality (secondary objectives) • Investigation of relative bioavailability of capsules versus aqueous solution (this objective was added with Amendment 1 to the protocol)
Methodology:	*Solution:* randomised, single-blind within dose groups, placebo-controlled within dose groups, single rising doses; *Capsules:* open, single-dose, uncontrolled
No. of subjects:	
planned:	entered: 80
actual:	entered: 80 (12 subjects out of 80 subjects who entered the single-rising-dose-part of the trial were re-dosed with capsules as defined in Amendment 1 to the protocol) Treatment BI 653048 H3PO4 solution: entered: 60 treated: 60 analysed (for primary endpoint): 60 Treatment BI 653048 H3PO4 capsules: entered: 12 treated: 12 analysed (for primary endpoint): 12 Treatment Placebo: entered: 20 treated: 20 analysed (for primary endpoint): 20

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 2 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Diagnosis and main criteria for inclusion:	Healthy male volunteers in the age range of ≥21 years and ≤50 years and with a body mass index (BMI) of ≥18.5 kg/m^2 and ≤29.9 kg/m^2 were included.
Test product:	• BI 653048 H3PO4 powder for preparation of an aqueous solution; solvent used for reconstitution: polyethylene glycol 400 (PEG 400), vitamin E polyethylene glycol succinate, anhydrous ethanol, and purified water • BI 653048 H3PO4 capsules of 25 mg and of 75 mg strength
dose:	• Aqueous solution (all doses refer to free base): 0.1 mg, 0.4 mg, 2 mg, 10 mg, 40 mg, 125 mg, 250 mg, 500 mg, 1000 mg, 1500 mg (appropriate aliquots of 7 different units strengths of reconstituted aqueous solution with concentrations of 0.5 mg/mL to 75 mg/mL BI 653048 H3PO4) • Capsules (all doses refer to free base): 50 mg, 150 mg (2 capsules each)
mode of admin.:	Oral
batch no.:	• Powder for preparation of an aqueous solution (12.5 mg LG01513, 50 mg LG01514, 157.0 mg LG01515, 315.3 mg LG01516, 636.3 mg LG01517, 1295 mg LG01518, 1977 mg LG01519) • Solvent: LG01520 • Capsules: 25 mg B093000216, 75 mg B093000217
Reference therapy:	Placebo to BI 653048 H3PO4 aqueous solution (solvent only, cf. test product)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	LG01521
Duration of treatment:	One day, single dose administration
Criteria for evaluation:	
Clinical pharmacology:	• Pharmacokinetic (PK) parameters of BI 653048 H3PO4 (if feasible): C_{max}, t_{max}, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{po}, CL/F, Vz/F, AUC_{0-tz}, AUC_{t1-t2}, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2,}$ dose-normalised C_{max} ($C_{max,\ Dnorm}$), and dose-normalised $AUC_{0-\infty}$ ($AUC_{0-\infty,\ Dnorm}$) • Pharmacodynamic (PD) parameters of cortisol, osteocalcin, white blood cell count (WBC), and differential cell count (if feasible for dose groups 10 mg to 1500 mg aqueous solution only): E_{min}, E_{max}, T_{min}, T_{max}, $AUEC_{below\_base}$, $AUEC_{above\_base}$ $AUEC_{t1-t2}$

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 3 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Clinical pharmacology (cont):	• Analysis of expression of glucocorticoid responsive genes (mRNA), i.e., analyses of the FKBP5, IL1R2, ZBTB, SDPR, ITGB3, and DDIT4 genes (for dose groups 10 mg to 1500 mg aqueous solution only)
Safety:	Physical examination, vital signs including blood pressure (BP), pulse rate (PR), respiratory rate (RR), and oral body temperature, 12-lead ECG, laboratory tests, adverse events (AE) and tolerability
Statistical methods:	Safety data, PK endpoints, PD biomarkers, and gene expression data were analysed by descriptive statistics. Dose proportionality of C_{max}, $AUC_{0-\infty}$, AUC_{0-tz}, and Ae_{0-24} of BI 653048 H3PO4 was explored using a regression model. A 95% confidence interval (CI) for the slope was computed. Relative bioavailability of capsules vs. aqueous solution was explored by comparison of $C_{max,\ Dnorm}$ and $AUC_{0-\infty,\ Dnorm}$. Point estimators (geometric means) of the median intra-subject ratios of $C_{max,\ Dnorm}$ and $AUC_{0-\infty,\ Dnorm}$ and their two-sided 90% CIs were calculated. The statistical model was an ANOVA on log-transformed parameters including effects for 'subject' and 'treatment'. Two-sided 90% CIs based on the t-distribution were computed. The PD parameter $AUEC_{below\_base}$ of osteocalcin was investigated by an ANCOVA with the covariates 'age' and 'baseline' and the factor 'treatment'. Moreover, osteocalcin and serum cortisol were correlated versus age, weight and BMI. Gene expression data were investigated by an ANCOVA including the covariate 'baseline' and the factor 'treatment'. Analysis of ECG endpoints was performed by an ANCOVA.

