Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim International GmbH		**Tabulated Study Report**	Boehringer Ingelheim
Name of finished product: Spiriva®			
Name of active ingredient: Tiotropium bromide		**Page 1 of 6**	
Report date: 26 JAN 07	**Study Number:** 205.301	**Study period (dates):** 15 DEC 04 – 19 APR 06	**Revision date::** 07 MAY 07

Title of study:	A 12-week randomised, double blind, placebo-controlled, parallel group trial evaluating the efficacy and safety of inhaled tiotropium 18 µg q.d. in patients with COPD and a concomitant diagnosis of asthma
Investigator:	[redacted]
Study centres:	Multi-centre study
Publication (reference):	Data of this study have not been published.
Clinical phase:	IV
Objectives:	The objective of the study was to demonstrate the efficacy and safety of tiotropium in patients with chronic obstructive pulmonary disease (COPD) and a concomitant diagnosis of asthma.
Methodology:	12-Week, randomised, double-blind, parallel group, placebo-controlled
No. of subjects: **planned:** **actual:**	entered: 432 enrolled: 566 entered: 472 Tiotropium inhalation capsules: entered: 228 treated: 228 analysed (for primary endpoint): 226 Placebo: entered: 244 treated: 244 analysed (for primary endpoint): 239
Diagnosis and main criteria for inclusion:	Female and male outpatients; ≥ 40 years old; diagnosis of COPD; diagnosis of asthma before the age of 30 years; post-bronchodilator FEV_1 < 80% of the predicted normal value; post-bronchodilator ratio of forced expiratory volume in 1 second to forced vital capacity (FEV_1/FVC) < 70%; increase in FEV_1 > 12% and at least 200 mL from baseline 30 min after 400 µg salbutamol or documented during the past 5 years; signed informed consent
Test product:	Tiotropium inhalation capsules
dose:	18 µg q.d.
mode of admin.:	Oral inhalation via the HandiHaler® device
batch no.:	404405 503470A (re-supply)

Duration of treatment:	12 weeks
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation via the HandiHaler® device
batch no.:	404403 407222 (re-supply)
Criteria for evaluation:	
Efficacy:	$FEV_1AUC_{0\text{-}6h}$, trough and peak FEV_1, $FVCAUC_{0\text{-}6h}$, trough and peak FVC, FEV_1 and FVC measurements at each time point, use of rescue medication, PEFR in the morning and in the evening
Safety:	Adverse events (AEs), vital signs, physical examination
Statistical methods:	Analysis of covariance with terms for treatment, centre, and baseline as a covariate
SUMMARY – CONCLUSIONS:	

Efficacy results:

The majority of patients were of Caucasian origin and the proportion of female patients was similar in both treatment groups with 38.9% (placebo) and 38.2% (tiotropium). The mean age was 59.6 (±9.6) years. Overall, the mean baseline FEV_1 was 1.550 L; the mean baseline percent predicted normal FEV_1 was 53.0%. No differences between treatment groups were discerned regarding weekly average use of rescue medication, disease background characteristics, duration of asthma and COPD, and concomitant therapy and diagnoses.

For pulmonary function tests and vital signs, baseline was defined as mean of the two pre-dose measurements (i.e. 30 min and 10 min prior to the first dose administration) on day 1. For all diary endpoints, baseline was defined as the average of the data obtained in the week immediately preceding visit 2, i.e. in the last week of the run-in period.

Primary endpoint

The primary analysis demonstrated that treatment with tiotropium was superior in bronchodilation to placebo in patients with COPD and concomitant asthma. The primary analysis showed that once daily dosing with tiotropium18 µg led to a statistically significant increase in $AUC_{0\text{-}6h}FEV_1$; the mean difference from placebo for the change from baseline on day 85 was 0.186 L (95% CI from 0.138 to 0.233 L, $p < 0.0001$).

Secondary endpoints

An improvement in mean $AUC_{0\text{-}6h}FEV_1$ with tiotropium was observed on day 1 (placebo-adjusted mean change from baseline: 0.159 L, $p < 0.0001$) and on day 29 (placebo-adjusted mean change from baseline: 0.184 L, $p < 0.0001$). At each time point at each visit, a statistically significant difference from placebo was seen for the mean change from baseline in FEV_1. The mean change from baseline in trough FEV_1 was by 0.098 L greater in the tiotropium group than in the placebo group on day 85 ($p < 0.0001$). The mean treatment difference for peak FEV_1 was 0.188 L on day 85 ($p < 0.0001$). The increase in the percent predicted normal FEV_1 as the mean difference from placebo was 5.9%-points for $AUCppnFEV_1$, 3.1%-points for trough $ppnFEV_1$, and 6.0%-points for peak $ppnFEV_1$ on day 85 (p-value for each of the parameters < 0.0001).

The same pattern as for FEV_1 was obtained for FVC. On day 85, the mean difference from placebo for $AUC_{0\text{-}6h}FVC$ was 0.232 L ($p < 0.0001$); the mean treatment difference for trough FVC was 0.128 L ($p=0.0002$) and for peak FVC 0.254 L ($p < 0.0001$).

