Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 1 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision** : Not applicable

Title of trial:	A randomised, open-label, 4-way crossover study to characterize the pharmacokinetics, safety and efficacy of FDC Tiotropium/Salmeterol, Tiotropium, Salmeterol and a free combination of Tiotropium *plus* Salmeterol following 4-week treatment periods in patients with COPD.
Principal/Coordinating Investigator:	[redacted]
Trial sites:	Atrium medical centre, Heerlen, The Netherlands; Private Practice, Genk, Belgium; Private Practice, Hasselt, Belgium.
Publication (reference):	Not applicable
Clinical phase:	III
Objectives:	The primary objective was to characterize the pharmacokinetics (*i.e.* systemic exposure to tiotropium and salmeterol) of the once-daily FDC Tiotropium/salmeterol (7.5 µg/25 µg) inhalation powder in comparison with the free combination of tiotropium (18 µg) inhalation powder once-daily *plus* salmeterol (50 µg) inhalation powder twice daily in separate devices as well as the single-agent therapies tiotropium (18 µg) inhalation powder once-daily or salmeterol (50 µg) inhalation powder twice daily in their marketed formulations and approved dose regimens in patients with COPD. The secondary objectives were to compare the safety, tolerability (adverse events, 12-lead ECG recordings) and efficacy (FEV_1, FVC) of tiotropium and salmeterol when administered as FDC Tiotropium/salmeterol Inhalation Powder, single-agent therapy or as free combination of the single agents in separate devices.
Methodology:	Open-label, randomised, 4-way crossover of 4-week treatment periods without washout periods.
No. of subjects:	
planned:	40 completed patients

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Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 2 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

actual:	Enrolled: 58 / entered: 50 / completed: 47 Treatment A (FDC Tiotropium/salmeterol) analysed for primary endpoint: 47 Treatment B (tiotropium) analysed for primary endpoint: 45 Treatment C (salmeterol) analysed for primary endpoint: 46 Treatment D (tiotropium + salmeterol) analysed for primary endpoint: 47
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥ 40 years with a diagnosis of COPD [postbronchodilator FEV_1 < 80% predicted (ECSC criteria) and post-bronchodilator FEV_1/FVC < 70%]; smoking history ≥ 10 pack-years; no history of asthma; eosinophil count < 600/mm3.
Test product:	Tiotropium/salmeterol Inhalation Powder, Hard Polyethylene Capsules
dose:	7.5 µg/25 µg once-daily
mode of admin.:	Oral inhalation via the Tiotropium/salmeterol HandiHaler®
batch no.:	B072000141
Reference therapy 1:	Tiotropium Inhalation Powder, hard gelatine capsule (Spiriva®)
dose:	18 µg once-daily
mode of admin.:	Oral inhalation via the Spiriva® HandiHaler®
batch no.:	707429 / 804675 (re-supply)
Reference therapy 2:	Salmeterol Multi-Dose Powder Inhaler (MDPI, Serevent® Diskus®)
dose:	50 µg twice daily
mode of admin.:	Oral inhalation from the Diskus®
batch no.:	R327947 / R347976 (re-supply)
Reference therapy 3:	Tiotropium Inhalation Powder (hard gelatine capsule) *plus* Salmeterol Multi-Dose Powder Inhaler (MDPI)
dose:	18 µg once-daily *plus* 50 µg twice daily
mode of admin.:	Oral inhalation via Spiriva® HandiHaler® *plus* oral inhalation from the MDPI (Diskus®)

