Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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®		**EudraCT No.:** 2009-018005-43	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 16	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Title of trial:	A Phase III randomised, double-blind, placebo-controlled, parallel-group trial to evaluate efficacy and safety of tiotropium inhalation solution delivered via Respimat® inhaler (2.5 and 5 µg once daily) compared with placebo and salmeterol HFA MDI (50 µg twice daily) over 24 weeks in patients with moderate persistent asthma
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multi-national trial in 124 sites in 11 countries
Publication (reference):	Data of this trial have not been published
Clinical phase:	III
Objectives:	This trial was 1 of 2 confirmatory Phase III trials with identical protocols (205.418 and 205.419). The objective of this trial was to evaluate the long-term efficacy and safety of 2 doses of tiotropium inhalation solution (2.5 µg and 5 µg) delivered by the Respimat® inhaler compared to placebo and to salmeterol (all treatments on top of medium-dose inhaled corticosteroid (ICS) maintenance therapy) in adults with moderate persistent asthma.
Methodology:	Randomised, double-blind, double-dummy, active- and placebo-controlled, parallel-group comparison of tiotropium (2.5 µg and 5 µg) once daily in the evening versus salmeterol (50 µg) twice daily and placebo on top of medium-dose ICS maintenance therapy over 24 weeks

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 2 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

No. of subjects:	
planned:	1000
actual:	enrolled: 2102 randomised: 1032 Placebo: randomised: 254 treated: 254 analysed (for primary endpoint): 253 Tiotropium bromide 2.5 µg (Tio R2.5): randomised: 258 treated: 257 analysed (for primary endpoint): 256 Tiotropium bromide 5 µg (Tio R5): randomised: 254 treated: 253 analysed (for primary endpoint): 252 Salmeterol: randomised: 266 treated: 266 analysed (for primary endpoint): 264
Diagnosis and main criteria for inclusion:	Male and female outpatients between 18 and 75 years of age with a current diagnosis of and with a minimum documented 3-month history of moderate, persistent asthma that was diagnosed before the age of 40; patients who had never smoked or who were ex-smokers with <10 pack-years and had stopped smoking at least 1 year prior to enrolment; symptomatic despite treatment with a medium, stable dose of inhaled corticosteroids (ICS) for at least 4 weeks prior to screening, pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≥60% and ≤90% of predicted; post-bronchodilator FEV_1 increase of ≥12% and ≥200 mL; variation in absolute FEV_1 values at Visit 1 (pre-bronchodilator) and Visit 2 (pre-dose) within ±30%; Asthma Control Questionnaire (ACQ) total score ≥1.5 at screening (Visit 1) and prior to randomisation (Visit 2); no asthma exacerbation or acute respiratory tract infection in the 4 weeks prior to screening.
Test product:	Tiotropium solution for inhalation
dose:	2.5 µg (ex-mouthpiece, 2 actuations of 1.25 µg, calculated as free cation) or 5 µg (ex-mouthpiece, 2 actuations of 2.5 µg, calculated as free cation), once daily in the evening

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 3 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B092000111-B092000094 (1.25 µg per actuation) B092000103-B092000094 (2.50 µg per actuation)
Reference therapy 1	Salmeterol hydrofluoroalkane (HFA 134a) metered dose inhaler (MDI)
dose:	50 µg (2 actuations of 25 µg) twice daily (morning and evening)
mode of admin.:	Oral inhalation via MDI
batch no.:	PH2274, OG1169, PC1980, PK2502, RA2332, RD0123
Reference therapy 2	Placebo solution for inhalation
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B092000097-B092000094
Reference therapy 3	Placebo MDI
dose:	Not applicable
mode of admin.:	Oral inhalation via MDI
batch no.:	B906475, B906475A
Duration of treatment:	A 4-week run-in period followed by a 24-week treatment period. Patients were followed up for 21 days after completion of the treatment period or in the event of early discontinuation of trial medication.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 4 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Criteria for evaluation:

Efficacy / clinical pharmacology:

Co-primary endpoints

The co-primary endpoints for this trial were the maximum FEV_1 within 3 h post-dosing (FEV_1 $peak_{0-3h}$) and pre-dose FEV_1 (trough FEV_1). Both were analysed as a response (change from trial baseline) after 24 weeks of treatment. For the analysis of pooled data from the twin trials 205.418 and 205.419, the primary endpoint was the (binary) responder rate as assessed by the Asthma Control Questionnaire (ACQ) total score determined after 24 weeks of treatment. This endpoint was analysed as a secondary endpoint in the individual trials.

