AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/Formoterol
Study Code	D5890L00035
Edition Number	1
Date	4 August 2011

Real life Effectiveness of Symbicort® Maintenance and Reliever Therapy (SYMBICORT SMART®) in Asthma Patients across Asia: SMARTASIA

Study dates: First subject enrolled: 10 July 2009
Last subject last visit: 19 August 2010

Phase of development: Therapeutic use (IV)

International Co-ordinating Investigator:

Sponsor's Responsible Medical Officer:

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

This study was conducted in 51 centres in 5 Asian countries and area: China (21 centres), India (12 centres), Indonesia (3 centres), Thailand (6 centres) and Taiwan (9 centres).

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables*
Primary Objective	**Primary outcome variables**
1. To compare, at a regional level, Symbicort SMART with partially controlled or uncontrolled asthma patient's previous therapy by assessing the changes in the ACQ-5 score	The change in overall ACQ-5 score from baseline (Visit 2) to the average of the scores during treatment period (Visits 3 to 5), and the change in ACQ-5 from baseline (Visit 2) to Week 4 of study (Visit 3)
Secondary Objectives	**Secondary outcome variable**s
1. To document the well-being of patients using Symbicort SMART in different countries/areas within the general practice setting, by assessing the change in ACQ-5 score from baseline at country/area level	The change in overall ACQ-5 score from baseline (Visit 2) to the average of the scores during treatment period (Visits 3 to 5), and from baseline to Week 4 of study (Visit 3) at the country/area level
2. To assess the clinical effectiveness of Symbicort SMART on patients' quality of life, by change in AQLQ domain and overall scores from baseline at regional level, using the AQLQ (S) - standardized version of the AQLQ	The change AQLQ(S) overall and domain scores from baseline (Visit 2) to the average of the scores during treatment period (Visits 3 to 5), and from baseline to Week 4 of study (Visit 3) at the regional, as well as country/area level.
3. To document the usage of Symbicort SMART, and to assess the change in: (i) asthma symptom score (ii) nights with awakening(s) due to asthma symptoms; and (iii) percentage of asthma-control and asthma symptom-free days	The average number of inhalations of Symbicort per day, percentage of as-needed medication free days, percentage of days using ≥ 3 inhalations, percentage of days using ≥ 5 inhalations and percentage of days using ≥ 9 inhalations of Symbicort Changes in asthma symptom score, number of nights with awakening(s) due to asthma symptoms, percentage of asthma asthma-control and symptom-free days from baseline run-in to treatment period (Week 3 to 5)
4. To determine impact of Symbicort SMART on lung function by assessing the changes in FEV_1 from baseline to treatment period	Changes in forced expiratory volume in one second (FEV1) from baseline (Visit 2) to treatment period (Visit 3 to 5)
5. To document the AEs including SAEs and discontinuations due to AEs (DAEs) during the study	The nature, incidence and severity of AEs including SAEs and discontinuations due to AEs (DAEs)

* The baseline value for the outcome variables was the value recorded following the run-in period and prior to initiation of study treatment.

Study design

This was a multi-centre open-label therapeutic Phase IV study to primarily assess the changes in the ACQ-5 score of patients after 12 weeks of Symbicort Maintenance and Reliever Therapy (Symbicort SMART).

Target subject population and sample size

The target subject population was subjects with confirmed diagnosis of asthma (GINA 2007 Guidelines) who have had asthma for at least 6 months, were on continuous asthma treatment within the 4 weeks preceding screening (Visit 1) and whose asthma condition was partly controlled or uncontrolled. Sample size was determined based on the precision with which the effect size may be reported. Based on the primary variable of this study (mean change in ACQ-5 score from baseline), a sample size of about 1000 patients was estimated to give a 95% confidence interval (CI) with an approximate width of 0.12 units when standard deviation (SD) is 1.0 unit. We eventually enrolled 1022 patients, of which 862 (84.3%) patients entered the study treatment period.

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

The investigational product is Symbicort (budesonide/formoterol fumarate dehydrate) Turbuhaler with delivered dose of 160/4.5 μg, administered b.i.d. and as needed in response to symptoms. Eight batches of the Symbicort Turbuhaler were used in this study.

Duration of treatment

Duration of treatment is 12 weeks.

Statistical methods

All analyses were performed on an intention-to-treat basis. The full analysis set comprised all patients who had taken at least one dose of Symbicort and had data collected after initiation of the drug treatment. The primary outcome variable, change in ACQ-5 score from baseline to treatment period, was analysed using paired t-test, with significance set at the 5% level. A change of ≥0.5 in the score was deemed clinically important. The changes in AQLQ(S) overall and domain scores were analysed in a similar way. FEV_1 and all secondary patient-reported outcomes were analysed as change from baseline using paired t-test.

