Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Title of trial:	A randomised, double-blind, crossover efficacy and safety comparison of Tiotropium/Salmeterol (7.5 µg/25 µg) Inhalation Powder in the morning (PE Capsule via tiotropium/salmeterol HandiHaler®), Tiotropium (18 µg) Inhalation Powder in the morning (gelatine capsule via Spiriva® HandiHaler®), Salmeterol (50 µg) Multi-Dose Powder Inhaler in the morning and evening and the free combination Tiotropium (18 µg) Inhalation Powder in the morning (gelatine capsule via Spiriva® HandiHaler®) *plus* Salmeterol (50 µg) Multi-Dose Powder Inhaler in the morning and evening following chronic administration (6-week treatment periods) in patients with COPD
Coordinating Investigator:	[redacted]
Trial sites:	This trial was conducted in 12 sites in Germany.
Publication (reference):	Data of this study have not been published.
Clinical phase:	III
Objectives:	The primary objective of this trial was to establish superiority of the fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg Inhalation Powder taken in the morning in daytime lung function response (FEV_1 AUC_{0-12} and peak FEV_1) and non-inferiority in night-time lung function response (FEV_1 AUC_{12-24} and trough FEV_1) compared with the single agent therapies in their established dose regimens (Tiotropium 18 µg in the morning and Salmeterol 50 µg in the morning and 50 µg in the evening) after treatment periods of 6 weeks. The secondary objective was to compare the safety of the once-daily fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg Inhalation Powder with those of the single agent therapies in their established dose regimens administered as single drugs or as the free combination. In addition, the 24-h FEV_1 profile of the free combination (Tiotropium 18 µg in the morning plus Salmeterol 50 µg in the morning and 50 µg in the evening) was characterised and compared with the 24-h profiles obtained with the other treatments.

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Methodology:	This was a randomised, multi-centre, double-blind (triple-dummy), 4-way crossover design of 4 consecutive 6-week treatment periods without washout periods conducted over 30 weeks. Following an initial screening visit, patients entered a 2-week run-in period. Patients who successfully completed this phase were randomised into 4 double-blind treatment periods of 6 weeks duration. Patients were evaluated for an additional 4-week period after the final dose of study medication. At the completion of each 6-week randomised treatment period, pulmonary function testing was conducted pre-dose and for 24 h following the morning dose of randomised treatment.
No. of subjects:	
planned:	entered: 120
actual:	enrolled: 203 All 4 treatment periods: entered: 147; treated: 146; completed: 123; analysed (for primary endpoint): 135 Fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg in the morning: entered: 147; treated: 132; completed: 129; analysed (for primary endpoint): 127 Tiotropium 18 µg in the morning: entered: 147; treated: 135; completed: 127; analysed (for primary endpoint): 128 Salmeterol 50 µg in the morning and 50 µg in the evening: entered: 147; treated: 137; completed: 128; analysed (for primary endpoint): 125 Free combination Tiotropium 18 µg morning plus Salmeterol 50 µg in the morning and 50 µg in the evening: entered: 147; treated: 132; completed: 129; analysed (for primary endpoint): 127
Diagnosis and main criteria for inclusion:	Patients with chronic obstructive pulmonary disease (COPD) of either sex, aged ≥40 years with a post-bronchodilator forced expiratory volume in 1 second (FEV_1) <80% of predicted normal and a post-bronchodilator FEV_1 <70% of post-bronchodilator forced vital capacity (FVC), a smoking history ≥10 pack-years, no history of asthma, and an eosinophil count <600/mm^3 were eligible for this study.

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Test product:	Tiotropium/Salmeterol Inhalation Powder, hard polyethylene capsules
dose:	7.5 µg/25 µg in the morning
mode of admin.:	Oral inhalation via the blue HandiHaler®
batch no.:	Verum: B072000141, B072000316
	Placebo: B072000118, B082000054
Reference therapy 1:	Tiotropium Inhalation Powder, hard gelatine capsules (Spiriva®)
dose:	18 µg in the morning
mode of admin.:	Oral inhalation via the grey Spiriva® HandiHaler®
batch no.:	Verum: 707429, B082000124
	Placebo: 707613
Reference therapy 2:	Salmeterol Multi-dose Powder Inhaler (Serevent® Diskus®)
dose:	50 µg in the morning and 50 µg in the evening
mode of admin.:	Oral inhalation from the Multi-dose Powder Inhaler (Serevent® Diskus®)
batch no.:	Verum: B072000252, R313320, R347976, R358405
	Placebo: B072000136, B072000213, B072000301, B082000090, B082000097, B082000112, B082000135, B0820001407, B092000019, B092000191
Reference therapy 3:	Tiotropium Inhalation Powder, hard gelatine capsules (Spiriva®) plus Salmeterol Multi-dose Powder Inhaler (Serevent® Diskus®)
dose:	Tiotropium 18 µg in the morning plus Salmeterol 50 µg in the morning and 50 µg in the evening
mode of admin.:	Oral inhalation via the grey Spiriva® HandiHaler® plus oral inhalation from the Multi-dose Powder Inhaler (Serevent® Diskus®)
batch no.:	See reference therapies 1 and 2
Duration of treatment:	Four 6-week treatment periods for a total treatment time of 24 weeks
Criteria for evaluation:	

