AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	Formoterol HFA pMDI		
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Protective Effect of Single Doses of Formoterol HFA pMDI Compared with Oxis® Turbuhaler® and Placebo on Exercise-Induced Bronchoconstriction (EIB) in Asthmatic Children, 6-11 Years of Age

Study centres

This study was conducted at 3 centres in total including Centres 1 and 4 (Denmark) and Centre 3 (Norway); another centre, although set up, did not start the study (Centre 2, Germany).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	6 June 2002	Therapeutic confirmatory (IIIa)
Last subject completed	27 January 2003	

Objectives

The primary objective of this study was to evaluate the magnitude and duration of the protective effect of formoterol hydrofluoroalkane (HFA) pressurised metered-dose inhaler (pMDI) 9 μg (2 x 4.5 μg) versus that of placebo on exercise-induced bronchoconstriction (EIB) in asthmatic children, 6-11 years of age, by assessment of the maximum fall in forced expiratory volume in one second (FEV_1) post-exercise, expressed as a percentage of pre-exercise FEV_1 ($Index_{EIB}$).

The secondary objectives were to further evaluate the magnitude and duration of the protective effect of formoterol HFA pMDI 9 μg versus that of placebo and Oxis Turbuhaler 9 μg, to evaluate the pre-exercise FEV_1 measured immediately before the post-dose exercise challenge test (ECT) versus that of Oxis Turbuhaler 9 μg and placebo; to compare safety versus that of Oxis Turbuhaler 9 μg and placebo, by assessment of adverse events and vital signs.

Study design

This was a randomised, double-blind, double-dummy, placebo-controlled, single dose study with a 3-way crossover design.

Target subject population and sample size

Boys and girls, aged 6-11 years with asthma diagnosed for at least 6 months were recruited to this study. When entering the study, subjects' asthma was to be in a stable phase, although on exercise challenge all subjects' lung function should have deteriorated. In total, it was planned to randomise a total of 24 subjects to study treatment; randomisation was stratified by centre with an equal allocation of subjects to each treatment sequence. The standard deviation for $Index_{EIB}$ was assumed to be between 8 and 10%. With 24 subjects completing the study, and using a 2-sided test at the 5% significance level, it was calculated that there would be an 80% chance of detecting a true difference of 8% between any 2 treatment comparisons.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Formoterol HFA pMDI, 4.5 μg per actuation, 120 actuations, Batch Numbers P6294, P6446; placebo to match formoterol HFA pMDI, 120 actuations, Batch Numbers P6309, P6445. Formoterol (Oxis®) Turbuhaler M2, 9 μg per dose, 60 doses, Batch Numbers P6477 (CH867); placebo to Oxis Turbuhaler M2, Batch Numbers P6475 (C140); Bricanyl (terbutaline sulphate) Turbuhaler, 0.5 mg per dose, 200 doses, Batch number P6480 (CE1183).

Duration of treatment

All study treatments were given as single dose inhalations.

Criteria for evaluation (main variables)

Efficacy

The primary variable was $Index_{EIB}$, the maximum fall in forced expiratory volume in one second (FEV_1) post-exercise, expressed as a percentage of pre-exercise FEV_1.

The secondary variables included: $Average_{EIB}$, the mean post-exercise FEV_1 (at 0-20 minutes) in relation to the pre-exercise FEV_1 (E_{pre}), at each timepoint; E_{min}/E_{pre}, the minimum post-exercise FEV_1 (E_{min}) as a ratio of the pre-exercise FEV_1 (E_{pre}), at each timepoint; $E_{pre,\ 15\ mins}$, the pre-exercise FEV_1 measured immediately before the 15-minute post-dose ECT.

Safety

The incidence, nature and intensity of all adverse events (AEs) was evaluated by means of an open, standardised question to each subject. Some clinical measurements were also performed including: changes in vital signs (pulse and blood pressure) from pre-dose to post-dose at Visits 2, 3 and 4; change from pre-exercise to post-exercise pulse at 15 minutes, 4, 8 and 12 hours post-dose at Visits 2, 3 and 4.