SUMMARY – CONCLUSIONS:

Clinical pharmacology results:

Pharmacokinetic results

At dose levels of 10 mg to 1500 mg, BI 653048 plasma concentrations were generally detectable and quantifiable until at least 48 h after dosing. The aqueous solution of BI 653048 H3PO4 was rapidly absorbed, plasma concentrations of BI 653048 reached a maximum at 1.5 h to 2.5 h after dosing. Elimination was characterised by more than a single phase; terminal phase time profiles were similar for the entire dose range. Oral clearance (CL/F) and volume of distribution did not differ relevantly between doses. A total of 5.5% to 9.0% of BI 653048 were excreted unchanged in urine within 48 h after dosing. The most important PK characteristics are summarised in the table below:

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 4 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Clinical pharmacology results (cont): *Pharmacokinetic results (cont).:*

Dose [mg]	$AUC_{0-\infty}$ [nmol*h/L]	$AUC_{0-\infty, Dnorm}$ [h*nmol/L/nmol]	C_{max} [nmol/L]	$C_{max, Dnorm}$ [nmol/L/nmol]	t_{max} [h]	$t_{1/2}$ [h]
	mean	mean	mean	mean	median	mean
			Aqueous solution			
10	1410	0.0726	117	0.00601	1.5	13.1
40	5130	0.0661	471	0.00607	2.5	11.1
125	13200	0.0544	1190	0.00489	1.5	12.9
250	28400	0.0586	2550	0.00525	1.5	10
500	60700	0.0626	5250	0.00541	1.5	10.7
1000	105000	0.0540	9580	0.00494	1.5	9.7
1500	173000	0.0594	17100	0.00587	1.5	8.2
			Capsules			
50	5590	0.0577	399	0.00411	2.5	12.4
150	19500	0.0671	1590	0.00547	1.5	12.2

$AUC_{0-\infty}$ (95% CI of the slope 0.9267, 1.0103) and C_{max} (95% CI of the slope 0.9928, 1.0434) increased proportional with dose in the range of 10 mg to 1500 mg BI 653048 H3PO4 aqueous solution. Comparison of relative bioavailability in subjects receiving 50 mg capsules who had previously received 40 mg solution (n=5) or 250 mg solution (n=1), and in subjects receiving 150 mg capsules who had previously received 125 mg solution (n=4) or 250 mg solution (n=2), revealed a median intra-subject ratio of 87.1% (90% CI 72.75, 104.35) for $C_{max, Dnorm}$ and of 104.2% (90% CI 92.72, 117.12) for $AUC_{0-\infty, Dnorm}$ No noticeable differences in t_{max} and terminal phase $t_{1/2}$ became apparent between the formulations.

Pharmacodynamic results:

Serum cortisol and plasma osteocalcin as well as absolute counts of lymphocytes, eosinophils, and monocytes declined quickly after dosing of BI 653048 H3PO4 in the dose range of 40 mg to 1500 mg, while WBC and neutrophils increased.

The maximum treatment-induced PD effects (E_{min}/E_{max}) occurred later than the maximum plasma concentrations of BI 653048 (medians for dose range 10 mg to 1500 mg: t_{max} 1.5 h to 2.5 h, T_{min} cortisol 12 h to 24 h, T_{min} osteocalcin 8 h to 24 h, T_{min} lymphocytes 4 h to 6 h, T_{min} eosinophils 4 h to 24 h, T_{min} monocytes 2 h to 6 h; T_{max} WBC and T_{max} neutrophils 12 h to 24 h).

