AstraZeneca

Drug product:	Oxis	**SYNOPSIS**	(For national authority use only)
Drug substance(s):	Formoterol fumarate dihydrate		
Document No.:	SD-037-CR-0708	Referring to part of the dossier	
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Study code:	SD-037-0708		
Date:	29 March, 2004		

Lung deposition and efficacy of formoterol inhaled via Turbuhaler® in patients with chronic obstructive pulmonary disease (COPD).

Publications

None at the time of writing this report.

Study dates:

First subject enrolled 19 July, 2001

Last subject completed 5 May, 2003

Phase of Development

Clinical pharmacology (I)

Objectives

The primary objective of the study was to assess lung deposition, determined as the absolute pulmonary bioavailability, of formoterol inhaled via Turbuhaler in patients with chronic obstructive pulmonary disease (COPD).

The secondary objectives were

- to evaluate the effect of formoterol on lung function parameters. The variables were forced expiratory volume in one second (FEV_1) and trapped gas volume.
- to describe the relationships between lung deposition and effects on lung function parameters.
- to estimate the patients ability to inhale via Turbuhaler. The variables were peak inspiratory flow (PIF) and inhaled volume (IV).
- to evaluate the influence of FEV_1 at visit 2 on total lung deposition.

Study design

The lung deposition and efficacy of formoterol inhaled via Turbuhaler were investigated in a double-blind, partly randomised, placebo-controlled crossover study in patients with COPD.

Target patient population and sample size

Patients, aged between 40 and 80 years, with a clinical diagnosis of COPD were to be included in the study. The patients had to be either current or previous smokers with smoking history equivalent to at least 10 pack years. The patients had to have a forced expiratory volume in one second (FEV_1) less than 80% of predicted and at least 800 mL and FEV_1/FVC less than 70% at inclusion. Positive reversibility, defined as an increase of 200 mL in FEV_1 after inhalation compared to the prior FEV_1 value, was to be shown. In an amendment of the study after inclusion of 12 patients, the criterion of positive reversibility was withdrawn.

Patients with history of asthma and/or seasonal allergic rhinitis with disease onset before 40 years of age or patients who have had a significant exacerbation of COPD in the last 2 months prior to enrolment or patients that require regular use of oxygen were to be excluded.

A total of 28 randomised patients were to be included in the study. The randomisation was to be stratified on 2 groups with at least 10 patients in each of the groups:

- Patients with baseline FEV_1 between 50 and 80% of predicted
- Patients with baseline FEV_1 below 50% of predicted

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Investigational product

Single doses of 4.5, 9, 18 and 36 µg formoterol fumarate dihydrate (delivered dose) inhaled via Oxis Turbuhaler® 4.5 µg (batch Nos. CC 22 and DB 24). Single intravenous infusion of formoterol fumarate dihydrate, 2 mL 5 µg/mL during 5 minutes.

Comparator

Single doses of placebo inhaled via Turbuhaler®.

Duration of treatment

Six single doses administered on six separate occasions with a wash-out period of at least one and not more than three weeks in between.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable
  The primary variable was the total amount of formoterol excreted in urine within 32 hours after administration.
- Secondary variables
  The secondary variables were
  - FEV_1 and trapped gas volume
  - PIF and IV
- Other variables
  Other variables were forced vital capacity (FVC), functional residual capacity (FRC_{HE}, FRC_{BP}), residual volume (RV_{HE}, RV_{BP}) and total lung capacity (TLC_{HE}, TLC_{BP}) determined by helium dilution and body plethysmography and inspiratory vital capacity (IVC) and specific airway conductance (sG_{aw}).

Safety

Adverse events were collected by means of standard questions.

Statistical methods

The full analysis set was used for pharmacokinetic and efficacy analyses. All hypothesis testing was performed using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

Absolute pulmonary bioavailability was estimated for the different dose levels using a multiplicative analysis of variance (ANOVA) model with patient, period and treatment as fixed factors. Dose proportionality was investigated by fitting a straight line to the adjusted means (on the log scale) versus logged delivered dose using weighed linear regression.

The effect of formoterol on all lung function parameters except trapped gas volume were compared between treatments using multiplicative ANOVA models with patient, period and treatment as fixed factors, and using baseline of the study day as a covariate. Trapped gas volume was analysed using a similar additive ANOVA model. Delivered dose-response relationships for FEV_1, FVC, IVC and sG_{aw} were investigated by fitting straight lines to the adjusted means (on the log scale) versus logged delivered dose using weighed linear regression. Relationships between lung deposition and effects on lung function variables were described graphically, and expressed by linear mixed effect models.

