AstraZeneca

Clinical Study Report Synopsis	
Drug Substance	SYMBICORT® pMDI
Study Code	D589CC00003
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A Phase IIIB, 12-Month, Double-Blind, Double-Dummy, Randomized, Parallel-Group, Multicenter Exacerbation Study of SYMBICORT® pMDI 160/4.5 µg x 2 Actuations Twice-daily and 80/4.5 µg x 2 Actuations Twice-daily Compared to Formoterol TBH 4.5 µg 2 Inhalations Twice-daily in COPD Patients

Study dates: First Patient enrolled: 02 January 2007
Last Patient last visit: 27 August 2009

Phase of development: IIIB

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

Study centers

This study was conducted in the United States (90 investigational sites), South America (51 investigational sites), and South Africa (20 investigational sites).

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	**Primary**
To compare efficacy of SYMBICORT pressurized metered-dose inhaler (pMDI) 160/4.5 µg x 2 actuations twice daily (BID) and SYMBICORT pMDI 80/4.5 µg x 2 actuations BID to formoterol Turbuhaler (TBH) 4.5 µg x 2 inhalations BID in chronic obstructive pulmonary disease (COPD) patients. The primary variable was the number of COPD exacerbations over the randomized treatment period.	The primary efficacy variable was the number of exacerbations. Secondary efficacy variables were time to first exacerbation; pre-dose forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC); morning and evening peak expiratory flow (PEF); COPD symptoms including breathlessness, cough, sputum and nighttime awakenings; rescue medication use; St George's Respiratory Questionnaire (SGRQ); and direct and indirect health economic resource utilization measurements. The efficacy objective were to be met by showing that patients using SYMBICORT pMDI had significantly fewer number of exacerbations than patients using formoterol TBH. Support for that objective was to be provided by the superiority of SYMBICORT to formoterol TBH in the secondary variables as demonstrated by larger lung function tests, lower symptom scores, less rescue medication use, better responses to patient reported outcomes (PROs), and less utilization of health economic resources.
Secondary	**Secondary**
To demonstrate the safety of both SYMBICORT pMDI doses compared to that of formoterol TBH in patients with COPD.	Safety variables were adverse events (AEs), serious adverse events (SAEs), laboratory tests, vital signs, electrocardiograms (ECGs), and physical examinations. The safety objective was to be met by showing that SYMBICORT pMDI had a similar safety profile to formoterol TBH.

Study design

This was a 12-month, double-blind, double-dummy, randomized, parallel-group, multicenter efficacy study comparing SYMBICORT pMDI 160/4.5 µg x 2 actuations BID and

80/4.5 µg x 2 actuations BID with that of formoterol TBH 4.5 µg x 2 inhalations BID in COPD patients.

The study consisted of an initial screening visit, 2-week run-in enrollment visits, 7 visits during a 12 month randomized treatment period (including randomization visit), and a follow-up telephone call 2 weeks after study treatment cessation.

Target patient population and sample size

Approximately 1200 male and female patients ≥40 years of age with a clinical diagnosis of COPD were to be randomized to treatment. In addition, patients had to demonstrate a pre-bronchodilator FEV_1 of ≤50% of predicted value and have a score of at least 2 on the Modified Medical Research Council (MMRC) dyspnea scale at Visit 2.

The sample size calculation was based on a normal approximation (standard square root transformation) to the Poisson regression model. A sample size of approximately 400 patients in each treatment group would allow 90% power to detect a reduction from 1.07 to 0.74 (about 30% reduction) in the number of exacerbations, adjusting for over dispersion (deviance) of 2.3.

