Clinical Study Synopsis for Public Disclosure

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**Name of company:**
Boehringer Ingelheim International GmbH

**Name of finished product:**
SPIRIVA®

**Name of active ingredient:**
Tiotropium bromide

**Report date:**
14 NOV 2005

**Study Number:**
205.273

**Study period (dates):**
08 OCT 03 – 04 AUG 04

**Date of Revision:**

**Title of study:**
A Six-Week, Randomised, Double-Blind, Triple-Dummy, Parallel Group, Multiple Dose, Pilot Study Comparing Tiotropium Inhalation Capsules to Salmeterol Inhalation Aerosol Combined with Fluticasone Inhalation Aerosol in Patients with Chronic Obstructive Pulmonary Disease (COPD).

**Investigator:**
Multi-centre

**Study center(s):**
12 centres in South Africa

**Publication (reference):**

**Clinical phase:**
IV

**Objectives:**
Primary objective: to estimate the comparative bronchodilator effect size and variability for tiotropium and salmeterol/fluticasone in COPD patients. Secondary objective: to explore the clinical safety of tiotropium compared with salmeterol/fluticasone in COPD patients.

**Methodology:**
Randomised, double-blind, triple-dummy parallel group design.

**No. of subjects:**
planned:
entered: 100 (50 per treatment group)
enrolled: 143

actual:
Tiotropium:
entered: 56
analyased (for primary endpoint): 56
Salmeterol/fluticasone:
entered: 51
analyased (for primary endpoint): 49

**Duration of treatment:**
42 days

**Diagnosis and main criteria for inclusion:**
Outpatients of either sex, aged ≥ 40 years with a diagnosis of COPD (GOLD criteria); post-bronchodilator FEV₁ < 80% predicted [ECSC criteria] and FEV₁/FVC < 70% at Visit 1, pre-dose FEV₁ ≤ 65% predicted at Visit 2, smoking history of > 10 pack-years, no history of asthma.

**Test product:**
dose:
18 µg tiotropium per day (one capsule)

mode of admin.:
Inhalation via the HandiHaler® device

**batch no.:**
207452 (expiry 11/2004)
### Table: Study Report Details

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**Reference therapy:** Salmeterol / fluticasone propionate combination

**dose:**
- Salmeterol 50 µg (two puffs of 25 µg each) b.i.d., and
- Fluticasone propionate 250 µg (two puffs of 125 µg each) b.i.d.

**mode of admin.:** Inhalation via MDI

**batch no.:**
- Salmeterol: 2L770 (expiry 10/2004)
- Fluticasone: 3A069 (expiry 04/2004), 326 (expiry 02/2005)

**Criteria for evaluation:**

**Efficacy:**
- Primary endpoint: FEV₁ AUC₀-₁₂
- FEV₁, FVC, rescue medication use.

**Safety:**
- Adverse events, vital signs, physical examination.

**Statistical methods:**
- Analysis of covariance with terms for treatment, centre and baseline.
- Descriptive statistics.

**SUMMARY – CONCLUSIONS:**

**Efficacy results:**
The two treatment groups were not comparable with respect to baseline efficacy characteristics. Patients treated with tiotropium 18 µg q.d. had a lower FEV₁ (SD) [1.31 L (0.47)] compared to patients allocated to the salmeterol 50 µg b.i.d plus fluticasone 250 µg b.i.d group [1.46 L (0.53)]. The FEV₁ (SD) predicted normal was 45.90 % (12.57) and 48.75 % (12.34) respectively. The pre-dose FVC (SD) was 2.66 L (0.89) in the tiotropium group and 2.88 L (0.96) in the combination arm.

The primary endpoint of the study was the forced expiratory volume area under the curve for the time period 0 to 12 hours (FEV₁ AUC₀-₁₂), measured after 6 weeks of treatment at the final study visit (Visit 4). The adjusted means (SE) of FEV₁ AUC₀-₁₂ were 1.55 L (0.03) in the tiotropium group and 1.57 L (0.04) in the salmeterol /fluticasone combination group. The difference in mean (SE) was -0.02 (0.05) [95% CI: -0.12, 0.07]. The results did not change when the treatment by centre interaction was included in the model. In addition, the adjusted means for the PP analysis were comparable with those obtained in the FAS population.
Secondary endpoints: Adjusted mean (SE) trough FEV₁ was statistically significantly higher (p-value 0.0294, 95% CI: -0.17, -0.01) in the salmeterol/fluticasone combination group [1.55 L (0.03)] compared to the tiotropium group [1.46 L (0.03)] at Day 22. A substantial, but statistically insignificant difference (p-value 0.0721, 95% CI: -0.17, -0.01) was also noted at Day 43: tiotropium 1.46 L (0.03) vs. salmeterol/fluticasone 1.54 L (0.03).

