AstraZeneca

BN-00S-0011

SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Symbicort® Turbuhaler®

ACTIVE INGREDIENT: budesonide/formoterol

Trial title (number): Effects of Symbicort Single Inhaler Therapy on top of a regular daily dose on Bronchial Hyperresponsiveness, asthma control and safety in mild to moderate asthmatics in general practice, compared to usual care therapy.

Developmental phase: IIIb
First subject recruited: 23 September 2003
Last subject completed: 30 October 2006
Approval date: 25 January 2008

OBJECTIVES

The primary objectives were:
1) to compare in asthmatic patients the effects of budesonide/formoterol (Symbicort®) Single inhaler Therapy ("SiT", presently named "Symbicort as Maintenance And Reliever Therapy" or "SMART") and treatment according to The Netherlands General Practitioners Guidelines ("NHG") with respect to their effects on bronchial hyperresponsiveness (PD_{20}-histamine), and
2) to validate the Bronchial Hyperresponsiveness Questionnaire (BHQ).

Secondary objectives of the study were:
1) to compare the efficacy of this SMART treatment with treatment according to NHG-guidelines by evaluating several aspects of asthma treatment: Lung function (FEV_1), Asthma symptom scores (day and night), Number of awakenings due to asthma, Number of asthma-control days, Time to first mild asthma exacerbation, Number of mild asthma exacerbation days, Home recordings of Peak Expiratory Flow (PEF, morning and evening), Asthma Control Questionnaire (ACQ), Satisfaction with Asthma Treatment Questionnaire (SATQ), Number of inhalations of inhaled glucocorticosteroids (ICS), Mean dose of ICS and
2) to investigate safety by assessing the nature, incidence, and severity of adverse events (AEs) within the treatment groups.

Study design

A 12-month randomised, active-control, parallel-group, open, stratified, multi-centre study in patients with mild to moderate persistent asthma who are hyperresponsive to inhaled histamine despite regular use of ICS.

After an initial Run-In period of one month, patients were randomised to either treatment using the budesonide/formoterol SMART approach or to treatment according to the NHG guidelines for 12 months. The NHG treatment represented a "real life" situation. Bronchial hyperresponsiveness (the provocative dose of histamine, inducing a 20% fall in FEV_1: PD_{20} histamine) and lung function (FEV_1) was measured at the start and end of the 12 months treatment period. Diaries with twice daily assessed lung function (PEF), symptoms and medication use were kept for 4 weeks during the Run-In period, the first, third, sixth and twelfth treatment month. Questionnaires were completed at the start and end of the 12 months' treatment period. The patients remained

under supervision of their own General Practitioner GP), and were additionally seen by the investigators at the start of the Run-In period, at the start of the treatment period and after 1 and 12 months of treatment. A telephonic contact was made with the investigators after 3 and 6 months treatment.

Target subject population and sample size

Adults with mild to moderate persistent asthma and with documented symptoms despite use of ICS. A total of 100 patients was to be studied.

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

In the SMART treatment group: budesonide/formoterol 100/6 µg/inhalation (Symbicort® Turbuhaler®, the dose expressed as "metered dose" which is equivalent with 80/4.5 µg/inhalation as "delivered dose"), two inhalations once daily in the evening. On top of that the patient was free to use extra inhalations if needed. Batch numbers: EA46, EI71, FB86 and FK203.
In the NHG treatment group: no medication was provided by AstraZeneca, the patients' own ICS and when required other medication was used in a dose, as judged appropriate and adjusted by the patient's GP.
For reversibility testing terbutaline was used (Bricanyl® Turbuhaler®), batch numbers EA1201 and 3521325.

Duration of treatment

12 months

Criteria for evaluation (main variables)

Efficacy and pharmacokinetics
Primary variables:

- Bronchial hyperresponsiveness, assessed with a histamine provocation test, resulting in a value of PD_{20}-histamine at the start and end of the 12 months' treatment period
- Validating the Bronchial Hyperresponsiveness Questionnaire (BHQ): comparing the changes form start to end of treatment in the BHQ with changes in PD_{20}-histamine.

Secondary variables:

- Lung function (FEV_1), Asthma symptom scores (day and night), Number of asthma-control days, Nights with awakenings due to asthma, Time to first mild asthma exacerbation, Number of mild asthma exacerbation days, PEF (morning and evening), Number of inhalations with ICS, Mean dose of ICS,
- Patient reported outcomes (PROs): Bronchial Hyperresponsiveness Questionnaire (BHQ) score, Asthma Control Questionnaire (ACQ) score, Satisfaction with Asthma Treatment Questionnaire (SATQ) score
- Health economics: Healthcare resource utilisation, Sick-leave.

