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 Trial Report | Boehringer Ingelheim |
|---|---|---|---|
| **Name of finished product:** BEA 2180 BR Inhalation Solution, Respimat® Inhaler | | **EudraCT No.:** 2007-001946-42 | **Synopsis No.:** |
| **Name of active ingredient:** BEA 2180 BR | | **Page:** 1 of 6 | |
| **Module:** | | **Volume:** {hyperlink } | |
| **Report date:** 17 DEC 2009 | **Trial No. / U No.:** 1205.14 / U09-1587-01 | **Date of trial:** 06 SEP 2007 – 05 MAY 2009 | **Date of revision:** Not applicable |



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|---|---|
| **Title of trial:** | A multinational, randomized, double-blind, placebo- and active-controlled, parallel group efficacy and safety comparison over 24 weeks of three doses (50 µg , 100 µg, 200 µg) of BEA 2180 to tiotropium 5 µg and placebo delivered by the Respimat® inhaler in patients with chronic obstructive pulmonary disease (COPD) |
| **Coordinating Investigator:** | [redacted] |
| **Trial sites:** | Multicentre study, [redacted] |
| **Publication (reference):** | Data of this study has not been published |
| **Clinical phase:** | IIb |
| **Objectives:** | The primary objective of this study was to compare the bronchodilator efficacy (standard lung function) of three doses (50 micrograms [mcg], 100 mcg and 200 mcg) of BEA 2180 inhalation solution delivered by the Respimat® inhaler once daily against placebo and tiotropium (5 mcg) for 24 weeks in patients with chronic obstructive pulmonary disease (COPD). As secondary endpoints, the effects on dyspnoea and health status after 24 weeks were characterized. A sub-study in approximately 300 patients included additional lung function measurements to characterize the onset of action and the pharmacodynamic steady state of BEA 2180 BR. |
| **Methodology:** | Randomized, double-blind, placebo- and active-controlled, parallel group design |
| **No. of subjects:** | |
| **planned:** | entered: 1950 |

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|---|---|
| **actual:** | enrolled: 2702<br>Treatment 50 mcg BEA 2180 BR:<br>entered: 419 treated: 419 analysed (for primary endpoint): 417<br>Treatment 100 mcg BEA 2180 BR:<br>entered: 415 treated: 415 analysed (for primary endpoint): 409<br>Treatment 200 mcg BEA 2180 BR:<br>entered: 390 treated: 390 analysed (for primary endpoint): 387<br>Treatment Placebo:<br>entered: 429 treated: 429 analysed (for primary endpoint): 421<br>Treatment 5 mcg tiopropium:<br>entered: 427 treated: 427 analysed (for primary endpoint): 423 |
| **Diagnosis and main criteria for inclusion:** | Outpatients of either sex, aged ≥40 years with a diagnosis of COPD and post-bronchodilator FEV1 <80% predicted (ECSC criteria) and FEV1/FVC ≤70%. |
| **Test product:** | BEA 2180 BR inhalation solution |
| **dose:** | 50 mcg (2 inhalations x 25 mcg ), 100 mcg (2 inhalations x 50 mcg ) and 200 mcg (2 inhalations x 100 mcg) BEA 2180 BR once daily |
| **mode of admin.:** | Oral inhalation via the Respimat® inhaler |
| **batch nos.:** | Cartridge: B062000697, B062000704, B06200705<br>Inhaler: B062000464-B062000709 |
| **Reference therapy:** | Placebo |
| **dose:** | Not applicable |
| **mode of admin.:** | Oral inhalation via the Respimat® inhaler |
| **batch nos.:** | Cartridge: B062000699<br>Inhaler: B062000666-B06200708 |

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|---|---|
| **Reference therapy:** | Tiotropium Bromide |
| **dose:** | 5 mcg |
| **mode of admin.:** | Oral inhalation via the Respimat® inhaler |
| **batch nos.:** | Cartridge/inhaler: 609410-6L0034; B062000707-B062000708 |
| **Duration of treatment:** | 24 weeks |
| **Criteria for evaluation:** | |
| **Efficacy / clinical pharmacology:** | FEV1 (trough, $AUC_{0-3h}$, peak), FVC (trough, $AUC_{0-3h}$, peak), twice daily PEFRs, rescue medication use, Mahler TDI, SGRQ (total score), global evaluations, COPD exacerbations. |
| **Safety:** | Adverse events, vital signs, laboratory evaluations, ECG testing and physical examinations |
| **Statistical methods:** | The statistical hypotheses for the primary endpoint of trough $FEV_1$ response were tested in a stepwise manner. First, the three doses of BEA 2180 (50 mcg, 100 mcg and 200 mcg) were tested for superiority to placebo. If the superiority of BEA 2180 over placebo was established, then the BEA 2180 doses were tested for non-inferiority to tiotropium 5 mcg. The statistical methods used included analysis of covariance with terms for center, treatment, and baseline as covariate; and descriptive statistics. |

