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®		**EudraCT No.:** 2010-018471-26	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 SEP 2012	**Trial No. / U No.:** 205.380 / U12-2075-02	**Dates of trial:** 19 NOV 10 – 09 JAN 12	**Date of revision:** 15 FEB 13

Title of trial:	A Phase II randomised, double-blind, placebo controlled, crossover efficacy and safety comparison of three doses of tiotropium inhalation solution delivered via Respimat® inhaler (1.25, 2.5, and 5 µg once daily) versus placebo in patients with moderate persistent asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre trial in 19 sites in 3 European countries including Germany, Austria, and Ukraine
Publication (reference):	Data from this study has not been published
Clinical phase:	II
Objectives:	The objective of this study was to evaluate the efficacy and safety of 3 doses of tiotropium solution for inhalation (1.25 µg [Tio R1.25], 2.5 µg [Tio R2.5], and 5 µg [Tio R5] once daily in the evening) in comparison to placebo delivered by the Respimat® inhaler in adult patients with moderate persistent asthma on top of maintenance therapy with inhaled corticosteroids (ICS)
Methodology:	Randomised, placebo-controlled, double-blind, crossover trial with four 4-week treatment periods without wash-outs

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat®		**EudraCT No.:** 2010-018471-26	
Name of active ingredient: Tiotropium bromide		**Page:** 2 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 SEP 2012	**Trial No. / U No.:** 205.380 / U12-2075-02	**Date of trial:** 19 NOV 10 – 09 JAN 12	**Date of revision:** 15 FEB 2013

No. of subjects:	
planned:	entered: 120
actual:	enrolled: 224 entered: 149
	Pharmacokinetic (PK) set single dose (SD): 53, multiple dose (MD): 52
	Tio R1.25: treated: 146 analysed (for primary endpoint): 146 PK set SD: 13, MD: 52
	Tio R2.5: treated: 147 analysed (for primary endpoint): 147 PK set SD: 14, MD: 51
	Tio R5: treated: 146 analysed (for primary endpoint): 145 PK set SD: 14, MD: 49
	Placebo: treated: 144 analysed (for primary endpoint): 144 PK set SD: 12, MD: 51
Diagnosis and main criteria for inclusion:	Male and female outpatients between 18 and 75 years old with at least a 3-month history of asthma that was diagnosed before the age of 40. Patients must have never smoked or must have been ex-smokers with less than 10 pack-years who had quit smoking at least 1 year prior to enrolment. A diagnosis of moderate, persistent asthma was required, and patients must have been symptomatic despite treatment with a medium, stable dose of ICS for at least 4 weeks prior to screening; in order to be considered symptomatic, patients needed to have an Asthma Control Questionnaire (ACQ) mean score of ≥1.5 at screening (Visit 1) and randomisation (Visit 2). Patients should have had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) of ≥60% and ≤90% of predicted normal at screening (Visit 1), and an increase in pre-bronchodilator FEV_1 of ≥12% and ≥200 mL at a time point 15 min to 30 min after the inhalation of 400 µg of salbutamol (albuterol). Variability between the pre-bronchodilator FEV_1 at Visit 1 and Visit 2 had to be within ±30%. Patients were not eligible if they had an asthma exacerbation or acute respiratory tract infection in the 4 weeks prior to screening and/or during the screening period.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat®		**EudraCT No.:** 2010-018471-26	
Name of active ingredient: Tiotropium bromide		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 SEP 2012	**Trial No. / U No.:** 205.380 / U12-2075-02	**Date of trial:** 19 NOV 10 – 09 JAN 12	**Date of revision:** 15 FEB 2013

