Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat®		**EudraCT No.:** 2009-018006-21	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 7	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 DEC 2012	**Trial No. / U No.:** 205.420 / U12-2227-01	**Dates of trial:** 05 JUL 10 – 19 AUG 11	**Date of revision:** Not applicable

Title of trial:	A Phase II, randomised, double-blind, placebo controlled, crossover efficacy and safety comparison of tiotropium 5 µg administered once daily (in the evening) and tiotropium 2.5 µg administered twice daily delivered by the Respimat® inhaler for four weeks versus placebo in patients with moderate persistent asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre trial including 15 sites in 5 countries (Czech Republic, Estonia, Latvia, Austria, and Germany)
Publication (reference):	Data of this study have not been published
Clinical phase:	II
Objectives:	The objective of this study was to demonstrate the 24-h bronchodilator efficacy and safety of tiotropium 5 µg administered once daily (in the evening) [Tio R5 qd] delivered by the Respimat® inhaler for 4 weeks in comparison to placebo in patients with moderate persistent asthma. The study further aimed to evaluate the efficacy and safety of tiotropium 2.5 µg administered twice daily [Tio R2.5 bid] in comparison to placebo and to Tio R5 qd delivered by the Respimat® inhaler for 4 weeks.
Methodology:	Randomised, double-blind, placebo-controlled, crossover design comparing different dose regimens of tiotropium with placebo for 4 weeks on top of maintenance therapy with a medium-dose inhaled corticosteroid (ICS) controller medication

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Name of finished product: Spiriva® − Respimat®		**EudraCT No.:** 2009-018006-21	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide		**Page:** 2 of 7	
Module:		**Volume:**	
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No. of subjects:	
planned:	entered: 90
actual:	enrolled: 182 entered: 94 PK subset: 30 PK subset with efficacy data: 28 Tio R2.5 bid: treated: 90 analysed (for primary endpoint): 89 Tio R5 qd: treated: 90 analysed (for primary endpoint): 90 Placebo: treated: 92 analysed (for primary endpoint): 91
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 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) score of ≥1.5 at screening (Visit 1) and randomisation (Visit 2). Patients had to have 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 15 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%. Maintenance treatment with medium-dose ICS (stable for at least 4 weeks prior to Visit 1) was required.
Test product:	Tiotropium solution for inhalation
dose:	2.5 µg (2 actuations of 1.25 µg), twice daily (Tio R2.5 bid) 5 µg (2 actuations of 2.5 µg), once daily in the evening (Tio R5 qd) Both doses were ex mouthpiece and calculated as the free cation
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	1.25 µg: 807988 − 7L0048; 2.5 µg: 707916 − 7L0048

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Name of active ingredient: Tiotropium bromide		**Page:** 3 of 7	
Module:		**Volume:**	
Report date: 11 DEC 2012	**Trial No. / U No.:** 205.420 / U12-2227-01	**Dates of trial:** 05 JUL 10 – 19 AUG 11	**Date of revision:** Not applicable

Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	708067 − 7L0049
Duration of treatment:	A 4-week run-in period was followed by a 12-week treatment period, including three 4-week treatment periods without washouts (off-treatment periods) between treatments
Criteria for evaluation:	
Efficacy / clinical pharmacology:	The primary endpoint was the area under the curve (AUC) from 0 to 24 h for FEV_1 (FEV_1 $AUC_{0–24h}$). It was analysed as an absolute value and as a response (change from study baseline). Secondary endpoints that were assessed during clinic visits included FEV_1 AUC_{0-12h}, FEV_1 AUC_{12-24h}, FEV_1 $peak_{0–24h}$, trough FEV_1, trough FVC, FVC AUC_{0-12h}, FVC AUC_{12-24h}, FVC AUC_{0-24h}, FVC $peak_{0–24h}$, PEF AUC_{0-24h}, all of which were determined as a response at the end of each 4-week period of randomised treatment. Secondary endpoints that were assessed using the Asthma Monitor AM2+® included daily morning and evening peak expiratory flow (PEF_{am} and PEF_{pm}), PEF variability, use of rescue salbutamol, and weekly mean number of night-time awakenings, all of which were determined as a weekly mean response from study baseline during the last week of each 4-week treatment period. Other endpoints related to efficacy included the ACQ score, which was determined at the end of each 4-week treatment period, and the pre-dose morning and evening FEV_1 ($FEV_{1\ am}$ and $FEV_{1\ pm}$) from the AM2+®, which were analysed as a weekly mean response from study baseline during the last week of each 4-week treatment period. In a subset of patients, pharmacokinetic (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.

