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.:** Not applicable	
Name of active ingredient: BI 224436 CL		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 Jan 2011	**Trial No. / U No.:** 1277.1 / U11-3013-01	**Date of trial:** 03 NOV 2009 – 04 MAR 2010	**Date of revision** (if applicable)**:** Not applicable.

Title of trial:	Safety and pharmacokinetics of single rising oral doses of BI 224436 ZW at 6.2 mg, 12.5 mg, 25 mg, 50 mg, 100 mg, 200 mg, 400 mg, 600 mg, 900 mg and 1200 mg dose levels in healthy male volunteers (randomized, double-blind, placebo-controlled within dose groups) The trial (Part 1) was held after 6 dose cohorts because the predicted geometric mean for AUC_{0-24} or C_{max} for the next higher dose cohort exceeded the one-half NOAEL limits (trial holding criterion specified in the protocol). Subsequently the sponsor decided not to recommence the trial (as Part 2). Therefore, this report presents data from the first 6 planned dose cohorts only (6.2 mg, 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg).
Principal Investigator:	[redacted]
Trial sites:	[redacted]
Publication (reference):	Data of this study has not been published
Clinical phase:	I
Objectives:	To investigate safety and pharmacokinetics of BI 224436 ZW
Methodology:	Randomized, double-blind, placebo controlled within dose groups, single rising dose, single center
No. of subjects:	
planned:	entered: 80
actual:	enrolled: 105 entered: 48, thereof Treatment BI 224436 ZW 6.2, 12.5, 25, 50, 100 and 200 mg in each cohort: entered: 6 treated: 6 analyzed (for primary endpoint): 6 Treatment Placebo: entered: 12 treated: 12 analyzed (for primary endpoint): 12

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Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤50 years, BMI range ≥18.5 to ≤29.9 kg/m^2
Test product:	BI 224436 CL Powder for Oral Solution reconstituted with Tartaric acid, aqueous solution, 0.5%
dose:	6.2 mg, 12.5 mg, 25 mg, 50 mg, 100 mg and 200 mg of BI 224436 ZW
mode of admin.:	Oral
batch no.:	Powder for Oral Solution: B093000661, B093000662, B093000663 and B093000664. Tartaric acid, aqueous solution, 0.5%: B091002871.
Reference therapy:	Placebo (Tartaric acid, aqueous solution, 0.5%)
dose:	Not applicable
mode of admin.:	Oral
batch no.:	B091002871
Duration of treatment:	Single dose
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Efficacy criteria were not assessed. Primary pharmacokinetic parameters: • C_{max} (maximum measured concentration of the analyte in plasma) and • AUC_{0-24} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to 24). Secondary pharmacokinetic parameters: • $AUC_{0-\infty}$ (area under the concentration-time curve of the analyte in plasma over the time interval from 0 extrapolated to infinity), • AUC_{0-tz} (area under the concentration-time curve of the analyte in plasma over the time interval from 0 to the last measurable concentration-time point) • C_{24} (minimum observed concentration at 24 hours),

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	• $t_{1/2}$ (terminal half-life of the analyte in plasma), • t_{max} (time from dosing to maximum measured concentration of the analyte in plasma). • CL/F (apparent clearance of the analyte in plasma), • V_z/F (apparent volume of distribution during the terminal phase λ_z), • Vd (apparent volume of distribution), • MRT_{po} (mean residence time of the analyte in the body after single oral administration), • λ_z (terminal rate constant in plasma), • C_{tz} (the last measurable concentration in the concentration-time profile), • $AUC_{tz-\infty}$ (the extrapolated AUC from the time of the last measurable concentration in the concentration-time profile to ∞), • $\%AUC_{tz-\infty}$ (the percentage of the $AUC_{tz-\infty}$ that is determined by extrapolation), • Ae_{0-4} (amount of analyte that is eliminated in urine from the time point t_0 to time point t_4), • Ae_{4-8} (amount of analyte that is eliminated in urine from the time point t_4 to time point t_8), • Ae_{8-12} (amount of analyte that is eliminated in urine from the time point t_8 to time point t_{12}), • Ae_{12-24} (amount of analyte that is eliminated in urine from the time point t_{12} to time point t_{24}), • fe_{0-24} (fraction of analyte eliminated in urine from time point t_0 to time point t_{24}) and • CLR_{0-24} (renal clearance of the analyte from the time point t_0 until the time point t_{24}).
Safety:	Physical examination, vital signs (BP, PR, RR, oral body temperature), 12-lead ECG, laboratory tests and adverse events.
Statistical methods:	Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality of BI 224436 was explored using a regression model. A 95% confidence interval for the slope was computed.

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results: Plasma BI 224436 C_{max}, $AUC_{0-\infty}$, AUC_{0-24}, and AUC_{0-tz} increased in a dose proportional manner over the dose range of 6.2 to 200 mg. Variability (geometric CV%) was low and less than 33% for these pharmacokinetics parameters (gCV% range: C_{max}, 13.1 – 31.5%; $AUC_{0-\infty}$, 20.2 – 31.7%; AUC_{0-24}, 18.3 – 28.8%; and AUC_{0-tz}, 20.3 – 32.9%). BI 224436 was rapidly absorbed with T_{max} occurring quickly after oral administration with an overall median and range of 0.5 h and 0.25 – 1.5 h, respectively. Relatively high exposures (C_{max} and AUC) were achieved with each dose. The C_{max}/C_{24} ratio for each dose cohort was high and ranged from about 22 (50 mg dose cohort) to 31 (12.5 mg dose cohort). Arithmetic mean terminal elimination half-life ($t_{1/2}$) was consistent across the 6 dose groups and ranged from 6.38 h to 7.85 h (arithmetic mean 7.11 h); variability (arithmetic CV%) was low and less than 24% (range 11.5 – 23.5%). Excretion of BI 224436 in urine over the 24-h urine collection interval was low and accounted for less than 3% of the administered dose in each of the 6 dose groups (range of gMean: 1.40 – 2.60%; range of gCV%: 22.7 – 46.3%).

Safety results: Four mild AEs were observed within 72 hours of administration of BI 224436 (headache [n = 1] and upper abdominal pain [n = 1] in 25 mg dose cohort and oral paresthesia [n = 2] in 50 mg cohort) without any dose related trend. There were no SAEs recorded during the trial. No clinically relevant changes in ECG, vital signs and laboratory parameters were observed.

Conclusions: Based on the single-dose pharmacokinetic profile, the 100 mg dose provided the desirable therapeutic plasma drug concentration (geometric mean C_{24} of 496 nmol/L [range 314 – 867 nmol/L]) relative to the target therapeutic C_{min} of 500 nmol/L. No safety concerns of BI 224436 were identified and a dose-limiting toxicity could not be established. In conclusion, BI 224436 was safe and provided adequate plasma concentrations at doses up to 200 mg in this first-in-human single rising dose trial.