AstraZeneca

DRUG PRODUCT	Oxis Turbuhaler	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Formoterol fumarate dihydrate	REFERRING TO PART	
DOCUMENT NO.	37-CR-3040	OF THE DOSSIER	
VERSION NO.	01		
STUDY CODE	37-3040		
DATE	25 February, 2002		

FINAL

Protective effect of salbutamol against methacholine bromide in asthmatic patients pre-treated with formoterol Turbuhaler® or salmeterol Diskhaler®

STUDY CENTRE(S)

Multicentre study

Centre 1 Sweden

Centre 2 The Netherlands

PUBLICATION (REFERENCE)

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STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	April 8, 1998	IV
- **DATE OF LAST PATIENT COMPLETED**	March 23, 2000	

OBJECTIVES

To evaluate whether pre-treatment with formoterol (full β_2-agonist) or salmeterol (partial β_2-agonist) influences the protective effect of salbutamol against methacholine in asthmatic patients.

STUDY DESIGN

Double-blind, double-dummy, crossover and randomised design. After enrolment, the patients were treated with formoterol Turbuhaler 9 μg (delivered dose, 12 μg metered dose) b.i.d. At visit 2, after two (max three) weeks of treatment with formoterol, FEV_1 as well as PC_{20} were measured 1 hour after the morning dose of formoterol. The patients who fulfilled all inclusion and exclusion criteria were randomised into the study and treated with formoterol Turbuhaler 9 μg b.i.d. or salmeterol Diskhaler 50 μg b.i.d, for two (max three) weeks prior to visit 3. For each pre-treatment, there were four methacholine challenge days. At visits 3-10, the patients inhaled the morning dose of formoterol or salmeterol (reference time). Spirometry for baseline FEV_1 was performed 60 (±5) minutes after the morning dose. A single dose of salbutamol Turbuhaler 200, 400 or 800 μg or placebo was inhaled 70 (±5) minutes after the reference time. Methacholine challenge testing started 15 (max 20) minutes after the salbutamol/placebo inhalation. At least 48 hours (due to the risk of developing methacholine refractivity if shorter intervals) but not more than 14 days separated each methacholine challenge. Treatment with formoterol or salmeterol continued during the methacholine challenge periods.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Male and female asthmatic patients treated with a constant dose of inhaled steroids ≥200 μg/day were to be included in the study. The patients had to have a baseline FEV_1 ≥40% of predicted normal values. After two weeks of treatment with formoterol Turbuhaler 9 μg b.i.d., the patients had to have a FEV_1 ≥70% of predicted normal values (one hour after the morning dose) and a PC_{20} ≤9.8 mg/mL. The patients had to have no change in prescribed asthma medication within one month prior to visit 1 or hospitalised due to exacerbation of asthma within two months prior to visit 1.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Formoterol fumarate dihydrate (Oxis), 9 μg/dose (delivered dose, metered dose 12 μg/dose) b.i.d. inhaled via Turbuhaler.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Salmeterol (Serevent), 50 μg/dose (metered dose) b.i.d. inhaled via Diskhaler.
Salbutamol sulphate (Inspiryl), 100 μg/dose (metered dose) inhaled via Turbuhaler.

Placebo for Inspiryl Turbuhaler.

DURATION OF TREATMENT

The study duration ranged from 58 to 117 days. A run-in period with formoterol Turbuhaler b.i.d. during two (max three) weeks. Two periods with treatment of formoterol Turbuhaler or salmeterol Diskhaler b.i.d. After two (max three) weeks of treatment, four single treatments with salbutamol Turbuhaler 200, 400 or 800 μg or placebo were added to the maintenance treatment of formoterol or salmeterol with at least 48 hours and not more than 14 days in between.

MAIN MEASUREMENT(S) AND VARIABLE(S):

- **PHARMACOKINETIC**

Not applicable.

- **PHARMACODYNAMIC**

The primary variable was the concentration of methacholine bromide causing a 20% fall in FEV_1 (PC_{20}) determined after single doses of salbutamol or placebo and pre-treatment with formoterol or salmeterol.

- **SAFETY**

Adverse events were collected by means of standard questions.

At enrolment (visit 1) and at follow-up (visit 10), health checks were performed including physical examination, measurements of pulse and blood pressure, ECG and laboratory tests.

