Drug product:	Symbicort	**SYNOPSIS**	
Drug substance(s):	Budesonide/formoterol		
Edition No.:	1.0		
Study code:	D5890L00007		
Date:	24 April 2007		

A comparative, placebo-controlled, double-blind, double-dummy, cross-over, single centre, phase IIIb study between formoterol alone (Oxis® Turbuhaler® 4.5 µg) and the fixed combination of formoterol and budesonide (Symbicort® Turbuhaler®160/4.5 µg) on airway responsiveness and airway inflammation induced by repeated low-dose allergen challenge in allergic patients with mild asthma – SMILDA.

Principal investigator

Study centre

Publications

None at the time of writing this report

Study dates

First patient enrolled 22 October 2004

Last patient completed 10 May 2006

Phase of development

Therapeutic confirmatory (III b)

Objectives

Primary:

To compare the effects of formoterol alone (Oxis® Turbuhaler®) and the fixed combination of formoterol and budesonide (Symbicort® Turbuhaler®) on airway responsiveness induced by repeated low dose allergen challenge in allergic patients with mild asthma.

Secondary:

To compare the effects of the three treatments on lung function, exhaled nitric oxide (eNO) and to assess the effect of repeated low-dose exposure on markers of inflammation in blood and sputum.

Study design

The study was designed as a double-blind, double-dummy, placebo-controlled, three-arm cross-over study between Symbicort Turbuhaler (fixed combination product with formoterol and budesonide), Oxis Turbuhaler (formoterol alone) and placebo.

Target patient population and sample size

Male and female patients, aged between 18 and 55 years, with mild allergic asthma since at least 6 months, were enrolled in the study. The disease had to have been stable for the last 4 weeks.

In a previous study, the standard deviation for the change in log10-transformed PD_{20} (the provocative dose causing a 20% fall in forced expiratory volume in one second (FEV_1)) from before to after allergen challenge was 0.23. With a similar standard deviation, using a significance level of 5% and a two-sided alternative hypothesis, a cross-over study with 12 completed patients would detect a between-treatment difference (increase) of 83% in PD_{20} with 80% power. The drop-out rate was expected to be 20% and 16 randomised patients were required.

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

Treatment was administered in a randomised order once daily as:

- 2 inhalations of each of Oxis (formoterol fumarate dihydrate 4.5 µg) and $placebo_{Symbicort}$ or
- 2 inhalations of each of $placebo_{Oxis}$ and Symbicort (budesonide 160 µg/formoterol fumarate dihydrate 4.5 µg) or
- 2 inhalations of each of $placebo_{Oxis}$ and $placebo_{Symbicort}$

Study treatment was given in inhalations of the following doses (batch #): Symbicort (budesonide 160 µg/formoterol fumarate dihydrate 4.5 µg (FE36)), $placebo_{Symbicort}$ (FE18), Oxis (formoterol fumarate dihydrate 4.5 µg (FH27)), $placebo_{Oxis}$ (FH39).

Duration of treatment

7 days with each of the 3 treatment cross-over periods, separated by wash-out periods of 15 days.

Criteria for evaluation (main variables)

Efficacy

Primary variable:

- Change in PD_{20} methacholine (MCh) during each treatment period.

Secondary variables:

- Change in eNO and change in FEV_1 during each treatment period.
- Explorative part: change in total number and differential count of cells, eosinophilic cationic protein (ECP) and biomarkers in induced sputum and blood during each treatment period and evaluation of blood for basophilic activity and saliva for lipid mediators.

Patient reported outcomes (PRO):

- Diary recordings of asthma symptom scores, FEV_1 and β_2-agonist inhalations.

Safety

Incidence of serious adverse events (SAEs) and discontinuations due to adverse events (DAEs).

Statistical methods

The primary variable, PD_{20} MCh, was log-transformed and then analysed using an analysis of covariance (ANCOVA) model with patient, period and treatment as fixed factors and each period's baseline value of PD_{20} MCh (log-transformed) as covariate. Treatment differences, 95% confidence intervals for these and p-values were calculated from the model.

The secondary variables, average and minimal FEV_1 and average eNO, were analysed and compared between treatments in the same way and with the same analysis model, but without log-transformation. The PRO, i.e. diary data on asthma scores, FEV_1 and number of β_2-agonists doses, were analysed based on individual patient averages and analysed as above.

Safety variables and baseline data were presented by descriptive statistics.

The explorative immunological part of the study will be reported later in a separate Appendix "Immunological Markers". The variables will be compared between treatments using a multiplicative analysis of variance model with patient, period and treatment as fixed factors and each period's baseline value as covariate. Adjusted mean treatment difference will be estimated and 95% confidence intervals will be calculated. No adjustment for multiple comparisons will be done, since the nature of these variables is exploratory and measuring different aspects.

