Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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 7**	
Report date: 31 OCT 2005	**Trial Number:** 205.259	**Study period (dates):** 24 JAN 02 - 07 MAY 04	**Date of Revision**

Title of study:	**S**piriva® **A**ssessment of **FE**V_1 (SAFE). The effect of inhaled tiotropium bromide (18 mcg once daily) on the change in FEV_1 during long-term treatment in patients with COPD. A one-year parallel group, double-blind, randomised, placebo-controlled study
Investigator:	[redacted]
Study center:	Multicentre study.
Publication (reference):	Data of this study has not been published
Clinical phase:	IIIb
Objectives:	To evaluate whether the effect of one-year (48 weeks) treatment with inhaled tiotropium bromide (18 µg once daily) on the change in trough FEV_1, compared to placebo in patients with COPD, is affected by smoking status.
Methodology:	Parallel group, double-blind, randomised, placebo-controlled study
No. of subjects: **planned:** **actual:**	 entered: 1000 enrolled: 1294 Treatment A: Tiotropium entered: 608 treated: 608 analysed (for primary endpoint): 587 Treatment B: Placebo entered: 306 treated: 305 analysed (for primary endpoint): 287
Diagnosis and main criteria for inclusion:	Outpatients of either sex, ≥40 years of age, FEV_1 ≤65% predicted (Morris), FEV_1/FVC ≤70%, smoking history ≥10 pack years with a diagnosis of chronic obstructive pulmonary disease.
Test product:	Tiotropium
dose: **mode of admin.:**	18 mcg Powder inhalation via the HandiHaler
batch no.:	103115 (original); 207452 (re-supply)
Duration of treatment:	48 weeks (336 days)

Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Powder inhalation via the HandiHaler
batch no.:	009586 (original); 205907 (re-supply)
Criteria for evaluation:	
Efficacy:	Primary; trough FEV_1 at 48 weeks Secondary; trough FEV_1 at interim visits, FVC, FEV_6 (at selected sites), FEV_1/FVC, incidence, severity and duration of COPD exacerbations, incidence and duration of hospitalisations due to COPD exacerbations, use of rescue medication, number of short courses of steroids/antibiotics, COPD symptom scores, physician's global evaluation and SGRQ.
Safety:	Adverse events and vital signs
Statistical methods:	One way ANCOVA with baseline as a covariate

SUMMARY – CONCLUSIONS:

Efficacy results:

The primary endpoint for the trial was trough FEV_1 at 48 weeks of treatment. The planned analysis also allowed for a stepwise further analysis of the differences in trough FEV_1 at 48 weeks in the smoker and ex-smoker groups if a positive signal was demonstrated in the overall population.

The results of the pre-specified primary parametric treatment comparison for trough FEV_1 at 48 weeks of treatment for all patients, smokers and ex-smokers, based on an ANCOVA model with baseline as a covariate, are presented below (Table 1);

Efficacy results (continued):

Table 1: Adjusted mean (SE) in FEV_1 (L) over time for FAS patients, smokers and ex-smokers (imputed)

	Study Phase	Tiotropium (N = 587)	Placebo (N = 287)	Difference	p-value	95% Confidence Interval
Overall	Day 0	0.97 #	0.97 #			
	Week 48*	1.07 (0.01)	0.97 (0.01)	0.10 (0.02)	<.0001	(0.07, 0.14)
Smokers	Day 0	1.03 #	1.03 #			
	Week 48*	1.18 (0.02)	1.04 (0.03)	0.14 (0.04)	0.0007	(0.06, 0.22)
Ex-Smokers	Day 0	0.94 #	0.94 #			
	Week 48*	1.02 (0.01)	0.94 (0.01)	0.08 (0.02)	<.0001	(0.05., 0.12)

1:Based on the ANCOVA model with term treatment and using baseline FEV_1 as a covariate
#:Common mean across groups at Day 0 (baseline, Visit 2)
*:Defined as the primary endpoint

There was a statistically significant increase in FEV_1 at 48 weeks in the tiotropium group compared with the placebo group in all three groups analyzed (overall, smoking and ex-smoking groups) (Table 1). These differences were first seen after two weeks of multiple dosing and were maintained at a steady state throughout the trial.

There were similar statistically significant increases in FVC (180 mL $p<0.0001$) and FEV_6 (130 mL, $p<0.05$)at 48 weeks in the tiotropium group compared with the placebo group in the overall patients. Again, these differences were first seen after two weeks of multiple dosing and were maintained at a steady state throughout the trial. There was also an increase FEV_1/FVC ratio with a trend towards significance at Week 48 (mean difference 1.1%, $p = 0.051$).