Test product:	Tiotropium solution for inhalation
dose:	1.25 or 2.5 or 5 µg (as 2 actuations per dose, calculated as free cation, ex mouthpiece), once daily, evening dosing
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	0.625 µg: 002380-8L0023; 1.25 µg: 906546-8L0013; 2.5 µg: 906154-8L0013
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	906238 - 8L0013
Duration of treatment:	A 4-week run-in period followed by four 4-week treatment periods no washouts (off-treatment periods) between treatments
Criteria for evaluation:	
Efficacy / clinical pharmacology:	Primary endpoint: peak FEV_1 within 3 h post-dosing (FEV_1 $peak_{0–3h}$) as a response (change from study baseline) Secondary endpoints included: Peak forced vital capacity (FVC) measured within 3 h post-dosing (FVC $peak_{0–3h}$), trough (pre-dose) FVC, trough FEV_1, areas under the curve from 0 to 3 h for FEV_1 (FEV_1 $AUC_{0–3h}$) and FVC (FVC $AUC_{0–3h}$), individual FEV_1, FVC, and peak expiratory flow (PEF) measurements, daily morning and evening PEF (PEF_{am} and PEF_{pm}), PEF variability, use of rescue salbutamol, and weekly mean number of night-time awakenings. In a subset of patients: FEV_1 $AUC_{0–12h}$, FEV_1 $AUC_{12–24h}$, FEV_1 $AUC_{0–24h}$, FVC $AUC_{0–12h}$, FVC $AUC_{12–24h}$, FVC $AUC_{0–24h}$. Other endpoints were pre-dose morning and evening FEV_1 ($FEV_{1\,am}$ and $FEV_{1\,pm}$) and ACQ. All endpoints (except for ACQ) were analysed as a response. Blood and urine samples were obtained from 53 patients for pharmacokinetic (PK) analysis of a single dose and from 52 patients for PK analysis of multiple doses. Samples were obtained following the administration of the first dose (Visit 2) and at the end of each 4-week treatment period.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat®		**EudraCT No.:** 2010-018471-26	
Name of active ingredient: Tiotropium bromide		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 SEP 2012	**Trial No. / U No.:** 205.380 / U12-2075-02	**Date of trial:** 19 NOV 10 – 09 JAN 12	**Date of revision:** 15 FEB 2013

Safety:	Adverse events (AEs), vital signs (blood pressure and pulse rate), physical examination, routine blood chemistry, haematology, 12-lead electrocardiogram (ECG)
Statistical methods:	The superiority of treatment with tiotropium (5 µg once daily followed by 2.5 µg and 1.25 µg once daily) over treatment with placebo was tested in terms of FEV_1 $peak_{0–3h}$ response in a sequential, hierarchical fashion at the level of α=0.025 (1-sided). The primary analysis was a 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. Secondary endpoints were analysed using the MMRM as described above for the primary efficacy endpoint. All calculated p-values for secondary endpoints were to serve an exploratory function. All other endpoints were analysed descriptively.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	Out of the 149 treated patients, 141 patients (94.6%) completed the planned treatment time. The study population was White (100%) and contained slightly more female patients (55.0%). The mean age was 49.3 years and the mean duration of asthma (from date of first diagnosis) was 23.8 years. The primary endpoint of (adjusted mean) FEV_1 $peak_{0–3h}$ response (change from baseline after 4 weeks of treatment) was 0.255 L for Tio R1.25, 0.244 L for Tio R2.5, 0.304 L for Tio R5, and 0.116 L for placebo. The observed difference to placebo for Tio R1.25 was 0.138 L, for Tio R2.5 0.128 L, and for Tio R5 0.188 L. Differences from placebo were statistically significant ($p<0.0001$) for all doses. Analyses of the secondary endpoints trough FEV_1, FEV_1 $AUC_{0–3h}$, FVC $peak_{0–3h}$, FVC $AUC_{0–3h}$, PEF_{am} and PEF_{pm} responses showed results consistent with those observed for the primary endpoint (p-value for treatment difference always <0.05). However, no significant difference between tiotropium treatment and placebo was shown for use of rescue medication at night or night-time awakenings ($p>0.05$). Similarly, no clinically relevant differences between active treatments and placebo were found in terms of PEF variability ($p>0.05$).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat®		**EudraCT No.:** 2010-018471-26	
Name of active ingredient: Tiotropium bromide		**Page:** 5 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 SEP 2012	**Trial No. / U No.:** 205.380 / U12-2075-02	**Date of trial:** 19 NOV 10 – 09 JAN 12	**Date of revision:** 15 FEB 2013

Efficacy / clinical pharmacology results (continued):

In terms of FEV_1 and PEF measurements at each time point analysed as a response, all 3 tiotropium treatments were superior to placebo in an exploratory way at all time points ($p<0.0001$). For the other endpoint ACQ score, statistically significant differences between all 3 tiotropium treatments and placebo in favor of tiotropium could be shown ($p\leq0.0043$). However, the treatment differences in terms of ACQ score were below the currently defined minimal clinically important difference for the ACQ score of 0.5.

