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.:** 2009-016251-21	
Name of active ingredient: Tiotropium bromide		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 28 NOV 2013	**Trial No. / U No.:** 205.458 / U13-1531-01	**Date of trial:** 19 OCT 2010 – 21 JUN 2011	**Date of revision:** Not applicable

Title of trial:	A multicentre, randomised, placebo- and active-controlled, 5-way crossover trial to characterise the pharmacokinetics and evaluate the bronchodilator efficacy and safety of once-daily tiotropium delivered (double-blind) from the Respimat® inhaler as solution for inhalation (1.25, 2.5, 5µg or placebo) and as inhalation powder (18µg) from the HandiHaler® (open-label) after 4 week-treatment periods in patients with Chronic Obstructive Pulmonary Disease (COPD)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study
Publication (reference):	Data of this study has not been published
Clinical phase:	II
Objectives:	To (a) compare the pharmacokinetics of 5 µg tiotropium solution for inhalation delivered by the Respimat® Inhaler (Tio R 5) with tiotropium powder for inhalation 18 µg delivered by the HandiHaler® and (b) evaluate dose-ranging efficacy (FEV_1, FVC) and safety (Holter monitoring) of tiotropium solution for inhalation delivered from the Respimat® Inhaler, at steady state in COPD patients.
Methodology:	Multi-centre, randomised, placebo- and active-controlled, double-blind within the 4 Respimat® treatments but open label for HandiHaler® treatment, 5-way crossover

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No. of subjects:	
planned:	entered: 142 randomised patients (each patient to receive each of the 5 treatments). 112 randomised patients for the primary PK analysis.
actual:	enrolled: 210 patients; entered/randomised: 154 patients; treated: 154 patients Placebo: treated: 147 analysed (for primary endpoint): 113 Tiotropium Respimat® 1.25 µg: treated: 147 analysed (for primary endpoint): 115 Tiotropium Respimat® 2.5 µg: treated: 145 analysed (for primary endpoint): 113 Tiotropium Respimat® 5 µg: treated: 150 analysed (for primary endpoint): 113 Tiotropium HandiHaler® 18 µg: treated: 146 analysed (for primary endpoint): 113
Diagnosis and main criteria for inclusion:	Male or female patients aged 40 years or above with a diagnosis of COPD with a post bronchodilator $FEV_1 \leq 80\%$ of predicted normal and <70% of post bronchodilator FVC at screening.
Test product:	Tiotropium solution for inhalation, Respimat®
dose:	- 1.25 µg (Tio R 1.25, 0.625 µg given as two actuations once daily) - 2.5 µg (Tio R 2.5, 1.25 µg given as two actuations once daily) - 5 µg (Tio R 5, 2.5 µg given as two actuations once daily) - Placebo
mode of admin.:	Oral inhalation via the Respimat®
batch no.:	B09000113, B0902000111, B092000103, 902692
Reference therapy:	Tiotropium powder for inhalation, HandiHaler®
dose:	18 µg (Tio HH 18)
mode of admin.:	Oral inhalation via the HandiHaler®
batch no.:	909298
Duration of treatment:	20 weeks

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Criteria for evaluation:

Pharmacokinetics: Plasma and urine samples for the quantification of tiotropium were obtained for 6 hours post-dosing following the administration of multiple doses of tiotropium (for 4 weeks) to steady-state at visits 3, 5, 7, 9 and 11 in a subset of pharmacokinetic patients. The pharmacokinetics of tiotropium following inhalation via Respimat® (doses to be tested: 1.25, 2.5 and 5 µg) and via HandiHaler® (18 µg) were evaluated. The primary endpoints were $C_{max,ss}$ and $AUC_{0-6,ss}$.

Efficacy / clinical pharmacology: Efficacy was primarily determined by FEV1 AUC_{0-6h} following 4 weeks of treatment administration in COPD patients. FEV1 trough, FEV1 AUC_{0-3h}, FVC AUC_{0-6h}, FVC trough and FVC AUC_{0-3h} were also evaluated. Each Respimat® dose was compared to placebo.

Safety: ECG (using Holter monitoring), adverse events, serious adverse events, adverse events leading to treatment discontinuation.