The patients ability to inhale via Turbuhaler was estimated by measurements of PIF and IV during inhalations of study drug. Relationships between lung deposition, PIF, IV, baseline FEV_1 or baseline FVC were described graphically and expressed by linear mixed effects models.

Adverse events (AEs) were evaluated by means of descriptive statistics and qualitative analysis.

Patient population

Table S1. Patient population and disposition

		Total
Population		
N randomised and treated (N planned)		19 (28)
- group 1 (baseline FEV_1 between 50 and 80% of predicted)		11
- group 2 (baseline FEV_1 below 50% of predicted)		8
Demographic characteristics		
Sex (% of patients)	Male	18 (94.7%)
	Female	1 (5.3%)
Mean Age (range)		64.4 (44-81)
Baseline characteristics		
Baseline FEV_1 (% pred.), group 1 (range)		61.5 (50.9-69.6)
Baseline FEV_1 (% pred.), group 2 (range)		41.4 (33.0-47.0)
FEV_1/FVC (%), group 1 (range)		55.4 (41.6-64.2)
FEV_1/FVC (%), group 2 (range)		42.2 (37.5-51.9)
Disposition		
N (%) of patients who	completed	18 (94.7%)
	discontinued	1 (5.3%)
N analysed for safety		19
N analysed for pharmacokinetics, primary objective		18
N analysed for efficacy, secondary objective		19

Efficacy and pharmacokinetic results

The response of single doses of formoterol Turbuhaler and placebo on lung function parameters are shown in Figure S1. All formoterol dose levels exhibited statistically significant increases in FEV_1, FVC, IVC and sG_{aw} compared to placebo. Furthermore, 18 and 36 µg formoterol statistically significantly decreased FRC_{HE} and RV_{HE} compared to placebo. No statistically significant differences versus placebo were observed for trapped gas volume.

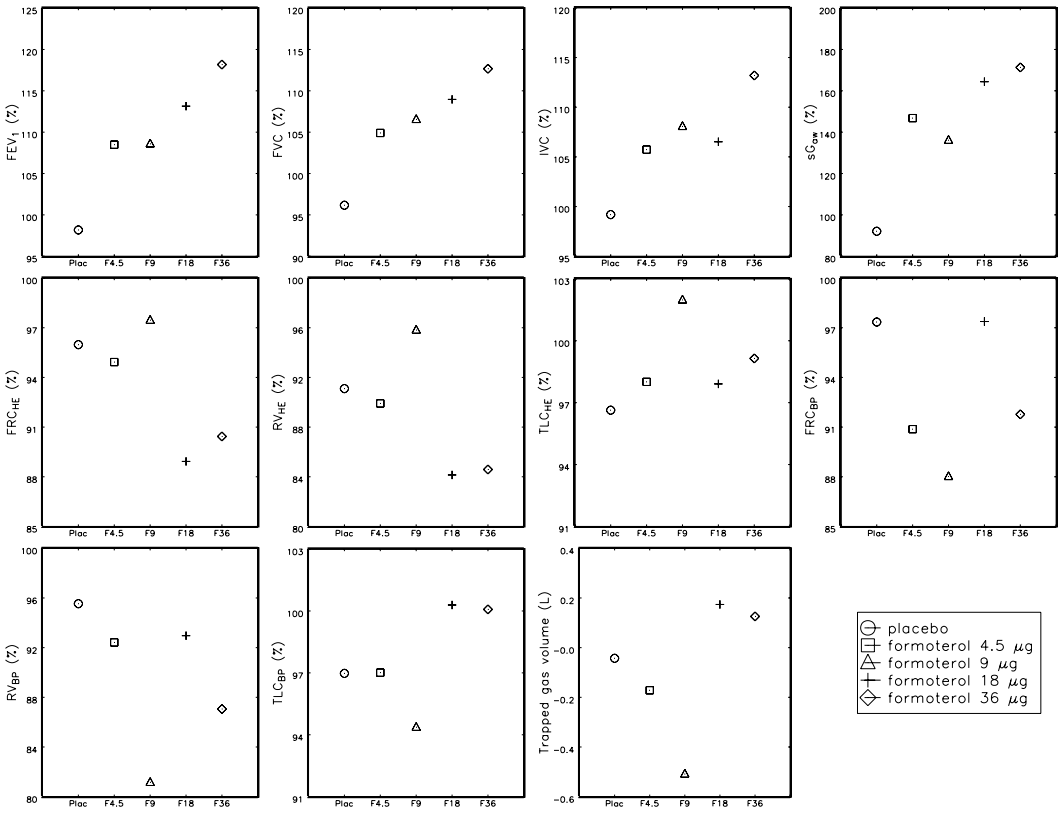

Figure S1. Response of single doses of formoterol Turbuhaler and placebo on lung function parameters as mean change from baseline for trapped gas volume and geometric mean baseline ratio for the other parameters

