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-0739		
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STUDY CODE	SD-037–0739		
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FINAL

A six months, randomised, open, parallel group, multicentre study to examine efficacy and safety of as needed versus maintenance use of Oxis® Turbuhaler® (formoterol) 9 μg in subjects well controlled on maintenance treatment with inhaled corticosteroids and long-acting β_2-agonist

STUDY CENTRE(S)

This was a multicentre study conducted in France, Israel, Norway and South Africa with a total of 36 centres. The number of centres in each country was 13, 5, 12 and 6, respectively.

PUBLICATION (REFERENCE)

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **DATE OF FIRST PATIENT ENROLLED**	June 05, 2001	Therapeutic confirmatory
- **DATE OF LAST PATIENT COMPLETED**	July 01, 2002	

OBJECTIVES

The primary objective of this study was to examine whether subjects well controlled on inhaled corticosteroids (ICSs) and maintenance use of long-acting β_2-agonist (LABA), could change from maintenance to only as needed use of Oxis® Turbuhaler® 9 μg by assessment of percentage of subjects who had a treatment failure during 6 months.

Treatment failure was defined as occurrence of at least one of the following:
- an asthma related serious adverse event
- changed maintenance dose of ICSs
- use of oral corticosteroids due to worsening of asthma
- treatment at a medical care unit due to worsening of asthma

The aim was to show that the number of treatment failures in the Oxis Turbuhaler 9 μg as needed group did not exceed the number of treatment failures in the control group with more than 20 %.

The secondary objective was to compare the efficacy of Oxis Turbuhaler 9 μg used only as needed with Oxis Turbuhaler 9 μg twice daily plus as needed by assessment of; asthma symptoms, nocturnal awakenings due to asthma symptoms, investigational product consumption and health-related quality of life (HRQL). Safety was assessed by incidence, type and intensity of adverse events.

STUDY DESIGN

This was a 6-month open, randomised, controlled, parallel group multicentre study in asthmatic patients well controlled on ICSs and LABA.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

This was an asthma study. Subjects who fulfilled the following inclusion criteria and none of the exclusion criteria were judged eligible.

Inclusion criteria:
1. Provision of written informed consent.
2. Out-patient, male or female, age ≥12 years.
3. Asthma diagnosed according to American Thoracic Society for more than 6 months (6).
4. $FEV_1 \geq 70$ % of predicted normal value after inhalation of one dose Oxis Turbuhaler 9 μg at the clinic, or ≤ 2 hours after inhalation of short-acting bronchodilator or ≤ 6 hours after inhalation of long-acting bronchodilator at home.
5. Use of ICS (any brand) at a daily dose 200 - 2000 μg the last 3 months.
6. Use of inhaled LABA during the last 3 months.

The day of randomisation was not regarded as one of the last 10 days of the run-in period. For randomisation in the study (visit 2), subjects had to fulfil all of the following criteria:

7. Use of Oxis Turbuhaler 9 μg used as needed ≤ 5 of the last 10 calendar days of the run-in period.
8. No day with > 2 doses of Oxis Turbuhaler 9 μg used as needed during the last 10 calendar days of the run-in period.
9. Daytime asthma symptom score (daytime or night-time) = 0 on a scale from 0 to 3 on ≥ 5 of the last 10 calendar days of the run-in period.
10. No day with asthma symptom score (daytime or night-time) > 1 during the last 10 days of the run-in period.
11. PEF diurnal variation ≤ 10 % on ≥ 8 of the last 10 calendar days of the run-in period.

12. Maximum 2 asthma related nocturnal awakenings the last 10 days of the run-in period.
13. Absence of significant respiratory infection during the run-in period, as judged by the investigator.
14. Unchanged prescription of asthma medication during the run-in period.

Exclusion criteria:

1. A history of smoking ≥ 10 pack-years.
2. Use of any β-blocker (including eye drops).
3. Changed dosing of ICSs the last month prior to visit 1.
4. Respiratory infection affecting the asthma within 1 month prior to visit 1, as judged by the investigator.
5. Any significant disease or disorder (e.g. pulmonary disease other than asthma, cardiovascular disease, gastrointestinal, liver, renal, neurological, musculoskeletal, endocrine, metabolic, malignant, psychiatric, major physical impairment) which in the investigator's opinion, may put the subject at risk because of participation in the study, may influence the results of the study, or the subjects ability to participate in the study.
6. Pregnancy or lactation.
7. When applicable, females of childbearing potential not using medically accepted contraceptive measures, as judged by the investigator.
8. Subjects who are scheduled to undergo hospitalisation due to surgery during the study.
9. Conditions associated with poor compliance, including alcohol or drug abuse.
10. Participation in a clinical study of any investigational product 1 month prior to visit 1 or during the study.
11. Previous allocation of a subject number in this study.

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Oxis (formoterol fumarate dihydrate) Turbuhaler 9 μg for inhalation, batch: CA 776, taken as needed. Will be referred to as Oxis in this report below.