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Efficacy:

The primary efficacy variable was FEV_1. The 4 co-primary endpoints were responses in:

- area under the curve for FEV_1 in the daytime (FEV_1 AUC_{0-12}),
- peak FEV_1,
- area under the curve for FEV_1 in the night-time (FEV_1 AUC_{12-24}), and
- trough FEV_1

measured at the end of each 6-week treatment period.

The secondary endpoints were responses in:

- FEV_1 AUC_{0-24},
- FVC AUC_{0-12}, peak FVC, FVC AUC_{12-24}, trough FVC, FVC AUC_{0-24},
- peak expiratory flow (PEF) AUC_{0-12}, peak PEF, PEF AUC_{12-24}, trough PEF, PEF AUC_{0-24}, and
- individual FEV_1, FVC, and PEF over a 24-h observation period

measured at the end of each 6-week treatment period and responses in

- morning and evening PEF and FEV_1 recorded by the patients at home,
- number of days with rescue medication use and number of puffs of rescue medication (daytime, night-time, and 24 h), and
- number of awakenings due to shortness of breath (SOB), number of days with night-time awakenings, number of days with night-time awakenings due to SOB, and average SOB score at night

measured in the days following the first 3 weeks of each 6-week treatment period.

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Safety:	Adverse events were recorded throughout the study. Vital signs (blood pressure and pulse rate) were recorded on pulmonary function test days. Marked changes in vital signs were defined for the project as follows: • increase in systolic blood pressure of ≥25 mm Hg above baseline, • decrease in systolic blood pressure below 100 mmHg if not at that level at baseline and a decrease of >10 mmHg below baseline, • increase in diastolic blood pressure above 90 mmHg and an increase of >10 mmHg above baseline, • decrease in diastolic blood pressure below 60 mmHg if not at that level at baseline and a decrease of >10 mmHg below baseline, • increase in pulse above 100 bpm if not at that level at baseline and an increase in pulse of >10 bpm above baseline, and • decrease in pulse below 60 bpm if not at that level at baseline and a decrease of >10 bpm below baseline.
Statistical methods:	Lung function responses after 6 weeks treatment with Tiotropium/Salmeterol Inhalation Powder 7.5 µg/25 µg in the morning were compared with responses after 6 weeks treatment with the single agent therapies in their established dose regimens (Tiotropium 18 µg in the morning and Salmeterol 50 µg in the morning and 50 µg in the evening) using the testing sequence shown below based on adjusted means from ANOVA. Fixed sequence testing was used to control type I error rate. Each step was considered confirmatory providing all previous steps were successful. The non-inferiority margin for FEV_1 endpoints was defined as δ=0.050 L. 1. superiority for FEV_1 AUC_{0-12}: Tiotropium/Salmeterol 7.5 µg/25 µg vs Salmeterol 50 µg 2. superiority for FEV_1 AUC_{0-12}: Tiotropium/Salmeterol 7.5 µg/25 µg vs Tiotropium 18 µg 3. superiority for peak FEV_1: Tiotropium/Salmeterol 7.5 µg/25 µg vs Salmeterol 50 µg 4. superiority for peak FEV_1:

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Tiotropium/Salmeterol 7.5 µg/25 µg vs Tiotropium 18 µg

5. non-inferiority for FEV_1 AUC_{12-24}:
   Tiotropium/Salmeterol 7.5 µg/25 µg vs Salmeterol 50 µg
6. non-inferiority for FEV_1 AUC_{12-24}:
   Tiotropium/Salmeterol 7.5 µg/25 µg vs Tiotropium 18 µg
7. non-inferiority for trough FEV_1:
   Tiotropium/Salmeterol 7.5 µg/25 µg vs Salmeterol 50 µg
8. non-inferiority for trough FEV_1:
   Tiotropium/Salmeterol 7.5 µg/25 µg vs Tiotropium 18 µg

Analysis of variance with terms for centre, patient within centre, treatment, and period was performed for all continuous efficacy endpoints. Adjusted means, standard error (SE), and treatment contrasts were presented with 95% confidence intervals. The α-level was set to 0.025 (one-sided).