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Name of active ingredient: Tiotropium bromide		**Page:** 4 of 7	
Module:		**Volume:**	
Report date: 11 DEC 2012	**Trial No. / U No.:** 205.420 / U12-2227-01	**Dates of trial:** 05 JUL 10 – 19 AUG 11	**Date of revision:** Not applicable

Safety:	Measurement of safety and tolerability was based on the incidence of adverse events (AEs), changes in vital signs (including blood pressure and pulse rate), changes in physical examination reported as AEs, changes in haematology parameters reported as AEs (for patients who participated in the PK portion of the trial only), and changes in 12-lead electrocardiogram (ECG) reported as AEs.
Statistical methods:	**Primary endpoint** The superiority of treatment with tiotropium (5 µg once daily followed by 2.5 µg twice daily) over treatment with placebo was tested in terms of FEV_1 $AUC_{0–24h}$ in a sequential, hierarchical fashion at the level of α=0.025 (1-sided). The primary analysis was a mixed model repeated measures (MMRM) that compared the mean FEV_1 $AUC_{0–24h}$. The statistical model included 'treatment' and 'period' as fixed effects and 'patient' as a random effect; study baseline was included as covariate. **Secondary and other endpoints** All continuous secondary endpoints were analysed using the MMRM as described above for the primary efficacy endpoint. Adjusted mean values as well as treatment contrasts were calculated together with the 95% confidence intervals (CIs). All calculated p-values were to serve an exploratory function. All other endpoints were analysed descriptively.
SUMMARY – CONCLUSIONS:	
Efficacy / clinical pharmacology results:	Out of the 94 treated patients, 89 patients (94.7%) completed the planned treatment time. The study population was White (100%) and contained slightly more female patients (58.5%) than male patients (41.5%). The mean age in the treated set was 44.3 years and the mean duration of asthma (from date of first diagnosis) was 21.3 years. In general, concomitant diagnoses at screening, concomitant medications at screening, and other baseline efficacy variables were as expected for a population of adult patients with moderate, not fully controlled, persistent asthma (mean baseline FEV_1: 2.513 L, mean baseline percent of predicted FEV_1: 76.779%). Overall, mean treatment compliance was high and similar between the tiotropium and placebo treatment groups (Tio R5 qd: 95.66%, Tio R2.5 bid: 96.47 %, placebo: 96.43%).

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Name of active ingredient: Tiotropium bromide		**Page:** 5 of 7	
Module:		**Volume:**	
Report date: 11 DEC 2012	**Trial No. / U No.:** 205.420 / U12-2227-01	**Dates of trial:** 05 JUL 10 – 19 AUG 11	**Date of revision:** Not applicable

Efficacy / clinical pharmacology results (continued):

Primary endpoint

For the primary efficacy endpoint FEV_1 $AUC_{0–24h}$ response, inhalation of tiotropium resulted in statistically significant ($p<0.0001$) adjusted mean treatment differences from placebo of 0.158 L for patients who took Tio R5 qd and 0.149 L for patients who took Tio R2.5 bid. In the exploratory analysis, no significant difference between Tio R5 qd and Tio R2.5 bid was observed in terms of FEV_1 $AUC_{0–24h}$ (0.009 L; [95% CI: -0.038, 0.056]).

Secondary and other endpoints

Significant treatment differences between treatments in favour of tiotropium (both Tio R5 qd and Tio R2.5 bid) over placebo were also observed for the secondary spirometry endpoints of adjusted mean FEV_1 $AUC_{0\text{-}12h}$ ($p<0.0001$), FEV_1 $AUC_{12\text{-}24h}$ ($p<0.0001$), FEV_1 $peak_{0–24h}$ ($p<0.0001$), trough FEV_1 ($p<0.0001$), FVC $AUC_{0\text{-}24h}$ ($p\leq0.004$), FVC $AUC_{0\text{-}12h}$ ($p\leq0.002$), FVC $AUC_{12\text{-}24h}$ ($p\leq0.0123$), and PEF $AUC_{0\text{-}24h}$ ($p<0.0001$) responses. For the secondary endpoints of adjusted mean trough FVC and FVC $peak_{0–24h}$ responses, treatment differences were always in favour of tiotropium (Tio R5 qd and Tio R2.5 bid) over placebo, but statistical significance could not always be shown. No significant differences between Tio R5 qd and Tio R2.5 bid were observed for any of the secondary spirometry endpoints measured in the clinic.