There were no pharmacokinetic, pharmacodynamic or genetic parameters assessed.

Safety

Safety was assessed by investigating adverse events by nature, incidence and severity.

Statistical methods

The full analysis set, as defined in the International Conference of Harmonisation E9 guidelines, was used in all efficacy analyses. The change in log transformed PD_{20} histamine from visit 2 to visit 4 was analysed by analysis of variance with baseline data included as covariate in the analysis. BHQ was validated by calculating Pearson correlation coefficients for the correlation with log transformed PD_{20} at visit 2 and Receiver Operating Curves for the ability of BHQ to define the severity of hyperresponsiveness of patients at visit 2. The same was done for the change in BHQ from visit 2 to visit 4 compared to the change in log transformed PD_{20} from visit 2 to visit 4.

The changes in FEV_1, ACQ and SATQ were compared between treatments using analysis of variance. For diary variables, PEF (morning and evening), asthma symptom scores (day and night), nights with awakenings due to asthma and asthma-control days, the mean change was compared between treatments using analysis of variance. Time to first mild asthma exacerbation was compared between treatments using a log-rank test. The total number of mild asthma exacerbations was compared using Poisson regression. The total number of inhalations with ICS and the mean dose of ICS used during the treatment period were compared between treatments using analysis of variance.

The safety variables were analysed by means of descriptive statistics.

Subject population

From a total of 32 practises of General Practitioners 164 patients were enrolled in the study of whom 102 were randomised to one of the two study treatments.

Table S1 Subject population and disposition

		SMART		NHG		Total	
Population							
N randomised (N planned)		54	(50)	48	(50)	102	(50)
Demographic characteristics							
Sex (n and % of subjects)	Male	22	(41%)	17	(35%)	39	(38%)
	Female	32	(59%)	31	(65%)	63	(62%)
Age (years)	Mean (SD)	44.7	(13.2)	40.6	(12.0)	42.8	(12.7)
	Range	18 to 66		19 to 63		18 to 66	
Race (n and % of subjects)	Caucasian	51	(94%)	48	(100%)	99	(97%)
	Oriental	3	(6%)	0		3	(3%)
Baseline characteristics							
Mean (SD) FEV_1 (L) at enrolment, Visit 1		3.23	(0.89)	3.46	(0.98)	3.34	(0.94)
	Range	1.71 to 5.39		1.67 to 5.47		1.67 to 5.47	
Mean (SD) FEV_1 (% predicted), Visit 1		96.0	(16.0)	101.5	(17.5)	98.6	(16.9)
	Range	65.5 to 65.0		65.0 to 147.7		65.0to 147.7	
Mean (SD) Reversibility FEV_1 (% predicted)		7.0	(5.3)	6.4	(4.5)	6.7	(4.9)
	Range	-1.6 to 21.8		-6.1 to 20.0		-6.1 to 21.8	
Mean (SD) ICS dose (µg/day), Visit 1,		566	(302)	506	(226)	538	(269
	Range	200 to 1600		200 to 1000		200 to 1600	

		SMART		NHG		Total	
Mean (SD) FEV_1 (% predicted), Visit 2		96.9	(17.2)	101.6	(17.4)	99.1	(17.3)
Geometric Mean (range) PD_{20} , Visit 2		0.31	0.01 to 3.68	0.49	0.01 to 4.22	0.39	0.01 to 4.22
Mean (SD) ICS dose (µg/day), Visit 2		533	(299)	496	(214)	526	(263)
Mean (SD) Asthma-Control days (%), Run-In		68.0	(34.5)	54.6	(38.7)	61.6	(37.0)
Disposition							
N (%) of subjects who	Completed	46	(85%)	44	(92%)	90	(88%)
	Discontinued	8	(15%)	4	(8%)	12	(12%)
N analysed for safety[a]		54		48		102	
N analysed for efficacy		54		48		102	

[a] Number of subjects who took at least 1 dose of study treatment and had at least 1 data point after dosing

Efficacy and pharmacokinetic results

The first primary objective in the study was to investigate and compare the effects on bronchial hyperresponsiveness with as efficacy parameter the PD_{20}-histamine, measured at the start and the end of the 12 months treatment period. In both groups there was a small and clinically not relevant increase (improvement) in PD_{20} from 0 to 12 months. Within the SMART treatment group the ratio of PD_{20}-histamine values at 12 months / 0 months was 1.047 (95% Confidence Interval 0.704 and 1.556), within the NHG treatment group this ratio was 1.455 (95% CI 0.952 and 2.222). The difference between the two treatments was not significant: the ratio SMART / NHG was 0.719 (95% CI 0.402 and 1.288, p=0.2543).