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## SUMMARY – CONCLUSIONS:

**Efficacy / clinical pharmacology results:**

The main objective of this trial was to demonstrate the superior bronchodilator efficacy of three doses (50 mcg, 100 mcg, 200 mcg) of BEA 2180 compared to placebo with respect to $FEV_1$ trough response after 24 weeks of treatment. If superiority of BEA doses versus placebo was demonstrated for $FEV_1$ trough response then non-inferiority of BEA doses versus tiotropium would be tested.

BEA 2180 at doses of 50 mcg, 100 mcg and 200 mcg were significantly better than placebo for the primary endpoint of $FEV_1$ trough response after 24 weeks of treatment.

Only the highest dose of BEA 2180, 200 mcg, was shown to be non-inferior to tiotropium for $FEV_1$ trough response after 24 weeks of treatment.

BEA 2180 doses demonstrated clear dose separation for $FEV_1$ trough response but not for $FEV_1$ AUC response or $FEV_1$ peak response.

All active treatments, BEA 2180 and tiotropium, had significantly greater PEFR response compared to placebo. No separation of active treatment was observed.

BEA doses had earlier onset of action as compared to tiotropium with the BEA 200 mcg dose having the slowest onset of BEA doses. The median time to onset of action was lowest for BEA 100 followed by, in ascending order, BEA 50, BEA 200 and tiotropium.

In the sub-study of 276 patients evaluating the early onset of action there was an inverse dose- response relationship between BEA doses and percentage responders during the first thirty minutes after dosing. For observations at one hour or later there was a positive dose- response relationship between BEA doses and percentage responders.

All active treatments had lower rescue medication as compared to placebo with the BEA 200 mcg dose consistently having the lowest usage.

Symptom assessments, as measured by SGRQ, TDI, SF-36 and PGE were consistently improved for active treatments versus placebo but there was little separation among active treatments.

COPD exacerbation rates and time to first exacerbation are reduced in all active treatments and reaching statistical significance for BEA 50 mcg and BEA 200 mcg doses.

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**Safety results:**

Overall, the safety profile of BEA 2180 was consistent with the patient population and with the known side effect profile of the study drug.

One percent, 20 of the 2,080 patients, died on treatment or within 30 days of stopping treatment. Five patients received placebo, 13 received BEA 2180, and 2 received Tio. Two patients died post-study; both were randomized to Tio.

SAEs were consistent across all treatment groups.

Reported AEs were consistent across all treatment groups; however, among the AEs judged to be drug-related, the incidence of cough was greater with BEA 2180 and the incidence of dry mouth was greater with Tio.

The most commonly reported AE was COPD and was reported in fewer BEA-treated patients than placebo-treated patients.

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**Conclusions:**

BEA at all three doses was significantly better than placebo for the primary endpoint of FEV1 trough response after 24 weeks of treatment. Only the 200 mcg dose of BEA was non-inferior to tiotropium after 24 weeks of treatment.

For the secondary endpoint of PEFR response compared to placebo, all active treatments had significantly greater PEFR response than placebo with no separation between any of the active treatments (BEA or tiotropium). All active treatments also had lower rescue medication usage than placebo, with BEA 200 mcg dose consistently having the lowest usage. Symptom assessments including SGRQ, TDI, SF-36 and PGE were improved for all four active treatments versus placebo, with little separation among treatment groups. COPD exacerbation rates and time to first exacerbation were reduced in all active treatments, reaching statistical significance only for the BEA 50 and 200 mcg doses.

Regarding safety, the incidence of adverse events and serious adverse events was consistent across all treatment groups. The most commonly reported AE overall was COPD, which was reported in fewer BEA-treated patients than placebo-treated patients. Among AEs reported to be drug related, the most common AE in BEA was cough, and dry mouth was the most comment event reported with tiotropium.

There was a death rate of 1% reported, with the most (1.8%) reported in the BEA 200 group and the fewest (0.5%) in the tiotropium group. None of the events leading to death were considered to be related to study medication, and the causes of death were consistent with those expected in a patient population of >10 pack year smokers.

Evaluation of clinical laboratory assessments and vital signs did not indicate any negative effect on these assessments due to the active treatments in the trial. ECG changes were small, and were mostly consistent across treatment groups.

Overall, both BEA and tiotropium were effective at improving lung function and reducing the symptoms of COPD. Only the 200 mcg dose of BEA was comparable to tiotropium at improving lung function as shown by the trough FEV1 response. All active treatments were safe at the doses studied in this trial.