Drug Product	Symbicort	**SYNOPSIS**	
Drug Substance	Budesonide/formoterol		
Study Code	D5890L00017		
Edition Number	01		
Date	07 November2008		

A comparison of budesonide/formoterol Turbuhaler® 160/4.5 µg 2 inhalations BID plus as needed (Symbicort Maintenance and Reliever Therapy) to budesonide Turbuhaler® 320 µg 2 inhalations BID plus terbutaline Turbuhaler® 0.4 mg as needed for the prevention of asthma relapse following emergency department discharge due to an asthma exacerbation. An 8 week, randomized, double blind, parallel group, active controlled, multicentre phase IIIB efficacy study in adult asthmatic patients.

Study centre(s)

A total of 20 hospitals across Canada were recruited to participate in this study.

Publications

None

Study dates		**Phase of development**
First subject enrolled	31 May 2006	IIIb
Last subject completed	15 May 2007	

The study was terminated prematurely due to slower than expected recruitment with only 41 out of the originally planned 600 patients randomized.

Objectives

Primary:

The primary objective of this study was to compare the efficacy of budesonide/formoterol as maintenance and reliever therapy to budesonide and terbutaline following emergency department discharge due to an asthma exacerbation by evaluating the time to first asthma relapse as the primary outcome variable.

Secondary:

The secondary objectives were:

- to determine if budesonide/formoterol as maintenance and reliever therapy reduces the need for rapid acting β_2-agonists compared to budesonide and terbutaline following emergency department discharge due to an asthma exacerbation.
- to determine if budesonide/formoterol as maintenance and reliever therapy improves the Asthma Control Questionnaire (ACQ5) score compared to budesonide and terbutaline following emergency department discharge due to an asthma exacerbation.
- to summarize the incidence, severity and types of all adverse events.

Study design

This was a randomized, double-blind, parallel group, active controlled, multicentre efficacy study comparing budesonide/formoterol Turbuhaler® 160/4.5 µg 2 inhalations BID plus as needed (Symbicort Maintenance and Reliever Therapy) to budesonide Turbuhaler® 320 µg 2 inhalations BID plus terbutaline Turbuhaler® 0.4 mg as needed for the prevention of asthma relapse following emergency department discharge due to an asthma exacerbation.

Target subject population and sample size

Male and female patients between 18-65 years of age, already receiving a low- or moderate-dose of inhaled corticosteroids at the time of their exacerbation and discharged from the emergency department following treatment for an asthma exacerbation.

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

Budesonide/formoterol Turbuhaler® 160/4.5 µg 2 inhalations twice-daily (BID) as maintenance therapy plus as needed for relief of asthma symptoms.

Comparator, dosage and mode of administration

Budesonide Turbuhaler® 320 µg 2 inhalations twice-daily (BID) as maintenance therapy plus terbutaline Turbuhaler® 0.4 mg for relief of asthma symptoms.

Duration of treatment

The treatment period was designed to last for 8 weeks.

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics

- Primary variable: - Time to first asthma relapse. An asthma relapse was defined as an unscheduled medical visit initiated by the patients' perceived need for further asthma treatment.
- Secondary variables:
  - Mean use of reliever medication.
  - Asthma Control Questionnaire (ACQ5) score.
  - Complete AE and SAE collection.

Safety

Adverse events were collected by means of a standard question: "Have you had any health problems since the previous visit or phone call?" The question was put to each patient during phone contacts 1 and 2 as well as at Visits 2 and 3.The patients' response to this question and spontaneously reported and/or observed AE were recorded in the CRF. The following information was collected, AE name, start date, seriousness, causality rating (yes or no), action taken related to the investigational product, discontinuation from the study due to this AE (yes or no), stop date or ongoing at the last visit, final outcome (if applicable).

Statistical methods

Efficacy was not evaluated in this abbreviated report. AEs were described using frequency and percentages.

The safety analysis comprised all subjects who took at least one dose of the randomised treatment.

During the study period, over 670 patients with asthma were approached, of which 41 patients were enrolled and randomized. The most common reasons for exclusion were not being on ICS treatment (30%), already receiving LABA as combination therapy (28%), admission to hospital (6%), history of smoking more than 10 pack years (5%), infection or co-morbidity (4%), history of COPD (4%) and PEF >80% (3%).

