AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D589DC00007
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A phase III, 12-week, double-blind, randomised, parallel-group, active-controlled, multinational, efficacy and safety study of Symbicort® Turbuhaler® 160/4.5 µg 2 inhalations bid compared to Oxis® Turbuhaler 4.5 µg 2 inhalations bid in patients with chronic obstructive pulmonary disease (COPD)

Study dates: First subject enrolled: 28 January 2010
Last subject last visit: 30 March 2011

Phase of development: Therapeutic confirmatory (III)

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

This submission /document contains trade secrets and confidential commercial information, disclosure of which is prohibited without providing advance notice to AstraZeneca and opportunity to object.

Study centre(s)

This study was conducted at 163 centres from 9 countries including Japan (80 centres), Korea (5 centres), Taiwan (8 centres), Philippines (7 centres), Viet Nam (4 centres), India (10 centres), Russia (20 centres), Poland (19 centres) and Ukraine (10 centres).

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 show that Symbicort Turbuhaler, administered as 160/4.5 µg 2 inhalations bid is effective in patients with COPD, when compared to Oxis Turbuhaler 4.5 µg 2 inhalations bid.	**Primary variable** • Pre-dose FEV_1 measured with the spirometer at the clinic visits **Secondary variables** • COPD symptoms: breathlessness, cough, night-time awakenings due to symptoms • 1 hour post-dose FEV_1 at the clinic visits • Pre-dose and 1 hour post-dose FVC at the clinic visits • COPD exacerbations – Time to first COPD exacerbation defined as worsening in symptoms requiring treatment with a course of systemic steroid or hospitalisation. – Number of COPD exacerbations over the randomised treatment period • Rescue medication use • HRQL based on the SGRQ • Morning and evening PEF measured by the patients at home • Morning and evening FEV_1 measured by the patients at home	Efficacy
Secondary	**Secondary**	
To compare the safety of Symbicort Turbuhaler 160/4.5 µg 2 inhalations bid with Oxis Turbuhaler 4.5 µg 2 inhalations bid in patients with COPD.	**Secondary variables** • Adverse events (nature, incidence and severity) • 12-lead ECG • Vital signs • Physical examinations • Clinical chemistry, haematology and urinalysis	Safety

Study design

This was a 12-week, double-blind, randomised, parallel-group, active-controlled, multinational Phase III study.

Target subject population and sample size

Male or female subjects, ≥40 years of age, with a current clinical diagnosis of COPD, and with documented COPD symptoms for more than 2 years

A total of 1260 patients (630 patients per treatment group) including 300 patients (150 patients per treatment group) in Japan were to be randomised.

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

Symbicort Turbuhaler 160/4.5 µg 2 inhalations twice daily: Batch number: 09-002661AZ

Oxis Turbuhaler 4.5 µg 2 inhalations twice daily: Batch number: 09-003068AZ and 09-003110AZ

Additional non-investigational drug, dosage and mode of administration

Salbutamol 100 µg 2 inhalations for COPD symptoms relief (rescue medication), inhaled from pMDI

Duration of treatment

The total duration of the study for a subject was between 13 and 18 weeks, an enrolment visit, 1-2 weeks run-in period and 12 weeks of randomised treatment period.

Statistical methods

The analysis set for efficacy was based on the Full Analysis Set in line with the International Conference on Harmonisation (ICH) E9 guidelines. The comparison between treatment groups was performed on the primary variable, mean change from baseline value in pre-dose FEV_1 measured at the clinic visits, using a multiplicative Analysis of Covariance (ANCOVA) model including country and treatment as fixed factors, and the baseline value as a covariate. For other lung functions, diary variables and SGRQ, the change was compared between treatment groups with methods similar to those used for the primary variables. Time to first COPD exacerbation was described using Kaplan-Meier curves, and compared between treatments using a log-rank test. The incidence of adverse events was calculated and results from laboratory safety measurements, vital signs, and ECG were analysed primarily by means of descriptive statistics.

