Boehringer Ingelheim

Clinical Study Synopsis for Public Disclosure

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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.

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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 Study Report**		
Name of finished product: Salmeterol xinafoate inhalation powder, hard polyethylene capsule				
Name of active ingredient: Salmeterol xinafoate		**Page:**	**Number:**	
Ref. to Documentation:	**Volume:**	**Page:**		**Addendum No.:**
Report date: 20 July 2007	**Number:** U07-1417	**Study period (dates):** 09 SEP 2005 to 07 FEB 2006		EudraCT No.: 2005-000918-13

Title of study:	A single dose, placebo-controlled, randomized, double-blind, double-dummy, crossover efficacy, pharmacokinetics and safety comparison of salmeterol inhalation powder (12.5 µg, 25 µg and 50 µg salmeterol), administered as the xinafoate salt from hard polyethylene capsules 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 centres:	13 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 two doses [25 µg (1 capsule) and 50 µg (2 capsules of 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. A hard capsule with half the strength (12.5 µg) was included to investigate a dose ordering effect. The secondary objectives were to characterize the pharmacokinetics of salmeterol inhalation powder delivered by HandiHaler® 2 from the PE hard capsule(s) and salmeterol xinafoate delivered by Serevent® Diskus®, and to compare the safety of the different pharmaceutical forms and/or doses.
Methodology:	A single dose, placebo-controlled, multicentre, randomized, double-blind, double-dummy, five-way crossover design.
No. of subjects: **planned:** **actual:**	 110 completed enrolled: 180, entered: 136; completed 132. Primary analysis: Placebo: 133; Salm 12.5 µg (PE); 133 Salm 25 µg (PE); 135 Salm 50 µg (PE): 133; Salm 50 µg (DPI): 132

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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 (at first, one capsule of 25 µg salmeterol was inhaled, and then one placebo capsule)
mode of admin.:	Oral inhalation via the HandiHaler® 2
batch no.:	0502002; 0506003
Reference therapy:	Salmeterol 12.5 µg inhalation powder, hard capsule
dose:	12.5 µg salmeterol, administered as the xinafoate; single dose (at first, one capsule of 12.5 µg salmeterol was inhaled, and then one placebo capsule)
mode of admin.:	Oral inhalation via the HandiHaler® 2
batch no.:	0502003; 0507001
Reference therapy:	Salmeterol 50 µg inhalation powder, two hard PE capsules of 25 µg each
Dose:	50 µg salmeterol, administered as the xinafoate; single dose (two capsules of 25 µg salmeterol were inhaled one after the other)
mode of admin.:	Oral inhalation via the HandiHaler® 2
batch no.:	0502002; 0506003
Reference therapy:	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; 5C803
Reference therapy:	Placebo
dose:	N/A
mode of admin.:	Oral inhalation via the Diskus® and the HandiHaler® 2, respectively

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batch no.:	Placebo matching Serevent Diskus®:B052000165 (Bulk), B052000251 (Device); B052000315 (Device) Placebo matching Salmeterol hard PE capsules: 0501001
Duration of treatment:	Five single doses separated by generally at least one week, in single cases at least four days; total number of treatment days: 5 days
Criteria for evaluation:	
Efficacy:	FEV_1: $AUC_{0\text{-}12h}$ (primary), peak, 12-h profile; FVC: $AUC_{0\text{-}12h}$, peak, 12-h profile
Safety:	Adverse events, vital signs, salmeterol plasma and urine pharmacokinetics, 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 50 µg (PE) over a 12 hour observation period was shown to be superior in terms of lung function improvement (FEV_1, FVC) compared to treatment with salmeterol 50 µg (DPI) in patients with COPD. Furthermore, the efficacy of treatment with salmeterol 25 µg (PE) was demonstrated to be non-inferior to that obtained with salmeterol 50 µg (DPI). Results of FEV_1 and FVC over the 12-hour observation period demonstrated superior efficacy of all active treatments over placebo from the first measurement (i.e. 15 minutes post dosing) until the end of the 12-hour observation period. Mean differences between salmeterol 12.5 µg, 25 µg and 50 µg (PE) were suggestive of a dose response relationship.

