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® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 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 73 sites in 14 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)

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 2 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

actual:	enrolled: 656 entered: 459 Tiotropium solution for inhalation (5 µg) entered: 237 treated: 237 analysed (for primary endpoint): 237 analysed (for 24 h pulmonary function test): 90 Placebo: entered: 222 treated: 222 analysed (for primary endpoint): 222 analysed (for 24 h pulmonary function test): 86
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.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

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 71 patients after a single dose and at pharmacokinetic steady state (4 weeks).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

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 459 patients were randomised and treated with either tiotropium 5 µg (237 patients) or placebo (222 patients). Of the treated patients, 10% discontinued prematurely (tiotropium: 11.0%, placebo: 9.0%). The most frequent reason for discontinuation was 'other', i.e. not related to AEs, lack of efficacy, non-compliance, loss to follow-up, or withdrawn consent (tiotropium: 3.0%, placebo: 3.2%). 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: 1.578 L, mean baseline percent of predicted FEV_1: 55.64%, mean baseline ACQ: 2.7).

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

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 0.086 L (p=0.0110) for adjusted mean FEV_1 $peak_{0–3h}$ response and 0.088 L (p=0.0050) for adjusted mean trough FEV_1 response were statistically significant and in favour of tiotropium. A significant difference between treatments in favour of tiotropium in terms of adjusted mean FEV_1 $peak_{0–3h}$ response was also observed at most other visits during the treatment period ($p \leq 0.0347$ in most cases), with the exception of Visits 2 (Day 1; p=0.0830) and 5 (Week 16; p=0.0561). A significant difference between treatments in favour of tiotropium in terms of adjusted mean trough FEV_1 response was observed at Visits 6 (Week 24, above) and 7 (Week 32; p=0.0042), but not at any other visit.

Secondary endpoints

As compared with placebo, tiotropium significantly reduced the risk of first severe asthma exacerbation by 30% (hazard ratio: 0.70, p=0.0499) and the risk of first asthma exacerbation by 28% (hazard ratio: 0.72, p=0.0095) in patients with severe, persistent asthma who had a history of at least 1 asthma exacerbation in the past year. Patients who took tiotropium had a longer median time to first asthma exacerbation than patients who took placebo (tiotropium: 317.0 days, placebo: 181.0 days).

The treatment differences between tiotropium and placebo for 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; $p \leq 0.0333$ in every case). At all other visits and timepoints the treatment differences were in favour of tiotropium, but statistical significance was not always shown. With the exception of the adjusted mean FVC response measured 1 h after inhalation (p=0.0612), treatment differences for all secondary FVC endpoints (adjusted mean FVC $peak_{0–3h}$, trough FVC, FVC $AUC_{0–3h}$, and individual FVC responses) were significant and in favour of tiotropium at Visit 6 (Week 24; $p \leq 0.0362$). At all other visits and timepoints, the treatment difference was in favour of tiotropium, but statistical significance was not always shown.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

Efficacy / clinical pharmacology results (continued):

For FEV_1 endpoints measured during the 24 h lung function measurements for the FAS24 (tiotropium: 90 patients, placebo: 86 patients) treatment differences were always in favour of tiotropium and statistically significant in most cases. 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} (22.293 L/min; $p<0.0001$), PEF_{pm} 23.267 L/min ($p<0.0001$), $FEV_{1\ am}$ (0.117 L, $p<0.0001$), and $FEV_{1\ pm}$ (0.124 L, $p<0.0001$) responses during the last 7 days before Visit 6 (after approximately 24 weeks of treatment). With the exception of Week 4 (at which no statistical significance was reached for the adjusted weekly mean $FEV_{1\ am}$ and $FEV_{1\ pm}$ responses), significant differences between the treatment groups in favour of tiotropium were observed for these AM3® lung function endpoints at all weeks of the treatment period as well ($p\leq0.0340$ in all cases).

