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..

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
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Module:		**Volume:**	
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Title of trial:	A Randomised, Double-Blind, Placebo-Controlled, Parallel-Group Study to Assess Long Term (one-year) Efficacy and Safety of Tiotropium Inhalation Solution 5 µg (2 puffs of 2.5 µg) Delivered by the Respimat® Inhaler in Patients with Chronic Obstructive Pulmonary Disease (COPD)
Coordinating Investigator:	[redacted]
Trial sites:	Multinational and multicentre study (31 countries, 336 sites)
Publication (reference):	Data of this study have not been published.
Clinical phase:	IIIb
Objectives:	The objective was to evaluate the long term (one-year) safety and efficacy of Tiotropium Inhalation Solution delivered by the Respimat® inhaler compared to placebo in patients with COPD.
Methodology:	Randomised, double-blind, placebo controlled, parallel group design study
No. of subjects:	
planned:	entered: 3000
actual:	enrolled: 5483 entered: 3991 treated: 3917 Tiotropium 5 µg entered: 1989 treated: 1989 analysed (for primary endpoint): 1939 Placebo: entered: 2002 treated: 2002 analysed (for primary endpoint): 1953
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥40 years with a diagnosis of COPD (pre-bronchodilator FEV_1 ≤60% predicted [ECSC criteria] and FEV_1 ≤70% of FVC), current or ex-smoker (smoking history ≥10 pack years)
Test product:	Tiotropium Inhalation Solution
dose:	5 µg (2 puffs of 2.5 µg)
mode of admin.:	Oral inhalation by the Respimat® inhaler

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batch no.:	Refer to Appendix 16.1.6
Reference therapy:	Placebo
dose:	Not applicable
mode of admin.:	Oral inhalation by the Respimat® inhaler
batch no.:	Refer to Appendix 16.1.6
Duration of treatment:	48 weeks
Criteria for evaluation:	
Efficacy:	Trough FEV_1, time to first COPD exacerbation, number of COPD exacerbations (exposure adjusted and unadjusted), number of patients with at least 1 COPD exacerbation, time to first hospitalisation due to COPD exacerbation, number of hospitalisations due to COPD exacerbations, number of patients with at least 1 hospitalisation due to COPD exacerbation (exposure adjusted and unadjusted), St. George's Respiratory Questionnaire (SGRQ, total and domain scores), and trough FVC
Safety:	Adverse events, clinical laboratory, vital signs (pulse rate and blood pressure), physical examination, and 12-lead ECG
Statistical methods:	Analysis of covariance with terms for centre, LABA use, treatment, and baseline as a covariate. Cox's proportional hazards regression model with terms for centre, LABA use, and treatment. Log rank test via the life table method adjusting for LABA use and treatment. Wilcoxon-Mann-Whitney non-parametric test. Generalised linear (assuming both a Poisson and a negative binomial distribution) regression with terms for centre, LABA use, and treatment, offset by logged treatment exposure. Logistic regression with terms for centre, LABA use, treatment, and treatment exposure. Fisher's exact test for comparing proportions.

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SUMMARY – CONCLUSIONS:

Efficacy:

The two treatment groups were generally well balanced at randomisation with respect to demographics, smoking history, history of COPD diagnosis and concomitant inhaled corticosteroids, oral corticosteroids, LABA use at randomisation, and pulmonary function at screening.

Co-primary endpoints

Superiority of tiotropium over placebo was demonstrated for both co-primary endpoints. The mean improvement in trough FEV_1 (at Day 337) was 102 mL ($p<0.0001$). The treatment differences to placebo were also statistically significant irrespective of LABA use.

There was an increase in the time to first COPD exacerbation and a 31% reduction in the risk of an exacerbation in the tiotropium group relative to the placebo group (HR = 0.69; 95% CI 0.63, 0.77; $p<0.0001$). A subgroup analysis by LABA use at randomisation showed favourable hazard ratios for tiotropium, irrespective of LABA use.

Secondary endpoints

A statistically significant increase in trough FEV_1 response at Days 29 and 169 was observed in the tiotropium group ($p<0.0001$) compared with placebo. A subgroup analysis by LABA use showed significantly greater improvements in the tiotropium group than in the placebo group, irrespective of LABA use.

