Drug Substance	Budesonide/formoterol	**SYNOPSIS**	(For national authority use only)
Study Code	D5892C00012		
Edition Number	1		
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A randomized, double-blind, double-dummy, two-way cross-over study evaluating systemic bioavailability and airway clearance of Symbicort® Turbuhaler® 320/9 µg/inhalation versus Seretide™ Diskus™ 50/500 µg/inhalation after single inhalations in patients with Chronic Obstructive Pulmonary Disease (COPD) and healthy volunteers

Study centres

This study was conducted in the United Kingdom (1 centre), Germany (1 centre) and Sweden (2 centres).

Study dates		**Phase of development**
First subject enrolled	04 September 2006	Clinical pharmacology (IV)
Last subject completed	22 July 2007	

End of study was defined as database lock, which is the time point after which no subject was exposed to study related activities.

Objectives

The primary objective was to evaluate airway tissue availability of budesonide via Symbicort Turbuhaler and fluticasone via Seretide Diskus in severe COPD patients and healthy volunteers, using area under the curve (AUC) of the plasma concentrations of the steroid components as surrogate marker.

In addition to the primary objective there was a number of planned exploratory analyses:

- to investigate the amount of budesonide and fluticasone (% of delivered dose) spontaneously expectorated in sputum,
- to investigate correlation between weight of spontaneously expectorated sputum and AUC for budesonide and fluticasone, and
- to investigate correlation between baseline lung function in COPD patients and AUC for plasma concentrations of budesonide and fluticasone.

Study design

This was a double-blind, double-dummy, randomised, two-way cross-over single dose multicentre study in patients with chronic obstructive pulmonary disease (COPD) and in healthy volunteers.

Target subject population and sample size

A total of 27 COPD patients (men or women ≥40 years of age) and 27 healthy volunteers (men or women ≥18 years of age) were planned to be randomized in order to get 24 evaluable subjects in each group.

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

Test product: Symbicort Turbuhaler, budesonide/formoterol 320/9 µg per inhalation, one inhalation. Batch number: GL 388

Comparator product: Seretide Diskus, salmeterol/fluticasone 50/500 µg per inhalation, one inhalation. Batch numbers: R187842, R225098

Duration of treatment

Two single dose treatments, Symbicort Turbuhaler and Seretide Diskus, which were separated by a wash-out period of 4 to 14 days.

Variables

Pharmacokinetics

The primary variable was AUC for plasma concentrations of budesonide and fluticasone in COPD patients and healthy volunteers.

In addition, spontaneously expectorated sputum from COPD patients was analysed for budesonide and fluticasone concentrations.

Safety

Safety was monitored by collecting serious adverse events (SAEs) and discontinuation of treatment with investigational product due to adverse events (DAEs) during the study.

Statistical methods

A multiplicative linear mixed effect model with treatment, group (COPD patient or healthy volunteers), and period as fixed factors, and subject as a random effect, was fitted to the individual area under the plasma concentration-time curves (AUC)s. From this model the ratio of the mean ratio of AUC between fluticasone and budesonide in COPD patients and the mean ratio of AUC between fluticasone and budesonide in healthy volunteers are estimated and presented with the associated 95% confidence limits.

The retrieved amount of budesonide and fluticasone (% of estimated lung deposited dose) expectorated in sputum during 6 hours after inhalation, in patients with COPD, was compared using a similar model with patient as a fixed factor. Influence of this individual AUC fluticasone/budesonide ratio was investigated using linear regression on log ratios and the variable in question, and influence of amount expectorated sputum and steroid on individual AUCs was investigated using linear regression on log AUCs and log sputum weight or log steroid amount.

Subject population

A total of 46 COPD patients were enrolled at three centres. Twenty-eight patients were randomised to treatment and 26 completed the study period. The first patient entered the study 5 January 2007 and the last patient finished the study 22 July 2007.

A total of 44 healthy volunteers were enrolled at one centre. Twenty-seven healthy volunteers were randomised to treatment and 26 completed the study. The first subject entered the study 4 September 2006 and the last subject finished the study 29 September 2006.

