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.

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..

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Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Spiriva® – Respimat® inhaler		**EudraCT No.:** 2008-001414-25	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 07 NOV 2013	**Trial No. / U No.:** 205.417 / U12-1987-02	**Dates of trial:** 03 NOV 08 – 22 JUL 11	**Date of revision:** 25 APR 2013

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 (5 µg/day) over 48 weeks as add-on controller therapy on top of usual care in patients with severe persistent asthma
Coordinating Investigator:	[redacted]
Trial sites:	Multinational trial in 75 sites in 15 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 (205.416 and 205.417). The objective of this trial was to evaluate the long-term efficacy and safety of tiotropium solution for inhalation (5 µg) delivered by the Respimat® inhaler in comparison to placebo (both treatments on top of usual care) in adult patients with severe, uncontrolled, persistent asthma
Methodology:	Randomised, placebo-controlled, double-blind, parallel-group comparison of tiotropium (5 µg) once daily in the morning versus placebo (both treatments on top of usual care) over 48 weeks
No. of subjects:	
planned:	entered: 300 (planned in CTP) 400 (planned in CTP after interim analysis)

actual:	enrolled: 679 entered: 453 Tiotropium solution for inhalation (5 µg): entered: 219 treated: 219 analysed (for primary endpoint): 216 analysed (for 24 h pulmonary function test): 82 Placebo: entered: 234 treated: 234 analysed (for primary endpoint): 232 analysed (for 24 h pulmonary function test): 91
Diagnosis and main criteria for inclusion:	Male and female outpatients between 18 and 75 years old with a current diagnosis of severe, persistent asthma; a minimum documented 5-year history of asthma diagnosed before the age of 40; never smokers or ex-smokers who had quit smoking at least 1 year prior to enrolment and who had a smoking history of <10 pack-years; symptomatic despite treatment with a high, stable dose of inhaled corticosteroids (ICS) and a long-acting β_2-adrenergic agonist (LABA) for at least 4 weeks prior to screening; forced expiratory volume in 1 second (FEV_1) ≤80% of predicted and ≤70% of the forced vital capacity (FVC) 30 min after the inhalation of 400 µg salbutamol (albuterol); Asthma Control Questionnaire (ACQ) ≥1.5 at screening (Visit 1) and prior to randomisation (Visit 2); a history of 1 or more asthma exacerbations in the past year that required treatment with systemic corticosteroids, with no asthma exacerbations in the 4 weeks prior to screening (Visit 1) or during the 4-week screening period.
Test product:	Tiotropium solution for inhalation
dose:	5 µg (ex mouthpiece, as 2 actuations of 2.5 µg, calculated as free cation), once daily (qd) in the morning (am)
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B072000278−B072000334
Reference therapy:	Placebo solution for inhalation
dose:	Not applicable
mode of admin.:	Oral inhalation via the Respimat® inhaler
batch no.:	B072000280−B072000335

Name of company: Boehringer Ingelheim		Tabulated Trial Report	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001414-25	
Name of active ingredient: Tiotropium bromide		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
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Duration of treatment: A 4-week screening period was followed by a 48-week treatment period. Patients were followed-up for 30 days.

Criteria for evaluation:

Efficacy / clinical pharmacology:

Co-primary endpoints included: maximum FEV_1 within 3 h post-dosing (FEV_1 $peak_{0–3h}$) and trough (pre-dose) FEV_1. Both of these co-primary endpoints were analysed as a response (change from study baseline) after 24 weeks of treatment. The third co-primary endpoint was time to first severe asthma exacerbation during the 48-week treatment period; this was considered primary only in the analysis of pooled data from the 2 twin trials 205.416 and 205.417 and is presented in a separate report.

Secondary endpoints included: maximum FVC measured within 3 h post-dosing (FVC $peak_{0–3h}$), trough FVC, FEV_1 area under the curve from 0 to 3 h (FEV_1 $AUC_{0–3h}$), and FVC $AUC_{0–3h}$. These endpoints were reported as a response after 24 weeks of treatment. Further secondary endpoints analysed during the 48 week treatment period were the time to first asthma exacerbation (including severe, non-severe; symptomatic, asymptomatic; i.e. any exacerbation), time to first severe asthma exacerbation, ACQ, and the Standardised Asthma Quality of Life Questionnaire (AQLQ(S)). Pre-dose morning and evening peak expiratory flow (PEF_{am} and PEF_{pm}), pre-dose morning and evening FEV_1 ($FEV_{1\,am}$ and $FEV_{1\,pm}$), PEF variability, use of rescue medication as needed, and asthma symptoms were secondary endpoints measured at home using the Asthma Monitor (AM3®). These AM3® endpoints were analysed as a weekly mean response during the 48-week treatment period (i.e. Weeks 1, 2, 3...) and during the last 7 days before Visit 6 (i.e. after approximately 24 weeks of treatment, but not necessarily the weekly mean response of Week 24). In a subset of patients who underwent 24 h spirometry, 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 $AUC_{12–24h}$ were also secondary endpoints that were analysed as a response after 24 weeks of treatment.

