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.:** 2009-018004-18	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 16	**Synopsis No.:**
Module:		**Volume:**	
Report date: 10 APR 2013	**Trial No. / Doc. No. (legacy doc. no.):** 205.418 / c02036039-03 (U12-2466-01)	**Dates of trial:** 07 SEP 2010 – 13 NOV 2012	**Date of revision:** 23 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 114 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

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No. of subjects:	
planned:	1000
actual:	enrolled: 2015 randomised: 1071 Placebo: randomised: 269 treated: 269 analysed (for primary endpoint): 265 Tiotropium bromide 2.5 µg (Tio R2.5): randomised: 262 treated: 262 analysed (for primary endpoint): 259 Tiotropium bromide 5 µg (Tio R5): randomised: 265 treated: 264 analysed (for primary endpoint): 261 Salmeterol: randomised: 275 treated: 275 analysed (for primary endpoint): 271
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

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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.

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Criteria for evaluation:

Efficacy / clinical

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.

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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 249 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 438 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 285 patients). Other endpoints Other endpoints included pharmacokinetic (PK) parameters of tiotropium. These parameters were evaluated in blood and urine samples in a subset of 140 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.

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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).

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Statistical methods (continued):	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. 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:	**Baseline patient characteristics** A total of 2015 patients were enrolled, 1071 patients were randomised, and 1070 patients were treated in this trial (placebo: 269 patients, Tio R2.5: 262 patients, Tio R5: 264 patients, salmeterol: 275 patients). Of these, 998 patients (93.3%) completed the 24-week treatment period (placebo: 92.2%, Tio R2.5: 95.0%, Tio R5: 91.3%, salmeterol: 94.5%), and 72 patients (6.7%) prematurely discontinued trial medication (placebo: 7.8%, Tio R2.5: 5.0%, Tio R5: 8.7%, salmeterol: 5.5%). The most frequent reasons for premature discontinuation apart from 'other' reasons (placebo: 2.2%, Tio R2.5: 1.9%, Tio R5: 3.4%, salmeterol: 2.5%) was the occurrence of AEs (placebo: 3.0%, Tio R2.5: 1.5%, Tio R5: 3.0%, salmeterol: 1.1%). The demographic characteristics were generally well balanced between the 4 treatment groups. Overall, 59.3% of the patients were female, the majority of the population was White (48.4%) or Asian (42.2%), and the mean age was 43.3 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] FEV_1: 2.240 L, mean baseline percent of predicted FEV_1: 74.72%, mean baseline ACQ total score: 2.18).

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Efficacy / clinical pharmacology results (continued):

Overall, median treatment compliance was high (93.3%) and similar between the 4 treatment groups (placebo: 93.0%, Tio R2.5: 93.6%, Tio R5: 92.8%, salmeterol: 93.6%).

Co-primary endpoints

Both Tio R5 and Tio R2.5 were shown to be superior over placebo for the co-primary endpoints 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: 0.053 L, Tio R2.5: 0.289 L, Tio R5: 0.250 L, salmeterol: 0.266 L). The treatment difference in the adjusted mean FEV_1 $peak_{0-3h}$ response was 0.236 L between Tio R2.5 and placebo and 0.198 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: 0.036 L, Tio R2.5: 0.148 L, Tio R5: 0.115 L, salmeterol: 0.086 L). The treatment difference in the adjusted mean trough FEV_1 response after 24 weeks of treatment was 0.185 L between Tio R2.5 and placebo and 0.152 L between Tio R5 and placebo; both of these treatment differences were statistically significant ($p<0.0001$). Sensitivity analyses confirmed these results. The treatment differences between salmeterol and placebo in the adjusted mean FEV_1 $peak_{0-3h}$ response (0.213 L) and adjusted mean trough FEV_1 response (0.123 L), which were analysed for descriptive purposes only, were also statistically significant ($p<0.0001$ in each case) 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 0.0359 to <0.0001).