The peak FEV₁ results were comparable between the two arms. The adjusted mean (SE) peak FEV₁ was 1.68 L (0.04) in the tiotropium group and 1.66 L (0.04) in the salmeterol/fluticasone combination group [95% CI: -0.09, 0.12].

Similar to the primary endpoint, the adjusted mean (SE) for FVC AUC0-12 was comparable in the tiotropium group [3.06 L (0.06)] and the salmeterol/fluticasone group [3.07 L (0.06)].

FVC trough response was similar in the two treatment groups. No differences were detected at both Day 22 (tiotropium 2.99 L (0.06) vs. salmeterol/fluticasone 3.02 L (0.06) [95% CI: -0.19, 0.13] and Day 43 (tiotropium 2.93 L (0.05) vs. salmeterol/fluticasone 2.97 L (0.05) [95% CI: -0.19, 0.10].

Similar to FEV₁, peak FVC at Day 43 tended to be higher in the tiotropium group [3.30 L (0.06)] compared to the salmeterol/fluticasone group [3.26 L (0.07)]. The difference in mean was 0.04 L (0.09) with 95% CI: -0.14, 0.23.

There were no significant differences between the two groups regarding the amount of salbutamol rescue therapy inhaled during the treatment period.
Safety results:

Adverse events were experienced by 45 (42.1%) patients. Of this total, 23 (41.1%) patients were treated with tiotropium 18 µg q.d., while 22 (43.1%) were treated with fluticasone 250 µg b.i.d. plus salmeterol 50 µg b.i.d.

The more frequently occurring adverse events in the tiotropium group were bronchitis (3; 5.4%), pharyngitis (3; 5.4%), dry mouth (2; 3.6%), viral infection (2; 3.6%), skin laceration (2; 3.6%), insomnia (2; 3.6%), COPD exacerbation (2; 3.6%), hoarseness (2; 3.6%) and influenza (2; 3.6%). Dry mouth, influenza, pharyngitis and hoarseness were of mild intensity, while all other adverse events were of mild to moderate severity. Dry mouth and hoarseness were considered related to administration of trial drug.

In the salmeterol/fluticasone combination group, the more common adverse events reported were hoarseness (4; 7.8%), headache (3; 5.9%), COPD exacerbation (3; 5.9%), dry mouth (2; 3.9%), nausea (2; 3.9%) and throat irritation (2; 3.9%). Dry mouth, nausea, throat irritation, headache and hoarseness were mostly of mild intensity. Moderate COPD exacerbation was reported in 2 of the 3 cases. Dry mouth in one patient, throat irritation in one patient, as well as all incidences of hoarseness, were considered related to administration of trial drug.

Serious adverse events occurred in 3 (2.8%) patients during the treatment period. Two patients (one with acute myocardial infarction and one with prostatitis) received tiotropium, while one patient with lumbar spondylosis received salmeterol plus fluticasone. Hospitalisation was required in all three cases, while the acute myocardial infarction was also reported as life-threatening. None of these SAEs were considered to be related to administration of trial drugs or placebo.

Adverse events which led to discontinuation of trial drug occurred in one patient who received the salmeterol/fluticasone combination. This patient discontinued the study six days after initiation of treatment due to moderate cough and hoarseness. Both these adverse events appeared at onset of treatment, were characterised as drug related and resolved after discontinuation of trial drug.

The number of patients experiencing adverse events which were considered by the investigator to be related to trial drugs was 13 (12.1%). Five (8.9%) patients were in the tiotropium group, while 8 (15.7%) patients were in the combination group.
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**Conclusions:**

There were no clinically significant changes in vital signs, physical findings and other observations related to safety during the study period.

This pilot study in COPD patients comparing tiotropium 18 μg q.d. to salmeterol 50 μg b.i.d. plus fluticasone 250 μg b.i.d. revealed that:

- treatments were generally comparable with regard to 12h spirometry after 6 weeks of treatment,
- duration of action, as indicated by trough and >4h lung function tests, tended to be longer with salmeterol plus fluticasone,
- conclusions are limited due to a) baseline differences and b) overall small groups,
- the general aim of the study, i.e. to check the range of lung function responses between tiotropium and salmeterol plus fluticasone in a head-to-head design, was achieved and results allow for planning of powered studies in the future.