The lung deposition, determined as the absolute pulmonary bioavailability, of formoterol inhaled via Turbuhaler is summarised in Table S2. The F_{pulm} was determined to be 20.5, 27.0, 24.4 and 23.7 % after inhalation of 4.5, 9, 18 and 36 µg formoterol, respectively. The values didn't exhibit any dose dependency in lung deposition, as shown in Table S3. The mean lung deposition based on all four dose levels was 24.0%.

Table S2. Descriptive statistics of absolute pulmonary bioavailability of formoterol

Parameter	Treatment	n	Treatment mean	Treatment (range)	Adjusted[1] means
F_{pulm} (%)	formoterol 4.5 µg	18	21.01	(4.8 - 100.7)	20.46
	formoterol 9 µg	18	27.21	(8.4 - 116.4)	27.01
	formoterol 18 µg	18	24.38	(11.1 - 41.2)	24.36
	formoterol 36 µg	18	22.69	(12.6 - 36.6)	23.67

1. from ANOVA

Table S3. Dose-proportionality of F_{pulm}: estimated regression parameters

Intercept	Slope	95% conf. lim.
3.04	0.049	(-0.091 - 0.188)

Delivered dose-response and lung dose-response relationships for FEV_1, FVC, IVC and sG_{aw} are presented in Figures S2 and S3. Statistically significant delivered dose-response relationships were observed for FEV_1, FVC and sG_{aw}, but not for IVC, whereas statistically significant lung dose-response relationships were shown for all four parameters. The confidence intervals of the slopes for FEV_1, FVC, IVC and sG_{aw} were more narrow for the lung dose-response relationships than for the delivered dose-response relationships, indicating that the effects on lung function were better described by lung deposition than by delivered dose.