Among all biomarkers assessed, cortisol demonstrated the least effect variability and largest response to BI 653048 H3PO4 in the dose range investigated.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 5 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Clinical pharmacology results (cont):	*Pharmacodynamic results (cont.):* While the maximum circadian cortisol suppression (E_{min}) did not differ largely between the 125 mg to 1500 mg doses, $AUEC_{below\_base}$ showed a clear increase with the administered dose. Cortisol remained suppressed for about 24 h after dosing in the 40 mg to 125 mg dose groups, for about 48 h in the 250 mg dose group, and for at least 72 h in the 500 mg to 1500 mg dose groups. Osteocalcin levels did not indicate a consistent dose-response relationship over the entire range of doses. Only for high doses of BI 653048 H3PO4 (500 mg to 1500 mg) osteocalcin tended to decrease in a dose-dependent manner, while $AUEC_{below\_base}$ remained rather constant for the 40 mg to 500 mg doses. The osteocalcin responses to BI 653048 H3PO4 were independent of age. WBC and differential cell counts were mainly affected by doses exceeding 250 mg showing a maximum effect at 24 h after dosing and a protracted approach to baseline up to 72 h. Analysis of the expression of glucocorticoid responsive genes revealed a trend towards a dose-dependent increase vs. baseline in placebo-corrected gene expression of the investigated genes FKBP5, IL1R2, ZBTB, SDPR, ITGB3, and DDIT4. IL1R2 was the most responsive gene showing a higher than 30-fold increase in gene expression at a dose of 1500 mg BI 653048 H3PO4. Except for IL1R2, the upregulation of all genes was reversible after 24 h. IL1R2 demonstrated an upregulation for more than 24 h after dosing of 1500 mg.
Safety results:	All 80 healthy male subjects completed the trial. The dose groups did not differ to a relevant extent in their demographic data and baseline characteristics. *Adverse events:* Overall, 23 AEs were reported by 19/80 subjects. A total of 11 AEs in 9 subjects were assessed by the investigator as related to treatment with BI 653048 H3PO4. This concerned 1 AE of hyperhidrosis (10 mg), 1 AE of asthenia (125 mg), 1 AE of viral infection (500 mg), 3 AEs of rash (500 mg), 1 AE of fluid retention (1500 mg), and 3 AEs of headache (1 AE each for 500 mg , 1500 mg, and 50 mg). Except for 1 AE of severe headache, all AEs were mild to moderate in intensity. Two subjects received comedication for their AEs. All AEs had resolved at the end of the observation period. None of them required treatment discontinuation. Serious AEs and deaths were not observed. Most of the observed AEs could theoretically be caused by the PD properties of a corticosteroid. Yet, also a causal relationship to the trial conditions (headache, which is common in healthy subjects) or unspecific reasons (viral infection, asthenia) are not unlikely. Headache was not associated with BP increases.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 6 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Safety results (cont.):	*Laboratory data:* A few subjects showed decreases in haematocrit potentially indicative of fluid retention. In agreement with PD effects expected for corticosteroids, WBC and neutrophils increased and lymphocytes decreased. Transient increases in liver/pancreatic function tests vs. normal/low baseline levels were observed in single subjects with BI 653048 H3PO4 (SGPT n = 2, GLDH n = 5, lipase n = 2) and with placebo (amylase n = 1, lipase n = 1). None of these increases exceeded 3 times upper normal limit. No subject developed treatment-induced changes in safety laboratory data resulting in the documentation of an AE. *Vital signs:* BP and PR showed some diurnal variation for BI 653048 H3PO4 and for placebo. No subject experienced clinically relevant orthostatic reactions with BI 653048 H3PO4. Vital signs did not indicate consistent, treatment or dose-related, clinically relevant untoward effects. None of the observed changes in vital signs was documented as an AE. *ECG:* No clinically relevant ECG abnormalities were detected. The baseline-adjusted, placebo-corrected means in mean changes from baseline in QTcF after dosing of BI 653048 H3PO4 did not exceed 6.53 ms in any of the assessed time periods and dose groups (ANCOVA results). The predicted QTcF changes from baseline at the geometric mean C_{max} ranged between -2.9 and +2.3 ms for all dose groups. No subject showed a baseline or post-treatment QTcF interval longer than 450 ms. Notable findings regarding the PQ or QRS intervals were not observed for subjects treated with BI 653048 H3PO4. *Global tolerability:* The investigator assessed the overall tolerability as 'good' in all subjects for all treatments.
Conclusions:	This single-rising-dose first-in-man trial in 80 healthy male subjects indicated dose proportionality based on C_{max} and $AUC_{0-\infty}$ for BI 653048 in the dose range of 10 mg to 1500 mg of an aqueous solution. The major PK characteristics did not differ relevantly between the capsule formulations and the aqueous solution. Among all biomarkers assessed, cortisol demonstrated the least effect variability and largest response to BI 653048 H3PO4 in the dose range investigated. Cortisol remained suppressed for 24 h after dosing in the dose range of 40 mg to 125 mg BI 653048 H3PO4 and until 72 h after dosing for doses higher than 500 mg. For doses lower than 500 mg, the PD effects on osteocalcin did not evidently increase with the administered dose. BI 653048 H3PO4 induced dose-dependent changes from baseline in gene expression of glucocorticoid responsive target genes as indicated by the markers FKBP5, IL1R2, ZBTB, SDPR, ITGB3, and DDIT4.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Not applicable		**EudraCT No.:** 2008-004809-34	
Name of active ingredient: BI 653048 H3PO4		**Page:** 7 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 18 MAY 2010	**Trial No. / U No.:** 1262.1 / U10-1785-01	**Date of trial:** 17 NOV 2008 – 15 JUN 2009	**Date of revision:** Not applicable

Conclusions (cont.):	BI 653048 H3PO4 was safe and well tolerated in the entire dose range. The PK, PD, and safety results of this trial support to select the dose range of 25 mg to 200 mg or even higher doses for future clinical trials.