Subject population

The disposition and demographic and key baseline characteristics of the patients in this study are summarised in Table S 2. In total, 1710 patients were enrolled and 1293 patients were randomised to either of the two treatment groups. Of the 1293 randomised patients, 1195 patients completed the study and 98 patients discontinued study treatment. The number of analysed patients was 1293 in the FAS and safety analysis set. The treatment groups were well-balanced with regards to demography and other patient characteristics.

Table S 2 Patient population and disposition (all randomised patients)

Demographic characteristics		Symbicort n=636	Oxis n=657	Total n=1293
Population				
Number of randomised (Number of planned)		636 (630)	657 (630)	1293 (1260)
Demographic characteristics				
Age(years)	Mean (SD)	64.5 (9.0)	65.6 (9.3)	65.0 (9.1)
	Range	(40 to 89)	(40 to 87)	(40 to 89)
Sex	Male	557 (87.6%)	593 (90.3%)	1150 (88.9%)
	Female	79 (12.4%)	64 (9.7%)	143 (11.1%)
Race	White	293 (46.1%)	291 (44.3%)	584 (45.2%)
	Asian	343 (53.9%)	366 (55.7%)	709 (54.8%)
Population	Japanese	147 (23.1%)	165 (25.1%)	312 (24.1%)
	non-Japanese	489 (76.9%)	492 (74.9%)	981 (75.9%)
Smoking pack years	Mean (SD)	43.4 (24.4)	44.7 (27.3)	44.1 (25.9)
	Range	(10 to 160)	(0 to 300)	(0 to 300)
Duration of disease	Mean (SD)	5.63 (4.46)	5.80 (4.51)	5.71 (4.49)
(years)	Range	(0.1 to 31.9)	(0.1 to 31.8)	(0.1 to 31.9)
Number of exacerbations	Mean (SD)	1.5 (1.5)	1.5 (1.3)	1.5 (1.4)
within a year	Range	(0 to 30)	(1 to 20)	(0 to 30)
Baseline characteristics				
FEV_1 (L) [1), 3)]	Mean (SD)	1.137 (0.381)	1.111 (0.364)	1.124 (0.373)
	Range	(0.36 to 2.65)	(0.24 to 2.67)	(0.24 to 2.67)
FEV_1/FVC [1), 3)]	Mean (SD)	44.88 (10.64)	44.43 (10.62)	44.65 (10.63)
	Range	(20.8 to 75.9)	(16.8 to 100.0)	(16.8 to 100.0)
FEV_1% of PN [2), 3)]	Mean (SD)	36.2 (10.4)	36.3 (10.4)	36.3 (10.4)
	Range	(10 to 68)	(11 to 66)	(10 to 68)
FEV_1% reversibility (%) [3)]	Mean (SD)	14.1 (19.0)	13.2 (15.1)	13.6 (17.2)
	Range	(-22 to 303)	(-57 to 104)	(-57 to 303)
Disposition				
Number (%) of patients who completed		594 (93.4%)	601 (91.5%)	1195 (92.4%)
Number (%) of patients who discontinued		42 (6.6%)	56 (8.5%)	98 (7.6%)
Number of analysed patients for safety		636	657	1293
Number of analysed patients for FAS		636	657	1293

1) post-bronchodilator
2) pre-bronchodilator
3) Oxis group: n=656, Total: n=1292
PN: predicted normal

Summary of efficacy results

The descriptive statistics in pre-dose FEV_1 as primary variable and the results of comparison between treatment groups using ANCOVA are presented in Table S 3 and Table S 4, respectively. The increase in pre-dose FEV_1 was statistically significantly greater in the Symbicort group than in the Oxis group (p=0.0011).