METHODS FOR DATA EVALUATION

FEV_1 measured after the morning dose of formoterol or salmeterol

FEV_1 values, measured one hour after the morning dose of formoterol or salmeterol, were compared between the two pre-treatments using a multiplicative (i.e. log-transformation of the response was used) analysis of variance model with patient, period and pre-treatment as fixed factors. The mean treatment ratio was estimated and 95% confidence limits were calculated.

FEV_1 measured after salbutamol or placebo

Geometric mean FEV_1 values (as ratio versus FEV_1 at visit 2) were estimated using a multiplicative analysis of variance model with patient, period and treatment as fixed factors. The levels within treatment were the eight combinations of pre-treatment and placebo/ salbutamol dose. The eight treatments were compared in pairs and treatment differences were described with geometric mean ratios and 95% confidence intervals.

PC_{20}

The concentration of methacholine bromide causing a 20% fall in FEV_1 from the post-saline value (PC_{20}) was calculated from the lowest FEV_1 value measured after each methacholine concentration. Log-linear interpolation of the dose versus % fall in FEV_1 curve was used to calculate PC_{20}.

Geometric mean PC_{20} values (as mg/mL or as ratio versus PC_{20} at visit 2) were estimated using a multiplicative analysis of variance model with patient, period and treatment as fixed factors. The levels within treatment were the eight combinations of pre-treatment and placebo/salbutamol dose. The eight treatments were compared in pairs and treatment differences were described with geometric mean ratios and 95% confidence intervals.

Various nonlinear models were fitted to the estimated means using weighted least squares regression.

PATIENTS

	Total
No. planned	40
No. randomized and treated	39
Males/Females	14/25
Mean age (years) (range)	38 (21-66)
Baseline FEV_1 (%)	85 (n=37)
No. analysed for efficacy	37
No. analysed for safety	39
No. completed	37

SUMMARY

- **PHARMACOKINETIC RESULTS**

Not applicable.

- **PHARMACODYNAMIC RESULTS**

Lung function by means of FEV_1 (measured 1 hour after the morning dose of formoterol or salmeterol) was 2.2% (95% confidence interval 1.2-3.2) higher after treatment with formoterol Turbuhaler 9 μg b.i.d. compared to salmeterol Diskhaler 50 μg b.i.d. for at least 2 weeks.

An additional bronchodilating effect of salbutamol was indicated after pre-treatment with formoterol Turbuhaler 9 μg b.i.d. or salmeterol Diskhaler 50 μg b.i.d., Figure 1. Inhalation of salbutamol 800 μg via Turbuhaler increased FEV_1 statistically significantly compared to placebo after both pre-treatments. The mean FEV_1 increased 2.8 and 3.4% after salbutamol 800 μg compared to placebo after pre-treatment with formoterol and salmeterol, respectively. The additional bronchodilating effect of salbutamol did not differ statistically significantly between pre-treatment with formoterol and salmeterol.

