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		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2012-001873-10	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 8	
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Title of trial:	A randomised, double-blind, 2-way crossover study to determine 24-hour FEV_1-time profile of inhaled tiotropium, delivered via the Respimat® inhaler, after 4 weeks of once daily (5 µg in the evening [2 actuations of 2.5 µg]) or twice daily (2.5 µg in the morning and evening [2 actuations of 1.25 µg]) administration in patients with moderate persistent asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre trial including 22 sites in 4 countries (Austria 4, Germany 11, Hungary 5, and Slovenia 2)
Publication (reference):	Data from this trial have not been published
Clinical phase:	II
Objectives:	The primary objective of this trial was to determine the 24-hour forced expiratory volume in 1 second (FEV_1)-profile of tiotropium solution for inhalation after two 4-week treatment periods of 5 µg tiotropium administered once daily (q.d.) in the evening and 2.5 µg tiotropium administered twice daily (b.i.d.; morning and evening) with the Respimat® inhaler. In addition, the pharmacokinetics (PK) of tiotropium were characterised in a subset of the study population. The objective of this sub-investigation was to compare the 24-hour PK profile of 5 µg tiotropium administered q.d. and 2.5 µg tiotropium administered b.i.d.
Methodology:	This was a randomised, double-blind, 2-way crossover study comparing two daily dose regimens of tiotropium for 4 weeks in addition to maintenance therapy with a medium dose of an inhaled corticosteroid (ICS) controller medication. There was no washout between treatment periods. Patients who participated in the PK evaluation had blood and urine samples taken after the first dose of the first treatment period, and at the end of each 4-week treatment period. All patients participated in the study for 15 weeks, comprising a 4-week screening period, two 4-week treatment periods, and then a follow-up 21 days after completion of the randomised treatment periods or early discontinuation.

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No. of patients:	
planned:	entered: 92
actual:	enrolled: 125 entered: 98 PK subset: 35 Tiotropium 2.5 µg b.i.d. (Tio R2.5 b.i.d.): entered 98 treated: 98 analysed (for primary endpoint): 98 Tiotropium 5 µg q.d. (Tio R5 q.d.): entered: 98 treated: 98 analysed (for primary endpoint): 97
Diagnosis and main criteria for inclusion:	Male and female outpatients between 18 and 75 years old with at least a 3-month history of moderate persistent asthma (according to Global Initiative for Asthma [GINA] guidelines) that was diagnosed before the age of 40. Patients had to have never smoked or had to be ex-smokers with less than 10 pack-years who had stopped smoking at least 1 year prior to enrolment. Patients had to be symptomatic despite treatment with a medium, stable dose of ICS for at least 4 weeks prior to screening; to be considered symptomatic, patients needed to have an Asthma Control Questionnaire (ACQ) score of ≥1.5 at screening (Visit 1) and randomisation (Visit 2). Patients had to have a pre-bronchodilator FEV_1 of ≥60% and ≤90% of predicted normal at screening, and an increase in post-bronchodilator FEV_1 of ≥12% and ≥200 mL 15 to 30 minutes after the inhalation of 400 µg of salbutamol.
Test product:	Tiotropium solution for inhalation (Spiriva® – Respimat®)
dose:	2.5 µg twice daily: 2 actuations of 1.25 µg tiotropium in the morning and in the evening (total daily dose of 5 µg) or 5 µg once daily: 2 actuations of 2.5 µg tiotropium in the evening and 2 actuations of placebo in the morning (total daily dose of 5 µg) Both doses were ex mouthpiece and calculated as the free cation
mode of admin.:	Oral inhalation via the Respimat® inhaler