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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	250	-0.033 (0.020)			
	Tio R2.5	247	0.192 (0.020)	0.224 (0.027)	0.171, 0.278	<0.0001
	Tio R5	241	0.163 (0.020)	0.195 (0.027)	0.141, 0.249	<0.0001
	Salmeterol	259	0.182 (0.020)	0.215 (0.027)	0.162, 0.268	<0.0001
FVC $peak_{0-3h}$ [L]						
	Placebo	250	0.045 (0.022)			
	Tio R2.5	247	0.219 (0.022)	0.174 (0.030)	0.114, 0.233	<0.0001
	Tio R5	241	0.148 (0.023)	0.102 (0.031)	0.042, 0.162	0.0008
	Salmeterol	259	0.168 (0.022)	0.123 (0.030)	0.064, 0.182	<0.0001
Trough FVC [L]						
	Placebo	250	-0.039 (0.025)			
	Tio R2.5	247	0.086 (0.026)	0.125 (0.032)	0.062, 0.189	0.0001
	Tio R5	241	0.036 (0.026)	0.076 (0.033)	0.012, 0.140	0.0200
	Salmeterol	259	0.028 (0.025)	0.067 (0.032)	0.004, 0.130	0.0359
FVC AUC_{0-3h} [L]						
	Placebo	250	-0.066 (0.023)			
	Tio R2.5	247	0.092 (0.023)	0.158 (0.029)	0.100, 0.215	<0.0001
	Tio R5	241	0.041 (0.024)	0.106 (0.029)	0.049, 0.164	0.0003
	Salmeterol	259	0.062 (0.023)	0.128 (0.029)	0.071, 0.184	<0.0001
Trough PEF [L/min]						
	Placebo	250	2.913 (3.641)			
	Tio R2.5	247	40.819 (3.664)	37.907 (4.994)	28.113, 47.700	<0.0001
	Tio R5	241	36.590 (3.712)	33.677 (5.023)	23.825, 43.529	<0.0001
	Salmeterol	259	31.317 (3.596)	28.404 (4.940)	18.716, 38.093	<0.0001

[1]Number of patients with measurements available at Week 24 in the full analysis set (FAS)
[2]FEV_1 AUC_{0-3h}, 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

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Efficacy / clinical pharmacology results (continued):

For the secondary endpoints related to questionnaires, the adjusted mean ACQ total score improved (decreased) from trial baseline (2.176) to Week 24 in all 4 treatment groups (placebo: 1.563, Tio R2.5: 1.362, Tio R5: 1.431, salmeterol: 1.302); in each treatment group, the minimal clinically important difference (0.5) was met. The treatment difference in the adjusted mean ACQ total score at Week 24 was -0.202 points between Tio R2.5 and placebo (p=0.0007), -0.113 points between Tio R5 and placebo (p=0.0262), and -0.262 points between salmeterol and placebo (p<0.0001). The proportion of responders (binary) based on the mean ACQ total score at Week 24 was comparable in the active treatment groups and larger than in the placebo group (placebo: 53.2%, Tio R2.5: 62.5%, Tio R5: 66.7%, salmeterol: 68.6%). The difference was statistically significant compared to placebo for each of the active treatments (Tio R2.5: p=0.0377, Tio R5: p=0.0022, salmeterol: p=0.0003).

The AQLQ(S) total score also improved (increased) from trial baseline (4.845) to Week 24 in all 4 treatment groups (placebo: 5.449, Tio R2.5: 5.522, Tio R5: 5.519, salmeterol: 5.654). Compared to placebo, the treatment difference was statistically significant for salmeterol (0.204 points, p=0.0019) but not for Tio R2.5 or Tio R5 (Tio R2.5: 0.073 points, p=0.2717; Tio R5: 0.070 points, p=0.2956).

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<0.0001). For $FEV_{1\ am}$ and $FEV_{1\ pm}$, the treatment differences compared to placebo favoured each active treatment but were only statistically significant for Tio R2.5 and salmeterol ($FEV_{1\ am}$, Tio R2.5: p=0.0069, Tio R5: p=0.0810, salmeterol: p=0.0012; $FEV_{1\ pm}$, Tio R2.5: p=0.0363, Tio R5: p=0.2077, salmeterol: p=0.0188).

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Efficacy / clinical pharmacology results (continued):