The number of patients with adverse events during the treatment periods was summarised. Vital signs (blood pressure and pulse rate) for each treatment were presented using descriptive statistics.

SUMMARY – CONCLUSIONS:

Efficacy results:

In this study, 203 patients were enrolled, 147 were randomised, and 146 were treated. Twenty-three patients discontinued treatment prematurely – 3 patients each (2.3%) in the fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg and free combination Tiotropium 18 µg plus Salmeterol 50 µg groups, 8 patients (5.9%) in the Tiotropium 18 µg group, and 9 patients (6.6%) in the Salmeterol 50 µg group. The most frequent reason for discontinuation was worsening of the study disease (11 patients, 7.5%).

The mean age was 61.4 years, 63.7% of the patients were male, and 97.9% of patients were white. The mean duration of COPD was 9.7 years, the mean smoking history was 43.07 pack-years, and 53.4% of patients were current smokers. Before bronchodilation, the mean FEV_1 was 1.36 L (46.1% of predicted normal) and the mean FEV_1/FVC ratio was 48.8%. Forty-five minutes

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Efficacy results (continued):

after 4 puffs of salbutamol 100 µg, the mean post bronchodilator FEV_1 was 1.54 L (52.3% of predicted normal) and the mean FEV_1/FVC ratio was 50.6%. The mean reversibility was 0.18 L or 14.7% above the pre-bronchodilator FEV_1. Inhaled corticosteroids were used by 51.4% of the patients at randomisation.

Primary analysis

After 6 weeks treatment in patients with COPD, the fixed dose combination Tiotropium/Salmeterol 7.5 µg/25 µg in the morning was superior to both single agent therapies in their established dose regimens (Tiotropium 18 µg in the morning and Salmeterol 50 µg in the morning and 50 µg in the evening) in daytime lung function response (FEV_1 AUC_{0-12} and peak FEV_1) and was non-inferior in night-time lung function response (FEV_1 AUC_{12-24} and trough FEV_1). Adjusted mean (SE) treatment difference in FEV_1 responses (including the secondary endpoint FEV_1 AUC_{0-24}) in favour of the fixed-dose combination compared with both single agent therapies and p-values for superiority (daytime and 24 h) non-inferiority (night-time) are shown in the table below.

Treatment differences in co-primary endpoints

	Tiotropium/Salmeterol 7.5 µg/25 µg compared with	
	Tiotropium 18 µg	Salmeterol 50 µg
FEV_1 response (L)		
AUC_{0-12}	0.070 (0.014) p<0.0001*	0.130 (0.014) p<0.0001*
Peak	0.066 (0.016) p<0.0001*	0.134 (0.016) p<0.0001*
AUC_{12-24}	0.064 (0.015) p<0.0001#	0.064 (0.015) p<0.0001#
Trough	-0.028 (0.031) p<0.0001#	0.058 (0.017) p<0.0001#
AUC_{0-24}§	0.067 (0.013) p<0.0001*	0.097 (0.014) p<0.0001*

*p-value for superiority
#p-value for non-inferiority
§FEV_1 AUC_{0-24} is a secondary endpoint

Secondary analysis

Treatment differences in FEV_1 AUC_{0-24} response in favour of Tiotropium/Salmeterol 7.5 µg/25 µg were statistically significant (p<0.05) compared with both single agent therapies as shown in the table above.

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Efficacy results (continued):

Adjusted mean (SE) treatment differences in response in FVC and PEF (at the end of each 6-week treatment period) as well as pre-dose FEV_1 and PEF and night-time rescue medication use (averaged over the days following the first 3 weeks of each 6-week treatment period) for Tiotropium/Salmeterol 7.5 µg/25 µg compared with Tiotropium 18 µg and Salmeterol 50 µg and p values for superiority are shown in the table below.