Table S 3 Descriptive statistics in pre-dose FEV_1 (L) (FAS)

Treatment	Period	n	G-mean	CV	Median	Min	Max
Symbicort	Baseline	635	0.971	38.254	0.980	0.33	2.53
	Mean over Visit 4-6	619	1.021	41.361	1.033	0.35	3.29
	Ratio to baseline (%)	618	104.6	18.7	102.6	37.4	311.1
Oxis	Baseline	657	0.945	37.963	0.950	0.31	2.61
	Mean over Visit 4-6	635	0.968	38.628	0.967	0.32	2.58
	Ratio to baseline (%)	635	101.5	16.6	100.7	35.1	218.5

Baseline: pre-dose value at visit 3
The available data without imputation are used.

Table S 4 Comparison between treatment groups for the change from baseline to the mean of treatment period in pre-dose FEV_1 (L) using ANCOVA (FAS)

		95% confidence interval		
Comparison	**Adjusted ratio**	**Lower**	**Upper**	**p-value**
Symbicort vs Oxis	1.032	1.013	1.052	0.0011

Baseline: pre-dose value at visit 3
ANCOVA (Multiplicative model): including country and treatment as fixed factors, and log (baseline value) as covariate
The available data without imputation are used.

The results of comparison between treatment groups within each sub-group for the ratio from baseline to the mean during treatment period in pre-dose FEV_1 using ANCOVA by population (Japanese / non-Japanese) are shown in Table S 5. Similar results for pre-dose FEV_1 were seen in the Japanese and non-Japanese populations. No interaction between treatment and population was observed (p=0.8899).

Table S 5 Comparison between treatment groups within each sub-group for the ratio from baseline to the mean during treatment period in pre-dose FEV_1 (L) using ANCOVA by population (Japanese / non-Japanese) (FAS)

Population	Comparison	Adjusted ratio	95% confidence interval Lower	Upper	p-value	Interaction p-value
Japanese	Symbicort vs Oxis	1.029	0.989	1.071	0.1582	0.8899
non-Japanese	Symbicort vs Oxis	1.032	1.010	1.055	0.0045	

Baseline: pre-dose value at visit 3
ANCOVA (Multiplicative model): including treatment, population and treatment*population as fixed factors, and log (baseline value) as covariate
The available data without imputation are used.

The results of comparison between treatment groups for the ratio from baseline to the mean during treatment period in 1 hour post-dose FEV_1, and pre-dose and 1 hour post-dose FVC using ANCOVA are shown in Table S 6. The increases in 1 hour post dose FEV_1 and FVC were statistically significantly greater in the Symbicort group than in the Oxis group (p=0.0019 and p=0.0337, respectively). No statistically significant differences in pre-dose FVC were observed between Symbicort and Oxis groups (p=0.0857).

Table S 6 Comparison between treatment groups for the ratio from baseline to the mean during treatment period in 1 hour post-dose FEV_1 (L), and pre-dose and 1 hour post-dose FVC (L) using ANCOVA (FAS)

Variable	Comparison	Adjusted ratio	95% confidence interval Lower	Upper	p-value
1 hour post-dose FEV_1 (L)	Symbicort vs Oxis	1.026	1.010	1.043	0.0019
Pre-dose FVC (L)	Symbicort vs Oxis	1.016	0.998	1.034	0.0857
1 hour post-dose FVC (L)	Symbicort vs Oxis	1.016	1.001	1.032	0.0337

Baseline: pre-dose value at visit 3
ANCOVA (Multiplicative model): including country and treatment as fixed factors, and log (baseline value) as covariate
The available data without imputation are used.

Kaplan Meier curves for time to first COPD exacerbation are shown in Figure S 1. Comparison between treatment groups for time to first COPD exacerbation is shown in Table S 7. The Symbicort group statistically significantly prolonged the time to first exacerbation compared with the Oxis group as analysed using Log-rank test and Cox proportional hazards model (Log-rank test: p=0.0085, Cox proportional hazards model: p=0.0094). The estimated hazard ratio of 0.679 translates to a 32.1% reduction in the instantaneous risk of having an exacerbation when this patient population is treated with Symbicort instead of Oxis.

