Boehringer Ingelheim

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..

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Title of trial:	A randomized, double-blind, placebo-controlled, parallel group study to evaluate the effects of a 4-week treatment of 15 and 30 mg b.i.d BIBW2948 BS (inhalation powder, hard capsule for HandiHaler®) on epithelial mucin stores and the safety and efficacy in COPD patients with symptoms associated with chronic bronchitis
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study, [redacted]
Publication (reference):	None
Clinical phase:	IIa
Objectives:	The general aim of this study was to evaluate the effects of a 4-week treatment of BIBW 2948 BS on epithelial mucin stores in patients with COPD associated with symptoms of chronic bronchitis. Additionally, the safety and tolerability of a 15 and 30 mg twice daily (b.i.d.) dose of BIBW 2948 BS via the HandiHaler® device was evaluated.
Methodology:	Randomized, double-blind, placebo-controlled, parallel group study, 4 week study
No. of subjects:	
planned:	entered: 60

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actual:	enrolled: 101 Treatment BIBW 2948 BS 30 mg b.i.d.: entered: 12 treated: 12 analysed (for primary endpoint):10 Treatment BIBW 2948 BS 15 mg b.i.d. : entered: 13 treated: 13 analysed (for primary endpoint): 6 Treatment Placebo 30 mg b.i.d.: entered: 12 treated: 12 analysed (for primary endpoint):12 Treatment Placebo 15 mg b.i.d. : entered: 11 treated: 10 analysed (for primary endpoint): 10 Primary endpoint analysis included patients with evaluable bronchoscopy samples at both baseline and end of treatment
Diagnosis and main criteria for inclusion:	Male or female (of non-child bearing potential) COPD patients with symptoms associated with chronic bronchitis having cough and sputum production on most days for 3 consecutive months for at least 2 years. Patients must be between the ages 40-70 years old, be actively smoking with a history of 10 or more pack-years. Patients must have a diagnosis of COPD post-bronchodilator forced expiratory volume in 1 second/forced vital capacity $FEV_1/FVC < 70\%$ and $FEV_1 \geq 40\%$ predicted).
Test product:	BIBW 2948 BS inhalation powder, hard capsules for HandiHaler®
dose:	15 mg b.i.d. BIBW 2948 BS (b.i.d. 2 capsules of 7.50 mg each) 30 mg b.i.d. BIBW 2948 BS (b.i.d. 4 capsules of 7.50 mg each)
mode of admin.:	Oral inhalation vial the HandiHaler®
batch no.:	B062000091, B072000103
Reference therapy:	Placebo inhalation powder, hard capsules for HandiHaler®
dose:	15 mg b.i.d. BIBW 2948 BS (b.i.d. 2 capsules of 7.50 mg each) 30 mg b.i.d. BIBW 2948 BS (b.i.d. 4 capsules of 7.50 mg each)

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mode of admin.:	Oral inhalation via the HandiHaler®
batch no.:	B062000057, B072000096
Duration of treatment:	4-weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary efficacy variable for the study was the volume of mucin per surface area of basal lamina (Vs mu,bala). Vs mu,bala was determined by stereologic quantification of periodic acid Schiff's reagent AB/PAS staining in endobronchial biopsies at Visit 2 (baseline) and at the end of the 4-week period of randomised treatment (Visit 5). Secondary endpoints (Bronchoscopic Measures): 1) Volume of mucin per volume of epithelium (Vv mu, ep) in endobronchial biopsies 2) Total and differential cell counts in bronchoalveolar lavage (BAL) 3) Mucin gene, and epidermal growth factor receptor (EGFR) gene expression (RNA) in epithelial brushings 4) EGFR Internalization Assay in epithelial brushings 5) Goblet cell size and number in endobronchial biopsies 6) Interleukin-8 (IL-8) levels in bronchoalveolar lavage 7) Myeloperoxidase (MPO) levels in bronchoalveolar lavage. Pharmacokinetic parameters were evaluated after single and multiple doses; pharmacokinetic/pharmacodynamic relationship was explored.
Safety:	Peak expiratory flow rate (PEFR), physical examination, pulse oximetry, vital signs, electrocardiogram (ECG), pulmonary function testing [FEV_1, FVC, FEV_1/FVC, FEF_{25-75}], laboratory tests, adverse events.

