Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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Name of company: Boehringer Ingelheim		**Tabulated Study Report**		
Name of finished product: Salmeterol xinafoate inhalation powder, hard polyethylene capsule		**BI study: 1184.10** **EudraCT: 2004-005238-37**		
Name of active ingredient: Salmeterol xinafoate		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 20 July 2007	**Number:** U07-1416	**Study period (dates):** 06 SEP 05 to 16 FEB 06		

Title of study:	A single dose, placebo-controlled, randomized, double-blind, double-dummy, crossover efficacy, pharmacokinetics and safety comparison of salmeterol inhalation powder (25 µg salmeterol), administered as the xinafoate salt from a hard polyethylene capsule via the HandiHaler® 2, and Serevent® Diskus® (50 µg salmeterol) in patients with chronic obstructive pulmonary disease (COPD)
Investigator:	Multi-centre, mono-national (Germany)
Study center(s):	14 study sites
Publication (reference):	Not yet published
Clinical phase:	II
Objectives:	The primary objective of this trial was to establish non-inferiority of lung function response to 25 µg salmeterol, administered as the xinafoate salt, in an inhalation powder delivered from hard PE capsules via the HandiHaler® 2 compared to Serevent® Diskus® (salmeterol 50 µg, administered as the xinafoate salt) following single dose inhalation in patients with COPD. The secondary objectives were to characterize the pharmacokinetics of salmeterol inhalation powder delivered by HandiHaler® 2 from the PE hard capsule and salmeterol xinafoate delivered by Serevent® Diskus®, and to compare the safety of the two pharmaceutical forms.
Methodology:	A single dose, placebo-controlled, multicentre, randomized, double-blind, double-dummy, three-way crossover design.
No. of patients:	
planned:	85 completed
actual:	Enrolled: 169/ 111 entered/ 107 completed Primary analysis: Placebo 108; Salm 25 µg (PE) 109; Salm 50 µg DPI 110
Diagnosis and main criteria for inclusion:	Outpatients of either sex, aged ≥ 40 years with a diagnosis of COPD [screening, pre-bronchodilator $FEV_1 \leq 60\%$ predicted (ECSC criteria) and $FEV_1/FVC \leq 70\%$]; smoking history of > 10 pack-years, no history of asthma, rhinitis or atopic disease; eosinophil count < 600/mm^3; FEV_1 response to salbutamol ≥ 12% of pre-bronchodilator FEV_1.
Test product:	Salmeterol 25 µg inhalation powder, hard PE capsule
dose:	25 µg salmeterol, administered as the xinafoate; single dose

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mode of admin.:	Oral inhalation via the HandiHaler® 2
batch no.:	0502002
Reference therapy 1:	Serevent® Diskus®(dry powder inhaler, DPI)
dose:	50 µg salmeterol, administered as the xinafoate; single dose
mode of admin.:	Oral inhalation; administration from the Diskus®
batch no.:	4H744
Reference therapy 2:	Placebo
dose:	N/A
mode of admin.:	Oral inhalation via the Diskus® and the HandiHaler® 2, respectively
batch no.:	0501001, B052000165 (Bulk), B052000251 (Device)
Duration of treatment:	Three single doses separated generally at least one week (in single cases at least two days); total number of treatment days: 3 days; total trial participation: 16 days.
Criteria for evaluation:	
Efficacy:	FEV_1: AUC_{0-12h} (primary), peak, AUC_{12-24h}, AUC_{0-24h}, 24-h profile; FVC: AUC_{0-12h}, peak, AUC_{12-24h}, AUC_{0-24h}, 24-h profile
Safety:	Adverse events, vital signs, pharmacokinetic profile in plasma and urine, physical examination, ECG
Statistical methods:	Analysis of covariance with terms for centre, patient within centre, test-day baseline, treatment and period. Descriptive statistics.

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SUMMARY – CONCLUSIONS:

Efficacy results:

Pharmacodynamic results

The efficacy of treatment with salmeterol 25 µg (PE) over a 24h hour observation period was shown to be non-inferior in terms of lung function improvement (FEV_1, FVC) compared to treatment with salmeterol 50 µg dry powder inhaler (DPI) in patients with COPD. There was no evidence of differences between salmeterol 25 µg (PE) and salmeterol 50 µg (DPI) at any time point for FEV_1. However, for FVC there was a suggestion of slightly better efficacy in favour of salmeterol 25 µg (PE).