Secondary endpoints

Secondary endpoints included maximum forced vital capacity measured within 3 h post-dosing (FVC $peak_{0-3h}$), pre-dose (trough) FVC, FEV_1 area under the curve from 0 to 3 h (FEV_1 AUC_{0-3h}), FVC AUC_{0-3h}, and pre-dose peak expiratory flow (trough PEF), analysed as a response (change from trial baseline after 24 weeks of treatment); ACQ total score, ACQ responder rate, and Standardised Asthma Quality of Life Questionnaire (AQLQ(S)) total score after 24 weeks of treatment; and the AM3® endpoints (measured by the patient at home) pre-dose morning (PEF_{am}) and evening peak expiratory flow (PEF_{pm}), PEF variability, pre-dose morning ($FEV_{1\ am}$) and evening FEV_1 ($FEV_{1\ pm}$), daily use of salbutamol, and asthma symptom-free days, analysed as the weekly mean response at Week 24. Secondary endpoints for the pooled analysis were time to first severe asthma exacerbation and time to first asthma exacerbation.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 5 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology (continued):	Further efficacy endpoints Further efficacy endpoints measured in the clinic included individual FEV_1, FVC, and PEF measurements at each time point; FEV_1 and FVC ($peak_{0-3h}$, trough, and AUC_{0-3h}), PEF ($peak_{0-3h}$ and AUC_{0-3h}) at all visits; FEV_1 AUC_{0-12h}, FEV_1 AUC_{0-24h}, FEV_1 $AUC_{12-24\,h}$, FVC AUC_{0-12h}, FVC AUC_{0-24h}, and FVC AUC_{12-24h} after 24 weeks of treatment (in a subset of 334 patients); individual FEV_1 and FVC measurements at each time point including the 5- and 15-min time points after 16 weeks of treatment (in a subset of 383 patients); the AM3® endpoints PEF_{am}, PEF_{pm}, PEF variability, and $FEV_{1\,am}$, $FEV_{1\,pm}$ at each week during the 24-week treatment; use of rescue medication (daytime, night-time, entire 24-h day), asthma symptoms, and asthma symptom-free days during each week of the 24-week treatment period; ACQ total score, ACQ6, and AQLQ(S) scores at all visits, ACQ6 and AQLQ(S) responder rates; time to first asthma exacerbation (including severe, non-severe; symptomatic, asymptomatic; i.e. any exacerbation), time to first symptomatic asthma exacerbation, time to first severe asthma exacerbation, number of exacerbations (any/symptomatic/severe) per patient, and number of patients with at least 1 exacerbation (any/symptomatic/severe) during the 24-week treatment period; patient satisfaction and preference questionnaire (PASAPQ) after 24 weeks of treatment (in a subset of 351 patients). Other endpoints Other endpoints included pharmacokinetic (PK) parameters of tiotropium. These parameters were evaluated in blood and urine samples in a subset of 100 patients after the first dose and at pharmacokinetic steady state (4 weeks).
Safety:	Safety was determined based on the incidence and intensity of adverse events (AEs), changes in vital signs (seated blood pressure and pulse rate), changes in 12-lead electrocardiogram (ECG), physical examination, and laboratory tests (reported as AEs), and vital status information.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 6 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Statistical methods:

The co-primary endpoints for each of the twin trials 205.418 and 205.419 were tested as part of a sequential testing scheme versus placebo. Testing of the ACQ response was based on the pooled data from the twin trials. Each step of the following 6 hypotheses was only to be considered confirmatory if all the previous steps had been successful. To be successful, test results from steps 1, 2, 4, and 5 had to be significant in each of the twin trials and test results from steps 3 and 6 had to significant for the pooled data.