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

Endpoint	Treatment	Response 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	238	-10.159 (3.537)			
	Tio R2.5	247	20.432 (3.547)	30.591 (4.520)	21.726, 39.455	<0.0001
	Tio R5	236	13.501 (3.587)	23.660 (4.533)	14.772, 32.549	<0.0001
	Salmeterol	254	22.467 (3.491)	32.627 (4.478)	23.846, 41.407	<0.0001
PEF_{pm} [L/min]						
	Placebo	239	-9.181 (3.245)			
	Tio R2.5	245	18.978 (3.245)	28.160 (4.447)	19.440, 36.880	<0.0001
	Tio R5	236	15.188 (3.273)	24.370 (4.462)	15.619, 33.120	<0.0001
	Salmeterol	252	19.727 (3.190)	28.909 (4.405)	20.271, 37.546	<0.0001
PEF variability [%]						
	Placebo	237	-1.400 (0.437)			
	Tio R2.5	244	-1.958 (0.434)	-0.558 (0.603)	-1.740, 0.624	0.3550
	Tio R5	234	0.180 (0.441)	1.580 (0.608)	0.388, 2.771	0.0094
	Salmeterol	252	-2.300 (0.427)	-0.900 (0.598)	-2.072, 0.272	0.1322
$FEV_{1\ am}$ [L]						
	Placebo	238	0.021 (0.022)			
	Tio R2.5	247	0.101 (0.022)	0.081 (0.030)	0.022, 0.139	0.0069
	Tio R5	236	0.073 (0.022)	0.052 (0.030)	-0.006, 0.111	0.0810
	Salmeterol	254	0.117 (0.021)	0.096 (0.030)	0.038, 0.154	0.0012
$FEV_{1\ pm}$ [L]						
	Placebo	239	-0.000 (0.022)			
	Tio R2.5	245	0.065 (0.022)	0.065 (0.031)	0.004, 0.126	0.0363
	Tio R5	236	0.039 (0.022)	0.039 (0.031)	-0.022, 0.100	0.2077
	Salmeterol	252	0.072 (0.022)	0.072 (0.031)	0.012, 0.133	0.0188

[1]Number of patients with data available at Week 24 in the FAS
[2]PEF_{pm}, PEF variability, and $FEV_{1\ am}$ adjusted for treatment, pooled centre, week, baseline, treatment by week and baseline by week; PEF_{am} adjusted for treatment, country, week, baseline, treatment by week and baseline by week; $FEV_{1\ pm}$ adjusted for treatment, 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

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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 -0.962 for placebo, -1.124 for Tio R2.5, 0.818 for Tio R5, and -1.416 for salmeterol. The treatment difference compared to placebo was statistically significant for salmeterol (-0.454 puffs, p=0.0010) but not for Tio R2.5 (-1.162 puffs, p=0.2447) or Tio R5 (0.144 puffs, p=0.3046). 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 0.162 for placebo, 0.207 for Tio R2.5, 0.157 for Tio R5, and 0.266 for salmeterol. Compared to placebo, the treatment differences in the weekly mean asthma symptom-free days response was statistically significant for salmeterol (0.105 days, p=0.0002) but not for Tio R2.5 (0.045 days, p=0.1178) or Tio R5 (-0.004 days, p=0.8880).

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.

Pharmacokinetics

Tiotropium was rapidly absorbed following oral inhalation with a median t_{max} of approximately 5 min post-dosing following administration of the first dose and at steady-state. The exposure increased in a dose proportional manner between the 2.5 and 5 µg doses. Pharmacokinetic steady state was found to be reached at the latest 7 days following the start of dosing. Overall, an average of 4.57 to 5.32% of the dose following the administration of the first dose and an average of 15.7 to 16.0% 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. Dosing to steady-state resulted in approximately 1.2 fold higher C_{max}, 1.24- to 1.45-fold higher $AUC_{0-0\,5}$, but 2.89- to 3.51-fold higher Ae_{0-24} values compared to the values found after the first dose. The gMean terminal elimination half-life ranged between 34.5 to 47.3 h.

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Safety results:

The median duration of treatment was 169 days (24 weeks) in all 4 treatment groups. Most patients (93.3%) completed the 24-week treatment period.

The percentage of patients reporting AEs was similar among the treatment groups (placebo: 59.5%, Tio R2.5: 53.1%, Tio R5: 56.1%, salmeterol: 52.4%). The most frequently reported AEs were asthma (placebo: 21.9%, Tio R2.5: 13.7%, Tio R5: 22.7%, salmeterol: 18.9% of patients), peak expiratory flow rate decreased (placebo: 19.0%, Tio R2.5: 10.7%, Tio R5: 12.9%, salmeterol: 10.5%), nasopharyngitis (placebo: 8.2%, Tio R2.5: 6.9%, Tio R5: 8.3%, salmeterol: 5.8%), and upper respiratory tract infection (placebo: 7.1%, Tio R2.5: 6.1%, Tio R5: 2.7%, salmeterol: 9.1%). Most AEs were of mild or moderate intensity; AEs of severe intensity were reported for a total of 42 patients (3.9%) during the treatment phase of this trial (placebo: 4.5%, Tio R2.5: 2.7%, Tio R5: 4.5%, salmeterol: 4.0%). The most frequently reported AE of severe intensity was asthma.