Statistical methods

Data for subjects who received at least one dose of investigational product, and for whom data were collected after randomisation, have been included in both the safety and efficacy analyses. Subjects who were enrolled in the study, but who never received investigational product, were not included in the analyses. For the safety analyses, subjects were analysed according to the treatment they actually received whereas for the efficacy analyses they were analysed according to their randomised treatment. AEs, pulse and blood pressure have been analysed primarily by means of descriptive statistics.

The primary study objective was to evaluate the magnitude and duration of the protective effect of formoterol HFA pMDI on EIB and to test for a statistically significant difference between formoterol HFA pMDI and placebo. Treatments were compared using an analysis of variance (ANOVA) model with subject, visit and treatment as fixed effects. Ninety-five percent confidence intervals (CIs) were constructed for each pairwise comparison and each timepoint was analysed separately.

Subject population

In total, 25 subjects were enrolled, randomised, received study treatment and completed all study treatments. There were 16 boys and 9 girls with a mean age of 9 years (range 6 to 11 years) with a mean duration of asthma of 6 years. All subjects received the correct dose of study treatment. There were no discontinuations due to AEs from study treatment. Details of the subject population and disposition are summarised in Table S1 below.

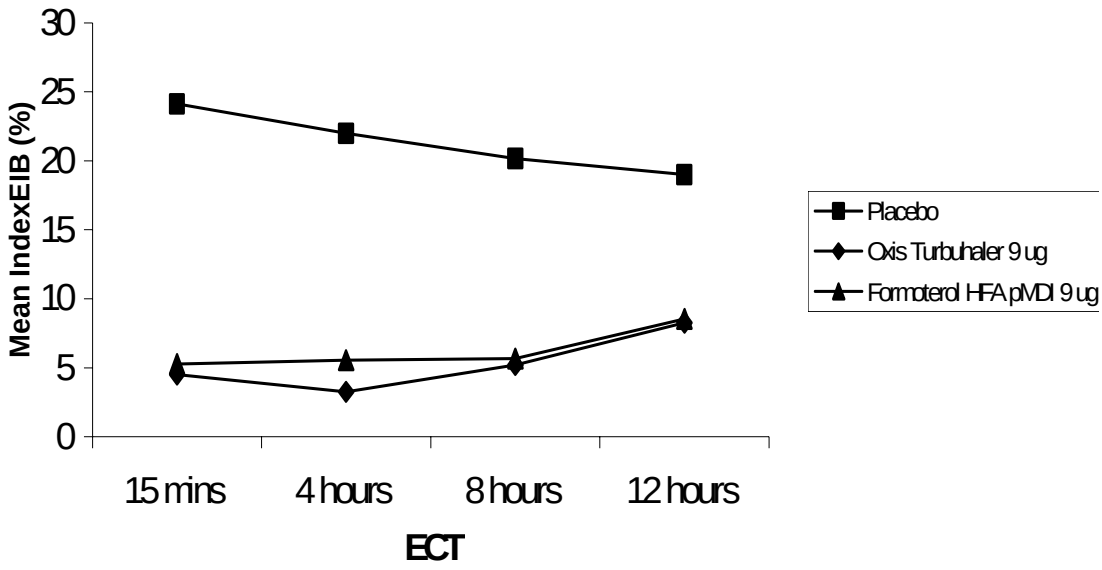
Table S1 Subject population and disposition

		Total
Population		
Number randomised		25
Demographic Characteristics		
Sex (N and % of subjects)	Male	16 (64%)
	Female	9 (36%)
Age (years)	Mean (SD)	8.8 (1.51)
	Range	6.0 to 11.0
Race (N and % of subjects)	Caucasian	24 (96%)
	Black	0 (0%)
	Oriental	1 (4%)
	Other	0 (0%)
Enrolment Characteristics		
FEV_1 (L)	Mean (SD)	1.83 (0.42)
FEV_1 as a % of Predicted FEV_1	Mean (SD)	94.7 (10.5)
$Index_{EIB}$ (%)	Mean (SD)	37.9 (12.0)

Efficacy results

The largest mean value of $Index_{EIB}$ (%) at each ECT was consistently that of placebo which was much higher than both formoterol HFA pMDI and Oxis Turbuhaler indicating a greater percentage fall in FEV_1 post-exercise after inhalation of placebo than after either active treatment. There appeared to be little difference between formoterol HFA pMDI and Oxis Turbuhaler at each ECT (Figure S1).