1. Mean FEV_1 $peak_{0\text{-}3h}$ response after 24 weeks treatment with tiotropium (5 µg)
2. Mean trough FEV_1 response after 24 weeks treatment with tiotropium (5 µg)
3. Probability of ACQ response after 24 weeks treatment with tiotropium (5 µg)
4. Mean FEV_1 $peak_{0\text{-}3h}$ response after 24 weeks treatment with tiotropium (2.5 µg)
5. Mean trough FEV_1 response after 24 weeks treatment with tiotropium (2.5 µg)
6. Probability of ACQ response after 24 weeks treatment with tiotropium (2.5 µg)

For steps 1, 2, 4, and 5, the superiority of treatment with tiotropium over placebo was tested at the level of α=0.025 (1-sided).

The primary analysis was a restricted maximum likelihood (REML)-based mixed effect model with repeated measures (MMRM) approach that included 'treatment', 'centre (pooled)', 'visit', and 'treatment-by-visit' interaction as fixed, categorical effects and 'baseline' as well as 'baseline-by-visit interaction' as continuous, fixed covariates.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 7 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Statistical methods (continued):

Patient was included as a random effect in the model. A spatial power structure for unequally spaced visits was used to model the within-patient errors. Adjusted mean values as well as treatment contrasts were calculated together with 95% confidence intervals (CIs). Comparisons of salmeterol versus placebo and tiotropium versus salmeterol were performed for descriptive purposes only. The analysis of the ACQ total score responder rate based on the pooled data from the twin trials is described in a separate report.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Baseline patient characteristics

A total of 2102 patients were enrolled, 1032 patients were randomised, and 1030 patients were treated in this trial (placebo: 254 patients, Tio R2.5: 257 patients, Tio R5: 253 patients, salmeterol: 266 patients). Of these, 974 patients (94.6%) completed the 24-week treatment period (placebo: 94.5%, Tio R2.5: 95.3%, Tio R5: 94.9%, salmeterol: 93.6%), and 56 patients (5.4%) prematurely discontinued trial medication (placebo: 5.5%, Tio R2.5: 4.7%, Tio R5: 5.1%, salmeterol: 6.4%). The most frequent reasons for premature discontinuation were the occurrence of AEs (placebo: 2.0%, Tio R2.5: 0.8%, Tio R5: 0.8%, salmeterol: 2.6%) and 'other' reasons (placebo: 1.2%, Tio R2.5: 1.6%, Tio R5: 2.0%, salmeterol: 1.1%).

The demographic characteristics were generally well balanced between the treatment groups. Overall, 58.6% of the patients were female, the majority of the population was White (47.3%) or Asian (42.8%), and the mean age was 42.9 years (standard deviation 12.9 years). Other characteristics were as expected for a population of adult patients with not fully controlled, moderate, persistent asthma at trial baseline (mean baseline [pre-dose] FEV1: 2.295 L, mean baseline percent of predicted FEV1: 75.41%, mean baseline ACQ total score: 2.18).

Overall, median treatment compliance was high (93.9%) and similar between the 4 treatment groups (placebo: 93.9%, Tio R 2.5: 92.7%, Tio R 5: 93.6%, salmeterol: 94.5%).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 8 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology results (continued):

Co-primary endpoints

Both Tio R5 and Tio R2.5 were shown to be superior over placebo for the co-primary endpoints of FEV_1 $peak_{0–3h}$ and trough FEV_1 response after 24 weeks of randomised treatment. Based on the MMRM analysis, the adjusted mean FEV_1 $peak_{0-3h}$ response was comparable in the 2 tiotropium groups (placebo: 0.075 L, Tio R2.5: 0.287 L, Tio R5: 0.244 L, salmeterol: 0.252 L). The treatment difference in the adjusted mean FEV_1 $peak_{0-3h}$ response was 0.211 L between Tio R2.5 and placebo and 0.169 L between Tio R5 and placebo; both of these treatment differences were statistically significant ($p<0.0001$).