Other endpoints included pharmacokinetic parameters of tiotropium. These parameters were evaluated in blood and urine samples in a subset of 76 patients after a single dose and at pharmacokinetic steady state (4 weeks).

Safety:	Measurement of safety and tolerability was based on the incidence and intensity of adverse events (AEs), changes in vital signs (including pulse rate and seated blood pressure), changes in physical examination reported as AEs, and vital status information. Vital status information was only assessed for prematurely discontinued patients who consented to be contacted regarding vital status.
Statistical methods:	The superiority of treatment with tiotropium (5 µg) over treatment with 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 repeated measures (MMRM) approach that included 'treatment', 'pooled centre', 'visit', and 'treatment by visit' interaction as fixed, categorical effects and 'baseline' and 'baseline by visit' interaction as continuous, fixed covariates. A spatial power structure was used to model the within-patient errors. Adjusted mean values as well as treatment contrasts were calculated together with 95% confidence intervals (CIs). As mentioned above, the superiority of treatment with tiotropium (5 µg) over treatment with placebo was also tested in terms of time to first severe asthma exacerbation. This analysis was based on the pooled data from the twin trials 205.416 and 205.417 and is described in a separate report. For this endpoint a pre-planned interim analysis of the hazard ratio of first severe asthma exacerbation was performed with the option to adapt the sample size. Based on the interim analysis, which was conducted by an independent data monitoring committee, the sample size was increased from 300 to 400 patients per trial.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:	A total of 453 patients were randomised and treated with either tiotropium 5 µg (219 patients) or placebo (234 patients). Of the treated patients, 11.5% discontinued prematurely (tiotropium: 9.6%, placebo: 13.2%). The most frequent reason for discontinuation was due to refusal to continue taking trial medication (tiotropium: 3.2%, placebo: 5.1%). Overall, the demographic profile was balanced between the treatment groups, and study baseline characteristics were as expected for a population of adult patients with severe, uncontrolled, persistent asthma (mean baseline FEV_1: 1.628 L, mean baseline percent of predicted FEV_1: 56.29%, mean baseline ACQ: 2.6).

Efficacy / clinical pharmacology results (continued):

Co-primary endpoints

Superiority of tiotropium over placebo was demonstrated for both co-primary endpoints of adjusted mean FEV_1 $peak_{0–3h}$ and trough FEV_1 response after 24 weeks of treatment. The observed treatment differences of 0.154 L ($p<0.0001$) for adjusted mean FEV_1 $peak_{0–3h}$ response and 0.111 L ($p=0.0002$) for adjusted mean trough FEV_1 response were statistically significant and in favour of tiotropium. Significant differences between treatments in favour of tiotropium in terms of adjusted mean FEV_1 $peak_{0–3h}$ and trough FEV_1 response were also observed at all other visits during the treatment period ($p\leq0.0173$ in every case).

Secondary endpoints

As compared with placebo, tiotropium significantly reduced the risk of first asthma exacerbation by 34% (hazard ratio: 0.66, $p=0.0011$), but did not significantly reduce the risk of first severe asthma exacerbation (hazard ratio 0.89, $p=0.4788$) in patients with severe, persistent asthma who had a history of at least 1 asthma exacerbation in the past year. Less than 50% of patients were reported with severe asthma exacerbations, so median time to first severe exacerbation could not be calculated. Patients who took tiotropium had a longer median time to first asthma exacerbation than placebo patients (tiotropium: 299.0 days, placebo: 181.0 days).

The treatment differences between tiotropium and placebo for other secondary FEV_1 endpoints measured in the clinic (adjusted mean FEV_1 $AUC_{0–3h}$ and individual FEV_1 responses at each timepoint) were significant and in favour of tiotropium at Visit 6 (Week 24; $p<0.0001$ in every case), and, with the exception of the adjusted mean FEV_1 response measured 30 min after inhalation at Visit 2 (Day 1; $p=0.1032$), at all other visits and timepoints ($p\leq0.0371$ in every case). Treatment differences between tiotropium and placebo for all secondary FVC endpoints (adjusted mean FVC $peak_{0–3h}$, trough FVC, FVC $AUC_{0–3h}$, and individual FVC responses) were also significant and in favour of tiotropium at Visit 6 (Week 24; $p\leq 0.0275$). At all other visits and timepoints, the treatment differences were always in favour of tiotropium, but statistical significance was not always shown.

Efficacy / clinical pharmacology results (continued):

For FEV_1 endpoints measured during the 24 h lung function measurements for the FAS24 (tiotropium: 82 patients, placebo: 91 patients) treatment differences were always statistically significant ($p \leq 0.0088$) and in favour of tiotropium. The 24 h lung function measurements confirmed the 24 h bronchodilator efficacy of tiotropium.