A statistically significant consistent pattern in favour of tiotropium was shown in the measures of COPD exacerbations. The hazard ratios for time to first hospitalisation due to a COPD exacerbation, moderate or severe COPD exacerbation, and COPD exacerbation (as defined by study 205.266) were significantly decreased in the tiotropium group compared with the placebo group. The reduced risks were in the range of 27% to 30%. Significant reductions in risk were noted regardless of LABA use, except for patients not taking LABAs for the time to first hospitalisation endpoint.

A statistically significant decrease was seen in all 4 assessments of number of COPD exacerbations in the tiotropium group compared with the placebo group. The reductions in relative rates were between 19% and 22% in favour of tiotropium.

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	Statistically significant decreases were also achieved in the number of patients with at least one COPD exacerbation, moderate or severe COPD exacerbation, and COPD exacerbation (as defined in study 205.266). For these, the odds of at least one COPD exacerbation in tiotropium were in the range of 0.70 to 0.73 of the odds in placebo. The odds of at least one hospitalisation due to COPD exacerbation in tiotropium was 0.82 of the odds in placebo ($p = 0.0728$). Statistically significant improvements in health-related quality of life as assessed by SGRQ were shown for the tiotropium group compared with the placebo group, both for the total score and all 3 individual domain scores (impact, activities, and symptoms). The treatment difference to placebo was −2.9 for the total score, −2.8 for impact, −3.0 for activities, and −4.0 for symptoms. The largest difference was demonstrated for the symptoms domain. However, the improvement in total SGRQ score did not achieve the minimal clinically important difference of 4.0 units. Statistically significant improvements were also observed in all scores irrespective of LABA use, again with the symptoms score showing the greatest reduction (post hoc analysis). The proportions of SGRQ responders were significantly higher in the tiotropium group than in than in the placebo group. Also, there were statistically significantly more patients who achieved a minimal clinical important difference of at least 4 units in the tiotropium group than in the placebo group compared with baseline ($p<0.0001$). At all measured time points the improvements in trough FVC were statistically significantly greater in the tiotropium group than in the placebo group ($p<0.0001$) and of comparable magnitude. The mean treatment difference to placebo at Day 337 was 0.168 L. A subgroup analysis by LABA use showed comparable results. Overall, the study demonstrates that tiotropium 5 µg delivered once daily by the Respimat® inhaler provides effective bronchodilation, increases time to first COPD exacerbation, reduces COPD exacerbations, and improves health-related quality of life as measured by the SGRQ.
Safety results:	The mean exposure to the study medication was slightly higher in the tiotropium group (308.5 days) than in the placebo group (299.5 days). The median exposure was 337 days in both groups with a range of 1 to 460 days in the tiotropium group and 1 to 455 days in the placebo group. A large majority of patients completed or nearly completed their planned exposure to the drug (>330 days, the planned exposure was 337 days): 78.5% of patients of the tiotropium group

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and 75.3% of patients of the placebo group. The duration of exposure was 1648.6 patient years in the tiotropium group.

Overall, the numbers of patients reported with adverse events and serious adverse events were similar in both treatment groups, except for fatal events and other significant AEs (acc. to ICH E3), details are given below. In total, 1369 patients (70.1%) in the tiotropium and 1361 patients (69.3%) in the placebo group were reported with at least one AE. The rate ratio was 0.99 (95% CI 0.92, 1.07) with p = 0.7601. The most frequently reported AEs were due to respiratory causes (COPD exacerbation, nasopharyngitis, dyspnoea, and upper respiratory tract infection). The frequencies of the most common AEs were balanced between both treatment groups except for COPD exacerbations and dry mouth. More patients in the placebo group (759 patients, 38.6%) experienced a COPD exacerbation compared with the tiotropium group (641 patients, 32.8%). Conversely, dry mouth occurred more often in patients treated with tiotropium (60 patients, 3.1%) than in those treated with placebo (27 patients, 1.4%).

