AstraZeneca

DRUG PRODUCT DRUG SUBSTANCE(S) Formoterol Turbuhaler DOCUMENT NO. SD-037-CR-0714 VERSION NO. 1 STUDY CODE SD-037-0714 DATE 11 November, 2002	**Synopsis** REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)

FINAL

A 12-month comparison of Oxis® (formoterol) Turbuhaler® and Bricanyl® (terbutaline) Turbuhaler® both used as needed in patients with asthma on anti-inflammatory treatment

STUDY CENTRE(S)

This was a multicentre study performed in Czech Republic, Portugal, Slovak Republic and South Africa with a total of 48 centres actively randomising subjects.

PUBLICATION (REFERENCE)

-

STUDY PERIOD		PHASE OF DEVELOPMENT
- DATE OF FIRST PATIENT ENROLLED	December 22, 2000	Therapeutic confirmatory
- DATE OF LAST PATIENT COMPLETED	July 9, 2002	

OBJECTIVES

The primary objective of the study was to show that Oxis® Turbuhaler® , used as needed, is non-inferior to Bricanyl® Turbuhaler® , used as needed. The primary variable was average morning peak expiratory flow (PEF) over the entire 12-month treatment period.

The secondary objective was to compare the efficacy and safety of 12 months treatment with Oxis Turbuhaler and Bricanyl Turbuhaler, both used as needed.

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 before randomisation, stratified according to their age into three groups, 6-11 years, 12-17 years and ≥18 years. Subjects were randomised to either proceed with the same treatment or shifted to Oxis Turbuhaler, 4.5 μg, as needed during 12 months in a double-blind manner.

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

Two subgroups of the subjects at the age of ≥12 years attended the clinic for more than 9 visits. One group tested the tolerability of a high single dose of the study medication at one occasion. The second group attended the clinic at two occasions one before randomisation and a second one after 10-12 months treatment for methacholine challenge tests. Subjects participated only in one of the subgroups. Children at the age of 6-11 years did not participate in any of the subgroup tests.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Inclusion criteria

Visit 1

1. Males and females with an age of ≥6 years with diagnosis of asthma according to American Thoracic Society (ATS) (1)
2. Baseline FEV_1 ≥80 % of predicted normal value (2, 3)
3. Stable inhaled steroid dose of ≥200 but ≤500 μg/day, nedocromyl or cromoglycate treatment for at least 4 weeks prior to enrolment

Visit 2

4. Use of the as needed medication drug between ≥3 times/week and ≤4 times/day during the run in period (The term "times" was clarified in an electronic mail sent to all monitors 9 February, 2001; times/week = inhalation occasions/week, times/day = no. of inhalations/day).

Exclusion Criteria

Visit 1

1. Use of long-acting β_2-agonists within 3 months prior to visit 1
2. Use of a β-blocker including eye drops
3. Subjects with a history of smoking ≥10 pack-years

Visit 2

4. Less than 16 morning PEF values recorded in the diaries during the run-in (Change, compared with study protocol according to Global Amendment no. 2).
5. Any significant respiratory infection during run-in, as judged by the investigator
6. Change in prescribed asthma medication during run-in

TEST PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Oxis® (formoterol fumarate dihydrate)Turbuhaler® 4.5 μg used as needed. Batch numbers: CC22, BI20, BF 319/1 BA19, AH18

COMPARATOR PRODUCT, BATCH NUMBER, DOSAGE AND MODE OF ADMINISTRATION

Bricanyl® (terbutaline sulphate) Turbuhaler® 0.5 mg as needed. Batch numbers: CA19, CA20, BB16.

DURATION OF TREATMENT

12 months

MAIN VARIABLE(S):

- **EFFICACY**

Primary variable

Average morning PEF over the entire 12-month treatment period.

