**SD-037-0709**

**STUDY REPORT SUMMARY**

**ASTRAZENECA PHARMACEUTICALS**

**FINISHED PRODUCT:** Oxis®

**ACTIVE INGREDIENT:** formoterol

**Trial title (number):** A 6-month study to compare the efficacy and safety of 9µg formoterol (Oxis) Turbuhaler b.i.d. with placebo b.i.d. in patients with Chronic Obstructive Pulmonary Disease (COPD). Furthermore to compare formoterol 4.5µg as needed with terbutaline 0.5 mg as needed.

**Development phase**:IIIA
**First subject recruited**: 28 July 2000
**Last subject completed**: 07 November 2001
**Approval date**: 08 April 2002

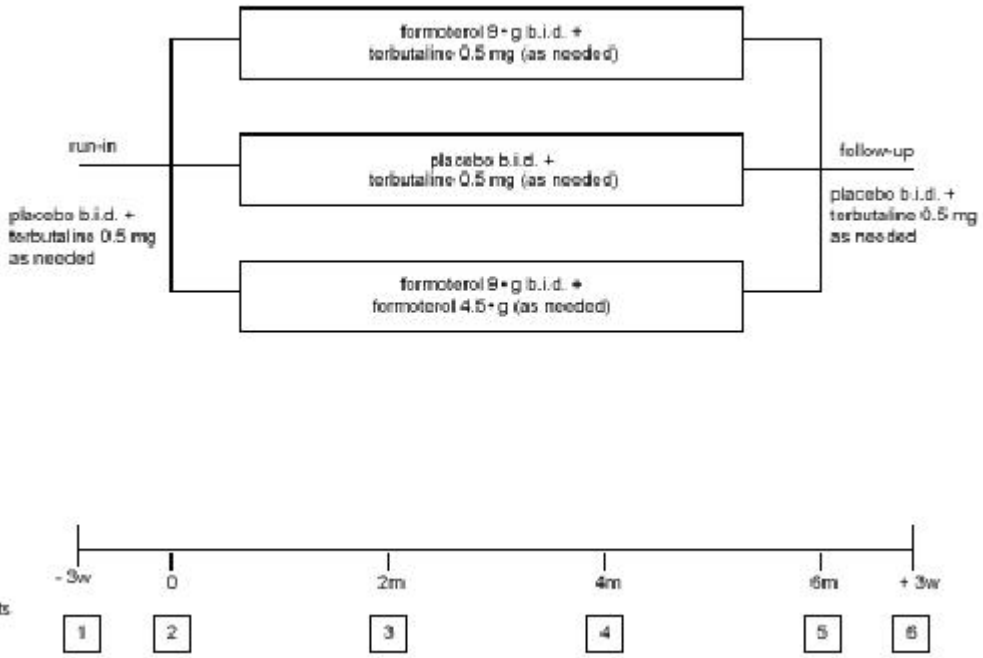
**OBJECTIVES**

The aim of the study was to compare formoterol 9µg b.i.d. with placebo b.i.d. (both with terbutaline 0.5 mg as rescue medication) and to compare formoterol 4.5µg as needed with terbutaline 0.5 mg as needed (both on top of regular treatment with formoterol 9µg b.i.d.). There were two primary efficacy variables, $FEV_1$ and the sum of breathlessness and chest tightness scores.

Secondary objective was safety assessed by ECG, vital signs, clinical chemistry and haematology and a standard adverse event (AE) question.

**METHODS**

Study Design:
Double-blind, randomized, placebo controlled, three parallel groups




Formoterol b.i.d.+ terbutaline as needed (Form+Terb)
placebo b.i.d.+ terbutaline as needed (Plac+Terb)
formoterol b.i.d. + formoterol as needed (Form+Form)
Diagnosis and Main Criteria for Inclusion/Exclusion
Out-patients with COPD.

Inclusion Criteria

- Clinical diagnosis of COPD with symptoms≥2 years prior to enrolment
- Men or women ≥40 years of age
- Pre-bronchodilator $FEV_1$ ≥40 and≤70% of predicted normal
- Pre-bronchodilator $FEV_1$ / VC <70%
- A sum of breathlessness and chest tightness scores of ≥2 per day during at least 10 days of the run-in period
- Current or previous smoker with a history of smoking equivalent to 10 or more pack years (1 pack year = 20 cigarettes smoked per day for one year or equivalent)

Exclusion Criteria

- A history of asthma or seasonal allergic rhinitis with disease onset before 40 years of age
- Changed dose of inhaled steroids or use of oral steroids within 4 weeks prior to enrolment

- Patients with significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure, uncontrolled hypertension or any other relevant cardiovascular disorder as judged by the investigator
- Any respiratory tract disorder other than COPD, which was considered by the investigator to be clinically relevant
- A significant exacerbation of COPD in the last 30 days prior to enrolment, requiring hospitalization, a course of antibiotics, use of oral steroids or change in inhaled steroid dosage
- A requirement for domiciliary oxygen

Test Prodcut, Dosage and Mode of Administration
Oxis®(formoterol) Turbuhaler® 9µg b.i.d.
Oxis®(formoterol) Turbuhaler® 4.5µg as needed.

Comparator Product, Dosage and Mode of Administration
Placebo Turbuhaler b.i.d.

Bricanyl (terbutaline) Turbuhaler® 0.5 mg as needed.

Duration of Treatment
6 months

Main Variable(s):
- Efficacy
The primary efficacy variables were $FEV_1$ from the clinic visits and the sum of breathlessness and chest tightness scores from the diary.

Secondary efficacy variables were time to first COPD exacerbation, VC, morning PEF, COPD symptom scores, use of rescue medication and HRQL assessed by the St.George's Respiratory Questionnaire (SGRQ).