One hundred and thirty-six patients (male: 83, female: 53) 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 61.2 (± 8.6) years, median duration of COPD of 9.0 (range 1 - 35) years and mean smoking history of 41.3 (± 18.8) pack-years. Most of the patients (61.8 %) were current smokers.

At the screening visit the mean FEV_1 was 1.30 L (45.0 % of predicted normal FEV1). The mean FEV_1/FVC ratio was 49.2 %. The highest individual FEV1 expressed as percent predicted was 59.6 % and the largest FEV_1/FVC ratio was 69.6 %.

Forty-five minutes after administration of salbutamol 400 µg (4 puffs of 100 µg) the mean FEV_1 and FEV_1/FVC ratio was 1.65 L (57.1 % of predicted normal FEV_1) and 53.3 % respectively. The mean reversibility was 0.35 L or 28.1 % above the pre-bronchodilator FEV1 and all patients showed an increase of at least 12%.

Treatment with salmeterol 50 µg (PE) was shown to be statistically superior to salmeterol 50 µg (DPI) in FEV_1 $AUC_{0\text{-}12h}$ (mean difference = 0.039 L; 95% CI [0.017, 0.061]; p=0.0006), which consequently nullified the planned test of non-inferiority. Moreover, non-inferiority of salmeterol 25 µg (PE) compared to salmeterol 50 µg (DPI) in FEV_1 $AUC_{0\text{-}12h}$ was confirmed (mean difference 0.005 L; 95% CI [-0.018, 0.027]; p<0.0001).

Results of the superiority test between treatment with salmeterol 25 µg (PE) and 12.5 µg (PE) demonstrated a significant difference in FEV_1 AUC_{0-12h} in favour of salmeterol 25 µg (PE) (mean difference = 0.036 L; 95% CI [0.014, 0.058]; p-value=0.0015). The results of the PP analysis confirmed the results of the ITT analysis.

Peak FEV_1 showed a statistically significant increase following both salmeterol 50 µg (PE) and salmeterol 50 µg (DPI) compared to placebo (0.179 L; p<0.0001 and 0.138 L; p<0.0001, respectively). The test of non-inferiority between salmeterol 50 µg (PE) and salmeterol 50 µg (DPI) was nullified by the corresponding test for superiority, which showed a significant difference in favour of salmeterol 50 µg (PE) (mean difference = 0.041 L; 95% CI [0.013, 0.069]; p=0.0046). Furthermore, non-inferiority of salmeterol 25 µg (PE) compared to salmeterol 50 µg (DPI) was confirmed (mean difference 0.005 L; 95% CI [-0.023, 0.033]; p<0.0001).

Results of the superiority test between treatment with salmeterol 25 µg (PE) and 12.5 µg (PE) demonstrated a statistically significant difference in peak FEV_1 in favour of treatment with salmeterol 25 µg (PE) (mean difference = 0.038 L; 95% CI [0.010, 0.066]; p=0.0072).

FVC results closely reflected those obtained for FEV_1. In terms of FVC AUC_{0-12h} salmeterol 50 µg (PE) was shown to be statistically superior to salmeterol 50 µg (DPI) (mean difference = 0.073 L; 95% CI [0.035, 0.111]; p=0.0002). Salmeterol 25 µg (PE) demonstrated a statistically significant improvement compared to salmeterol 12.5µg (PE) (mean difference = 0.055 L, 95% CI [0.017, 0.093], p=0.0047) and appeared to be comparable to salmeterol 50 µg (DPI) (mean difference = 0.013 L; 95% CI [-0.025, 0.051]; p=0.5021).

Compared with placebo, a statistically significant difference was found for peak FVC after treatment with both salmeterol 50 µg (PE) and salmeterol 50 µg (DPI) (0.245 L; p<0.0001 and 0.169 L; p<0.0001 respectively). Salmeterol 50 µg (PE) was shown to be superior to salmeterol 50 µg (DPI) (mean difference = 0.077 L; 95% CI [0.027, 0.126]; p=0.0025). No relevant difference was found between salmeterol 25 µg (PE) and salmeterol 50 µg (DPI) (mean difference 0.028 L; 95% CI [-0.022, 0.077]; p=0.2747).