Statistical methods: ANOVA (analysis of variance) suitable for crossover trials using mixed effects model.

SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Pharmacokinetics

- The exposure to tiotropium following the use of Tio R 5 was lower compared to Tio HH 18. Using the parameters $AUC_{0-6,ss}$ and $C_{max,ss}$, bioequivalence was not established between Tio R 5 and Tio 18 HH. The ratio of $AUC_{0-6,ss}$ (Tio R 5/ Tio HH 18) was 75.99% (90% confidence interval of (70.44, 81.98)). The ratio of $C_{max,ss}$ was 80.66% (90% confidence interval of (73.49, 88.52)).
- The shape of the plasma concentration time profile of tiotropium following inhalation via HandiHaler® and Respimat devices® was similar. Tiotropium was rapidly absorbed following inhalation via the two devices with a median $t_{max,ss}$ value ranging between 5-7 minutes post-dosing. The plasma profile and amount excreted in the urine following inhalation via the HandiHaler® was higher than all doses of Respimat®.

Efficacy / clinical pharmacology results (continued):

Pharmacokinetics (continued)

- Based on plasma and urinary PK parameters, exposure to tiotropium following inhalation via the Respimat device did not appear to deviate relevantly from dose proportionality.
- The $C_{pre,ss}$ values were 6.43% lower for Tio R 5 compared to Tio HH 18.
- The amount of tiotropium excreted in urine over 6 hours post-dosing was 25.86% lower for Tio R 5 compared to Tio HH 18. Hence, the urinary excretion data supported the primary exposure conclusions based on $AUC_{0-6,ss}$.
- The renal clearance of tiotropium exceeded glomerular filtration rate, indicating active secretion in the urine.

Efficacy / clinical pharmacology results (continued):

Efficacy

The analysis of each spirometry endpoint on both the FAS and PPS supported the following conclusions:

- Dose ordering among the Respimat doses was observed.
- Tio R 5 was significantly better than placebo.
- Tio R 2.5 was significantly better than placebo.
- Tio R 1.25 provided significantly less bronchodilation compared to Tio HH 18 in all endpoints.
- Although numerically lower compared to the other Respimat doses Tio R 1.25 cannot be regarded ineffective compared to placebo. Note that in order for Tio R 1.25 to be declared an ineffective dose compared to placebo, the upper bound of the 95% confidence interval for the treatment difference 'Tio R 5 – placebo' had to lie below 0.1 litres.

Each tiotropium solution for inhalation dose (Tio R 1.25, Tio 2.5 and Tio R5) was also compared to Tio HH 18, although this was not a main objective and the study was not designed for these comparisons (due to Tio HH 18 being open-label). Tio R 5 was shown to be the most comparable dose to Tio HH 18 in terms of FEV_1 and FVC trough, AUC_{0-6h} and AUC_{0-3h}. Tio R 2.5 provided FEV_1 and FVC AUC_{0-6h} and AUC_{0-3h} values which were comparable to Tio HH 18, although the mean FEV_1 and FVC values appeared notably lower than those for Tio HH 18 in the first 60 minutes post-inhalation. The mean trough FEV_1 value for Tio R 2.5 was significantly less than the mean value for Tio HH 18, while the mean trough FVC value was numerically less only.

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Safety results:

The overall safety profile as observed in the present study indicates that, compared to Tio HH 18 as well as to placebo, inhalation of Tio R 1.25, Tio R 2.5 and Tio R 5 during a 4-week treatment period was safe and well tolerated in patients with COPD.

Adverse events

The incidence of adverse events reported was generally balanced between the five treatment periods and there was no evidence for a treatment dependent increase in either the frequency or the intensity of adverse events during the four tiotropium treatment periods. The most commonly occurring adverse events were those due to respiratory causes, including dyspnoea and exacerbation of chronic obstructive pulmonary disease, which were reported with higher frequency during the placebo period compared with any of the tiotropium periods.

