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.

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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: 22 May 2007	**Number:** U06-2288	**Study period (dates):** 30 JAN 06 to 18 APR 06		

Title of study:	Safety, tolerability and pharmacokinetics of multiple rising inhaled doses (7.5 to 60 mg daily for 12 days) of BIBW 2948 BS inhalation powder, hard capsule for HandiHaler® in healthy male volunteers (randomised, double-blind placebo-controlled within dose groups)
Investigator:	[redacted]
Study center:	Human Pharmacology Centre, Boehringer Ingelheim Pharma GmbH & Co. KG, Germany
Publication (reference):	None
Clinical phase:	I
Objectives:	To investigate safety, tolerability, and pharmacokinetics of BIBW 2948 BS after repeated dosing
Methodology:	Randomised, double-blind and placebo-controlled within dose groups, multiple rising dose, single centre
No. of subjects:	
planned:	entered: 36
actual:	entered: 36 BIBW 2948 BS: treated: 27, analysed (for primary endpoint): 26 Placebo: treated: 9, analysed (for primary endpoint): 9
Diagnosis and main criteria for inclusion:	Healthy male volunteers, age ≥21 and ≤50 years, BMI range: ≥18.5 and ≤29.9 kg/m^2, actively smoking (<10 cigarettes or <3 cigars <3 pipes/day) for > 1 year
Test product:	BIBW 2948 BS inhalation powder, hard capsule for HandiHaler®
dose:	Repeated doses 7.5, 30 mg once daily and 30 mg twice daily
mode of admin.:	Oral inhalation via the HandiHaler® device for BIBW 2948 BS
batch no.:	BIBW 2948 BS 7.5 mg: 0508002 HandiHaler®: 4C0032
Duration of treatment:	Twelve days at each dose level/subject
Reference therapy:	Placebo inhalation powder, hard capsule for HandiHaler®

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dose:	Not applicable
mode of admin.:	Oral inhalation via the HandiHaler® device for BIBW 2948 BS
batch no.:	Placebo: 0409001
Criteria for evaluation:	
Efficacy:	Pharmacokinetic parameters: After the first dose: C_{max}, t_{max}, $AUC_{\tau,1}$, $AUC_{0-\infty}$, $\%AUC_{tz-\infty}$, λ_z, $t_{1/2}$, MRT_{ih}, CL/F, V_z/F; After the last dose: $C_{max,ss}$, $t_{max,ss}$, $C_{min,ss}$, $AUC_{\tau,ss}$, $\lambda_{z,ss}$, $t_{1/2,ss}$, $MRT_{ih,ss}$, CL/F_{ss}, $V_z/F_{ss;}$ Accumulation ratio: $R_{A,AUC}$, $R_{A,Cmax}$, and linearity index (LI); Attainment of steady state, dose proportionality of pharmacokinetics; Pharmacodynamic endpoint: induced sputum (e.g. amount of cells)
Safety:	Physical examination including ophthalmological examination, vital signs (BP, PR, orthostatic test), ECG, laboratory tests, adverse events and tolerability
Statistical methods:	Descriptive statistics for safety and PK endpoints. 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:	Because BIBW 2948 BS itself is not stable in plasma, the pharmacokinetic evaluation in plasma and urine was done for the major metabolite BIBW 3056 ZW after quantitative cleavage representing the sum of BIBW 2948 BS and BIBW 3056 ZW. Generally, BIBW 2948 BS was rapidly absorbed and initial plasma concentration peaks were observed approximately 5 minutes after inhalation. Plasma concentrations of BIBW 3056 ZW were measurable at least up to 24 hours after single dose administration of 7.5 mg qd, and at all time points sampled in the 30 mg qd and bid dose groups. After multiple inhalation of the 7.5 mg qd dose for ten days, plasma concentrations of BIBW 3056 ZW were measurable in all subjects until at least 24 hours post-dose. In dose groups 30 mg qd and bid, BIBW 3056 ZW could be measured at all time points for the ten days of treatment and even up to 72 hours after the last dose was inhaled. The shape of the plasma concentration-time profiles was comparable after single and multiple dose administration. A comparison of key pharmacokinetic parameters after multiple dose administration (steady state) of BIBW 2948 BS is shown in the table below.

