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: Not applicable		**EudraCT No.:** 2007-005134-36 (1184.14) 2007-005107-17 (1184.15)	**Synopsis No.:**
Name of active ingredient: Tiotropium bromide + salmeterol xinafoate		**Page:** 1 of 8	
Module:		**Volume:**	
Report date: 04 FEB 2010	**Trial No. / U No.:** 1184.14/1184.15 U10-1141-01	**Date of trials:** 15 APR 2008 – 21 NOV 2008	**Date of revision** (if applicable): Not applicable

Title of trial:	A 24-week (+ 24 week extension) placebo-controlled (only 1st 12-week period), double–blind, parallel-group, efficacy and safety comparison of FDC Tiotropium/Salmeterol, Tiotropium, Salmeterol and FDC Tiotropium/Salmeterol *plus* Salmeterol in COPD patients
Principal/Coordinating Investigators:	[redacted] Heerlen, The Netherlands (1184.14) and [redacted] Royal University Hospital, Saskatoon, Saskatchewan, Canada (1184.15).
Trial sites:	Multi-centre, multinational study.
Publication (reference):	No.
Clinical phase:	III
Objectives:	The primary objectives of these long-term efficacy and safety studies were to assess the bronchodilator efficacy as determined by FEV_1, the effect on dyspnoea as determined by the Mahler BDI and TDI, the effect on the health status as determined by the SGRQ and the effect on COPD exacerbations after administration of FDC Tiotropium/salmeterol, tiotropium, salmeterol and FDC Tiotropium/salmeterol *plus* salmeterol. The secondary objective was to compare the safety of once-daily FDC tiotropium/salmeterol (7.5 µg/25 µg) inhalation powder versus single-agent therapy of its components and versus combination therapy of FDC tiotropium/salmeterol (7.5 µg/25 µg) (morning) *plus* salmeterol (25 µg) (evening).
Methodology:	24-week (+ 24-week extension +4 week follow-up), multinational, randomised, double-blind, placebo- (only 1st 12-week period) and active-controlled, parallel-group study. Clinical visits were scheduled for 4, 12, 18, 24, 36 and 48 weeks following randomisation.
No. of subjects:	
planned:	entered: 3000 patients per study

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actual:	Enrolled (screened): 978 (133 sites have enrolled patients) Entered (randomised): 427 (220 patients in 1184.14 and 207 patients in 1184.15) 1) Treatment FDC tiotropium/salmeterol 7.5 µg/25 µg (QD): entered/treated/analysed (for primary endpoint): 81 2) Treatment tiotropium 18 µg (QD): entered/treated/analysed (for primary endpoint): 83 3) Treatment salmeterol 25 µg (BID): entered/treated/analysed (for primary endpoint): 91 4) Treatment FDC tiotropium/salmeterol 7.5 µg/25 µg (QD) *plus* salmeterol 25 µg (QD): entered/treated/analysed (for primary endpoint): 85 5) Treatment tiotropium: placebo (BID) entered/treated/analysed (for primary endpoint): 87
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged $\geq$ 40 years with a diagnosis of COPD [post-bronchodilator FEV1 < 80% of predicted normal (ECSC criteria) and post-bronchodilator FEV_1 < 70% of post-bronchodilator FVC]; smoking history ≥ 10 pack-years; no history of asthma and eosinophil count < 600/mm^3
Test product:	Tiotropium/salmeterol inhalation powder, hard polyethylene (PE) capsule
dose:	7.5 µg/25 µg once-daily (morning)
mode of admin.:	Oral inhalation via the tiotropium/salmeterol HandiHaler®
batch no.:	B072000141
Reference therapy:	Tiotropium inhalation powder, hard gelatine capsule (Spiriva®)
dose:	18 µg once-daily (morning)
mode of admin.:	Oral inhalation via Spiriva® HandiHaler®
batch no.:	707429