Ten patients reported one or more serious adverse events (SAE) during at least one treatment period (Pbo and Tio R 5: 3 patients each, Tio R 1.25 and Tio HH 18: 2 patients each, no patient on Tio R 2.5). Six patients had AEs that led to their discontinuation of trial drug (Tio R 1.25 and Tio R 5: 1 patient each, Pbo and Tio HH 18: 2 patients each, no patient on Pbo and Tio R 2.5:). Pneumonia or worsening of COPD requiring hospitalisation was the most commonly reported SAE. Causal relationship to treatment was not reported in any of these cases. There were no fatal events in this study.

ECG evaluation

Holter (arrhythmia) analysis: The Holter arrhythmia analyses did not suggest any clinically relevant untoward effects associated with the tiotropium Respimat® and HandiHaler® treatments in the given dose range. Maximum and mean HR (evaluated over 6.5 h as well as by hourly intervals) were comparable between tiotropium Respimat® doses, HandiHaler® and placebo. There were no relevant differences across treatments regarding the number of patients with SVPB runs, pairs, and single premature beats as well the number of patients with VPB pairs and single premature beats assessed over 6.5 h and during the first hour after inhalation (when the highest plasma levels of tiotropium were observed). More patients experienced VPB runs (including ventricular tachycardia, ideoventricular rhythm, and other events with at least 3 subsequent ventricular beats) on the higher dose levels of tiotropium (Tio R 5: 10 patients, Tio HH 18: 9 patients) compared with the lower dose levels (Tio R 1.25: 5 patients, Tio R 2.5: 4 patients) or on placebo (3 patients).

Safety results (continued):

ECG evaluation (continued)

Holter (arrhythmia) analysis (cont.): This observation was not confirmed in evaluations from tiotropium trials 205.254 and 205.255 with tiotropium Respimat® doses up to Tio R 10 and trial 205.284 with Tio HH 18, nor in a restrospective analysis of an additional Holter recording period within the current trial on another steady state day (day 26). None of the events was sustained (defined as extending over more than 30 s), the longest event had a duration of 7 s. The median HR of the fastest VPB run as well as the median number of beats in the longest VPB run did not consistently differ between active treatments and placebo.

Evaluation of ECG intervals and heart rate: The analyses of the QT / QTcN and PR intervals as well as the QRS complex did not reveal any relevant effects associated with the tiotropium treatments as compared with placebo. All upper 90% confidence limits of the placebo-corrected adjusted mean QTcN intervals between trough and 45 min after inhalation were well below the threshold of 10 ms suggested by the ICH guideline E14 [R05-2311].

Overall cardiologic assessment: The most frequent abnormalities across all treatments including placebo were ectopies (25.9 to 36.5%) and conduction defects (24.3 to 34.5%) followed by irregularities in rhythm and T wave abnormalities. Sinus tachycardia (defined as HR >100 bpm at any time point on treatment) seemed slightly more frequent on tiotropium (9.7 to 11.3%) compared with placebo (7.0%), irrespective of the dose level administered. The mean values, however, of the endpoints 'maximum HR evaluated over the entire 6.5 h Holter monitoring period' (109 to 110 bpm) as well as 'mean HR evaluated over the entire 6.5 h Holter monitoring period' (77 to 78 bpm) were nearly identical for all active treatments and placebo. First degree AV-block was more frequent on active treatment (18.3 to 20.7%) than on placebo (11.3%); a dose-dependency of these findings was not evident. The analysis of central tendency of PR intervals did show slight increases compared to placebo of up to 3 ms at single time points, without dose dependency. No corresponding findings on PR interval were observed in the TQT trial 205.302 assessing higher dose levels of up to 56 µg tiotropium administered by the HandiHaler.

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Conclusions:	In view of a slightly lower systemic exposure of Tio R 5, and comparable safety and bronchodilator efficacy of Tio R 5 and Tio HH 18, the data from this study indicate that the currently marketed dose of Tio R 5 is an optimal match to Tio HH 18 for the maintenance therapy of patients with COPD. Evaluation of safety did not reveal differences between the formulations. No safety findings of clinical concern arose from the analysis of ECG intervals and Holter monitoring for Tio R 1.25 to Tio R 5 and Tio HH 18.