For the secondary endpoint of adjusted mean ACQ score, an improvement was reported for both treatment groups from study baseline (2.666) to Week 48 (tiotropium: 1.986, placebo: 2.107), but the difference between the treatment groups of −0.121 was not significant ($p=0.0727$) 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 to 5 min post-inhalation. Approximately 5.35% and 11.3% 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 1.45-fold higher C_{max}, 1.62-fold higher $AUC_{0-0\ 5}$, and 2.25-fold higher Ae_{0-24} at steady state as compared to single dose.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

Safety results:

Mean exposure was similar for both treatment groups (tiotropium: 315.2 days, placebo: 321.1 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 70.5% of tiotropium and 76.6% of placebo patients reporting at least 1 AE. The most frequently reported treatment-emergent AEs included asthma (tiotropium: 38.4%, placebo: 49.1%), PEF rate decreased (tiotropium: 20.7%; placebo: 26.1%), and nasopharyngitis (tiotropium: 8.0%; placebo: 9.0%). AEs assessed as being drug related by the investigator were reported for 5.5% of patients taking tiotropium and 4.1% of placebo patients; all were of mild or moderate intensity, and none were considered to be serious. 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 5 placebo patients, while AEs leading to discontinuation were reported for 6 patients in each treatment group. Finally, serious AEs (SAEs) were reported for 7.6% of patients in the tiotropium group and 6.8% of patients in the placebo group; none of these SAEs were considered to be immediately life threatening. Three patients (all in the tiotropium group) were reported with cerebrovascular and/or cardiovascular SAEs (1 patient with cerebrovascular accident, 1 patient with atrial fibrillation, and 1 patient with coronary artery occlusion and stenosis, ventricular tachycardia, and supraventricular arrhythmia); none of these were drug-related and all 3 patients had significant co-morbidities at baseline. There were no deaths or pregnancies during the course of this study. Of the 40 patients who had an available vital status, 38 (tiotropium: 21, placebo: 17) were reported as alive and 2 (both in the placebo group) were reported as lost to follow-up.

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: 20.3%, placebo: 12.6%); 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.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product: Spiriva® − Respimat® inhaler		**EudraCT No.:** 2008-001413-14	
Name of active ingredient: Tiotropium bromide		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 13 AUG 2012	**Trial No. / U No.:** 205.416 / U12-1986-02	**Dates of trial:** 30 OCT 08 – 25 JUL 11	**Date of revision:** 25 APR 2013

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 both first severe and 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 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 $_{(0\text{-}3)}$ response at 24 weeks (primary endpoint) Trough FEV_1 response at 24 weeks (primary endpoint) FEV_1 peak $_{(0\text{-}3)}$ response at all visits (secondary endpoint) Trough FEV_1 response at all visits (secondary endpoint) FEV_1 $AUC_{(0\text{-}3)}$ 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 $_{(0\text{-}3)}$ response at all visits (secondary endpoint) Trough FVC response at all visits (secondary endpoint) FVC $AUC_{(0\text{-}3)}$ 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	222	0.261 (0.026)			
		Tio R5	237	0.318 (0.024)	0.057 (0.033)	(-0.007, 0.122)	0.0830
	AUC (0-3h)	Placebo	222	0.164 (0.024)			
		Tio R5	237	0.215 (0.023)	0.051 (0.031)	(-0.010, 0.112)	0.0997
Week 4	Trough	Placebo	213	0.043 (0.024)			
		Tio R5	225	0.076 (0.024)	0.033 (0.031)	(-0.028, 0.094)	0.2861
	Peak (0-3h)	Placebo	213	0.293 (0.026)			
		Tio R5	225	0.371 (0.025)	0.078 (0.033)	(0.013, 0.143)	0.0188
	AUC (0-3h)	Placebo	213	0.208 (0.024)			
		Tio R5	225	0.281 (0.023)	0.073 (0.031)	(0.012, 0.134)	0.0189
Week 8	Trough	Placebo	213	0.076 (0.024)			
		Tio R5	227	0.125 (0.024)	0.048 (0.031)	(-0.012, 0.109)	0.1187
	Peak (0-3h)	Placebo	213	0.322 (0.026)			
		Tio R5	226	0.397 (0.025)	0.075 (0.033)	(0.010, 0.141)	0.0240
	AUC (0-3h)	Placebo	213	0.234 (0.024)			
		Tio R5	226	0.307 (0.023)	0.072 (0.031)	(0.011, 0.134)	0.0206