Tiotropium was rapidly absorbed following single and multiple inhalations of 1.25 µg, 2.5 µg and 5 µg once daily via the Respimat® inhaler. Median $t_{max(,ss)}$ values ranged from 0.0720 h to 0.196 h and 0.0830 h to 0.114 h following single and multiple dosing, respectively. An at least bi-exponential decline in plasma profile was observed following multiple dosing. On an average, 4.79% to 7.41% of the tiotropium dose was excreted unchanged in the urine over 24 h following the inhalation of a single dose of 1.25 µg to 5 µg tiotropium. At steady-state, an average of 10.6% to 11.3% of the dose was excreted unchanged in the urine over 24 h. Administration of multiple doses of tiotropium did not result in accumulation in C_{max} and AUC values. However, there was approximately 2- to 2.6-fold accumulation based on fe_{0-24} values. A slightly less than dose proportional increase was observed for geometric mean (gMean) $C_{max,ss}$ and $AUC_{0-0\ 167,ss}$ values. In contrast, dose proportional behaviour was observed for $fe_{0-24,ss}$ values. The renal clearance (gMean 162 mL/min to 254 mL/min) of tiotropium was higher than the creatinine clearance, indicating active secretion into the urine. The patient's sex, age and renal function (data from patients with normal renal function and mild renal impairment were available in this trial) did not influence $C_{max(,ss)}$ and $fe_{0-24(,ss)}$ values. Also the body weight, height, and pre-dose FEV_1 percent predicted had no impact on the $C_{max(,ss)}$ and $fe_{0-24(,ss)}$ values.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat®		**EudraCT No.:** 2010-018471-26	
Name of active ingredient: Tiotropium bromide		**Page:** 6 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 SEP 2012	**Trial No. / U No.:** 205.380 / U12-2075-02	**Date of trial:** 19 NOV 10 – 09 JAN 12	**Date of revision:** 15 FEB 2013

Safety results:

The mean exposure to study medication was comparable for all 4 treatments, ranging from 29.4 days (placebo) to 30.1 days (Tio R1.25).

The overall frequency of AEs was well balanced between all 4 treatments, and no dose-dependent AE trends were noted. A total of 14.6% of patients were reported with AEs while taking placebo, 9.6% of patients while taking Tio R1.25, 13.6% of patients while taking Tio R2.5, and 15.8% of patients while taking Tio R5. The most frequently reported treatment-emergent AEs included asthma (placebo: 5 patients, Tio R1.25: 1 patient, Tio R2.5: 3 patients, Tio R5: 4 patients) and nasopharyngitis (placebo: 2 patients, Tio R1.25: 2 patients, Tio R2.5: 1 patient, Tio R5: 5 patients). Two patients on Tio R5 were reported with AEs of severe intensity (alcohol abuse and panic attack, and inguinal hernia), all of which were also considered to be SAEs. Furthermore, a single patient experienced one SAE during screening (intervertebral disc protrusion). All SAEs required hospitalisation of the patients. None of the SAEs were considered drug-related, and none were fatal or life-threatening. Drug-related events were reported for 2 patients during treatment with placebo, 2 patients during treatment with Tio R1.25, and 3 patients during treatment with Tio R5. A single patient was reported with AEs leading to discontinuation of trial drug during treatment with Tio R5. A single patient reported dry mouth while taking Tio R5.

Mean systolic and diastolic blood pressure and pulse rate were comparable between treatments; no clinically relevant change in mean vital signs associated with tiotropium treatment was seen. The post-study ECG recording did not indicate any study drug-related changes.

Conclusions:

Tiotropium solution for inhalation via the Respimat® inhaler was a safe and effective bronchodilator as add-on therapy to ICS in a population of adult patients with uncontrolled moderate persistent asthma. Based on efficacy, safety, and pharmacokinetic evaluations of this study, 5 µg tiotropium administered via the Respimat® inhaler appeared to be the preferred dose. The pharmacokinetics of tiotropium did not deviate relevantly from dose proportionality.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the results of additional secondary endpoints, as summarised below. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format; therefore, results for a total of 10 secondary endpoints are provided in the Trial Synopsis and the following tables.