Subject population

A total of 1022 eligible asthma patients were enrolled. Amongst them, 862 (84.3%) patients who have had asthma for a mean duration of 10.73 ± 12.03 years entered into treatment period. These 862 patients who took at least one dose of Symbicort formed the set of subjects for both efficacy and safety analysis (Table S2). Amongst them, 66 patients (7.7%) discontinued from the study. Demographic and baseline characteristics of the subjects are summarised in Table S3.

Table S2 Study Population (Full Analysis Set)

	China	India	Indonesia	Taiwan	Thailand	All
Patients in full analysis set (FAS)	407	162	61	103	129	862
Patients in safety analysis set	407	162	61	103	129	862

Table S3 Demographic characteristics of patients

Demographic characteristic		Number (%) of patients[a] N = 862
Sex	Male	407 (47.2)
	Female	455 (52.8)
Age (years)	n	862
	Mean (SD)	44.7 (13.7)
	Range	18 - 81
Race	Asian	862 (100.0)
BMI (kg/m^2)	n	862
	Mean (SD)	24.36 (4.10)
	Range	14.2 - 47.5
Time since diagnosis (years)	n	862
	Mean (SD)	10.73 (12.03)
	Range	0.1 - 60.0
Smoking	Non smoker	744 (86.3)
	Ex-smoker	84 (9.7)
	Occasional smoker	18 (2.1)
	Habitual smoker	16 (1.9)
Pack-years	n	116
	Mean (SD)	4.8 (2.9)
	Range	0 - 15
Inhaled GCS at entry: dose (µg / day)	n	19
	Mean (SD)	541.9 (339.9)
	Range	2 - 1200
FEV_1 (L)	n	862
	Mean (SD)	2.063 (0.709)
	Range	0.69 - 4.63
FEV_1 % of predicted normal *	n	862
	Mean (SD)	70.38 (17.37)
	Range	22.4 - 124.3
FEV_1 % Reversibility	n	862
	Mean (SD)	26.50 (15.15)
	Range	9.8 - 139.5

[a] FAS: All enrolled subjects except for screening failure
* Predicted normal FEV1 value (post-bronchodilator) was calculated according to ERS (Quanjer et al 1993)

Summary of efficacy results

Primary outcome variable: Change in ACQ-5 score from baseline at regional level

At the regional level, during treatment with Symbicort SMART, patients' asthma control significantly improved. This is reflected by the consistent reduction in mean overall ACQ-5 score from baseline to 4, 8, and 12 weeks of the therapy (Table S4). A significant decrease in ACQ-5 score was evident from 4 weeks (indicating-early onset of improvement in asthma control) post-initiation of treatment with Symbicort SMART,. During the treatment period, overall mean ACQ-5 score fell significantly by 0.58 ± 0.93 (95% CI, -0.64 to -0.51; P<0.0001). Clinically important improvement in ACQ-5 score (change ≥ MID of 0.5) was observed by 8 weeks of treatment. During treatment, 48.2% of the patients experienced improvement in symptoms, while 8.8% had symptoms worsened.

Table S4 Summary of mean values of overall ACQ (5) score at a regional level

Variable	Visit	Observed value			Change from Visit 2			95% CI		Paired t-test
		N	Mean	SD	N	Mean	SD	Lower	Upper	p-value
Overall score	2	854	1.62	1.00	-	-	-	-	-	-
	3	833	1.16	0.88	826	-0.46	0.96	-0.52	-0.39	<.0001
	4	803	1.01	0.85	796	-0.60	1.01	-0.67	-0.53	<.0001
	5	794	0.92	0.85	787	-0.69	1.09	-0.77	-0.62	<.0001
	Mean of 3-5	841	1.04	0.75	834	-0.58	0.93	-0.64	-0.51	<.0001

Secondary Outcome variables

Change in ACQ-5 score from baseline at country/area level

Table S5 Summary of period means of overall ACQ (5) score for mean of Visit 3-5 at country/area level

Overall score		N	Visit 2		Mean of Visit 3-5		Mean change	95% confidence interval		Paired t-test
			Mean	Range	Mean	Range		Lower	Upper	p-value
Country/Area	China	386	1.72	0.0 - 5.0	1.14	0.0 - 4.4	-0.58	-0.67	-0.49	<.0001
	India	159	1.87	0.0 - 5.4	1.12	0.0 - 3.3	-0.74	-0.92	-0.57	<.0001
	Indonesia	61	1.78	0.0 - 3.8	0.61	0.0 - 2.9	-1.18	-1.40	-0.95	<.0001
	Taiwan	100	1.11	0.0 - 4.8	0.89	0.0 - 2.9	-0.22	-0.38	-0.06	0.0089
	Thailand	128	1.31	0.0 - 3.6	0.95	0.0 - 2.9	-0.36	-0.48	-0.23	<.0001

Significant reduction in ACQ-5 score was observed in all 5 participating countries during the Symbicort SMART treatment period (P<0.0001 to P=0.0089), indicating significant improvements in asthma control across the region (Table S5). Statistically significant changes were observed from as early as 4 weeks into treatment period. Change in ACQ-5 scores

differed significantly between countries (P<0.0001); it was highest in Indonesia, followed by India, China, Thailand and Taiwan. Improvement in asthma control reached clinical importance (change ≥ MID of 0.5) in China, India and Indonesia; in China and Indonesia, it was achieved by 4 weeks post-initiation of treatment with Symbicort SMART.