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Efficacy results:

Compared with the single dose administration, the extent of exposure was higher at steady state, resulting in a low to moderate accumulation of BIBW 3056 ZW of 1.18 ($R_{A,AUC,10}$) for the 7.5 mg qd dose group, 1.29 ($R_{A,AUC,10}$) for the 30 mg qd dose group and 1.77 ($R_{A,AUC,19}$) for the 30 mg bid dose group. The linearity index was close to 1 for the 7.5 mg qd dose group and slightly above 1 for the 30 mg qd and bid dose groups.

Excretion of BIBW 3056 ZW/ BIBW 2958 BS in urine was less than 2% of the administered dose after single dose and at steady-state.

Table 1: Comparison of key pharmacokinetic parameters of BIBW 2948 BS at steady state

BIBW 3056 ZW	7.5 mg qd gMean	7.5 mg qd gCV [%]	30 mg qd gMean	30 mg qd gCV [%]	30 mg bid gMean	30 mg bid gCV [%]
$AUC_{\tau,ss}$ [ng·h/mL]	20.0	34.1	109	31.0	121	23.9
$C_{max,ss}$ [ng/mL]	3.24	31.8	17.9	27.3	20.5	25.5
$t_{max,ss}$ [1] [h]	0.250	0.0830 - 0.750	0.117	0.0670 - 0.783	0.117	0.0670 - 2.03
$t_{½,ss}$ [h]	14.5	44.0	19.6	28.7	23.8	22.2
$CL/F_{,ss}$ [mL/min]	6490	34.1	4750	31.0	4280	23.9
$V_z/F_{,ss}$ [L]	8120	41.6	8080	28.4	8820	24.4
$fe_{0-24,ss}$ [%]	1.10	33.3	1.09	87.5	1.47	82.8

[1] median and range

Steady-state was achieved on day four after multiple administration of BIBW 2948 BS. Evaluation of dose proportionality of dose groups 7.5 mg qd and 30 mg qd by the power model indicated that $AUC_{\tau,1,}$ $AUC_{\tau,ss}$ and C_{max} increased proportionally with dose and only $C_{max,ss}$ increased slightly more than proportionally with dose.

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Safety results:	During the study period, a total of 23 AEs in 18 subjects were reported, 4 AEs in four subjects receiving placebo (4/9, 44.4%) and 19 AEs in 14 subjects receiving BIBW 2948 BS (14/27, 51.9%) at the administered doses. The most frequent adverse event was headache, reported seven times by seven subjects. The majority of AEs were of mild intensity, three subjects experienced a severe AE, and six subjects experienced a moderate AE. None of the severe AEs were related to study treatment. One subject discontinued the study prematurely due to an adverse event (periodontal abscess) on day 8 of the study period. All of the subjects recovered from their adverse events and no dose dependency could be discerned. The investigator noted a possible drug relationship to the adverse event in six subjects, two subjects treated with placebo (22.2%) and four subjects treated with BIBW 2948 BS (14.8%). These were an elevation in ALT levels (two subjects, 30 mg bid), cough (two subjects, 30 mg bid and placebo), and fatigue (two subjects, 7.5 mg qd and placebo). One post-study serious adverse event (acute peri-myocarditis) was reported 36 days after the subject had completed the end-of-study examination. The subject was treated with 7.5 mg BIBW 2948 BS and completed the study as planned. Clinically relevant elevations / deviations in ALT were reported for two subjects exposed to the 30 mg bid dose. No AE due to a clinically relevant change in any laboratory parameter was reported for any of the other subjects. No adverse effects were revealed upon evaluation of vital signs. Evaluation of the QT interval, based on single recordings during the treatment period, did not suggest a QTc prolongation effect.
Conclusions:	BIBW 2948 BS was rapidly absorbed reaching initial peak plasma concentrations approximately 5 minutes after inhalation. Steady-state was reached on day four after multiple dosing of BIBW 2948 BS. Accumulation was minimal to moderate and the linearity index was close to one, indicating no change in pharmacokinetic parameters up to ten days of treatment. No dose dependency for any of the observed adverse events could be discerned. With the exception of two subjects showing a clinically relevant elevation in ALT, there were no clinically relevant elevations / deviations in laboratory parameters or vital signs. Evaluation of the ECG (cardiac axis, heart rate, QTc interval, PQ interval, QRS interval) did not reveal any clinically relevant changes in subjects exposed to BIBW 2948 BS or placebo. Overall, the safety and tolerability of BIBW 2948 BS administered for ten days in healthy male volunteers was good.