Subject population

Table S1 Subject population and disposition

		SMART		BUD + SABA		Total	
Population							
N randomised (N planned)		21	(300)	20	(300)	41	(600)
Demographic characteristics							
Sex (n and % of subjects)	Male	11	(52.4)	9	(45.0)	20	(48.8)
	Female	10	(47.6)	11	(55.0)	21	(51.2)
Age (years)	Mean (SD)	30.1	(7.7)	32.2	(10.6)	31.1	(9.2)
	Range	20 to 48		18 to 51		18 to 51	
Race (n and % of subjects)	Caucasian	20	(95.2)	17	(85.0)	37	(90.2)
	Black	0	(0)	1	(5.0)	1	(2.4)
	Oriental	1	(4.8)	0	(0)	1	(2.4)
	Other	0	(0)	2	(10.0)	2	(4.9)
Baseline characteristics							
Mean (SD) FEV_1 (L)		2.7	(0.7)	2.6	(0.7)	2.6	(0.7)
Disposition							
N (%) of subjects who	Completed	14	(66.7)	13	(65.0)	27	(65.9)
	Discontinued	7	(33.3)	7	(35.0)	14	(34.1)
N analysed for safety[a]		21		20		41	
N analysed for efficacy (ITT)		21		20		41	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing
ITT=Intention to treat; N=Number

Efficacy and pharmacokinetic results

No analysis of the efficacy results was performed since the study was prematurely terminated.

Table S2 Number of asthma relapses by treatment (ITT)

Event		SMART (N=21)	BUD + SABA (N=20)
Asthma relapse (total)	No. of subjects	3 (14.3%)	3 (15.0%)
	No. of events	4	3
	No. with 1 event	2	3
	No. with > 1 event	1	0
	Max events/subject	2	1
New asthma relapse	No. of subjects	3	3
	No. of events	3	3
Continuation from previous asthma relapse	No. of subjects	1	0
	No. of events	1	0

Table S3 Mean use of reliever medication (inhalation/day) by visit (ITT)

		SMART (n=21)	BUD + SABA (n=20)
Telephone contact 1	N	19	19
	Mean	2.8	2.8
	Range	0-8	0-8
Telephone contact 2	N	19	18
	Mean	1.2	2.0
	Range	0-4	0-6
Visit 2	N	16	15
	Mean	1.6	2.1
	Range	0-5	0-8
Visit 3	N	16	13
	Mean	1.0	2.5
	Range	0-6	0-6

Table S4 Mean overall ACQ5 by baseline and treatment period (ITT)

	Baseline (Visit 1)			Treatment period average		
Treatment	**n**	**Mean**	**(Range)**	**n**	**Mean**	**(Range)**
SMART	21	3.25	(0.8 - 6.0)	17	1.28	(0.3 - 2.7)
BUD + SABA	20	3.55	(1.8 - 5.2)	15	1.26	(0.0 - 3.0)

Safety results

Table S5 Number (%) of subjects who had at least 1 adverse event in any category, and total numbers of adverse events (safety analysis set)

Category of adverse event	N (%) of subjects who had an adverse event in each category[a]			
	SMART (n=21)		BUD + SABA (n=20)	
Any adverse events	12	(57.1)	8	(40.0)
Serious adverse events	0	(0)	0	(0)
Serious adverse events leading to death	0	(0)	0	(0)
Serious adverse events not leading to death	0	(0)	0	(0)
Discontinuations of study treatment due to adverse events (DAE)	1	(4.8)	0	(0)
Other significant adverse events				
	Total number of adverse events			
Adverse events	28		18	
Serious adverse events	0		0	
Other significant adverse events	1		0	

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

Table S6 Number (%) of subjects with the most commonly reported[a] adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set)

Adverse event (preferred term)	Number (%) of subjects who had an adverse event			
	SMART (n=21)		BUD + SABA (n=20)	
Headache	1	(4.8)	3	(15.0)
Myalgia	3	(14.3)	0	(0)
Back pain	0	(0)	2	(10.0)
Nasopharyngitis	1	(4.8)	1	(5.0)
Pharyngolaryngeal pain	2	(9.5)	0	(0)
Productive cough	1	(4.8)	1	(5.0)
Upper respiratory tract infection	1	(4.8)	1	(5.0)

[a] Events with a total frequency of ≥4% across all treatment groups are included in this table.