AstraZeneca

SD-037-0345

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Oxis®

ACTIVE INGREDIENT: formoterol

Trial title (number): Oxis (formoterol) and Pulmicort (budesonide) Turbuhaler in the management of asthma - OPTIMA

Development phase: IV
First subject recruited: 20 January 1998
Last subject completed: 17 February 2000
Approval date: 01 August 2001

OBJECTIVES

Group A, phase I: To compare the effect of Oxis (4.5µg b.i.d.) and Pulmicort Turbuhaler (100µg b.i.d.) versus Pulmicort Turbuhaler (100µg b.i.d.) alone and placebo alone in steroid-free patients with mild asthma.

Group B, phase I: To compare the effect of Oxis (4.5µg b.i.d.) and Pulmicort Turbuhaler (100 and 200µg b.i.d.) versus Pulmicort Turbuhaler (100 and 200µg b.i.d.) in steroid treated patients with mild-to-moderate asthma.

Groups A & B, phase II: To study the management of asthma by allowing any asthma medication to be added to respective allocated study medications. This was studied after the patient had been treated for the first severe asthma exacerbation.

METHODS

STUDY DESIGN
The study was of a randomized, double-blind and parallel-group design, with a total duration of 13 months, including a one-month run-in period. The treatment period was divided in two phases. The duration of phase I and II varied for each patient depending on when the first severe asthma exacerbation occurred. After the first exacerbation, the patient entered phase II. During this phase, the patient continued with the allocated study medication and any other asthma medication could be added. The study consisted of 9 scheduled visits: start of run-in, start of treatment and 1, 2, 4, 6, 8, 10 and 12 months after visit 2.

Patients who had not used any steroids 3 months prior to visit 1 were allocated to Group A. Patients who had used inhaled GCS daily (e.g. maximum daily dose ≤400µg Pulmicort Turbuhaler or equivalent) were allocated to Group B.

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION

Major inclusion criteria:

- Diagnosis of stable asthma, according to the American Thoracic Society (ATS).
- Group A: GCS-free during the last 3 months prior to visit 1.
  Pre-bronchodilator FEV_1 ≥70% of predicted normal value (local) at visit 1. 15 min post-bronchodilator FEV_1 ≥80% of predicted normal value (local) at visit 1 (2x0.5 mg Bricanyl Turbuhaler).
- Group B: Daily use of inhaled GCSs for the last 3 months with a maximum daily dose of 400µg Pulmicort Turbuhaler or 400µg Fluticasone or 800µg Pulmicort pMDI or 1000µg BDP, irrespective of device, or the equivalent dose of other steroids. The dose should be constant 6 weeks prior to visit 1. Pre-bronchodilator FEV_1 ≥ 50% of predicted normal value (local) at visit 1. 15 min post-bronchodilator FEV_1 ≥70% of predicted normal value (local) at visit 1 (2x0.5 mg Bricanyl Turbuhaler).
- Randomization criteria: Total need of at least 2 inhalations per week of short-acting β_2-agonist during the last 2 weeks or PEF variability of≥15% during the last 2 weeks or≥12% reversibility in FEV_1 15 min post bronchodilator at visit 1 or 2 (2x0.5 mg Bricanyl Turbuhaler).

Major exclusion criteria:

- Use of oral GCS within 3 months prior to visit 1.
- Beta-blocker therapy (eyedrops included).
- Pregnant and/or lactating women or women not using acceptable contraceptives as judged by the investigator.
- Patients with a history of smoking > 15 pack-years.
- Randomization criteria: ≥7 morning PEF values missing in the diary during the last 14 days or signs of respiratory infection during run-in, as judged by the investigator or change in prescribed asthma medication during run-in.

TEST PRODUCT, DOSAGE AND MODE OF ADMINISTRATION
Pulmicort (budesonide) Turbuhaler, 100 or 200µg per dose
Oxis (formoterol) Turbuhaler, 4.5µg per dose

COMPARATOR PRODUCT, DOSAGE AND MODE OF ADMINISTRATION
Placebo for Pulmicort Turbuhaler
Placebo for Oxis Turbuhaler
Bricanyl (terbutaline) Turbuhaler, used for rescue medication

DURATION OF TREATMENT
Run-in period: 1 month; Treatment period: 12 months

MAIN VARIABLE(S):
- EFFICACY
Primary variables: Time to first severe asthma exacerbation, expessed as the risk for a first severe exacerbation, and rate (proportion) of poorly controlled days.

Secondary variables: Forced Expiratory Volume in one second (FEV_1), rate of severe exacerbations, number of patients with added asthma medication, kind and amount of added medication, morning Peak Expiratory Flow (PEF), number of rescue inhalations, number of awakenings due to nocturnal asthma and days with asthma symptoms.

- SAFETY
Primary variable: Adverse Events evaluated by means of an open standard question to the patient at the clinic visits.

STATISTICAL METHODS
The approach for statistical analysis was an Intent-To-Treat analysis.
Time to first severe exacerbation was analysed by use of a Cox semi-parametric model for proportional hazards, where the results of the analysis is expressed as hazard ratios (risk ratios) between treatments. Poorly controlled days was analyzed by means of a Poisson regression model. Diary data were analyzed by use of an ANCOVA model for change during treatment and with baseline value as covariate.