Trial Synopsis - Appendix

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

Results for	**presented in**
Disposition of patients	Table 15.1.1: 2
Trough FEV_1 at the end of each treatment period	Table 15.2.1: 3
FEV_1 AUC_{0-6h} at the end of each treatment period	Table 15.2.1: 1
FEV_1 AUC_{0-3h} at the end of each treatment period	Table 15.2.1: 5
FEV_1 at each planned time at the end of each treatment period	Table 15.2.1: 7
Trough FVC at the end of each treatment period	Table 15.2.2: 3
FVC AUC_{0-6h} at the end of each treatment period	Table 15.2.2: 1
FVC AUC_{0-3h} at the end of each treatment period	Table 15.2.2: 5
FVC at each planned time at the end of each treatment period	Table 15.2.2: 7

Table 15.1.1: 2 Termination of trial medication and patient participation

	Placebo N (%)	Tio R 1.25 N (%)	Tio R 2.5 N (%)	Tio R 5 N (%)	Tio HH 18 N (%)	Study total N (%)
Enrolled						210
Not randomised						56
Randomised						154
Not treated						0
Treated	147 (100.0)	147 (100.0)	145 (100.0)	150 (100.0)	146 (100.0)	154 (100.0)
Not prematurely discontinued from period medication	144 (98.0)	144 (98.0)	145 (100.0)	145 (96.7)	141 (96.6)	
Prematurely discontinued from period medication	3 (2.0)	3 (2.0)	0 (0.0)	5 (3.3)	5 (3.4)	
Adverse events	2 (1.4)	1 (0.7)	0 (0.0)	1 (0.7)	2 (1.4)	
Unexpected worsening of COPD	1 (0.7)	0 (0.0)	0 (0.0)	1 (0.7)	1 (0.7)	
Worsening of other pre-existing disease	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	
Other adverse event	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	
Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.7)	
Lost to follow-up	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Consent withdrawn not due to adverse events	0 (0.0)	1 (0.7)	0 (0.0)	2 (1.3)	1 (0.7)	
Other	1 (0.7)	1 (0.7)	0 (0.0)	2 (1.3)	1 (0.7)	
Completed planned observation time (Week 21)						140 (90.9)
Patient discontinued due to:						14 (9.1)
Adverse event						5 (3.2)
Unexpected worsening of COPD						2 (1.3)
Worsening of other pre-existing disease						1 (0.6)
Other adverse event						2 (1.3)
Non compliant with protocol						0 (0.0)
Lost to follow-up						0 (0.0)
Consent withdrawn not due to adverse events						5 (3.2)
Other						4 (2.6)

For the treatment columns, data from the termination period 1/2/3/4/5 medication pages were used.
For the Total column, data from the trial completion pages were used.
Patients discontinued from one study period for a non-drug-related reason were allowed to continue with the other treatments.
Only the total number of randomised patients is shown, because patients were randomised to treatment sequences rather than to single treatments.

Table 15.2.1: 3 Day 29 trough FEV1 [litres] ANOVA results (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	143	143	144	143	142
Adjusted*mean (SE)	1.345 (0.045)	1.432 (0.045)	1.446 (0.045)	1.466 (0.045)	1.473 (0.045)
Comparison vs Placebo					
Adjusted* mean (SE)		0.087 (0.014)	0.101 (0.014)	0.121 (0.014)	0.128 (0.014)
95% Confidence interval*		(0.060 , 0.114)	(0.074 , 0.128)	(0.094 , 0.148)	(0.101 , 0.155)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.041 (0.014)	-0.027 (0.014)	-0.007 (0.014)	
95% Confidence interval*		(-0.068 , -0.014)	(-0.055 , -0.000)	(-0.034 , 0.020)	

* Adjusted for 'sequence', 'patients within sequences', 'period' and 'treatment'.
The effect 'patients within sequences' was considered as random, while the other effects were considered as fixed.
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.1: 1 Day 29 FEV1 AUC0-6 [litres] ANOVA results (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	143	143	144	143	142
Adjusted*mean (SE)	1.371 (0.046)	1.535 (0.046)	1.556 (0.046)	1.562 (0.046)	1.567 (0.046)
Comparison vs Placebo					
Adjusted* mean (SE)		0.165 (0.012)	0.185 (0.012)	0.191 (0.012)	0.196 (0.012)
95% Confidence interval*		(0.141 , 0.189)	(0.161 , 0.209)	(0.167 , 0.216)	(0.172 , 0.220)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.031 (0.012)	-0.011 (0.012)	-0.005 (0.012)	
95% Confidence interval*		(-0.055 , -0.007)	(-0.035 , 0.013)	(-0.029 , 0.019)	