Pharmakinetic Results

No formal statistical examination of the pharmacokinetic data was planned.

However, the geometric mean test/reference ratios [salmeterol 12.5 µg (PE) / salmeterol 50 µg (DPI)] were calculated to be 0.52, 0.37 and 0.54 for C_{max}, $AUC_{0-3\ 083}$, and $Ae_{0-3\ 083}$, respectively. Similarly, the geometric mean test/reference ratios [salmeterol 25 µg (PE) / salmeterol 50 µg (DPI)] were calculated to be 1.03, 0.79 and 0.87 for C_{max}, $AUC_{0-3\ 083}$, and $Ae_{0-3\ 083}$, respectively. Also, the geometric mean test/reference ratios [salmeterol 50 µg (PE)] / salmeterol 50 µg (DPI)] were calculated to be 1.93, 1.69 and 1.53 for C_{max}, $AUC_{0-3\ 083}$, and $Ae_{0-3\ 083}$, respectively.

Safety:

Based on the observations made in the present study, inhalation of all study treatments including a single dose of salmeterol 12.5 µg (PE), 25 µg (PE) or 50 µg (PE); 2 capsules of 25 µg) was shown to be safe and well tolerated.

Twenty-nine out of 136 patients treated (21.3%) reported adverse events at some time point during the whole study. 11 patients (8.1%) reported 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 five treatment periods.

The greatest number of patients reported treatment emergent adverse events categorized in the SOC nervous system disorders- 4 patients (2.9%): 1 patient with headache on placebo ([redacted]) and on Salm 12.5 µg (PE) ([redacted]) ,1 patient with headache on Salm 25 µg (PE) ([redacted]), 2 patients with headache on Salm50 µg (PE) ([redacted]), one patient with headache on Salm50 µg (DPI) ([redacted]) and one patient with dizziness on placebo treatment ([redacted]). Following were a number of patients with reported treatment emergent adverse events in the SOC respiratory, thoracic and mediastinal disorders - 3 patients (2.2%)- 1 patient with reported chronic obstructive pulmonary disease meaning exacerbations on Salm 25 µg (PE) ([redacted]), one patient with pharolaryngeal pain on Salm12.5 µg (PE) treatment ([redacted])and one patient on Salm50 µg (PE) treatment ([redacted]), dysphonia reported by the latter patient ([redacted]) on Salm50 µg (PE) treatment.

There were three patients with AEs judged related to treatment by the investigator: one patient on Salm12.5 µg (PE) treatment (0.8%) with pharyngolaryngeal pain ([redacted])(the intensity was moderate, treatment was continued and the patient recovered from the event within one day), one patient (0.7%) on Salm25 µg (PE) treatment with headache([redacted], the intensity was mild, treatment was continued, the patient recovered from the event within one day) and one patient (0.8%) on Salm50 µg (PE) treatment with headache ([redacted], the intensity was mild, treatment was continued and the patient recovered within 2 days).

There were two patients with serious adverse events reported during the study: one (0.7%) with two SAEs- hypokalaemia and hyponatraemia in the post treatment period and one on Salm50 µg (PE) who died on the evening of the treatment day. The cause of death was unknown. Outside the usual follow-up period (therefore not included into the data base but reported according to BI SAE procedures) three serious adverse events were reported for one patient (one of them fatal [oesophageal cancer]). All SAEs were classified as not related to trial drug.

Significant adverse events were not defined for this study. Patients with AEs termed as other significant according to ICH E3, leading to discontinuation, were not reported in this study . Two patients dropped out prematurely due to administrative reasons: one (patient [redacted]) due to non-compliance with the protocol (Placebo) and one (patient [redacted]) who withdrew consent [Salmeterol 25 µg (PE)] and two further patients withdrew from the study for other reasons, including one patient ([redacted]), mentioned above, who died on 19th October 2005 after completing visit 4 [Salmeterol 50 µg (PE)] and one (patient [redacted]) who refused to schedule another visit after not complying with the stability criteria [Salmeterol 25 µg (PE)] (refer to Table 10.1.1:2 section 10).