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

Dosage, mode of administration and batch numbers: Treatments were given in a double dummy fashion because of the difference in devices. Patients were randomly assigned to 1 of the 3 following treatment groups: (1) SYMBICORT pMDI (budesonide/formoterol) 160/4.5 µg (delivered dose) per actuation, 2 actuations administered twice daily (BID), and placebo pMDI, 2 actuations administered BID. Batch numbers of SYMBICORT pMDI 160/4.5 µg were 3000060E00, 300076E00, 06-006505AZ, and 06-010292AZ; (2) SYMBICORT pMDI (budesonide/formoterol) 80/4.5 µg (delivered dose) per actuation, 2 actuations administered BID, and placebo pMDI, 2 actuations administered BID. Batch numbers of SYMBICORT pMDI 80/4.5 µg were 2000036E00, 200044D00, 05-005495AZ, and 06-010296AZ; (3) Formoterol TBH 4.5µg (delivered dose) per inhalation, 2 inhalations administered BID, and placebo pMDI, 2 actuations administered BID. Batch numbers of formoterol TBH were IH803, KA830, 06-009524AZ, and 07-011329AZ.

Duration of treatment

The study consisted of an initial screening visit, a 2-week run-in period, a 12-month randomized treatment period, and a follow-up telephone call 2 weeks after the last dose of study medication.

Statistical methods

The primary efficacy variable was the number of COPD-related exacerbations. The analyses of the secondary efficacy endpoints provided additional supportive data compared to formoterol TBH to characterize the complete efficacy profile of SYMBICORT.

To maintain the experiment-wise Type I error rate at no greater than 5%, a sequential approach to hypothesis testing and the interpretation of unadjusted p-values was taken. SYMBICORT pMDI 160/4.5 µg x 2 BID, was first compared with formoterol TBH for COPD-related exacerbations. If the associated null hypothesis was rejected at the 5% level, then testing would proceed to the secondary variables for the higher dose. The secondary variables (in hierarchical order: morning PEF, evening PEF, pre-dose FEV_1, dyspnea, rescue medication use, and SGRQ) were tested at the 5% significance level. Testing for these variables was stopped when a comparison did not achieve statistical significance at the 5% level. If each of these 6 comparisons were significant at the 5% level then the SYMBICORT pMDI 80/4.5 µg x 2 BID would also be tested against formoterol TBH in the same sequence as for the higher dose.

All efficacy analyses were performed on an efficacy analysis set population using 2-sided tests at the 5% level of significance. The efficacy analysis set included all randomized patients who took at least 1 dose of randomized treatment and contributed sufficient data for at least 1 efficacy outcome variable. The numbers of exacerbations were expressed as the mean number of exacerbations per patient treatment year. Differences were compared using a Poisson regression model (logarithmic link function), with treatment and country as factors allowing for over dispersion (using the deviance estimate), if necessary. Differential treatment exposure was adjusted for by using the natural logarithm of the number of days during the randomized period (since first dose of randomized treatment) divided by 365.25 as an offset variable. Time to first COPD exacerbation was described using a Kaplan-Meier plot and was analyzed using a log-rank test to compare the curves between treatment groups. This was further described using a Cox proportional hazards model (Cox PHM) with treatment as factor and stratified by county, if appropriate. Patients who did not report an exacerbation were censored at the last day of the randomized period regardless of whether the patient completed the study or were withdrawn early. For all secondary variables, the primary comparison was between both SYMBICORT pMDI doses and formoterol. Other continuous secondary variables were analyzed with methods similar to those used for the primary variables. Count data were analyzed using a Poisson regression model adjusting for treatment, country, time in study, and overdispersion. Safety variables were analyzed with descriptive statistics, shift tables, and ANCOVA models using all patients who received at least 1 dose of randomized treatment and for whom any data were available after randomization (safety analysis set).