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Statistical methods: Primary endpoint will be analysed using analysis of covariance with terms for treatment, centre and baseline as covariate. Exploratory analyses were performed for daily diary and cough and sputum assessment questionnaire (CASA-Q) symptom score.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

The primary endpoint was the change of volume of mucin per surface area of basal lamina from baseline to week 4 of treatment. Upon evaluation, there were no clear differences across treatment groups and the variability of the change from baseline was high. Sensitivity analyses revealed that, although not statistically significant, there was the suggestion of a reduction in the mucin volume in the high dose group (BIBW 30 mg b.i.d.) compared to the pooled placebo and the lower BIBW 15 mg b.i.d. group. In addition, this same pattern of result was seen for the change from baseline volume of mucin per volume of epithelium, a secondary endpoint.

The EGFR internalization assay findings demonstrated statistical differences between the pooled placebo group and the pooled treatment groups for the change from baseline measures for all EGFR internalization parameters evaluated. Likewise, there were statistical differences between the pooled placebo and the BIBW 30 mg b.i.d groups. No differences were observed for the 15 mg b.i.d. group across all measures of EGFR internalization. When statistically tested across treatment groups, the 30 mg b.i.d. was statistically different for 3 of 5 of the EGFR internalization measures.

Statistical significance was noted in the sensitivity analyses for the change in IL-8 levels from baseline to end of treatment in the lower dose group of 15 mg b.i.d. compared to placebo. No significant differences in IL-8 were shown for the higher dose group. Additionally statistical differences were observed for the MUC5B endpoint at the 30 mg b.i.d. BIBW 2948 BS dose group as compared to 30 mg b.i.d. or pooled placebo.

There were no notable changes from baseline to end of study therapy for the

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following secondary endpoints: total and differential cell counts in bronchoalveolar lavage, log mucin gene expression levels from MUC2, MUC5AC, goblet cell size and number in endobronchial biopsies, and myeloperoxidase levels in bronchioalveolar lavage.

Further exploratory analyses were performed based on findings from the sensitivity analyses for the primary endpoint, change in mucin per surface area of basal lamina and the change from baseline volume of mucin per volume of epithelium, as well as the EGFR internalization assay findings. There were positive correlations (Pearson coefficient > 0.6) between the inhibition of the numbers of EGFR spots at the nucleus per cell with marker as a percentage change from baseline and the primary endpoint, volume of mucin per surface area of basal lamina and secondary endpoints, volume of mucin per volume of epithelium, and the MUC 5AC gene copy number.

Exploratory PK/PD correlation analyses linked exposure to BIBW 2948 BS (as assessed by AUC0-6,ss values for the major metabolite BIBW 3056 ZW) with the efficacy endpoints. Correlations were however seen in the 30 mg b.i.d. group only, and were driven by the two patients with the highest AUC0-6,ss values, suggesting that concentrations of BIBW 3056 ZW exceeding a threshold value reached only in some patients of the 30 mg b.i.d. dose group were associated with a reduction of EGFR activation and less mucin volume.

Pharmacokinetic conclusions

The shape of mean plasma concentration profiles of BIBW 3056 ZW was similar for both dose groups, and following single and multiple inhalations. Maximum plasma concentrations in both dose groups were reached approximately 15 to 50 minutes after drug inhalation. After rapid absorption there was an at least bi-exponential decline of plasma concentrations with the second phase beginning between 6 and 24 hours after inhalation. Taking into account the high variability in the 15 mg b.i.d. dose group, geometric mean terminal half-lives at steady state in both dose groups were similar (15 mg b.i.d. group: 16.7 h [gCV: 62.8%], 30 mg group: 13.8 h [gCV: 30.4%]). Systemic