Similarly, in terms of the adjusted mean trough FEV_1 response after 24 weeks of randomised treatment, a comparable effect was observed for the 2 tiotropium doses (placebo: -0.012 L, Tio R2.5: 0.164 L, Tio R5: 0.121 L, salmeterol: 0.094 L). The treatment difference in the adjusted mean trough FEV_1 response was 0.176 L between Tio R2.5 and placebo and 0.133 L between Tio R5 and placebo; both of these treatment differences were statistically significant ($p<0.0001$). The sensitivity analysis performed on the PPS confirmed these results. The treatment differences between salmeterol and placebo in the adjusted mean FEV_1 $peak_{0-3h}$ response (0.176 L) and adjusted mean trough FEV_1 response (0.106 L), which were included for descriptive purposes only, were also statistically significant for both co-primary endpoints ($p<0.0001$ and $p=0.0002$, respectively) and comparable to the tiotropium groups in terms of the magnitude of effect.

Secondary endpoints

For the secondary lung function endpoints measured in the clinic (FEV_1 AUC_{0-3h}, FVC $peak_{0-3h}$, trough FVC, FVC AUC_{0-3h}, and trough PEF), the adjusted mean responses after 24 weeks of treatment were comparable in the active treatment groups and larger than in the placebo group (see Table 1 below). For all of these endpoints, the treatment differences between Tio R2.5 and placebo and between Tio R5 and placebo were statistically significant, as were the treatment differences between salmeterol and placebo (p values ranging from 0.0312 to <0.0001).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 9 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology results (continued):

Table 1 Efficacy responses for secondary lung function endpoints (clinic assessment) after 24 weeks − FAS

Endpoint	Treatment	N[1]	Response Adjusted[2] mean (SE)	Active treatment − placebo Adjusted[2] mean difference (SE)	95% CI	p-value[3]
FEV_1 AUC_{0-3h} [L]						
	Placebo	242	-0.005 (0.019)			
	Tio R2.5	245	0.196 (0.019)	0.201 (0.026)	0.150, 0.252	<0.0001
	Tio R5	240	0.158 (0.019)	0.163 (0.026)	0.112, 0.215	<0.0001
	Salmeterol	251	0.173 (0.019)	0.178 (0.026)	0.127, 0.229	<0.0001
FVC $peak_{0-3h}$ [L]						
	Placebo	242	0.071 (0.022)			
	Tio R2.5	245	0.181 (0.022)	0.110 (0.030)	0.052, 0.168	0.0002
	Tio R5	240	0.160 (0.022)	0.089 (0.030)	0.030, 0.147	0.0031
	Salmeterol	251	0.188 (0.021)	0.116 (0.030)	0.058, 0.174	<0.0001
Trough FVC [L]						
	Placebo	242	-0.048 (0.027)			
	Tio R2.5	245	0.039 (0.027)	0.087 (0.032)	0.025, 0.149	0.0061
	Tio R5	240	0.035 (0.027)	0.083 (0.032)	0.021, 0.146	0.0093
	Salmeterol	251	0.020 (0.027)	0.068 (0.032)	0.006, 0.130	0.0312
FVC AUC_{0-3h} [L]						
	Placebo	242	-0.065 (0.024)			
	Tio R2.5	245	0.043 (0.024)	0.108 (0.029)	0.052, 0.164	0.0002
	Tio R5	240	0.024 (0.025)	0.089 (0.029)	0.033, 0.145	0.0019
	Salmeterol	251	0.066 (0.024)	0.131 (0.028)	0.075, 0.186	<0.0001
Trough PEF [L/min]						
	Placebo	242	7.938 (3.659)			
	Tio R2.5	245	36.698 (3.614)	28.759 (4.963)	19.025, 38.494	<0.0001
	Tio R5	240	36.117 (3.646)	28.178 (4.985)	18.401, 37.956	<0.0001
	Salmeterol	251	29.352 (3.572)	21.414 (4.955)	11.695, 31.133	<0.0001