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 3 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

batch no.:	707429 + R327947 / 804675 + R347976 (re-supply)
Duration of treatment:	Four 4-week treatment periods; total treatment period: 16 weeks
Criteria for evaluation:	
Pharmacokinetics:	Co-primary endpoints: C_{max}, AUC_{0-8} and; C_{max}, AUC_{0-8} and Ae_{0-8} (tiotropium). Secondary endpoints: AUC_{t1-t2} , t_{max}, λ_z, $t_{½}$, MRT_{ih}, CL/F, V_z/F, Ae_{t1-t2}, fe_{t1-t2}, $CL_{R,t1-t2}$
Efficacy / clinical pharmacology:	FEV_1 AUC_{0-8h}, peak and trough FEV_1, FVC AUC_{0-8h}, peak and trough FVC
Safety:	12-lead ECG, blood pressure, adverse events, laboratory tests and physical examination
Statistical methods:	Confidence intervals. Analysis of variance with terms for centre, patients within centre, treatment and period. Descriptive statistics.
SUMMARY – CONCLUSIONS:	

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Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 4 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

Efficacy / clinical pharmacology results:

Pharmacokinetics

With respect to tiotropium, administration of once-daily FDC Tiotropium/salmeterol resulted in statistically significantly higher $C_{max,ss}$ values compared to the reference treatments: 47.06 % higher compared to once-daily tiotropium and 40.49 % higher compared to the free combination of once-daily tiotropium *plus* salmeterol twice daily. There was no statistically significant difference in the $AUC_{0-8,ss}$ values of the FDC Tiotropium/salmeterol and tiotropium (gMean ratio of 111.77). However, the $AUC_{0-8,ss}$ values for the FDC Tiotropium/salmeterol were slightly but significantly higher than that of free combination of tiotropium *plus* salmeterol with a gMean ratio of 117.64. The $Ae_{0-8,ss}$ values achieved with FDC Tiotropium/salmeterol were statistically significantly higher than those of the 2 reference treatments.

With respect to salmeterol, administration of once-daily FDC Tiotropium/salmeterol resulted in statistically significantly higher $C_{max,ss}$ values compared to the reference treatments: 33.04 % higher compared to salmeterol twice daily and 24.15 % higher compared to the free combination of once-daily tiotropium *plus* salmeterol twice daily, and statistically significantly lower $AUC_{0-8,ss}$ values compared to the reference treatments (59.64% compared to salmeterol and 57.74% compared to the free combination of tiotropium *plus* salmeterol).

Pharmacodynamics

Once-daily FDC Tiotropium/salmeterol was superior to tiotropium or salmeterol alone in FEV_1 AUC_{0-8h} [by 0.099 mL and 0.160 mL ($p<0.0001$), respectively], trough [by 0.056 mL and 0.075 mL ($p<0.02$), respectively] and peak FEV_1 [by 0.101 mL and 0.167 mL ($p<0.0001$), respectively].

With respect to FVC AUC_{0-8h} [0.116 mL and 0.261 mL ($p<0.001$), respectively] and peak FVC [0.103 mL and 0.267 mL ($p<0.006$), respectively] the results paralleled the results found for FEV_1; for trough FVC a statistically significant difference was only observed between the FDC Tiotropium/salmeterol and salmeterol mono-therapy [0.182 mL ($p<0.0001$)] and no difference versus single-agent therapy with tiotropium [0.065 mL ($p=0.14$)].

No relevant and statistically significant differences were found between once-daily FDC Tiotropium/salmeterol and the free combination of tiotropium *plus*.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 5 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

Efficacy / clinical pharmacology results (cont.):

salmeterol in terms of the FEV_1 (<0.02 L, p>0.60) and FVC-derived endpoints (<0.04 L, p>0.45).

Safety results:

Based on the observations made in the present study, therapy with once-daily FDC Tiotropium/salmeterol during a 4-week treatment period was shown to be safe and well tolerated compared to 4-week treatments with each of the single-agents or with free combination therapy of tiotropium *plus* salmeterol.

