# 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:** Boehringer Ingelheim | | **Tabulated Trial Report** | Boehringer Ingelheim |
| **Name of finished product:** Not applicable | | **EudraCT No.:** 2008-005150-20 | |
| **Name of active ingredient:** BIBW 2992 | | **Page:** 1 of 5 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 22 OCT 2009 | **Trial No. / U No.:** 1200.35 / U09-2233-02 | **Dates of trial:** 13 JAN 2009 – 27 APR 2009 | **Date of revision** 25 APR 2012 |



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| **Title of trial:** | Relative bioavailability of a single dose of 20 mg BIBW 2992 administered as tablet (final formulation) compared to BIBW 2992 drinking solution and BIBW 2992 tablet (trial formulation II) following oral administration to healthy male volunteers (an open-label, randomised, single-dose, three-way crossover phase I study) |
| **Principal Investigator:** | [redacted] |
| **Trial site:** | Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany |
| **Publication (reference):** | Data of this trial have not been published. |
| **Clinical phase:** | I |
| **Objective:** | The primary objective of the study was to investigate the relative bioavailability and pharmacokinetics of 20 mg BIBW 2992 administered as film-coated immediate release tablet (final formulation, i.e. phase III/to-be-marketed formulation) to healthy subjects in comparison with the drinking solution and in comparison with the trial formulation II tablet, which was administered in phase II clinical trials and also partly in phase I trials. |
| **Methodology:** | The study was performed in an open-label, randomised, 3-way crossover design. In each treatment period, a single dose of 20 mg BIBW 2992 was administered. |
| **No. of subjects:** | |
| **planned:** | entered: 22 |
| **actual:** | entered: 22 |
| | 20 mg BIBW 2992 as tablet (FF):<br>treated: 21 analysed (for primary endpoints): 21 |
| | 20 mg BIBW 2992 as tablet (TFII):<br>treated: 20 analysed (for primary endpoints): 20 |
| | 20 mg BIBW 2992 as drinking solution:<br>treated: 22 analysed (for primary endpoints): 22 |
| **Diagnosis and main criteria for inclusion:** | Subjects were healthy male volunteers at the age of 21 to 55 years with a body mass index (BMI) of 18.5 to 29.9 kg/m$^2$. |

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| **Test products:** | BIBW 2992 as tablets (FF/TFII) |
| **dose:** | 20 mg |
| **mode of admin.:** | Oral administration with 240 mL water |
| **batch no.:** | FF: B071003953 / TFII: B081002939 |
| **Reference therapy:** | BIBW 2992 as drinking solution |
| **dose:** | 20 mg (as powder dissolved in 80 mL aqueous 0.2% hydroxyethyl cellulose solution) |
| **mode of admin.:** | Oral administration with 160 mL water |
| **batch no.:** | B081004461 (solvent: B071002338) |
| **Duration of treatment:** | Single-dose administration in each treatment period with pharmacokinetic blood sampling for 96 h. The 3 treatments were separated by wash-out phases of at least 3 weeks. |
| **Criteria for evaluation:** | |
| **Clinical pharmacology:** | Pharmacokinetic parameters:<br>Primary endpoints: $AUC_{0-\infty}$ and $C_{max}$<br>Secondary endpoints: $AUC_{0-tz}$, $\%AUC_{tz-\infty}$, $AUC_{0-24}$, $t_{max}$, $\lambda_z$, $t_{1/2}$, $MRT_{po}$, CL/F, $V_z$/F |
| **Safety:** | Safety was evaluated based on physical examinations, blood pressure, pulse rate, 12-lead electrocardiogram (ECG), laboratory tests, adverse events (AEs), and tolerability. |
| **Statistical methods:** | Point estimators (geometric means [gMean]) of the median intrasubject ratios of $AUC_{0-\infty}$ and $C_{max}$ and their 2-sided 90% confidence intervals (CIs) were calculated. The statistical model was an analysis of variance (ANOVA) on log-transformed parameters including effects for 'sequence', 'subjects nested within sequences', 'period', and 'treatment'.<br>For all other parameters, descriptive statistics were calculated. |

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**SUMMARY – CONCLUSIONS:**

**Clinical pharmacology results:**

Twenty-two healthy male subjects were entered in the trial. Of these, 20 subjects were administered the TFII tablet, 21 subjects were administered the FF tablet, and 22 subjects were administered the drinking solution.