Efficacy results continued):

Tiotropium had no statistically significant effect on the incidence of COPD exacerbations, with 0.88 exacerbations per patient year in the tiotropium group compared with 0.92 exacerbations per patient year in the placebo group ($p = 0.599$). Nor did tiotropium have any effect on; the number of exacerbation days per patient year (tiotropium 16.13, placebo 16.19, $p = 0.843$); the percentage of patients with at least one exacerbation (tiotropium 44.1%, placebo 41%, $p = 0.395$); or on the percentage of patients with at least one exacerbation after adjusting for severity.

Tiotropium had no statistically significant effect on the number of hospitalizations due to a COPD exacerbation (tiotropium 0.13, placebo 0.15, $p = 0.557$). Nor did tiotropium have any effect on the number of hospitalization days (tiotropium 1.14, placebo 1.16, $p = 0.774$), or on the percentage of patients with at least one hospitalization due to a COPD exacerbation (tiotropium 8.4%, placebo 8.2%, $p = 1.0$).

Tiotropium had no effect on the number of short courses of antibiotics (tiotropium 1.02, placebo 1.00, $p = 0.756$) or oral corticosteroids (tiotropium 0.58, placebo 0.55, $p = 0.599$) taken for a COPD exacerbation.

Tiotropium significantly improved shortness of breath as measured by COPD symptom scores at Week 48 (mean difference -0.11, $p<0.05$), but had no significant effect on wheezing, coughing or tightness of chest at the same time point.

Tiotropium significantly improved the total (tiotropium 40.9%, placebo 43.7% $p<0.005$), symptoms (tiotropium 44.4%, placebo 49.3% $p<0.005$) and impacts (tiotropium 28.5%, placebo 31.3% $p<0.01$) domains of the St. George's Respiratory Questionnaire at Week 48, but had no significant effect on the activities score.

Tiotropium had a marginal effect on the Physician's Global Evaluation performed at Week 48 (tiotropium 5.2%, placebo 5.1% $p = 0.063$).

Tiotropium significantly reduced the mean weekly total (range of mean weekly differences 0.76-1.07) and day-time (range of mean weekly differences 0.65-0.98) use of rescue medication per day, but had no effect on the mean weekly night-time (range of mean weekly differences 0.03-0.15) use of rescue medication per day.

Safety results:

A total of 913 patients were randomized and received at least one dose of trial medication. Six hundred and eight (608) patients were randomized to tiotropium and 305 patients were randomized to placebo. Patients in the tiotropium group had a longer mean exposure to trial medication (287.2 days) compared with patients in the placebo group (268.4 days).

The percentage of patients reporting at least one treatment emergent adverse event was slightly higher in the tiotropium group (78.9%) compared with placebo (74.1%). Overall, the most frequently occurring adverse events were in the lower and upper respiratory system and gastrointestinal system organ classes. The most common events were dyspnoea, cough, purulent sputum, wheezing, and chest discomfort, with 45.7%, 43.8%, 31.4%, 28.0% and 26.4% of all patients reporting these events, respectively. COPD exacerbation was also one of the most commonly reported adverse events in this trial with a total of 27.2% of all patients reporting this as an adverse event. There were a slightly lower percentage of patients reporting COPD exacerbations in the tiotropium group (26.5%) compared with the placebo group (28.5%) but there were a higher percentage of patients reporting both bronchitis (tiotropium 17.3%, placebo 15.4%) and pneumonia (tiotropium 8.2%, placebo 4.9%) in the tiotropium group compared with the placebo group.

There were a similar percentage of patients reporting dry mouth between the two groups (tiotropium 3.5%, placebo 3.6%), a slightly higher percentage of patients reporting both sinusitis (tiotropium 3.5%, placebo 1.3%) and pharyngitis (tiotropium 7.6%, placebo 6.6%) in the tiotropium group compared with the placebo group, and a slightly lower percentage of patients reporting upper respiratory tract infections in the tiotropium group (2.8%) compared with the placebo group (3.9%).

Overall, 7.3% of the patients reported at least one adverse event which was considered by the investigator as related to treatment with the trial medication (related adverse event). The percentage of patients with a related adverse event was 6.9% in the tiotropium group and 8.2% in the placebo group. The most common event reported as related was dyspnoea, which was reported by a lower percentage of patients in the tiotropium group (1.6%) compared with the placebo group (3.3%). Dry mouth was reported equally in both treatment groups (tiotropium 2.5%, placebo 2.6%) as being related to trial medication.