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Reference therapy:	Salmeterol inhalation powder, hard PE capsule
dose:	25 µg twice-daily (morning and evening)
mode of admin.:	Oral inhalation via the tiotropium/salmeterol HandiHaler®
batch no.:	B072000085
Reference therapy:	Tiotropium/salmeterol inhalation powder, hard polyethylene capsule, *plus* salmeterol inhalation powder, hard PE capsule
dose:	7.5 µg/25 µg once-daily (morning) *plus* 25 µg once-daily (evening)
mode of admin.:	Oral inhalation via the tiotropium/salmeterol HandiHaler®
batch no.:	B072000141/B072000085
Reference therapy:	Placebo inhalation powder, hard PE capsule/hard gelatine capsule
dose:	NA
mode of admin.:	Oral inhalation of PE capsule via the tiotropium/salmeterol HandiHaler® and gelatine capsule via the Spiriva® HandiHaler®
batch no.:	B072000118/707613
Duration of treatment:	24 weeks + 24-week extension (+ 4 week follow-up); total treatment period: 48 weeks

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Criteria for evaluation:

Following a critical re-evaluation of new regulatory authority information Boehringer Ingelheim decided to discontinue the two ongoing sister studies 1184.14 and 1184.15. This decision was not based on any safety or efficacy decision. It became clear after initiation of the studies that the required justification and the acceptance criteria for registering a once-a-day posology for a bronchodilator or its combination product had been tightened. From this point of view the ongoing studies 1184.14 and 1184.15 would not lead to a successful profiling and registration of the FDC tiotropium/salmeterol as a once-a-day product. In consequence, the ongoing studies had become futile.

On 15 April 2008 the first patient was enrolled. The decision to terminate the 48-week trials 1184.14 and 1184.15 was made on 11 September 2008, i.e. relatively short after initiation of the trials, meaning that not only a limited number of patients had been randomised to study drug but also that only a few patients had completed the first 12-week treatment period and, therefore, a primary endpoint analysis as originally defined (refer to Section 9.7 of this report) had become futile. On 21 November 2008 the last patient terminated the study.

For this reason it was decided to prepare an abbreviated report based on combined data of trials 1184.14 and 1184.15. The analyses on available data were changed and are detailed in Section 9.8 of this report.

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Efficacy / clinical pharmacology:	Visit 2 (randomisation visit - first dose effect) FEV_1 AUC (0-8h), peak FEV_1, FVC AUC (0-8h), peak FVC, PEF AUC (0-8h), peak PEF, and individual FEV_1, FVC and PEF measurements at each time point. Visit 3 (effects after 4-week treatment period) FEV_1 AUC (0-8h), trough and peak FEV_1, FVC AUC (0-8h) , trough and peak FVC, PEF AUC (0-8h), trough and peak PEF, and individual FEV_1, FVC and PEF measurements at each time point, TDI focal score, SGRQ. Diary-based endpoints (AM2+) were: Weekly mean morning pre-dose and evening pre-dose PEF and FEV_1; Weekly mean number of puffs of as-needed salbutamol/albuterol per day (i.e. 24-h period), daytime (i.e. from morning dose till evening dose of study medication) and night-time (i.e. from evening dose till morning dose); Weekly mean number of COPD-related night-time awakenings. The limited data collected after the 12-week treatment period (Visit 4) were listed.
Safety:	Adverse events, ECG recording (with additional ECGs in subgroup), Holter recordings (subgroup), vital signs (pulse rate and blood pressure), routine blood chemistry, haematology and urinalysis
Statistical methods:	Analysis of covariance with terms for centre, treatment and baseline as covariates; logistic regression, life table methods, methods for count data, descriptive statistics.
SUMMARY – CONCLUSIONS:	

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Efficacy / clinical pharmacology results:

Due to limited data only adjusted mean (SE) trough FEV_1, peak FEV_1 and FEV_1 AUC (0-8h) response (L) after 4-week treatment period (Visit3) is presented in the synopsis:

	T+S_PE	Tio18Gel	Salm25PE	T+S_PE/S25PE	Placebo
Trough	0.117 (0.032)	0.075 (0.030)	0.101 (0.030)	0.124 (0.030)	0.000 (0.030)
Peak (0-3h)	0.353 (0.038)	0.267 (0.037)	0.251 (0.037)	0.331 (0.036)	0.111 (0.036)
AUC (0-8h)	0.277 (0.034)	0.185 (0.033)	0.167 (0.033)	0.248 (0.033)	0.027 (0.033)

Adjusted mean (SE) differences and 95% confidence intervals of trough FEV_1, peak FEV_1 and FEV_1 AUC (0-8h) (L) after 4-week treatment period (Visit 3):

