AstraZeneca

D5890C0007

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort® Turbuhaler®

ACTIVE INGREDIENT: Budesonide/formoterol

Trial title (number): Onset of relief of dyspnoea after methacholine provocation with single doses of one inhalation of Symbicort®Turbuhaler®160/4.5 mcg/inhalation, two inhalations of Ventoline™ via pMDI 100mcg/actuation, or placebo in adults with asthma - a randomised, double-blind, cross-over, phase IIIB study.

Developmental phase: III
First subject recruited: 13 July 2004
Last subject completed: 14 January 2005

OBJECTIVES

The primary objective of this study was to compare the onset of relief of dyspnoea provided by a single dose of 1 inhalation of Symbicort® Turbuhaler® 160/4.5 mcg/inhalation, 2 inhalations of Ventoline™ via pMDI (pressurised Metered Dose Inhaler) 100 mcg/actuation, or placebo in methacholine-induced bronchoconstriction.

METHODS

Study design

This was a randomised, double-blinded, placebo-controlled, cross-over study comparing the onset of relief of dyspnoea after methacholine-induced bronchoconstriction in adults with asthma.

Target patient population and sample size

Male and female patients, 18 to 50 years of age, with a documented history of asthma of at least 6 months, a baseline $FEV_1$of >1.5 L and >60% of predicted normal. In addition, patients had to show a 20% fall in FEV_1following provocation with methacholine at a concentration (PC20-MCh) ≤8 mg/mL and a demonstrated fall in $FEV_1$of >30% upon continuation of the provocation test.It was estimated that a total of 30 randomised and evaluable patients, derived from an estimated 60 enrolled, were required for 80% power to detect a difference between treatments of 0.36 in change in Borg score from immediately before study drug administration to 1 minute after study drug administration.

Investigational product and comparators: dosage, mode of administration and batch numbers

One inhalation of Symbicort Turbuhaler (budesonide/formoterol), 160/4.5 mcg/inhalation (delivered dose), powder for inhalation; batch number EG 32 (P6853).
Two actuations of Ventoline (salbutamol) pMDI, 100 mcg/actuation (metered dose), suspension for inhalation; batch number (P6997).
One inhalation of placebo Turbuhaler, powder for inhalation; batch numbers EG 16 (P6876), FD 17 (P7001).
Two actuations of placebo pMDI, suspension for inhalation; batch numbers P6909 (P7005).

Duration of treatment

The patients received single doses of study drug on 3 of the 4 clinic visits (Visits 2-4), separated by intervals of 3 to 14 days.

Criteria for evaluation (main variables)

Efficacy

- Primary outcome variable:
  - change in Borg score from immediately before study drug administration to 1 minute after study drug administration
- Secondary outcome variables:
  - time to 50% recovery in Borg score
  - change in FEV_1 from immediately before study drug administration to 1 minute after study drug administration
  - time to 85% recovery in FEV_1

Safety

Safety was assessed by monitoring adverse events.

Statistical methods

The full analysis set, as defined in the International Conference on Harmonisation E9 guidelines, was used in all efficacy analyses. The change in Borg score from immediately before study drug administration to 1 minute after study drug administration was compared between treatments using an additive analysis of variance model with patient, period, and treatment as factors and the Borg score immediately before study drug administration as a covariate.

RESULTS

Patient population

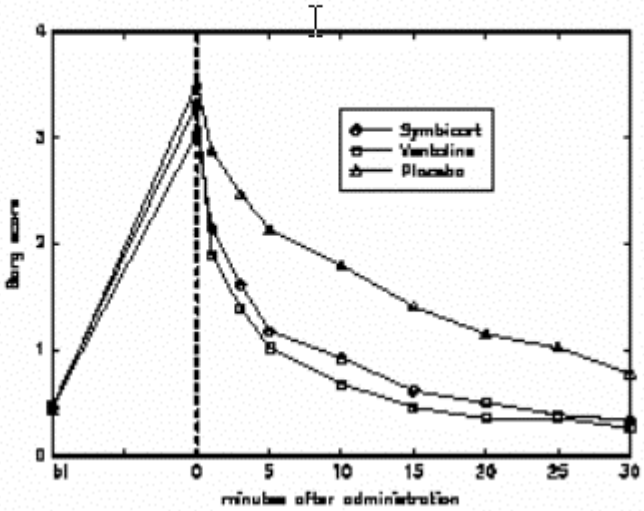
Table S1 Patient population, demographics, and disposition