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Oxis (formoterol) Turbuhaler 9 μg for inhalation, batch: CA 776, taken twice daily plus as needed. Will be referred to as Oxis+Oxis in this report below.

DURATION OF TREATMENT

1 month run-in was followed by 6 months treatment.

MAIN VARIABLE(S):

- **EFFICACY**

Primary variable was the percentage of subjects who had a treatment failure.

- **SAFETY**

The main variables for safety was incidence, type and intensity of adverse events during the study.

STATISTICAL METHODS

Primarily, descriptive statistics was used to evaluate efficacy. For the primary variable, the percentage of treatment failures, 95 % confidence intervals was constructed for the percentage within each group and for the difference in percentage between groups. Distribution of consumption of investigational product and asthma symptoms, was presented graphically as histograms. Secondary endpoints was compared using analysis of variance with treatment and country/centre as fixed factors and using the run-in mean as covariate. The statistical analysis followed the intention-to-treat approach, i.e. include all treated subjects with data from the treatment period. All tests was two-sided at a 5 % significance level. Adverse events were analysed by means of descriptive statistics and qualitative analysis.

SUBJECTS

Table 1. Treatment group comparison of patient flow and baseline characteristics.

	OXIS	**OXIS + OXIS**	**Total**
No. planned	150	150	300
No. randomized	166	155	321
Males/Females	67/99	73/82	140/181
Mean age (range)	40 (12-77)	41 (12-78)	40 (12-78)
FEV_1 (L) post bronchodilator	2.89 (1.23 –5.62)	2.84 (1.32 –5.14)	2.87 (1.23 –5.62)
FEV_1 (%P.N.) post bronchodilator	92 (55 –170)	90 (60 –120)	91 (55 –170)
Mean no.of inh.	2.1 (0.0 –4.0)	2.1 (1.8 –4.0)	2.1 (0.0 –4.0)
Mean symptom score	0.1 (0.0 –1.2)	0.1 (0.0 –1.0)	0.1 (0.0 –1.2)
No. analysed for efficacy	166	155	321
No. analysed for safety	166	154	320
No. completed	153	133	286

SUMMARY

- EFFICACY RESULTS

For the primary efficacy variable, the percentage of subjects with treatment failure, the pre-defined treatment difference of 0.2 (20%) between Oxis and Oxis+Oxis was not exceeded. In the Oxis and Oxis+Oxis groups 14/166 (8.4%) and 16/155 (10.3%), respectively, of the subjects had treatment failures. The estimated treatment difference between the Oxis and Oxis+Oxis group (–0.02 (-0.08, 0.05)) was not statistically significant.

There were 13/166 (7.8%) and 21/155 (13.5%) withdrawals in the Oxis and Oxis+Oxis group respectively. However, no treatment difference in withdrawal rates could be demonstrated (p=0.090).

The subjects treated with Oxis increased their daytime asthma symptom score with 0.16 compared with 0.06 in the Oxis+Oxis group. The estimated treatment difference was 0.10 (p=0.0017). For symptom free days the pattern was similar. The percentage of symptom free days decreased from 88% to 74.2% and from 89.4% to 83.9% for subjects treated with Oxis and Oxis+Oxis, respectively. The estimated treatment difference was 9.0 percentage units (p<0.001).

The consumption of investigational product was considerably reduced for the subjects in the Oxis group, compared with the Oxis+Oxis group. The subjects in the Oxis group consumed 1.3 (p<0.001) inhalations less per day than the Oxis+Oxis group subjects.

For neither night-time asthma score nor the percentage awakenings, a treatment difference could be demonstrated between Oxis and Oxis+Oxis.

Health-related quality of life, as measured by the Asthma Quality of Life Questionnaire, standardised version (AQLQ(S)), was not shown to differ between the treatment groups as assessed over the whole treatment period.

In summary, there were no treatment differences in neither treatment failures, night-time asthma symptom score, nocturnal awakenings due to asthma, withdrawal rates nor HRQL between the Oxis and the Oxis+Oxis group. However, Oxis treatment in comparison with Oxis+Oxis treatment, exhibited slightly increased asthma daytime symptom score, somewhat fewer symptom free days and a large reduction in investigational product consumption.

- **SAFETY RESULTS**

- The frequency of subjects reporting adverse events was low (40%) and equal between the 2 treatment groups.
- There was no apparent difference in the adverse event pattern and in the proportion of reported system organ classes and adverse events between the 2 treatment groups. As expected, most reported adverse events were associated with the respiratory system.
- The number of subjects discontinuing the study due to adverse events was low; 4 in each treatment group.
- During randomised treatment, 7 subjects (4%) in the Oxis group and 5 (3%) subjects in the Oxis+Oxis group reported 12 serious adverse events. No serious adverse events were considered to be related to study treatment by the investigator or sponsor, and none of the subjects discontinued due to these events.

The 6 month safety profile between Oxis treatment, compared with Oxis+Oxis treatment, was comparable. The treatments were considered safe and well tolerated, and no new or clinically important drug related safety findings were observed.