Significant differences between the treatment groups in favour of tiotropium were observed for the AM3® endpoints of adjusted weekly mean PEF_{am} (20.654 L/min, $p<0.0001$), PEF_{pm} 32.453 L/min ($p<0.0001$), $FEV_{1\ am}$ (0.090 L, $p=0.0027$), and $FEV_{1\ pm}$ (0.137 L, $p<0.0001$) responses during the last 7 days before Visit 6 (after approximately 24 weeks of treatment). With the exception of Week 2 (at which no statistical significance was reached for the adjusted weekly mean PEF_{am} response), significant differences between the treatment groups in favour of tiotropium were observed for adjusted weekly mean PEF_{am}, $PEF_{pm,}$ and $FEV_{1\ pm}$ responses at all weeks of the treatment period ($p \leq 0.0389$ in all cases). For adjusted weekly mean $FEV_{1\ am}$ response, significant differences between the treatment groups in favour of tiotropium were observed starting at Week 21 and every week thereafter ($p \leq 0.0255$ in all cases); prior to Week 21, the treatment difference was always in favour of tiotropium, but statistical significance was not always shown.

For the secondary endpoint of adjusted mean ACQ score, an improvement was reported for both treatment groups from study baseline (2.591) to Week 48 (tiotropium: 2.027, placebo: 2.159), but the difference between the treatment groups of −0.133 was not significant ($p=0.0533$) and the minimal clinically important difference of 0.5 was not met. Similar results were observed for other patient-reported outcomes (e.g. AQLQ(S), asthma symptoms, and use of rescue medication measured at home using the AM3®).

Pharmacokinetics

Tiotropium was rapidly absorbed with a median $t_{max(,ss)}$ of 4.5 to 5 min post-inhalation. Approximately 6.61% and 6.93% of the inhaled dose was excreted unchanged in the urine over 24 h ($fe_{0-24(,ss)}$) following the inhalation of a single dose and at steady-state, respectively. Dosing to steady state led to slight accumulation compared to administration of a single dose and resulted in a 1.23-fold higher C_{max}, 1.69-fold higher $AUC_{0-0\ 5}$, and 1.46-fold higher Ae_{0-24} at steady state as compared to single dose.

Safety results:

Mean exposure was similar for both treatment groups (tiotropium: 323.1 days, placebo: 317.2 days). During the treatment period, the overall incidence of AEs was slightly higher in the placebo group than in the 5 µg tiotropium group, with 76.7% of tiotropium and 83.8% of placebo patients reporting at least 1 AE. The most frequently reported treatment-emergent AEs included asthma (tiotropium: 41.6%; placebo: 52.6%), PEF rate decreased (tiotropium: 20.1%; placebo: 27.4%) and nasopharyngitis (tiotropium: 14.6%; placebo: 15.4%). AEs assessed as being drug-related by the investigator were reported for 5.9% of patients taking tiotropium and 5.1% of placebo patients. Almost all drug-related AEs were of mild or moderate intensity; the only exceptions to this were 3 patients who were reported with drug-related asthma of severe intensity (tiotropium: 2 patients, placebo: 1 patient). Only 1 of the drug-related AEs was considered to be serious; this case of asthma [exacerbation], which was reported by a patient in the tiotropium group, was of moderate intensity and required hospitalisation. This SAE had 2 different causality assessments by the investigator (drug-related in clinical database, not drug-related in SAE form). However, the local monitor confirmed with the investigator that there was no causal relationship between the SAE and drug intake.

Other significant AEs (according to ICH E3), which were defined as those non-serious and non-significant AEs that led to discontinuation or dose reduction of the study drug, were reported for 3 tiotropium patients and 7 placebo patients, while AEs leading to discontinuation were reported for 2 tiotropium patients and 8 placebo patients. Finally, serious AEs (SAEs) were reported for 8.7% of patients in the tiotropium group and 10.7% of patients in the placebo group. Three patients (all in the tiotropium group) were reported with life-threatening SAEs (1 patient with cerebral infarction, 1 patient with hypotension, shock, and renal failure [after hospitalisation for a non-life-threatening asthma exacerbation], and 1 patient with acute respiratory failure and asthma [exacerbation]); none of these were considered to be drug-related by the investigator. Two patients were reported with pregnancies that began while patients were on treatment, and 2 patients were reported with pregnancies that began after patients had stopped taking study drug. Healthy babies were delivered in all 4 cases. There were no deaths during the course of this study. Of the 50 patients who had an available vital status, 49 (tiotropium: 21 patients, placebo: 28 patients) were reported as alive and 1 (placebo group) was reported as lost to follow-up.

