AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D589LC00001
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A comparison of Symbicort® Maintenance and Reliever Therapy (Symbicort Turbuhaler® 160/4.5 µg, one inhalation bid plus as needed) and Symbicort Turbuhaler 160/4.5 µg, one inhalation bid plus terbutaline Turbuhaler 0.4 mg/inhalation as needed, for treatment of asthma – a 12-month, randomized, double-blind, parallel group, active-controlled, multinational phase III study in asthmatic patients aged 16 years and above.

Study dates: First patient enrolled: February 2009
Last patient last visit: February 2011

Phase of development: Therapeutic confirmatory (III)

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

Study centre(s)

The study was conducted at 148 centres in Japan and in 12 other countries in Asia, America and Europe.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To compare the efficacy of Symbicort SMART (Symbicort Turbuhaler 160/4.5 µg, one inhalation bid plus as needed) with Symbicort Turbuhaler 160/4.5 µg, one inhalation bid plus terbutaline Turbuhaler 0.4 mg as needed, as asthma therapy.	**Primary variable** • Time to first asthma exacerbation **Secondary variables** • Number of asthma exacerbations • Morning Peak Expiratory Flow (PEF) • Evening PEF • Forced expiratory volume in one second (FEV_1) • Use of as-needed medication • Asthma symptom score • Nights with awakening(s) due to asthma symptoms • Time to first mild asthma exacerbations • Number of mild asthma exacerbation days • Percentage of symptom-free days (no symptoms and no awakenings) • Percentage of as-needed-free days • Percentage of asthma-control days (no asthma symptoms, no awakenings, and no as-needed use) • Asthma Control Questionnaire (ACQ)	Efficacy
Secondary	**Secondary**	
To investigate safety of Symbicort SMART and of Symbicort 160/4.5 µg, one inhalation bid plus terbutaline Turbuhaler 0.4 mg as needed.	• Adverse events (AEs: nature, incidence and severity) • Clinical chemistry • Haematology • Urinalysis • Morning p-cortisol • 12-lead ECG • Pulse rate • Blood pressure	Safety

Study design

This was a 12-month, randomized, double-blind, parallel-group, active-controlled, multinational phase III study comparing Symbicort SMART to Symbicort maintenance treatment plus terbutaline Turbuhaler as needed in symptomatic patients with asthma not adequately controlled despite use of inhaled glucocorticosteroids.

Target subject population and sample size

Men and women ≥16 years of age, with asthma not adequately controlled despite use of inhaled glucocorticosteroids.

The power calculation was based on the outcome variable "time to first asthma exacerbation" and a log-rank test of time to event in groups followed for a fixed time assuming constant hazard ratio.

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

- Symbicort® Turbuhaler® 160/4.5 µg one inhalation bid plus Symbicort® Turbuhaler® 160/4.5 µg as needed (Batch number: see Appendix 12.1.6)

- Symbicort® Turbuhaler® 160/4.5 µg one inhalation bid plus terbutaline Turbuhaler® 0.4 mg as needed (Batch number: see Appendix 12.1.6)

Additional study drug: dosage, mode of administration and batch numbers

- terbutaline Turbuhaler® 0.4 mg 120 inhalation as reliever medication during the run-in period and also to be used for the reversibility test. (Batch number: see Appendix 12.1.6)

Duration of treatment

A 1-week enrolment period followed by a 2-week run-in period and a 52-week treatment period.

Statistical methods

The analysis set for efficacy was based on the Full Analysis Set in line with the ICH E9 guidelines.

Time to first asthma exacerbation was described using Kaplan-Meier curves, and compared between treatments using a log-rank test.

The mean number of asthma exacerbations per patient was compared between treatments using Poisson regression model.

For diary variables the mean change from run-in to treatment period were compared between treatments using ANCOVA model. Change in FEV_1 was compared between treatments using

ANCOVA. Time to first mild asthma exacerbation was analysed in the same way as time to first asthma exacerbation.

The incidence of adverse events was calculated and results from laboratory safety measurements, vital signs, ECG and morning p-cortisol were analysed primarily by means of descriptive statistics.

