AstraZeneca

Drug product:		**SYNOPSIS**	
Drug substance(s):	Formoterol HFA pMDI		
Document No.:	D5125C00344		
Edition No.:	01		
Study code:	SD-037-0344		
Date:	6 August 2003		

A 3-Month, Multi-centre, Double-blind, Double-dummy, Randomised, Parallel Group, Phase III Study to Investigate the Efficacy and Safety of Formoterol HFA pMDI Compared with Placebo and Oxis® Turbuhaler® in Subjects with Asthma

Study centres

This study was performed in 48 centres across 7 countries (Argentina, Brazil, Greece, Mexico, Philippines, Poland, South Africa).

Publications

None at the time of writing this report.

Study dates		**Phase of development**
First subject enrolled	2 May 2002	Therapeutic confirmatory (III)
Last subject completed	3 December 2002	

Objectives

Primary objective

The primary objective of this study was to show that formoterol hydrofluoroalkane (HFA) pressurised metered-dose inhaler (pMDI) 9 μg, twice daily (bid), was effective in subjects aged 12 years and older, with asthma, when compared to placebo, based on morning peak expiratory flow (mPEF).

Secondary objectives

The secondary objectives were to show that formoterol HFA pMDI 9 μg, bid, was also effective compared to placebo based on forced expiratory volume in one second (FEV_1), evening peak expiratory flow (ePEF), time to first asthma exacerbation and other criteria; and was therapeutically equivalent to Oxis® Turbuhaler® 9 μg, bid, based on mPEF. In addition the secondary objectives were to compare the efficacy of formoterol HFA pMDI 9 μg, bid, with Oxis Turbuhaler 9 μg, bid, based on FEV_1, ePEF, time to first asthma exacerbation, and other criteria; and to compare the safety profile to Oxis Turbuhaler 9 μg, bid, and to placebo.

Study design

This was a randomised, double-blind, double-dummy, parallel-group, placebo-controlled, multicentre, 12-week study with a 2-week run-in period, comparing the efficacy and safety of formoterol HFA pMDI 9 μg (2 × 4.5 μg) bid with Oxis Turbuhaler 9 μg (2 × 4.5 μg) bid in subjects with asthma.

Target subject population and sample size

Male or female asthmatic subjects aged 12 years and older with approximately 25% of subjects aged between 12 and 17 years. Subjects were to have been treated with 200 to 1000 μg/day of inhaled steroids for the previous 3 months and on a stable dose for 30 days prior to the start of the run-in period. For inclusion to the treatment period, subjects had to have a total asthma symptom score (night-time plus day-time) of ≥1 on at least 4 of the last 7 days of the run-in period. It was planned to randomise 600 subjects into this study involving approximately 10 subjects from each centre.

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

The investigational product was as follows: Formoterol 9 μg via HFA pMDI. Subjects received 9 μg (2 inhalations x 4.5 μg) bid (Batch numbers: P6294, P6295, P6296, P6446, P6447, P6449 and P6450).

The comparator products were as follows: Formoterol 9 μg via Turbuhaler. Subjects received 9 μg (2 inhalations x 4.5 μg) bid (Batch number: P6486). Placebo to formoterol HFA pMDI (Batch numbers: P6309, P6445) and Turbuhaler (Batch number: P6487), bid.

Duration of treatment

There was a 2-week run-in period after which the subjects entered a 12-week treatment period.

Criteria for evaluation (main variables)

Efficacy

- Primary variable: The change from baseline (mean over last 10 days of run-in period) to treatment (mean for the 12-week treatment period) in mPEF before inhalation of study treatment.

- Secondary variables: These included the change from baseline (mean over last 10 days of run-in period) to treatment (mean of the 12-week treatment period) in ePEF, use of reliever medication (day and night, and daily) and asthma symptom score (day and night); the change from baseline (start of treatment period) to treatment (mean value after 4, 8 and 12 weeks of treatment) in FEV_1 measured 30 minutes after study drug inhalation; the time from baseline (start of treatment period) to the first asthma exacerbation; the percentage of nights with awakenings due to asthma symptoms; the percentage of symptom-free days; the percentage of asthma control days; and the percentage of reliever-free days.

Safety

The incidence, nature and intensity of adverse events (AEs) during the 12-week treatment period.