Subject population

This study was conducted at 180 investigational sites in the United States and 8 other countries. The study population was representative of the target patient population with moderate to very severe COPD. A total of 2183 patients were screened for possible study participation, 1219 of whom were subsequently randomized at 161 investigational sites. Demographic and baseline characteristics were generally well-balanced across the 3 treatment groups (Table S2). Among randomized patients, there was a greater proportion of male than female patients (62% versus 38%), consistent with the disease prevalence in adults. Most patients were white (82.3%). Most patients had taken oral corticosteroid treatment (72.2%) or antibiotic treatment (81.2%) 1 to 12 months before randomization. Among randomized

patients, the overall withdrawal rate was highest in the formoterol TBH treatment group (32.9%); followed by the SYMIBICORT 80/4.5 x2 BID treatment group (28.9%) and the SYMBICORT 160/4.5 x2 BID treatment group (28.7%). Overall, the most common reason for discontinuation from the randomized treatment period of the study was due to voluntary discontinuation by the patient (12.0%), followed by discontinuation due to an AE (10.6%).

Table S2 Demographic and key characteristics (safety analysis set)

	Treatment group[a]			
Demographic or key characteristic	**SYM 160/4.5 x2 BID (N=407)**	**SYM 80/4.5 x2 BID (N=408)**	**FOR 4.5 x2 BID (N=403)**	**Total (N=1219)**
Sex (n and % of patients)				
Male	262 (64.4)	264 (64.7)	229 (56.8)	755 (62.0)
Female	145 (35.6)	144 (35.3)	174 (43.2)	463 (38.0)
Age group (years) (n and % of patients)				
40 to <65	206 (50.6)	236 (57.8)	232 (57.6)	674 (55.3)
65 to <75	152 (37.3)	124 (30.4)	129 (32.0)	405 (33.3)
≥75	49 (12.0)	48 (11.8)	42 (10.4)	139 (11.4)
Age (years)				
Mean (SD)	63.8 (9.40)	62.8 (9.22)	62.5 (9.36)	63.0 (9.34)
Median	64.0	63.0	63.0	63.0
Range	40 to 86	40 to 84	40 to 87	40 to 87
Race (n and % of patients)				
White	338 (83.0)	332 (81.4)	332 (82.4)	1002 (82.3)
Black or African American	14 (3.4)	15 (3.7)	19 (4.7)	48 (3.9)
Asian	7 (1.7)	4 (1.0)	3 (0.7)	14 (1.1)
American Indian or Alaska Native	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)
Other	48 (11.8)	56 (13.7)	48 (11.9)	152 (12.5)
Smoking status (n and % of patients)				
Ex-smoker	269 (66.1)	265 (65.0)	249 (61.8)	783 (64.3)
Occasional smoker	8 (2.0)	8 (2.0)	16 (4.0)	32 (2.6)
Habitual smoker	130 (31.9)	135 (33.1)	138 (34.2)	403 (33.1)
Number of pack years (years)				
Mean (SD)	52.6 (30.45)	52.0 (30.94)	52.2 (31.10)	52.3 (30.81)
Median	46.0	44.0	43.0	45.0
Range	10 to 200	10 to 280	10 to 258	10 to 280