N randomized		**32**
Demographic characteristics		
Sex	**Male**	**15**
	Female	**17**
Age (years)	**Mean**	**33.5**
	Range	**18 – 50**
Race (n)	**Caucasian**	**30**
	Black	**1**
	Oriental	**1**
Time since diagnosis (years)	**Median**	**14**
	Range	**1 – 48**
Inhaled GCS use	**Number of patients**	**29**
	Mean daily dose (mcg)	**677**
	Daily dose range (mcg)	**100 – 2000**
Baseline characteristics		
FEV_1 (L)	**Mean**	**3.40**
	Range	**1.83 – 5.22**
FEV_1 (% P.N.)	**Mean**	**93.6**
	Range	**61 – 126**
PC_{20} (mg/ml)	**Geometric mean**	**0.47**
	Range	**0.1 – 6.7**
Disposition		
N (%) of patients who	**Completed**	**31 (97)**
	Discontinued	**1 (3)**
N analysed for safety		**32**
N analysed for efficacy		**31**

Efficacy results

Both 1 inhalation of Symbicort and 2 inhalations of Ventoline statistically significantly decreased Borg score 1 minute after study drug administration compared with placebo. The decrease after 1 minute was statistically significantly greater for Ventoline than for Symbicort (mean Borg score difference: 0.41, 95% CI: 0.06-0.77, p = 0.0243); however, higher Borg scores prior to administration of Ventoline gave this treatment greater room for recovery and may have influenced the results (Figure S1).

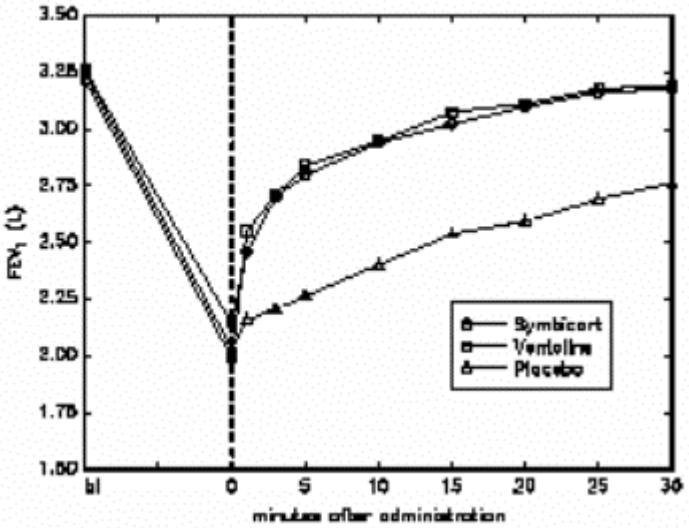
Figure S1 **Mean Borg score**



Median time to 50% recovery in Borg score was similar for Symbicort and Ventoline, 3 and 2 minutes respectively, and considerably shorter than for placebo (10 minutes). Symbicort and Ventoline both shortened time to 50% recovery in Borg score statistically significantly compared to placebo. There was no statistically significant difference between Symbicort and Ventoline in time to recovery.

FEV1 1 minute after study drug administration was statistically significantly increased both after Symbicort and Ventoline treatments compared to placebo. The increase after 1 minute was statistically significantly greater for Ventoline than for Symbicort (mean ratio Symbicort vs Ventoline: 0.95, 95% CI: 0.90-0.99); however, lower FEV1 values prior to administration of Ventoline gave this treatment greater room for recovery and may have influenced the results (Figure S2).

Figure S2 **Geometric mean FEV_1**



Median time to 85% recovery in $FEV_1$was similar for Symbicort and Ventoline, 3.7 and 3.2 minutes respectively, and considerably shorter than for placebo (22 minutes). Symbicort and Ventoline both shortened time to 85% recovery in FEV_1statistically significantly compared to placebo. There was no statistically significant difference between Symbicort and Ventoline in time to recovery.

Safety results

The number of adverse events were few and occurred with all 3 treatments. All adverse events were of mild or moderate intensity. No serious adverse events or discontinuations due to adverse events appeared during the study. In total, the treatments were well tolerated by the patients.

REFERENCE

RE Jonkers, TA Bantje, R Aalbers. Onset of relief of dyspnoea with budesonide/formoterol or salbutamol following methacholine-induced severe bronchoconstriction in adults with asthma: a double-blind, placebo-controlled study. Respir Res. 2006;7:141-150.

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 Symbicort™ (budesonide/formoterol), Healthcare Professionals should view their specific country information.