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	exposure as assessed by AUC0-6(,ss), AUCτ(,ss) and Cmax(,ss) values between 15 mg and 30 mg increased by a factor of 2.2–2.7. A profound assessment of dose-dependency was not possible with only two different dose levels however, the slightly more than dose-proportional increase of systemic exposure is assumed to be related to the high variability of plasma concentrations rather than to non-linear kinetics. Accumulation of BIBW 3056 ZW in plasma upon multiple dosing of BIBW 2948 BS twice daily accounted for a factor of 1.24–1.73.
Safety results:	The overall adverse event frequencies were comparable in the BIBW 2948 BS (84.0%) and placebo (78.3%) treated groups. The most frequently occurring adverse events in this study population were respiratory system events. The majority of the observed respiratory events were balanced between BIBW 2948 BS and placebo, although a higher incidence (12.0% vs. 8.7%) of exertional dyspnoea occurred among the BIBW 28948 BS dose groups compared to placebo treated patients. The investigator determination of drug related events was slightly higher in the BIBW 2948 BS group with 28.0% of patients having an investigator defined drug related event as compared to the overall placebo group where 21.7% patients had a related adverse event. There was a significant imbalance in the frequency of serious adverse events that occurred during the treatment period in this study between the placebo and active-treated groups. There were a total of 4 patients with serious adverse events (SAEs) (8.3%), all of whom were receiving treatment with active drug. Only one of the events, increases in clinical lab enzymes, was thought to be related to study drug. There were no deaths that occurred during the study. The two patients found to have liver enzyme elevations after 4 weeks of treatment with 30 mg b.i.d. BIBW 2948 BS (patient nos. 103 and 409) after the first dose had systemic exposure to BIBW 3056 ZW well within the range of the other patients in that dose group. After multiple inhalations, they however showed the highest– although not strikingly elevated – systemic exposure (1.2- to 1.6-fold higher than the respective group median value).

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A large imbalance in adverse events leading to discontinuation of study treatment was also observed. There was 1 of 23 (4.3%) patient discontinued from the placebo group, while 6 of 25 (24%) patients in the BIBW 2948 BS groups were discontinued from treatment due to an adverse event. Patients receiving active therapy were more likely to be discontinued due to increased cough and dyspnea than those receiving placebo treatment. The majority of the discontinuations occurred in the 15 mg b.i.d. dose group where 5 of 13 (38.5%) of patients were discontinued from treatment due to an adverse event.

One patient from the BIBW 2948 BS 30 mg b.i.d. dose group experienced a pre-defined significant adverse event.

For clinical laboratory testing, three cases of reversible increases in liver enzymes were reported during this trial. Two cases were unblinded and the patients were found to be receiving active drug at a dose of 30 mg bid, and the third case was receiving 30 mg b.i.d placebo. There were no apparent differences in vital signs, physical examinations, or ECGs between active and placebo treated patients, and there were no further clinical laboratory findings in the treated patients.

There was a transient decline in FEV_1 that was observed at Visit 5 between the 15 mg and 30 mg BIBW 2948 BS and 15 and 30 mg b.i.d. placebo groups. Results of exploratory statistical analysis showed a clinically (222.2 mL FEV_1) and statistically significant (0.0094) decline in FEV_1 for the 30 mg b.i.d. dose group as compared to the 30 mg placebo dose group. Additionally there was a clinically significant (93.4 mL) but statistically non- significant (p=0.3013) decline for the 15 mg dose group as compared to placebo.

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Conclusions:

Systemic exposure to BIBW 3056 ZW in patients treated with 30 mg b.i.d. BIBW 2948 was 2.2–2.7 fold higher than for patients treated with 15 mg b.i.d., and was comparable to the exposure of healthy volunteers treated at the same dose. The *a priori* efficacy endpoints for the study were not achieved, although a clear inhibition of the EGFR internalization, and presumably EGFR tyrosine kinase activity, was observed. The effects of this inhibition on mucus production could not conclusively be established, although a slight signal was observed. BIBW 2948 BS was poorly tolerated as compared to placebo with respect to having a clinically significant effect on lung function, and the possibility exists that a link between EGFR inhibition, and thereby mucin reductions, caused a transient decrease of post bronchodilator FEV1. Furthermore BIBW 2948 BS potentially causes transient elevations in liver aminotransferases. Otherwise the compound was well tolerated, and did not exhibit the hallmark adverse events associated with oral EGFR TK inhibitors.