One-hundred and eleven patients (male: 74, female: 37) were randomised and treated, all of whom were included in the full analysis set for the evaluation of efficacy. Only 4 patients failed to complete all visits. All patients were white with a mean age (± SD) of 59.9 (± 8.6) years, median duration of COPD of 9.0 (range 1 - 34) years and mean smoking history of 44.9 (± 24.3) pack-years. Most of the patients (63.1 %) were current smokers.

At the screening visit the mean pre- bronchodilator FEV_1 was 1.29 L (43.0 % of predicted normal FEV_1). The mean FEV_1/FVC ratio was 46.2 %. The highest individual FEV_1 expressed as percent predicted was 59.7 %.

Treatment with salmeterol 25 µg (PE) demonstrated a significant improvement for FEV_1 AUC_{0-12h} compared to placebo (0.191; $p<0.0001$). Moreover, non-inferiority of salmeterol 25 µg (PE) compared to salmeterol 50 µg (DPI) was confirmed (mean difference 0.007 L; 95% CI [-0.022, 0.036]; $p<0.0001$). The results of the PP analysis confirmed the results of the ITT analysis.

The peak FEV_1 within 3 hours after the morning dose of study medication showed a statistically significant increase after treatment with either salmeterol 25 µg (PE) or salmeterol 50 µg (DPI) compared to placebo (0.194 L; $p<0.0001$ and 0.192 L; $p<0.0001$ respectively). The mean difference between salmeterol 25 µg (PE) and salmeterol 50 µg (DPI) was 0.003 L with $p=0.0021$ for the test of non-inferiority. Treatment with both, salmeterol 25 µg (PE) and salmeterol 50 µg (DPI), significantly improved the FEV_1 AUC_{0-24h} compared to placebo. The mean treatment differences were 0.145 L ($p<0.0001$) and 0.140 L ($p<0.0001$) respectively. The analysis also demonstrated non-inferiority of salmeterol 25 µg (PE) to salmeterol 50 µg (DPI) (mean difference 0.006 L; $p<0.0001$).FEV_1 AUC_{12-24h} was statistically significantly improved following treatment with salmeterol 25 µg (PE) compared to placebo (0.100 L; $p<0.0001$). The mean difference between salmeterol 25 µg (PE) and salmeterol 50 µg (DPI) was 0.004 L (non-inferiority $p<0.0001$).

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Pharmacokinetic results

The main pharmacokinetic results obtained during this study have been summarized below:

			Salm. 25 µg PE		Salm. 50 µg (DPI)	
		N	gMean	gCV [%]	gMean	gCV [%]
C_{max}	**[pg/mL]**	33/32	34.6	48.4	32	42.2
AUC_{0-3}	**[pg·h/mL]**	33/32	56.3	42.2	69	42.7
$AUC_{0-3.083}$	**[pg·h/mL]**	33/32	57.2	42.4	70.5	43
AUC_{0-tz}	**[pg·h/mL]**	33/32	78.6	66.4	104	71.4
t_{max}**	**[h]**	33/32	0.117	0.0330-1.62	1.11	0.433-3.12
$Ae_{0-3.083}$	**[pg]**	26/29	25600	42.4	26700	69.2

** Median and Range

Source data: Table: 15.5.2.1: 1-4

No formal statistical examination of the pharmacokinetic data was planned to test for relative bioavailability. The geometric mean test/reference ratios [salmeterol 25 µg (PE) / salmeterol 50 µg (DPI)] were found to be 1.11 and 0.82 for C_{max} and $AUC_{0-3\,083}$, respectively. Urinary excretion data ($Ae_{0-3\,083}$) of salmeterol supported the plasma data with geometric mean test/reference ratio [salmeterol 25 µg (PE) / salmeterol 50 µg (DPI)] of 0.96.

Hence, salmeterol inhaled from 25 µg salmeterol (PE) resulted in a similar systemic exposure as 50 µg salmeterol (DPI).

Safety results:

Based on the observations made in the present study, inhalation of all study treatments including a single dose of salmeterol 25 µg (PE) was shown to be safe and well tolerated.

There were 28 out of 111 treated patients (25.2%) with reported adverse events at some timepoint during the whole study, 14 patients (12.6%) with treatment emergent AEs .