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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	211	0.086 (0.025)			
		Tio R5	225	0.128 (0.024)	0.041 (0.031)	(-0.020, 0.102)	0.1837
	Peak (0-3h)	Placebo	211	0.331 (0.026)			
		Tio R5	225	0.395 (0.025)	0.064 (0.034)	(-0.002, 0.130)	0.0561
	AUC (0-3h)	Placebo	211	0.248 (0.024)			
		Tio R5	225	0.310 (0.023)	0.062 (0.032)	(0.000, 0.124)	0.0489
Week 24	Trough	Placebo	211	0.056 (0.025)			
		Tio R5	217	0.144 (0.024)	0.088 (0.031)	(0.027, 0.149)	0.0050
	Peak (0-3h)	Placebo	211	0.315 (0.026)			
		Tio R5	217	0.401 (0.025)	0.086 (0.034)	(0.020, 0.152)	0.0110
	AUC (0-3h)	Placebo	211	0.229 (0.024)			
		Tio R5	217	0.315 (0.024)	0.086 (0.032)	(0.024, 0.149)	0.0067
Week 32	Trough	Placebo	209	0.068 (0.025)			
		Tio R5	218	0.158 (0.024)	0.090 (0.031)	(0.028, 0.151)	0.0042
	Peak (0-3h)	Placebo	209	0.308 (0.026)			
		Tio R5	218	0.401 (0.025)	0.092 (0.034)	(0.026, 0.159)	0.0067

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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	209	0.229 (0.025)			
		Tio R5	218	0.321 (0.024)	0.092 (0.032)	(0.030, 0.155)	0.0039
Week 40	Trough	Placebo	207	0.072 (0.025)			
		Tio R5	211	0.133 (0.025)	0.061 (0.032)	(-0.001, 0.123)	0.0541
	Peak (0-3h)	Placebo	207	0.287 (0.026)			
		Tio R5	211	0.388 (0.026)	0.102 (0.034)	(0.034, 0.169)	0.0031
	AUC (0-3h)	Placebo	207	0.215 (0.025)			
		Tio R5	211	0.304 (0.024)	0.088 (0.032)	(0.025, 0.151)	0.0061
Week 48	Trough	Placebo	204	0.087 (0.025)			
		Tio R5	213	0.129 (0.025)	0.042 (0.032)	(-0.021, 0.104)	0.1896
	Peak (0-3h)	Placebo	204	0.295 (0.026)			
		Tio R5	213	0.367 (0.026)	0.073 (0.034)	(0.005, 0.140)	0.0347
	AUC (0-3h)	Placebo	204	0.217 (0.025)			
		Tio R5	213	0.289 (0.024)	0.073 (0.032)	(0.009, 0.136)	0.0247

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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	222	0.143 (0.024)			
		Tio R5	237	0.167 (0.023)	0.025 (0.032)	(-0.037, 0.086)	0.4363
	1:00	Placebo	222	0.171 (0.025)			
		Tio R5	237	0.222 (0.024)	0.051 (0.032)	(-0.012, 0.114)	0.1128
	2:00	Placebo	222	0.203 (0.025)			
		Tio R5	237	0.262 (0.024)	0.060 (0.033)	(-0.005, 0.124)	0.0684
	3:00	Placebo	222	0.192 (0.026)			
		Tio R5	237	0.276 (0.025)	0.083 (0.033)	(0.018, 0.149)	0.0124
Week 4	0:30	Placebo	213	0.175 (0.024)			
		Tio R5	225	0.246 (0.023)	0.072 (0.032)	(0.009, 0.134)	0.0244
	1:00	Placebo	213	0.221 (0.025)			
		Tio R5	225	0.290 (0.024)	0.070 (0.032)	(0.006, 0.133)	0.0318
	2:00	Placebo	213	0.237 (0.025)			
		Tio R5	225	0.318 (0.024)	0.081 (0.033)	(0.017, 0.146)	0.0138
	3:00	Placebo	213	0.234 (0.026)			
		Tio R5	225	0.319 (0.025)	0.086 (0.034)	(0.020, 0.151)	0.0107
Week 8	0:30	Placebo	213	0.212 (0.025)			
		Tio R5	226	0.278 (0.024)	0.066 (0.032)	(0.003, 0.129)	0.0390
	1:00	Placebo	213	0.250 (0.025)			
		Tio R5	226	0.313 (0.024)	0.063 (0.033)	(-0.001, 0.126)	0.0547