The number of patients who reported AEs of severe intensity was comparable for both treatments: 327 patients (16.8%) tiotropium vs. 316 patients (16.1%) placebo.

The numbers of AEs assessed as drug-related by the investigator were balanced between both treatment groups and reported by 115 patients (5.9%) in the tiotropium group and 121 patients (6.2%) in the placebo group. The most frequently reported AEs considered as drug-related occurred in the SOCs gastrointestinal disorders (44 patients, 2.3% tiotropium vs. 27 patients, 1.4% placebo), lower respiratory system disorders (34 patients, 1.7% tiotropium vs. 48 patients, 2.4% placebo), and upper respiratory system disorders (22 patients, 1.1% tiotropium vs. 12 patients, 0.6% placebo). Differences between treatments were found in the SOCs cardiac disorders, gastrointestinal disorders, nervous system disorders, renal and urinary disorders, lower and upper respiratory disorders, and vascular disorders. More patients in the placebo group compared with the tiotropium group were reported with AEs in the SOCs cardiac disorders and lower respiratory system disorders. More patients with adverse events in the SOCs gastrointestinal disorders, nervous system disorders, renal and urinary disorders, upper respiratory system disorders, and vascular disorders were attributed to tiotropium compared with placebo.

Adverse events leading to discontinuation were reported for 136 patients (7.0%)

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in the tiotropium group and 149 patients (7.6%) in the placebo group. The most commonly reported AEs leading to discontinuation were in the SOCs cardiac disorders (25 patients, 1.3% tiotropium vs. 17 patients, 0.9% placebo) and lower respiratory tract disorders (60 patients, 3.1% tiotropium vs. 94 patients, 4.8% placebo). The main SOCs that had more patient discontinuations in the tiotropium group than in the placebo group were cardiac disorders, renal and urinary disorders, and other and upper respiratory system disorders.

The overall number of patients with other significant AEs as defined by ICH E3 was lower in the tiotropium group than in the placebo group (61 patients, 3.1% vs. 88 patients, 4.5%), this difference was mainly due to a higher number of patients with lower respiratory system disorders in the placebo group (29 patients, 1.5% vs. 63 patients, 3.2%).

AEs of special interest were defined post-hoc as non-fatal events known to be related to anticholinergics, cardiac events, and respiratory events. The evaluation suggested a trend towards an increased risk for angina and cardiac ischaemic events excluding myocardial infarction (non-MI events) with tiotropium, but a decreased risk for the more serious ischaemic outcome of myocardial infarction. Overall, the pattern and the wide confidence intervals, despite combined terms, did not allow for definitive conclusions. For heart failure, all endpoints showed a trend towards a reduced risk for the composite events for tiotropium; however, the risk estimates were imprecise. All endpoints for dysrhythmias, except one composite term “other arrhythmias”, which encompassed a variety of terms (excluding life-threatening tachyarrhythmia), showed a tendency towards a reduced risk with tiotropium. For the composite term other arrhythmias, a trend towards a higher rate with tiotropium was observed (mainly due to higher rates for the preferred terms bundle branch block left, bundle branch block right, and supraventricular extrasystoles). There was no evidence for an increased risk of stroke with tiotropium compared with placebo (rate ratio = 0.89; 95% CI 0.38, 2.10).

A composite endpoint of major cardiovascular events was evaluated which included all fatal events in the SOC cardiac disorders and SOC vascular disorders as well as the preferred terms ‘sudden death’, ‘cardiac death’ and ‘sudden cardiac death’ (not coded in the cardiac SOC), combined with non-fatal myocardial infarction, and non-fatal stroke. The incidence rates and rate ratio for the composite cardiovascular endpoint were similar for this major cardiovascular

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endpoint (rate ratio = 1.08, 95% CI 0.66, 1.77).

There were increased incidence rate ratios of tiotropium over placebo consistent with systemic anticholinergic pharmacology: urinary retention and dry mouth. Other gastrointestinal manifestations were inconsistently imbalanced. For the SOC upper respiratory system disorders, there was no or minimal imbalance.