Safety results (continued):	Overall, mean systolic and diastolic blood pressure and pulse rate were comparable between the treatment groups at baseline, over 3 h post-dose, and over the 48 weeks of the study. More tiotropium patients than placebo patients were reported with a marked increase in diastolic blood pressure (tiotropium: 19.2%, placebo: 14.1%); however, this was not accompanied by an imbalance between the treatment groups in terms of AEs related to blood pressure (e.g. the PTs blood pressure increased and hypertension). In all other cases, the difference between the groups in terms of frequency of patients with marked changes in vital signs was minimal.
Conclusions:	Tiotropium solution for inhalation via the Respimat® inhaler was safe and effective as an add-on therapy to a high dose of ICS and LABA in a population of adult patients with uncontrolled, severe, persistent asthma with a history of at least 1 exacerbation in the preceding year. Tiotropium was superior to placebo in its ability to improve adjusted mean FEV_1 $peak_{0-3h}$ and trough FEV_1 responses (co-primary endpoints) after 24 weeks of treatment. Further, tiotropium significantly reduced the risk of first asthma exacerbation as compared with placebo. The safety profiles for tiotropium and placebo on top of ICS and LABA were similar. Pharmacokinetic evaluation of tiotropium following inhaled administration revealed rapid absorption, and dosing to steady-state resulted in slight accumulation compared to single dose administration.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide some of the results for secondary endpoint statements in the synopsis. The number of secondary endpoints defined for this trial was too large to allow meaningful presentation in this format; therefore, results for up to a total of 10 secondary efficacy endpoints are provided in the following tables.

Results for	**presented in**
FEV_1 $peak_{0\text{-}3h}$ response at 24 weeks (primary endpoint) Trough FEV_1 response at 24 weeks (primary endpoint) FEV_1 $peak_{0\text{-}3h}$ response at all visits (secondary endpoint) Trough FEV_1 response at all visits (secondary endpoint) FEV_1 $AUC_{0\text{-}3h}$ response at all visits (secondary endpoint)	Table 15.2.1.1.3: 3
FEV_1 individual measurements: response at each time point and visit (secondary endpoint)	Table 15.2.1.1.3: 2
FVC $peak_{0\text{-}3h}$ response at all visits (secondary endpoint) Trough FVC response at all visits (secondary endpoint) FVC $AUC_{0\text{-}3h}$ response at all visits (secondary endpoint)	Table 15.2.1.2.1: 3
FVC individual measurements: response at each time point and visit (secondary endpoint)	Table 15.2.1.2.1: 2

Table 15.2.1.1.3: 3 FEV1 peak (0-3h) response [L], trough FEV1 response [L], FEV1 AUC (0-3h) response [L] at all visits - MMRM results - FAS

					Tio R5 vs Placebo		
Timepoint	Endpoint statistic	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Day 1	Peak (0-3h)	Placebo	232	0.252 (0.023)			
		Tio R5	216	0.344 (0.025)	0.092 (0.031)	(0.030, 0.153)	0.0036
	AUC (0-3h)	Placebo	232	0.157 (0.022)			
		Tio R5	216	0.238 (0.023)	0.081 (0.029)	(0.023, 0.138)	0.0062
Week 4	Trough	Placebo	227	0.068 (0.022)			
		Tio R5	213	0.137 (0.023)	0.069 (0.029)	(0.012, 0.127)	0.0173
	Peak (0-3h)	Placebo	227	0.284 (0.024)			
		Tio R5	213	0.388 (0.025)	0.104 (0.032)	(0.042, 0.166)	0.0010
	AUC (0-3h)	Placebo	227	0.200 (0.022)			
		Tio R5	213	0.297 (0.023)	0.097 (0.029)	(0.039, 0.155)	0.0010
Week 8	Trough	Placebo	228	0.055 (0.022)			
		Tio R5	209	0.158 (0.023)	0.103 (0.029)	(0.046, 0.160)	0.0004
	Peak (0-3h)	Placebo	228	0.285 (0.024)			
		Tio R5	208	0.416 (0.025)	0.131 (0.032)	(0.069, 0.193)	<.0001
	AUC (0-3h)	Placebo	228	0.198 (0.022)			
		Tio R5	208	0.316 (0.023)	0.119 (0.030)	(0.061, 0.177)	<.0001

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.1.3: 3 FEV1 peak (0-3h) response [L], trough FEV1 response [L], FEV1 AUC (0-3h) response [L] at all visits - MMRM results - FAS

					Tio R5 vs Placebo		
Timepoint	Endpoint statistic	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 16	Trough	Placebo	222	0.070 (0.022)			
		Tio R5	208	0.151 (0.023)	0.080 (0.029)	(0.023, 0.138)	0.0064
	Peak (0-3h)	Placebo	222	0.278 (0.024)			
		Tio R5	208	0.401 (0.025)	0.123 (0.032)	(0.060, 0.185)	0.0001
	AUC (0-3h)	Placebo	222	0.198 (0.022)			
		Tio R5	208	0.313 (0.023)	0.115 (0.030)	(0.056, 0.173)	0.0001
Week 24	Trough	Placebo	218	0.044 (0.022)			
		Tio R5	204	0.155 (0.023)	0.111 (0.030)	(0.053, 0.169)	0.0002
	Peak (0-3h)	Placebo	218	0.248 (0.024)			
		Tio R5	205	0.401 (0.025)	0.154 (0.032)	(0.091, 0.217)	<.0001
	AUC (0-3h)	Placebo	218	0.164 (0.022)			
		Tio R5	204	0.307 (0.023)	0.143 (0.030)	(0.084, 0.202)	<.0001
Week 32	Trough	Placebo	212	0.032 (0.022)			
		Tio R5	199	0.129 (0.023)	0.097 (0.030)	(0.038, 0.156)	0.0012
	Peak (0-3h)	Placebo	212	0.233 (0.024)			
		Tio R5	199	0.387 (0.025)	0.154 (0.032)	(0.090, 0.218)	<.0001