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

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Conclusions

The primary objective of the present study was to establish non-inferiority of lung function response to two doses [25 µg (1 capsule) and 50 µg (2 capsules of 25 µg)] of salmeterol, formulated as inhalation powder in the hard PE capsule and delivered via the HandiHaler® 2, compared to salmeterol 50 µg, formulated as inhalation powder and delievered from the DPI (Serevent® Diskus®), following single dose inhalation in patients with COPD. A PE capsule with half the strength (salmeterol 12.5 µg) was included to investigate a dose ordering effect.

To achieve this primary objective, the study was designed as a double-blind, placebo-controlled, randomized, crossover study with five treatments. On the 5 test-days the 12-hour lung function profiles and pharmacokinetics were evaluated following inhalation of placebo and the four salmeterol treatments. The test-days were separated by a washout period of at least four days.

A total of 136 COPD patients (male: 83 / female: 53) were randomised and treated. Only 4 patients failed to complete all visits. All patients were caucasians and the mean age of the patient population was 61.2 years. The median duration of COPD was 9.0 years and the mean smoking history was 41.3 pack-years. Most of the patients (61.8 %) were current smokers. At the screening visit the mean pre- bronchodilator FEV_1 was 1.30 L (45.0 % of predicted normal FEV_1) and the mean FEV_1/FVC ratio was 49.2 %.

Two patients dropped out prematurely due to administrative reasons: one (patient [redacted]) due to non-compliance with the protocol (Placebo) and one (patient [redacted]) who withdrew consent [Salmeterol 25 µg (PE)] and two further patients withdrew from the study for other reasons, including one patient ([redacted]) who died on 19th October 2005 after completing visit 4 [Salmeterol 50 µg (PE)] and one (patient [redacted]) who refused to schedule another visit after not complying with the stability criteria [Salmeterol 25 µg (PE)].

Twenty-nine out of 136 patients treated (21.3%) reported adverse events at some time point during the whole study, 11 patients (8.1%) reported AEs counted as on treatment. There were two patients with serious AEs- one patient (0.8%) in the Salm50 µg (PE) treatment group with a fatal SAE and one patient (0.7%) during the post-treatment period. Outside the usual follow-up period three serious adverse events were reported for one patient (one of them fatal). All Serious Adverse Event were judged non-related to the study-medication.

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 five treatment periods.

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Conclusions (cont.)

There were three patients with adverse events judged related to treatment by the investigators: one patient on Salm12.5PE treatment (0.8%) with pharyngolaryngeal pain ([redacted], the intensity was moderate, treatment was continued, the patient recovered from the event within one day), one patient (0.7%) on Salm25PE treatment with headache ([redacted], the intensity was mild, treatment was continued, the patient recovered from the event within one day) and one patient (0.8%) on Salm50PE treatment with headache ([redacted], the intensity was mild, treatment was continued, the patient recovered within 2 days).

The efficacy of treatment with salmeterol 50 µg (PE) over a 12 hour observation period was shown to be superior in terms of lung function improvement (FEV_1, FVC) compared to treatment with salmeterol 50 µg (DPI) in patients with COPD. Furthermore, the efficacy of treatment with salmeterol 25 µg (PE) was demonstrated to be non-inferior to that obtained with salmeterol 50 µg (DPI). Results of FEV_1 and FVC over the 12-hour observation period demonstrated superior efficacy of all active treatments over placebo from the first measurement (i.e. 15 minutes post dosing) until the end of the 12-hour observation period. Mean differences between salmeterol 12.5 µg, 25 µg and 50 µg (PE) were suggestive of a dose response relationship.

Inhalation of salmeterol 25 µg (PE) resulted in a similar systemic exposure as salmeterol 50 µg (DPI). However, inhalation of salmeterol 12.5 µg (PE) resulted in a lower while inhalation of salmeterol 50 µg (PE) resulted in a higher systemic exposure compared to salmeterol 50 µg (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 12.5 µg (PE), 25 µg (PE) or 50 µg (PE; 2 capsules of 25 µg) was shown to be safe and well tolerated.

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 12.5 µg (PE), salmeterol 25 µg (PE) or salmeterol 50 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.

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