[1]Number of patients with measurements available at Week 24 in the full analysis set (FAS)
[2]FEV_1 AUC_{0-3h} and FVC $peak_{0-3h}$, and trough PEF adjusted for treatment, pooled centre, week, baseline, treatment by week and baseline by week; trough FVC, and FVC AUC_{0-3h} adjusted for treatment, country, week, baseline, treatment by week and baseline by week
[3]2-sided p-value
Note: the comparison of salmeterol vs placebo is provided for descriptive purposes only

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	
Name of active ingredient: Tiotropium bromide		**Page:** 10 of 16	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology results (continued):

For the secondary endpoints related to questionnaires, the adjusted mean ACQ total score improved (decreased) from trial baseline (2.181) to Week 24 in all 4 treatment groups (placebo: 1.442, Tio R2.5: 1.315, Tio R5: 1.359, salmeterol: 1.318); in each treatment group, the minimal clinically important difference (0.5) was met. Compared to placebo, the treatment difference in the adjusted mean ACQ total score at Week 24 was statistically significant for Tio R2.5 (-0.127 points, p=0.0305), and salmeterol (-0.124 points, p=0.0339), but not for Tio R5 (-0.083 points, p=0.1602). The proportion of responders (binary) based on the mean ACQ total score at Week 24 was similar in all 4 treatment groups (placebo: 62.5%, Tio R2.5: 66.4%, Tio R5: 61.9%, salmeterol: 64.4%). The AQLQ(S) total score improved (increased) from trial baseline (4.799) to Week 24 in all 4 treatment groups (placebo: 5.551, Tio R2.5: 5.562, Tio R5: 5.548, salmeterol: 5.634). For both the proportion of responders based on the mean ACQ total score and the AQLQ(s) total score, the differences between active treatment and placebo were not statistically significant ($p \geq 0.4012$).

For the secondary endpoints measured at home using the AM3® device, the adjusted mean responses for PEF_{am} and PEF_{pm} after 24 weeks of treatment were comparable in the active treatment groups and larger than in the placebo group (see Table 2 below). The treatment differences compared to placebo were statistically significant for all 3 active treatments (p=0.0099 to <0.0001). For $FEV_{1\ am}$ and $FEV_{1\ pm}$, the treatment differences compared to placebo favoured each active treatment and were statistically significant with the exception of salmeterol vs placebo for $FEV_{1\ pm}$ ($FEV_{1\ am}$, Tio R2.5: p=0.0111, Tio R5: p=0.0395, salmeterol: p=0.0071; $FEV_{1\ pm}$, Tio R2.5: p=0.0357, Tio R5: p=0.0422, salmeterol: p=0.1214).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 11 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology results (continued):

Table 2 Efficacy responses for secondary lung function endpoints (home assessment) at Week 24 – FAS

