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
Name of finished product: Spiriva®		**EudraCT No.:** 2007-001840-33	
Name of active ingredient: Tiotropium		**Page:** 1 of 6	**Synopsis No.:**
Module:		**Volume:**	
Report date: 02 AUG 2010	**Trial No. / U No.:** 205.389 / U10-2159-02	**Dates of trial:** 28 JAN 2008 – 01 APR 2010	**Date of revision:** 17 June 2011

Title of trial:	Effect of inhalation of tiotropium once daily 18 mcg versus salmeterol twice daily 50 mcg on time to first exacerbation in COPD patients (a randomised, double-blind, double-dummy, parallel group, one-year study) The POET-COPD® study - Prevention Of Exacerbations with Tiotropium
Coordinating Investigator:	[redacted]
Trial sites:	Multicentre study (752 sites in 25 countries)
Publications (reference):	Beeh KM, Hederer B, Glaab T et al. Int J Chron Obstruct Pulmon Dis. 2009; 4:119-125 [P09-03705]. Vogelmeier C, Hederer B, Glaab T et al. N Engl J Med. 2011; 364:1093-103 [P11-03885]
Clinical phase:	IV
Objectives:	To compare the effect of tiotropium (18 µg, Spiriva® HandiHaler®) once daily and salmeterol (50 µg, Serevent® HFA-MDI) twice daily on COPD exacerbations.
Methodology:	One-year randomised, double-blind, double-dummy, parallel group design. Visits: at screening; at randomisation; after 2, 4, 8, and 12 months. Telephone calls monthly between the visits.
No. of subjects:	
planned:	entered: 7350 evaluable patients; 3675 patients for each treatment
actual:	enrolled: 8293 Treatment tiotropium: entered: 3711, treated (analysed for primary endpoint): 3707 completed treatment: 3122 Treatment salmeterol: entered: 3673 treated (analysed for primary endpoint): 3669 completed treatment: 3021
Diagnosis and main criteria for inclusion:	Diagnosis of COPD (post-bronchodilator FEV_1 ≤70% predicted and FEV_1/FVC ≤70%), smoking ≥10 pack years, age ≥40 years, at least 1 COPD exacerbation in the previous year.

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Test product:	Tiotropium
dose:	18 µg once daily
mode of admin.:	Inhalation (powder) via the HandiHaler®
batch no.:	Tiotropium capsules: 701980B072000133, 707429B082000005, 804675B082000121, 902164B092000034 Placebo capsules matching tiotropium: 701840B072000132, 704110B072000222 Inhalation device: 7C1112B072000252, 6C2115B062000646
Reference therapy:	Salmeterol
dose:	50 µg (2 actuations of 25 µg) twice daily
mode of admin.:	Inhalation (suspension) via HFA-MDI
batch no.:	Salmeterol: M05001B072000340, NB1670B082000073, NH0372B082000200, NI2392B082000273, OD0451B092000075 Placebo matching salmeterol: 703874AB082000068, 703874AB082000327, 703874AB082000146, 809795B092000065
Duration of treatment:	360 days, preceded by a 2-week run-in phase
Criteria for evaluation:	
Efficacy:	Primary endpoint: time to first (moderate or severe) COPD exacerbation An exacerbation was defined as an increase or new onset of more than 1 symptom (cough, sputum, wheezing, dyspnoea, chest tightness), with at least 1 symptom lasting at least 3 days and requiring treatment with systemic steroids and/or antibiotics (moderate exacerbation) or hospitalisation (severe exacerbation). Secondary endpoints: Time-to-event endpoints: time to (a) first severe COPD exacerbation, (b) first moderate COPD exacerbation, (c) premature discontinuation of trial medication, (d) first COPD exacerbation or discontinuation of study medication because of worsening of underlying disease, whichever comes first, (e) first COPD exacerbation treated with systemic steroids, (f) first COPD exacerbation treated with antibiotics, (g) first COPD exacerbation treated with systemic steroids and antibiotics.