Significant differences between the treatment groups in favour of tiotropium (both Tio R5 qd and Tio R2.5 bid) were observed for the AM2+® endpoints of adjusted weekly mean PEF_{am} ($p<0.0001$), PEF_{pm} ($p<0.0001$), $FEV_{1\ am}$ ($p\leq0.0449$), and $FEV_{1\ pm}$ ($p\leq0.0002$) responses; once again, no significant differences between the two tiotropium regimens were noted for any of these endpoints. No significant differences were noted between tiotropium (Tio R5 qd and Tio R2.5 bid) and placebo in terms of adjusted mean PEF variability, use of rescue medication, or night-time awakenings score responses.

For the other endpoint of adjusted mean ACQ score, an improvement (decrease) was reported for all treatment groups from study baseline (2.317) after 4 weeks of treatment (placebo: 1.808, Tio R2.5 bid: 1.618, Tio R5 qd: 1.535). While the statistical significance of treatment with tiotropium (Tio R5 qd and Tio R2.5 bid) over treatment with placebo was shown ($p\leq0.0072$) for adjusted mean ACQ score, the minimal clinically important difference of 0.5 between the treatment groups was not met.

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Name of active ingredient: Tiotropium bromide		**Page:** 6 of 7	
Module:		**Volume:**	
Report date: 11 DEC 2012	**Trial No. / U No.:** 205.420 / U12-2227-01	**Dates of trial:** 05 JUL 10 – 19 AUG 11	**Date of revision:** Not applicable

Efficacy / clinical pharmacology results (continued):	**Pharmacokinetics** Tiotropium was rapidly absorbed following inhalation. Following the administration of a single dose, t_{max} was achieved approximately 2 to 6 min (median) post-dosing. At steady state t_{max} was achieved approximately 5 to 6 min post-dosing. Following the administration of a single dose, the total exposure over 24 h was comparable between Tio R2.5 bid and Tio R5 qd based on Ae_{0-24} values. Geometric mean AUC and C_{max} values did not appear to be dose-proportional. At steady-state, the total exposure was comparable between Tio R2.5 bid and Tio R5 qd based on $Ae_{0-24,ss}$ and $AUC_{0-24,ss}$ values. The steady state $C_{max,ss}$ values following TioR2.5 bid as morning and evening dosing were 39 to 47% lower, respectively, than the value observed following Tio R5 qd evening dosing. In the Tio R2.5 bid treatment group, the morning $C_{max,ss}$ and AUC values were higher than those of the evening. Approximately 2-fold accumulation was observed following dosing to steady-state as compared to administration of a single dose with Tio R5 qd. With the Tio R2.5 bid regimen, there was less than 2-fold accumulation based on C_{max} and $AUC_{0-0\,5}$ values and about 4-fold accumulation based on 24-h urinary excretion.
Safety results:	The mean exposure to study treatment was comparable for all 3 treatments and ranged from 29.0 days (Tio R5 qd) to 29.8 days (Tio R2.5 bid). During the treatment period, the overall frequency of AEs was well balanced, with 28.3% of placebo patients, 28.9% of Tio R2.5 bid patients, and 24.4% of Tio R5 qd patients reported with at least 1 AE. The most frequently reported treatment-emergent AEs were headache (placebo: 4.3%, Tio R2.5 bid: 7.8%, Tio R5 qd: 5.6%) and nasopharyngitis (placebo: 4.3%, Tio R2.5 bid: 3.3%, Tio R5 qd: 3.3%). AEs assessed as being drug related by the investigator were reported for 4 patients who took Tio R5 qd, 3 patients who took Tio 2.5 bid, and 3 patients who took placebo; all were of mild or moderate intensity, and none were considered to be serious. Other significant AEs (according to ICH E3) and AEs leading to discontinuation were reported for 2 patients in the placebo treatment group (1 patient with hypertension, 1 patient with diarrhoea); no other significant AEs were reported for patients taking tiotropium.

