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 International GmbH | | Tabulated Trial Report | Boehringer Ingelheim |
|---|---|---|---|
| **Name of finished product:** Spiriva® | | **EudraCT No.:** 2006-000822-30 | |
| **Name of active ingredient:** Tiotropium bromide Inhalation Capsules | | **Page:** 1 of 4 | **Synopsis No.:** |
| **Module:** | | **Volume:** | |
| **Report date:** 10 MAR 2008 | **Trial No. / U No.:** 205.346 / U08-3233-02 | **Date of trial:** 04 OCT 2006 – 08 OCT 2007 | **Date of revision :** 02 SEP 2008 |



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| **Title of trial:** | A randomized, double-blind, double-dummy, parallel group trial comparing 12 weeks treatment with tiotropium inhalation capsules 18 mcg via HandiHaler® once daily to Combivent® Inhalation Aerosol CFC MDI 2 actuations q.i.d. in COPD patients currently prescribed Combivent® Inhalation Aerosol CFC MDI |
| **Principal/Coordinating Investigator:** | [redacted]. |
| **Trial sites:** | 39 sites in Argentina, Lithuania, Slovakia, UK, and US. |
| **Publication (reference):** | Not applicable |
| **Clinical phase:** | IV |
| **Objectives:** | The objective of the study is to evaluate the efficacy and safety of 12 weeks treatment with tiotropium HandiHaler® 18 mcg daily compared to Combivent® MDI CFC Inhalation Aerosol 2 actuations q.i.d. in COPD patients currently prescribed Combivent® MDI. |
| **Methodology:** | 12-week, randomized, double-blind, double-dummy, parallel group design |
| **No. of subjects:** | |
| **planned:** | enrolled: 490 entered: 325 |
| **actual:** | enrolled: 477 entered: 327<br>Treatment Tiotropium:<br>entered: 163 treated: 163 analysed (for primary endpoint): 150<br>Treatment Combivent®:<br>entered: 164 treated: 164 analysed (for primary endpoint): 151 |
| **Diagnosis and main criteria for inclusion:** | Male or female, ≥40 years of age with COPD, pre-bronchodilator $FEV_1$ ≤65% of predicted, $FEV_1$/FVC ≤70%, smoking history ≥10 pack-years, no history of asthma and was using Combivent® CFC MDI prior to enrolling into the trial |

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| **Test product:** | Tiotropium Inhalation Capsules |
| **dose:** | 18 mcg qd |
| **mode of admin.:** | Oral inhalation via the HandiHaler® |
| **batch no.:** | B062000002, B062000724 |
| **Reference therapy:** | Combivent® inhalation aerosol CFC |
| **dose:** | 2 puffs q.i.d.<br>18 mcg ipratropium bromide monohydrate/103 mcg albuterol sulfate per actuation, mouthpiece delivery (21 mcg ipratropium bromide monohydrate/ 120 mcg albuterol sulfate, valve delivery) |
| **mode of admin.:** | Oral inhalation via the CFC Metered Dose Inhaler (MDI) |
| **batch no.:** | B063000200, B063000644 |
| **Duration of treatment:** | 12 weeks |
| **Criteria for evaluation:** | |
| **Efficacy / clinical pharmacology:** | Primary endpoints: Trough $FEV_1$ and $FEV_1$ $AUC_{0-6}$ after 12 weeks.<br>Secondary endpoints: Peak $FEV_1$ at 12 weeks; peak $FEV_1$, $FEV_1$ $AUC_{0-6}$ after first dose and 6 weeks, trough $FEV_1$ at 6 weeks; FVC (trough, peak, $AUC_{0-6}$) at each week; $FEV_1$ and FVC at each time point; albuterol use; Patient and Physician Global Evaluations; morning and evening PEFR. |
| **Safety:** | Adverse events, vital signs |
| **Statistical methods:** | Analysis of covariance with treatment and center as fixed effects and baseline measurements as a covariate, descriptive statistics. |

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**SUMMARY – CONCLUSIONS:**

**Efficacy / clinical pharmacology results:**

Treatment with tiotropium inhalation capsules inhaled via the HandiHaler® device was shown to be superior to Combivent® inhalation aerosol MDI with respect to mean trough $FEV_1$ response after 12 weeks of treatment.

Treatment with tiotropium inhalation capsules inhaled via the HandiHaler® device was shown to be non-inferior to Combivent® inhalation aerosol MDI with respect to mean $FEV_1$ $AUC_{0-6}$ response after 12 weeks of treatment.

Treatment with tiotropium inhalation capsules inhaled via the HandiHaler® device was not superior to Combivent® inhalation aerosol MDI with respect to mean $FEV_1$ $AUC_{0-6}$ response after 12 weeks of treatment.

Treatment with Combivent® MDI was shown to be superior to treatment with tiotropium HandiHaler® with respect to mean $FEV_1$ peak response after 12 weeks of treatment.

FVC parameters were assessed as secondary outcome measures. FVC trough and $AUC_{0-6}$ responses were similar for tiotropium versus Combivent® treatment groups.

Rescue medication was assessed as a secondary endpoint. No significant differences in rescue medication were observed between treatment with tiotropium versus Combivent® for total daily usage, daytime usage and nighttime usage.

The weekly means for total albuterol use (scheduled plus rescue) were significantly greater for patients receiving Combivent® versus patients receiving tiotropium throughout the twelve weeks of study.

No differences in patient global evaluations, physician global evaluations and shortness of breath assessments were observed between treatment with tiotropium versus Combivent®.

Morning PEFR measurements were greater for patients receiving tiotropium versus Combivent®. No difference between treatments was observed for evening PEFR measurements.

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| **Safety results:** | A similar proportion of patients in the Combivent® group (27.4%) experienced adverse events compared to the tiotropium group (24.5%). A notable imbalance in COPD exacerbations was observed which was reported in 13 Combivent patients and 7 tiotropium patients. There were 2 deaths in this trial; one in each treatment group. One death (COPD) occurred in the Combivent® group. The death in the tiotropium group was due to renal failure. There were 4 patients with serious COPD exacerbations in the Combivent® group and 1 in the tiotropium group. There were no imbalances between the groups with respect to marked change from baseline for diastolic and systolic blood pressure or for heart rate.<br><br>In summary the results of this study are consistent with the known safety profile of tiotropium and Combivent®; however, there is evidence from the safety evaluation that tiotropium may be more effective than Combivent in preventing exacerbations of COPD. |
| **Conclusions:** | In summary the results of this study are consistent with the known safety and efficacy profile of tiotropium and Combivent®. All patients participating in the trial were to have used Combivent® regularly for at least 4 weeks prior to screening. The study results indicate that patients switched to tiotropium achieve superior bronchodilator benefits when they awaken in the morning and achieve at least equivalent benefit over the day time hours. This occurs despite the comparison of tiotropium administered only once daily to a product (Combivent®) having two bronchodilators of differing mechanisms administered 4 times each day. Furthermore, the use of tiotropium results in an overall reduction of the total amount of beta-agonist use (prn and scheduled) suggesting a reduction in the risk of COPD exacerbations. In conclusion, the trial provided evidence suggesting that tiotropium is a safe and effective alternative to Combivent® in COPD. |