AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort®
ACTIVE INGREDIENT: Budesonide/formoterol

Study No: D5890L00004
A comparison of Symbicort® SMART (Symbicort® 200 Turbuhaler® 1 inhalation b.i.d. plus as-needed) and conventional best practice for the treatment of persistent asthma in adolescents and adults – a 26-week, randomised, open-label, parallel group, multicentre study

Developmental phase: IIIb
Study Completion Date: Last subject completed: 7 October 2005
Date of Report: August 22, 2007

OBJECTIVES:

The primary objective of the study was to compare the effectiveness of Symbicort® Maintenance and Reliever Therapy (Symbicort® SMART) in asthma with treatment according to conventional best practice. The secondary objective was safety.

METHODS:

Study design

This was a randomized, open-label, phase IIIB, multicentre study with a parallel-group design. Subjects were treated with either Symbicort® Maintenance and Reliever Therapy (Symbicort® SMART) i.e. Symbicort® Turbuhaler® 160/4.5 µg/inhalation (delivered dose), 1 inhalation b.i.d. plus as-needed, or Conventional Best Practice (CBP) according to the investigator's judgement, following the Canadian Asthma Consensus Report[1,2]. The study comprised the following periods: 2-week run-in period and 26-week randomized treatment period.

Figure 1 Study flow chart

Run-in Treatment period

Symbicort® SMART : 160/4.5 µg/ inhalation (delivered dose) + as-needed

Subject's usual asthma therapy	Conventional best practice			
Visit				
1	2	3	4	5
Weeks				
-2	0	4	13	26

Target subject population and sample size

Male and female, adolescent (≥ 12 years of age) and adult subjects with persistent asthma, currently treated with inhaled glucocorticosteroids (IGCSs) or IGCS and long-acting β_2-agonist (LABA).

Using a log-rank test, a sample size of 650 subjects per treatment group (a total of 1300 randomized subjects) was required in order to detect a difference between the two treatment groups with 80% probability. It was under the assumption that, at the end of the study, 13% of the patients would have experienced a severe exacerbation in one treatment group and 8.2% of the patients would have experienced a severe exacerbation on the other treatment group. In order to compensate for an estimated 15% dropout rate during the run-in period, a total of 1530 subjects were to be enrolled in this study.

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

Investigational medication was Symbicort® Turbuhaler® 160/4.5 µg/ inhalation (delivered dose), 1 inhalation b.i.d. as maintenance dosing plus as-needed, in response to symptoms.

Comparators were conventional best practice medications according to the investigator's judgement, following the Canadian Asthma Consensus Report[1,2].

Batch number was: Symbicort® 200 Turbuhaler® (160/4.5 µg) – FB 611

Duration of treatment

The treatment period lasted for 26 weeks.

Criteria for evaluation (main variables)

Efficacy

Primary variable

- Time to first severe asthma exacerbation

Secondary variables

- Number of severe asthma exacerbations
- Mean use of as-needed medication
- Prescribed asthma medications

Other Efficacy Variable

- Peak Expiratory Flow

Patient reported outcomes (PRO)

- Asthma Control Questionnaire (ACQ) score
- Patient's satisfaction with the treatment

Health Economics

- Health care resource use
- Out-of-pocket expenses
- Time lost from paid and unpaid work

Safety

Safety variables were incidence and type of adverse events (AEs).

Statistical methods

All efficacy analyses were based on the full analysis set, as defined in the ICH E9 guidelines.

Time to first severe asthma exacerbation was described using Kaplan-Meier curves and compared between treatments using a log-rank test and Cox proportional hazards (Cox PH) model with treatment as a factor. The mean number of severe asthma exacerbations per patient was compared between treatments using a Poisson regression model. The overall asthma control questionnaire (ACQ) score, use of inhaled steroids, use of as-needed medication and PEF were analysed by an analysis of variance model. Prescribed asthma medications, patient's satisfaction with the treatment and health care resource use were compared between treatments and presented descriptively. The annual asthma medication costs and annual total costs were compared between treatments using the bootstrapping method. Safety data was analysed by means of descriptive statistics.