The second primary objective in the study was to validate the bronchial hyperresponsiveness questionnaire (BHQ). This was primarily done by comparing the change in BHQ from 0 to 12 months' treatment with the change in PD_{20}-histamine from 0 to 12 months' treatment. In this comparison the data form the two treatment groups was combined. The relation between the change in BHQ (the overall score) and the change in PD_{20} was statistically significant: Pearson's r was –0.301 (95% CI –0.476 and –0.102). Also the changes in the two subscales of BHQ had a significant relation with the change in PD_{20} : for BHQ symptoms : r = -0.275 (95% CI –0.455 and –0.075) and for BHQ stimuli r = -0.246 (95% CI –0.430 and –0.042).

The secondary parameters showed the following effects:
Lung function: FEV_1: during the 12 months of SMART treatment FEV_1 decreased slightly: -0.03 L (95% CI –0.08 and +0.03 L), and during NHG treatment a decrease of –0.06 L was observed (95% CI –0.012 and 0.00 L), the difference between the two treatments was not significant : 0.04 L (95% CI –0.05 and +0.12 L, p=0.401). Expressed in % of predicted FEV_1 did not change either: -1.1% during SMART treatment (95% CI –2.9 and +0.6%) and –1.8% during NHG treatment (95% CI –3.6 and 0.0 %). The difference was not significant: 0.7% (95% CI –1.8 and +3.2%, p=0.579).

Asthma symptom scores, as reported in the diaries on a 0 – 3 scale, showed no change from the Run-In period to the Treatment period: for the SMART treatment group the change in day-time symptom score was +0.02 (95% CI –0.06 and +0.09) and for the NHG treatment group –0.02 (95% CI –0.10 and +0.06), the difference between treatments being not significant: 0.04 (95% CI –0.07 and +0.14, p=0.522). The change in night-time symptom score was for the SMART treatment group +0.01 (95% CI –0.05 and +0.07) and for the NHG treatment group 0.00 (95% CI –0.06 and +0.06), the difference between treatments being not significant: 0.01 (95% CI –0.08 and +0.09, p=0.865). The proportion of nights with awakenings due to asthma did not show differences either. The change in the % of nights with awakenings was for the SMART treatment group -0.27 (95% CI –1.71 and +1.17) and for the NHG treatment group –0.39 (95% CI –1.91 and

+1.12), the difference between treatments being not significant: 0.12 (95% CI –1.97 and +2.21, p=0.910).

Morning and evening Peak Expiratory Flow (PEF) as measured daily by the patient at home and recorded in the diaries, did show a large difference between the two treatments. The change in morning PEF was for the SMART treatment group 19.2 L/min (95% CI 10.9 and 27.4 L/min) and for the NHG treatment group –3.9 L/min (95% CI –12.7 and +4.8), the difference between treatments was statistically significant: 23.1 L/min (95% CI 11.0 and 35.2 L/min, p=0.0003). The change in evening PEF was for the SMART treatment group 11.5 L/min (95% CI 3.7 and 19.4 L/min) and for the NHG treatment group –5.0 L/min (95% CI –13.3 and +3.3), the difference between treatments was statistically significant: 16.5 L/min (95% CI 5.0 and 28.0 L/min, p=0.005).

The number of Asthma Control days was calculated from the above mentioned asthma symptoms scores as a day with both day-time and night-time symptoms scores as zero and no awakening due to asthma. Days with missing data were by definition no Asthma Control day. The proportion of Asthma Control days did not show great differences. The change in the % of Asthma Control days was for the SMART treatment group -1.79 (95% CI –8.20 and +4.62) and for the NHG treatment group –0.75 (95% CI –7.56 and +6.06), the difference between treatments being not significant: -1.04 (95% CI –10.5 and +8.39, p=0.827).