Figure S 1 Kaplan-Meier plot of time to first COPD exacerbation (FAS)

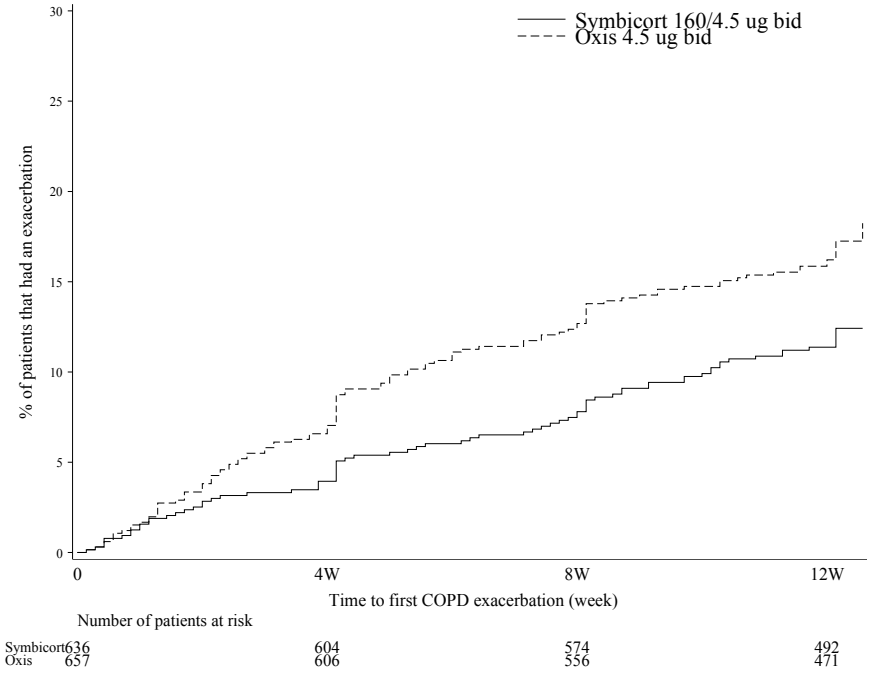

Table S 7 Statistical analysis of time to first COPD exacerbation (FAS)

		Log-rank test	Cox proportional hazards model			
			Hazard	95% confidence Interval		
Variable	**Comparison**	**p-value**	**ratio**	**Lower**	**Upper**	**p-value**
Any exacerbation	Symbicort vs Oxis	0.0085	0.679	0.507	0.909	0.0094
Due to hospitalisation	Symbicort vs Oxis	0.4437	0.816	0.477	1.397	0.4590
Due to the use of GCS treatment	Symbicort vs Oxis	0.0028	0.638	0.472	0.862	0.0034

GCS: Glucocorticosteroid

Table S 8 shows the descriptive statistics in number of COPD exacerbations over the randomised treatment period. Table S 9 shows the statistical analysis of total number of COPD exacerbations. There were 93 exacerbations experienced by 76 (11.9%) of the patients in the Symbicort group, and there were 151 exacerbations experienced by 111 (16.9%) of the patients in the Oxis group. Symbicort treatmemt results in a statistically significant reduction in total number of COPD exacerbations over the randomised treatment period compared with the Oxis group (p=0.0006). The estimated rate ratio o f 0.638 translates to a 36.2% reduction in the exacerbation rate.