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Name of active ingredient: Tiotropium		**Page:** 3 of 6	**Synopsis No.:**
Module:		**Volume:**	
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Efficacy (continued):	Number of patients with events: occurrence of (a) at least 1 COPD exacerbation (moderate or severe), (b) at least 1 severe COPD exacerbation, (c) premature discontinuation of trial medication. Number of events: number of (a) COPD exacerbations (moderate or severe), (b) severe COPD exacerbations, (c) moderate COPD exacerbations, (d) COPD exacerbations treated with systemic steroids, (d) COPD exacerbations treated with antibiotics, (e) COPD exacerbations treated with systemic steroids and antibiotics. Weekly mean of pre-dose morning Peak Expiratory Flow Rate (PEFR) measured by patients at home and recorded in a patient diary during the first 4 months of randomised treatment.
Safety:	Serious adverse events (SAEs); adverse events (AEs) leading to treatment discontinuation; study drug-related AEs (following an amendment to the trial protocol). In addition in Poland all AEs and in Norway unexpected study drug-related AEs were collected. Fatal AEs were adjudicated by an independent mortality adjudication committee. All-cause mortality during treatment with study medication; all-cause mortality including follow-up of vital status from patients who prematurely discontinued treatment. Cardiovascular safety (composite safety endpoints based on SAEs), vital signs, physical examination.
Statistical methods:	Primary endpoint: Cox's proportional hazards model Secondary endpoints: Time-to-event endpoints: Cox's proportional hazards model Number of patients with events: Cochran-Mantel-Haenszel-test Number of events: Poisson regression model correcting for overdispersion PEFR rate: mixed effects model for repeated measures Mortality: Cox's proportional hazards model
SUMMARY – CONCLUSIONS:	
Efficacy results:	The treatment groups were balanced with respect to demographics, COPD characteristics, pulmonary medication use at baseline, and concomitant diagnoses (74.6% of treated patients were men, 99.6% white, and 48.1% current smokers; the mean age was 62.9 years and the mean FEV_1 was 49.3% predicted). During the study, concomitant use of pulmonary and other medication was also balanced between both treatment groups

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Name of active ingredient: Tiotropium		**Page:** 4 of 6	**Synopsis No.:**
Module:		**Volume:**	
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Efficacy results (continued):

Patients were allowed to continue inhaled corticosteroid (ICS) therapy during the trial and the use of ICS during the trial (overall 45.1% of treated patients) was also balanced between treatment groups

The study demonstrated superiority of tiotropium over salmeterol for the primary endpoint: tiotropium significantly reduced the risk of the first moderate or severe COPD exacerbation (for hazard ratio, see table below). Sensitivity analyses on the primary endpoint (on the per-protocol set of patients or excluding COPD exacerbations with imaging-confirmed pneumonia) confirmed the results of the primary analysis.

The effect of tiotropium was consistent across a set of secondary endpoints assessing exacerbations (see table below for p-values). Compared to salmeterol, tiotropium reduced the risk of both a moderate and severe (i.e. hospitalised) exacerbation ($p<0.001$) and tiotropium reduced the number of exacerbations ($p<0.05$ for moderate and/or severe exacerbations). The pattern of benefit with tiotropium was consistently observed in all major subgroups considered in this trial (i.e. age, gender, GOLD stage, smoking status, BMI, pulmonary medication use at baseline). The Kaplan-Meier analyses of time to first moderate or severe exacerbation demonstrated that the benefit with tiotropium became manifest as early as about 1 month after onset of treatment, and was maintained over the entire study period of 1 year.

	Ratio (95% CI) tiotropium vs. salmeterol	p-value
Primary endpoint:		
Time to first moderate or severe COPD exacerbation	0.83 (0.77, 0.90) [1]	<0.0001
Secondary endpoints		
Number of moderate or severe COPD exacerbations	0.89 (0.83, 0.96) [2]	0.0017
Time to first severe COPD exacerbation	0.72 (0.61, 0.85) [1]	<0.0001
Number of severe COPD exacerbations	0.73 (0.66, 0.82) [2]	<0.0001
Time to first moderate COPD exacerbation	0.86 (0.79, 0.93) [1]	0.0004
Number of moderate COPD exacerbations	0.93 (0.86, 1.00) [2]	0.0479

[1] Hazard ratio: Cox's proportional hazards model; p-value: Wald's Chi-square test
[2] Rate ratio based on Poisson regression model correcting for overdispersion

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Name of active ingredient: Tiotropium		**Page:** 5 of 6	**Synopsis No.:**
Module:		**Volume:**	
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Safety results:

Vital status information was available for 99.1% of patients in both treatment groups at the end of the study (with confirmed vital status at Day 360 for those who prematurely discontinued study medication). Tiotropium was associated with a lower risk of premature discontinuation of trial medication (hazard ratio: 0.88; 95% CI: 0.78, 0.98; p = 0.0242).

