AstraZeneca

DRUG PRODUCT	Oxis Turbuhaler	**Synopsis**	(FOR NATIONAL AUTHORITY USE ONLY)
DRUG SUBSTANCE(S)	Formoterol	REFERRING TO PART OF THE DOSSIER	
DOCUMENT NO.	SD-037-CR-0724		
VERSION NO.	01		
STUDY CODE	SD-037-0724		
DATE	27 August, 2002		

FINAL

Comparison of formoterol (Oxis®) via Turbuhaler® with salbutamol via pressurized metered dose inhaler and spacer in subjects with acute asthma presenting to the Emergency Department

STUDY CENTRE(S)

This study was run in 4 centres in Australia.

PUBLICATION (REFERENCE)

To be decided.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST Subject ENROLLED**	12 March 2001	Therapeutic use
- **DATE OF LAST Subject COMPLETED**	16 October 2001	

OBJECTIVES

The primary objective of this study was to compare the efficacy of formoterol 36 μg administered as two divided doses (18 μg + 18 μg) via Turbuhaler and salbutamol 1600 μg administerd as two divided doses (800 μg + 800 μg) via pressurized metered dose inhaler (pMDI) and spacer device in the treatment of subjects with acute asthma presenting to the Emergency Department (ED).

The secondary objectives of the study were to further assess the efficacy and safety of formoterol and salbutamol within the first 4 hours after administration of the first dose of study drug.

STUDY DESIGN

The design of the study was double-blind, double-dummy, randomized, reference-controlled with parallel groups.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Subjects presenting at the ED with acute bronchoconstriction and the diagnosis of asthma were eligible for the study after consenting if their age was > 18 and ≤ 70, if they had an FEV_1 of > 30 % predicted normal value, and if their pulse rate was ≥ 100 beats per minute (only if ≥ 50 years of age).

Subjects were excluded if their acute bronchoconstriction required treatment with nebulized or IV β_2-agonists and if transfer to the intensive care unit was required at initial assessment. Other exclusion criteria were oxygen saturation (SaO_2) < 93% on room air as well as any known severe cardiovascular disorder such as ischemic heart disease, tachyarrhythmias or severe heart failure.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Formoterol (Oxis®), inhalation powder, via Turbuhaler®, 4.5 μg/inhalation (delivered dose, corresponding to 6 μg metered dose), cumulative doses (batch Nos: BA19, CC22). Total dose was 36 μg administered as four inhalations on two occasions (18 μg/occasion).

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Salbutamol, via pMDI and spacer, 100 μg/inhalation, cumulative doses (batch No; AAR99A). Total dose was 1600 μg administered as four inhalations on two occasions (800 μg/occasion).

DURATION OF TREATMENT

The study drug was administered as cumulative doses at time 0 and 30 minutes after first dose. Efficacy and safety were assessed up to four hours after administration of the first dose.

MAIN VARIABLE(S):

The primary variable was forced expiratory volume in one second (FEV_1 percent predicted) measured 45 minutes after administration of the first dose of study drug.

- **EFFICACY**

Secondary efficacy variables were:

change in FEV_1 (at other time points than 45 minutes)
PEF percent predicted at 45 minutes
change in PEF (at 15, 75, 90, 120, 180 and 240 minutes)
number of subjects withdrawn from the study within 4 hours after administration of the first dose

- **SAFETY**

The variables used to assess safety were:

adverse events (AEs)
pulse/blood pressure/respiratory rate
oxygen saturation
ECG; heart rate, QTc
serum potassium

STATISTICAL METHODS

The primary efficacy variable was the FEV_1 percent predicted at 45 minutes after administration of the first dose of study drug. Secondary efficacy variables were the changes in FEV_1 and PEF and maximum and average post study drug values for FEV_1 and PEF from 45 to 240 minutes. Treatments were compared using an additive analysis of variance model with fixed factors treatment and centre and FEV_1 at baseline as a covariate. The number of subjects withdrawn within 4 hours after first drug administration was compared using the χ2-test.

Safety parameters, the minimum and average post study drug values for serum potassium and diastolic blood pressure were compared between treatments as well as the maximum and average post study drug values for systolic blood pressure, heart rate and QTc. Additive ANOVA models were used to assess differences between treatments regarding safety. The assessments of ECG i.e. sinus rhythm and overall evaluation are presented as descriptive statistics.

SUBJECTS, BASELINE DATA

	Formoterol Turbuhaler	Salbutamol pMDI	Total
No. planned	40	40	80
No. randomized and treated	38	40	78
Males/Females	16/22	10/30	26/52
Mean age (range), years	36 (18-69)	37 (19-67)	37 (18-69)
BMI, kg/m^2	28 (17-57)	27 (16-61)	28 (16-61)
IGCS at study entry, N	25	23	48
IGCS at study entry, μg	1313 (200-3200)	908 (50-2000)	1092 (50-3200)
FEV_1at study entry, L	1.90 (0.59-4.10)	1.77 (0.65-3.37)	1.83 (0.59-4.10)
FEV_1 % predicted normal	57 (31-101)	60 (30-107)	59 (30-107)
SaO_2 %	96 (93-100)	97 (93-100)	97 (93-100)
Pulse, beats per minute	102 (67-136)	99 (72-138)	100 (67-138)
No. analyzed for efficacy	38	39	77
No. analyzed for safety	38	40	78
No. completed*	29	27	56

* Completed refers to the No. of subjects who participated throughout the entire 4 hour study period.

SUMMARY

- EFFICACY RESULTS

The analysis of the primary variable, change in FEV_1 % predicted normal (p.n.) value at 45 minutes (E_{45}) after the first dose of study drug (i.e. 15 minutes after the last dose), did not show a statistically significant difference between the treatments (see Table 1). The average change, adjusted difference, (E_{av}) was 4.4% (-20.8 to 31.0) in the formoterol group and 7.4% (-11.4 to 45.9) in the salbutamol group.

Table 1. Descriptive statistics, FEV_1

Variable	Mean diff form-salb	95% conf.limits	p-value
FEV_1 (%p.n.) E_{45}	-3.00	(-7.99, 2.00)	0.24
FEV_1 (%p.n.) E_{15}	-1.91	(-6.31, 2.49)	0.39
FEV_1 (%p.n.) E_{av}	-1.52	(-7.23, 4.19)	0.6
FEV_1 (%p.n.) E_{max}	-2.34	(-8.24, 3.56)	0.43

E= Effect

The change in PEF percent predicted normal (PEF, E_{av}) was similar to the change in FEV_1 percent predicted normal, though the difference between treatments -5.2% (-10.5 to 0.0) was statistically significant in favour of salbutamol at 15 minutes (PEF, E_{15}) after first dose of

study drug (p=0.05). No difference between the treatments was shown for any of the following PEF assessments during the study.

- **SAFETY RESULTS**

Twenty seven AEs were reported and 8 subjects discontinued due to an AE (3 in the formoterol group and 5 in the salbutamol group). The most commonly reported AE was asthma aggravated (3 in the formoterol group and 4 in the salbutamol group).

The number of SAEs reported was 4 in the formoterol group and 7 in the salbutamol group.

No statistically significant nor any clinically relevant difference between treatments was displayed regarding heart rate, QTc and serum potassium.