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-0716		
VERSION NO.	01		
STUDY CODE	SD-037-0716		
DATE	21 October, 2002		

FINAL

A 12-month comparison of Oxis® (formoterol) Turbuhaler® and Bricanyl® (terbutaline) Turbuhaler both used as needed in subjects with asthma not using anti-inflammatory treatment

STUDY CENTRE(S)

54 centres in 8 countries (Estonia, Germany, Latvia, Lithuania, Poland, Russia, the United Kingdom, and Ukraine) randomised subjects into the study.

STUDY PERIOD		**PHASE OF DEVELOPMENT**
- **FIRST SUBJECT ENROLLED**	February 2001	Therapeutic confirmatory
- **LAST SUBJECT COMPLETED**	June 2002	

PUBLICATION (REFERENCE) (NOT APPLICABLE)

OBJECTIVES

The primary objective of the study was to show that Oxis Turbuhaler, used as needed, is non-inferior to Bricanyl Turbuhaler, as needed, regarding asthma control in subjects with mild intermittent asthma. The primary variable was the average morning peak expiratory flow (PEF) over the entire 12-month treatment period. Non-inferiority was to be declared if the lower limit of the two-sided 95% confidence interval for the difference between Oxis Turbuhaler and Bricanyl Turbuhaler did not exceed -10 L/min.

The secondary objective was to compare the efficacy and safety of 12-month treatment with as needed Oxis Turbuhaler with that of as needed Bricanyl Turbuhaler.

STUDY DESIGN

Subjects who fulfilled all inclusion criteria and none of the exclusion criteria at Visit 1 entered a three-week run-in period during which they received Bricanyl Turbuhaler 0.5 mg as needed in a single-blind manner. Those who completed the run-in period according to the protocol, were stratified according to their age into three groups, children (6-11 years), adolescents (12-17 years), and adults (≥18 years), before randomisation. Subjects were randomised to either proceed with the same treatment or shift to Oxis Turbuhaler 4.5 μg as needed during 12 months in a double-blind manner.

During the study the subjects attended the clinic on 9 occasions: one screening visit, one visit at the end of run-in, and after 1, 2, 4, 6, 8, 10, and 12 month's treatment. Between the visits, the subjects were contacted by telephone to check adverse events (AEs) and compliance with study procedure.

Two subgroups including at least 60 subjects each aged ≥12 years, attended the clinic for more visits. One group tested the tolerability of a single high dose of the study drug on one occasion, after 10-12 months' treatment. The second group attended the clinic on two extra occasions, one before randomisation and a second one after 10-12 months' treatment for methacholine challenge tests. Subjects participated only in one of the two subgroups. Children age 6-11 years did not participate in any of these subgroups.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria

Visit 1

1. Males and females with an age of ≥6 years and a diagnosis of asthma according to the American Thoracic Society
2. Baseline forced expiratory flow in one second (FEV_1) ≥80% of predicted normal value
3. Informed consent obtained before conducting any study-related procedures

Visit 2

4. Use of short acting β_2-agonist on two to six occasions during the last 14 days in the run-in period

Main exclusion criteria

Visit 1

1. Use of inhaled steroids or other anti-inflammatory treatment within 3 months prior to Visit 1
2. Use of long-acting β_2-agonist within 3 months prior to Visit 1
3. Use of a β-blocker including eye drops
4. Respiratory infection affecting the asthma within 4 weeks prior to enrolment, as judged by the investigator

5. Subjects with a history of smoking ≥10 pack-years
6. Use of unallowed medication

Visit 2

7. <16 morning PEF values in the diary during run-in
8. Any significant respiratory infection during run-in, as judged by the investigator
9. Change in prescribed asthma medication during run-in

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Oxis (formoterol fumarate dihydrate) Turbuhaler, batch nos. 6128 and 6189, 4.5 μg as needed, inhalation

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Bricanyl (terbutaline sulphate) Turbuhaler, batch nos. 6127 and 6188, 0.5 mg as needed, inhalation

DURATION OF TREATMENT

12 months

MAIN VARIABLE(S):

- **EFFICACY**

Primary

The primary variable was the average morning PEF over the entire 12-month treatment period.