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.1.3: 3 FEV1 peak (0-3h) response [L], trough FEV1 response [L], FEV1 AUC (0-3h) response [L] at all visits - MMRM results - FAS

					Tio R5 vs Placebo		
Timepoint	Endpoint statistic	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 32	AUC (0-3h)	Placebo	212	0.149 (0.023)			
		Tio R5	199	0.295 (0.024)	0.145 (0.030)	(0.086, 0.205)	<.0001
Week 40	Trough	Placebo	207	0.040 (0.022)			
		Tio R5	199	0.149 (0.023)	0.109 (0.030)	(0.050, 0.169)	0.0003
	Peak (0-3h)	Placebo	207	0.242 (0.024)			
		Tio R5	199	0.384 (0.025)	0.143 (0.033)	(0.079, 0.207)	<.0001
	AUC (0-3h)	Placebo	207	0.162 (0.023)			
		Tio R5	199	0.298 (0.024)	0.136 (0.031)	(0.076, 0.196)	<.0001
Week 48	Trough	Placebo	204	0.063 (0.023)			
		Tio R5	198	0.155 (0.023)	0.092 (0.030)	(0.032, 0.151)	0.0026
	Peak (0-3h)	Placebo	205	0.245 (0.025)			
		Tio R5	198	0.397 (0.026)	0.152 (0.033)	(0.087, 0.217)	<.0001
	AUC (0-3h)	Placebo	204	0.172 (0.023)			
		Tio R5	198	0.310 (0.024)	0.138 (0.031)	(0.078, 0.199)	<.0001

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.1.3: 2 FEV1 [L] individual measurements response at each time point and visit
– MMRM results – FAS

Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Tio R5 vs Placebo: Adjusted* mean of difference (SE)	95% CI	p-value
Day 1	0:30	Placebo	232	0.135 (0.022)			
		Tio R5	216	0.184 (0.023)	0.048 (0.030)	(-0.010, 0.107)	0.1032
	1:00	Placebo	232	0.171 (0.023)			
		Tio R5	216	0.235 (0.024)	0.064 (0.031)	(0.004, 0.125)	0.0371
	2:00	Placebo	232	0.178 (0.023)			
		Tio R5	216	0.289 (0.024)	0.111 (0.031)	(0.050, 0.172)	0.0004
	3:00	Placebo	232	0.183 (0.023)			
		Tio R5	216	0.293 (0.025)	0.110 (0.032)	(0.048, 0.172)	0.0005
Week 4	0:30	Placebo	227	0.177 (0.022)			
		Tio R5	213	0.261 (0.023)	0.084 (0.030)	(0.025, 0.142)	0.0049
	1:00	Placebo	227	0.212 (0.023)			
		Tio R5	213	0.293 (0.024)	0.080 (0.031)	(0.020, 0.141)	0.0095
	2:00	Placebo	227	0.218 (0.023)			
		Tio R5	213	0.335 (0.024)	0.117 (0.031)	(0.055, 0.178)	0.0002
	3:00	Placebo	227	0.223 (0.024)			
		Tio R5	213	0.327 (0.025)	0.104 (0.032)	(0.042, 0.166)	0.0010
Week 8	0:30	Placebo	228	0.182 (0.022)			
		Tio R5	208	0.276 (0.023)	0.094 (0.030)	(0.036, 0.153)	0.0017
	1:00	Placebo	228	0.211 (0.023)			
		Tio R5	208	0.314 (0.024)	0.103 (0.031)	(0.042, 0.163)	0.0010

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.1.3: 2 FEV1 [L] individual measurements response at each time point and visit
– MMRM results – FAS

Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Tio R5 vs Placebo: Adjusted* mean of difference (SE)	95% CI	p-value
Week 8	2:00	Placebo	228	0.217 (0.023)			
		Tio R5	208	0.351 (0.025)	0.134 (0.031)	(0.072, 0.196)	<.0001
	3:00	Placebo	228	0.214 (0.024)			
		Tio R5	208	0.354 (0.025)	0.140 (0.032)	(0.077, 0.202)	<.0001
Week 16	0:30	Placebo	222	0.174 (0.022)			
		Tio R5	208	0.274 (0.023)	0.100 (0.030)	(0.041, 0.159)	0.0009
	1:00	Placebo	222	0.209 (0.023)			
		Tio R5	208	0.317 (0.024)	0.108 (0.031)	(0.047, 0.169)	0.0006
	2:00	Placebo	222	0.218 (0.024)			
		Tio R5	208	0.341 (0.025)	0.123 (0.032)	(0.061, 0.185)	0.0001
	3:00	Placebo	222	0.221 (0.024)			
		Tio R5	208	0.354 (0.025)	0.134 (0.032)	(0.071, 0.197)	<.0001
Week 24	0:30	Placebo	218	0.152 (0.022)			
		Tio R5	205	0.284 (0.023)	0.132 (0.030)	(0.072, 0.191)	<.0001
	1:00	Placebo	218	0.168 (0.023)			
		Tio R5	205	0.308 (0.024)	0.140 (0.032)	(0.078, 0.202)	<.0001
	2:00	Placebo	218	0.178 (0.024)			
		Tio R5	205	0.328 (0.025)	0.150 (0.032)	(0.088, 0.213)	<.0001
	3:00	Placebo	218	0.191 (0.024)			
		Tio R5	205	0.344 (0.025)	0.152 (0.032)	(0.089, 0.216)	<.0001

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.1.3: 2 FEV1 [L] individual measurements response at each time point and visit
– MMRM results – FAS

Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Tio R5 vs Placebo: Adjusted* mean of difference (SE)	95% CI	p-value
Week 32	0:30	Placebo	212	0.122 (0.023)			
		Tio R5	199	0.262 (0.024)	0.140 (0.031)	(0.080, 0.201)	<.0001
	1:00	Placebo	212	0.161 (0.024)			
		Tio R5	199	0.299 (0.025)	0.139 (0.032)	(0.076, 0.201)	<.0001
	2:00	Placebo	212	0.167 (0.024)			
		Tio R5	199	0.328 (0.025)	0.162 (0.032)	(0.098, 0.225)	<.0001
	3:00	Placebo	212	0.175 (0.024)			
		Tio R5	199	0.320 (0.025)	0.146 (0.033)	(0.082, 0.210)	<.0001
Week 40	0:30	Placebo	207	0.142 (0.023)			
		Tio R5	199	0.271 (0.024)	0.129 (0.031)	(0.068, 0.189)	<.0001
	1:00	Placebo	207	0.174 (0.024)			
		Tio R5	199	0.289 (0.025)	0.115 (0.032)	(0.052, 0.178)	0.0004
	2:00	Placebo	207	0.179 (0.024)			
		Tio R5	199	0.330 (0.025)	0.151 (0.033)	(0.087, 0.215)	<.0001
	3:00	Placebo	207	0.184 (0.024)			
		Tio R5	199	0.335 (0.025)	0.151 (0.033)	(0.086, 0.216)	<.0001
Week 48	0:30	Placebo	205	0.152 (0.023)			
		Tio R5	198	0.287 (0.024)	0.134 (0.031)	(0.073, 0.196)	<.0001
	1:00	Placebo	205	0.174 (0.024)			
		Tio R5	198	0.321 (0.025)	0.147 (0.032)	(0.084, 0.211)	<.0001

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.1.3: 2 FEV1 [L] individual measurements response at each time point and visit
– MMRM results – FAS

					Tio R5 vs Placebo		
Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 48	2:00	Placebo	205	0.183 (0.024)			
		Tio R5	198	0.329 (0.025)	0.146 (0.033)	(0.081, 0.210)	<.0001
	3:00	Placebo	205	0.191 (0.025)			
		Tio R5	198	0.343 (0.026)	0.152 (0.033)	(0.087, 0.217)	<.0001

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.628 (0.539)

Table 15.2.1.2.1: 3 FVC peak (0-3h) response [L], trough FVC response [L], FVC AUC (0-3h) response [L] at all visits - MMRM results - FAS

					Tio R5 vs Placebo		
Timepoint	Endpoint statistic	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Day 1	Peak (0-3h)	Placebo	232	0.331 (0.031)			
		Tio R5	216	0.404 (0.033)	0.073 (0.042)	(-0.008, 0.155)	0.0786
	AUC (0-3h)	Placebo	232	0.180 (0.029)			
		Tio R5	216	0.260 (0.031)	0.080 (0.039)	(0.004, 0.157)	0.0390
Week 4	Trough	Placebo	227	0.091 (0.030)			
		Tio R5	213	0.118 (0.031)	0.027 (0.040)	(-0.052, 0.106)	0.4964
	Peak (0-3h)	Placebo	227	0.377 (0.031)			
		Tio R5	213	0.451 (0.033)	0.073 (0.042)	(-0.008, 0.155)	0.0780
	AUC (0-3h)	Placebo	227	0.237 (0.029)			
		Tio R5	213	0.312 (0.031)	0.075 (0.039)	(-0.001, 0.152)	0.0539
Week 8	Trough	Placebo	228	0.059 (0.030)			
		Tio R5	209	0.158 (0.031)	0.098 (0.040)	(0.019, 0.177)	0.0148
	Peak (0-3h)	Placebo	228	0.360 (0.031)			
		Tio R5	208	0.452 (0.033)	0.092 (0.042)	(0.010, 0.174)	0.0277
	AUC (0-3h)	Placebo	228	0.219 (0.029)			
		Tio R5	208	0.315 (0.031)	0.096 (0.039)	(0.019, 0.172)	0.0146
Week 16	Trough	Placebo	222	0.070 (0.030)			
		Tio R5	208	0.138 (0.032)	0.068 (0.041)	(-0.012, 0.148)	0.0940
	Peak (0-3h)	Placebo	222	0.360 (0.031)			
		Tio R5	208	0.432 (0.033)	0.072 (0.042)	(-0.011, 0.154)	0.0881