The number of patients experiencing SAEs was also comparable between treatments: 342 patients (17.5%) on tiotropium vs. 336 patients (17.1%) on placebo. The most frequently reported SAEs were due to respiratory or cardiac causes, as expected in this patient population. Lower respiratory system disorders were the most common SAEs, with 191 patients (9.8%) in the tiotropium group and 211 patients (10.7%) in the placebo group. The second most common SAE was in the SOC cardiac disorders, reported for 60 patients (3.1%) in the tiotropium group and 48 patients (2.4%) in the placebo group. There was an imbalance in the SOC of other respiratory system disorders with 1.3% of patients on tiotropium vs. 0.8% on placebo. This imbalance was predominantly due to respiratory neoplasms, 17 patients in the tiotropium group compared with 8 patients in the placebo group. Neoplasms other than lung cancer were reported more frequently in the tiotropium group (29 patients, 1.5%) vs. placebo (18 patients, 0.9%) too. The preferred terms reported were quite diverse and all categories of neoplasm had low event rates, with the vast majority of preferred terms having a frequency not exceeding 0.1%. The difference in numbers of events between the two treatment groups did not exceed 2 cases per preferred term. Furthermore, there is no pre-clinical evidence of a risk for tiotropium to induce or promote cancer growth and the time to cancer diagnosis was not different between the treatment groups. Considering the biology and the chronology of the formation and growth of neoplasms, the diversity of types of cancers and the timing of the diagnoses in relation to the patient's randomisation into the studies, it is very likely that the onset of these neoplasms predated the study entry. Thus, there is no biological plausibility of a causal relation between the increased number of cancer diagnoses and the treatment assignment.

Similar trends were observed when the fatal events were analysed in 4 different treatment intervals or using different censoring rules. Following the pre-defined evaluation for the planned randomised treatment period of 337 Days, censored at this date is reported. The total number of deaths was 52 (incidence density 2.94

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per 100 patient-years) in the tiotropium group and 38 (incidence density 2.13) in the placebo group (rate ratio 1.38, 95% CI 0.91, 2.10, p = 0.1297). The most common causes of death were general disorders and administration site conditions (31 patients, 0.8%), lower respiratory system disorders (25 patients, 0.6%) and cardiac disorders (13 patients, 0.3%). An imbalance favouring placebo was seen in the SOC cardiac disorders (9 patients tiotropium vs. 4 patients placebo), general disorders and administration site conditions, which includes the preferred terms death/unexplained death and sudden death (19 patients tiotropium vs. 12 patients placebo) and lung or other neoplasms (9 patients tiotropium vs.2 patients placebo). The event rate was lower for tiotropium than placebo in the SOC lower respiratory system disorders (9 patients tiotropium vs. 16 patients placebo), which included mainly COPD exacerbations, respiratory failure and pneumonias and in the SOC infections and infestations (3 patients tiotropium vs. 5 patients placebo).

With regard to fatal cases of lung or other neoplasm, 5 of the tiotropium treated patients who died were treated for less than 100 days or diagnosed within this period. The remaining four patients received treatment for about 200 to 300 days. As was discussed for neoplasms as serious adverse events above, there is no biological plausibility to assume a causal relationship with tiotropium treatment, and it is very likely that the onset of these neoplasms predated the study entry.

Subgroup analyses were performed to determine whether patterns of events would suggest specific populations at risk. Regarding concomitant respiratory medication, it appears that LABA use and especially LABA only use (based on small numbers), or no ICS at randomisation was associated with a higher risk in the tiotropium group, whereas ICS only (again this group based on small numbers) was associated with a higher risk in the placebo group. Subgroup analyses based on age and smoking status did not reveal any interactions which would require special consideration.