- Safety
The main safety variables were changes in ECG, vital signs, clinical chemistry and haematology and the general pattern of AE collected through a standard question addressed to the subjects.

**STATISTICAL METHODS**
The study aimed at comparing formoterol maintenance treatment with 9µg b.i.d. with placebo and also at comparing formoterol 4.5µg with terbutaline 0.5 mg, both used as needed on top of maintenance treatment with formoterol. These two comparisons were treated separately when testing for statistical significance. For spirometry variables, the primary endpoints were the changes from baseline (visit 2) to the mean of values from visits 4 and 5. For diary card variables, the primary endpoints were the changes from the mean during run-in to the mean over the last 90 days of treatment. Treatments were compared using analysis of variance (ANOVA) model with treatment and country as fixed factors and baseline as covariate. Time to first severe COPD

exacerbation was compared between treatments using a Cox proportional hazards model. For the comparison between Form+Terb and Plac+Terb both primary efficacy variables must show statistical significance in order to declare effect of the drug. For the comparison between Form+Form and Form+Terb, Form+Form was first compared with Plac+Terb, and if this was statistically significant, the two formoterol groups were compared. No corrections for multiple tests were made. All analyses were performed according to the intention-to-treat approach and all tests were two-sided on a 5% significance level. AEs were analysed by means of descriptive statistics and qualitative analysis. Assessments of effects on laboratory variables, vital signs and ECG were based on mean and individual changes from baseline to end-of treatment and on treatment emergent laboratory abnormalities/changes.

**RESULTS**

Subjects:

It was planned to include 690 randomized subjects. Nine-hundred and six (906) were enrolled and 657 were randomized at 73 centres in Bulgaria, Hungary, Israel, Romania, the Netherlands, Spain, Sweden and the UK.

| | Form+Terb | Plac+ Terb | Form+Form | Total |
|---|---|---|---|---|
| No. enrolled | | | | 906 |
| No. randomized and treated | 215 | 217 | 225 | 657 |
| Males/Females | 131/84 | 159/58 | 160/65 | 450/207 |
| Mean age (range) | 60 | 60 | 60 | 60 |
| Baseline values | | | | |
| $FEV_1$ (% P.N) | 53 | 54 | 54 | 54 |
| $FEV_1$ (% VC) | 54 | 55 | 55 | 54 |
| No. analysed for efficacy | 215 | 217 | 225 | 657 |
| No. analysed for safety | 215 | 217 | 225 | 657 |
| No. completed | 184 | 178 | 195 | 557 |

Efficacy Results:

For the comparison between formoterol maintenance (Form+Terb) and placebo (Plac+Terb); formoterol was statistically significantly better on both primary variables, $FEV_1$ (difference 6.5%; p=0.001) and the sum of breathlessness and chest tightness scores (difference 0.27 units; p=0.01). On the secondary efficacy variables, formoterol was statistically significantly better on VC, breathlessness score, chest tightness score, cough score, sleep score, daily use of rescue medication and morning PEF (Table 1). No differences were found on severe COPD exacerbations or SGRQ. For the comparison between formoterol as needed (Form+Form) and Form+Terb, the former was statistically significantly better on $FEV_1$ and the symptom domain of the SGRQ questionnaire. Numerically, the Form+ Form group was better than the Form+Terb group on most of the other efficacy variables. Withdrawal of formoterol both as maintenance and as reliever on top of maintenance resulted in increased COPD symptoms, declines in lung function and impaired HRQL.

Table 1. Summary of the efficacy results ( Mean difference from baseline)

| Treatment Comparison | $FEV_1$ (%) | VC | PEF morning (l/min) | Combined symtoms (score 0-8) | Daily use of rescue medication | Severe COPD exacerbations, hazard ratio[b] |
|---|---|---|---|---|---|---|
| Form+Terb vs Plac+Terb | +6.5** | +4.6[a] | +14.8*** | -0.27* | -0.48* | 1.01 |
| Form+ Form vs Plac+Terb | +11.8*** | +6.7[a] | +20.4*** | -0.32** | -0.62** | 0.62 |
| Form+ Form vs Form+Terb | +5.00[a] | +2.0 | + 5.6 | -0.05 | -0.14 | 0.613 |

***P <0.001**P <0.01*P<0.05 versus placebo; a p<0.05 Form+Form vs Form+Terb; b 1.0 = equal risk

Safety Results

- The frequency of subjects reporting AEs was low and similar when comparing the 3 treatment groups. The most commonly reported system organ class (SOCs) and adverse events (AEs) occurred in a similar pattern in all treatment groups with regard to type and frequency, and most common were AEs related to the respiratory system.
- Three deaths occurred during randomised treatment in the formoterol groups. In addition, 2 deaths occurred post-treatment. None of the deaths were assessed as being related to the investigational products.
- Twenty-six subjects reported a serious adverse events (SAE), other than death, during randomised treatment; in total 17 (4%) SAEs in the 2 formoterol groups and 9 (4%) in the placebo group. Most of these SAEs were related to the subjects' underlying diseases. For 2 of the SAE cases, the investigator assessed the causal relationship as related to study treatment.
- The frequency of subjects who discontinued the study due to AEs was low and similar between the treatment groups.
- There were no clinically relevant differences between the treatment groups regarding laboratory values, ECG, pulse or blood pressure.

**REFERENCES**

Campbell M, Eliraz A, Johansson G, Tornling G, Nihlén U, Bengtsson T, Rabe KF. Formoterol for maintenance and as-needed treatment of chronic obstructive pulmonary disease. Respir Med 2005; 99: 1511-1520.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Oxis® (formoterol), Healthcare Professionals should view their specific country information.