Parameter	Treatment	N[1]	Response Adjusted[2] mean (SE)	Active treatment − placebo Adjusted[2] mean difference (SE)	95% CI	p-value[3]
PEF_{am} [L/min]						
	Placebo	235	2.764 (3.292)			
	Tio R2.5	238	23.377 (3.267)	20.613 (4.496)	11.795, 29.431	<0.0001
	Tio R5	236	27.521 (3.294)	24.757 (4.513)	15.907, 33.607	<0.0001
	Salmeterol	247	19.779 (3.219)	17.015 (4.477)	8.236, 25.795	0.0001
PEF_{pm} [L/min]						
	Placebo	236	-0.072 (3.328)			
	Tio R2.5	238	15.919 (3.303)	15.991 (4.547)	7.074, 24.908	0.0004
	Tio R5	236	21.175 (3.330)	21.247 (4.561)	12.302, 30.193	<0.0001
	Salmeterol	247	11.617 (3.256)	11.689 (4.528)	2.808, 20.569	0.0099
PEF variability [%]						
	Placebo	232	-0.448 (0.484)			
	Tio R2.5	237	-1.401 (0.480)	-0.953 (0.598)	-2.125, 0.220	0.1114
	Tio R5	234	-0.627 (0.487)	-0.178 (0.600)	-1.355, 0.999	0.7665
	Salmeterol	244	-1.518 (0.472)	-0.069 (0.594)	-2.234, 0.095	0.0719
$FEV_{1\ am}$ [L]						
	Placebo	235	0.020 (0.023)			
	Tio R2.5	238	0.099 (0.023)	0.079 (0.031)	0.018, 0.140	0.0111
	Tio R5	236	0.084 (0.023)	0.064 (0.031)	0.003, 0.126	0.0395
	Salmeterol	247	0.103 (0.022)	0.083 (0.031)	0.023, 0.144	0.0071
$FEV_{1\ pm}$ [L]						
	Placebo	236	-0.002 (0.024)			
	Tio R2.5	238	0.066 (0.023)	0.068 (0.032)	0.005, 0.131	0.0357
	Tio R5	236	0.064 (0.024)	0.066 (0.032)	0.002, 0.129	0.0422
	Salmeterol	247	0.048 (0.023)	0.050 (0.032)	-0.013, 0.112	0.1214

[1]Number of patients with data available at Week 24 in the FAS
[2]PEF_{am} ,PEF_{pm}, $FEV_{1\ am}$, and $FEV_{1\ pm}$ adjusted for treatment, pooled centre, week, baseline, treatment by week and baseline by week; PEF variability adjusted for treatment, country, week, baseline, treatment by week and baseline by week
[3]2-sided p-value
Note: the comparison of salmeterol vs placebo is provided for descriptive purposes only

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 12 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology results (continued):

After 24 weeks of treatment, the adjusted weekly mean number of puffs of rescue medication used in 24 h had decreased in all treatment groups; the 24-h weekly mean response at Week 24 was -0.952 for placebo, -1.123 for Tio R2.5, -0.843 for Tio R5, and -1.078 for salmeterol. The adjusted weekly mean asthma symptom-free days response had increased after 24 weeks of treatment in all treatment groups; the weekly mean response at Week 24 was 0.189 for placebo, 0.164 for Tio R2.5, 0.196 for Tio R5, and 0.195 for salmeterol. Compared to placebo, the treatment differences in the weekly mean number of puffs of rescue medication and asthma symptom-free days were not statistically significant for any of the active treatment groups ($p \geq 0.1927$).

Further endpoints

Treatment differences in favour of the active treatments over placebo were observed for the further lung function endpoints (clinic and home assessments), questionnaires, and asthma exacerbations, although statistical significance was not always shown. For rescue medication use, asthma symptoms, and asthma symptom-free days, the differences between the active treatment groups and placebo were mostly non-significant. The subset of patients who completed the PASAPQ after 24 weeks of treatment expressed a clear preference for the Respimat® inhaler over the MDI in terms of the PASAPQ performance score.