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

Table S1 Subject population and disposition

Demographic or baseline characteristic		**Treatment group**			
		COPD patients (n=28)		**Healthy volunteers (n=27)**	
Demographic characteristics					
Sex (n and % of subjects)	Male	21	(75%)	11	(41%)
	Female	7	(25%)	16	(59%)
Age (years)	Mean	65.0		30.9	
	Range	48-80		20-65	

Table S1 Subject population and disposition

Demographic or baseline characteristic		Treatment group	
		COPD patients (n=28)	**Healthy volunteers (n=27)**
Race (n)	Caucasian	28	27
Baseline characteristics			
BMI (kg/m^2)	Mean	26.5	23.1
	Range	21-32	18-29
FEV_1 (L)	Mean	1.097	3.846
	Range	0.50-1.91	2.27-5.94
FEV_1 (% P.N.)	Mean	37.5	103.3
	Range	24-51	84-131
VC (L)	Mean	2.751	4.610
	Range	1.18-5.22	3.46-6.57
FVC (L)	Mean	2.679	(NA)
	Range	1.06-4.91	(NA)
FEV_1 (% FVC)	Mean	42.4	(NA)
	Range	27-60	(NA)
FEV_1 (% VC)	Mean	41.6	83.1
	Range	26-63	66-103
Time since diagnosis (years)	Median	8.8	(NA)
	Range	1-37	(NA)
Pack-years	Median	40	(NA)
	Range	10-64	(NA)
Smoking status (n)	Previous	16	(NA)
	Habitual	22	(NA)
Inhaled GCS at entry	n	18	(NA)
	Mean	777.2	(NA)
	Range	160-1600	(NA)
Disposition			
N (%) of subjects who	Completed	26 (92.9%)	26 (96.3%)
	Discontinued	2 (7.1%)	1 (3.7%)

NA Not applicable

Three subjects discontinued the study, two patients (adverse event [AE], disallowed medication) and one healthy volunteer (AE).

Summary of pharmacokinetic results

The bioavailability of budesonide and fluticasone was compared after exposure of respective steroid. There was a tendency for both drugs to appear in lower plasma concentration in COPD patients than in healthy volunteers. The mean AUC for fluticasone over budesonide was estimated to be about 18% for healthy volunteers and 20% for COPD patients (Table S2), indicating similar uptake in COPD patients compared to healthy volunteers for budesonide in relation to fluticasone.

The healthy volunteer/COPD patient ratio of the fluticasone/budesonide ratios was estimated to 89%, and there was not sufficient evidence to claim that there was a true difference between the drugs.

Table S2 Geometric mean ratios for dose-adjusted AUC

Parameter	Geometric mean ratios	95% C.I.
FLU/BUD for HV	0.180	(0.133, 0.243)
FLU/BUD for COPD	0.202	(0.148, 0.276)
FLU/BUD for HV/COPD	0.890	(0.578, 1.37)
HV/COPD for BUD	2.02	(1.48, 2.76)
HV/COPD for FLU	1.80	(1.32, 2.45)

FLU Fluticasone, BUD Budesonide, HV Healthy volunteer, CI Confidence interval

The correlation between baseline lung function in COPD patients and AUC for plasma concentrations of budesonide and fluticasone was investigated. There was a tendency that AUC for budesonide increased relative to fluticasone with increasing lung obstruction and with increasing number of pack-years. Statistical significance was not derived.

The amount of budesonide and fluticasone (% estimated lung deposited dose [ELDD]) spontaneously expectorated in sputum was compared. Fluticasone was expectorated over a much longer period and the average expectorated amount of fluticasone was higher than budesonide, whereas there was no difference in average weight of sputum expectorated during both treatments. An analysis of the geometric mean of the total amount (% ELDD) of drug expectorated is given in Table S3. It shows that more fluticasone was expectorated (% ELDD) than budesonide, with a ratio estimated to about 5.

Table S3 Statistical analysis of amount of budesonide and fluticasone (% of ELDD) in expectorated sputum during 0 to 6 hours post-dose. Adjusted geometric means and treatment ratio

Parameter	Estimate	95% C.I.	P-value
Budesonide	1.11	(0.52,2.37)	
Fluticasone	5.78	(2.59,12.9)	
Fluticasone/Budesonide	5.21	(1.72,15.8)	0.006

CI Confidence interval

The correlation between weight of spontaneously expectorated sputum and AUC for plasma concentrations of budesonide and fluticasone was plotted. The expectorated amount did not seem to affect exposure for budesonide, whereas there were indications that the fluticasone exposure diminished when more substance was expectorated. Budesonide was present in expectorated sputum mainly shortly after inhalation, whereas fluticasone was expectorated over a longer period. Budesonide is more rapidly absorbed in the airway tissue compared to fluticasone as demonstrated by pharmacokinetic data.

Summary of safety results

No deaths, SAEs and other significant adverse events occurred in the study. Two subjects discontinued the study due to AEs. One event was reported in a healthy volunteer during the wash-out period following Seretide treatment. The other event was reported in a COPD patient during run-in and the patient discontinued the study after first intake of investigational product. No AE was judged by the investigator to be causally related to the investigational product.

There were no safety concerns during the conduct of the study and both treatments were well tolerated.