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batch no.:	1.25 µg per actuation: B102000044-B092000043 2.5 µg per actuation: B102000049-B082000285 Placebo: B102000083-B082000164
Reference therapy:	Not applicable
Duration of treatment:	A 28-day screening period was followed by two 4-week treatment periods, i.e. total treatment duration of 8 weeks. There was no washout period between treatments. All patients were followed up for 21 days after completion of the randomised treatment periods or early discontinuation.
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the area under the curve (AUC) from 0 to 24 hours (relative to evening dosing) for FEV_1 (FEV_1 $AUC_{0–24h}$) (L) determined at the end of each 4-week randomised treatment period. It was analysed as the change from study baseline (i.e. response). Secondary endpoints included FEV_1 AUC_{0-12h}, FEV_1 AUC_{12-24h}, $FEV_1Peak_{0–24h}$, trough FEV_1, forced vital capacity (FVC) AUC_{0-24h}, FVC AUC_{0-12h}, FVC AUC_{12-24h}, FVC $Peak_{0–24h}$, trough FVC, and peak expiratory flow (PEF) AUC_{0-24h}. All these endpoints were determined as a response at the end of each 4-week period of randomised treatment. Other endpoints included individual FEV_1, FVC and PEF values at each timepoint over 24 hours at the end of each 4-week period of randomised treatment. Morning and evening PEF recordings (home assessment via the asthma monitor AM3®), PEF variability (home assessment), morning and evening FEV_1 recordings (home assessment), use of salbutamol rescue medication, night-time awakenings, and ACQ were also evaluated. In a subset of patients, PK parameters of tiotropium were evaluated in blood and urine samples following the administration of the first dose and at the end of each 4-week treatment period.
Safety:	Incidence of adverse events (AEs), changes in 12-lead electrocardiogram (ECG), and changes in vital signs (seated blood pressure and pulse rate).

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Statistical methods:	**Primary endpoint**: The primary endpoint, FEV_1 $AUC_{0–24h}$ response, was analysed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM). The statistical model included 'treatment' and 'period' as fixed effects and 'patient' as a random effect; study baseline was included as covariate. Adjusted means (with standard error [SE] and treatment contrasts [Tio R5 q.d. – Tio R2.5 b.i.d.]) with 95% confidence intervals (CIs) are presented. No p-values are presented as no formal statistical hypothesis was tested. **Secondary and other endpoints:** The secondary and other endpoints were analysed and summarised in the same way as the primary endpoint. Individual daily (morning and evening) measurements used in computation of weekly means for the endpoints derived from home assessment AM3® device data are listed only. **PK endpoints:** Non-compartmental PK analyses were carried out using a validated software program, e.g. WinNonlin™. Descriptive statistics were calculated for all analyte concentrations as well as for all primary and secondary PK parameters.
SUMMARY – CONCLUSIONS:	
Efficacy/clinical pharmacology results:	**Disposition:** A total of 125 patients were enrolled, with 98 patients randomised to receive treatment with Tio R5 q.d. and Tio R2.5 b.i.d. in a crossover manner using a predefined randomisation sequence. Overall, 97 patients (99.0%) completed the trial according to the clinical trial protocol (CTP), with 1 patient (1.0%) prematurely discontinuing trial medication due to an AE (see safety section). **Demographics:** The study population contained slightly more male patients (55.1%) than female patients (44.9%); all patients were White. The mean (standard deviation [SD]) age was 43.8 (21.1) years and the mean body mass index (BMI) was 27.7 kg/m². The majority of patients had never smoked (69.4%). The mean age at onset of asthma was 23.6 years (range 0-40 years). The mean duration of asthma (from date of first diagnosis to inclusion in the study) was 20.2 years (range 0.3-54.0 years). The mean FEV_1 reversibility was 23.5% at screening (Visit 1). At study baseline (Visit 2), 98.0% patients had a FEV_1 ≥60% and ≤90% of predicted normal.

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Efficacy/clinical pharmacology results (cont.):

Concomitant diagnoses were as expected for an asthmatic population, with allergic rhinitis (33.7%) reported most frequently. All 98 randomised patients were taking a medium stable dose of ICS within the 3 months prior to study participation and continued taking ICS throughout the trial. Almost all treated patients (94.9%) had taken β_2-adrenergic agonists prior to the study (65.3% of patients were taking regular long-acting and 66.3% of patients were taking regular on short-acting β_2-adrenergic agonists).

Primary endpoint: Mean (SD) FEV_1 AUC_{0-24h} at study baseline was 2.634 L (0.733). Inhalation of both daily dose regimens of tiotropium resulted in notable bronchodilation compared to baseline, with a similar effect size for FEV_1 AUC_{0-24h} response being observed compared to baseline: mean increase in FEV_1 AUC_{0-24h} in the Tio R2.5 b.i.d. period of 0.219 L, and in the Tio R5 q.d. period of 0.217 L (FAS). The difference in adjusted means between the two treatments was -0.002 L (95% CI: -0.038, 0.034). Comparable results were seen in the PPS analysis: difference in adjusted means of -0.001 L (95% CI: -0.038, 0.037).