Secondary

- FEV_1 before and after inhalation of investigational product at the clinic
- Evening PEF
- Average daily number of inhalations of investigational product
- Day-time asthma symptoms
- Night-time asthma symptoms
- Time to first severe asthma exacerbation
- Provocative cumulative dose of methacholine giving a 20% fall in FEV_1 (PD_{20}) (subgroup)

- **SAFETY**

- AEs
- Clinical chemistry, hematology and urinalysis
- ECG
- Systolic and diastolic blood pressure

- Blood pressure, ECG, S-potassium, B-glucose and AEs after single high dose administration (subgroup)

STATISTICAL METHODS

The primary efficacy variable, morning PEF, was compared between treatments using an analysis of variance (ANOVA) model with treatment and country as factors and baseline as a covariate. Non-inferiority was declared if the lower limit of the two-sided 95% confidence interval for the difference between Oxis Turbuhaler and Bricanyl Turbuhaler did not exceed -10 L/min. The non-inferiority decision was based on the per protocol (PP) population. An intention-to-treat (ITT) analysis was also performed. The non-inferiority test was followed by an ordinary test for superiority.

For the secondary efficacy variables only an ITT-analysis was performed, except for evening PEF for which both ITT- and PP-analyses were performed. The same ANOVA model was used for the analysis of other diary card variables as for morning PEF. FEV_1 before and after one dose of investigational product at the clinic visits were compared using multiplicative ANOVA models with treatment and country as factors and baseline as a covariate. Time to first severe asthma exacerbation was compared using a Cox proportional hazards model and time to withdrawal was compared using the log-rank test.

PD_{20} was compared between treatments using a multiplicative ANOVA model with fixed factors country and treatment and using baseline PD_{20} as a covariate. Pharmacodynamic parameters (E_{av}, E_{max}, and E_{min} as well as C_{av}, C_{max}, and C_{min}) for the various variables measured during the single high dose tests were compared using additive ANOVA models with fixed factors treatment and country and using baseline of the study day (value pre-dose) as a covariate.

All hypothesis testing was done using two-sided alternative hypotheses. P-values less than 5% were considered statistically significant.

AEs were analysed by means of descriptive statistics and qualitative analysis.

SUBJECTS

Five-hundred subjects (250 in each group) were planned to be randomised at 65 centres.

	Oxis	**Bricanyl**	**Total**
No. planned	250	250	500
No. randomised and treated	333	342	675
Males/Females	194/139	208/134	402/273
Mean age (range)	23 (6-73)	24 (6-87)	24 (6-87)
No. analysed for efficacy	333	339	672
No. analysed for safety	333	341	674
No. completed	310	314	624

SUMMARY

- EFFICACY RESULTS

Oxis Turbuhaler proved to be non-inferior to Bricanyl Turbuhaler when used as needed in subjects with mild intermittent asthma. The lower limit of the 95% confidence interval for the difference in morning PEF was -3.2 L/min (test limit was -10 L/min). Numerically, morning PEF was highest in the Oxis group, but no statistically significant difference was found.

No statistically significant difference between Oxis Turbuhaler and Bricanyl Turbuhaler was found on any of the secondary efficacy variables: evening PEF, asthma symptom, use of investigational product, pre- and post-bronchodilator FEV_1 or severe asthma exacerbations.

After administration of a high single dose of the investigational product in a subset of subjects, there were statistically significant differences between the two treatment groups on serum potassium (larger decrease after Bricanyl Turbuhaler), systolic blood pressure, heart rate and QTc (larger increases after Bricanyl Turbuhaler).

In another subset of subjects, performing methacholine challenges during run-in and near end-of-treatment, there was no statistically significant difference between the groups in PD_{20}.

- SAFETY RESULTS

The frequency of subjects reporting AEs during the as needed treatment, as well as the pattern of these AE, were similar between the two treatment groups. Most common were different infections and allergy symptoms in the respiratory system.

Both the frequency of subjects reporting AEs (33% and 67%, respectively) and the number of AEs that were reported during the single high dose day (26 and 56, respectively) were much lower in the Oxis group compared with the Bricanyl group. The frequency of tremor was much higher in the Bricanyl group than in the Oxis group (54% and 15%, respectively).

Six subjects in each treatment group reported one SAE each. None of the SAEs were assessed as being related to study treatment, and none of the events caused the subject to discontinue the study.

Only 2 AEs lead to study discontinuation, both occurring in the Bricanyl group.

Laboratory values, ECG and blood pressure over a 12-month period as well as after single high doses showed no clinically relevant differences between the treatment groups. However, on the parameters where a statistical difference between the treatments was found after single high doses, these differences were to Oxis' advantage.