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)

Table 15.2.1.2.1: 3 FVC peak (0-3h) response [L], trough FVC response [L], FVC AUC (0-3h) response [L] at all visits - MMRM results - FAS

					Tio R5 vs Placebo		
Timepoint	Endpoint statistic	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 16	AUC (0-3h)	Placebo	222	0.230 (0.029)			
		Tio R5	208	0.306 (0.031)	0.077 (0.039)	(-0.001, 0.154)	0.0521
Week 24	Trough	Placebo	218	0.044 (0.030)			
		Tio R5	204	0.150 (0.032)	0.106 (0.041)	(0.025, 0.186)	0.0099
	Peak (0-3h)	Placebo	218	0.323 (0.032)			
		Tio R5	205	0.416 (0.033)	0.094 (0.042)	(0.010, 0.177)	0.0275
	AUC (0-3h)	Placebo	218	0.187 (0.030)			
		Tio R5	204	0.295 (0.031)	0.109 (0.040)	(0.031, 0.187)	0.0063
Week 32	Trough	Placebo	212	0.035 (0.031)			
		Tio R5	199	0.121 (0.032)	0.086 (0.041)	(0.005, 0.167)	0.0384
	Peak (0-3h)	Placebo	212	0.310 (0.032)			
		Tio R5	199	0.419 (0.033)	0.109 (0.043)	(0.025, 0.193)	0.0112
	AUC (0-3h)	Placebo	212	0.182 (0.030)			
		Tio R5	199	0.293 (0.031)	0.111 (0.040)	(0.032, 0.190)	0.0058
Week 40	Trough	Placebo	207	0.070 (0.031)			
		Tio R5	199	0.166 (0.032)	0.096 (0.042)	(0.014, 0.178)	0.0213
	Peak (0-3h)	Placebo	207	0.321 (0.032)			
		Tio R5	199	0.417 (0.034)	0.097 (0.043)	(0.012, 0.181)	0.0258
	AUC (0-3h)	Placebo	207	0.192 (0.030)			
		Tio R5	199	0.300 (0.032)	0.108 (0.040)	(0.029, 0.187)	0.0078

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)

Table 15.2.1.2.1: 3 FVC peak (0-3h) response [L], trough FVC response [L], FVC AUC (0-3h) response [L] at all visits - MMRM results - FAS

					Tio R5 vs Placebo		
Timepoint	Endpoint statistic	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 48	Trough	Placebo	204	0.072 (0.031)			
		Tio R5	198	0.142 (0.032)	0.071 (0.042)	(-0.012, 0.153)	0.0933
	Peak (0-3h)	Placebo	205	0.305 (0.033)			
		Tio R5	198	0.420 (0.034)	0.114 (0.044)	(0.029, 0.200)	0.0088
	AUC (0-3h)	Placebo	204	0.190 (0.031)			
		Tio R5	198	0.299 (0.032)	0.109 (0.041)	(0.029, 0.189)	0.0074

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)

Table 15.2.1.2.1: 2 FVC [L] individual measurements response at each time point and visit
– MMRM results – FAS

					Tio R5 vs Placebo		
Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Day 1	0:30	Placebo	232	0.170 (0.030)			
		Tio R5	216	0.219 (0.031)	0.048 (0.040)	(-0.030, 0.126)	0.2281
	1:00	Placebo	232	0.197 (0.030)			
		Tio R5	216	0.261 (0.032)	0.064 (0.041)	(-0.016, 0.144)	0.1168
	2:00	Placebo	232	0.200 (0.031)			
		Tio R5	216	0.312 (0.033)	0.112 (0.042)	(0.030, 0.193)	0.0077
	3:00	Placebo	232	0.192 (0.032)			
		Tio R5	216	0.298 (0.033)	0.106 (0.042)	(0.023, 0.189)	0.0119
Week 4	0:30	Placebo	227	0.240 (0.030)			
		Tio R5	213	0.284 (0.031)	0.045 (0.040)	(-0.034, 0.123)	0.2661
	1:00	Placebo	227	0.253 (0.030)			
		Tio R5	213	0.310 (0.032)	0.057 (0.041)	(-0.024, 0.137)	0.1656
	2:00	Placebo	227	0.250 (0.031)			
		Tio R5	213	0.347 (0.033)	0.098 (0.042)	(0.015, 0.180)	0.0200
	3:00	Placebo	227	0.241 (0.032)			
		Tio R5	213	0.346 (0.033)	0.105 (0.042)	(0.022, 0.189)	0.0129
Week 8	0:30	Placebo	228	0.211 (0.030)			
		Tio R5	208	0.302 (0.031)	0.091 (0.040)	(0.012, 0.170)	0.0240
	1:00	Placebo	228	0.231 (0.030)			
		Tio R5	208	0.312 (0.032)	0.080 (0.041)	(-0.000, 0.161)	0.0504