Both study medications are approved and have well established safety profiles. Therefore, for this large phase IV trial, only serious adverse events and certain categories of non-serious adverse events were systematically collected. Non-serious AEs were collected if they led to treatment discontinuation. Beyond, investigators had the freedom to report any non-serious AE as deemed appropriate by them. In addition, there were local requirements for AE recording. In Poland, all non-serious AEs were to be collected; in Norway, unexpected study drug-related AEs were to be collected. No study-drug related AE was reported in Norway. Overall the frequency of AEs was balanced across the treatment groups (tiotropium: 24.5%, salmeterol: 27.3%).

Serious adverse events were reported for a smaller proportion of patients in the tiotropium group (14.7%) than in the salmeterol group (16.5%); the incidence rate ratio was 0.86 (95% CI: 0.77, 0.97; p = 0.0139). The most frequently reported SAEs were either respiratory or cardiac in nature. Patients in the tiotropium group had a reduced risk for respiratory disorders (incidence rate ratio: 0.79, 95% CI: 0.68, 0.92) at a frequency of 8.1% of patient in the tiotropium groups versus 10.0% of patients in the salmeterol group. The frequency of cardiac disorders was comparable between treatment groups (incidence rate ratio: 1.12, 95% CI: 0.84, 1.50). On MedDRA preferred term level, the most frequently reported SAE was COPD with a reduced risk for tiotropium patients (incidence rate ratio: 0.77, 95% CI: 0.66, 0.91) at a frequency of 7.3% of patient in the tiotropium group versus 9.1% in the salmeterol group.

Fatal events (including vital status of prematurely discontinued patients until Day 360) occurred in 1.7% and 2.1% of tiotropium and salmeterol treated patients. The most frequent adjudicated primary causes of death on MedDRA system organ class (SOC) level were general disorders and respiratory disorders. Various mortality analyses were performed, based on different definitions of treatment periods and based on either adjudicated or investigator-reported causes of death. There were numerically fewer fatal cases in the tiotropium group relative to the salmeterol group for each of the analyses; however, in all cases the 95% CI of the hazard ratio included the value 1.

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Safety results (continued):	Additional analyses were performed to evaluate the cardiovascular safety of tiotropium and salmeterol by means of 3 composite safety endpoints. These were the composite endpoints of major adverse cardiovascular events (MACE), fatal MACE, and stroke, based on a pre-defined, project-specific collapsing of MedDRA terms. Hazard ratios and confidence intervals based on Cox's regression for time to an endpoint did not show a difference in cardiovascular risk between the 2 treatments (MACE: hazard ratio: 1.10; 95% CI: 0.74, 1.64; fatal MACE: hazard ratio 0.88; 95% CI: 0.48, 1.62; stroke: hazard ratio 0.90; 95% CI: 0.42, 1.92).
Conclusions:	The results of the POET-COPD® study demonstrate that tiotropium is more effective than salmeterol in reducing exacerbations in patients with moderate to very severe COPD and a history of at least 1 exacerbation in the preceding year. This effect of tiotropium was substantiated by significant improvements in a set of related primary and secondary endpoints characterising the risk of moderate or severe exacerbations of COPD, including time to first exacerbation or hospitalisation as well as reductions in the number of exacerbations or hospitalisations. Tiotropium reduced the risk of premature discontinuation of trial medication. Overall, the frequencies of serious adverse events and adverse events leading to treatment discontinuation were lower in the tiotropium group and reflected the advantage in the respiratory system organ class. There were no statistically significant differences in mortality and overall cardiovascular safety between tiotropium and salmeterol.

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 additional secondary endpoints, as summarised below.