Subject population

Table S 2 Treatment group comparison of demographic and disease data

Variable		Symbicort SMART n = 1049		Symbicort + Terbutaline n = 1042		All n = 2091	
n, randomized		1049		1042		2091	
Sex	N	1049		1042		2091	
	Male	327	(31.2%)	350	(33.6%)	677	(32.4%)
	Female	722	(68.8%)	692	(66.4%)	1414	(67.6%)
Age (yrs)	N	1049		1042		2091	
	Mean (SD)	45.7	(14.5)	45.6	(14.5)	45.6	(14.5)
	Range	16	-84	16	-85	16	-85
	<65	943	(89.9%)	943	(90.5%)	1886	(90.2%)
	65-	106	(10.1%)	99	(9.5%)	205	(9.8%)
Race	N	1049		1042		2091	
	White	332	(31.6%)	332	(31.9%)	664	(31.8%)
	Black	7	(0.7%)	11	(1.1%)	18	(0.9%)
	Asian	652	(62.2%)	650	(62.4%)	1302	(62.3%)
	Islanders	1	(<0.1%)	0		1	(<0.1%)
	American Indian	56	(5.3%)	49	(4.7%)	105	(5.0%)
	Other	1	(<0.1%)	0		1	(<0.1%)
Height (cm)	N	1049		1042		2091	
	Mean (SD)	160.6	(9.4)	160.7	(9.4)	160.6	(9.4)
	Range	138	-190	135	-197	135	-197
Weight (kg)	N	1049		1042		2091	
	Mean (SD)	66.2	(15.6)	66.0	(16.0)	66.1	(15.8)
	Range	34	-127	31	-135	31	-135

Table S 2 Treatment group comparison of demographic and disease data

Variable		Symbicort SMART n = 1049		Symbicort + Terbutaline n = 1042		All n = 2091	
Body mass index (BMI) (kg/m^2)	N	1049		1042		2091	
	Mean (SD)	25.6	(5.2)	25.5	(5.2)	25.5	(5.2)
	Range	15	-50	13	-55	13	-55
Time since diagnosis (yrs)	N	1049		1042		2091	
	Median	12		12		12	
	Range	1	-67	1	-74	1	-74
Smoking Status	N	1049		1042		2091	
	Never	890	(84.8%)	890	(85.4%)	1780	(85.1%)
	Current	40	(3.8%)	42	(4.0%)	82	(3.9%)
	Former	119	(11.3%)	110	(10.6%)	229	(11.0%)
Pack-years for current and former smokers	N	159		152		311	
	Median	5		5		5	
	Range	0	-9	0	-9	0	-9
Number of days since previous exacerbation before entry [a]	N	1048		1042		2090	
	Median	143		146		144	
	Range	3	-366	9	-366	3	-366
Inhaled GCS dose at entry (µg)	N	1049		1042		2091	
	Mean (SD)	662.2	(208.5)	659.2	(208.7)	660.7	(208.5)
	Median	640		640		640	
	Range	160	-1600	200	-1600	160	-1600
BDP dose before entry (µg)	N	1049		1042		2091	
	Mean (SD)	1025.2	(325.2)	1020.8	(324.2)	1023.0	(324.6)
	Median	1000		1000		1000	
	Range	200	-2500	400	-2500	200	-2500
LABA prior to study entry (Yes/No)	N	1049		1042		2091	
	Yes	636	(60.6%)	650	(62.4%)	1286	(61.5%)
	No	413	(39.4%)	392	(37.6%)	805	(38.5%)
FEV_1 (L)	N	1049		1042		2091	
	Mean (SD)	1.93	(0.64)	1.93	(0.65)	1.93	(0.64)
	Range	0.7	-4.6	0.7	-5.0	0.7	-5.0
FEV_1 (%PN)	N	1049		1042		2091	
	Mean (SD)	70.18	(14.65)	69.64	(13.75)	69.91	(14.21)
	Range	44.0	-156.6	43.8	-150.0	43.8	-156.6