Safety results (continued):

Overall, 12.3% of the patients reported a treatment emergent adverse event for which the action taken with the test medication for the event was recorded as discontinued and this was comparable between the two treatment groups (tiotropium 11.5%, placebo 12.1%). The most frequently occurring adverse events that led to treatment discontinuation were lower respiratory system, and general disorders. For the lower respiratory system disorders system organ class, the percentages were similar in both treatment groups (tiotropium 8.4%, placebo 8.2%) as were those for general disorders (tiotropium 3.8%, placebo 3.6%). The most common event leading to treatment discontinuation was dyspnoea, which was reported by 6.9% of patients in the tiotropium group, and 6.6% of patients in the placebo group.

Overall, 17.4% of the patients reported a treatment emergent serious adverse event. There were a higher percentage of patients reporting a serious adverse event in the tiotropium group (18.4%) compared with the placebo group (14.1%). The most frequently occurring serious adverse events were lower respiratory system disorders and cardiac disorders. For the lower respiratory system disorders system organ class, there was a higher percentage in the tiotropium group (13.7%) compared with the placebo group (9.5%). For the cardiac disorders system organ class, there was a slightly higher percentage in the tiotropium group (3.0%) compared with the placebo group (2.6%).

The most common serious adverse events were COPD exacerbations and pneumonia. Serious COPD exacerbations were reported by 8.6% of patients in the tiotropium group compared with 6.2% of patients in the placebo group while pneumonia was reported by 4.9% of patients in the tiotropium group compared with 3.0% of patients in the placebo group. Additionally, there were 3.0% of patients in the tiotropium group reporting serious cardiac disorders compared with 2.6% in the placebo group. Of these, the majority of cardiac events were comparable between the two groups, with the exception of myocardial infarction which occurred in 1% of patients in the tiotropium group compared with 0.3% of patients in the placebo group.

Fatal adverse events were reported for 22 patients. Two of the fatal events had onsets during the screening period and the patients were not yet randomized. One fatal event occurred while patient was receiving treatment (placebo) but the onset of the event (liver cancer) was considered to have been present prior to randomization of the patient. There were 15 fatalities (tiotropium 13 [2.1%], placebo 2 [0.7%]) during the treatment period (including the thirty-day period after the last medication dose), and 4 fatalities in the post-trial period.

Safety results (continued):	In all cases, the fatal adverse events were not considered by the investigator as related to treatment with the test medication. Evaluation of vital signs (individual patient marked changes and mean changes from baseline) indicated that changes from baseline were minimal and no effect of treatment was observed.
Conclusions:	In summary, the primary endpoint of this trial was met. There was a statistically significant increase in FEV_1 at 48 weeks in the tiotropium group compared with the placebo group in all three groups analyzed (overall, smoking and ex-smoking groups). These differences were first seen after two weeks of multiple dosing and were maintained at a steady state throughout the trial. There were also similar increases in FVC, FEV_6, FEV_1/FVC ratio at 48 weeks in the tiotropium group compared with the placebo group in the overall patients. Additionally, tiotropium had no effect on the incidence, duration or severity of COPD exacerbations, incidence and duration of hospitalizations due to a COPD exacerbation, or the number of short courses of antibiotics or oral corticosteroids taken for a COPD exacerbation. Tiotropium also significantly improved shortness of breath as measured by COPD symptom scores at Week 48, but had no significant effect on wheezing, coughing or tightness of chest at the same time point. Tiotropium significantly improved all domains of the St. George's Respiratory Questionnaire at Week 48, with the exception of the activities score, and had a marginal effect on the Physician's Global Evaluation performed at Week 48. Finally, tiotropium significantly reduced the mean weekly total and day-time use of rescue medication per day, but had no effect on the mean weekly night-time use of rescue medication per day. Evaluation of all of the safety data collected from this trial revealed an unexpected increase in the percentages of adverse events, serious adverse events and fatalities in the tiotropium group compared to placebo, that have not been previously seen in the tiotropium clinical program. The increased numbers of adverse events and serious adverse events, observed in the tiotropium group, appear to be driven by individual lower respiratory events (e.g., bronchitis and pneumonia). Additionally, there were a slightly higher percentage of patients experiencing a myocardial infarction in the tiotropium group compared to the placebo group, and a higher number of fatalities from various reasons were also observed in the tiotropium group compared with the placebo group. The efficacy and safety of tiotropium is being investigated further in ongoing long-term trials.