AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Formoterol
Study Code	D5127C00001
Edition Number	1
Date	3 January 2011

A randomised, placebo-controlled, double-blind (double-dummy technique), crossover, multi-centre study, to evaluate onset of effect in patients with Chronic Obstructive Pulmonary Disease (COPD) treated with formoterol Turbuhaler® 9 µg, compared with Serevent® Diskus® 50 µg

Study dates: First subject enrolled: 18 January 2010
Last subject last visit: 5 May 2010

Phase of development: Therapeutic exploratory (II)

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Fourteen (14) centres in 3 countries participated in this study: Sweden (4 centres), Italy (6 centres) and Spain (4 centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
The primary objective was to evaluate time to onset of effect of formoterol, 9 µg single dose, compared with salmeterol, 50 µg single dose, in patients with moderate COPD	Forced Expiratory Volume in 1 second (FEV_1) measured by spirometry 5 minutes post dose	Efficacy
	Secondary	
	Average FEV_1 during the first 15 minutes (area under the FEV_1 curve from 0 to 15 minutes)	Efficacy
	Average FEV_1 during 120 minutes (area under the FEV_1 curve from 0 to 120 minutes)	Efficacy
	Proportion of patients who has achieved at least 12% increase in FEV_1 at 5 minutes post dose	Efficacy
	Proportion (cumulative) of patients who has achieved at least 12 % increase in FEV_1 at each time point between 10 to 120 minutes post dose	Efficacy
	Time to at least 12 % increase in FEV_1	Efficacy
Secondary		
The secondary objective of the study was to evaluate safety	Adverse events (nature, incidence and intensity)	Safety
	Pulse rate	Safety
	Blood pressure	Safety

Study design

This was a randomised, placebo-controlled, double-blind (double-dummy) crossover, multi-centre phase II study comparing onset of effect for inhaled formoterol, 9 µg single dose, with inhaled salmeterol, 50 µg single dose, in patients with moderate COPD.

Target subject population and sample size

Eligible patients, female and male, had to be ≥ 40 years of age, with a clinical diagnosis of COPD according to GOLD guidelines (2008) and current COPD symptoms. They should be current or previous smokers with a smoking history equivalent to 10 or more pack years, have a forced expiratory volume in 1 second (FEV_1) in the range ≥ 50 to ≤ 80 % of predicted normal, and a ratio between FEV_1 and forced vital capacity (FEV_1/FVC) < 70 % (both post-bronchodilator)

In order to achieve 80 % power for demonstrating a difference on the natural logarithmic scale between formoterol and salmeterol in FEV_1 5 minutes post-dose, a total of 90 patients with data on both treatments are needed. This estimate was based on an assumption of a true 5 % difference between treatments. It was assumed that 5 % of the patients would not contribute with data from both treatments and to compensate for this a total of 95 patients would be required.

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

The investigational product was formoterol Turbuhaler® powder for inhalation 9 µg (batch number 09-002583AZ), which was inhaled as a single dose of 9 µg.
The comparator drug was salmeterol Diskus® powder for inhalation 50 µg (GlaxoSmithKline, batch 09-004061AZ), which was inhaled as a single dose of 50 µg.
Placebo in appropriate inhalation devices was used: placebo Turbuhaler (batch 09-002533AZ) and placebo Diskus (batch 09-004883AZ), which was inhaled as single doses.
Terbutaline Turbuhaler powder for inhalation 0.5 mg (batch 09-004059AZ) was used for reversibility testing and as reliever medication during the study.

Duration of treatment

Single dose, 3-way crossover (washout periods 2-7 days).

Statistical methods

The primary variable, FEV_1 5 minutes post-dose (expressed as a percentage of the pre-dose value), was compared between treatments using a multiplicative ANOVA model (ie, data were log-transformed) with factors for patient, period and treatment. Treatment differences (ratios of treatment effects) were estimated from the model and 95 % confidence intervals were calculated. All pair-wise differences were estimated; the primary comparison was however between formoterol and salmeterol.