Results for	**presented in**
Patient disposition	Table 15.1.1: 1
Time to first hospitalised COPD exacerbation during randomised treatment	Table 15.2.2.1.1: 1
Time to premature discontinuation of trial medication	Table 15.2.2.1.2: 1
Time to first COPD exacerbation or time to discontinuation of study medication because of worsening of underlying disease	Table 15.2.2.1.3: 1
Time to first COPD exacerbation treated with systemic steroids	Table 15.2.2.1.5: 1
Time to first COPD exacerbation treated with antibiotics	Table 15.2.2.1.6: 1
Time to first COPD exacerbation treated with systemic steroids and antibiotics	Table 15.2.2.1.7: 1
Number of patients with at least one COPD exacerbation	Table 15.2.2.2.1: 1
Number of patients with at least one hospitalised COPD exacerbation	Table 15.2.2.2.2: 1
Number of patients with premature discontinuation of trial medication	Table 15.2.2.2.3: 1
Number of COPD exacerbations	Table 15.2.2.3.1: 1

Table 15.1.1: 1 Disposition of patients

	Tiotropium N (%)	Salmeterol N (%)	Total N (%)
Enrolled			8293
Not entered/randomised			909
Entered/randomised	3711	3673	7384
Not treated	4	4	8
Treated	3707 (100.0)	3669 (100.0)	7376 (100.0)
Not prematurely discontinued from trial medication	3122 (84.2)	3021 (82.3)	6143 (83.3)
Prematurely discontined from trial medication	585 (15.8)	648 (17.7)	1233 (16.7)
Due to adverse events	264 (7.1)	292 (8.0)	556 (7.5)
Worsening of disease under study	122 (3.3)	147 (4.0)	269 (3.6)
Worsening of other pre-existing disease	25 (0.7)	16 (0.4)	41 (0.6)
Other adverse event	117 (3.2)	129 (3.5)	246 (3.3)
Due to lack of efficacy	32 (0.9)	24 (0.7)	56 (0.8)
Due to administrative reasons	289 (7.8)	332 (9.0)	621 (8.4)
Non compliant with protocol	66 (1.8)	74 (2.0)	140 (1.9)
Lost to follow-up	7 (0.2)	15 (0.4)	22 (0.3)
Consent withdrawn not due to adverse events	192 (5.2)	209 (5.7)	401 (5.4)
Other	24 (0.6)	34 (0.9)	58 (0.8)

Source data: Appendix 16.2.1, Listing 2

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Table 15.2.2.1.1: 1 Time to first hospitalised COPD exacerbation: Cox regression model - treated set

	Tiotropium N (%)	Salmeterol N (%)
Total patients	3707 (100.0)	3669 (100.0)
Patients with at least one hospitalised COPD exacerbation	262 (7.1)	336 (9.2)
Censored patients	3445 (92.9)	3333 (90.8)
Hazard ratio* [Tio/Sal] (95% CI)		0.72 (0.61, 0.85)
p-value**		<.0001

Only COPD exacerbations with onset during actual treatment are counted
Hospitalized COPD exacerbations are severe COPD exacerbations
*Hazard ratio adjusted for (pooled) centre and treatment
**based on Wald´s Chi-square test

Table 15.2.2.1.2: 1 Time to premature discontinuation of trial medication: Cox regression model - treated set

	Tiotropium N (%)	Salmeterol N (%)
Total patients	3707 (100.0)	3669 (100.0)
Patients with premature discontinuation of trial medication	585 (15.8)	648 (17.7)
Censored patients	3122 (84.2)	3021 (82.3)
Hazard ratio* [Tio/Sal] (95% CI)		0.88 (0.78, 0.98)
p-value**		0.0242

*Hazard ratio adjusted for (pooled) centre and treatment
**based on Wald´s Chi-square test

Table 15.2.2.1.3: 1 Time to first COPD exacerbation or time to discontinuation of study medication because of worsening of underlying disease (whichever comes first): Cox regression model - treated set

	Tiotropium N (%)	Salmeterol N (%)
Total patients	3707 (100.0)	3669 (100.0)
Patients with at least one COPD exacerbation or time to discontinuation of study medication because of worsening of underlying disease	1316 (35.5)	1448 (39.5)
Censored patients	2391 (64.5)	2221 (60.5)
Hazard ratio* [Tio/Sal] (95% CI)		0.84 (0.78, 0.91)
p-value**		<.0001

Only COPD exacerbations with onset during actual treatment are counted
*Hazard ratio adjusted for (pooled) centre and treatment
**based on Wald´s Chi-square test