Subject population

Table S1 Subject population and disposition

		SMART (772)	CBP (766)	Total (1538)
Sex (n and % of subject)	Male	326 (42.2)	287 (37.5)	613 (39.8)
	Female	446 (57.8)	479 (62.5)	925 (60.2)
Age	Mean (SD)	42.1 (16.4)	43.1 (16.0)	42.6 (16.2)
	Range	12-92	12-94	12-94
Age Groups (n and % of subject)	12 - 17	53 (6.9)	38 (5)	91 (5.9)
	18 - 64	641 (83)	652 (85.1)	1293 (84.1)
	>=65	78 (10.1)	76 (9.9)	154 (10)
Race (n and % of subject)	Caucasian	728 (94.3)	726 (94.8)	1454 (94.5)
	Black	18 (2.3)	25 (3.3)	43 (2.8)
	Oriental	17 (2.2)	13 (1.7)	30 (1.9)
	Other	9 (1.2)	2 (0.3)	11 (0.7)
Body Mass Index (BMI)	Mean (SD)	28.9 (6.9)	29 (6.7)	29 (6.8)
	Range	15.1-62.4	16.2-64.5	15.1-64.5
Use of LABA	N (%)	564 (73%)	573 (75%)	1137 (74%)
IGCS dose/day (μg) during run-in	Mean (SD)	566 (207)	572 (229)	569 (218)
	Range	250-1600	160-2400	160-2400
IGCS dose/day (μg) before randomization[a]	Mean (SD)	565 (203)	571 (224)	568 (214)
	Range	250-1600	160-2400	160-2400
Median time since diagnosis (yrs)	Median	15.6	15	15.1
	Range	0.3-69	0.3-68	0.3-69
Time since most recent exacerbation (months)	Median	9.6	9.6	9.6
	Range	0-528	0-468	0-528
No of as-needed inhalations/day				
ICS alone	Mean (SD)	1.58 (1.75)	1.75 (1.89)	1.67 (1.82)
Combo[b]	Mean (SD)	1.13 (1.62)	1.04 (1.58)	1.09 (1.60)
Total	Mean (SD)	1.25 (1.67)	1.22 (1.69)	1.24 (1.68)
	Range	0-13.2	0-12.2	0-13.2
As-needed free days (%)	Mean (SD)	53.7 (38.3)	55.7 (38.2)	54.67 (38.3)
	Range	0-100	0-100	0-100
Smoking Status (n and % of subject)	Non Smoker	468 (60.6)	483 (63.1)	951 (61.8)

		SMART (772)	CBP (766)	Total (1538)
	Ex-Smoker	202 (26.2)	197 (25.7)	399 (25.9)
	Occasional Smoker	30 (3.9)	22 (2.9)	52 (3.4)
	Habitual Smoker	72 (9.3)	64 (8.4)	136 (8.8)
# pack year	Mean (SD)	4.8 (2.9)	4.8 (2.8)	4.8 (2.8)
	Range	0-10	0-10	0-10
PEF(L/min) pre BD	Mean (SD)	408 (118)	405 (117)	406 (117)
	Range	100-820	110-800	100-820
PEF(L/min) post BD	Mean (SD)	434 (122)	428 (119)	431 (121)
	Range	110-840	110-820	110-840
PEF % predicted normal (%) pre BD	Mean (SD)	94.8	94.1	94.5
	Range	22 - 197	26 - 186	22-197

[a] all IGCS recorded in the med log prior to randomization were included in the calculation
[b] Including combination drugs (i.e., Symbicort or Advair) and ICS + LABA

RESULTS:

Efficacy results

The time to first severe asthma exacerbation was not significantly different between the Symbicort® SMART arm and Conventional Best Practice arm, with a hazard ratio of 0.989 (p=0.952).

The number of severe exacerbations for Symbicort® SMART and CBP was 19 versus 21 events/year/100 patients, p=0.634. There were numerically fewer exacerbations based on emergency room visits/hospitalizations with Symbicort SMART (4.4 versus 7.5 events/100 patients/yr; 41% reduction, p = 0.09). Mean as-needed use was significantly lower with Symbicort® SMART versus the CBP group (0.94 inh./day versus 1.09 inh./day, p=0.0036). The percentage of subjects with greater than 8 as-needed inhalations on at least one day was lower in the Symbicort® SMART arm when compared to the CBP arm (2% versus 4%).

The mean daily dose of inhaled steroid use was significantly lower in the Symbicort® SMART arm versus the CBP arm (478 versus 585 µg/day, p<0.0001). The mean daily dose of inhaled steroid use expressed as BDP equivalent was also significantly lower in the Symbicort® SMART arm versus the CBP arm (748 versus 1015 µg/day, p<0.0001).

A total of 82 % of the subjects in the CBP arm were prescribed a combination treatment of an inhaled glucocorticosteroid and long acting Beta-2 agonist (in combination therapy or as mono products). The PEF measurements improved slightly during the treatment period, with no significant differences between the two treatment groups.

