Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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..

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Name of company: Boehringer Ingelheim International GmbH		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: SPIRIVA ®, Respimat®		**EudraCT No.:** 2005-005615-21	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 4	**Synopsis No.:**
Module:		**Volume:**	
Report date: 22 OCT 2008	**Trial No. / U No.:** 205.341 / U08-2081-01	**Dates of trial:** 07 AUG 2006 - 08 NOV 2007	**Date of revision** (if applicable):

Title of trial:	A Randomised, Double-Blind, Placebo-Controlled, Crossover Efficacy and Safety Evaluation of 8-Week Treatment Periods of Two Doses [5 µg (2 actuations of 2.5 µg) and 10 µg (2 actuations of 5 µg)] of Tiotropium Inhalation Solution Delivered by the Respimat® Inhaler as Add-on Therapy in Patients with severe persistent Asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre, multi-national study at 16 sites in 3 countries (Denmark, Germany and The Netherlands)
Publication (reference):	Data from this study have not been published yet.
Clinical phase:	IIA
Objectives:	The primary objective of this study was to examine the efficacy and safety of tiotropium compared with placebo as add-on therapy in severe asthmatics according to Global Initiative for Asthma (GINA, 2005) step 4 classification.
Methodology:	Randomised, double-blind, placebo-controlled, 3-way cross-over design.
No. of subjects:	
planned:	150 to be enrolled, 115 to be randomised and 84 completed patients
actual:	enrolled: 132 patients randomised: 107 patients 5 µg Tiotropium Inhalation Solution: treated 104 patients; analysed (for primary endpoint) 104 patients 10 µg Tiotropium Inhalation Solution: treated 103 patients; analysed (for primary endpoint) 103 patients Placebo: treated 103 patients; analysed (for primary endpoint) 103 patients

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Diagnosis and main criteria for inclusion:	Outpatients of either sex, age 18 – 75 years, with a history of asthma of at least 5 years and a current diagnosis of severe, persistent asthma (GINA 2005 step 4) and a post bronchodilator (400 µg salbutamol) forced expiratory volume in 1 second (FEV_1) ≤80% predicted (European Coal and Steel and Community [ECSC] criteria). In addition, patients had to have a FEV_1 ≤70% of forced vital capacity (FVC), smoking history <10 pack years and ≥1 year smoking cessation, symptomatic (based on Asthma Control Questionnaire [ACQ] score ≥1.5) and at least 4 weeks on a high, stable dose of inhaled corticosteroids plus a long-acting beta adrenergic.
Test product:	Tiotropium inhalation solution
dose:	5 µg or 10 µg once daily (q.d.) in the morning
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	2.5 µg B052000510; 5 µg B052000647
Reference therapy:	Placebo inhalation solution
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B052000504
Duration of treatment:	Two-week run-in period followed by three 8-week treatment periods giving a total treatment period of 24 weeks
Criteria for evaluation:	
Efficacy / clinical pharmacology:	**Primary:** Clinic assessment: peak FEV_1 (within 3 hours post-dosing) **Secondary:** Clinic assessment: peak FVC, trough FEV_1 (pre-dose), trough FVC, FEV_1 (AUC_{0-3h}), FVC (AUC_{0-3h}), individual FEV_1/FVC measurements, mini-asthma quality of life questionnaire (AQLQ)

	Home assessment: peak expiratory flow ($PEF_{am/pm}$), $FEV_{1\ am/pm}$, PEF variability, use of PRN rescue medication, daytime and nocturnal symptoms, asthma symptoms and QOL assessed by asthma e-diary incorporated in Asthma Monitor®-2 (AM2) system In a subset of patients: FEV_1 (AUC_{0-12h}), FEV_1 (AUC_{12-24h}), FEV_1 (AUC_{0-24h}), FVC (AUC_{0-12h}), FVC (AUC_{12-24h}), FVC (AUC_{0-24h})
Safety:	Physical examination, vitals signs (blood pressure and pulse rate), laboratory tests and the incidence and intensity of adverse events (AEs)
Statistical methods:	Analysis of covariance (ANCOVA) with terms for FEV_1, pooled centre, patient within pooled centre, period and treatment.

SUMMARY – CONCLUSIONS:

Efficacy results:

The primary endpoint of peak FEV_1 response (adjusted mean) after 8 weeks of treatment was 0.451 L for 5 µg tiotropium, 0.483 L for 10 µg tiotropium and 0.313 L for placebo (all treatments were given on top of usual care of at least a long-acting ß-agonist [LABA] and an inhaled corticosteroid [iCS]). The observed difference to placebo was 0.170 L and 0.139 L for 10 µg and 5 µg tiotropium, respectively. The differences between the active dose groups and the placebo group were statistically significant ($p<0.0001$), but between the tiotropium dose groups, no statistical difference could be shown.

Safety results:

During the treatment phase, the overall occurrence of AEs was similar between the placebo and 5 µg tiotropium groups (39.8% and 42.3% of patients, respectively, reported at least one AE), but slightly higher in the 10 µg tiotropium group (49.5% of patients reported at least one AE). The most common treatment-emergent AEs were nasopharyngitis and asthma (MedDRA preferred term classification including aggravated asthma and exacerbation of asthma), with both being reported overall by 28 patients (26.2%).

Very few of the AEs were considered drug-related, with only one patient (1.0%) in both the placebo and 5 µg tiotropium groups and 5 patients (4.9%) in the 10 µg tiotropium group reporting drug-related AEs. The only treatment-emergent AE reported in more than one patient was dry mouth, which was considered drug-related in 4 patients (3.9%) in the 10 µg tiotropium group.

A total of 6 patients (5.6%) were withdrawn from the study due to an AE, with slightly more patients in the 5 µg tiotropium group (4 patients, 3.8%) compared with the 10 µg tiotropium and placebo groups (1 patient each, 1.0%). The most common AE leading to withdrawal from the study was worsening of asthma, which was the reason for withdrawal for 4 patients.

A total of 5 patients (4.7%) had at least one SAE during the study, with 2 patients having SAEs during placebo treatment, 2 having SAEs during 5 µg tiotropium treatment and 1 having an SAE during 10 µg tiotropium treatment. None of the SAEs were considered drug-related and none were fatal or life-threatening.

No clinically relevant change in mean vital sign values associated with tiotropium treatment was seen.

Conclusions:

The primary endpoint of peak FEV_1 response showed statistically significant superiority for both doses of tiotropium compared with placebo, with these results supported by the analysis of secondary endpoints. Thus, tiotropium via the Respimat® inhaler was an effective broncholdilator as add-on therapy in a population of patients with symptomatic severe persistent asthma. The 5 µg tiotropium inhalation solution administered via the Respimat® inhaler in addition revealed a safety profile similar to placebo (at least LABA and iCS).