Subgroup analyses according to the presence or absence of known cardiac disease, coronary artery disease, cardiac rhythm disorders, and use of cardiovascular medications at baseline did not distinguish a group at increased risk of any adverse event or a serious adverse event on an SOC level. For fatal events however, there was a higher rate ratio in those patients who had a history of cardiac disease (RR= 4.03), and arrhythmia at baseline (RR = 8.61). This was

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	not observed based on presence of coronary artery disease and not consistent based on use of cardiovascular medications at inclusion. The rate ratio for a composite endpoint of major cardiovascular events was balanced in patients with known cardiac disease (0.99), while this endpoint was unbalanced (RR=1.72) for patients with known arrhythmia at baseline. Evaluation of clinical laboratory results and vital signs did not reveal any clinically relevant changes in mean values or treatment differences. Overall, treatment with tiotropium was well tolerated as reflected in adverse events and serious adverse events and the overall crude rate for fatal events for this one-year trial was low (2.3%). However all-cause fatal events were imbalanced in favour of placebo, predominantly based on the SOCs cardiac disease, general (death unexplained / sudden death) and neoplasms. These imbalances were partly compensated by a lower rate for tiotropium in the SOCs lower respiratory events and infections. There is no plausible biological mechanism to suggest a causal relationship of the increased rate of neoplasms to the tiotropium treatment assignment. The observed higher rate of fatal events in the tiotropium group appeared to be concentrated among a subgroup of patients having cardiac disorders at inclusion, especially rhythm disorders.
Conclusions:	Treatment with tiotropium 5 µg inhaled from the Respimat® inhaler provided statistically significant improvements in both co-primary endpoints of trough FEV_1 at 48 weeks (Day 337) and time to first COPD exacerbation. Treatment with tiotropium was associated with an improvement in lung function, a reduced risk of a COPD exacerbation and associated hospitalisation, and an improvement in health related quality of life (St. George's Respiratory Questionnaire) relative to the control group. Treatment with tiotropium was shown to be effective irrespective of concomitant LABA use. Overall, treatment with tiotropium was well tolerated. However all-cause fatal events were imbalanced in favour of placebo, predominantly based on the SOCs cardiac disease and general (death unexplained / sudden death). The observed higher rate of fatal events in the tiotropium group appeared to be concentrated among a subgroup of patients having cardiac disorders at inclusion, especially rhythm disorders.

Trial Synopsis - Appendix

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

Results for	**presented in**
Patient disposition	Table 15.1.1: 2
Trough FEV_1 response after 4 weeks Trough FEV_1 response after 24 weeks Trough FEV_1 response after 48 weeks	Table 15.2.1: 2
Time to first hospitalised COPD exacerbation during randomised treatment	Table 15.2.2.1: 10
Number of patients with at least one COPD exacerbations during randomised treatment	Table 15.2.2.3: 1
Number of patients with at least one moderate or severe COPD exacerbations during randomised treatment	Table 15.2.2.3: 9
Number of COPD exacerbations per patient during randomised treatment	Table 15.2.2.2: 1
Number of hospitalisations for COPD exacerbations per patient during randomised treatment	Table 15.2.2.3: 7
Number of patients with at least 1 hospitalisation for COPD exacerbation during randomised treatment	Table 15.2.2.3: 5
SGRQ after 24 and 48 weeks (total and domain scores)	Table 15.2.3: 2
Trough FVC response after 4 weeks Trough FVC response after 24 weeks Trough FVC response after 48 weeks	Table 15.2.4: 2