Mild exacerbation days were calculated from the diary recordings in the study, as a day with either morning PEF below 80% of the mean PEF in the Run-In period or with a night with awakening due to asthma. The number of mild asthma exacerbation days did not show large differences. During SMART treatment, in a total follow-up of 15.2 patient years 249 days fulfilled the mild asthma exacerbation criterion and during NHG treatment, in a total follow-up of 14.4 patient years 241 days. The difference between the two treatments in events (SMART: 16.37 days/year, 95% CI 14.46 and 18.53, NHG: 16.76 days/year, 95% CI 14.77 and 19.01) was not significant: 0.98 (95% CI 0.82 and 1.17, p=0.796).

The time to first mild asthma exacerbation was calculated during the first treatment month, since diary recordings were stopped thereafter for one month. Within the SMART treatment group 6 of 54 patients (11%) had such a mild exacerbation, against 7 of 48 patients (15%) in the NHG group. The Hazard ratio for the difference between treatments in the time to this first exacerbation as SMART / NHG ratio was 1.31 (95% CI 0.44 and 3.88) and was not significant (p=0.632).

Severe asthma exacerbations (systemic corticosteroid treatment for at least 3 days) occurred in 8 patients (2 in the SMART group and 6 in the NHG treatment group). No hospitalisations or emergency room treatments for asthma exacerbations were necessary. Since one patient in the SMART group experienced 3 severe asthma exacerbations and one patient in the NHG group experienced 2 exacerbations the total number of severe asthma exacerbations was 4 in the SMART group and 7 in the NHG group. With a follow-up of 50.1 years and 45.0 years respectively, the incidence became 0.08 exacerbations/patient/year in the SMART treatment group (95% CI 0.03 and 0.21) and 0.16 exacerbations/patient/year in the NHG treatment group (95% CI 0.07 and 0.33). The ratio of the two incidences of the two treatments (SMART / NHG) was 0.51 (95% CI 0.15 and 1.75 asthma exacerbations/patient/year). No statistical comparison for this parameter was foreseen or performed due to the expected low numbers.

The number of inhalations of the inhaled corticosteroid (ICS) and of the rescue medication was recorded in the diaries, within the SMART treatment group obviously as one combined number of inhalations. From the number of inhalations the daily ICS dose was calculated, for the SMART treatment group a mean dose of 263 µg/day was calculated (95% CI 221 to 304 µg/day), and for the NHG treatment group 523 µg/day (95% CI 479 and 567). The ICS dose was statistically significant lower in the SMART treatment group (-260 µg/day, 95% CI –321 and –199, p<0.0001). Expressed in µg/day of BDP equivalents (taking an approximate equivalence of 1000 µg/day BDP = 800 µg/day budesonide = 500 µg/day fluticasone propionate) the mean ICS dose was during SMART treatment 326 µg/day BDP (95% CI 254 and 399 µg/day) and during NHG treatment 798 µg/day BDP (95% CI 721 and 875 µg/day). The difference between treatments (59% lower during SMART) was highly significant (-472 µg/day BDP, 95% CI –587 and –366, p<0.0001). The

number of rescue inhalations was low throughout the study and changed slightly during the study, within the SMART treatment group the number of rescue inhalations changed form 0.55/day in the Run-In to 0.78/day in the treatment period, within the NHG treatment group the rescue use changed form 0.42/day in the Run-In to 0.44/day in the treatment period. It must be noted that the number of rescue inhalations in the SMART treatment group was defined as the number of inhalations on top of the planned 2 inhalations. No statistical comparison was foreseen or performed on this parameter.

In the Patient Reported Outcomes the following data were obtained.

The Bronchial Hyperresponsiveness Questionnaire (BHQ) changed hardly during the study. For both treatment groups combined overall BHQ changed from a mean value of 1.47 to 1.46, BHQ-symptoms from 1.32 to 1.31 and BHQ-stimuli from 1.67 to 1.67. No statistical comparison between groups was foreseen since the present study was considered necessary to validate the BHQ in greater detail.

The average Asthma Control Questionnaire (ACQ) did hardly change during the study. Within the SMART treatment group the mean ACQ changed from 0 to 12 months treatment with 0.00 (95% CI –0.18 and +0.18), within the NHG treatment group with 0.06 (95% CI –0.13 and +0.25). The difference between the two treatments was not significant (-0.06, 95% CI –0.32 and +0.21, p=0.673). At the end of the study, 15% and 17% of patients in the SMART and NHG treatment groups respectively had a clinically meaningful improvement in ACQ (>0.5 points) while 17% respectively 15% had a clinically meaningful deterioration.