Both groups showed similar improvement in asthma symptoms as measured by improvement in ACQ score. A total of 94% of the patients in the Symbicort® SMART

arm were satisfied or better with their treatment and 98% of patients in the CBP arm were satisfied or better with their treatment.

Health economic results

No patients were hospitalized in the Symbicort® SMART arm versus 1 in the CBP arm. Emergency room visits were 18 on Symbicort® SMART versus 27 on CBP treatment. The number of specialist visits and healthcare professional visits were 84 in Symbicort® SMART versus 78 in CBP and the number of tests was greater, 48 versus 40 on Symbicort® SMART than the CBP.

Total out-of-pocket expenses were less in the Symbicort® SMART arm ($810 versus $974 in CBP arm). The number of days lost by subject was 311 in the Symbicort® SMART arm versus 205 in the CBP arm. The asthma medication and the total costs per patient per year were 28% and 23% lower, respectively with Symbicort® SMART versus CBP. The difference between the Symbicort® SMART group and CBP arm regarding asthma medication cost was $ 353.60 and the difference regarding total yearly societal cost was $ 315.55. The total yearly societal cost includes all healthcare costs both direct and indirect costs (eg. Visit to family physician, specialists etc.).

Safety results

All treatments in both groups were considered safe and well tolerated. No clinically important drug related safety findings were identified in this study. The study collected data on AEs, SAEs and DAEs. The number of subjects who had an adverse event that started in the treatment phase was similar for both treatment groups. Similarly, the number of subjects with serious adverse events that started in the treatment phase was similar for both treatment groups. The number of subjects that discontinued the study due to an adverse event was higher in the Symbicort® SMART arm when compared to the CBP arm.

Table S2 Number(%) of subjects who had an adverse event in any category (safety analysis set)

	N(%) of subjects who had an adverse event in each category[1]							
	SMART (n= 772)				CBP (n= 766)			
	Run-in		Tx-emergent		Run-in		Tx-emergent	
Category of adverse event	n	(%)	n	(%)	n	(%)	n	(%)
Any adverse events	83	(10.8%)	474	(61.4%)	61	(8.0%)	491	(64.1%)
Serious adverse events	2	(0.3%)	17	(2.2%)	2	(0.3%)	15	(2.0%)
Serious adverse events leading to death	0	(0.0%)	1	(0.1%)	0	(0.0%)	2	(0.3%)
Serious adverse events not leading to death	2	(0.3%)	16	(2.1%)	2	(0.3%)	13	(1.7%)
Discontinuations of study treatment due to adverse events[2]	1	(0.1%)	27	(3.5%)	1	(0.1%)	6	(0.8%)
Total number of adverse events								
Any adverse events	101		109		78		1088	

	N(%) of subjects who had an adverse event in each category[1]							
	SMART (n= 772)				CBP (n= 766)			
	Run-in		Tx-emergent		Run-in		Tx-emergent	
Category of adverse event	n	(%)	n	(%)	n	(%)	n	(%)
			8					
Serious adverse events	2		20		2		18	
Serious adverse events leading to death	0		1		0		2	
Serious adverse events not leading to death	2		19		2		16	
Discontinuations of study treatment due to adverse events[2]	1		37		1		7	

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[1]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.

[2]Discontinuation due to AE was based on the data collected in the AELOG module

Table S3 Number (%) of subjects who had at least 1 adverse event in any system organ class[a], sorted by decreasing order of frequency over all treatment groups (safety analysis set)

	SMART (n= 772)				**CBP (n= 766)**			
	Run-in		Tx-emergent		Run-in		Tx-emergent	
System organ class	n	(%)	n	(%)	n	(%)	n	(%)
Infections and infestations	39	(5.1%)	320	(41.5%)	23	(3.0%)	339	(44.3%)
Respiratory, thoracic and mediastinal disorders	13	(1.7%)	81	(10.5%)	5	(0.7%)	68	(8.9%)
Musculoskeletal and connective tissue disorders	8	(1.0%)	70	(9.1%)	5	(0.7%)	65	(8.5%)
Gastrointestinal disorders	9	(1.2%)	61	(7.9%)	9	(1.2%)	66	(8.6%)
Nervous system disorders	10	(1.3%)	50	(6.5%)	9	(1.2%)	54	(7.0%)
Injury, poisoning and procedural complications	5	(0.6%)	50	(6.5%)	6	(0.8%)	42	(5.5%)

[a] Top six System organ class with a least 1 adverse event.