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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 8	2:00	Placebo	213	0.257 (0.025)			
		Tio R5	226	0.339 (0.024)	0.083 (0.033)	(0.018, 0.148)	0.0124
	3:00	Placebo	213	0.256 (0.026)			
		Tio R5	226	0.345 (0.025)	0.089 (0.034)	(0.023, 0.155)	0.0082
Week 16	0:30	Placebo	211	0.232 (0.025)			
		Tio R5	225	0.275 (0.024)	0.044 (0.032)	(-0.019, 0.107)	0.1731
	1:00	Placebo	211	0.252 (0.025)			
		Tio R5	225	0.314 (0.024)	0.063 (0.033)	(-0.001, 0.127)	0.0554
	2:00	Placebo	211	0.271 (0.026)			
		Tio R5	225	0.350 (0.025)	0.079 (0.033)	(0.014, 0.145)	0.0173
	3:00	Placebo	211	0.281 (0.026)			
		Tio R5	225	0.341 (0.025)	0.060 (0.034)	(-0.007, 0.126)	0.0784
Week 24	0:30	Placebo	211	0.202 (0.025)			
		Tio R5	217	0.271 (0.024)	0.069 (0.032)	(0.005, 0.133)	0.0333
	1:00	Placebo	211	0.245 (0.025)			
		Tio R5	217	0.322 (0.025)	0.077 (0.033)	(0.012, 0.141)	0.0206
	2:00	Placebo	211	0.254 (0.026)			
		Tio R5	217	0.348 (0.025)	0.094 (0.034)	(0.028, 0.160)	0.0052
	3:00	Placebo	211	0.258 (0.026)			
		Tio R5	217	0.365 (0.025)	0.107 (0.034)	(0.040, 0.174)	0.0018

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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 32	0:30	Placebo	209	0.204 (0.025)			
		Tio R5	218	0.291 (0.024)	0.086 (0.033)	(0.023, 0.150)	0.0080
	1:00	Placebo	209	0.239 (0.025)			
		Tio R5	218	0.335 (0.025)	0.096 (0.033)	(0.031, 0.161)	0.0038
	2:00	Placebo	209	0.252 (0.026)			
		Tio R5	218	0.353 (0.025)	0.100 (0.034)	(0.034, 0.166)	0.0031
	3:00	Placebo	209	0.261 (0.026)			
		Tio R5	218	0.343 (0.026)	0.082 (0.034)	(0.015, 0.150)	0.0168
Week 40	0:30	Placebo	207	0.186 (0.025)			
		Tio R5	211	0.270 (0.024)	0.084 (0.033)	(0.020, 0.148)	0.0106
	1:00	Placebo	207	0.225 (0.026)			
		Tio R5	211	0.311 (0.025)	0.085 (0.033)	(0.019, 0.151)	0.0111
	2:00	Placebo	207	0.240 (0.026)			
		Tio R5	211	0.335 (0.025)	0.095 (0.034)	(0.029, 0.162)	0.0051
	3:00	Placebo	207	0.242 (0.027)			
		Tio R5	211	0.343 (0.026)	0.101 (0.035)	(0.033, 0.169)	0.0035
Week 48	0:30	Placebo	204	0.203 (0.025)			
		Tio R5	213	0.258 (0.025)	0.055 (0.033)	(-0.010, 0.119)	0.0974
	1:00	Placebo	204	0.221 (0.026)			
		Tio R5	213	0.300 (0.025)	0.079 (0.034)	(0.013, 0.145)	0.0195

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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	204	0.233 (0.026)			
		Tio R5	213	0.317 (0.025)	0.084 (0.034)	(0.017, 0.151)	0.0140
	3:00	Placebo	204	0.243 (0.027)			
		Tio R5	213	0.323 (0.026)	0.080 (0.035)	(0.012, 0.148)	0.0218

