# 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***.

## 2. SYNOPSIS

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| **Name of company:** Boehringer Ingelheim | | **Tabulated Study Report** | | **(For National Authority Use only)** |
| **Name of finished product:** Not applicable | | | | |
| **Name of active ingredient:** BIIF 1149 BS | | **Page:** | **Number:** | |
| **Ref. to Documentation:** | **Volume:** | **Page:** | | **Addendum No.:** |
| **Report date:** 8 June 2001 | **Number:** 1157.4 | **Study period (years):** 11/99 – 02/00 | | |

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| **Title of study:** | A single increasing dose safety, tolerability and pharmacodynamics (citric acid challenge) study after oral administration of BIIF 1149 BS (single doses as tablets: 40, 65, 100 mg) in healthy young male volunteers (randomised, double-blind within each dose group, placebo-controlled, parallel groups). |
| **Investigator:** | [redacted] |
| **Study centre:** | Human Pharmacology Centre Ingelheim, Boehringer Ingelheim Pharma KG, Germany |
| **Publication (reference):** | Data of the trial has not been published |
| **Clinical phase:** | I |
| **Objectives:** | Safety, tolerability, pharmacodynamics and pharmacokinetics |
| **Methodology:** | Randomised, double-blind (within each dose group), placebo-controlled, parallel groups |
| **No. of subjects entered:** | |
| **total:** | Twenty-four (24) |
| **each treatment:** | Eight subjects (six on BIIF 1149 BS, two on placebo) per each of the three dose levels |
| **Diagnosis and main criteria for inclusion:** | Healthy male volunteers, age 21 – 50, Broca-Index: ± 20% |
| **Test product:** | BIIF 1149 BS tablets at 5 mg and 25 mg |
| **dose:** | Single doses: 40, 65, 100 mg of BIIF 1149 BS |
| **mode of admin.:** | Oral |
| **batch no.:** | B990704 (5 mg), B990511 (25 mg) |
| **Duration of treatment:** | Two days separated by an interval of at least fifteen days |
| **Reference therapy:** | BIIF 1149 BS placebo tablets |
| **dose:** | Not applicable |
| **mode of admin.:** | Oral |
| **batch no.:** | B99805 (5 mg), B990515 (25 mg) |

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| **Name of active ingredient:** BIIF 1149 BS | | **Page:** | **Number:** | |
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**Criteria for evaluation:**

**Efficacy:** Not applicable

**Safety:** Blood pressure, pulse rate, ECG, adverse events, laboratory tests, measurement of pharmacodynamic activity by means of citric acid challenge, preliminary PK

**Statistical methods:** ANOVA, descriptive analysis

**SUMMARY - CONCLUSIONS:**

**Efficacy results:** Not applicable

**Safety results:**

The results of this study show that increasing doses of 40 mg to 100 mg BIIF 1149 BS administered did not produce any clinically relevant changes in the vital parameters, ECG and standard safety laboratory.

Eleven of the 24 treated subjects reported fifteen adverse events which were of mild to moderate intensity. Although the most frequent adverse event "tiredness" was regarded as drug-related by the investigator, there was no evidence of a drug dependent increase in frequency or intensity of adverse events. Moreover, most subjects who reported tiredness on their first treatment day did not report tiredness on their second treatment day (at least 15 days after the first dosing).

**Pharmacokinetics:**

In plasma the pharmacologically active metabolite BIIF 1148 BS is the predominant compound with a slower elimination phase compared to the parent compound BIIF 1149 BS. Plasma concentrations of both compounds increased quickly (for all doses median $t_{max}$ = 1.5 h - 2 h) after administration. The mean terminal half-life of BIIF 1148 BS and BIIF 1149 BS was estimated consistently between 65 to 70 hours and between 8 to 9 hours, respectively. Highest plasma concentrations ($C_{max}$) were observed at 430 ng/ml for BIIF 1148 BS and at 385 ng/ml for BIIF 1149 BS. Mean $C_{max}$ of BIIF 1148 BS and BIIF 1149 BS at 100 mg (tablet) dose level was 341 ng/mL and 192 ng/mL, respectively. The interindividual variability with respect to $C_{max}$, $AUC_{0-24h}$ and $AUC_{0-\infty}$ was moderate (BIIF 1148 BS: range of 13.2% - 32.4% gCV; BIIF 1149 BS: range of 26.8% - 51.6% gCV). If $AUC_{0-\infty}$ is considered, plasma concentrations of parent compound BIIF 1149 BS represented up to around 9% of those of the metabolite BIIF 1148 BS. Urinary excretion of BIIF 1149 BS and BIIF 1148 BS was up to about 0.18% and 7.8% of dose, respectively. The renal clearance ($CL_{ren.\ 0-24h}$) for both compounds is low (BIIF 1149 BS: 0.8-2.1 mL/min; BIIF 1148 BS: 5.7-7.2 mL/min).

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**Conclusions:**

It is concluded, that BIIF 1149 BS was well tolerated in all dose groups. The used method of citric acid challenge was not able to show a possible antitussive effect of BIIF 1149 BS.
Pharmacokinetic results of this second step single rising dose study (40 - 100 mg) are similar and consistent to those obtained in the first single rising dose study (0.1 - 25 mg). BIIF 1148 BS is the predominant compound in plasma reflecting an extensive first pass metabolism of BIIF 1149 BS. Urinary excretion of BIIF 1149 BS and BIIF 1148 BS is of minor relevance. The point estimates of the slope b (0.652 and 0.631, respectively) indicate that $C_{max}$ and $AUC_{0-\infty}$ of BIIF 1149 BS may increase less than proportional with the dose. The point estimates of the slope b (0.668 and 0.574, respectively) indicate that $C_{max}$ and $AUC_{0-\infty}$ of BIIF 1148 BS increase less than proportional with the dose.