	Difference (SE)	95% Confidence Interval	P−value (non−inf.)	P−value (sup.)
		Trough FEV_1		
T+S_PE −				
Tio18GEL	0.041 (0.038)	(-0.033, 0.116)	0.0169	0.2764
Salm25PE	0.016 (0.039)	(-0.060, 0.092)	0.0900	0.6840
T+S_PE/S25PE	-0.008 (0.038)	(-0.082, 0.067)	0.2658	0.8396
PLA	0.117 (0.038)	(0.041, 0.192)		0.0025
		Peak FEV_1		
T+S_PE −				
Tio18GEL	0.085 (0.041)	(0.006, 0.165)	0.0010	0.0359
Salm25PE	0.101 (0.041)	(0.020, 0.182)	0.0003	0.0146
T+S_PE/S25PE	0.021 (0.040)	(-0.058, 0.101)	0.0789	0.5984
PLA	0.241 (0.041)	(0.161, 0.321)		<.0001
		FEV_1 AUC_{0-8h}		
T+S_PE −				
Tio18GEL	0.092 (0.037)	(0.020, 0.164)	0.0001	0.0125
Salm25PE	0.110 (0.037)	(0.037, 0.184)	<.0001	0.0033
T+S_PE/S25PE	0.029 (0.037)	(-0.043, 0.101)	0.0309	0.4242
PLA	0.250 (0.037)	(0.178, 0.323)		<.0001

FEV_1, FVC and PEF results after the first dose (Visit 2) as well as FVC, PEF, TDI focal score, SGRQ score and diary- based endpoints after 4-week treatment period (Visit 3) are described in Section 11.

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Safety results:

The safety profiles observed were concordant with the known safety characteristics of tiotropium and salmeterol. No unexpected safety issues arose during the conduct of the studies.

The frequencies of reported adverse events were generally comparable between the treatment groups. The most frequently reported adverse events were nasopharyngitis (ranging from 2.2 – 5.9 %), chronic obstructive pulmonary disease (i.e. COPD exacerbations, ranging from 1.2 – 8.4 %) and headache (ranging from 0 – 2.3 %).

The frequency of adverse events classified as related to the study medication was slightly higher in the tiotropium group (8.4% versus 2.5-4.6% in the other treatment groups; the lowest frequency was observed in the FDC Tiotropium/salmeterol group). The frequencies of reported adverse events leading to permanent treatment discontinuation or serious adverse events were slightly higher in the salmeterol group (3.3% and 6.6%, respectively, versus 0 – 1.2 % and 1.2 – 3. 4 % in the other treatment groups).

Fifteen patients suffered from a serious adverse event: 12 patients following randomisation to study drug and prior to Visit 4 (i.e. clinic visit after 12-week treatment period) and 3 patients during the screening phase. Two fatal cases were reported during treatment with study drug; one patient died during treatment with FDC Tiotropium/salmeterol + salmeterol (due to artherosclerotic heart disease and emphysema) and one patient died during salmeterol treatment (due to pancreatic cancer). Two other patients died during the post-study period; one patient due to cardiac failure (during the treatment period on salmeterol) and one patient due to respiratory failure (during treatment period on tiotropium); all cases were considered not related to the study medication.

Two related SAEs were reported (both on placebo treatment): one patient was hospitalised for palpitations and nausea, while another patient suffered from angle closure glaucoma. Six patients discontinued the study due to an AE.

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Conclusions:

The results of the combined studies 1184.14 and 1184.15 are limited due to early study termination by the sponsor.

In term of lung function improvement (FEV_1, FVC, PEF) the results of the FDC Tiotropium/salmeterol (7.5 µg/25 µg) group were more favourable as compared to the results of the mono therapies (tiotropium 18µg GEL, salmeterol 25 µg PE and placebo), whereas the results of the FDC Tiotropium/salmeterol (7.5 µg/25 µg) group seemed to be non-inferior to the results of the FDC Tiotropium/salmeterol (7.5 µg/25 µg) + salmeterol 25 µg PE group.

Due to the low number of patients per treatment arm at the time of study termination no conclusions can be drawn regarding the outcome parameters TDI focal score and SGRQ total score, time to first moderate-to-severe COPD exacerbation as well as the diary-based endpoints.

Although data is limited, the safety profile observed for the FDC Tiotropium/salmeterol (7.5 µg/25 µg) was concordant with the known safety characteristics of tiotropium and salmeterol. No unexpected safety issues arose during the conduct of the studies.