The Satisfaction with Asthma Treatment Questionnaire (SATQ) was analysed as overall score and in three subscales. Overall SATQ score improved slightly during SMART treatment (+0.20, 95% +0.03 and +0.37) and less during NHG treatment (+0.06, 95% CI –0.11 and +0.24), the difference was not statistically significant (0.14, 95% CI –0.11 and +0.38, p=0.268). SATQ score on “Effectiveness” improved similar during SMART treatment (+0.28, 95% +0.01 and +0.55) and during NHG treatment (+0.27, 95% CI –0.02 and +0.55), the difference was not statistically significant (0.01, 95% CI –0.39 and +0.41, p=0.948). SATQ score on “Ease of Use” improved during SMART treatment (+0.35, 95% +0.14 and +0.55) and was unchanged during NHG treatment (+0.02, 95% CI –0.19 and +0.24), with a statistically significant difference between treatments (0.32, 95% CI 0.03 and +0.55, p=0.034). SATQ score on “Burden of Asthma Medication” was unchanged during both SMART treatment (-0.01, 95% -0.25 and +0.23) and during NHG treatment (-0.03, 95% CI –0.27 and +0.22), the difference was not statistically significant (0.02, 95% CI –0.33 and +0.36, p=0.924). SATQ score on “Side-effects and Worries” was slightly improved during both SMART treatment (+0.14, 95% -0.13 and 0.41) and slightly decreased during NHG treatment (-0.10, 95% CI –0.38 and 0.19), the difference was not statistically significant (0.24, 95% CI –0.15 and +0.63, p=0.228).

A preliminary Health Economics analysis showed that medication costs were lower during SMART treatment than during NHG treatment (22,603 versus 23,795 € for the entire treatment groups), that other health care utilisation was lower during SMART treatment (274 versus 483 €) and that the costs of sick-leave (full-time an part-time employees only and costs of leave of care-givers) were lower during SMART treatment (708 versus 8971 €). Total costs per treatment year became 471 € for the SMART treatment and 57% higher: 739 € per year for the NHG treatment. A statistical comparison was not foreseen or performed, a detailed analysis will be done outside the scope of the present Clinical Study Report.

Safety results

The 54 patients randomised to budesonide /formoterol SMART treatment were followed for a total of 18,311 days or 50.1 years (mean 339 days per patient) and the 48 patients randomised to NHG treatment were followed for a total of 16,429 days or 45.0 years (mean 342 days per patient).

Table S2 **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=54)		NHG (n=48)		Total (n=102)	
Any adverse events N (%)	40	(74%)	42	(88%)	82	(80%)
Serious adverse events	1	(2%)	2	(4%)	3	(3%)
Serious adverse events leading to death	0		0		0	
Serious adverse events not leading to death	1	(2%)	2	(4%)	3	(3%)
Discontinuations of study treatment due to adverse events	4	(7%)	0		4	(4%)
Other significant adverse events	0		0		0	
	Total number of adverse events					
Adverse events	88		86		174	
Serious adverse events	1		2		3	
Other significant adverse events	0		0		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.

There were no deaths during the study and there were 3 SAE's observed (a pulmonary embolism, gastritis and an intervertebral disk protrusion) of which the first SAE (pulmonary embolism on day 2 of SMART treatment) also resulted in treatment discontinuation. Four patients discontinued study treatment due to an adverse event: the above mentioned patient with a pulmonary embolism, one patient with palpitations and tremor and two patients due to deterioration of their asthma, all four during SMART treatment.

The most commonly reported adverse events are shown in the Table below.

Table S3 **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 the adverse event					
	SMART (n=54)		NHG (n=48)		Total (n=102)	
Nasopharyngitis	17	(31%)	25	(52%)	42	(41%)
Influenza	4	(7%)	4	(8%)	8	(8%)
Back pain	2	(4%)	3	(6%)	5	(5%)
Sinusitis	3	(6%)	2	(4%)	5	(5%)
Seasonal allergy	3	(6%)	1	(2%)	4	(4%)

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

There were no apparent differences between the two treatments. The incidence of discontinuations due to AE's was somewhat higher in the SMART group (4 versus 0) of which 2

discontinuations were due to asthma exacerbations. However, the overall incidence of severe asthma exacerbations was lower in the SMART treatment group. For the patients in the NHG treatment group, withdrawal from NHG treatment was impossible, though withdrawal from the study was possible. The higher incidence of episodes of nasopharyngitis in the NHG treatment group (52% versus 31%) was considered to have no clinical relevance.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Seroquel™ (quetiapine), Healthcare Professionals should view their specific country information.