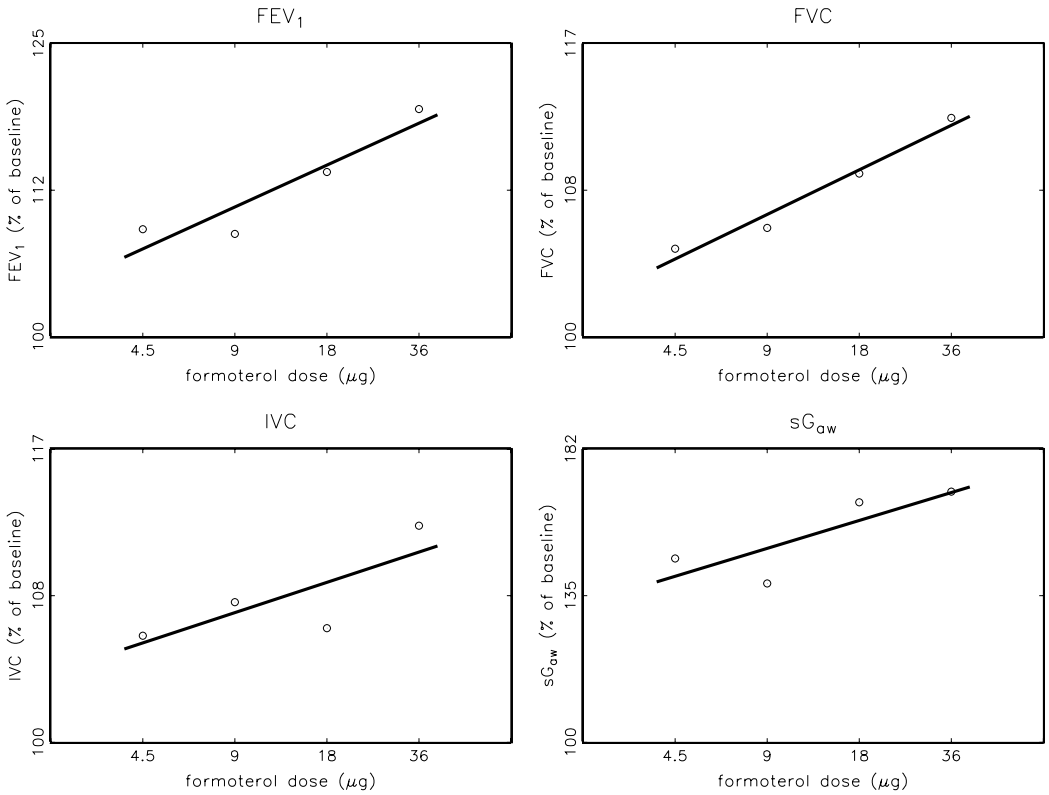

Figure S2. Delivered dose-response relationships for lung function parameters

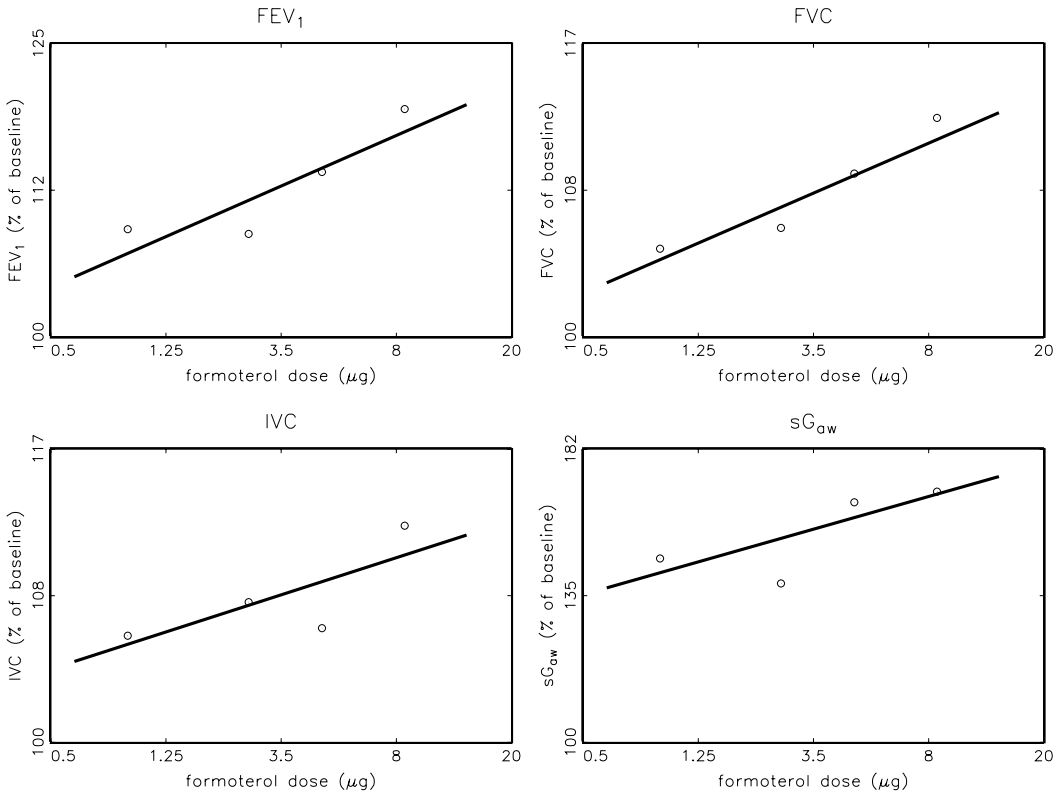

Figure S3. Lung dose-response relationships for lung function parameters

PIF and IV were measured for each of the eight inhalations at all study visits with inhaled treatments. The mean PIF and IV were 58.9 L/min (patient range: 44.9-73.2 L/min) and 2.20 L (patient range: 1.39-3.42 L), respectively. Disease severity, determined as baseline FEV_1, was significantly correlated with IV but not with PIF. A lower IV was observed for patients with more severe disease. No statistically significant correlations between lung deposition and baseline FEV_1, PIF or IV were observed.

Safety results

All treatments were well tolerated. In total, 7 AEs (6 different preferred terms) were reported after intake of investigational product, all started during the run-in or wash-out periods. Except for arthritis (reported for formoterol 9 µg and placebo, by the same patient) all other symptoms were reported only once. The AEs were evenly distributed between the treatments, however none was reported during the formoterol 36 µg treatment. Two of the AEs were assessed as being of a severe intensity; both were Serious Adverse Events (SAEs) due to hospitalisation (one case of cerebrovascular disorder, and one cholelithiasis), and considered by the investigator as not related to the study treatment. The SAEs occurred in the wash-out

periods after formoterol 4.5 µg and formoterol 18 µg treatment, respectively. Both patients recovered without sequela. No discontinuations due to AEs were reported in the study.