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 Study Report**		
Name of finished product:				
Name of active ingredient: BIBW 2948 BS		**Page:**	**Number:**	
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Report date: 13 March 2006	**Number:** U06-1163	**Study period (dates):** 31 March 2005 to 26 July 2005		

Title of study:	A randomised, double-blind, placebo-controlled (within dose groups) study to evaluate safety, tolerability, and pharmacokinetics of single rising inhaled doses BIBW 2948 BS (0.75 to 150 mg inhalation powder, hard capsule for HandiHaler®) in healthy male volunteers.
Investigator:	[redacted]
Study center(s):	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, 55216 Ingelheim am Rhein, Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	To investigate the safety, tolerability, and pharmacokinetics of BIBW 2948 BS
Methodology:	Randomised, double-blind, and placebo controlled within dose groups, single rising dose, single centre
No. of subjects:	
planned:	entered: 96
actual:	enrolled: 96 treated: 91 (21subjects exposed to placebo and 70 subjects exposed to BIBW 2948 BS) Dose levels 0.75, 2.25, 4.5, 15, 30, 45, 60, 82.5, 105, 127.5 mg BIBW 2948 BS treated: 6 subjects per dose group; analysed (for primary endpoint): 6 Dose levels 7.5 and 150 mg BIBW 2948 BS treated: 5 subjects per dose group; analysed (for primary endpoint): 5
Diagnosis and main criteria for inclusion:	Healthy male volunteers, between ≥21 and ≤50 years of age, with a BMI between ≥18.5 and ≤30 kg/m^2
Test product:	BIBW 2948 BS inhalation powder, hard capsule for HandiHaler® in two dosage strengths, 0.75 mg and 7.5 mg.
dose:	0.75 mg, 2.25 mg, 4.5 mg, 7.5 mg, 15 mg, 30 mg, 45 mg, 60 mg, 82.5 mg, 105 mg, 127.5 mg, 150 mg
mode of admin.:	oral inhalation via the HandiHaler® device for BIBW 2948 BS
batch no.:	0.75 mg powder capsule: 0409002 7.5 mg powder capsule: 0409003

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Duration of treatment:	One day (single dose) for each treatment
Reference therapy:	Placebo inhalation powder, hard capsule for HandiHaler®
dose:	Not applicable
mode of admin.:	oral inhalation via the HandiHaler® device for BIBW 2948 BS
batch no.:	placebo powder capsule: 0409001
Criteria for evaluation:	
Efficacy:	Pharmacokinetic parameters: AUC_{0-tz}, AUC_{t1-t2}, C_{max}, t_{max}, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2;}$ If feasible: λ_Z, $t_{½}$, $AUC_{0-\infty}$, MRT_{ih}, CL/F, V_z/F
Safety:	Physical examination, vital signs (BP, PR, RR, body temperature, orthostasis test), ECG, airway resistance (R_{aw}), laboratory tests, adverse events and tolerability.
Statistical methods:	Descriptive statistics for safety and pharmacokinetic endpoints were calculated. Dose proportionality of BIBW 3056 ZW was explored using a regression model. A 95 % confidence interval for the slope was computed.
SUMMARY – CONCLUSIONS:	
Efficacy results:	Only male Caucasian subjects participated in this trial. The different dosing groups and placebo were comparable in terms of subjects' age, height, weight, and BMI. The mean age of the randomised subjects was 33.5 years, with a mean height of 181.6 cm, a mean body weight of 81.6 kg, and a mean BMI of 24.7 kg/m^2. <u>Pharmacokinetics</u> For pharmacokinetic evaluation, the plasma and urine concentrations of BIBW 3056 ZW were determined after alkaline hydrolysis of remaining BIBW 2948 BS. Thus, all of the described concentrations and pharmacokinetic parameters refer to the sum of BIBW 2948 BS and BIBW 3056 ZW. Plasma concentrations of subjects receiving placebo were below the limit of quantification (1 ng/mL). No pharmacokinetic parameters were determined for subjects receiving 0.75 mg and 2.25 mg BIBW 2948 BS as the plasma concentrations of BIBW 3056 ZW were either not detectable or close to the limit of quantification. In dose groups 4.5 to 150 mg, a t_{max} of approximately 0.2 hours indicated fast initial absorption and distribution from the lung.

