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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat® inhaler		**EudraCT No.:** 2008-001413-14 and 2008-001414-25	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 6	
Module:		**Volume:**	
Report date: 31 AUG 2012	**Trial No. / U No.:** 205.416 and 205.417 / U12-2037-01	**Dates of trial:** 30 OCT 2008 – 25 JUL 2011	**Date of revision:** Not applicable

Title of trials:	A Phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (5 µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multi-centre, multi-national trials; 148 sites in 15 countries
Publication (reference):	Data of the combined analysis of these trials have not been published
Clinical phase:	III
Objectives:	The objective of this trial was to evaluate the long-term efficacy and safety of tiotropium solution for inhalation (5 µg) delivered by the Respimat® inhaler in comparison to placebo (both treatments on top of usual care) in adult patients with severe, uncontrolled, persistent asthma
Methodology:	Randomised, placebo-controlled, double-blind, parallel-group comparison of tiotropium (5 µg) daily in the morning versus placebo on top of usual care over 48 weeks
No. of subjects:	
planned:	entered: 600 (planned in CTP) 800 (planned for interim analysis in CTP)
actual:	enrolled: 1335
	Tiotropium inhalation solution (5 µg) entered: 456 treated: 456 analysed (for primary endpoint): 453 Placebo: entered: 456 treated: 456 analysed (for primary endpoint): 454

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Diagnosis and main criteria for inclusion:	Male and female outpatients between 18 and 75 years old with a current diagnosis of severe, persistent asthma; patients needed a minimum documented 5-year history of asthma diagnosed before the age of 40; patients who had never smoked or ex-smokers with <10 pack-years who had quit smoking at least 1 year prior to enrolment; symptomatic despite treatment with a high, stable dose of inhaled corticosteroids (ICS) and a long-acting β_2-adrenergic agonist (LABA) for at least 4 weeks prior to screening; forced expiratory volume in 1 second (FEV_1) ≤80% of predicted and ≤70% of the forced vital capacity (FVC) 30 min after the inhalation of 400 µg salbutamol (albuterol); Asthma Control Questionnaire (ACQ) ≥1.5 at screening (Visit 1) and prior to randomisation (Visit 2). All patients had a history of 1 or more asthma exacerbations in the past year that required treatment with systemic corticosteroids, with no asthma exacerbations in the 4 weeks prior to screening (Visit 1) or during the 4-week screening period.
Test product:	Tiotropium inhalation solution
dose:	5 µg (ex mouthpiece, as 2 actuations of 2.5 µg, calculated as free cation), once daily (qd) in the morning (am)
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	See individual clinical trial reports of 205.416 and 205.417
Reference therapy:	Placebo inhalation solution
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	See individual clinical trial reports of 205.416 and 205.417
Duration of treatment:	A 4-week screening period was followed by a 48-week treatment period. Patients were followed-up for 4 weeks.
Criteria for evaluation:	

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Efficacy / clinical pharmacology:	Primary endpoint for the pooled analysis: Time to first severe asthma exacerbation during the 48-week treatment period
Efficacy / clinical pharmacology (continued):	Secondary endpoints for the pooled analysis: • Time to first asthma exacerbation during the 48-week treatment period (including severe, non-severe; symptomatic, asymptomatic; i.e. any exacerbation) • Number of patients with at least 1 severe asthma exacerbation • Number of patients with at least 1 asthma exacerbation • Number of severe asthma exacerbations per patient • Number of asthma exacerbations per patient
Safety:	Safety was determined based on the incidence and intensity of AEs, changes in vital signs, including pulse rate and seated blood pressure, and changes in physical examination reported as AEs.
Statistical methods:	The analyses were based on the pooled data from the replicate trials 205.416 and 205.417. The superiority of treatment with tiotropium (5 µg) over treatment with placebo was tested in terms of time to first severe asthma exacerbation. For this endpoint a pre-planned interim analysis of the hazard ratio of time to first severe asthma exacerbation was performed with the option to adapt the sample size. Based on the interim analysis which was conducted by an independent data monitoring committee, the sample size was increased from 300 to approximately 400 patients for each trial.

SUMMARY – CONCLUSIONS:

