# 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***.

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| **Name of company:**<br>Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:**<br>Not applicable | | **EudraCT No.:**<br>2008-006789-27 | |
| **Name of active ingredient:**<br>BI 60732 | | **Page:**<br>1 of 5 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:**<br>30 JUN 2010 | **Trial No. / U No.:**<br>1267.1 / U10-2000-01 | **Dates of trial:**<br>25 FEB 2009 – 03 JULY 2009 | **Date of revision:**<br>Not applicable |



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| **Title of trial:** | Investigation of safety, tolerability, pharmacokinetics and pharmacodynamics of single rising oral doses of 0.25, 0.5, 1, 2, 4, 20, 50, 100, 150 and 200 mg BI 60732 Powder in Bottle (PIB) administered to healthy male volunteers in a randomised, double blind, placebo controlled phase I trial<br>This trial was prematurely discontinued due to the Sponsor's decision to discontinue clinical development |
| **Principal Investigator:** | [redacted] |
| **Trial site:** | Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany |
| **Publication (reference):** | Data of this study have not been published |
| **Clinical phase:** | I |
| **Objectives:** | Evaluation of safety, tolerability, pharmacokinetics and pharmacodynamic effects on coagulation parameters for oral administration of single doses of the Factor Xa inhibitor BI 60732 (First-in-Human study) |
| **Methodology:** | Randomised, placebo-controlled, double-blind, single rising dose (SRD) study |
| **No. of subjects:** | |
| **planned:** | Total entered: 80 |
| **actual:** | Total entered: 56<br>Treatment: BI 60732<br>entered: 42 treated: 42 analysed (for primary endpoint): 42<br>Treatment: placebo<br>entered: 14 treated: 14 analysed (for primary endpoint): 14 |
| **Diagnosis and main criteria for inclusion:** | Healthy male volunteers, age ≥18 to ≤45 years, BMI range: ≥18.5 and ≤29.9 kg/$m^2$ |

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| **Test product:** | BI 60732 Powder-in-Bottle (PIB) in tartaric acid solution |
| **dose:** | 0.25, 0.5, 1, 2, 4, 20, and 50 mg (100, 150 and 200 mg doses were not administered due to discontinuation of the trial) |
| **mode of admin.:** | Oral administration after an overnight fast |
| **batch no.:** | LG01523 (BI 60732); B071001886 (tartaric acid solution) |
| **Reference therapy:** | Placebo tartaric acid solution |
| **dose:** | Not applicable |
| **mode of admin.:** | Oral administration after an overnight fast |
| **batch no.:** | LG01522 (empty vials); B071001886 (tartaric acid solution) |
| **Duration of treatment:** | Single dose |
| **Criteria for evaluation:** | |
| **Safety:** | The primary endpoints for this trial were safety and tolerability. Evaluation of safety included physical examination, vital signs (BP, PR), ECG, laboratory tests including coagulation parameters and faecal occult blood testing (FOB plus®), adverse events monitoring and assessment of tolerability. |
| **Clinical pharmacology:** | Key secondary endpoints for the trial were pharmacokinetic (PK) and pharmacodynamic (PD) parameters, including PK measurements of $C_{max}$, $t_{max}$, $AUC_{0-\infty}$, $t_{1/2}$, and $\lambda_z$, and PD measurements of activated partial thromboplastin time (aPTT), prothrombin time (PT), Heptest®, Russel's Viper Venom Test and endogenous thrombin potential. |
| **Statistical methods:** | Descriptive statistics for safety and PK endpoints were calculated. Dose proportionality was explored using a regression model, and a 95% confidence interval for the slope was computed. |

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**SUMMARY – CONCLUSIONS:**

**Clinical pharmacology results:**

In this trial, BI 60732 was administered to only 7 of the planned 10 dose groups, because the sponsor decided to terminate clinical development of the drug. Thus, the highest dose administered was 50 mg. Plasma exposure to BI 60732 was lower than expected; therefore, according to the substantial Clinical Trial Protocol Amendment 3, no PK analysis was done for Dose Groups 1 and 2 and no pharmacodynamic effects were evaluated in Dose Groups 1 to 4.