Pharmacokinetics

Tiotropium was rapidly absorbed following oral inhalation with a median t_{max} of 4.17 to 4.86 min post-dosing following administration of the first dose and at steady-state. Following the administration of a single dose, the C_{max}, AUC, and Ae_{0-24} values increased in a less than dose proportional manner with doubling of the dose from 2.5 to 5 µg. At steady-state, $C_{max,ss}$, $AUC_{0-\tau,ss}$, and $Ae_{0-24,ss}$ values showed approximately a dose proportional increase. Pharmacokinetic steady-state was found to be reached by at the latest 7 days following the start of dosing. Overall, an average of 3.66 to 4.85% of the dose following the administration of the first dose and an average of 11.5 to 13.3% of the dose following the administration of multiple doses (after 4 weeks) to steady-state was excreted unchanged in urine within 24 h post-dose.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 13 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Efficacy / clinical pharmacology results (continued):	Dosing to steady-state resulted in approximately 1.3-fold higher C_{max}, 1.24- to 1.47-fold higher $AUC_{0-0\,5}$, but 2.73- to 2.97-fold higher Ae_{0-24} values compared to the values found after the first dose. The gMean terminal elimination half-life ranged between 39.6 to 48.0 h.
Safety results:	The median duration of treatment was 169 days (24 weeks) in all 4 treatment groups. Most patients (94.6%) completed the 24-week treatment period. The percentage of patients reporting AEs was slightly higher in the Tio R2.5 group than in the other treatment groups (placebo: 58.7%, Tio R2.5: 63.4%, Tio R5: 58.5%, salmeterol: 56.4%). The most frequently reported AEs were asthma (placebo: 22.0%, Tio R2.5: 17.9%, Tio R5: 20.2%, salmeterol: 19.9% of patients), nasopharyngitis (placebo: 10.2%, Tio R2.5: 12.1%, Tio R5: 7.5%, salmeterol: 9.4%), peak expiratory flow rate decreased (placebo: 11.0%, Tio R2.5: 8.2%, Tio R5: 9.9%, salmeterol: 6.8%), and upper respiratory tract infection (placebo: 8.7%, Tio R2.5: 4.3%, Tio R5: 4.7%, salmeterol: 6.0%). Most AEs were of mild or moderate intensity. AEs of severe intensity were reported for a total of 38 patients (3.7%) during the treatment phase of this trial (placebo: 2.4%, Tio R2.5: 3.1%, Tio R5: 6.3%, salmeterol: 3.0%). The most frequently reported AE of severe intensity was asthma. Drug-related AEs (as assessed by the investigator) were reported for a total of 89 patients (8.6%). The incidence was highest in the Tio R5 group and lowest in the placebo group (placebo: 6.7%, Tio R2.5: 9.3%, Tio R5: 11.1%, salmeterol: 7.5%). The most frequent drug-related AE was thirst (placebo: 2 patients, Tio R2.5: 2 patients, Tio R5: 5 patients, salmeterol: 3 patients). Other drug-related AEs that were reported for more than 2 patients overall were asthma (6 patients), dysphonia (6 patients), gamma-glutamyl transferase increased (6 patients), cough (5 patients), alanine aminotransferase increased (5 patients), throat irritation (4 patients), dry mouth (4 patients), dry throat (3 patients), aspartate aminotransferase increased (3 patients), blood glucose abnormal (3 patients), headache (3 patients), and muscle spasms (3 patients).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 14 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Safety results (continued):

At the preferred term (PT) level, none of the severe or drug-related AEs occurred at a markedly higher incidence on tiotropium than on placebo or salmeterol. There were 2 drug-related AEs of severe intensity; both were cases of asthma (Tio R 2.5: 1 patient, Tio R5: 1 patient). The event in the Tio R2.5 group lead to treatment discontinuation.

A total of 16 patients (1.6%) experienced AEs that led to premature discontinuation of trial medication; the incidence was slightly higher in the placebo and salmeterol groups than in the tiotropium groups (placebo: 5 patients [2.0%], Tio R2.5: 2 patients [0.8%], Tio R5: 2 patients [0.8%], salmeterol: 7 patients [2.6%]). The most frequently reported AE that led to premature discontinuation was asthma, reported for 7 patients (placebo: 3 patients [1.2%], Tio R2.5: 1 patient [0.4%], salmeterol: 3 patients [1.1%]). No patient discontinued prematurely due to asthma in the Tio R5 group.

Patients with an elevation of AST and/or ALT ≥3 fold the upper limit of normal (ULN) combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw were not reported. Any patients with elevated liver enzymes (although not fulfilling the definition for hepatic injury) were followed up with the sites and assessed to ensure that potential drug induced liver injury (DILI) could be ruled out. It was confirmed that there were no DILI cases in this trial.