Change in AQLQ (S) domains and overall scores from baseline (regional level)

During the Symbicort SMART treatment period, overall AQLQ(S) score increased by 0.70 ± 0.89 (95% CI, 0.64 to 0.76) from baseline (P<0.0001), demonstrating a significant improvement in patient's quality of life. Significant improvement was evident from as early as 4 weeks into the therapy, and the level was sustained throughout the treatment period. Clinically important change (≥ MID of 0.5) was evident from 8 weeks post-initiation of Symbicort SMART. While 52.9% of the patients experienced improvement in everyday functioning and well-being, 5.1% experienced worsened conditions. Overall scores for symptoms, activity limitations, emotion function and response to environmental stimuli were likewise increased during the treatment period (P<0.0001). Significant improvement was observed from as early as 4 weeks after start of treatment, showing early impact on patient's quality of life.

Change in AQLQ (S) domains and overall scores from baseline (country/area level)

Statistically significant change in overall AQLQ(S) score was observed in all 5 participating countries/area during treatment with Symbicort SMART (P<0.0001 to P=0.0002). Significant changes were observed by 4 weeks of treatment (P<0.0001 to P=0.0252). The change differed significantly between the countries/area (P<0.0001); it was highest in Indonesia, followed by India, China, Thailand and Taiwan. Clinically important change (difference ≥ MID of 0.5) in AQLQ(S) score was observed in Indonesia, Thailand, China and India. Significant improvement in symptoms, activity limitations, emotional function and response to environmental stimuli during treatment was also observed in all 5 countries/area.

Asthma symptom score, days with awakening(s) during the night, inhalations of medications, asthma-control and asthma symptom-free days

During treatment with Symbicort SMART, asthma symptoms score was significantly reduced (P<0.0001). From run-in to treatment period, night- and day-time symptom score changed -0.32 ± 0.54 (95% CI, -0.35 to -0.28) and -0.30 ± 0.52 (95% CI, -0.34 to -0.27), respectively, The percentage of days with awakening(s) due to asthma symptoms during the night was reduced by -11.09 ± 26.13% (95% CI, -12.85 to -9.34%; P<0.0001), while the percentage of asthma-control and symptom-free days increased by 20.90 ± 34.40% (95% CI, 18.59 to 23.21%) and 23.89 ± 34.62% (95% CI, 21.56 to 26.21%), respectively (P<0.0001). Along with that, the number of inhalations of as-needed reliever medications for night- and day-time was significantly changed by -0.30 ± 0.82 (95% CI, -0.35 to -0.24) inhalations and -0.30 ± 0.97 (95% CI, -0.36 to-0.23) inhalations, respectively (P<0.0001). Concurrently, the percentage of as-needed medication free days increased by 11.90 ± 44.65 % (95% CI, 8.90 to 14.89 %; P<0.0001).

Change in forced expiratory volume in one second (FEV_1) from baseline

During the Symbicort SMART treatment period, patients' pulmonary function was significantly improved. A significant increase in FEV_1 G-mean value from baseline level was observed as early as 4 weeks post-initiation of treatment, indicating an early onset in recovery of impaired pulmonary function. During the 12 weeks of treatment, the overall increase in mean FEV_1 from baseline was 0.17 ± 0.35 (95% CI, 0.15 - 0.20) L; the corresponding increase in G-mean FEV_1 was 1.10 ± 19.33 (95% CI, 0.08 - 0.10) L. G-mean FEV_1 significantly increased from baseline level during Symbicort SMART treatment ($P<0.0001$).

Summary of safety results

Amongst 862 patients, 171 patients (19.8%) reported AEs, and 12 patients (1.4%) reported SAEs. The most frequently reported AE was nasopharyngitis (3.4%), followed by upper respiratory tract infection (3.2%), and asthma (1.4%). The majority of the AEs were of mild intensity. Thirteen patients (1.5%) had their study medication discontinued because of AEs. In total 15 SAEs were reported in 12 patients (1.4%). Two of the SAEs resulted in death, one was asthma exacerbation and the other was myocardial infarction. Both deaths were considered unrelated to the study treatment.