Table S 2 Treatment group comparison of demographic and disease data

Variable		Symbicort SMART n = 1049	Symbicort + Terbutaline n = 1042	All n = 2091
Reversibility in FEV_1 (%)	N	1049	1042	2091
	Mean (SD)	23.24 (12.46)	22.41 (10.80)	22.82 (11.67)
	Range	-4.5 -141.9	10.4 -109.6	-4.5 -141.9
As-needed use (total), inh/day	N	1043	1031	2074
	Mean (SD)	2.41 (1.55)	2.43 (1.58)	2.42 (1.56)
	Range	0.0 -9.3	0.1 -9.4	0.0 -9.4
Symptom score (total)	N	1044	1030	2074
	Mean (SD)	1.96 (0.99)	1.99 (1.01)	1.97 (1.00)
	Range	0.0 -6.0	0.0 -5.8	0.0 -6.0
Symptom-free days (%)	N	1044	1031	2075
	Mean (SD)	10.31 (20.02)	9.83 (19.50)	10.07 (19.76)
	Range	0.0 -100.0	0.0 -100.0	0.0 -100.0
As-needed-free days (%)	N	1043	1031	2074
	Mean (SD)	9.33 (14.72)	9.39 (15.01)	9.36 (14.86)
	Range	0.0 -100.0	0.0 -90.0	0.0 -100.0
Asthma-control days (%)	N	1044	1031	2075
	Mean (SD)	6.22 (12.42)	6.37 (12.45)	6.30 (12.43)
	Range	0.0 -90.0	0.0 -60.0	0.0 -90.0
Awakenings (%)	N	1034	1030	2064
	Mean (SD)	31.54 (35.68)	31.85 (36.89)	31.70 (36.28)
	Range	0.0 -100.0	0.0 -100.0	0.0 -100.0

For categorical data, frequencies are given, for other data mean values and ranges are given
a Number of days since previous exacerbation before entry is computed from visit 2
PN: Predicted normal value, inh: Inhalation
Data derived from Table 1-6, Section 11.

- The study included enough patients to achieve the aim in the power calculation, and the treatment groups were balanced at baseline.
- The study included asthma patients with asthma not adequately controlled despite use of inhaled GCSs and thus for whom treatment with Symbicort Turbuhaler is appropriate.
- The study included the intended number of Japanese patients with asthma that were not adequately controlled despite use of inhaled GCSs.

Summary of efficacy results

Table S 3 Statistical analysis of asthma exacerbations

Variable	Analysis	Treatment or treatment comparison	Hazard ratio, rate, or rate ratio[a]	95% CL		P-value
				Lower	Upper	
Asthma exacerbations	Log-rank test	Symbicort SMART vs Symbicort+terbutaline	-	-	-	0.0007
	Cox PH model	Symbicort SMART vs Symbicort+terbutaline	0.695	0.570	0.848	0.0003
	Poisson reg.	Symbicort SMART	0.214	0.185	0.247	-
		Symbicort+terbutaline	0.307	0.270	0.349	-
		Symbicort SMART vs Symbicort+terbutaline	0.696	0.592	0.818	<.0001
Oral steroids	Log-rank test	Symbicort SMART vs Symbicort+terbutaline	-	-	-	0.0129
	Cox PH model	Symbicort SMART vs Symbicort+terbutaline	0.742	0.590	0.933	0.0106
	Poisson reg.	Symbicort SMART	0.149	0.125	0.177	-
		Symbicort+terbutaline	0.205	0.175	0.240	-
		Symbicort SMART vs Symbicort+terbutaline	0.727	0.599	0.882	0.0012
Hospitalizations[b]	Log-rank test	Symbicort SMART vs Symbicort+terbutaline	-	-	-	0.0007
	Cox PH model	Symbicort SMART vs Symbicort+terbutaline	0.326	0.165	0.646	0.0013
	Poisson reg.	Symbicort SMART	n.a.	n.a.	n.a.	n.a.
		Symbicort+terbutaline	n.a.	n.a.	n.a.	n.a.
		Symbicort SMART vs Symbicort+terbutaline	n.a.	n.a.	n.a.	n.a.
ER treatment[b]	Log-rank test	Symbicort SMART vs Symbicort+terbutaline	-	-	-	0.0068
	Cox PH model	Symbicort SMART vs Symbicort+terbutaline	0.688	0.539	0.879	0.0028
	Poisson reg.	Symbicort SMART	0.164	0.140	0.191	-
		Symbicort+terbutaline	0.248	0.219	0.282	-
		Symbicort SMART vs Symbicort+terbutaline	0.659	0.540	0.803	<.0001
ER or hospitalization	Log-rank test	Symbicort SMART vs Symbicort+terbutaline	-	-	-	0.0031
	Cox PH model	Symbicort SMART vs Symbicort+terbutaline	0.677	0.534	0.858	0.0013
	Poisson reg.	Symbicort SMART	0.172	0.148	0.200	-
		Symbicort+terbutaline	0.265	0.234	0.299	-
		Symbicort SMART vs Symbicort+terbutaline	0.649	0.535	0.787	<.0001