Table S2 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]			
	SYM 160/4.5 x2 BID (N=407)	SYM 80/4.5 x2 BID (N=408)	FOR 4.5 x2 BID (N=403)	Total (N=1219)
MMRC Scale				
Mean (SD)	2.9 (0.88)	3.0 (0.88)	3.1 (0.89)	3.0 (0.88)
Median	3.0	3.0	3.0	3.0
Range	2 to 5	2 to 5	2 to 5	2 to 5
Number of exacerbations in past 1 to 12 months (n and % of patients)				
1	244 (60.0)	243 (59.6)	234 (58.1)	721 (59.2)
2	95 (23.3)	94 (23.0)	99 (24.6)	288 (23.6)
3	36 (8.8)	40 (9.8)	38 (9.4)	114 (9.4)
4	22 (5.4)	12 (2.9)	19 (4.7)	53 (4.4)
≥5	10 (2.5)	19 (4.7)	13 (3.2)	42 (3.4)
Months since first COPD symptoms				
Mean (SD)	125.6 (86.71)	121.6 (81.78)	119.5 (86.45)	122.2 (84.97)
Median	102.0	97.0	96.0	98.0
Pre-dose FEV_1 (L) at Visit 2				
N	402	400	399	1201
Mean (SD)	0.98 (0.37)	0.97 (0.35)	0.95 (0.36)	0.97 (0.36)
Range	0.30 to 3.00	0.22 to 2.07	0.31 to 2.76	0.22 to 3.00
Percent predicted pre-dose FEV_1 at Visit 2				
N	402	400	397	1199
Mean (SD)	32.96 (10.45)	32.34 (9.80)	32.38 (10.07)	32.56 (10.10)
Range	12.05 to 72.57	8.09 to 57.73	12.11 to 61.40	8.09 to 72.57
Percent predicted post-dose FEV_1 at Visit 2				
N	402	398	395	1195
Mean (SD)	37.94 (11.83)	37.62 (11.60)	37.52 (12.39)	37.70 (11.93)
Range	13.28 to 76.50	8.19 to 67.50	11.75 to 74.50	8.19 to 76.50
Percent pre-dose FEV_1/FVC at Visit 2				
N	402	400	399	1201
Mean (SD)	45.85 (11.25)	46.08 (11.17)	46.06 (11.06)	46.00 (11.15)
Range	19.84 to 73.00	10.82 to 98.91	20.00 to 87.58	10.82 to 98.91

Table S2 Demographic and key characteristics (safety analysis set)

Demographic or key characteristic	Treatment group[a]			
	SYM 160/4.5 x2 BID (N=407)	SYM 80/4.5 x2 BID (N=408)	FOR 4.5 x2 BID (N=403)	Total (N=1219)
Reversibility in FEV_1 (L) at Visit 2				
N	402	398	397	1197
Mean (SD)	0.15 (0.14)	0.16 (0.17)	0.15 (0.18)	0.15 (0.17)
Range	-0.16 to 0.68	-0.49 to 1.18	-0.33 to 1.24	-0.49 to 1.24
Reversibility in FEV_1 (%) at Visit 2				
N	402	398	397	1197
Mean (SD)	16.24 (15.59)	17.58 (19.55)	17.10 (19.73)	16.97 (18.37)
Range	-22.03 to 73.24	-45.79 to 135.63	-18.97 to 151.43	-45.79 to 151.43

[a] SYM 160 x2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; SYM 80 x2 BID: SYMBICORT pMDI 80/4.5 µg x 2 actuations BID; FOR 4.5 x2 BID: formoterol TBH 4.5 µg x 2 inhalations BID.

Abbreviations: BID: twice daily; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; MMRC: Modified Medical Research Council; N: number; pMDI: pressurized metered-dose inhaler SD: standard deviation; TBH: Turbuhaler®.

Summary of efficacy results

Results of the primary efficacy results are summarized in Table S3 and Table S4.

Table S3 Summary of protocol-defined exacerbations (efficacy analysis set)

Parameter	Treatment[a]			
	SYM 160/4.5 x2 BID (N=404)	SYM 80/4.5 x2 BID (N=403)	FOR 4.5 x2 BID (N=403)	Total (N=1210)
At least 1 exacerbation, n (%) of patients	169 (41.8)	173 (42.9)	182 (45.2)	524 (43.3)
Total number of exacerbations	250	275	357	882
Total number of patient-treatment year	334	326	313	972
Total number of exacerbations per patient-treatment year	0.75	0.84	1.14	0.91
Total days of exacerbations per patient-treatment year	7.49	7.98	10.42	8.60
Total days of exacerbations per patient				
Mean (SD)	6.18 (17.68)	6.44 (10.75)	8.10 (13.59)	6.91 (14.31)

Table S3 Summary of protocol-defined exacerbations (efficacy analysis set)

Parameter	Treatment[a]			
	SYM 160/4.5 x2 BID (N=404)	SYM 80/4.5 x2 BID (N=403)	FOR 4.5 x2 BID (N=403)	Total (N=1210)
Range	0 to 297	0 to 71	0 to 105	0 to 297

[a] SYM 160/4.5 x2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; SYM 80/4.5 x2 BID: SYMBICORT pMDI 80/4.5 µg x 2 actuations BID; FOR 4.5 x2 BID: formoterol TBH 4.5 µg x 2 inhalations BID.

