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®		**EudraCT No.:** 2006-004086-33	
Name of active ingredient: Tiotropium bromide, BA 679 BR		**Page:** 1 of 5	**Synopsis No.:**
Module:		**Volume:** {hyperlink }	
Disclosure Synopsis date: 14 OCT 2013	**Trial No. / U No.:** 205.334 / U09-1780-01	**Date of trial:** 13 SEP 2007 – 29 JAN 2009	**Date of revision :** Not applicable

Title of trial:	Effect of inhalation of a free combination of tiotropium once daily 18 mcg and salmeterol twice daily 50 mcg versus a fixed combination of fluticasone and salmeterol twice daily (500/50 mcg) on static lung volumes and exercise tolerance in COPD patients (a randomised, double-blind, double dummy, 16 (2 x 8) weeks, crossover study)
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Multicenter, multinational study (40 centers in 7 countries)
Publication (reference):	Data of this study has not been published.
Clinical phase:	IV
Objectives:	To investigate whether treatment with tiotropium plus salmeterol improves static lung volumes and exercise tolerance in COPD patients more than a fixed combination of fluticasone and salmeterol.
Methodology:	Randomised, double-blind, verum-controlled, crossover study
No. of patients:	
planned:	entered: 368
actual:	enrolled: 422
	Treatment Tiotropium 18 mcg + Salmeterol 100 mcg: entered and treated: 344, analysed (for primary endpoint): 309
	Treatment Fluticasone/Salmeterol 1000/100 mcg: entered and treated: 344, analysed (for primary endpoint): 309
Diagnosis and main criteria for inclusion:	Outpatients of either sex, between 40 and 75 years old, with a diagnosis of chronic obstructive pulmonary disease and the presence of static lung hyper-inflation.

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Test product:	Tiotropium	Salmeterol
dose:	18 mcg daily (18 mcg o.d.)	100 mcg daily (50 mcg b.i.d.)
mode of admin.:	Powder inhalation via the HandiHaler®	Powder inhalation via Diskus/Accuhaler®
batch no.:	For further Details, cf. Appendix 16.1.6	For further Details, cf. Appendix 16.1.6
Reference therapy:	Fluticasone/Salmeterol (fixed combination)	
dose:	1000/100 mcg daily (500/50 mcg b.i.d.)	
mode of admin.:	Powder inhalation via Diskus/Accuhaler®	
batch no.:	Data are on file at Boehringer Ingelheim.	
Duration of treatment:	16 weeks in total, 8 weeks per investigational treatment period	
Criteria for evaluation:		
Efficacy / clinical pharmacology:	Thoracic Gas Volume Functional Residual Capacity [TGV(FRC)], Constant work rate exercise endurance time, body plethysmographic parameters (inspiratory capacity [IC], inspiratory reserve capacity [IRV], total lung capacity [TLC], reserve volume [RV]), exertional dyspnoea and leg discomfort during constant work rate exercise, spirometric parameters (Forced Expiratory Volume in the first second [FEV_1], Forced Vital Capacity [FVC], Slow Vital Capacity [SVC])	
Safety:	Adverse events, physical examination, vital signs	
Statistical methods:	Analysis of variance with terms for sequence, patient within sequence, treatment and period; Wilcoxon signed rank test; descriptive statistics	

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SUMMARY – CONCLUSIONS:

Efficacy / clinical pharmacology results:

Regarding the two co-primary endpoints post-dose TGV(FRC) and exercise endurance time, both after 8 weeks of treatment, post-dose TGV(FRC) showed a statistically significant difference on the 5% significance level in favour of the free combination tiotropium + salmeterol when compared with the fixed combination fluticasone + salmeterol (mean difference: Tio+Sal vs. Flu+Sal -0.087 litres; 95% CI -0.174, -0.001; p=0.0482).

Having reached a statistically significant result for post-dose TGV(FRC) the pre-specified two-step testing procedure foresaw testing for treatment differences between Tio+Sal and Flu+Sal with respect to exercise endurance time. For this co-primary endpoint no statistical significance was observed (median difference Tio+Sal vs. Flu+Sal 3.0 seconds; 95% CI -9.5; 27.5; p=0.3407). The analysis of endurance time was based on a non-parametric approach using Wilcoxon's signed rank test. A parametric sensitivity analysis for the logarithms of the endurance times with the same ANOVA model as for post-dose TGV(FRC) confirmed that no significant treatment difference existed between Tio+Sal and Flu+Sal after 8 weeks. However, although not statistically significant, the observed difference in endurance times between Tio+Sal and Flu+Sal showed a numerical trend that suggests a prolonged endurance time in favour of Tio+Sal. Moreover, regarding the reasons for termination of exercise, a shift from stopping for breathing discomfort to stopping for leg discomfort was observed which was more pronounced in Tio+Sal than in Flu+Sal.