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 1.578 (0.542)

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	222	0.311 (0.032)			
		Tio R5	237	0.380 (0.031)	0.070 (0.042)	(-0.012, 0.151)	0.0933
	AUC (0-3h)	Placebo	222	0.169 (0.030)			
		Tio R5	237	0.238 (0.029)	0.069 (0.039)	(-0.008, 0.145)	0.0778
Week 4	Trough	Placebo	213	0.027 (0.031)			
		Tio R5	225	0.117 (0.031)	0.089 (0.039)	(0.012, 0.167)	0.0238
	Peak (0-3h)	Placebo	213	0.319 (0.032)			
		Tio R5	225	0.451 (0.031)	0.132 (0.042)	(0.050, 0.214)	0.0016
	AUC (0-3h)	Placebo	213	0.196 (0.030)			
		Tio R5	225	0.319 (0.029)	0.123 (0.039)	(0.046, 0.199)	0.0017
Week 8	Trough	Placebo	213	0.073 (0.031)			
		Tio R5	227	0.156 (0.030)	0.082 (0.039)	(0.005, 0.160)	0.0368
	Peak (0-3h)	Placebo	213	0.368 (0.032)			
		Tio R5	226	0.443 (0.031)	0.075 (0.042)	(-0.007, 0.158)	0.0727
	AUC (0-3h)	Placebo	213	0.241 (0.030)			
		Tio R5	226	0.319 (0.029)	0.078 (0.039)	(0.001, 0.155)	0.0479
Week 16	Trough	Placebo	211	0.070 (0.031)			
		Tio R5	225	0.153 (0.031)	0.083 (0.040)	(0.005, 0.161)	0.0361
	Peak (0-3h)	Placebo	211	0.365 (0.033)			
		Tio R5	225	0.450 (0.031)	0.085 (0.042)	(0.002, 0.167)	0.0458

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.710 (0.916)

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	211	0.249 (0.031)			
		Tio R5	225	0.332 (0.029)	0.084 (0.040)	(0.006, 0.161)	0.0345
Week 24	Trough	Placebo	211	0.022 (0.031)			
		Tio R5	217	0.157 (0.031)	0.136 (0.040)	(0.058, 0.214)	0.0007
	Peak (0-3h)	Placebo	211	0.355 (0.033)			
		Tio R5	217	0.445 (0.032)	0.089 (0.043)	(0.006, 0.173)	0.0362
	AUC (0-3h)	Placebo	211	0.230 (0.031)			
		Tio R5	217	0.328 (0.030)	0.098 (0.040)	(0.020, 0.176)	0.0139
Week 32	Trough	Placebo	209	0.069 (0.032)			
		Tio R5	218	0.179 (0.031)	0.111 (0.040)	(0.032, 0.189)	0.0056
	Peak (0-3h)	Placebo	209	0.357 (0.033)			
		Tio R5	218	0.441 (0.032)	0.084 (0.043)	(0.000, 0.168)	0.0499
	AUC (0-3h)	Placebo	209	0.242 (0.031)			
		Tio R5	218	0.329 (0.030)	0.087 (0.040)	(0.009, 0.166)	0.0297
Week 40	Trough	Placebo	207	0.069 (0.032)			
		Tio R5	211	0.168 (0.031)	0.099 (0.040)	(0.020, 0.178)	0.0142
	Peak (0-3h)	Placebo	207	0.325 (0.033)			
		Tio R5	211	0.450 (0.032)	0.125 (0.043)	(0.040, 0.210)	0.0038
	AUC (0-3h)	Placebo	207	0.215 (0.031)			
		Tio R5	211	0.333 (0.030)	0.118 (0.040)	(0.039, 0.197)	0.0036

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.710 (0.916)

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	0.062 (0.032)			
		Tio R5	213	0.173 (0.031)	0.111 (0.040)	(0.031, 0.190)	0.0063
	Peak (0-3h)	Placebo	204	0.337 (0.033)			
		Tio R5	213	0.462 (0.032)	0.125 (0.043)	(0.040, 0.210)	0.0039
	AUC (0-3h)	Placebo	204	0.223 (0.031)			
		Tio R5	213	0.344 (0.030)	0.122 (0.041)	(0.042, 0.201)	0.0027