There was no evidence for a treatment dependent increase either in frequency or in intensity of adverse events (AEs). A comparable number of patients reported adverse events during the four 4-week periods, ranging from 10 (20.8%) and 12 patients (25.0%) during the tiotropium and FDC Tiotropium/salmeterol periods, respectively, to 18 patients (37.5%) during the salmeterol as well as during the free combination period of tiotropium *plus* salmeterol. The most frequently reported adverse events, occurring in 4% or more of the patients in at least one of the treatment periods, were nasopharyngitis [ranging from 2 (tiotropium) to 8 patients (free combination tiotropium *plus* salmeterol], dizziness (only in salmeterol period in 2 patients), dyspnoea [ranging from 1 (1 patient each in FDC Tiotropium/salmeterol and tiotropium periods) to 4 patients (salmeterol period)], COPD exacerbation [ranging from 1 (free combination of tiotropium *plus* salmeterol) to 3 patients (salmeterol period)] , cough [ranging from no report in the tiotropium period to 2 patients each during FDC Tiotropium/salmeterol and free combination period of tiotropium *plus* salmeterol)], dry throat [ranging from no report during tiotropium and salmeterol periods to 2 patients during free combination period of tiotropium *plus* salmeterol)] , epistaxis (only occurring in salmeterol period in 2 patients), and diarrhoea (only in free combination period of tiotropium *plus* salmeterol in 2 patients).

For 2 patients AEs were classified by the investigator as related to the study medication; for 1 patient during the tiotropium period (dry mouth; patient continued in the study) and for 1 patient in the salmeterol period (dyspnoea,

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Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 6 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

Safety results (cont.):

nausea; patient discontinued the study due to these adverse events). In addition, 1 patient discontinued the study during the tiotropium period due to an exacerbation of COPD.

Four patients suffered from a non-fatal serious adverse event (SAE) during one of the 4-week treatment periods, which were considered not related to the study drug. Two SAEs occurred during treatment with the FDC Tiotropium/salmeterol (lateral cervical cyst, metastatic non-small cell lung carcinoma) and two SAEs occurred during the tiotropium period (chest pain which was considered not of cardiac origin, claudicatio intermittens).

The safety parameters blood pressure and heart rate did not reveal any relevant treatment differences; analysis of the standard laboratory tests did not reveal any relevant findings.

In terms of QTcF small differences were observed between the three salmeterol-containing treatments and tiotropium as single-agent therapy (which was used in the analysis as a surrogate placebo). The mean difference from tiotropium in the first hour post-dosing ranged from 1.27 ms (upper bound of two-sided 90% CI: 4.71ms) for the free combination of tiotropium *plus* salmeterol to 3.04 ms (upper bound of two-sided 90% CI: 6.45 ms) for the FDC Tiotropium/salmeterol, while on treatment with salmeterol a mean difference of 2.45 ms (upper bound of two-sided 90% CI: 5.89 ms) was observed.

Compared to tiotropium, the maximum difference in QTcF when on FDC Tiotropium/salmeterol was seen 10 min post-inhalation (4.30 ms with an upper bound of the two-sided 90% CI of 7.49 ms), which was slightly higher compared to the other two salmeterol-containing treatments. For single-agent therapy with salmeterol the maximum difference in QTcF of 3.92 ms was found 40 min post-inhalation (with upper bound of the two-sided 90% CI of 7.13 ms), while for the free combination of tiotropium *plus* salmeterol the maximum difference was seen 1 h post-inhalation (2.49 ms, upper bound of the two-sided 90% CI: 5.70 ms). Compared to tiotropium, the mean increases observed in QTcF are below 5 ms for all three salmeterol-containing treatments with the upper bound of the two-sided 90% CI below 10 ms, meaning that these increases are below the threshold level of regulatory concern as described in the ICH E14 guideline.

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Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 7 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

Conclusions:

Pharmacokinetics

Administration of once-daily FDC Tiotropium/salmeterol resulted in a statistically significantly higher tiotropium $C_{max,ss}$ compared to the reference treatments (47.06 % higher compared to tiotropium and 40.49 % higher compared to the free combination of tiotropium *plus* salmeterol). There was no statistically significant difference in the $AUC_{0-8,ss}$ values of the FDC Tiotropium/salmeterol and tiotropium (gMean ratio of 111.77). However, the $AUC_{0-8,ss}$ values for the FDC Tiotropium/salmeterol were slightly but significantly higher than that of free combination of tiotropium *plus* salmeterol with a gMean ratio of 117.64. Further, the $Ae_{0-8,ss}$ values achieved with FDC Tiotropium/salmeterol were statistically significantly higher than those of the 2 reference treatments.

