Boehringer Ingelheim

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**.

Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: BEA 2180 BR Inhalation Solution, Respimat® Inhaler				
Name of active ingredient: BEA 2180 BR		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 12 December 2006	**Number:** U06-3733	**Study period (dates):** 23 July 2005 - 09 May 2006		

Title of study:	A randomized, multiple-dose, double-blind, placebo- and active controlled, parallel group efficacy and safety study to determine the optimum dose of BEA 2180 BR delivered by the Respimat® inhaler in patients with Chronic Obstructive Pulmonary Disease (COPD)
Investigator:	[redacted]
Study centers:	Multicenter
Publication (reference):	N/A
Clinical phase:	IIb
Objectives:	The primary objective of this study was to determine the optimum dose of BEA 2180 BR inhalation solution delivered by the Respimat® inhaler once daily for four weeks in patients with COPD. As a secondary objective the safety and efficacy of the optimal dose was compared to placebo and tiotropium bromide 5 µg delivered by the Respimat.
Methodology:	Randomized, double-blind, placebo- and active-controlled, parallel design
No. of subjects:	
planned:	entered: 420
actual:	entered: 389 (enrolled: 656) placebo: entered: 55 treated: 55 analyzed (for primary endpoint): 53 BEA 2180 10 µg: entered: 56 treated: 56 analyzed (for primary endpoint): 55 BEA 2180 20 µg: entered: 56 treated: 56 analyzed (for primary endpoint): 55 BEA 2180 50 µg: entered: 51 treated: 51 analyzed (for primary endpoint): 51 BEA 100 µg: entered: 60 treated: 60 analyzed (for primary endpoint): 58 BEA 2180 200 µg: entered: 58 treated: 58 analyzed (for primary endpoint): 57 Tiotropium 5 µg: entered: 53 treated: 53 analyzed (for primary endpoint): 53

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Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥40 years with a diagnosis of COPD and a forced expiratory volume in one second (FEV_1) ≥30% and ≤60% predicted [European Coal and Steel and Community (ECSC) criteria] and FEV_1/forced vital capacity (FVC) ≤70% at Visit 1. Patients must have an increase in FEV_1 of at least 12% from baseline 45 minutes after 80 µg Atrovent®. At the randomization visit (Visit 2), the pre-dose FEV_1 must be within 15% of the pre-dose value at Visit 1.
Test product:	BEA 2180 BR inhalation solution
dose:	10, 20, 50, 100 and 200 µg BEA 2180 once daily
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B052000122 (5 µg): B052000134 (10 µg): B052000135 (25 µg): B052000146 (50 µg): B052000145 (100 µg)
Duration of treatment:	4 weeks
Reference therapy 1:	Placebo matching BEA 2180 inhalation solution
dose:	N/A
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B052000121
Reference therapy 2:	Tiotropium inhalation solution
dose:	5 µg once daily
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	303974
Criteria for evaluation:	
Efficacy:	FEV_1 [trough, area under the curve from 0 to 6 hours (AUC_{0-6h}), peak], FVC (trough, AUC_{0-6h}, peak), twice daily peak expiratory flow rate (PEFR), rescue medication use, COPD symptoms, Global Evaluations.
Safety:	Adverse events (AEs), vital signs, laboratory evaluations, electrocardiogram (ECG) testing and physical examinations.
Pharmacokinetic:	Plasma and urine concentrations of BEA 2180 or tiotropium

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Statistical methods: Analysis of covariance (ANCOVA) with terms for center, treatment and baseline as covariate; descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy results: In this trial the proof of concept (24 h duration of action) was shown after 4 weeks of treatment with a consistent data profile. The primary endpoint (trough FEV_1) was reached with a Δ >130 ml clinically meaningful difference with BEA 2180 100 µg and 200 µg.

Doses of BEA 2180 50 µg, 100 µg, and 200 µg were superior compared to placebo, with trough FEV_1, Δ = 121ml, 136 ml, 181 ml respectively at day 29, for tiotropium 5 µg the difference to placebo was 134 ml. FVC and diary data were consistent with FEV_1 results. The BEA 2180 200 µg group was numerically higher than tiotropium 5 µg Respimat® at trough FEV_1.

Pharmacokinetic results: Plasma concentrations increased approximately linearly with dose. Maximum plasma concentrations were generally measured 5 minutes after end of drug inhalation, and plasma concentrations declined rapidly to about one-tenth of the maximum plasma concentration within the first two hours after inhalation. After multiple dosing, trough concentrations increased within the first two weeks, while almost no accumulation was observed for Cmax. Plasma concentrations of BEA 2180 were further evaluated in a population pharmacokinetic analysis which is reported separately.

To evaluate the urinary excretion of BEA 2180, samples were collected in fixed time intervals, i.e. 0-6 h on Days 1, 8, 15, and 29. Around 3% was generally excreted unchanged in urine within the first 6 h after inhalation at steady state.

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Safety results:

The overall incidence of AEs was balanced among the active treatment groups. The placebo group had the highest incidence of AEs (47.3%). The two most common AEs overall were nasopharyngitis in 28 patients (7.2%) and COPD exacerbation in 28 patients (7.2%). Seven patients (1.8%) withdrew from the trial due to an AE and eleven patients (2.8%) had an event that was considered by the investigator to be related to study medication. Dry mouth is considered to be an anticholinergic side effect and was reported twice in the placebo group and twice in the BEA 2180 50 µg group.

Serious adverse events (SAEs) were reported in 13 patients (3.3%) and there was one death that occurred in the placebo group post-treatment. Only one SAE, COPD exacerbation, was reported by more than one patient. None of the SAEs were considered to be related to treatment by the investigator.

Evaluation of the clinical laboratory values and vital signs indicated that changes from baseline were minimal and were not dose dependent. Electrocardiogram changes during the study were balanced across treatment groups including placebo.

Conclusions:

In this trial the clinical proof of concept (24 h duration of action) was shown after 4 weeks of treatment with a consistent data profile. The primary endpoint (trough FEV_1) was reached with a Δ >130 ml clinically meaningful difference with BEA 2180 100 µg and 200 µg and with tiotropium 5 µg. The safety analyses did not raise any special concerns for BEA 2180 as compared to tiotropium or placebo. The most common adverse events reported were typical for this population and study duration. Future studies of BEA 2180 inhalation solution will identify a more complete evaluation of the safety profile