a Hazard ratio for Log-rank test and Cox PH model; annual event rate for individual treatment groups and rate ratio for treatment comparison for the Poisson regression model

b No country adjustment was performed

CL: Confidence limit, PH: Proportional hazard

Data derived from Table 3, Section 11.

Summary of safety results

Table S 4 Summary of AEs

	Symbicort SMART n = 1049		Symbicort+Terbutaline n = 1042		All n = 2091	
No. (%) of patients with AE	602	(57.4%)	599	(57.5%)	1201	(57.4%)
No. (%) of patients with SAE other than death	42	(4.0%)	74	(7.1%)	116	(5.5%)
No. of SAEs other than death[a]	45		85		130	
No. (%) of patients with SAE leading to death	1	(<0.1%)	1	(<0.1%)	2	(<0.1%)
No. of SAEs leading to death[a]	1		2[c]		3	
Max no. of SAEs/patient	2		4		4	
No. (%) of patients with OAE	0		0		0	
No. of OAEs	0		0		0	
No. (%) of patients with DAE[b]	11	(1.0%)	12	(1.2%)	23	(1.1%)
No. of DAEs[a,b]	15		13		28	
No. of AEs[a]	1400		1389		2789	
- Mild	1110		1066		2176	
- Moderate	261		276		537	
- Severe	29		47		76	
No. (%) of patients with drug-related AE	41	(3.9%)	36	(3.5%)	77	(3.7%)
No. of drug-related AEs[a]	52		42		94	
Max no. of AEs/patient	30		13		30	

a Events are counted by Preferred terms (PT); for patients with multiple events falling under the same PT, only one occurrence of the event is counted

b For 4 DAEs, the investigational product was not actively permanently stopped. This is applicable for the following AEs and patients: 1 AE that lead to death (septic chock, E5503016) in the Symbicort SMART group, and 2 AEs that lead to death (acute myocardial infarction and abdominal pain upper, E6301022) in the Symbicort+ Terbutaline as needed group and 1 AE reported post treatment (cognitive disorder, E8108012).

c One patient (E6301022) had 2 SAEs.

Data derived from Table 3-2, Section 11.

Table S 5 Number (%) of patients with the 10 most frequently reported AEs, by PTs

PT	Symbicort SMART n = 1049	Symbicort+Terbutaline n = 1042	All n = 2091
Nasopharyngitis	137 (13.1%)	133 (12.8%)	270 (12.9%)
Bronchitis	69 (6.6%)	78 (7.5%)	147 (7.0%)
Viral upper respiratory tract infection	60 (5.7%)	72 (6.9%)	132 (6.3%)
Asthma	49 (4.7%)	75 (7.2%)	124 (5.9%)
Pharyngitis	49 (4.7%)	58 (5.6%)	107 (5.1%)
Upper respiratory tract infection bacterial	41 (3.9%)	31 (3.0%)	72 (3.4%)
Headache	31 (3.0%)	28 (2.7%)	59 (2.8%)
Rhinitis seasonal	26 (2.5%)	23 (2.2%)	49 (2.3%)
Influenza	18 (1.7%)	27 (2.6%)	45 (2.2%)
Sinusitis	21 (2.0%)	22 (2.1%)	43 (2.1%)

Data derived from Table 3-6, Section 11.