AstraZeneca

SD-037-0695

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Oxis®

ACTIVE INGREDIENT: formoterol

Trial title (number): A 6 months comparison of the safety and efficacy profiles of Oxis (formoterol) Turbuhaler as needed and Bricanyl (terbutaline) Turbuhaler as needed in children with asthma on anti-inflammatory treatment.

Development phase:IIIb

First subject recruited: 27 January 2000

Last subject completed: 26 March 2001

Approval date: 13 December 2001

OBJECTIVES

Primary objectives:

To compare the safety and efficacy profiles of formoterol Turbuhaler 4.5µg/dose taken as needed and terbutaline Turbuhaler 0.25 mg/dose as needed in children/adolescents with asthma on inhaled glucocorticosteroid (IGCS), Disodium cromoglycate (DSCG) or nedocromil treatment. The primary variable was time to first asthma exacerbation.

METHODS

STUDY DESIGN

The design of the study was double-blind, parallel-group, reference controlled, and randomised. Subjects were stratified into two age groups, 6-11 and 12-17 years.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Subjects with bronchial asthma were included in the study.

INCLUSION CRITERIA

Girls and boys, aged 6-17 years with asthma were recruited for this study. To be eligible at the first visit, subjects were supposed to show reversibility in FEV_1 (12 % from baseline or 9 % of predicted normal value), to be on a stable dose of anti-inflammatory treatment and moreover, to demonstrate a need of ≥1 inhalation per day of a short-acting β_2-agonist during the run-in period. At visit 2, subjects had to show an average need of >1 inhalation/day of a short-acting β_2-agonist (study medication) during the last 14 days of run-in and to be compliant with the electronic diary prior to allocation to the 6-month treatment period.

EXCLUSION CRITERIA

Subjects who had lack of acceptable contraceptives or who were pregnant or breast-feeding were excluded at study entry. At visit 2, subjects were withdrawn from the study if they during the run-in period had: a need of >8 inhalations of the study medication during any single day; more than 3 days with a missing value for number of inhalations during the last 14 days of the run-in period; a significant respiratory tract infection had occurred.

TEST PRODUCT, DOSAGE AND MODE OF ADMINISTRATION

Formoterol Turbuhaler, 4.5µg, as needed (p.r.n.) for inhalation. Strength 4.5µg /dose.

COMPARATOR PRODUCT, DOSAGE AND MODE OF ADMINISTRATION

Terbutaline Turbuhaler, 0.25 mg as needed (p.r.n.) for inhalation. Strength 0.25 mg/dose.

DURATION OF TREATMENT

The duration of the treatment period was six months with study medication taken as needed.

MAIN VARIABLE(S):

The primary study variable was 'Time to first asthma exacerbation' which included bothmild and severe exacerbations.

- **EFFICACY**

The efficacy variables were: morning and evening PEF, number of inhalations of study medication, night time awakenings due to asthma, days when avoiding activity due to asthma symptoms, restrictions in activity (all collected in an electronic diary), $FEV_1$and Paediatric Asthma Quality of Life Questionnaire, standardised version, (PAQLQ(S)).

- **SAFETY**

The safety variables were: adverse events (AEs), ECG variables, pulse and blood pressure.

STATISTICAL METHODS

An Intention To Treat type of analysis was used. The primary analyses were performed of both age groups. Additional analyses investigated treatment differences in each age group. Time to first asthma exacerbation (mild or severe) was described and compared between the two treatment groups using a log-rank test. Additional descriptions, including descriptions for the different age groups, were made using Cox-regression models. Additional analyses were also made for the time to first severe asthma exacerbation. Diary variables were compared between the treatment groups by calculating the average value during the last 14 days of the run-in period and during the full treatment period. The change from run-in to the treatment period was analysed using an analysis of variance model with treatment and country as fixed factors and the run-in average as a covariate. Variables measured at clinic visits were analysed with respect to change from visit 2 to visit 5 using analysis of variance with treatment and country as fixed factors and the value at visit 2 as a covariate. An additive model was used for FEV_1. AEs were analysed by means of descriptive statistics and qualitative analysis.

RESULTS

SUBJECTS

It was estimated that 675 subjects had to be enrolled to obtain 500 evaluable subjects.

	Formoterol 4.5 µg	Terbutaline 0.25 mg	Total
No. planned	250	250	500
No. randomised and treated	277	275	552
Males/Females	178/99	180/95	358/194
Mean age (range)	11 (5-16)	11 (6-17)	11 (5-17)
IGCS at entry (µg)	395 (50-1400)	406 (100-1000)	401 (50-1400)
FEV_1	1.94 (0.75-4.12)	1.86 (0.77-3.92)	1.90 (0.75-4.12)
FEV_1 (% predicted)	83 (48-161)	80 (51-144)	82 (48-161)
Reversibility (%)	21 (2-62)	22 (3-66)	21 (2-66)
Mean No. of β_2-agonist inhalations	2.4 (0.5-7.7)	2.4 (1.1-7.0)	2.4 (0.5-7.7)
Mean symptom score	1.1 (0.0-6.0)	1.1 (0.0-4.1)	1.1 (0.0-6.0)
Symptom free days (%)	48 (0-100)	47 (0-100)	47 (0-100)
No. analysed for efficacy	277	275	552
No. analysed for safety	277	275	552
No. completed	260	257	517

EFFICACY RESULTS

No statistically significant difference could be shown between the treatment groups for the primary variable time to first exacerbation.

		Hazard		
Variable	Treatment	ratio	95 % Conf.Limits	P-value
Time to first exacerbation (mild or severe)	Formoterol 4.5 µg prn vs. Terbutaline	0.875	0.701 - 1.090	0.23
	0.25 mg prn			

The analysis of time to first exacerbation did not detect any statistically significant difference. In the formoterol group, 155 subjects (n=277) had an exacerbation and the corresponding figure in the terbutaline group was 161 (n=275). The mean time to first exacerbation (any kind) for subjects who experienced an exacerbation was 57 days in the formoterol group and 46 days in the terbutaline group. The corresponding figures for a severe exacerbation were 76 days for the formoterol group (n=51) and 83 days in the terbutaline group (n=51). For all analyses of diary variables, no statistically significant difference could be detected between the two treatment groups. The sub-group analyses of age groups 6-11 and 12-17 years were consistent with the result of the overall analyses. The analysis of health-related quality of life data did not detect any statistically significant difference between the treatment groups.

SAFETY RESULTS

The frequency of subjects who reported AEs was similar when comparing the two treatment groups. The most commonly reported system organ classes (SOCs) and AEs occurred in a similar pattern in the treatment groups with regard to type and frequency. Twenty-six subjects reported 29 serious adverse events (SAEs) during randomised treatment; 16 SAEs in 15 subjects (5 %) in the formoterol group and 13 SAEs in 11 subjects (4 %) in the terbutaline group. The frequency of subjects who discontinued the study due to AEs was low; 3 % in each treatment

group. There were no clinically important differences between the treatment groups regarding ECG, pulse or blood pressure.

REFERENCES

Villa, J, Kuna P, Egner J, Brander R. A 6-month comparison of the safety profiles of formoterol (Oxis®) Turbuhaler® as needed and terbutaline (Bricanyl®) Turbuhaler® as needed in asthmatic children on anti-inflammatory medication.Am J Respir Crit Care Med2002; 165(8)(Suppl): A746.

Villa J, Kuna P, Egner J, Brander R. Safety offormoterol reliever therapy compared with terbutaline in asthmatic children taking anti-inflammatory therapy.Eur Respir J 2002;20(Suppl 38):431s, Abs P2739.

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.