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Name of active ingredient: Tiotropium bromide		**Page:** 7 of 7	
Module:		**Volume:**	
Report date: 11 DEC 2012	**Trial No. / U No.:** 205.420 / U12-2227-01	**Dates of trial:** 05 JUL 10 – 19 AUG 11	**Date of revision:** Not applicable

Safety results (continued):	AEs of severe intensity were reported for 2 patients who took Tio R5 qd (1 patient with haemorrhage and rib fracture due to road traffic accident [all 3 were also considered to be serious AEs] and 1 patient with polyuria), for no patients who took Tio R2.5 bid, and for 1 patient who took placebo (hypertensive crisis [which was also considered to be an SAE]). A total of 3 patients were reported with a total of 5 SAEs during the course of this study; in addition to the hypertensive crisis reported for 1 patient in the placebo group and the haemorrhage and rib fracture due to road traffic accident reported for 1 patient in the Tio R5 qd group, 1 additional patient in the Tio R5 qd group was reported with venous thrombosis limb. All patients with SAEs required hospitalisation, but none of the SAEs were considered drug-related and none were fatal or life threatening. The incidence of dry mouth was low (placebo: 1 patient, Tio R2.5 bid: 1 patient, Tio R5 qd: 3 patients). Mean systolic and diastolic blood pressure and pulse rate were comparable between the treatment groups; no clinically relevant changes in mean vital signs associated with tiotropium were seen.
Conclusions:	Tiotropium solution for inhalation via the Respimat® inhaler was a safe and effective bronchodilator as add-on therapy to medium-dose ICS in adult patients with not fully controlled, moderate persistent asthma. Significant and comparable bronchodilation over a complete 24 h period was achieved following administration of a total daily dose of 5 µg tiotropium, regardless of whether it was administered as a once daily dose of 5 µg (in the evening) or a twice daily dose of 2.5 µg (in the morning and evening). At steady-state, administration of Tio R2.5 bid resulted in comparable total exposure, but $C_{max,ss}$ values for morning and evening dosing that were 39% to 47% lower, respectively, than the value observed following Tio R5 qd evening dosing.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the specific data results for patient disposition and for additional secondary endpoints, mentioned in the results section.

Results for	**presented in**
Patient Disposition	Table 15.1.1: 1
FEV_1 $AUC_{(0\text{-}12h)}$-response FEV_1 $AUC_{(12\text{-}24h)}$-response Peak $FEV_{1(0\text{-}24h)}$-response Trough FEV_1 response	Table 15.2.1.1.2: 1
FVC $AUC_{(0\text{-}12h)}$-response FVC $AUC_{(12\text{-}24h)}$-response FVC $AUC_{(0\text{-}24h)}$-response Trough FVC-response Peak FVC $_{(0\text{-}24h)}$- response	Table 15.2.1.2.1: 1
PEF AUC $_{(0\text{-}24h)}$-response	Table 15.2.1.3.1: 1
Mean Pre-Dose PEF-morning Mean Pre-Dose PEF-evening PER variability	Table 15.2.1.4.1: 1

Table 15.1.1: 1 Disposition of patients

	Placebo N (%)	Tio R2.5 bid N (%)	Tio R5 qd N (%)	Total N (%)
Enrolled				182
Not entered/randomized				88
Entered/randomized	94	94	94	94
Not treated	2	4	4	0
Treated	92 (100.0)	90 (100.0)	90 (100.0)	94 (100.0)
Not prematurely discontinued from trial medication	89 (96.7)	89 (98.9)	89 (98.9)	89 (94.7)
Prematurely discontinued from trial medication	3 (3.3)	1 (1.1)	1 (1.1)	5 (5.3)
Adverse events	2 (2.2)	0 (0.0)	0 (0.0)	2 (2.1)
Worsening of disease under study	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Worsening of other pre-existing disease	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)
Other adverse event	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non compliant with protocol	1 (1.1)	0 (0.0)	0 (0.0)	1 (1.1)
Lost to follow-up	0 (0.0)	1 (1.1)	1 (1.1)	2 (2.1)
Consent withdrawn not due to adverse events	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

All discontinued patients stopped trial medication during the first treatment period. These patients are presented under the treatment they were on at the time they withdrew.
All other patients have completed all three treatment periods.