In the daytime, treatment differences in FVC AUC_{0-12} response in favour of the fixed-dose combination were statistically significant compared with both single agent therapies, but improvements in peak FVC response were statistically significant only compared with Salmeterol 50 µg but not Tiotropium 18 µg. In the night-time, treatment differences in FVC AUC_{12-24} response in favour of the fixed-dose combination were statistically significant compared with both single agent therapies but treatment differences in trough FVC were not statistically significant. Over 24 h, treatment differences in FVC AUC_{0-24} response in favour of the fixed-dose combination were statistically significant compared with both single agent therapies.

In the daytime, treatment differences in both PEF AUC_{0-12} and peak PEF responses in favour of the fixed-dose combination were statistically significant compared with both single agent therapies. In the night-time, treatment differences in PEF AUC_{12-24} response in favour of the fixed-dose combination were statistically significant compared with both single agent therapies, but improvements in trough PEF response with the fixed-dose combination were statistically significant only compared with Salmeterol 50 µg but not Tiotropium 18 µg. Over 24 h, improvements in PEF AUC_{0-24} response with the fixed-dose combination were statistically significant compared with both single agent therapies.

Differences in FEV_1, FVC, and PEF responses in favour of Tiotropium/Salmeterol 7.5 µg/25 µg compared with both single agent therapies were statistically significant at most time points up to 24 h after inhalation.

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Efficacy results (continued):

Treatment differences in secondary endpoints

	Tiotropium/Salmeterol 7.5 µg/25 µg vs Tiotropium 18 µg	Tiotropium/Salmeterol 7.5 µg/25 µg vs Salmeterol 50 µg
FVC response (L)		
AUC_{0-12}	0.083 (0.025) p=0.0010	0.176 (0.025) p<0.0001
Peak	0.051 (0.030) p=0.0898	0.142 (0.030) p<0.0001
AUC_{12-24}	0.085 (0.027) p=0.0015	0.118 (0.027) p<0.0001
Trough	-0.028 (0.031) p=0.3652	0.042 (0.031) p=0.1816
AUC_{0-24}	0.084 (0.024) p=0.0005	0.147 (0.024) p<0.0001
PEF response (L/min)		
AUC_{0-12}	11.8 (2.5) p<0.0001	24.2 (2.5) p<0.0001
Peak	13.1 (3.0) p<0.0001	23.1 (3.0) p<0.0001
AUC_{12-24}	8.5 (2.5) p=0.0008	10.6 (2.5) p<0.0001
Trough	2.8 (3.2) p=0.3775	7.1 (3.2) p=0.0285
AUC_{0-24}	10.1 (2.3) p<0.0001	17.4 (2.3) p<0.0001
Pre-dose FEV_1 response (L)		
Morning	0.040 (0.016) p=0.0137	0.027 (0.016) p=0.0981
Evening	0.057 (0.018) p=0.0014	0.105 (0.018) p<0.0001
Pre-dose PEF response (L/min)		
Morning	5.7 (2.4) p=0.0182	6.3 (2.4) p=0.0091
Evening	11.0 (2.6) p<0.0001	23.3 (2.7) p<0.0001
Rescue use response (days)		
Daytime	-0.07 (0.02) p=0.0027	-0.02 (0.02) p=0.4587
Night-time	-0.09 (0.02) p=0.0002	-0.09 (0.03) p=0.0006
24 hours	-0.09 (0.02) p=0.0003	-0.07 (0.02) p=0.0042
Rescue use response (puffs)		
Daytime	-0.33 (0.11) p=0.0029	-0.36 (0.11) p=0.0012
Night-time	-0.17 (0.07) p=0.0115	-0.09 (0.07) p=0.1772
24 hours	-0.52 (0.16) p=0.0013	-0.47 (0.16) p=0.0040
Night-time awakenings and shortness of breath (SOB) response		
Awakenings† (no.)	0.00 (0.03) p=0.9980	0.02 (0.03) p=0.4618
Awakenings (days)	0.00 (0.01) p=0.9956	-0.01 (0.01) p=0.7100
Awakenings† (days)	-0.01 (001) p=0.4416	-0.01 (0.01) p=0.7058
Average SOB score‡	-0.02 (003) p=0.4206	0.00 (0.03) p=0.8723

† due to SOB ‡ 1=not at all; 2=a little bit; 3=somewhat; 4=quite a bit; 5=very much