The effect on FEV_1 over time was further described by means of descriptive statistics and appropriate graphs. Area under the FEV_1 curve from 0 to 15 minutes (AUC_{0-15}) and area under the FEV_1 curve from 0 to 15 minutes (AUC_{0-120}) were compared between treatments using the same model as described above.

The proportion of patients (cumulative over time) achieving at least a 12% improvement in FEV_1 was computed and presented for each of the treatments at each time point. At 5 minutes post-dose, the treatment groups were compared pair-wise using an exact McNemar's test.

The time to a 12 % increase in FEV_1 was calculated by linear interpolation between the first time-point with an increase of at least 12% and the last previous value. The times were then compared between treatment groups using a Cox proportional hazards model.

All tests were two-sided and p-values less than or equal to 0.05 were considered statistically significant.

AEs were analysed by means of descriptive statistics and qualitative analysis.

Pulse rate and blood pressure were measured before lung function assessments, and analysed by means of descriptive statistics.

All statistical analyses were performed at AstraZeneca R&D Lund using SAS® Version 9.1. (SAS Institute Inc, 100 SAS Campus Drive, Cary, NC 27513-2414, USA). There were no interim analyses.

Subject population

A total of 141 patients were enrolled at 14 centres in 3 countries. Of these patients, 109 patients with moderate COPD were randomised to one of six treatment sequences (3-way crossover study). All, but one patient completed the study.

Summary of efficacy results

The increase in FEV_1 5 minutes after dose (primary variable) compared to pre-dose was 7.2% for formoterol, 4.1% for salmeterol and 0.7% for placebo. The ratio for formoterol vs salmeterol was 1.030 and statistically significantly greater than 1 (p=0.009). Thus, in patients with moderate COPD, formoterol 9 µg has an onset of bronchodilatory effect that is faster than that of salmeterol 50 µg, based on the effect on FEV_1 at 5 minutes post-dose. The ratio for formoterol vs placebo was 1.064 and statistically significantly greater than 1 (p<0.001). Thus, formoterol 9 µg improved FEV_1 compared with placebo, indicating an onset of bronchodilatory effect within 5 minutes.

The results for the secondary variables support the results for the primary efficacy variable.

The average increase in FEV_1 during the first 15 minutes (AUC_{0-15}) relative to pre-dose was 6.4%, 4.1% and 1.2% for formoterol, salmeterol and placebo, respectively. The improvement with formoterol was significantly higher than with salmeterol (p=0.009) and placebo (p<0.001). The average increase in FEV_1 during the first 120 minutes (AUC_{0-120}) relative to pre-dose was 9.6%, 8.2% and 1.4% for formoterol, salmeterol and placebo, respectively. The improvement with formoterol was numerically higher than with salmeterol and significantly higher than with placebo (p<0.001).

The proportions of patients with at least 12% increase in FEV_1 5 minutes post-dose for each treatment were: 23.1%, 9.2% and 6.4% for formoterol, salmeterol and placebo, respectively. The statistical comparisons of these proportions (using the exact McNemar's test) showed that the proportion of patients achieving at least 12% increase in FEV_1 at 5 minutes post dose

was statistically significantly larger after treatment with formoterol than with salmeterol ($p=0.008$) or placebo ($p<0.001$).

The cumulative proportion of patients who achieved at least 12 % increase in FEV_1 was larger for formoterol than for salmeterol and placebo at each time-point between 10 to 120 minutes post dose.

Pairwise treatment comparisons showed that the time to at least 12 % increase in FEV_1 was significantly shorter for formoterol than for salmeterol ($p=0.002$) and placebo ($p<0.001$, Cox regression).

Summary of safety results

The reported AEs were few, of mild or moderate intensity, and with no consistent pattern. No adverse events of concern were identified after dosing. The most common adverse event, during all three treatment periods, was nasopharyngitis. No serious adverse events were identified.

One subject had an adverse event that led to discontinuation of investigational product (salmeterol) and withdrawal from the study, however, this DAE was not judged as causally related to study drug.

No differences between the three treatment periods could be detected with respect to blood pressure and pulse rate measured before intake of study drug. All numeric differences were small.