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.710 (0.916)

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	213	0.255 (0.033)			
		Tio R5	226	0.352 (0.031)	0.097 (0.042)	(0.014, 0.180)	0.0221
	3:00	Placebo	213	0.263 (0.033)			
		Tio R5	226	0.340 (0.032)	0.076 (0.043)	(-0.009, 0.161)	0.0795
Week 16	0:30	Placebo	211	0.238 (0.031)			
		Tio R5	225	0.311 (0.030)	0.073 (0.040)	(-0.005, 0.152)	0.0664
	1:00	Placebo	211	0.256 (0.032)			
		Tio R5	225	0.347 (0.030)	0.091 (0.041)	(0.011, 0.171)	0.0265
	2:00	Placebo	211	0.265 (0.033)			
		Tio R5	225	0.359 (0.031)	0.094 (0.043)	(0.011, 0.178)	0.0268
	3:00	Placebo	211	0.293 (0.034)			
		Tio R5	225	0.359 (0.032)	0.066 (0.044)	(-0.019, 0.152)	0.1293
Week 24	0:30	Placebo	211	0.206 (0.031)			
		Tio R5	217	0.291 (0.030)	0.085 (0.040)	(0.006, 0.164)	0.0360
	1:00	Placebo	211	0.251 (0.032)			
		Tio R5	217	0.328 (0.031)	0.077 (0.041)	(-0.004, 0.158)	0.0612
	2:00	Placebo	211	0.258 (0.033)			
		Tio R5	217	0.364 (0.032)	0.106 (0.043)	(0.022, 0.190)	0.0138
	3:00	Placebo	211	0.259 (0.034)			
		Tio R5	217	0.374 (0.033)	0.115 (0.044)	(0.028, 0.201)	0.0095

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.710 (0.916)

Table 15.2.1.2.1: 2 FVC [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	209	0.219 (0.031)			
		Tio R5	218	0.313 (0.030)	0.094 (0.041)	(0.015, 0.174)	0.0199
	1:00	Placebo	209	0.253 (0.032)			
		Tio R5	218	0.349 (0.031)	0.096 (0.042)	(0.015, 0.178)	0.0206
	2:00	Placebo	209	0.265 (0.033)			
		Tio R5	218	0.353 (0.032)	0.088 (0.043)	(0.003, 0.172)	0.0416
	3:00	Placebo	209	0.276 (0.034)			
		Tio R5	218	0.334 (0.033)	0.058 (0.044)	(-0.029, 0.145)	0.1879
Week 40	0:30	Placebo	207	0.200 (0.031)			
		Tio R5	211	0.290 (0.030)	0.090 (0.041)	(0.010, 0.170)	0.0280
	1:00	Placebo	207	0.222 (0.032)			
		Tio R5	211	0.347 (0.031)	0.125 (0.042)	(0.043, 0.207)	0.0029
	2:00	Placebo	207	0.241 (0.033)			
		Tio R5	211	0.363 (0.032)	0.122 (0.043)	(0.037, 0.207)	0.0050
	3:00	Placebo	207	0.227 (0.034)			
		Tio R5	211	0.371 (0.033)	0.144 (0.045)	(0.056, 0.231)	0.0013
Week 48	0:30	Placebo	204	0.211 (0.031)			
		Tio R5	213	0.320 (0.031)	0.109 (0.041)	(0.028, 0.189)	0.0080
	1:00	Placebo	204	0.224 (0.032)			
		Tio R5	213	0.351 (0.031)	0.127 (0.042)	(0.045, 0.209)	0.0026

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.710 (0.916)

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	204	0.245 (0.033)			
		Tio R5	213	0.374 (0.033)	0.129 (0.044)	(0.044, 0.215)	0.0031
	3:00	Placebo	204	0.254 (0.034)			
		Tio R5	213	0.379 (0.033)	0.125 (0.045)	(0.037, 0.213)	0.0054

* adjusted for treatment, (pooled) centre, visit, baseline, treatment*visit and baseline*visit
Baseline mean(sd) at visit 2 = 2.710 (0.916)