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)

Table 15.2.1.2.1: 2 FVC [L] individual measurements response at each time point and visit
– MMRM results – FAS

					Tio R5 vs Placebo		
Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 8	2:00	Placebo	228	0.234 (0.031)			
		Tio R5	208	0.337 (0.033)	0.104 (0.042)	(0.021, 0.186)	0.0138
	3:00	Placebo	228	0.244 (0.032)			
		Tio R5	208	0.343 (0.033)	0.099 (0.043)	(0.015, 0.182)	0.0202
Week 16	0:30	Placebo	222	0.208 (0.030)			
		Tio R5	208	0.284 (0.031)	0.076 (0.041)	(-0.004, 0.155)	0.0615
	1:00	Placebo	222	0.245 (0.031)			
		Tio R5	208	0.313 (0.032)	0.068 (0.041)	(-0.013, 0.149)	0.1018
	2:00	Placebo	222	0.248 (0.032)			
		Tio R5	208	0.332 (0.033)	0.084 (0.042)	(0.001, 0.167)	0.0471
	3:00	Placebo	222	0.258 (0.032)			
		Tio R5	208	0.330 (0.033)	0.072 (0.043)	(-0.012, 0.156)	0.0934
Week 24	0:30	Placebo	218	0.187 (0.030)			
		Tio R5	205	0.285 (0.032)	0.098 (0.041)	(0.018, 0.179)	0.0160
	1:00	Placebo	218	0.190 (0.031)			
		Tio R5	205	0.297 (0.032)	0.107 (0.042)	(0.025, 0.189)	0.0108
	2:00	Placebo	218	0.195 (0.032)			
		Tio R5	205	0.311 (0.033)	0.116 (0.043)	(0.032, 0.200)	0.0067
	3:00	Placebo	218	0.223 (0.032)			
		Tio R5	205	0.325 (0.034)	0.102 (0.043)	(0.017, 0.186)	0.0189

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)

Table 15.2.1.2.1: 2 FVC [L] individual measurements response at each time point and visit
– MMRM results – FAS

					Tio R5 vs Placebo		
Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 32	0:30	Placebo	212	0.161 (0.031)			
		Tio R5	199	0.274 (0.032)	0.113 (0.041)	(0.032, 0.194)	0.0062
	1:00	Placebo	212	0.201 (0.031)			
		Tio R5	199	0.299 (0.033)	0.098 (0.042)	(0.015, 0.181)	0.0205
	2:00	Placebo	212	0.198 (0.032)			
		Tio R5	199	0.324 (0.034)	0.126 (0.043)	(0.042, 0.211)	0.0035
	3:00	Placebo	212	0.208 (0.033)			
		Tio R5	199	0.309 (0.034)	0.101 (0.044)	(0.016, 0.187)	0.0206
Week 40	0:30	Placebo	207	0.191 (0.031)			
		Tio R5	199	0.283 (0.032)	0.092 (0.042)	(0.010, 0.174)	0.0272
	1:00	Placebo	207	0.206 (0.032)			
		Tio R5	199	0.295 (0.033)	0.089 (0.043)	(0.005, 0.173)	0.0369
	2:00	Placebo	207	0.199 (0.032)			
		Tio R5	199	0.320 (0.034)	0.121 (0.044)	(0.035, 0.206)	0.0057
	3:00	Placebo	207	0.212 (0.033)			
		Tio R5	199	0.334 (0.034)	0.121 (0.044)	(0.035, 0.208)	0.0061
Week 48	0:30	Placebo	205	0.175 (0.031)			
		Tio R5	198	0.299 (0.032)	0.124 (0.042)	(0.042, 0.206)	0.0031
	1:00	Placebo	205	0.199 (0.032)			
		Tio R5	198	0.301 (0.033)	0.102 (0.043)	(0.018, 0.186)	0.0178

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)

Table 15.2.1.2.1: 2 FVC [L] individual measurements response at each time point and visit
– MMRM results – FAS

					Tio R5 vs Placebo		
Timepoint	Planned time	Treatment	N	Adjusted* mean (SE)	Adjusted* mean of difference (SE)	95% CI	p-value
Week 48	2:00	Placebo	205	0.193 (0.033)			
		Tio R5	198	0.313 (0.034)	0.121 (0.044)	(0.035, 0.206)	0.0060
	3:00	Placebo	205	0.205 (0.033)			
		Tio R5	198	0.329 (0.034)	0.124 (0.044)	(0.037, 0.211)	0.0053

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.840 (0.882)