Results for	**presented in**
Pre-dose FEV_1 measured just prior to the last administration of randomised treatment (trough FEV_1), determined as a response from study baseline at the end of each 4-week treatment period	Table 15.2.1.1.2: 1
AUC from 0 to 3 h for FEV1 (FEV_1 AUC_{0-3h})	Table 15.2.1.1.2: 1
Maximum FVC measured within the first 3 h after dosing (FVC $Peak_{0-3h}$), determined as a response from study baseline at the end of each 4-week treatment period	Table 15.2.1.2.1: 1
Pre-dose FVC measured just prior to the last administration of randomised treatment (trough FVC), determined as a response from study baseline at the end of each 4-week treatment period	Table 15.2.1.2.1: 1
AUC from 0 to 3 h for FVC (FVC AUC_{0-3h})	Table 15.2.1.2.1: 1
Individual FEV_1 measurements, determined at each clinic visit	Table 15.2.1.1.2: 3
Individual FVC measurements, determined at each clinic visit	Table 15.2.1.2.1: 3
Individual PEF measurements, determined at each clinic visit	Table 15.2.1.3.1: 1
Pre-dose morning PEF_{am}, determined as a response from study baseline based on the weekly mean of the last week of treatment for each treatment period	Table 15.2.1.4.1: 1
Pre-dose evening PEF_{pm}, determined as a response from study baseline based on the weekly mean of the last week of treatment for each treatment period	Table 15.2.1.4.1: 1

Table 15.2.1.1.2: 1 Trough FEV1 response [L] and FEV1 AUC (0-3h) response [L]
- MMRM results (comparisons to placebo) - FAS

				Comparison vs Placebo		
Endpoint name	Treatment	N	Adjusted* Mean(SE)	Adjusted* mean of difference (SE)	95% CI	p-value* superiority
FEV1 Trough response	Placebo	144	0.006 (0.027)			
	Tio R1.25	144	0.131 (0.027)	0.125 (0.024)	(0.078, 0.173)	<.0001
	Tio R2.5	144	0.138 (0.027)	0.132 (0.024)	(0.084, 0.179)	<.0001
	Tio R5	143	0.149 (0.027)	0.143 (0.024)	(0.096, 0.191)	<.0001
FEV1 AUC (0-3h) response	Placebo	144	0.025 (0.027)			
	Tio R1.25	144	0.154 (0.027)	0.129 (0.023)	(0.083, 0.175)	<.0001
	Tio R2.5	144	0.152 (0.027)	0.127 (0.023)	(0.081, 0.172)	<.0001
	Tio R5	143	0.203 (0.027)	0.178 (0.023)	(0.132, 0.224)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 2.303 (0.690)

Table 15.2.1.2.1: 1 FVC Peak (0-3h) response [L], Trough FVC response [L], AUC (0-3h) response [L]
- MMRM results (comparisons to placebo) - FAS

				Comparison vs Placebo		
Endpoint name	Treatment	N	Adjusted* Mean(SE)	Adjusted* mean of difference (SE)	95% CI	p-value* superiority
FVC Peak (0-3h) response	Placebo	144	0.092 (0.034)			
	Tio R1.25	144	0.171 (0.034)	0.079 (0.027)	(0.026, 0.132)	0.0034
	Tio R2.5	144	0.163 (0.034)	0.071 (0.027)	(0.018, 0.124)	0.0087
	Tio R5	143	0.229 (0.034)	0.137 (0.027)	(0.085, 0.190)	<.0001
FVC Trough response	Placebo	144	0.004 (0.035)			
	Tio R1.25	144	0.058 (0.035)	0.054 (0.030)	(-0.005, 0.113)	0.0732
	Tio R2.5	144	0.076 (0.035)	0.072 (0.030)	(0.012, 0.131)	0.0177
	Tio R5	143	0.102 (0.035)	0.098 (0.030)	(0.039, 0.157)	0.0012
FVC AUC (0-3h) response	Placebo	144	-0.028 (0.034)			
	Tio R1.25	144	0.036 (0.034)	0.064 (0.026)	(0.013, 0.115)	0.0149
	Tio R2.5	144	0.047 (0.034)	0.075 (0.026)	(0.024, 0.126)	0.0043
	Tio R5	143	0.110 (0.034)	0.138 (0.026)	(0.086, 0.189)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 3.635 (0.981)

Table 15.2.1.1.2: 3 FEV1 [L] individual measurements response at each time point - MMRM results (comparisons to placebo) - FAS