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Efficacy / clinical pharmacology results:	A total of 912 patients were randomised and treated with either tiotropium 5 µg (456 patients) or placebo (456 patients). Of the treated patients, 10.7% discontinued prematurely (Tio R5: 10.3%, placebo: 11.2%). The most frequent reason for discontinuation was withdrawn consent (3.3%) (Tio R5: 3.3%, placebo: 3.3%). Overall, the demographic profile was balanced between the treatment groups. Baseline characteristics were as expected for a population of adult patients with severe, uncontrolled, persistent asthma (mean baseline FEV_1: 1.603 L, mean baseline FEV_1 %predicted: 55.96, mean baseline ACQ: 2.6).
Efficacy / clinical pharmacology results (continued):	Superiority of Tio R5 over placebo was demonstrated for the primary endpoint time to first severe asthma exacerbation. The hazard ratio of Tio R5 to placebo was found to be 0.79 which translated into a risk reduction of 21% (p=0.0343). The time to first severe exacerbation was increased to 282 days vs. 226 days (This is the time until at least 25% of the patients had a first severe exacerbation). Superiority of Tio R5 over placebo was demonstrated for the secondary endpoint time to first asthma exacerbation. The hazard ratio was found to be 0.69 which translated into a risk reduction of 31 % (p<0.0001). In terms of time to first asthma exacerbation a median time of 315.0 days was reported for Tio R5 patients versus 181.0 days for placebo patients. For the secondary endpoint number of patients with at least 1 severe asthma exacerbation, the odds ratio for Tio R5 versus placebo was found to be 0.75 (p=0.0592). The analysis of number of patients with at least 1 asthma exacerbation showed an odds ratio of 0.58 (p<0.0001). The ratio of number of severe asthma exacerbations per patient for Tio R5 versus placebo was found to be 0.80 (p=0.0458). The ratio of number of asthma exacerbations per patient for Tio R5 versus placebo was found to be 0.76 (p=0.0031).

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Safety results:

During the treatment period, the overall incidence of AEs was higher in the placebo group than in the Tio R5 group, with 73.5% of tiotropium and 80.3% of placebo patients reporting at least 1 AE. The most frequently reported treatment-emergent AEs included asthma (Tio R5: 39.9%, placebo: 50.9%), PEF rate decreased (Tio R5: 20.4%; placebo: 26.8%), and nasopharyngitis (Tio R5: 11.2%; placebo: 12.3%).

AEs reported as being drug related by the investigator were higher in patients taking Tio R5 than in patients taking placebo (Tio R5: 5.7%; placebo: 4.6%); all drug-related AEs were in general of mild or moderate intensity. Other significant AEs (according to ICH E3; Tio R5: 1.3%; placebo: 2.6%) and AEs leading to discontinuation (Tio R5: 1.8%; placebo: 3.1%) were reported infrequently.

Serious AEs (SAEs) were reported for 8.1% of patients in the Tio R5 and 8.8% of patients in the placebo group. The most frequently reported SAE in both treatment groups was asthma (Tio R5: 17 patients, placebo: 21 patients). Three patients (all in the Tio R5 group) were reported with life threatening SAEs (one patient with cerebral infarction, one patient with hypotension, shock and renal failure (following hospitalisation due to asthma exacerbation), and one patient with acute respiratory failure and asthma). None of these were considered drug-related by the investigator. There were no deaths reported during the course of this study.

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Conclusions:

In patients with severe, persistent asthma, still uncontrolled despite treatment with at least high-dose ICS and LABA, having had at least 1 severe asthma exacerbation in the year prior to trial participation, treatment with Tio R5 was superior to placebo for the primary endpoint time to first severe asthma exacerbations with a 21% risk reduction over 48 weeks of treatment. The time to first severe exacerbation was increased to 282 days vs. 226 days (This is the time until at least 25% of the patients had a first severe exacerbation). Superiority of Tio R5 could be demonstrated for number of severe asthma exacerbations per patient. Furthermore, Tio R5 was superior to placebo for the secondary endpoints time to asthma exacerbation, number of patients with at least 1 asthma exacerbation and the number of asthma exacerbations per patient. Overall Tio R5 was safe and well tolerated when administered to adult patients with severe, uncontrolled, persistent asthma.

Trial Synopsis - Appendix

The results table on the following page supplement the trial results presented in the Trial Synopsis. The appended tables provide detailed results for patient disposition in the synopsis.

Results for	presented in
Patient Disposition	Table 15.1.1: 1

Table 15.1.1: 1 Disposition of patients (Termination of trial medication)

Disposition	Placebo	Tio R5	Total
Enrolled			1335
Not entered/randomised			423
Entered/randomised	456	456	912
Not treated	0	0	0
Treated	456 (100.0)	456 (100.0)	912 (100.0)
Not prematurely discontinued from trial medication	405 (88.8)	409 (89.7)	814 (89.3)
Prematurely discontinued from trial medication	51 (11.2)	47 (10.3)	98 (10.7)
Adverse events	14 (3.1)	8 (1.8)	22 (2.4)
Worsening of disease under study	8 (1.8)	3 (0.7)	11 (1.2)
Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)
Other adverse event	6 (1.3)	5 (1.1)	11 (1.2)
Lack of efficacy	0 (0.0)	2 (0.4)	2 (0.2)
Non compliant with protocol	7 (1.5)	5 (1.1)	12 (1.3)
Lost to follow-up	3 (0.7)	1 (0.2)	4 (0.4)
Consent withdrawn not due to adverse events	15 (3.3)	15 (3.3)	30 (3.3)
Other	12 (2.6)	16 (3.5)	28 (3.1)