Administration of FDC Tiotropium/salmeterol resulted in a statistically significantly higher salmeterol $C_{max,ss}$ compared to the reference treatments (33.04 % higher compared to salmeterol and 24.15 % higher compared to the free combination of tiotropium *plus* salmeterol) and statistically significantly lower salmeterol $AUC_{0-8,ss}$ values compared to the reference treatments (59.64% compared to salmeteroland 57.74% compared to tiotropium *plus* salmeterol).

Although higher (during the approximate first 2 h post-dosing), the plasma concentration time profile of tiotropium from the FDC Tiotropium/salmeterol formulation was comparable and parallel to the two reference formulations during the terminal phase. The plasma profile of salmeterol in the FDC Tiotropium/salmeterol was very different from that of the two reference formulations being characterized by a very rapid t_{max} of approximately 5 mins (in comparison to the t_{max} at approximately 1 h post-dosing for the reference formulations), followed by a lower plasma concentration during the terminal phase. However, the plasma profile of the test formulation was parallel to that of the reference formulations during the terminal phase. Further, the plasma profile of the free combination (tiotropium *plus* salmeterol) was comparable to that of the reference formulations, i.e., the single-agents tiotropium and salmeterol. Hence, tiotropium and salmeterol were not found to alter each others pharmacokinetics on co-administration in patients with COPD.

Name of company: Boehringer Ingelheim		**Tabulated Trial Report**	Boehringer Ingelheim
Name of finished product:		**EudraCT No.:** 2007-000207-15	
Name of active ingredient: tiotropium bromide / salmeterol xinafoate		**Page:** 8 of 8	**Synopsis No.:**
Module:		**Volume:**	
Report date: 11 JUN 2010	**Trial No. / U No.:** 1184.24 / U10-1933-01	**Date of trial:** 13 MAY 2008 – 30 JUNE 2009	**Date of revision :** Not applicable

Conclusions (cont.):

Pharmacodynamics

Compared to single-agent therapy with once-daily tiotropium or salmeterol twice daily, the once-daily FDC Tiotropium/salmeterol provided significantly more bronchodilation in terms of FEV_1 AUC_{0-8h}, trough and peak FEV_1. With respect to FVC AUC_{0-8h} and peak FVC the results paralleled the results found for FEV_1; for trough FVC a statistically significant difference was only observed between the FDC Tiotropium/salmeterol and salmeterol twice daily. No relevant and statistically significantly differences were found between FDC Tiotropium/salmeterol and the free combination of tiotropium *plus* salmeterol in terms of the FEV_1 and FVC-derived endpoints.

The overall safety profile as observed in the present short-term study indicates that maintenance therapy of tiotropium *plus* salmeterol as fixed-dose combination or as free combination of the single-agents is safe and well tolerated in patients with COPD.

Overall conclusions

The FDC Tiotropium/salmeterol formulation resulted in a statistically significantly higher tiotropium peak and total exposure compared to tiotropium and the free combination of tiotropium *plus* salmeterol. Further, the FDC Tiotropium/salmeterol formulation resulted in a statistically significantly higher salmeterol peak exposure but lower total exposure compared to salmeterol and the free combination of tiotropium *plus* salmeterol. The two chemical entities, i.e., tiotropium and salmeterol, were not found to alter each others pharmacokinetics on co-administration as free combination of the single agents in patients with COPD.

Maintenance combination therapy of tiotropium *plus* salmeterol was found to be safe and effective for the treatment of COPD patients with moderate-to-very severe airflow obstruction.