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Efficacy results (cont.):	Maximum plasma concentrations ranged from 4.45 ng/mL (gMean, 4.5 mg dose) to 74.8 ng/mL (gMean 150 mg dose). Additional peaks were noted between 0-4 hours and 8-10 hours in the plasma concentration-time profiles. Plasma concentrations of the dose groups 7.5 mg to 150 mg were extrapolated to infinity. The $AUC_{0-\infty}$ increased from 43.8 ng*h/mL (gMean 7.5 mg dose) to 693 ng*h/mL (gMean 150 mg dose). The apparent volume of distribution and clearance ranged from 3240 to 6410 L and from 2970 to 5540 mL/min (gMean within dose groups). The terminal half-life ranged from 12 to 19 hours. Less than 2 % of the dose was excreted as BIBW 3056 ZW/BIBW 2948 BS in urine. $AUC_{0-\infty}$, AUC_{0-4}, and C_{max} appeared to increase in proportion with dose in subjects treated with 7.5 to 150 mg BIBW 2948 BS. Administration of the 4.5 mg dose using the 0.75 mg capsule suggests a slightly higher bioavailability.
Safety results:	Adverse events were reported in 28 subjects, 4 AEs in 2 subjects receiving placebo (2/21, 9.5%) and 33 AEs in 26 subjects receiving BIBW 2948 BS (26/70, 37.1%) at various concentrations. There were no serious adverse events and no discontinuations due to AEs. The most frequently occurring AEs (reported by more than 3 subjects) by preferred term were cough, reported in 18 patients, headache, reported in 4 patients, and dysgeusia (bitter/sour taste by lower level term), reported in 4 patients. These AEs were of short duration and subsided within minutes or hours. The majority of AEs were mild to moderate in severity and only 4 AEs were classified as severe (headache in 3 subjects and fracture of clavicle in one subject). A dose dependency was observed in subjects experiencing cough (all of mild severity), as only one cough was reported in doses up to 60 mg. Subjects receiving BIBW 2948 BS at doses of 82.5 mg and higher had to perform up to 20 actuations with the HandiHaler® in order to attain their required dose. No coughs were reported in subjects exposed to placebo. There was a higher number of AEs in subjects exposed to doses of 60 mg and above of BIBW 2948 BS. A cough constituted the majority of these reported AEs. This was not observed in subjects exposed to lower doses of the study drug. Dysgeusia (bitter or sour taste by lower level term) was reported by 4 subjects, exposed to 30 mg, 105 mg, and 150 mg. The AEs were considered mild and related to the study drug. No dose relationship could be discerned. It is possible that the bitter or sour taste may be a property of the study drug itself rather than an adverse reaction.

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Safety results (cont.):	Adverse events previously observed with orally administered EGFR inhibitors, such as diarrhoea, rash, dry skin, nausea, vomiting and pruritus were not reported. Acne, an AE frequently seen in orally administered EGFR inhibitors, was reported twice in this study; in one subject exposed to placebo and in one subject exposed to 60 mg BIBW 2948 BS. No dose relationship was observed and based on the data from this study, it is unlikely that the occurrence of acne is related to the study drug. There were no clinically relevant elevations / deviations in any of the laboratory parameters assessed. Also, no adverse effects were revealed upon evaluation of vital signs and body plethysmography. Evaluation of the ECG (cardiac axis, heart rate, PQ interval, QRS interval) did not reveal any clinically relevant changes in subjects exposed to BIBW 2948 BS or placebo. Generally a slight increase in heart rate was observed for all treatment groups and placebo from screening to baseline on day 1. No further increase of heart rate was observed during the treatment period and no drug effect was observed. Evaluation of the QT interval based on single recordings during the treatment phase did not suggest a prolongation effect. No dose effect on the QT interval was observed.
Conclusions:	Overall, safety and tolerability of BIBW 2948 BS was good and based on the data from this study there are no concerns to proceed with the multiple rising dose study.