After a single oral dose of BI 60732, the plasma concentrations of BI 60732 rapidly increased with a median time to maximum concentration of 2 to 3 h (for entire dose range tested) and approximately 2 h for doses between 4 and 50 mg. Plasma levels of BI 60732 then declined at a moderate rate, displaying a gMean $t_{1/2}$ of 8.8 to 12.8 h; the half-life appeared to be related to dose, with a longer $t_{1/2}$ at higher doses. For doses between 2 and 50 mg, the gMean $AUC_{0\text{-}tz}$ values were 29.1, 75.5, 371, and 1490 nmol*h /L, respectively; and the gMean $C_{max}$ concentrations were 3.56, 6.66, 29.3, and 118 nmol/L, respectively. For this dose range, an approximately proportional increase in $C_{max}$ with increasing dose was observed, and a supra-proportional increase in $AUC_{0\text{-}tz}$ with increasing dose was observed. Over the entire dose range tested, the gMean cumulative urinary excretion ($fe_{0\text{-}72}$) ranged from 9.3% to 14.7%, with no relationship between dose and renal excretion.

PK-PD analysis indicated that traditional coagulation tests such as aPTT and PT were insensitive to plasma BI 60732 concentration. In contrast, the HepTest® ratio appeared to be relatively sensitive, displaying a linear relationship to plasma BI 60732 concentration ($R^2$=0.76). The best indication of BI 60732 activity was provided by endogenous thrombin-generation related biomarkers. Inhibition of thrombin peak activity was well-correlated with plasma concentration of BI 60732, described by an $E_{max}$ model ($R^2$=0.93).

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**Safety results:**

All subjects received the assigned single dose of BI 60732 (ranging from 0.25 to 50 mg) or placebo. No deaths, other serious AEs, or other significant AEs (ICH E3 definition) were reported during the course of the study. No significant AEs were pre-specified for the study.

Overall, of 56 subjects entered in the study, 9 (16.1%) reported AEs. During screening, 3 of 56 subjects (5.4%) reported AEs. During treatment, of 14 subjects in the placebo group, 2 subjects (14.3%) reported AEs. Of the 42 actively-treated subjects, 4 (9.5%) reported AEs (moderate nasopharyngitis and moderate hypoacusis in Subject [redacted]; moderate nasopharyngitis in Subject [redacted]; mild paraesthesia and mild gastrointestinal haemorrhage in Subject [redacted]; and mild dyspepsia in Subject [redacted]). Given the pattern of bleeding, the mild gastrointestinal haemorrhage in Subject [redacted] appeared unlikely to be related to administration of study medication, and a subsequent colonoscopy indicated a non-study-related source of haemorrhage. All AEs were of mild or moderate intensity, and the investigator did not consider any AE related to treatment. Concomitant therapy was required for 3 AEs in 2 subjects (muscle tightness in Subject [redacted] during screening, and nasopharyngitis and hypoacusis in Subject [redacted] during active treatment).

There were no relevant mean changes in laboratory parameters. During screening, one subject had an abnormal laboratory result (mildly increased gamma-glutamyltransferase) that was classified as an AE. Resting 12-lead ECG analysis in Dose Groups 5 to 7 did not indicate any relevant prolongation in QTc interval, change in QTc interval, or change in R-R interval. Global tolerability was rated as 'good' for all 56 subjects participating in the study. There were no unexpected safety findings relative to the favourable preclinical assessment of safety.

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**Conclusions:**

Due to low plasma exposure to BI 60732, complete pharmacokinetic assessment was performed only for doses of 1 mg and greater (Dose Groups 3 to 7) and pharmacodynamic assessment was performed only for doses of 4 mg and greater (Dose Groups 5 to 7).

After a single oral dose of BI 60732 (PIB formulation), a median $t_{max}$ of 2 to 3 h was measured. The gMean half-life appeared to be dependent on dose, and ranged from 8.8 to 12.8 h. Over the dose range from 2 to 50 mg, an approximately proportional increase in $C_{max}$ with increasing dose was observed, and a supra-proportional increase in $AUC_{0-tz}$ was observed. Urinary excretion of BI 60732 was less than 15% of the administered dose.

Examination of the PK-PD relationship indicated that inhibition of thrombin peak activity ($E_{max}$ model, $R^2$=0.93) provided the best index of BI 60732 activity.

BI 60732 was safe and well-tolerated for single doses of 0.25 to 50 mg administered to healthy male subjects.