Secondary and other endpoints:

All the secondary endpoints of clinic PFTs (FEV_1, FVC, and PEF) were in line with the primary endpoint results, with no notable differences being seen between the two treatments (see table below).

When mean response at individual time points over 24 hours was evaluated, the maximum effect for FEV_1 for both treatments was observed during the daytime at 18 hours after inhalation of the last evening dose of study drug (adjusted mean FEV_1 responses 0.292 L and 0.313 L, respectively). The maximum effect of FVC for Tio R2.5 b.i.d. was observed at 16 hours after study drug inhalation (adjusted mean FVC response 0.152 L), with the maximum effect for Tio R5 q.d. being observed during the daytime at 18 hours after inhalation of the last evening dose of study drug (adjusted mean FVC response 0.123 L). Finally the maximum effect for mean PEF AUC_{0-24h} response for Tio R2.5 b.i.d. was observed at 16 hours after study drug inhalation (adjusted mean PEF response 57.792 L/min), with the maximum effect for Tio R5 q.d. being observed during the daytime at 18 hours after inhalation of the last evening dose of study drug (adjusted mean PEF response 52.031 L/min).

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Efficacy/clinical pharmacology results (cont.):

Parameter and treatment	N	Mean	Adjusted response[1] (SE)	Mean	(SE)	Adjusted difference between groups[1]: 95% CI
FEV_1 $AUC_{0–12h}$ [L]						
Tio R2.5 b.i.d.	98	0.182	(0.031)	0.010	(0.021)	(-0.032, 0.052)
Tio R5 q.d.	97	0.192	(0.031)			
FEV_1 $AUC_{12–24h}$ [L]						
Tio R2.5 b.i.d.	98	0.256	(0.033)	-0.014	(0.018)	(-0.050, 0.022)
Tio R5 q.d.	97	0.243	(0.033)			
FEV_1 $Peak_{0–24h}$ [L]						
Tio R2.5 b.i.d.	98	0.465	(0.031)	-0.014	(0.018)	(-0.051, 0.023)
Tio R5 q.d.	97	0.451	(0.031)			
Trough FEV_1 [L]						
Tio R2.5 b.i.d.	98	0.203	(0.033)	0.004	(0.032)	(-0.060, 0.068)
Tio R5 q.d.	97	0.207	(0.034)			
FVC $AUC_{0–24h}$ [L]						
Tio R2.5 b.i.d.	98	0.079	(0.032)	-0.005	(0.020)	(-0.044, 0.035)
Tio R5 q.d.	97	0.075	(0.032)			
FVC $AUC_{0–12h}$ [L]						
Tio R2.5 b.i.d.	98	0.056	(0.031)	-0.003	(0.023)	(-0.048, 0.042)
Tio R5 q.d.	97	0.053	(0.031)			
FVC $AUC_{12–24h}$ [L]						
Tio R2.5 b.i.d.	98	0.102	(0.034)	-0.006	(0.020)	(-0.047, 0.034)
Tio R5 q.d.	97	0.096	(0.034)			
FVC $Peak_{0–24h}$ [L]						
Tio R2.5 b.i.d.	98	0.328	(0.033)	-0.019	(0.026)	(-0.070, 0.032)
Tio R5 q.d.	97	0.309	(0.033)			
Trough FVC [L]						
Tio R2.5 b.i.d.	98	0.077	(0.034)	0.041	(0.035)	(-0.030, 0.111)
Tio R5 q.d.	97	0.118	(0.034)			
PEF $AUC_{0–24h}$ [L/min]						
Tio R2.5 b.i.d.	98	42.788	(5.923)	-1.389	(3.658)	(-8.651, 5.873)
Tio R5 q.d.	97	41.399	(5.933)			

Common mean (SD) of study baseline FEV_1 response (L) was 2 634 L (0 773), mean FVC at baseline was 3 964 L (1 027), and mean PEF at baseline was 414 398 L/min (111 531)
[1] Adjusted for treatment, period, patient, and baseline

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Efficacy/clinical pharmacology results (cont.):