When the time course of post-dose TGV(FRC) and endurance time over the 8 weeks of treatment with either Tio+Sal or Flu+Sal is regarded, the p-value for testing the difference between the treatments was smaller after 4 weeks compared to 8 weeks for TGV(FRC) whereas for endurance time no statistically significant difference between the treatments could be observed for 4 weeks as well.

For the other secondary PFT (pulmonary function test) endpoints, all post-dose measurements after 8 weeks reached statistical significance (in favour of Tio+Sal) except for TLC and FEV_1/FVC. It should be noted that with respect to the trough measurements after 8 weeks, additionally RV did not reach statistical significance.

Safety results:

The safety assessment from this trial was generally consistent with the known safety profile from previous tiotropium clinical trials. The trial did not identify any previously unsuspected important adverse effects of tiotropium.

A total of 344 patients were randomised and received at least one dose of trial medication. 172 patients received the free combination of tiotropium (18 mcg/day) plus salmeterol (100 mcg/day) and 172 patients received the fixed combination fluticasone + salmeterol (1000/100 mcg/day) in the first treatment period. 332 patients were treated with tiotropium + salmeterol and 329 patients with fluticasone + salmeterol during period one or two of this crossover study. During treatment with tiotropium + salmeterol 23 patients withdrew from the trial prior to completion and 19 patients during treatment with fluticasone + salmeterol.

The most common adverse events for treated patients were COPD exacerbation, headache, and nasopharyngitis. COPD exacerbations occurred in 29 patients during treatment with tiotropium + salmeterol and 24 patients during treatment with fluticasone + salmeterol. Corresponding numbers of patients with headache were 3 and 9, whereas for nasopharyngitis the numbers were 14 and 15.

No deaths occurred during the treatment period.

During treatment with tiotropium + salmeterol 12 patients experienced a Serious Adverse Event and during treatment with fluticasone + salmeterol 8 patients. None of these events was deemed related to study drugs by the investigators.

About 2000 symptom limited exercise endurance tests with a high level of workload were performed during this study. No clinical relevant adverse events were identified during these large number of exercise tests.

Insights into the safety of the drugs used during the study are limited. Nevertheless, some conclusions can be drawn. Under the precautions that this study was only a eight weeks study with 344 patients it can be concluded that tiotropium can be used safely in combination with salmeterol also in patients with moderate to severe COPD conducting strenuous exercise. This also applies to the fixed combination of fluticasone + salmeterol.

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Conclusions:

The present trial provides information regarding the characterisation of the clinical efficacy of the free combination of tiotropium plus salmeterol compared to the fixed combination of fluticasone + salmeterol on static lung volumes (TGV(FRC)) and exercise endurance time. Treatment with the free combination of tiotropium + salmeterol led to a statistically significant reduction of static lung volumes compared to the treatment with the fixed combination of fluticasone + salmeterol in patients with moderate to severe COPD, whereas differences in exercise endurance time were not statistically significant.

The safety assessment from this trial was generally consistent with the overall safety database from previous tiotropium clinical trials. The trial did not identify any previously unsuspected important adverse reaction to tiotropium nor to the other drugs used in this study.

Trial Synopsis - Appendix

The result tables on the following pages supplement the trial results presented in the Trial Synopsis. The appended tables provide the results of additional 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 a total of 11 secondary endpoints are provided in the Trial Synopsis and the following tables.

Results for	presented in
Analysis of trough TGV(FRC) [Litres] after 8 weeks	Table 15.2.2.1: 1
Analysis of trough RV [Litres] after 8 weeks	Table 15.2.2.2: 1
Analysis of post−dose RV [Litres] after 8 weeks	Table 15.2.2.2: 2
Analysis of trough IC [Litres] after 8 weeks	Table 15.2.2.3: 1
Analysis of post−dose IC [Litres] after 8 weeks	Table 15.2.2.3: 2
Analysis of trough IRV [Litres] after 8 weeks	Table 15.2.2.4: 1
Analysis of post−dose IRV [Litres] after 8 weeks	Table 15.2.2.4: 2
Analysis of trough TLC [Litres] after 8 weeks	Table 15.2.2.5: 1
Analysis of post−dose TLC [Litres] after 8 weeks	Table 15.2.2.5: 2
Analysis of trough RV/TLC [%] after 8 weeks	Table 15.2.2.6: 1
Analysis of post−dose RV/TLC [%] after 8 weeks	Table 15.2.2.6: 2

Table 15.2.2.1: 1 Analysis of trough TGV(FRC) [Litres] after 8 weeks
- FAS using imputed values