There was no indication for a clinically relevant increase of the number of patients with adverse events in relation to treatment nor an indication for an increase of the intensity of adverse events in relation to a certain treatment with respect to the three treatment periods.

The greatest number of patients reported treatment emergent AEs categorized in the MeDRA 9.0 system organ class (SOC) infections and infestations- 6 patients (5.4%) with nasopharyngitis, following were 4 patients (3.6%) with reported treatment emergent adverse events in the SOC respiratory, thoracic and mediastinal disorders- 3 patients (2.7%) with AEs reported as preferred term chronic obstructive pulmonary disease referring to exacerbations and 1 patient (0.9%) with exacerbated dyspnoea. Following were a number of patients with reported treatment emergent adverse events in the SOC Nervous system disorders- 2 patients (1.8%) with headache.

There were no serious adverse events reported during the study. Significant adverse events were not defined for this study. Outside the usual follow-up period (therefore not included into the data base but reported according to BI SAE procedures, Case 2006-DE-02042DE) about three months after last single treatment three serious adverse events were reported for one patient (one of them fatal) which were classified as not related to trial drug.

There were two patients that were discontinued due to adverse events (AEs termed as other significant according to ICH E3), both in the system organ class respiratory, thoracic and mediastinal disorders: one patient with the reported exacerbated dyspnoea on Salm 25 µg (PE) treatment ([redacted]) and one patient with reported dyspnoea in the post treatment period ([redacted]).

There were no adverse events judged related to treatment by the investigators.

Evaluation of measurements of blood pressure, pulse rate, ECG recordings and physical examination did not reveal any obvious clinically significant drug-related changes.

Conclusions:

The primary objective of this trial was to establish non-inferiority of lung function response of 25µg salmeterol, administered as the xinafoate salt in an inhalation powder delivered from PE hard capsules via the HandiHaler® 2 compared to salmeterol 50 µg, formulated as inhalation powder and delivered from the DPI (Serevent® Diskus®), following single dose inhalation in patients with COPD.

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To achieve this primary objective, the study was designed as a single dose, placebo-controlled, randomized, double-blind, double-dummy, crossover trial with three single dose treatments. On the 3 test-days the 24-hour lung function profiles and pharmacokinetics were evaluated following inhalation of placebo and the two salmeterol treatments (one treatment per visit). The test-days were separated by a washout period of at least one week generally, in single patients by a washout period of at least two days.

One-hundred and eleven COPD patients (male: 74, female: 37) were randomised and treated, all of whom were included in the full analysis set for the evaluation of efficacy. Only 4 patients failed to complete all visits. All patients were Caucasians with a mean age (± SD) of 59.9 (± 8.6) years, median duration of COPD of 9.0 (range 1 - 34) years and mean smoking history of 44.9 (± 24.3) pack-years. Most of the patients (63.1 %) were current smokers.

The efficacy of treatment with salmeterol 25 µg (PE) over a 24 hour observation period was shown to be non-inferior in terms of lung function improvement (FEV_1, FVC) compared to treatment with salmeterol 50 µg (DPI) in patients with COPD. There was no evidence of clinically meaningful differences between salmeterol 25 µg (PE) and salmeterol 50 µg (DPI) at any time point for FEV_1. However, for FVC there was a suggestion of slightly better efficacy in favour of salmeterol 25 µg (PE).

In terms of lung function improvement (FEV_1, FVC) both active formulations, salmeterol 50 µg (DPI) and sameterol 25 µg (PE) are comparable in patients with moderate-to-severe COPD. Also, inhalation of salmeterol 25 µg (PE) resulted in a similar systemic exposure as 50 µg salmeterol (DPI).

Based on the observations made regarding the overall safety profile in the present study, inhalation of all study treatments including a single dose of salmeterol 25 µg (PE) was shown to be safe and well tolerated.

Evaluation of measurements of blood pressure, pulse rate and ECG recordings did not reveal any obvious clinically significant drug-related changes.

The results of the present study do not raise objections to further clinical studies with the salmeterol PE capsule formulation in patients with COPD. It is concluded that a single dose of salmeterol 25 µg (PE) is safe and well tolerated in patients with COPD. The results of this study in a study population where the proposed precautions for marketed salmeterol were applied did not indicate the need for any special precautions for the conduct of future studies.