Other efficacy endpoints obtained using the AM3® device at home were also in line with the primary endpoint results, with no notable differences being seen between the adjusted weekly means of the two treatments: PEF_{am} 2.222 L/min (95% CI: -6.300, 10.743); PEF_{pm} -0.280 L/min (95% CI: -8.191, 7.630); PEF variability -0.847 L/min (95% CI: -2.100, 0.406); morning FEV_1 response 0.009 L (95% CI: -0.040, 0.059); and evening FEV_1 response 0.016 L (95% CI: -0.058, 0.090). Use of rescue medication decreased by a weekly mean of 1.5 puffs per 24-hour period when on Tio R2.5 b.i.d. and 1.7 puffs when on Tio R5 q.d. The score for night-time awakenings due to asthma also decreased during both treatments, with a weekly mean decrease from baseline for Tio R2.5 b.i.d. of -0.241 and for Tio R5 q.d. of -0.289. No notable differences were seen between the two tiotropium treatments for either assessment. ACQ scores improved to a similar level during the two treatments, from a mean score at baseline of 2.446 to a mean score of 1.465 after 4 weeks of treatment with Tio R2.5 b.i.d. and 1.373 following treatment with Tio R5 q.d. No notable difference was seen between the two treatments, with a difference in adjusted means between Tio R2.5 b.i.d. and Tio R5 q.d. of -0.092.

Pharmacokinetics:

Tiotropium was rapidly absorbed following administration of Tio R2.5 b.i.d. and Tio R5 q.d., with a median time from dosing to maximum plasma concentration at steady state ($t_{max,ss}$) of 0.083 to 0.100 hours post-inhalation. The daily total exposure (measured by $AUC_{0-\tau,ss}$) at steady-state was comparable if the dose was given as a single daily dose or split into a b.i.d. regimen. The b.i.d. regimen resulted in up to 4.29-fold accumulation and the q.d. regimen resulted in up to 2.7-fold accumulation based on urinary excretion. At steady-state, the maximum measured concentration in plasma at steady state ($C_{max,ss}$) and $AUC_{0-tau,ss}$ results were comparable following the morning and evening administrations of Tio R2.5 b.i.d. The steady-state $C_{max,ss}$ value with Tio R2.5 b.i.d. administration was approximately 35-37% lower than that of Tio R5 q.d.

Safety results:

The mean (SD) exposure to study treatment was comparable for both treatments (Tio R2.5 b.i.d. 29.4 [1.2] days, Tio R5 q.d. 29.5 [3.5] days). During the two treatment periods, the overall frequency of AEs was well balanced, with 19.4% of Tio R2.5 b.i.d. patients and 18.4% of Tio R5 q.d. patients reporting at least 1 AE. The most frequently reported treatment-emergent AEs were nasopharyngitis (both groups 4.1%) and headache (Tio R2.5 b.i.d. 2.0%, Tio R5 q.d. 3.1%).

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Safety results (cont.):	AEs that were considered drug-related by the investigator occurred in 2 patients (2.0%) during treatment with Tio R2.5 b.i.d. (both of dry mouth), and 1 patient (1.0%) during treatment with Tio R5 q.d. (headache). AEs of severe intensity were only reported for 1 patient during treatment with Tio R2.5 b.i.d.: this patient was found to have AEs of cervical dysplasia and cervix carcinoma in situ classed as severe following routine screening whilst receiving Tio R2.5 b.i.d.: both events were also classed as SAEs and led to premature discontinuation from the study (note: the AEs were reported while the patient was receiving Tio R2.5 b.i.d in the first period but the patient was withdrawn in the second period when they were receiving Tio R5 q.d.). No other patients had drug-related AEs, severe AEs, SAEs, or withdrew from the study. Mean systolic and diastolic blood pressure and pulse rate were comparable between the treatments, with no clinically relevant changes in mean vital signs associated with tiotropium being seen. Compared to the baseline ECG recording, no clinically significant changes in ECGs at end-of-treatment were observed. No pregnancies occurred during the course of the study.
Conclusions:	Tiotropium inhalation solution via the Respimat® inhaler was a well-tolerated bronchodilator as add-on therapy to medium-dose ICS in adult patients with not fully controlled, symptomatic, moderate persistent asthma. Comparable bronchodilation was seen following inhalation of both study treatments, as evaluated by the AUC FEV_1 over a 24-hour period, regardless of whether it was administered as a once daily dose of 5 µg (in the evening) or as a twice daily dose of 2.5 µg (in the morning and evening). The primary endpoint was supported by the secondary endpoints evaluated at the clinic and by at home assessments using the AM3® device. Pharmacokinetic evaluations showed that at steady-state, administration of Tio R2.5 b.i.d. resulted in a comparable total daily exposure but approximately 35 to 37% lower $C_{max,ss}$ compared to Tio R5 q.d.