The main pharmacokinetic parameters (gMean values and geometric coefficients of variation [gCV]) of the 3 formulations of BIBW 2992 are given in the following table. For $t_{max,}$ the median value and the range (min-max) are given.

| Parameter | Tablet FF | | Tablet TFII | | Drinking solution | |
|---|---|---|---|---|---|---|
| | gMean | gCV [%] | gMean | gCV [%] | gMean | gCV [%] |
| **$AUC_{0-\infty}$ [ng·h/mL]** | **103** | **65.5** | **115** | **37.6** | **114** | **37.5** |
| **$C_{max}$ [ng/mL]** | **4.14** | **65.6** | **5.02** | **38.2** | **4.93** | **31.5** |
| **$t_{max}$ [h]** | **5.00** | **2.02-12.0** | **5.00** | **2.02-6.00** | **5.00** | **0.517-10.0** |
| **$t_{1/2}$ [h]** | **28.9** | **20.9** | **30.4** | **16.0** | **27.5** | **13.3** |
| **$MRT_{po}$ [h]** | **35.9** | **17.3** | **35.9** | **15.9** | **34.2** | **12.1** |
| **CL/F [mL/min]** | **3230** | **65.5** | **2900** | **37.6** | **2920** | **37.5** |
| **$V_z$/F [L]** | **8100** | **64.4** | **7620** | **40.5** | **6960** | **34.8** |

The drinking solution showed higher gMean $AUC_{0-\infty}$ and $C_{max}$ values compared with the FF. Similarly, the TFII showed higher gMean $AUC_{0-\infty}$ and $C_{max}$ values compared with the FF. The interindividual variability was generally highest for the FF.

The statistical analysis of relative bioavailability was based on the parameters $AUC_{0-\infty}$ and $C_{max}$. When the FF and the drinking solution were compared, the adjusted gMean ratios FF/drinking solution for $AUC_{0-\infty}$ and $C_{max}$ were 92.24% (90% CI 76.30, 111.51) and 85.31% (90% CI 68.75, 105.88), respectively. Based on the arithmetic mean values, the ratios FF/drinking solution for $AUC_{0-\infty}$ and $C_{max}$ were 97.54% and 92.25%, respectively.

When the FF and the TFII were compared, the adjusted gMean ratios FF/TFII for $AUC_{0-\infty}$ and $C_{max}$ were 86.54% (90% CI 70.45, 106.31) and 80.27% (90% CI 64.71, 99.56), respectively. The arithmetic mean ratios FF/TFII for $AUC_{0-\infty}$ and $C_{max}$ were 96.75% and 88.64%, respectively.

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**Safety results:**

Of the 22 entered subjects, 20 subjects received 20 mg BIBW 2992 of each tested formulation, i.e. a total dose of 60 mg BIBW 2992 during the entire trial. One subject received 2 single doses of 20 mg BIBW 2992 (FF and drinking solution) and 1 subject received 1 single dose of 20 mg BIBW 2992 (drinking solution).

A total of 13 subjects (59.1%) experienced at least 1 AE during the study: 2 subjects (9.1%) during the screening period, 5 subjects (25.0%) during the TFII treatment, 5 subjects (23.8%) during the FF treatment, and 7 subjects (31.8%) during the treatment with the drinking solution.

AEs reported by more than 1 subject were headache (experienced by 8 subjects, 36.4%), rhinitis (3 subjects, 13.6%), arthralgia and influenza-like illness (2 subjects each, 9.1%). AEs reported by 1 subject each were nasopharyngitis, migraine, oropharyngeal pain, frequent bowel movements, and pityriasis rosea. The subject with pityriasis rosea was withdrawn from the trial for safety reasons. The event occurred about 7 weeks after administration of the drinking solution and was not considered drug-related.

In 2 subjects, headache was assessed as drug-related by the investigator: 1 subject reported headache during the TFII and FF treatments, the other subject reported headache during the treatment with the drinking solution. None of the other AEs was considered drug-related.

The severity of the AEs was assessed according to the 'Common Terminology Criteria for Adverse Events' (CTCAE). The majority of AEs were rated as CTCAE grade 1 or 2, whereas both cases of influenza-like illness were rated as grade 3. Both cases of drug-related headache were rated as CTCAE grade 1. No AEs of CTCAE grade 4 or 5 occurred in this trial.

Overall tolerability was assessed as 'good' for all exposed subjects. There were no clinically relevant findings with respect to the evaluation of laboratory parameters, vital signs, and ECG recordings.

**Conclusions:**

Single doses of 20 mg BIBW 2992 administered as final formulation tablet, trial formulation II tablet, and drinking solution to healthy male subjects were well tolerated and no differences between the 3 formulations were noted with respect to safety and tolerability.

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The adjusted gMean ratio (relative bioavailability) between final formulation and drinking solution was 85.31% (90% CI 68.75, 105.88) for $C_{max}$ and 92.24% (90% CI 76.30, 111.51) for $AUC_{0-\infty}$. Based on the arithmetic mean values, the ratios for $C_{max}$ and $AUC_{0-\infty}$ were 92.25% and 97.54%, respectively.

The adjusted gMean ratio between final formulation and trial formulation II was 80.27% (90% CI 64.71, 99.56) for $C_{max}$ and 86.54% (90% CI 70.45, 106.31) for $AUC_{0-\infty}$. Based on the arithmetic mean values, the ratios for $C_{max}$ and $AUC_{0-\infty}$ were 88.64% and 96.75%, respectively.

Due to the observed variability of the $C_{max}$ and $AUC_{0-\infty}$ values and a strong overlap of individual $C_{max}$ and $AUC_{0-\infty}$ values between the final formulation and the drinking solution as well as between the 2 tablet formulations, the differences between the gMean values and also between the arithmetic mean values for $C_{max}$ and $AUC_{0-\infty}$ are not considered clinically relevant.