Efficacy results continued:	Mean $AUC_{0\text{-}6h}FEV_1/FVC$ increased by 2.2%-points ($p < 0.0001$) and mean trough FEV_1/FVC increased by 1.2%-points ($p=0.0163$) on tiotropium relative to placebo (day 85). Only the mean difference from placebo for trough FEV_1/FVC on day 29 was not statistically significantly different from zero. Peak FEV_1/FVC slightly increased on treatment with tiotropium; the mean difference in change from baseline was 1.8%-points on day 85 compared with placebo ($p = 0.0006$). Weekly average morning and evening PEFR was observed to be higher in the tiotropium group than in the placebo group during all 12 weeks of randomised treatment. The mean difference from placebo in the change from baseline at week 12 was 20.3 L/min ($p < 0.0001$) for the morning measurement and 23.6 L/min ($p < 0.0001$) for the evening measurement. Weekly average number of puffs of rescue medication used during the daytime and the total daily number of puffs were observed to be lower in the tiotropium group than in the placebo group during the entire randomised treatment period. The mean weekly average of number of puffs of rescue medication used total daily was about half a puff lower in the tiotropium group than in the placebo group after 12 weeks of treatment; the treatment difference was statistically significant. For night-time use of rescue medication, a statistically significant decrease was observed only for week 1; from week 2 onwards, the p-values for the treatment difference in rescue medication at night-time were greater than 0.05. Overall, tiotropium showed statistically and clinically significant superiority over placebo.
Safety results:	Mean exposure (± SD) was similar in both treatment groups with 84.8 (± 14.1) days in the placebo group and 86.5 (± 8.5) days in the tiotropium group. The total exposure was 58.1 patient-years for placebo and 55.4 patient-years for tiotropium. The incidence of AEs within the 12-week treatment period was similar in both treatment groups; 89 patients (36.5%) in the placebo group experienced AEs and 87 patients (38.2%) in the tiotropium group had AEs. The vast majority of patients with AEs had events of mild or moderate intensity. The frequency of patients experiencing AEs of severe intensity was comparable between the two treatment groups (placebo: 11 patients, 4.5%; tiotropium: 9 patients, 3.9%).

Safety results continued:

Serious adverse events (SAEs) were recorded in 5 patients (2.0%) on treatment with placebo and in 10 patients (4.4%) on treatment with tiotropium. Five deaths occurred during the study. Two patients died during the run-in period and thus had not received any study medication. Two patients who passed away had been treated with placebo. One of these patients had experienced a COPD exacerbation on placebo and sepsis post-treatment; one patient died due to respiratory failure on treatment with placebo. One patient who had been treated with tiotropium died from respiratory insufficiency due to pneumothorax and COPD exacerbation. The death occurred about 6 month after the last intake of study drug; the patient was treated with commercially available tiotropium until 2 months prior to his death. All SAEs observed during the study were considered not related to study drug.

As expected for a study population comprising patients with COPD and concomitant asthma, respiratory system disorders was the system organ class with the highest incidence of AEs. Lower respiratory disorders were less common on tiotropium than on placebo (placebo: 20.1%; tiotropium: 12.7%); upper respiratory disorders were more frequently observed in the tiotropium group than in the placebo group (placebo: 5.7%; tiotropium: 13.2%). The total frequency of exacerbations of the underlying diseases COPD and/or asthma was considerably reduced in the tiotropium group (placebo: 28 patients, 11.5%; tiotropium: 15 patients, 6.6%). The incidence of bronchitis was lower for tiotropium than for placebo (placebo: 13 patients, 5.3%; tiotropium: 2 patients, 0.9%). A higher number of patients in the tiotropium group than in the placebo group experienced nasopharyngitis (placebo: 9 patients, 3.7%; tiotropium: 17 patients, 7.5%).

Gastrointestinal disorders were noted in a higher percentage of patients on tiotropium than on placebo (placebo: 14 patients, 5.7%; tiotropium: 22 patients, 9.6%). This was attributable to a higher incidence of dry mouth (placebo: 4 patients, 1.6%; tiotropium: 9 patients, 3.9%) and diarrhoea (placebo: 2 patients, 0.8%; tiotropium: 6 patients, 2.6%) in the tiotropium group than in the placebo group; dry mouth is an anti-cholinergic effect and was considered drug-related. No clinically relevant findings were discerned regarding vital signs and physical examination. A higher incidence of marked decreases in systolic blood pressure was observed with tiotropium than with placebo (placebo: 3 patients, 1.2%; tiotropium: 14 patients, 6.1%); this was considered a chance finding. The evaluation of laboratory values was only performed at screening but not during the course of the study.

Safety results continued:	In summary, the results of the safety evaluation were consistent with the known safety profile of tiotropium; there were no unexpected safety concerns. The analysis of AEs, vital signs, and physical examinations demonstrated that tiotropium was safe and well tolerated at the given dose in patients with COPD and concomitant asthma.
Conclusions:	Tiotropium 18 µg q.d. administered as inhalation capsules via the HandiHaler® device was efficacious in COPD patients with a concomitant diagnosis of asthma. Tiotropium led to a statistically significant improvement in forced expiratory volume in one second measured as the area under the curve of change from baseline to 6 h post dose ($AUC_{0-6h}FEV_1$); the treatment difference was 0.186 L ($p < 0.0001$) on day 85. The mean values for the secondary efficacy parameters $AUC_{0-6h}FEV_1$ on day 1 and 29, trough and peak FEV_1, $AUC_{0-6h}FVC$ (forced vital capacity), and trough and peak FVC were higher on treatment than at baseline; the increase was greater in the tiotropium group than in the placebo group (all p-values < 0.05). Efficacy was further corroborated by the observed increase in peak expiratory flow rate and decrease in the use of rescue medication in patients treated with tiotropium. The results of the safety evaluation were consistent with the known safety profile of tiotropium. It is concluded that tiotropium 18 µg q.d. is efficacious and safe in patients with COPD and concomitant asthma.