Table S 8 Number (%) of patients who had any COPD exacerbations over the randomised treatment period (FAS)

Variable		Symbicort n=636		Oxis n=657	
	Mean observation time (days)	83.1		81.9	
Any exacerbation	No. of patients who had at least 1 exacerbation	76	(11.9%)	111	(16.9%)
	Total No. of exacerbations	93		151	
	Total No. of days with exacerbations	653		1098	
Due to	No. of patients who had at least 1 exacerbation	24	(3.8%)	30	(4.6%)
hospitalisation	Total No. of exacerbations	24		38	
	Total No. of days with exacerbations	214		334	
Due to the use of	No. of patients who had at least 1 exacerbation	70	(11.0%)	109	(16.6%)
GCS treatment	Total No. of exacerbations	87		149	
	Total No. of days with exacerbations	552		1002	

GCS: Glucocorticosteroid

Table S 9 Statistical analysis of total number of COPD exacerbations over the randomised treatment period (FAS)

		Poisson regression model			
			95% confidence Interval		
Variable	Comparison	Rate ratio	Lower	Upper	p-value
Any exacerbation	Symbicort vs Oxis	0.638	0.493	0.826	0.0006
Due to hospitalisation	Symbicort vs Oxis	0.649	0.389	1.082	0.0972
Due to the use of GCS treatment	Symbicort vs Oxis	0.605	0.464	0.788	0.0002

GCS: Glucocorticosteroid

The results of comparison between treatment groups for the change from run-in period average to treatment period average in morning and evening PEF and FEV_1 measured by the subjects at home using ANCOVA are shown in Table S 10. The changes in morning and evening PEF and FEV_1 were statistically significantly greater in the Symbicort group than in the Oxis group ($p<0.0001$ in each case).

Table S 10 Comparison between treatment groups for the change from run-in period average to treatment period average in morning and evening PEF (L/min) and morning and evening FEV_1 (L) using ANCOVA (FAS)

Variable	Comparison	Adjusted difference	95% confidence interval Lower	Upper	p-value
morning PEF (L/min)	Symbicort vs Oxis	9.554	5.900	13.207	<0.0001
evening PEF (L/min)	Symbicort vs Oxis	8.373	4.677	12.069	<0.0001
morning FEV_1 (L)	Symbicort vs Oxis	0.061	0.040	0.082	<0.0001
evening FEV_1 (L)	Symbicort vs Oxis	0.056	0.034	0.078	<0.0001

Run-in period average is calculated as average recorded over the last 7 days of the run-in period.
ANCOVA (Additive model): including country and treatment as fixed factors, and the run-in period average as covariate
The available data without imputation are used.

The results of comparison between treatment groups for the change from run-in period average to treatment period average in COPD symptom score using ANCOVA are shown in Table S 11. The decreases in COPD symptom scores of night-time awakening, breathlessness and total COPD symptom score were statistically significantly greater in the Symbicort group than in the Oxis group (night-time awakening: p=0.0491, breathlessness: p=0.0008, total COPD symptom score: p=0.0118). No statistically significant difference in COPD symptom score of cough was observed between Symbicort and Oxis groups (p=0.2324).

Table S 11 Comparison between treatment groups for the change from run-in period average to treatment period average in COPD symptom score using ANCOVA (FAS)

Variable	Comparison	Adjusted difference	95% confidence interval Lower	Upper	p-value
Night-time awakening (points/day)	Symbicort vs Oxis	-0.063	-0.126	0.000	0.0491
Breathlessness (points/day)	Symbicort vs Oxis	-0.115	-0.182	-0.047	0.0008
Cough (points/day)	Symbicort vs Oxis	-0.040	-0.105	0.025	0.2324
Total COPD symptom score (points/day)	Symbicort vs Oxis	-0.207	-0.367	-0.046	0.0118

Each COPD symptom was assessed on a scale of 0 to 4.
Run-in period average is calculated as average recorded over the last 7 days of the run-in period.
ANCOVA (Additive model): including country and treatment as fixed factors, and the run-in period average as covariate
The available data without imputation are used.

The results of comparison between treatment groups for the change from run-in period average to treatment period average in use of rescue medication using ANCOVA are shown in

Table S 12. The decrease in use of rescue medication was statistically significantly greater in the Symbicort group than in the Oxis group (p=0.0033).