Patient population

Patient disposition is presented in Table S1 and baseline patient characteristics in Table S2. The randomised study population comprised 18 patients, of which one was discontinued due to poor compliance. The remaining 17 patients started treatment with investigational products. 2 patients were discontinued during or after the first treatment period: one due to AE, classified as SAE, during placebo treatment and one due to other reason during Oxis treatment. 15 patients completed the study and were included in the full analysis set for efficacy. All enrolled patients were included in the safety analysis set. There were no protocol deviations. The patients' demographic and baseline characteristics were representative of a patient population with mild allergic asthma, although most patients had a fairly long history, approximately 20 years, of asthma symptoms and diagnosis.

Table S1 Patient disposition

	Symbicort period	Oxis period	Placebo period	All periods
Number of patients enrolled				28
Number of patients randomised				18
Number of patients entering specific treatment	15	16	16	17
Number (%) of patients who discontinued during the specific treatment	0 (0.0%)	1 (6.3%)	2 (12.5%)	3
Reasons for discontinuation: n (%)				
Adverse event	0 (0.0%)	0 (0.0%)	1 (6.3%)	1
Other	0 (0.0%)	1 (6.3%)	1 (6.3%)	2
Number (%) of patients who completed the study period	15 (100.0%)	15 (93.8%)	15 (93.8%)	15

Note: Percentages calculated for each reason for discontinuation are based on the number of patients entering specific treatment. No percent is calculated for total. One patient in the placebo treatment discontinued before taking any drug.
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Table S2 Baseline demographic values. Full Analysis Set

Variable	All patients (N=15) Distribution			
Demographic characteristics				
Sex: n (%)				
Male	8 (53.3)			
Female	7 (46.7)			
Race: n (%)				
Caucasian	14 (93.3)			
Oriental	1 (6.7)			
Smoking status: n (%)				
Non Smoker	13 (86.7)			
Ex-Smoker	2 (13.3)			
	N	**Mean (SD)**	**Median**	**(Min,Max)**
Age (Years)	15	31.97 (10)	25.6	(25 , 56)
Pack Years	2	2.50 (.71)	2.5	(2 , 3)
Years since stopped smoking	2	25.00 (0)	25.0	(25 , 25)
Baseline asthma variables				
Years since first appearance of asthma symptoms	15	20.07 (7.9)	18.0	(10 , 35)
Years since asthma first diagnosed	15	18.07 (9.5)	17.0	(2 , 35)
Average expired NO at Visit 1	15	42.59 (31)	28.8	(10.1 , 98.2)
FVC at Visit 1 (L)	15	5.16 (1)	4.9	(3.85 , 6.93)
FEV_1 at Visit 1 (L)	15	4.03 (.85)	4.0	(3.07 , 5.42)
FEV_1 in % at Visit 1	15	106.2 (8.6)	106	(91.1 , 123)

Data derived from Table 11 and Table 12.

Efficacy results

Analysis of the primary variable, the change in PD_{20} MCh during each treatment period, showed a significant increase of PD_{20} MCh with Symbicort compared with placebo (p=0.01). There was no statistically significant difference between Oxis and placebo. Symbicort presented better numerically than Oxis, although it did not reach statistical significance. Symbicort treatment was significantly superior to placebo and Oxis in decreasing eNO (p=0.0002 and p=0.002, respectively). There was also a significant difference favouring Symbicort in change in FEV_1 compared to placebo and Oxis (p=0.002 and p=0.02). Diary recordings of asthma symptom scores showed no significant differences between Symbicort and Oxis, but both treatments were significantly better than placebo (p=0.02 and p=0.02, respectively). There were no statistical differences in diary recordings of FEV_1 and use of β_2-agonists for any of the treatments.

Safety results

The number of patients who had at least one adverse event (AE) in any category is summarised in Table S3. Generally, the study treatments were safe and well tolerated. In this study, only information regarding SAEs and DAEs was collected. The incidence of SAEs and DAEs was low. There was only one patient who experienced in all 3 SAEs, of which one led to discontinuation. The SAEs occurred after the first treatment period with placebo. The investigator considered the SAEs to be unrelated to the investigational product, other medication or study procedures. There were no deaths reported. No new safety concerns were identified in this study.

Table S3 Number (%) of patients who had an adverse event in any category. Safety Analysis Set

Category of adverse event	Number (%) of patients who had an adverse event in each category[a]					
	Symbicort (n=15)		Oxis (n=16)		Placebo (n=17)	
Serious adverse events	0	0%	0	0%	1	5.9%
Serious adverse events leading to death	0	0%	0	0%	0	0%
Serious adverse events not leading to death	0	0%	0	0%	1	5.9%
Discontinuations of study treatment due to adverse events	0	0%	0	0%	1	5.9%

a Patients with multiple events in the same category are counted only once in that category. Patients with events in more than 1 category are counted once in each of those categories.

Data derived from Table 24.

Conclusion(s)

Date of the report

24 April 2007