Drug-related AEs (as assessed by the investigator) were reported for a total of 41 patients (3.8%) during the treatment phase, and the incidence was similar among the treatment groups (placebo: 4.1%, Tio R2.5: 4.6%, Tio R5: 3.8%, salmeterol: 2.9%). The most frequent drug-related AEs were dry mouth (placebo: 2 patients, Tio R2.5: 2 patients, Tio R5: 2 patients), cough (placebo: 3 patients, Tio R5: 1 patient, salmeterol: 1 patient), and oropharyngeal discomfort (Tio R2.5: 2 patients, Tio R5: 1 patient, salmeterol: 2 patients).

Other drug-related AEs that were reported for more than 2 patients overall were palpitations (4 patients), headache (3 patients), thirst (3 patients), and urticaria (3 patients). There were 3 drug-related AEs of severe intensity: asthma in 1 patient treated with placebo, dry mouth in 1 patient treated with Tio R2.5, and urinary tract infection in 1 patient treated with salmeterol. The AE of urinary tract infection was the only serious drug-related AE. The AE of asthma lead to treatment discontinuation.

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Safety results (continued):

A total of 22 patients (2.1%) experienced AEs that led to premature discontinuation of trial medication (placebo: 3.0%, Tio R2.5: 1.5%, Tio R5: 2.7%, salmeterol: 1.1%). Asthma was the most frequently reported AE leading to premature discontinuation, reported for 8 patients (placebo: 4 patients, Tio R5: 3 patients, salmeterol: 1 patient).

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' AEs (defined according to the ICH E3 guideline as non-serious and non-significant AEs leading to discontinuation or dose reduction of the trial drug) were reported for a total of 18 patients (1.7%) in this trial (placebo: 1.9%, Tio R2.5: 1.1%, Tio R5: 2.7%, salmeterol: 1.1%). One patient in the Tio R2.5 group experienced an AE of upper respiratory tract infection leading to dose reduction. The AE was of mild intensity and assessed as not related to trial drug. All other patients prematurely discontinued treatment.

A total of 26 patients (2.4%) were reported with a total of 34 SAEs during the treatment phase of the trial. The incidence of SAEs was slightly higher in the placebo group than in the active treatment groups (placebo: 3.7 %, Tio R2.5: 1.9%, Tio R5: 1.5%, salmeterol: 2.5%). Five patients prematurely discontinued treatment due to SAEs (3 in the placebo group, 2 in the Tio R2.5 group). Only 1 SAE (urinary tract infection) in the salmeterol group was assessed as drug related. SAEs that occurred in more than 1 patient were cerebrovascular accident (placebo: 2 patients, salmeterol: 1 patient), asthma (placebo: 1 patient, salmeterol: 1 patient), and gastroenteritis (placebo: 1 patient, salmeterol: 1 patient). All other SAEs were single occurrences. No deaths were reported during the course of this trial.

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Safety results (continued):	Seven pregnancies were reported during the trial; all pregnancies began while the patients were on treatment with trial medication. Three pregnancies did not come to full term: of these, 2 cases were spontaneous abortions (1 each in the salmeterol and placebo groups); 1 case in the Tio R5 group was an induced abortion (at the patient's request). Of the other 4 pregnancies, a healthy baby was delivered by 1 patient in the salmeterol treatment group. Two patients in the Tio R5 group were still pregnant at the time of writing this CTR. For 1 patient in the placebo group, information on the outcome of the pregnancy is not available. 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 most frequently observed for increased diastolic blood pressure (placebo: 0.0 to 3.0% of patients, Tio R2.5: 0.0 to 3.4% of patients, Tio R5: 0.0 to 2.7% of patients, salmeterol: 0.4 to 2.5% of patients). The incidence of AEs related to increased blood pressure was slightly higher in the Tio R2.5 treatment group than in the other groups for the preferred term (PT) hypertension (placebo: 3 patients [1.1%], Tio R2.5: 6 patients [2.3%], Tio R5: 2 patients [0.8%], salmeterol: 2 patients [0.7%]) and similar among the treatment groups for the PT blood pressure increased (placebo: 3 patients [1.1%], Tio R2.5: 2 patients [0.8%], Tio R5: 1 patient [0.4%], salmeterol: 0 patients). One AE (hypertension in a patient in the salmeterol group) was considered related to treatment.

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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 approximately 5 min after administration of the first dose and at pharmacokinetic steady-state. The pharmacokinetics of tiotropium were dose proportional and a pharmacokinetic steady-state was reached at the latest 7 days following the start of dosing.