RESULTS

PATIENTS

Group A	Placebo	Pulmicort 100	Pulmicort 100 + Oxis 4.5	Total
No. randomized and treated	239	228	231	698
Males/Females	101 / 138	93 / 135	85 / 146	279 / 419
Mean age (range)	30.6 (12-69)	30.6 (12-70)	31.3 (12-76)	30.9 (12-76)
Adolescents	41	42	42	125
(12-17 years)				
Baseline values: Asthma	8.5	9.5	8.9	8.9
(years)	(0-46)	(0-52)	(0-41)	(0-52)
Mean FEV_1	89.9	90.1	89.1	89.7
(% of predicted)				
No. analysed for efficacy	237	226	227	690
No. completed for efficacy	191	179	184	554
No. analysed for safety	239	228	231	698
No. completed for safety	193	180	186	559

Group B	Pulmicort 100	Pulmicort 100 + Oxis 4.5	Pulmicort 200	Pulmicort 200 + Oxis 4.5	Total
No. randomized and treated	322	323	312	315	1272
Males/Females	141 / 181	144 / 179	133 / 179	129 / 186	547/725
Mean age	38.1	36.5	37.4	36.8	37.2
(range)	(12-80)	(12-82)	(12-80)	(11-74)	(11-82)
Adolescents	34	45	30	35	144
(12-17 years)					
Baseline values:					
Asthma	11.8	11.1	12.8	10.5	11.6
(years)	(0-59)	(0-60)	(0-68)	(0-48)	(0-68)
Mean FEV_1 (% of predicted)	86.3	86.4	87.0	86.5	86.6
No. analysed for efficacy	317	320	308	312	1257
No. completed for efficacy	276	273	267	276	1092
No. analysed for safety	322	323	312	315	1272
No. completed safety	280	275	271	279	1105

EFFICACY RESULTS

Group A (Corticosteroid-free patients)

Time to first severe asthma exacerbation: Pulmicort gave a statistically significant reduction in risk by 60% (risk ratio=0.40, 95% CI=0.27, 0.59) compared to placebo, while adding Oxis gave no additional statistically significant effect. Treatment with Pulmicort plus Oxis reduced the risk by 48% (risk ratio=0.52, 95% CI=0.36, 0.75) compared to placebo.

Rate of poorly controlled days: Pulmicort gave a statistically significant reduction in risk for a day to be poorly controlled by 48% (risk ratio=0.52, 95% CI=0.40, 0.67) compared to placebo. Treatment with Pulmicort plus Oxis gave a statistically significant reduction of risk by 41% (risk ratio=0.59, 95% CI=0.46, 0.76) compared to placebo.

There was also a reduction in the rate of severe asthma exacerbations, in asthma symptoms, nocturnal awakenings, and number of rescue inhalations of short-actingβ-agonists. Also, FEV_1 increased more in the budesonide group compared to the placebo.

Group B (Patients previously taking a low dose inhaled GCS)

Comparison of the groups taking budesonide 100μg b.i.d. and 200μg b.i.d. showed no statistically significant difference in the risk for a first severe exacerbation, rate of poorly controlled asthma days or rate of asthma exacerbations. However, asthma symptoms, FEV_1 and PEF Morning improved more with the higher dose of budesonide.

Time to first severe asthma exacerbation: Addition of Oxis to Pulmicort gave a statistically significant risk reduction by 43% (risk ratio=0.57, 95% CI=0.46, 0.72) compared to addition of placebo. The reduction in risk from giving the higher dose instead of the lower dose of Pulmicort was only of borderline significance. The lower dose of Pulmicort plus Oxis gave a statistically significant reduction in risk by 29% (risk ratio=0.71, 95% CI=0.52, 0.96) compared to the higher dose alone.

Rate of poorly controlled days: Addition of Oxis gave a statistically significant risk reduction in poorly controlled days by 30% (risk ratio=0.70, 95% CI=0.60, 0.82) compared to placebo. The reduction in risk from giving the higher dose instead of the lower dose of Pulmicort was only of borderline statistical significance. The lower dose of Pulmicort plus Oxis gave a statistically significant reduction in risk by 19% (risk ratio=0.81, 95% CI=0.66, 0.99).

Adding formoterol also increased FEV_1 and PEF Morning, reduced the rate of asthma exacerbations, the number of rescue inhalations of short actingβ-agonists and nocturnal awakenings, although the latter did not reach statistical significance. Adding formoterol to the higher dose of budesonide reduced the risk for a severe exacerbation more than when adding it to the lower dose.

SAFETY RESULTS

All treatments were safe and well controlled. The frequency of patients who reported Adverse Events was similar when comparing Groups A and B, and also between the different treatments. The β_2-agonist and inhaled steroid class effects were reported in a low and similar frequency of less than 2% during all treatments. 95 Serious Adverse Events (23 in group A and 72 in Group B) were reported by 85 patients (of totally 1970 patients, 698 in Group A and 1272 in Group B) during the randomized treatment. One death was reported in Group A . The probable cause of death was a septic chock. 27 discontinuations due to Adverse Events (DAEs) were reported in Group A and 26 in Group B.

REFERENCES

O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerström E, Sandström T, Svensson K, Tattersfield A. Low dose inhaled budesonide and formoterol in mild persistent asthma. The Optima randomized trial. Am J Respir Crit Care Med 2001;164:1392-1397.

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.