				Comparison vs Placebo		
Endpoint name	Treatment	N	Adjusted* Mean(SE)	Adjusted* mean of difference (SE)	95% CI	p-value* superiority
Timepoint -0:10	Placebo	144	0.006 (0.027)			
	Tio R1.25	144	0.131 (0.027)	0.125 (0.024)	(0.078, 0.173)	<.0001
	Tio R2.5	144	0.138 (0.027)	0.132 (0.024)	(0.084, 0.179)	<.0001
	Tio R5	143	0.149 (0.027)	0.143 (0.024)	(0.096, 0.191)	<.0001
Timepoint 0:30	Placebo	144	0.029 (0.028)			
	Tio R1.25	144	0.160 (0.028)	0.131 (0.025)	(0.081, 0.181)	<.0001
	Tio R2.5	144	0.163 (0.028)	0.134 (0.025)	(0.084, 0.184)	<.0001
	Tio R5	143	0.209 (0.028)	0.180 (0.025)	(0.130, 0.230)	<.0001
Timepoint 1:00	Placebo	144	0.026 (0.029)			
	Tio R1.25	144	0.148 (0.029)	0.122 (0.026)	(0.071, 0.173)	<.0001
	Tio R2.5	144	0.156 (0.029)	0.129 (0.026)	(0.078, 0.180)	<.0001
	Tio R5	143	0.205 (0.029)	0.179 (0.026)	(0.127, 0.230)	<.0001
Timepoint 2:00	Placebo	144	0.033 (0.029)			
	Tio R1.25	144	0.158 (0.029)	0.125 (0.025)	(0.076, 0.175)	<.0001
	Tio R2.5	144	0.149 (0.029)	0.116 (0.025)	(0.067, 0.166)	<.0001
	Tio R5	143	0.218 (0.029)	0.185 (0.025)	(0.136, 0.235)	<.0001
Timepoint 3:00	Placebo	144	0.013 (0.029)			
	Tio R1.25	144	0.160 (0.029)	0.146 (0.026)	(0.095, 0.198)	<.0001
	Tio R2.5	144	0.148 (0.029)	0.135 (0.026)	(0.083, 0.187)	<.0001
	Tio R5	143	0.191 (0.029)	0.178 (0.026)	(0.126, 0.230)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 2.303 (0.690)

Table 15.2.1.2.1: 3 FVC [L] individual measurements response at each time point - MMRM results (comparisons to placebo) - FAS

				Comparison vs Placebo		
Endpoint name	Treatment	N	Adjusted* Mean(SE)	Adjusted* mean of difference (SE)	95% CI	p-value* superiority
Timepoint -0:10	Placebo	144	0.004 (0.035)			
	Tio R1.25	144	0.058 (0.035)	0.054 (0.030)	(-0.005, 0.113)	0.0732
	Tio R2.5	144	0.076 (0.035)	0.072 (0.030)	(0.012, 0.131)	0.0177
	Tio R5	143	0.102 (0.035)	0.098 (0.030)	(0.039, 0.157)	0.0012
Timepoint 0:30	Placebo	144	-0.028 (0.035)			
	Tio R1.25	144	0.042 (0.035)	0.070 (0.029)	(0.012, 0.128)	0.0187
	Tio R2.5	144	0.060 (0.035)	0.088 (0.029)	(0.030, 0.146)	0.0029
	Tio R5	143	0.124 (0.035)	0.152 (0.029)	(0.094, 0.210)	<.0001
Timepoint 1:00	Placebo	144	-0.031 (0.036)			
	Tio R1.25	144	0.024 (0.036)	0.055 (0.029)	(-0.002, 0.112)	0.0607
	Tio R2.5	144	0.041 (0.036)	0.072 (0.029)	(0.015, 0.129)	0.0139
	Tio R5	143	0.112 (0.036)	0.143 (0.029)	(0.086, 0.201)	<.0001
Timepoint 2:00	Placebo	144	-0.022 (0.036)			
	Tio R1.25	144	0.037 (0.036)	0.059 (0.029)	(0.002, 0.116)	0.0416
	Tio R2.5	144	0.045 (0.036)	0.067 (0.029)	(0.010, 0.124)	0.0205
	Tio R5	143	0.119 (0.036)	0.141 (0.029)	(0.084, 0.198)	<.0001
Timepoint 3:00	Placebo	144	-0.050 (0.036)			
	Tio R1.25	144	0.036 (0.036)	0.086 (0.030)	(0.026, 0.145)	0.0047
	Tio R2.5	144	0.033 (0.036)	0.083 (0.030)	(0.024, 0.142)	0.0061
	Tio R5	143	0.078 (0.036)	0.128 (0.030)	(0.069, 0.188)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 3.635 (0.981)