Table 15.1.1: 2 Disposition of patients
- enrolled set

Termination from:		Tiotropium N (%)	Placebo N (%)	Total N (%)
	Enrolled			5483
	Not randomised			1492
	Randomised	1989	2002	3991
	Not treated	0	0	0
	Treated	1989 (100.0)	2002 (100.0)	3991 (100.0)
Treatment	NOT prematurely discontinued	1671 (84.0)	1629 (81.4)	3300 (82.7)
	Prematurely discontinued from trial medication	318 (16.0)	373 (18.6)	691 (17.3)
	Adverse events	143 (7.2)	156 (7.8)	299 (7.5)
	Worsening of disease under study	46 (2.3)	77 (3.8)	123 (3.1)
	Worsening of other pre-existing disease	14 (0.7)	7 (0.3)	21 (0.5)
	Other adverse event	83 (4.2)	72 (3.6)	155 (3.9)
	Lack of efficacy	28 (1.4)	67 (3.3)	95 (2.4)
	Non compliant with protocol	47 (2.4)	35 (1.7)	82 (2.1)
	Lost to follow-up	22 (1.1)	28 (1.4)	50 (1.3)
	Consent withdrawn	20 (1.0)	35 (1.7)	55 (1.4)
	Other	58 (2.9)	52 (2.6)	110 (2.8)
Trial	NOT prematurely discontinued	1667 (83.8)	1623 (81.1)	3290 (82.4)
	Prematurely discontinued from trial	4 (0.2)	6 (0.3)	10 (0.3)
	Adverse events	2 (0.1)	3 (0.1)	5 (0.1)
	Worsening of disease under study	0 (0.0)	0 (0.0)	0 (0.0)
	Worsening of other pre-existing disease	0 (0.0)	0 (0.0)	0 (0.0)
	Other adverse event	2 (0.1)	3 (0.1)	5 (0.1)
	Lack of efficacy	0 (0.0)	0 (0.0)	0 (0.0)
	Non compliant with protocol	0 (0.0)	0 (0.0)	0 (0.0)
	Lost to follow-up	2 (0.1)	0 (0.0)	2 (0.1)
	Consent withdrawn	0 (0.0)	1 (0.0)	1 (0.0)
	Other	0 (0.0)	2 (0.1)	2 (0.1)
	Prematurely terminated treatment*	318 (16.0)	373 (18.6)	691 (17.3)

* Patients prematurely discontinued from trial medication did not complete trial completion page.

Table 15.2.1: 2 Analysis of change from baseline to each test day in trough FEV1
- full analysis set (LOCF/WOCF)

ANCOVA results for Day 29

FEV1 [L]	Tiotropium (N=1879)	Placebo (N=1866)
Baseline		
Mean (SE)	1.111 (0.009)	1.106 (0.009)
Day 29		
Adjusted mean* (SE)	1.218 (0.005)	1.125 (0.005)
Change to Day 29		
Adjusted mean* (SE)	0.110 (0.005)	0.017 (0.005)
Difference to Placebo		
Adjusted mean* (SE)	0.093 (0.007)	
95% confidence interval	(0.080, 0.106)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.1.1

Table 15.2.1: 2 Analysis of change from baseline to each test day in trough FEV1
- full analysis set (LOCF/WOCF)

ANCOVA results for Day 169

FEV1 [L]	Tiotropium (N=1889)	Placebo (N=1870)
Baseline		
Mean (SE)	1.111 (0.009)	1.106 (0.009)
Day 169		
Adjusted mean* (SE)	1.230 (0.006)	1.127 (0.006)
Change to Day 169		
Adjusted mean* (SE)	0.121 (0.006)	0.018 (0.006)
Difference to Placebo		
Adjusted mean* (SE)	0.103 (0.008)	
95% confidence interval	(0.088, 0.118)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.1.1

Table 15.2.1: 2 Analysis of change from baseline to each test day in trough FEV1 - full analysis set (LOCF/WOCF)

ANCOVA results for Day 337

FEV1 [L]	Tiotropium (N=1889)	Placebo (N=1870)
Baseline		
Mean (SE)	1.111 (0.009)	1.106 (0.009)
Day 337		
Adjusted mean* (SE)	1.228 (0.007)	1.126 (0.007)
Change to Day 337		
Adjusted mean* (SE)	0.119 (0.007)	0.018 (0.007)
Difference to Placebo		
Adjusted mean* (SE)	0.102 (0.009)	
95% confidence interval	(0.085, 0.118)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.1.1

Table 15.2.2.1: 10 Time to first hospitalised COPD exacerbation during randomised treatment: Life-table method - full analysis set