Figure S1 Plot of ECT Data: Mean $Index_{EIB}$ (%) – ITT Population



The least square (LS) means indicated similar magnitudes of percentage falls in FEV_1 post-exercise as measured by $Index_{EIB}$ for formoterol HFA pMDI and Oxis Turbuhaler at 15 minutes (5.2% and 4.6%, respectively), 4 hours (5.7% and 3.2%, respectively), 8 hours (5.7% and 5.3%, respectively) and 12 hours (8.6% and 8.3%, respectively). In contrast, $Index_{EIB}$ was much larger for placebo at all timepoints (24.1%, 21.8%, 20% and 18.9% at 15 minutes, 4 hours, 8 hours and 12 hours, respectively).

The LS mean differences at 15 minutes for formoterol HFA pMDI and Oxis Turbuhaler versus placebo were -18.9% (95% CI -23.6, -14.1, p<0.001) and -19.5% (95% CI -24.2, -14.7, p<0.001), respectively (Table S2) indicating that both formoterol HFA pMDI and Oxis Turbuhaler offered greater protection for EIB than placebo (Table S2). The LS mean difference at 15 minutes for Formoterol HFA pMDI versus Oxis Turbuhaler indicated there was no statistically significant difference in protection of EIB (LS mean 0.62%, 95% CI -4.2, 5.4, p=0.795). The LS mean differences between formoterol HFA pMDI and placebo at 4, 8 and 12 hours were -16.1% (95% CI -21.7, -10.5, p<0.001), -14.3% (95% CI -19.2, -9.5, p<0.001) and -10.3% (95% CI -15.3, -5.3, p<0.001), respectively, indicating that at each timepoint there was a greater fall in FEV_1 post exercise after placebo than after formoterol HFA pMDI. Although the magnitude of these differences decreased over time, they were all statistically significant thus demonstrating that formoterol HFA pMDI continued to offer greater protection for EIB than placebo for at least 12 hours. The LS mean differences between Oxis Turbuhaler and placebo at the ECTs at 4, 8 and 12 hours were of similar magnitude to those between formoterol HFA pMDI and placebo (-18.6%, -14.8% and -10.5%, respectively; p-value <0.001 at each timepoint). Oxis Turbuhaler also provided greater protection in EIB than placebo for at least 12 hours with no statistically significant difference between formoterol HFA pMDI and Oxis Turbuhaler at any timepoint over the 12 hours.

Table S2 Summary of ECT data: $Index_{EIB}$ (ITT population)

Treatment or Comparison	N	Least Squares Mean or Difference	SE	95% Confidence Intervals	p-value
Placebo	25	24.07	1.665	(20.72,27.42)	
Oxis Turbuhaler 9 μg	25	4.60	1.668	(1.24, 7.95)	
Formoterol HFA pMDI 9 μg	25	5.21	1.670	(1.85, 8.58)	
Formoterol HFA pMDI 9 μg - Placebo	50	-18.9	2.361	(-23.6,-14.1)	<0.001
Oxis Turbuhaler 9 μg - Placebo	50	-19.5	2.355	(-24.2,-14.7)	<0.001
Formoterol HFA pMDI 9 μg - Oxis Turbuhaler 9 μg	50	0.62	2.367	(-4.15, 5.38)	0.795

There were no statistically significant differences in $Average_{EIB}$ or E_{min}/E_{pre} between formoterol HFA pMDI and Oxis Turbuhaler at any timepoint over the 12 hours indicating that there was no difference in either the magnitude or duration of protective effect on EIB between the 2 treatments.

Safety results

AEs were reported by 3 subjects, all of which commenced during the enrolment period; the AEs were rated mild and non-serious (elevated heart rate, impetigo and common cold) and also resolved prior to treatment apart from impetigo which was still ongoing at the end of the study. Both formoterol HFA pMDI and Oxis Turbuhaler treatments resulted in modest transient increases in heart rate.