Statistical methods

The primary objective was to determine whether formoterol HFA pMDI was effective by testing for a statistically significant difference between formoterol HFA pMDI and placebo in change from baseline in mPEF. A secondary objective was to demonstrate therapeutic equivalence between formoterol HFA pMDI and Oxis Turbuhaler in the change in mPEF from baseline. Equivalence limits of ±15 L/min in mPEF were used and therapeutic equivalence was declared if the 95% confidence interval for the difference between formoterol HFA pMDI and Oxis Turbuhaler fell within these limits. Treatments were compared using an analysis of covariance (ANCOVA) model adjusting for treatment and country, and with mean mPEF over the last 10 days of run-in as a covariate. The standard deviation of the change in mPEF was estimated to be 40 L/min. With 200 subjects per group, there was an 80% chance of detecting a true difference of 11 L/min between the treatments. The equivalence limit was set to ±15 L/min, giving an 80% chance of declaring therapeutic equivalence if the true difference between the treatments was at most 4 L/min.

The secondary objectives were to determine whether formoterol HFA pMDI was effective and to compare the efficacy between formoterol HFA pMDI and Oxis Turbuhaler. The mean ePEF was summarised and analysed as for mean mPEF. Time to first asthma exacerbation was compared between treatments using a Cox proportional hazards model. Asthma symptom scores (day and night-time scores; percentage of symptom-free days; percentage of nights with awakenings; percentage of asthma control days) were analysed using an ANCOVA model with treatment and country as fixed factors and the baseline value as a covariate. The logged geometric mean ratio of the mean treatment FEV_1 over the baseline FEV_1 was compared between treatments using an ANCOVA model with treatment and country as

factors and log-transformed baseline FEV_1 as a covariate. The results were transformed back to the linear scale. Use of reliever medication (change from baseline in mean day-time usage, change from baseline in mean night-time usage, change from baseline in mean daily usage, and percentage of reliever medication-free days) was compared between treatments using an ANCOVA model with treatment and country as factors, and mean reliever medication usage over the baseline period as a covariate. All efficacy analyses were performed on both the Per Protocol (PP) and Intention to Treat (ITT) populations, but the primary presentation of efficacy was based on the PP population

Adverse event data were analysed by means of descriptive statistics and qualitative analysis.

Subject population

The subject populations and key demographic and baseline characteristics of study subjects are summarised in Table S1.

Table S1 Subject population and disposition

		Formoterol HFA pMDI 9 μg	Oxis Turbuhaler 9 μg	Placebo	Total
Total enrolled					647
Total randomised		216	213	210	639
Safety population		216	213	210	639
Intention to treat population		218	212	209	639
Per Protocol population		215	209	207	631
Demographic Characteristics[a]					
Sex (N and % of subjects)	Male	107 (49%)	83 (39%)	90 (43%)	280 (44%)
	Female	111 (51%)	129 (61%)	119 (57%)	359 (56%)
Age (years)	Mean (SD)	34 (16.5)	35 (16.9)	37 (18.0)	35 (17.1)
	Range	12 to 77	12 to 79	12 to 80	12 to 80
Race (N and % of subjects)	Caucasian	145 (67%)	140 (66%)	136 (65%)	421 (66%)
	Black	3 (1%)	3 (1%)	3 (1%)	9 (1%)
	Oriental	47 (22%)	45 (21%)	45 (22%)	137 (21%)
	Other	23 (11%)	24 (11%)	25 (12%)	72 (11%)
Baseline Characteristics[a]					
Duration of Asthma (years)	Mean (SD)	14.2 (13.54)	13.8 (12.08)	14.8 (13.29)	14.2 (12.98)
Taking Inhaled GCS (N and % of subjects)		218 (100%)	208 (98%)	208 (100%)	634 (99%)

N Number; SD Standard Deviation, GCS Glucocorticosteroid.
Note : Duration of asthma is calculated from approximate imputed date of diagnosis to enrolment date
Note : Partial dates of diagnosis are imputed as the end of the month or the 31st December where relevant
[a] Subjects in the intention to treat population

Efficacy results

Mean mPEF at baseline (last 10 days of run-in period) and over the whole treatment period, the change from baseline to treatment, and the results of the treatment comparison between formoterol pMDI and placebo are summarised in Table S2.