* Adjusted for 'sequence', 'patients within sequences', 'period' and 'treatment'.
The effect 'patients within sequences' was considered as random, while the other effects were considered as fixed.
Tio R 1.25 will be considered an ineffective dose if the 95% confidence interval for 'Tio R 1.25 - placebo' lies entirely below 0.1 [L].
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.1: 5 Day 29 FEV1 AUC0-3 [litres] ANOVA results (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	143	143	144	143	142
Adjusted*mean (SE)	1.366 (0.046)	1.521 (0.046)	1.546 (0.046)	1.553 (0.046)	1.558 (0.046)
Comparison vs Placebo					
Adjusted* mean (SE)		0.155 (0.013)	0.180 (0.013)	0.187 (0.013)	0.191 (0.013)
95% Confidence interval*		(0.130 , 0.180)	(0.155 , 0.205)	(0.162 , 0.211)	(0.167 , 0.216)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.036 (0.013)	-0.011 (0.013)	-0.005 (0.013)	
95% Confidence interval*		(-0.061 , -0.012)	(-0.036 , 0.013)	(-0.029 , 0.020)	

* Adjusted for 'sequence', 'patients within sequences', 'period' and 'treatment'.
The effect 'patients within sequences' was considered as random, while the other effects were considered as fixed.
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.1: 7 Day 29 adjusted mean FEV1 [litres] at each planned time (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	143	143	144	143	142
Adjusted* mean (SE)					
0:00 (trough)	1.349 (0.045)	1.436 (0.045)	1.450 (0.045)	1.470 (0.045)	1.477 (0.045)
0:30	1.366 (0.046)	1.501 (0.046)	1.522 (0.046)	1.541 (0.046)	1.554 (0.046)
1:00	1.371 (0.046)	1.529 (0.046)	1.552 (0.046)	1.560 (0.046)	1.571 (0.046)
2:00	1.375 (0.046)	1.543 (0.046)	1.573 (0.046)	1.572 (0.046)	1.571 (0.046)
3:00	1.375 (0.047)	1.556 (0.047)	1.582 (0.047)	1.584 (0.047)	1.580 (0.047)
4:00	1.374 (0.047)	1.557 (0.047)	1.575 (0.047)	1.578 (0.047)	1.582 (0.047)
5:00	1.394 (0.047)	1.562 (0.047)	1.571 (0.047)	1.579 (0.047)	1.588 (0.047)
6:00	1.375 (0.047)	1.536 (0.048)	1.551 (0.047)	1.558 (0.047)	1.570 (0.048)

* Adjusted for period, planned time and period*planned time as fixed effects. Patient*planned time and patient*treatment*planned time are fitted as random effects with unstructured covariance matrices (ref model 3 of R10-5353).
Data recorded after the patient used rescue are imputed by the least favourable prior measurement, i.e. lowest value of the available test days.
The baseline (ie immediately prior to the first dose of randomised treatment) mean (sd) is 1.402 (0.542) litres.
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.2: 3 Day 29 trough FVC [litres] ANOVA results (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	142	143	143	143	142
Adjusted*mean (SE)	3.116 (0.077)	3.254 (0.077)	3.304 (0.077)	3.352 (0.077)	3.351 (0.077)
Comparison vs Placebo					
Adjusted* mean (SE)		0.138 (0.028)	0.188 (0.028)	0.236 (0.028)	0.235 (0.028)
95% Confidence interval*		(0.083 , 0.194)	(0.133 , 0.244)	(0.180 , 0.292)	(0.180 , 0.291)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.097 (0.028)	-0.047 (0.028)	0.000 (0.028)	
95% Confidence interval*		(-0.153 , -0.042)	(-0.103 , 0.009)	(-0.055 , 0.056)	