Table 15.2.1.1.2: 1 FEV1 AUC (0-12h) response [L], AUC (12-24h) response [L], peak (0-24h) response [L], trough FEV1 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 AUC (0-12h) response	Placebo	90	0.048 (0.044)			
	Tio R2.5 bid	89	0.217 (0.044)	0.169 (0.025)	(0.120, 0.218)	<.0001
	Tio R5 qd	90	0.233 (0.044)	0.185 (0.025)	(0.136, 0.234)	<.0001
FEV1 AUC (12-24h) response	Placebo	90	0.135 (0.044)			
	Tio R2.5 bid	89	0.264 (0.045)	0.129 (0.026)	(0.077, 0.181)	<.0001
	Tio R5 qd	90	0.266 (0.044)	0.131 (0.026)	(0.079, 0.183)	<.0001
FEV1 Peak (0-24h) response	Placebo	90	0.337 (0.045)			
	Tio R2.5 bid	89	0.469 (0.045)	0.132 (0.024)	(0.084, 0.179)	<.0001
	Tio R5 qd	90	0.468 (0.045)	0.131 (0.024)	(0.084, 0.179)	<.0001
FEV1 Trough response	Placebo	90	0.143 (0.044)			
	Tio R2.5 bid	89	0.254 (0.044)	0.111 (0.030)	(0.053, 0.170)	0.0002
	Tio R5 qd	90	0.275 (0.044)	0.133 (0.029)	(0.074, 0.191)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 2.524 (0.699)

Table 15.2.1.2.1: 1 FVC AUC (0-24h) response [L], AUC (0-12h) response [L], AUC (12-24h) response [L], peak (0-24h) response [L], trough FVC 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 AUC (0-24h) response	Placebo	90	0.003 (0.044)			
	Tio R2.5 bid	89	0.104 (0.044)	0.101 (0.023)	(0.055, 0.147)	<.0001
	Tio R5 qd	90	0.087 (0.044)	0.084 (0.023)	(0.038, 0.130)	0.0004
FVC AUC (0-12h) response	Placebo	90	-0.026 (0.046)			
	Tio R2.5 bid	89	0.099 (0.046)	0.125 (0.026)	(0.073, 0.177)	<.0001
	Tio R5 qd	90	0.074 (0.046)	0.100 (0.026)	(0.048, 0.152)	0.0002
FVC AUC (12-24h) response	Placebo	90	0.032 (0.045)			
	Tio R2.5 bid	89	0.108 (0.045)	0.076 (0.027)	(0.023, 0.129)	0.0051
	Tio R5 qd	90	0.100 (0.045)	0.068 (0.027)	(0.015, 0.120)	0.0123
FVC Peak (0-24h) response	Placebo	90	0.302 (0.045)			
	Tio R2.5 bid	89	0.380 (0.045)	0.077 (0.027)	(0.025, 0.130)	0.0042
	Tio R5 qd	90	0.350 (0.045)	0.048 (0.027)	(-0.005, 0.100)	0.0747
FVC Trough response	Placebo	90	0.112 (0.046)			
	Tio R2.5 bid	89	0.179 (0.046)	0.068 (0.035)	(0.000, 0.136)	0.0515
	Tio R5 qd	90	0.168 (0.046)	0.056 (0.035)	(-0.012, 0.124)	0.1058

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 3.951 (1.019)

Table 15.2.1.3.1: 1 PEF AUC (0-24h) response [L/min] - 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
PEF AUC (0-24h) response	Placebo	90	8.589 (6.870)			
	Tio R2.5 bid	89	38.831 (6.883)	30.242 (4.091)	(22.167, 38.317)	<.0001
	Tio R5 qd	90	42.899 (6.871)	34.310 (4.089)	(26.240, 42.380)	<.0001

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = 400.783 (106.681)

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 a.m. PEF response	Placebo	91	1.953 (5.864)			
	Tio R2.5 bid	89	23.281 (5.907)	21.328 (5.190)	(11.084, 31.573)	<.0001
	Tio R5 qd	88	24.310 (5.924)	22.357 (5.225)	(12.044, 32.670)	<.0001
Mean p.m. PEF response	Placebo	91	-1.560 (5.891)			
	Tio R2.5 bid	89	28.360 (5.932)	29.920 (5.026)	(20.001, 39.839)	<.0001
	Tio R5 qd	89	27.096 (5.931)	28.657 (5.042)	(18.707, 38.606)	<.0001
Mean PEF variability response	Placebo	91	0.296 (0.711)			
	Tio R2.5 bid	89	0.619 (0.718)	0.323 (0.769)	(-1.195, 1.841)	0.6747
	Tio R5 qd	88	0.685 (0.721)	0.389 (0.774)	(-1.138, 1.916)	0.6159

*adjusted for treatment, period, patient and study baseline
Baseline mean (sd) at visit 2 = Mean morning PEF: 372.678 (124.314), Mean evening PEF: 395.935 (125.968)
Mean PEF variability: 11.676 (6.867)