Secondary variables

- Pre- and post-dose FEV_1
- Evening PEF
- Day- and night-time use of study medication
- Day- and night-time asthma symptoms
- Time to first asthma exacerbation
- PD_{20} methacholine (subgroup)

- **SAFETY**

- Adverse events (AEs)

- Clinical chemistry, haematology and urinalysis
- Electrocardiography (ECG)
- Systolic and diastolic blood pressure
- Blood pressure, ECG, serum-potassium, blood-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 and Bricanyl did not exceed -10 L/min. The non-inferiority decision was based on the per protocol (PP) population. The non-inferiority test was followed by an ordinary test for superiority in the intention-to treat (ITT) population.

For the secondary efficacy variables only an ITT-analysis was performed, except for evening PEF for which both ITT- and per protocol (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 study medication 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.

The provocative cumulative dose (PD_{20}) was compared between treatments using a multiplicative ANOVA model with fixed factors centre and treatment and using baseline PD_{20} as a covariate. Pharmacodynamic parameters (E_{av}, E_{max}, E_{min}) for the various variables measured during the high dose tests were compared using additive ANOVA models with fixed factors treatment and centre 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

	Oxis Turbuhaler	Bricanyl Turbuhaler	All
Enrolled subjects			615
Not randomised			160
- Adverse event			9
- Eligibility criteria not fulfilled			151
Randomised	228	227	455
Discontinued	11	20	31
- Adverse event	2	3	5
- Eligibility criteria not fulfilled	2	3	5
- Study-specific discontinuation criteria	1	1	2
- Other reasons	6	13	19
Completers	217	207	424

SUMMARY

- EFFICACY RESULTS

The primary objective of this study was to show that Oxis Turbuhaler is non-inferior to Bricanyl, both treatments used as needed, regarding asthma control measured as morning PEF.

Oxis Turbuhaler proved to be non-inferior to Bricanyl Turbuhaler when used as needed in subjects with asthma on a stable dose of anti-inflammatory treatment. The lower limit of the 95% confidence interval for the difference in morning PEF was -3.7 L/min (test limit -10 L/min) (see table below). Numerically morning PEF was highest in the Oxis group, but no statistically significant difference was found.

	Oxis Turbuhaler vs. Bricanyl Turbuhaler		
Variable	Difference	95% conf. lim.	P-value
PEF (L/min)			
-morning	5.5	(-3.7, 14.7)	0.24
-evening	2.8	(-6.7, 12.2)	0.56

There was a statistically significant difference in favour of Oxis Turbuhaler on pre-dose FEV_1. No statistically significant differences between Oxis Turbuhaler and Bricanyl Turbuhaler were found on any of the other secondary efficacy variables: evening PEF (see table above), asthma symptom, use of study medication, post-bronchodilator FEV_1 or severe asthma exacerbations. However, there was a trend of less symptoms and less use of study medication during night-time in the Oxis group.

Because of recruitment problems, fewer subjects than planned performed the high dose test (9 subjects out of 60 planned) and the methacoline challenge test (17 out of 60 planned). No statistically significant differences between Oxis and Bricanyl were found but due to the low number of subjects, no conclusions can be drawn from these analyses.

- **SAFETY RESULTS**

- The frequency of subjects reporting AEs during the as-needed treatment was slightly higher in the Bricanyl group, the pattern, however, was comparable between the two groups. Most common were various infections and allergy symptoms in the respiratory system.
- The results during the high dose visit regarding AEs, laboratory values and vital signs did not raise any safety concerns for any of the treatments, although the low number of subjects precludes any reliable conclusions to be drawn.
- 12 subjects in the Oxis group and 13 subjects in the Bricanyl group reported SAEs. None of the serious AEs (SAEs) were assessed to be related to the study treatment. 3 of the SAEs lead to the subject discontinuing the study.
- Only 5 subjects had AEs that lead to study discontinuation (2 subjects in the Oxis group, 3 in the Bricanyl group).
- Lab values, ECG and blood pressure over a 12-month period showed no clinically relevant differences between the two treatment groups.