Table S2 Summary of mean mPEF (L/min) over baseline, the treatment period and treatment comparison (primary variable) for change from baseline in mean mPEF (L/min) over the treatment period (PP population)

Statistic or Comparison	Formoterol HFA pMDI 9 μg (n = 215)	Oxis Turbuhaler 9 μg (n = 209)	Placebo (n = 207)
Mean baseline mPEF (L/min)[a] (SD)	367.6 (97.45)	365.7 (92.89)	346.8 (100.17)
Mean treatment mPEF (L/min)(SD)	386.9 (101.89)	382.9 (93.8)	350.6 (99.37)
Change from baseline mPEF (L/min) (SD)	18.9 (37.19)	17.1 (36.83)	4.3 (35.09)
Treatment comparison (Formoterol HFA pMDI versus placebo)			
Number of subjects analysed	420	NA	NA
Least Squares mean	15.7	NA	NA
Lower 95% confidence limit	8.8	NA	NA
Upper 95% confidence limit	22.6	NA	NA
p-value[b]	<0.001	NA	NA

[a] Baseline was mean of available readings over the last 10 days of the run-in period.
[b] p-value based on ANCOVA.
NA Not Applicable; SD Standard Deviation.

Table S2 shows that the means for baseline mPEF were similar for formoterol HFA pMDI and Oxis Turbuhaler; mean baseline mPEF was lower for the placebo group. A pairwise treatment comparison of changes from baseline in mPEF showed a statistically significant greater improvement for formoterol HFA pMDI compared to placebo (LS Mean 15.7, 95% CI = 8.8, 22.6; $p<0.001$).

Table S3 presents the differences between formoterol HFA pMDI and Oxis Turbuhaler treatments, and between Oxis Turbuhaler and placebo treatments, in change from baseline (mean over last 10 days of run-in period) in mean mPEF.

Formoterol HFA pMDI and Oxis Turbuhaler were considered therapeutically equivalent since there was no statistically significant difference in the change from baseline in mPEF between the treatments and the 95% CI for the difference between the treatments fell within ±15 L/min.

Table S3 Treatment comparisons (secondary variables) for change from baseline in mean mPEF (L/min) over the treatment period (PP population)

Statistic or Comparison	Formoterol HFA pMDI 9 μg (n = 215)	Oxis Turbuhaler 9 μg (n = 209)	Placebo (n = 207)
Treatment comparison: Formoterol HFA pMDI versus Oxis Turbuhaler			
Number of subjects analysed	422	NA	NA
Least Squares mean	1.9	NA	NA
Lower 95% confidence limit	-5.0	NA	NA
Upper 95% confidence limit	8.7	NA	NA
p-value[a]	NA	NA	NA
Treatment comparison Oxis Turbuhaler versus placebo			
Number of subjects analysed	NA	414	NA
Least Squares mean	NA	13.8	NA
Lower 95% confidence limit	NA	6.9	NA
Upper 95% confidence limit	NA	20.8	NA
p-value[a]	NA	NA	NA

[a] p-value based on ANCOVA
NA Not Applicable; SD Standard Deviation.

For other secondary variables, lung function variables (ePEF, FEV_1) showed that formoterol HFA pMDI was effective compared with placebo, whereas the symptom-based variables (asthma symptom scores, reliever medication usage) generally showed improved efficacy for Oxis Turbuhaler compared to formoterol HFA pMDI.

Safety results

One subject, a 66-year-old male, died during this study, after 55 days of treatment with formoterol HFA pMDI 9 μg; the investigator considered that there was no relationship between study medication and death. Six subjects experienced a serious adverse event (SAE) during treatment and 8 subjects were discontinued from study treatment. Formoterol HFA pMDI 9 μg, Oxis Turbuhaler 9 μg and placebo treatments were well tolerated with a similar profile of reported AEs and there were no apparent differences between formoterol HFA pMDI and Oxis Turbuhaler.

A summary of AEs occurring during treatment, by category, and the total number of AEs during the treatment period are presented in Table S4.

Table S4 Number (%) of subjects who had at least one adverse event in any category and the total numbers of adverse events during the treatment period (Safety population)

Category of Adverse Event [a]	Formoterol HFA pMDI 9 μg (n=216)	Oxis Turbuhaler 9 μg (n=213)	Placebo (n=210)
Any adverse events	81 (38%)	74 (35%)	75 (36%)
Serious adverse events not leading to death	3 (1%)	2 (1%)	1 (0%)
Deaths	1 (0%)	0 (0%)	0 (0%)
Discontinuations of study treatment due to adverse events	2 (1%)	1 (0%)	5 (2%)
Other significant adverse event	0 (0%)	0 (0%)	0 (0%)
TOTAL NUMBER OF ADVERSE EVENTS			
Adverse events	143	132	119
Serious adverse events not leading to death	4	3	1
Deaths	1	0	0
Discontinuations of study treatment due to adverse events	2	2	5
Other significant adverse event	0	0	0

[a] Subjects with multiple events in the same category are counted only once in that category. Subjects with events in more than one category are counted once in each of those categories.