Table S 12 Comparison between treatment groups for the change from run-in period average to treatment period average in use of rescue medication using ANCOVA (FAS)

Variable	Comparison	Adjusted difference	95% confidence interval Lower	Upper	p-value
Use of rescue medication (times/day)	Symbicort vs Oxis	-0.223	-0.371	-0.074	0.0033

Run-in period average is calculated as average recorded over the last 7 days of the run-in period.
ANCOVA (Additive model): including country and treatment as fixed factors, and the run-in period average as covariate
The available data without imputation are used.

The distribution of categorised changes in SGRQ total score and the comparison between treatment groups were shown in Table S 13. Statistically significantly more patients improved in the Symbicort group than in the Oxis group (p=0.0240).

Table S 13 Comparison between treatment groups for the categorised change in SGRQ total score from baseline to last available score using chi-square test (FAS)

		Change in total score from baseline [1)]					χ^2 test
		Improved	Unchanged	Deteriorated	Improved,% (n)		p-value
Total score	Symbicort	350	90	181	56.4%	(350/621)	0.0240
	Oxis	317	88	229	50.0%	(317/634)	

Baseline: Visit 3
1) Improved: decrease of 4 units or more, Deteriorated: increase of 4 units or more

Summary of safety results

A summary of AEs in each category is presented in Table S 14. After randomisation, 299 AEs were reported for 193 of the 636 patients (30.3%) in the Symbicort group, and 332 AEs were reported for 214 of the 657 patients (32.6%) in the Oxis group. The majority of AE were of mild or moderate intensity. Four (4) deaths were reported in the Symbicort group, and 5 deaths were reported in the Oxis group. Serious AEs other than death were reported by 39 patients (6.1%) in the Symbicort group, and 41 patients (6.2%) in the Oxis group. Discontinuations of study treatment due to AEs were reported by 19 patients (3.0%) in the Symbicort group, and 26 patients (4.0%) in the Oxis group. There were no other significant AEs identified in this study. The incidence and nature of adverse events were similar in the Symbicort group and the Oxis group. The incidence of AEs and drug-related AEs in Japanese patients were higher than those in non-Japanese patients in both Symbicort and the Oxis

groups, however the nature of AEs (ie, severity and/or seriousness) were similar between Japanese and non-Japanese population.

Table S 14 Number (%) of patients who had any adverse events and number of adverse events (Safety analysis set)

	Symbicort			Oxis		
Category	Japanese n=147	non-Japanese n=489	Total n=636	Japanese n=165	non-Japanese n=492	Total n=657
Number of patients who had an AE in each category [1)]						
Any AEs	74 (50.3%)	119 (24.3%)	193 (30.3%)	98 (59.4%)	116 (23.6%)	214 (32.6%)
SAEs leading to death	0	4 (0.8%)	4 (0.6%)	2 (1.2%)	3 (0.6%)	5 (0.8%)
SAEs not leading to death	12 (8.2%)	27 (5.5%)	39 (6.1%)	15 (9.1%)	26 (5.3%)	41 (6.2%)
DAEs [2)]	8 (5.4%)	11 (2.2%)	19 (3.0%)	14 (8.5%)	12 (2.4%)	26 (4.0%)
OAEs	0	0	0	0	0	0
Drug-related AEs [3)]	20 (13.6%)	7 (1.4%)	27 (4.2%)	15 (9.1%)	4 (0.8%)	19 (2.9%)
Number of AEs [4)]						
Any AEs	127	172	299	163	169	332
Mild intensity	96	100	196	117	92	209
Moderate intensity	30	47	77	35	56	91
Severe intensity	1	25	26	11	21	32
SAEs leading to death	0	4	4	2	3	5
SAEs not leading to death	12	34	46	19	29	48
DAEs	9	11	20	14	12	26
OAEs	0	0	0	0	0	0
Drug-related AEs[3)]	27	8	35	18	5	23

1) Patients with multiple events in the same category are counted only once in that category. Patients with events in more than one category are counted once in each of those categories.
2) Three (3) patients in the Symbicort group and 4 patients in the Oxis group were discontinued study treatment due to AEs leading to death.
3) The causality was judged by the investigator.
4) Multiple occurrence of the same event in a patient is counted only once. Multiple events in the same category are counted multiple times in that category. Multiple events belonging to more than one category are counted in each of those categories.