Abbreviations: BID: twice daily; N: number; SD: standard deviation; TBH: Turbuhaler®.

Table S4 Analysis of the estimated number of protocol-defined exacerbations (efficacy analysis set)

Event	Treatment[a]	Comparisons		
		Estimate (SE)	95% CI	P-value
Estimate number of overall exacerbations per patient-treatment year[b]	SYM 160 x2 BID	0.700 (0.084)	0.554, 0.885	
	SYM 80 x2 BID	0.794 (0.092)	0.632, 0.997	
	FOR 4.5 x2 BID	1.072 (0.119)	0.863, 1.331	
	SYM 160 x2 BID vs FOR 4.5 x2 BID	0.654 (0.066)	0.535, 0.798	<0.001
	SYM 80 x2 BID vs FOR 4.5 x2 BID	0.741 (0.073)	0.610, 0.899	0.002

[a] SYM 160/4.5 x2 BID: SYMBICORT pMDI 160/4.5 µg x 2 actuations BID; SYM 80/4.5 x2 BID: SYMBICORT pMDI 80/4.5 µg x 2 actuations BID; FOR 4.5 x2 BID: formoterol TBH 4.5 µg x 2 inhalations BID.

[b] Statistics based on Poisson Regression and adjusted for differential treatment exposure using person-years as an offset variable.

Note: Statistics based on Poisson Regression weren't displayed for hospitalization exacerbation because the model did not converge.

Abbreviations: BID: twice daily; CI: confidence interval; pMDI: pressurized metered-dose inhaler; SE: standard error; TBH: Turbuhaler®.

There were statistically significant reductions in the number of overall exacerbations per patient-treatment year in both SYMBICORT treatment groups compared to the formoterol TBH treatment group. SYMBICORT 160/4.5 x2 BID treatment group demonstrated a statistically significantly increased time to first exacerbation compared to the formoterol TBH treatment group. The increases in morning and evening PEFs in both SYMBICORT treatment groups were not statistically significant compared to the formoterol TBH treatment group. Since the treatment group differences were not of statistical significance, all p-values for the

remaining secondary variables were to be interpreted as unadjusted only. Unadjusted p-values below 0.05 were not considered statistically significant, but can be considered as descriptive measures.

Summary of safety results

SYMBICORT pMDI was well tolerated relative to formoterol TBH in this study of 1218 patients with COPD. There were higher rates of drug-related AEs in both the SYMBCIORT pMDI treatment groups compared to the formoterol TBH treatment group. There were lower rates of COPD-related AEs leading to discontinuation in the SYMBICORT pMDI treatment groups. A total of 213 patients in the safety analysis set experienced SAEs during the randomized treatment period (SYBMICORT 160/4.5 x2 BID: 79 patients; SYMBICORT 80/4.5 x2 BID: 61 patients; formoterol TBH: 73 patients). Of these SAEs, a total of 64 patients discontinued from the study (SYMBICORT 160/4.5 x2 BID: 20 patients; SYMBICORT 80/4.5 x2 BID: 18 patients; formoterol TBH: 26 patients). A total of 26 patients in the safety analysis set experienced an SAE leading to death with onset during the randomization treatment period. There were no meaningful differences among the 3 treatment groups in terms of QT and QTc data. There were no meaningful differences in hematology, clinical chemistry, vital signs, and physical examination findings between patients treatment with either dose of SYMBICORT pMDI compared to the formoterol TBH treatment group.