Table 15.2.2.1.5: 1 Time to first COPD exacerbation treated with systemic steroids: Cox regression model - treated set

	Tiotropium N (%)	Salmeterol N (%)
Total patients	3707 (100.0)	3669 (100.0)
Patients with at least one COPD exacerbation treated with systemic steroids	715 (19.3)	852 (23.2)
Censored patients	2992 (80.7)	2817 (76.8)
Hazard ratio* [Tio/Sal] (95% CI)		0.77 (0.69, 0.85)
p-value**		<.0001

Only COPD exacerbations with onset during actual treatment are counted
*Hazard ratio adjusted for (pooled) centre and treatment
**based on Wald´s Chi-square test

Table 15.2.2.1.6: 1 Time to first COPD exacerbation treated with antibiotics: Cox regression model - treated set

	Tiotropium N (%)	Salmeterol N (%)
Total patients	3707 (100.0)	3669 (100.0)
Patients with at least one COPD exacerbation treated with antibiotics	1154 (31.1)	1259 (34.3)
Censored patients	2553 (68.9)	2410 (65.7)
Hazard ratio* [Tio/Sal] (95% CI)		0.85 (0.78, 0.92)
p-value**		<.0001

Only COPD exacerbations with onset during actual treatment are counted
*Hazard ratio adjusted for (pooled) centre and treatment
**based on Wald´s Chi-square test

Table 15.2.2.1.7: 1 Time to first COPD exacerbation treated with systemic steroids and antibiotics: Cox regression model - treated set

	Tiotropium N (%)	Salmeterol N (%)
Total patients	3707 (100.0)	3669 (100.0)
Patients with at least one COPD exacerbation treated with systemic steroids and antibiotics	562 (15.2)	671 (18.3)
Censored patients	3145 (84.8)	2998 (81.7)
Hazard ratio* [Tio/Sal] (95% CI)		0.76 (0.68, 0.86)
p-value**		<.0001

Only COPD exacerbations with onset during actual treatment are counted
*Hazard ratio adjusted for (pooled) centre and treatment
**based on Wald´s Chi-square test

Table 15.2.2.2.1: 1 Number of patients with at least one COPD exacerbation
- treated set

	Tiotropium N(%)	Salmeterol N(%)	Risk ratio (Tio/Sal)* Estimate	95%CI	p-value
Total treated	3707(100.0)	3669(100.0)			
At least one COPD exacerbation	1277(34.4)	1414(38.5)	0.90	(0.85; 0.95)	0.0002

*Cochran-Mantel-Haenszel test stratified by (pooled) centre

Table 15.2.2.2.2: 1 Number of patients with at least one hospitalised COPD exacerbation - treated set

	Tiotropium N(%)	Salmeterol N(%)	Risk ratio (Tio/Sal)* Estimate	95%CI	p-value
Total treated	3707(100.0)	3669(100.0)			
At least one COPD exacerbation	262(7.1)	336(9.2)	0.77	(0.66; 0.89)	0.0005

*Cochran-Mantel-Haenszel test stratified by (pooled) centre

Table 15.2.2.2.3: 1 Number of patients with premature discontinuation of trial medication - treated set

	Tiotropium N(%)	Salmeterol N(%)	Risk ratio (Tio/Sal)* Estimate	95%CI	p-value
Total treated	3707(100.0)	3669(100.0)			
Premature discontinuation of trial medication	585(15.8)	648(17.7)	0.90	(0.82; 1.00)	0.0406

*Cochran-Mantel-Haenszel test stratified by (pooled) centre

Table 15.2.2.3.1: 1 Number of COPD exacerbations: Poisson regression with overdispersion - treated set

	Tiotropium	Salmeterol
Total treated	3707	3669
Total number of events	2114	2297
Total exposure*[pt-yr]	3308.4	3209.6
Observed number of events**[per pt-yr]	0.64	0.72
Adjusted rate of events***[per pt-yr]		
Mean (95%CI)	0.64(0.61; 0.67)	0.72(0.68; 0.75)
Rate ratio[Tio/Sal] of events***		
Mean (SE)	0.89(0.03)	
95% CI	(0.83; 0.96)	
p-value	0.0017	

*Total time (sum over all patients) on actual treatment
**Total number of events divided by total exposure
***Poisson regression correcting for overdispersion and adjusted for treatment exposure