Trough TGV(FRC) [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	5.235 (0.077)	5.254 (0.077)
Comparison vs Sal+Flu		
Mean (SE)	-0.018 (0.056)	
95% Confidence interval	(-0.129, 0.093)	
p-value	0.7466	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 5.462 (0.076) based on 309 patients

Table 15.2.2.2: 1 Analysis of trough RV [Litres] after 8 weeks
- FAS using imputed values

Trough RV [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	4.226 (0.075)	4.252 (0.075)
Comparison vs Sal+Flu		
Mean (SE)	-0.026 (0.060)	
95% Confidence interval	(-0.145, 0.092)	
p-value	0.6622	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 4.462 (0.074) based on 308 patients

Table 15.2.2.2: 2 Analysis of post-dose RV [Litres] after 8 weeks
- FAS using imputed values

Post-dose RV [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	3.915 (0.068)	4.069 (0.068)
Comparison vs Sal+Flu		
Mean (SE)	-0.154 (0.047)	
95% Confidence interval	(-0.246, -0.062)	
p-value	0.0011	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 4.462 (0.074) based on 308 patients

Table 15.2.2.3: 1 Analysis of trough IC [Litres] after 8 weeks
- FAS using imputed values

Trough IC [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	2.329 (0.043)	2.231 (0.043)
Comparison vs Sal+Flu		
Mean (SE)	0.098 (0.034)	
95% Confidence interval	(0.032, 0.164)	
p-value	0.0039	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 2.151 (0.042) based on 309 patients

Table 15.2.2.3: 2 Analysis of post-dose IC [Litres] after 8 weeks
- FAS using imputed values

Post-dose IC [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	2.469 (0.044)	2.354 (0.044)
Comparison vs Sal+Flu		
Mean (SE)	0.115 (0.033)	
95% Confidence interval	(0.050, 0.180)	
p-value	0.0005	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 2.151 (0.042) based on 309 patients

Table 15.2.2.4: 1 Analysis of trough IRV [Litres] after 8 weeks
- FAS using imputed values

Trough IRV [Litres]	Tio+Sal	Sal+Flu
Number of patients	280	281
After 8 weeks		
Mean (SE)	1.475 (0.038)	1.410 (0.038)
Comparison vs Sal+Flu		
Mean (SE)	0.065 (0.030)	
95% Confidence interval	(0.005, 0.125)	
p-value	0.0324	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 1.358 (0.037) based on 281 patients

Table 15.2.2.4: 2 Analysis of post-dose IRV [Litres] after 8 weeks
- FAS using imputed values

Post-dose IRV [Litres]	Tio+Sal	Sal+Flu
Number of patients	280	281
After 8 weeks		
Mean (SE)	1.612 (0.041)	1.545 (0.041)
Comparison vs Sal+Flu		
Mean (SE)	0.067 (0.032)	
95% Confidence interval	(0.004, 0.130)	
p-value	0.0381	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 1.358 (0.037) based on 281 patients

Table 15.2.2.5: 1 Analysis of trough TLC [Litres] after 8 weeks
- FAS using imputed values

Trough TLC [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	7.470 (0.090)	7.394 (0.090)
Comparison vs Sal+Flu		
Mean (SE)	0.076 (0.060)	
95% Confidence interval	(-0.043, 0.195)	
p-value	0.2114	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 7.509 (0.089) based on 308 patients

Table 15.2.2.5: 2 Analysis of post-dose TLC [Litres] after 8 weeks
- FAS using imputed values

Post-dose TLC [Litres]	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	7.363 (0.087)	7.362 (0.087)
Comparison vs Sal+Flu		
Mean (SE)	0.000 (0.047)	
95% Confidence interval	(-0.093, 0.094)	
p-value	0.9944	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 7.509 (0.089) based on 308 patients

Table 15.2.2.6: 1 Analysis of trough RV/TLC [%] after 8 weeks
- FAS using imputed values

Trough RV/TLC	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	56.10 (0.54)	57.18 (0.54)
Comparison vs Sal+Flu		
Mean (SE)	-1.08 (0.39)	
95% Confidence interval	(-1.85, -0.31)	
p-value	0.0064	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 59.07 (0.53) based on 308 patients

Table 15.2.2.6: 2 Analysis of post-dose RV/TLC [%] after 8 weeks
- FAS using imputed values

Post-dose RV/TLC	Tio+Sal	Sal+Flu
Number of patients	309	309
After 8 weeks		
Mean (SE)	52.79 (0.54)	55.02 (0.54)
Comparison vs Sal+Flu		
Mean (SE)	-2.23 (0.39)	
95% Confidence interval	(-2.99, -1.47)	
p-value	<.0001	

ANOVA with fixed terms for sequence, treatment, and period and random term for subject within sequence
Baseline Mean (SE) is 59.07 (0.53) based on 308 patients