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Efficacy results (continued):	The fixed dose combination Tiotropium/Salmeterol 7.5 µg/25 µg provided comparable daytime (0-12 h; -0.024 L, p<0.09) bronchodilator effects, but significantly less bronchodilation during the night-time (12-24 h; -0.057 L, p=0.0001) compared to the free combination Tiotropium 18 µg plus Salmeterol 50 µg, resulting in less bronchodilation in terms of FEV_1 AUC_{0-24} following treatment with the fixed dose combination Tiotropium/Salmeterol 7.5 µg/25 µg (-0.041 L, p=0.0029).
Safety results:	The safety evaluation was based on the 146 patients in the treated set. Median exposure to study medication in all 4 treatment groups was 42.0 days. There was no evidence for a treatment-dependent increase either in the frequency or the intensity of adverse events for the Tiotropium/Salmeterol 7.5 µg/ 25 µg group. During the four 6-week treatment periods, adverse events were reported in 30 patients (22.7%) during treatment with Tiotropium/Salmeterol 7.5 µg/25 µg, compared with 41 patients (30.4%) with Tiotropium 18 µg, 38 patients (27.7%) with Salmeterol 50 µg, and 31 patients (23.5%) with the free combination of Tiotropium 18 µg plus Salmeterol 50 µg. The most frequently reported adverse events overall were nasopharyngitis (27 patients, 18.5%) and COPD (18 patients, 12.3%). By system organ class, infections and infestations (50 patients, 34.2%) was reported in the highest frequency of patients overall. Severe adverse events were reported in 15 patients (10.3%). The frequency of patients with severe adverse events ranged from 2 patients (1.5%) during treatment with Tiotropium/Salmeterol 7.5 µg/25 µg to 7 patients (5.2%) during treatment with Tiotropium 18 µg. The investigator considered 9 adverse events in 5 patients possibly related to the study medications – 2 adverse events in 2 patients (1.5%) during treatment with Tiotropium 18 µg, 3 adverse events in 2 patients (1.5%) during treatment with Salmeterol 50 µg, 4 adverse events in 2 patients (1.5%) during treatment with the free combination Tiotropium 18 µg plus Salmeterol 50 µg, and no adverse events during treatment with Tiotropium/Salmeterol 7.5 µg/25 µg. Sixteen patients (11.0%) discontinued the study medication due to an adverse event. The frequency of patients with discontinuation due to an adverse event

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Safety results (continued):	during treatment with the fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg (2 patients, 1.5%) was similar to that of the free combination Tiotropium 18 µg plus Salmeterol 50 µg (1 patient, 0.8%) and lower than those of the single agent therapies (Tiotropium 18 µg: 7 patients, 5.2%; Salmeterol 50 µg: 6 patients, 4.4%). The adverse events most frequently leading to discontinuation of study medication was COPD exacerbation (7 patients, 4.8%). Serious adverse events were reported in 13 patients (8.9%). One patient (0.7%) experienced fatal serious adverse events (intracranial aneurysm and subarachnoid haemorrhage) during treatment with Tiotropium 18 µg. One patient each did not recover from congestive cardiomyopathy, prostate cancer, hepatic neoplasm malignant, and colon cancer; all other patients recovered from the serious adverse events; all other patients recovered from the serious adverse events. The frequency of patients with serious adverse events during treatment with the fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg (1 patient, 0.8%) was similar to that of the free combination Tiotropium 18 µg plus Salmeterol 50 µg (2 patients, 1.5%) and lower than those of the single agent therapies (Tiotropium 18 µg: 7 patients, 5.2%; Salmeterol 50 µg: 4 patients, 2.9%). The investigator did not consider any of the serious adverse events possibly related to the study medications, whereas one serious adverse event (pneumonia) with Tiotropium 18 µg was reported to be related to study medication by the investigator and led to unblinding and reporting as a suspected unexpected serious adverse reaction. The most frequently reported serious adverse events were COPD exacerbations (4 patients, 2.7%) and pneumonia (3 patients, 2.1%). Comparisons of vital signs at thedid not reveal any obvious clinically significant drug-related changes.

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Conclusions:	After 6 weeks treatment in patients with COPD, the fixed-dose combination Tiotropium/Salmeterol 7.5 µg/25 µg in the morning was superior in daytime lung function response to both Tiotropium 18 µg in the morning and Salmeterol 50 µg in the morning and 50 µg in the evening. The fixed-dose combination was non-inferior in night-time lung function response to both single agent therapies. Analyses of the secondary efficacy endpoints were consistent with the primary endpoints. There was no evidence for a treatment-dependent increase either in frequency or in intensity of adverse events. All treatments were safe and well tolerated in patients with COPD.