The most commonly reported AEs (those with an incidence ≥2% on PT level in each of treatment groups) in the study are shown in Table S 15. The most commonly reported AEs were CHRONIC OBSTRUCTIVE PULMONARY DISEASE (Symbicort group: 8.0%, Oxis group: 9.4%) and NASOPHARYNGITIS (Symbicort group: 5.5%, Oxis group: 4.9%). The

incidences of NASOPHARYNGITIS and BRONCHITIS in Japanese patients were higher than those in non-Japanese patients for any of the treatment groups. The incidence of DYSPHONIA was higher in Japanese patients than that in non-Japanese patients only for the Symbicort group (Symbicort group: Japanese 7.5%, non-Japanese 0.0%, Oxis group: Japanese 0.6%, non-Japanese 0.2%).

Table S 15 Number (%) of patients with most commonly reported adverse events by preferred term (Safety analysis set)

	Symbicort			Oxis		
Preferred term [1), 2), 3)]	Japanese n=147	non-Japanese n=489	Total n=636	Japanese n=165	non-Japanese n=492	Total n=657
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	11 (7.5%)	40 (8.2%)	51 (8.0%)	17(10.3%)	45 (9.1%)	62 (9.4%)
NASOPHARYNGITIS	24 (16.3%)	11 (2.2%)	35 (5.5%)	25 (15.2%)	7 (1.4%)	32 (4.9%)
BRONCHITIS	8 (5.4%)	5 (1.0%)	13 (2.0%)	13 (7.9%)	2 (0.4%)	15 (2.3%)
UPPER RESPIRATORY TRACT INFECTION BACTERIAL	3 (2.0%)	4 (0.8%)	7 (1.1%)	3 (1.8%)	5 (1.0%)	8 (1.2%)
DYSPHONIA	11 (7.5%)	0	11 (1.7%)	1 (0.6%)	1 (0.2%)	2 (0.3%)
PHARYNGITIS	1 (0.7%)	3 (0.6%)	4 (0.6%)	5 (3.0%)	1 (0.2%)	6 (0.9%)
DIARRHOEA	3 (2.0%)	1 (0.2%)	4 (0.6%)	4 (2.4%)	0	4 (0.6%)
PNEUMONIA	3 (2.0%)	2 (0.4%)	5 (0.8%)	2 (1.2%)	1 (0.2%)	3 (0.5%)
RHINORRHOEA	0	2 (0.4%)	2 (0.3%)	4 (2.4%)	0	4 (0.6%)
BLOOD URINE PRESENT	3 (2.0%)	0	3 (0.5%)	2 (1.2%)	0	2 (0.3%)
OESOPHAGEAL CANDIDIASIS	3 (2.0%)	0	3 (0.5%)	0	0	0

1) This table used a cut-off of 2% in each of treatment groups.
2) A patient experiencing more than one AE within a PT was counted once within that PT.
3) MedDRA 14.0
Table was sorted by frequency of group total.

After randomisation, 4 deaths were reported in the Symbicort group, and 5 deaths were reported in the Oxis group. One (1) death (Cause of death; ACUTE MYOCARDIAL INFARCTION) in the Oxis group was judged as causally related to investigational product by the investigator.

There were no findings for clinical laboratory values, vital signs or ECG that gave any reason for concern regarding the safety of the Symbicort group and the Oxis group.