'Other significant' (defined according to the ICH E3 guideline as those non-serious and non-significant AEs which led to discontinuation or dose reduction of the trial drug were reported for a total of 15 patients (1.5%) in this trial (placebo: 4 patients, Tio R2.5: 4 patients, Tio R5: 1 patient, salmeterol: 6 patients. Two of these patients, both in the Tio R2.5 group, had AEs leading to dose reduction (mild dizziness assessed as not related to treatment, moderate palpitations assessed as related to treatment); all other patients prematurely discontinued treatment.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 15 of 16	
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Safety results (continued):

A total of 22 patients (2.1%) were reported with a total of 28 SAEs during the treatment phase of the trial (placebo: 1.6% of patients, Tio R2.5: 2.7%, Tio R5: 2.8%, salmeterol: 1.5%). None of the SAEs were considered to be drug-related by the investigator. Three SAEs, 1 each in the placebo, Tio R5, and salmeterol groups, led to discontinuation of the patient from the trial. The most frequent SAE was asthma, reported for 6 patients (placebo: 2 patients, Tio R2.5: 2 patients, Tio R5: 1 patient, salmeterol: 1 patient). All other SAEs were single occurrences. There were no deaths reported during the course of this trial.

Three pregnancies were reported for patients who had received trial medication. A healthy baby was delivered by 1 patient in the placebo group; 2 pregnancies did not come to full term (1 patient in the Tio R2.5 had an induced abortion following an ectopic pregnancy and 1 patient in the Tio R5 group had a spontaneous abortion). Three further patients became pregnant prior to randomisation and did not receive trial medication.

Overall, mean systolic blood pressure, diastolic blood pressure, and pulse rate were comparable between the treatment groups at baseline, and generally remained relatively stable over the 24 weeks of the treatment period. All 4 treatment groups showed some fluctuation in the magnitude of the changes from baseline; however, these changes were small. No time-related trends were observed. Marked changes in vital signs were recorded for 0.0 to 4.3% of patients (depending on vital sign parameter, time point and treatment group); however, this was not accompanied by an imbalance between the treatment groups in terms of AEs related to increased blood pressure, e.g. the PTs hypertension (placebo: 1 patient [0.4%], Tio R2.5: 4 patients [1.6%], Tio R5: 2 patients [0.8%], salmeterol: 5 patients [1.9%]) and blood pressure increased (placebo: 3 patients [1.2%], Tio R2.5: 1 patient [0.4%], Tio R5: 2 patients [0.8%], salmeterol: 1 patient [0.4%]). Two SAEs were reported in the vascular disorder system organ class (SOC): hypertension in a patient in the Tio R2.5 group and hypertensive crisis in a patient in the Tio R5 group. One AE (hypertension in a patient in the salmeterol group) was considered related to treatment.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018005-43	
Name of active ingredient: Tiotropium bromide		**Page:** 16 of 16	**Synopsis No.:**
Module:		**Volume:**	
Report date: 08 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.419 / c02036086-05 (U12-2467-02)	**Dates of trial:** 24 AUG 2010 – 07 NOV 2012	**Date of revision:** 22 MAY 2014

Conclusions: Tiotropium solution for inhalation via the Respimat® inhaler given on top of medium dose ICS maintenance therapy in a population of adult patients with moderate, persistent asthma was safe and effective. Tiotropium 5 µg and 2.5 µg administered once daily in the evening significantly improved adjusted mean FEV_1 $peak_{0\text{-}3h}$ and trough FEV_1 responses after 24 weeks of treatment as compared with placebo (co-primary endpoints). Comparable results were obtained for salmeterol. The safety profiles for tiotropium and placebo on top of ICS were similar, and both tiotropium doses were well tolerated over 24 weeks of treatment. Tiotropium was rapidly absorbed following oral inhalation with a median t_{max} of 4.17 to 4.86 min after administration of the first dose and at pharmacokinetic steady-state. The pharmacokinetics of tiotropium were dose proportional at steady-state and pharmacokinetic steady-state was reached at the latest 7 days following start of dosing.