	Tiotropium (N=1939)			Placebo (N=1953)		
	Number at risk	Number with exac.	Probability no exac. (%)	Number at risk	Number with exac.	Probability no exac. (%)
Day 1	1938	1	99.9	1953	0	100.0
Day 29	1881	20	99.0	1870	23	98.8
Day 57	1825	31	98.4	1796	50	97.3
Day 85	1781	49	97.4	1745	68	96.4
Day 113	1739	64	96.6	1692	80	95.7
Day 141	1711	79	95.7	1652	101	94.5
Day 169	1682	88	95.2	1604	122	93.3
Day 197	1661	99	94.6	1567	140	92.2
Day 225	1631	112	93.9	1546	155	91.3
Day 253	1607	122	93.3	1523	166	90.7
Day 281	1581	140	92.2	1499	178	90.0
Day 308	1559	152	91.5	1466	190	89.3
Day 337	1008	159	91.1	928	196	88.9
Time to first exacerbation [Days]						
Lower quartile (95% CI)*	NE (NE, NE)			NE (NE, NE)		
Median (95% CI)*	NE (NE, NE)			NE (NE, NE)		
P-value#	0.0191					

Exacerbations are counted if between the date of first dose of randomised treatment and the date of last dose of randomised treatment + 1 day (inclusive). Patients are censored at end of interval if no exacerbation has occurred.
NE = Non estimable
* Life-table values, lower quartile and median from unadjusted (for LABA) analysis
# P-value for treatment effect from log-rank test adjusting for the effect of LABA use at randomisation

Table 15.2.2.3: 1 Number of patients with at least one COPD exacerbations during randomised treatment
- full analysis set

	Tiotropium (N=1939)	Placebo (N=1953)
At least one exacerbation, N (%):		
Yes	685 (35.3)	842 (43.1)
No	1254 (64.7)	1111 (56.9)
Total patient years at risk*	1645.3	1607.8
Logistic regression estimates#:		
Odds ratio [tio/pbo] (95%CI)	0.70 (0.62, 0.80)	
P-value	<.0001	

* Period of risk from start of randomised treatment to the day after taking last dose of randomised treatment
\# Estimates from logistic regression model adjusting for time at risk, and LABA use

Table 15.2.2.3: 9 Number of patients with at least one moderate or severe COPD exacerbations during randomised treatment - full analysis set

	Tiotropium (N=1939)	Placebo (N=1953)
At least one exacerbation, N (%):		
Yes	538 (27.7)	666 (34.1)
No	1401 (72.3)	1287 (65.9)
Total patient years at risk*	1645.3	1607.8
Logistic regression estimates#:		
Odds ratio [tio/pbo] (95%CI)	0.73 (0.64, 0.84)	
P-value	<.0001	

* Period of risk from start of randomised treatment to the day after taking last dose of randomised treatment
\# Estimates from logistic regression model adjusting for time at risk, and LABA use

Table 15.2.2.2: 1 Number of COPD exacerbations during randomised treatment: Wilcoxon rank-sum test - full analysis set

	Tiotropium (N=1939)	Placebo (N=1953)
Total number of exacerbations (sum over all patients)	1168	1434
Naïve estimates [per patient]:		
Median number of exacerbations	0.00	0.00
Upper quartile number of exacerbations	1.00	1.00
P-value#	<.0001	
Total patient years at risk*	1645.3	1607.8
Adjusted for time at risk estimates [per patient year]:		
Median number of exacerbations	0.00	0.00
Upper quartile number of exacerbations	1.08	1.09
P-value#	<.0001	

P-value for treatment effect from Wilcoxon rank-sum test
* Period of risk from start of randomised treatment to the day after the last dose of randomised treatment

Table 15.2.2.3: 7 Number of patients with at least one hospitalised COPD exacerbations during planned randomised treatment - full analysis set

	Tiotropium (N=1939)	Placebo (N=1953)
At least one exacerbation, N (%):		
Yes	171 (8.8)	214 (11.0)
No	1768 (91.2)	1739 (89.0)
Total patient years at risk*	1761.3	1778.1
Logistic regression estimates#:		
Odds ratio [tio/pbo] (95%CI)	0.77 (0.62, 0.95)	
P-value	0.0166	

* Period of risk from start of randomised treatment to the day of the planned last dose of randomised treatment
\# Estimates from logistic regression model adjusting for time at risk, and LABA use

Table 15.2.2.3: 5 Number of patients with at least one hospitalised COPD exacerbations during randomised treatment - full analysis set