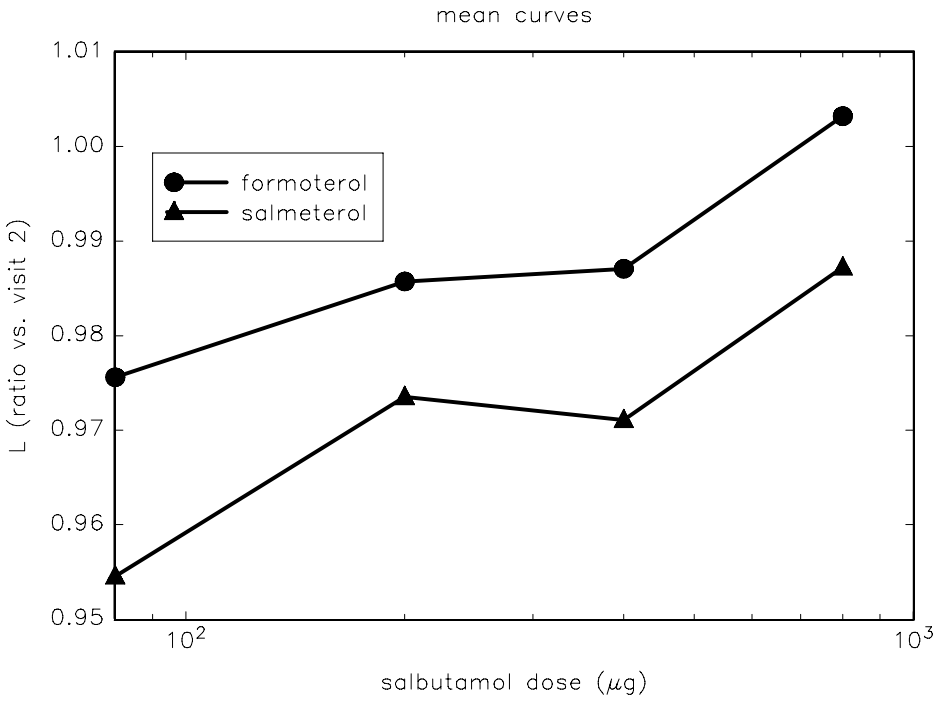

Figure 1. Mean dose response curves for FEV_1 after salbutamol and pre-treatment with formoterol Turbuhaler 9 μg b.i.d. or salmeterol Diskhaler 50 μg b.i.d.

An additional bronchoprotective effect of salbutamol against methacholine was indicated after pre-treatment with formoterol Turbuhaler 9 μg b.i.d. or salmeterol Diskhaler 50 μg b.i.d. for at least 2 weeks, Figure 2. The two highest doses of salbutamol, 400 and 800 μg, increased PC_{20} statistically significantly compared to placebo after both pre-treatments. The mean PC_{20} increased 27% and 34% after inhalation of salbutamol 800 μg compared to placebo, corresponding to 0.34 and 0.42 doubling doses, after pre-treatment of formoterol and salmeterol, respectively. The protective effect of salbutamol seemed to have reached maximum for the different doses of salbutamol. The additional protective effect of salbutamol against methacholine did not differ statistically significantly between pre-treatments with formoterol and salmeterol.

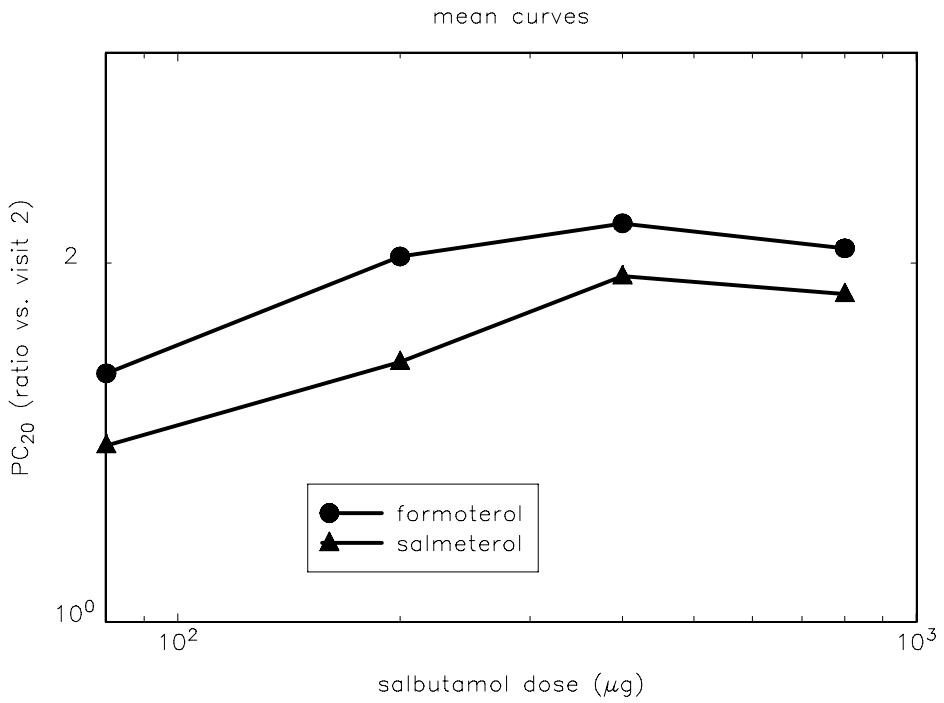

Figure 2. Mean dose response curves for PC_{20} after salbutamol and pre-treatment with formoterol Turbuhaler 9 μg b.i.d. or salmeterol Diskhaler 50 μg b.i.d.

- **SAFETY RESULTS**

The treatments were safe and well tolerated in this study. There were no serious adverse events reported after randomization and no other significant adverse events were identified. Only two patients discontinued the study due to adverse events, one during treatment with formoterol, and one during treatment with salmeterol.