* Adjusted for 'sequence', 'patients within sequences', 'period' and 'treatment'.
The effect 'patients within sequences' was considered as random, while the other effects were considered as fixed.
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.2: 1 Day 29 FVC AUC0-6 [litres] ANOVA results (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	142	143	143	143	142
Adjusted*mean (SE)	3.153 (0.079)	3.436 (0.078)	3.472 (0.078)	3.488 (0.078)	3.483 (0.079)
Comparison vs Placebo					
Adjusted* mean (SE)		0.283 (0.022)	0.319 (0.022)	0.335 (0.022)	0.330 (0.022)
95% Confidence interval*		(0.241 , 0.326)	(0.276 , 0.362)	(0.292 , 0.378)	(0.287 , 0.373)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.047 (0.022)	-0.011 (0.022)	0.005 (0.022)	
95% Confidence interval*		(-0.089 , -0.004)	(-0.054 , 0.032)	(-0.038 , 0.048)	

* Adjusted for 'sequence', 'patients within sequences', 'period' and 'treatment'.
The effect 'patients within sequences' was considered as random, while the other effects were considered as fixed.
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.2: 5 Day 29 FVC AUC0-3 [litres] ANOVA results (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	142	143	143	143	142
Adjusted*mean (SE)	3.140 (0.078)	3.421 (0.078)	3.465 (0.078)	3.479 (0.078)	3.480 (0.078)
Comparison vs Placebo					
Adjusted* mean (SE)		0.281 (0.023)	0.324 (0.023)	0.339 (0.023)	0.339 (0.023)
95% Confidence interval*		(0.236 , 0.325)	(0.279 , 0.369)	(0.294 , 0.384)	(0.295 , 0.384)
p-value*			<.0001	<.0001	<.0001
Comparison vs Tio HH 18**					
Adjusted* mean (SE)		-0.059 (0.023)	-0.015 (0.023)	-0.000 (0.023)	
95% Confidence interval*		(-0.103 , -0.014)	(-0.060 , 0.029)	(-0.045 , 0.044)	

* Adjusted for 'sequence', 'patients within sequences', 'period' and 'treatment'.
The effect 'patients within sequences' was considered as random, while the other effects were considered as fixed.
** Results to be interpreted with caution as Tio HH 18 was not blinded.

Table 15.2.2: 7 Day 29 adjusted mean FVC [litres] at each planned time (FAS, imputed data)

	Placebo	Tio R 1.25	Tio R 2.5	Tio R 5	Tio HH 18**
Number of patients in analysis set	143	143	144	143	142
Number of analysed patients	142	143	143	143	142
Adjusted* mean (SE)					
0:00 (trough)	3.118 (0.076)	3.255 (0.076)	3.307 (0.076)	3.356 (0.076)	3.351 (0.076)
0:30	3.131 (0.077)	3.390 (0.077)	3.435 (0.077)	3.473 (0.077)	3.496 (0.077)
1:00	3.152 (0.078)	3.449 (0.078)	3.484 (0.078)	3.488 (0.078)	3.499 (0.078)
2:00	3.146 (0.078)	3.443 (0.078)	3.489 (0.078)	3.499 (0.078)	3.487 (0.078)
3:00	3.156 (0.078)	3.466 (0.078)	3.513 (0.078)	3.516 (0.078)	3.497 (0.078)
4:00	3.161 (0.079)	3.468 (0.079)	3.495 (0.079)	3.505 (0.079)	3.501 (0.079)
5:00	3.191 (0.079)	3.459 (0.079)	3.467 (0.079)	3.501 (0.079)	3.488 (0.079)
6:00	3.168 (0.079)	3.417 (0.079)	3.470 (0.079)	3.473 (0.079)	3.469 (0.079)

* Adjusted for period, planned time and period*planned time as fixed effects. Patient*planned time and patient*treatment*planned time are fitted as random effects with unstructured covariance matrices (ref model 3 of R10-5353).
Data recorded after the patient used rescue are imputed by the least favourable prior measurement, i.e. lowest value of the available test days.
The baseline (ie immediately prior to the first dose of randomised treatment) mean (sd) is 3.208 (0.893) litres.
** Results to be interpreted with caution as Tio HH 18 was not blinded.