	Tiotropium (N=1939)	Placebo (N=1953)
At least one exacerbation, N (%):		
Yes	161 (8.3)	198 (10.1)
No	1778 (91.7)	1755 (89.9)
Total patient years at risk*	1645.3	1607.8
Logistic regression estimates#:		
Odds ratio [tio/pbo] (95%CI)	0.82 (0.66, 1.02)	
P-value	0.0728	

* Period of risk from start of randomised treatment to the day after taking last dose of randomised treatment
\# Estimates from logistic regression model adjusting for time at risk, and LABA use

Table 15.2.3: 2 Analysis of change from baseline to each test day in SGRQ scores
- full analysis set (LOCF)

ANCOVA results for Activities component, Day 169

	Tiotropium (N=1690)	Placebo (N=1668)
Baseline		
Mean (SE)	57.974 (0.353)	58.594 (0.360)
Day 169		
Adjusted mean* (SE)	54.787 (0.424)	57.081 (0.426)
Change to Day 169		
Adjusted mean* (SE)	-3.573 (0.432)	-1.218 (0.435)
Difference to Placebo		
Adjusted mean* (SE)	-2.355 (0.545)	
95% confidence interval	(-3.423, -1.286)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.3.1

Table 15.2.3: 2 Analysis of change from baseline to each test day in SGRQ scores
- full analysis set (LOCF)

ANCOVA results for Activities component, Day 337

	Tiotropium (N=1690)	Placebo (N=1668)
Baseline		
Mean (SE)	57.974 (0.353)	58.594 (0.360)
Day 337		
Adjusted mean* (SE)	55.173 (0.451)	58.168 (0.453)
Change to Day 337		
Adjusted mean* (SE)	-3.196 (0.456)	-0.226 (0.460)
Difference to Placebo		
Adjusted mean* (SE)	-2.970 (0.576)	
95% confidence interval	(-4.099, -1.841)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.3.1

Table 15.2.4: 2 Analysis of change from baseline to each test day in trough FVC
- full analysis set (LOCF/WOCF)

ANCOVA results for Day 29

FVC [L]	Tiotropium (N=1879)	Placebo (N=1866)
Baseline		
Mean (SE)	2.387 (0.017)	2.390 (0.018)
Day 29		
Adjusted mean* (SE)	2.564 (0.009)	2.413 (0.009)
Change to Day 29		
Adjusted mean* (SE)	0.176 (0.009)	0.025 (0.009)
Difference to Placebo		
Adjusted mean* (SE)	0.151 (0.012)	
95% confidence interval	(0.127, 0.174)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.4.1

Table 15.2.4: 2 Analysis of change from baseline to each test day in trough FVC
- full analysis set (LOCF/WOCF)

ANCOVA results for Day 169

FVC [L]	Tiotropium (N=1889)	Placebo (N=1870)
Baseline		
Mean (SE)	2.387 (0.017)	2.390 (0.018)
Day 169		
Adjusted mean* (SE)	2.568 (0.010)	2.408 (0.010)
Change to Day 169		
Adjusted mean* (SE)	0.179 (0.010)	0.019 (0.010)
Difference to Placebo		
Adjusted mean* (SE)	0.160 (0.013)	
95% confidence interval	(0.135, 0.186)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.4.1

Table 15.2.4: 2 Analysis of change from baseline to each test day in trough FVC
- full analysis set (LOCF/WOCF)

ANCOVA results for Day 337

FVC [L]	Tiotropium (N=1889)	Placebo (N=1870)
Baseline		
Mean (SE)	2.387 (0.017)	2.390 (0.018)
Day 337		
Adjusted mean* (SE)	2.556 (0.011)	2.388 (0.011)
Change to Day 337		
Adjusted mean* (SE)	0.168 (0.011)	-0.001 (0.011)
Difference to Placebo		
Adjusted mean* (SE)	0.168 (0.014)	
95% confidence interval	(0.141, 0.196)	
p-value	<.0001	

* Adjusted for baseline, pooled centre and LABA use at randomisation
Note: Patients without a baseline or an on-treatment value are excluded from the analysis
Source data: Appendix 16.1.9.2, Statdoc 6.4.1