Table 15.2.1.3.1: 1 PEF [L/min] individual measurements response at each time point - MMRM results (comparisons to placebo) - FAS

				Comparison vs Placebo		
Endpoint name	Treatment	N	Adjusted* Mean(SE)	Adjusted* mean of difference (SE)	95% CI	p-value* superiority
Timepoint -0:10	Placebo	144	11.038 (4.804)			
	Tio R1.25	144	30.567 (4.802)	19.528 (4.240)	(11.194, 27.863)	<.0001
	Tio R2.5	144	33.903 (4.804)	22.865 (4.234)	(14.543, 31.187)	<.0001
	Tio R5	143	34.787 (4.812)	23.749 (4.238)	(15.419, 32.078)	<.0001
Timepoint 0:30	Placebo	144	8.235 (4.949)			
	Tio R1.25	144	32.163 (4.947)	23.928 (4.305)	(15.467, 32.390)	<.0001
	Tio R2.5	144	37.149 (4.949)	28.914 (4.298)	(20.466, 37.363)	<.0001
	Tio R5	143	39.325 (4.957)	31.090 (4.302)	(22.634, 39.545)	<.0001
Timepoint 1:00	Placebo	144	6.095 (5.074)			
	Tio R1.25	144	34.070 (5.072)	27.974 (4.423)	(19.281, 36.668)	<.0001
	Tio R2.5	144	36.851 (5.074)	30.756 (4.416)	(22.076, 39.436)	<.0001
	Tio R5	143	41.260 (5.082)	35.164 (4.420)	(26.477, 43.852)	<.0001
Timepoint 2:00	Placebo	144	7.237 (5.039)			
	Tio R1.25	144	34.544 (5.037)	27.306 (4.479)	(18.502, 36.111)	<.0001
	Tio R2.5	144	36.972 (5.039)	29.735 (4.472)	(20.944, 38.526)	<.0001
	Tio R5	143	42.694 (5.047)	35.456 (4.476)	(26.658, 44.255)	<.0001
Timepoint 3:00	Placebo	144	5.046 (5.024)			
	Tio R1.25	144	34.620 (5.022)	29.574 (4.621)	(20.491, 38.657)	<.0001
	Tio R2.5	144	37.283 (5.024)	32.237 (4.614)	(23.167, 41.306)	<.0001
	Tio R5	143	40.624 (5.033)	35.577 (4.619)	(26.499, 44.655)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 366.041 (106.101)

Table 15.2.1.4.1: 1 Mean PEF a.m. response [L/min], PEF p.m. response [L/min] and PEF variability response [%]
- MMRM results (comparisons to placebo) - FAS

				Comparison vs Placebo		
Endpoint name	Treatment	N	Adjusted* Mean(SE)	Adjusted* mean of difference (SE)	95% CI	p-value* superiority
Mean PEF a.m. response	Placebo	142	4.395 (4.573)			
	Tio R1.25	146	22.944 (4.543)	18.550 (3.737)	(11.204, 25.895)	<.0001
	Tio R2.5	146	22.290 (4.543)	17.895 (3.737)	(10.550, 25.240)	<.0001
	Tio R5	144	25.241 (4.559)	20.846 (3.739)	(13.497, 28.195)	<.0001
Mean PEF p.m. response	Placebo	142	3.833 (4.363)			
	Tio R1.25	146	25.084 (4.331)	21.251 (3.770)	(13.840, 28.662)	<.0001
	Tio R2.5	146	18.410 (4.331)	14.577 (3.770)	(7.166, 21.988)	0.0001
	Tio R5	144	25.414 (4.348)	21.581 (3.773)	(14.166, 28.997)	<.0001
Mean PEF variability response	Placebo	142	-0.171 (0.615)			
	Tio R1.25	146	-0.285 (0.609)	-0.114 (0.635)	(-1.363, 1.134)	0.8574
	Tio R2.5	146	-0.711 (0.609)	-0.540 (0.635)	(-1.789, 0.708)	0.3954
	Tio R5	144	-0.248 (0.612)	-0.077 (0.636)	(-1.327, 1.173)	0.9034

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = Mean PEF a.m.: 328.381 (113.667), Mean PEF p.m.: 349.443 (116.873)
Mean PEF variability: 14.151 (8.726)