AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Budesonide/formoterol
Study Code	D589DC00008
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An open-label phase III, multi-centre 52-week, parallel-group study evaluating the safety and efficacy of Symbicort Turbuhaler 160/4.5 µg 2 inhalations twice daily compared with standard treatment in Japanese patients with chronic obstructive pulmonary disease (COPD)

Study dates:	First patient enrolled: 28 January 2010 Last patient last visit: 24 October 2011
Phase of development:	Therapeutic confirmatory (III)
International Co-ordinating Investigator:	Not applicable

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

Study centre(s)

This study was conducted at 60 centres in Japan.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Primary and secondary objectives and outcome variables are summarised in Table S1.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate the safety of Symbicort Turbuhaler 160/4.5 μg 2 inhalations bid and standard COPD treatment (JRS guideline and GOLD guideline) in a Japanese population of COPD patients treated for 52 weeks	AEs, vital signs, laboratory variables, ECG, physical examination	Safety
Secondary	**Secondary**	
To investigate the efficacy profile of Symbicort Turbuhaler 160/4.5 μg 2 inhalations bid and standard COPD treatment in patients treated for 52 weeks	FEV_1, FVC, PEF, COPD symptoms, use of rescue medication, SGRQ and COPD exacerbations	Efficacy

Study design

This was a multicentre, open, randomised, parallel-group, phase III study with Symbicort Turbuhaler 160/4.5 μg 2 inhalations bid or standard COPD therapy. The standard COPD treatment arm was the group to refer to when safety results of the Symbicort Turbuhaler arm was evaluated.

Target subject population and sample size

The target patient population was patients with COPD to whom treatment with inhaled GCS and LABA was recommended, with a reference to the guidelines. Specifically, COPD patients with ≤50% of pre-bronchodilator FEV_1 predicted normal were selected for the study.

Two hundred and forty patients with COPD (at least 120 patients in the Symbicort Turbuhaler group and at least 120 patients in the standard COPD therapy group) were to be enrolled to obtain 100 patients per arm for 1-year treatment.

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

- Investigational product

Symbicort Turbuhaler, 160/4.5 μg, 2 inhalations twice daily (Batch number: 09-002662AZ and 10-005848AZ)

- Comparator

Standard COPD treatment according to JRS guideline and GOLD guideline

- Reliever medication

Salbutamol: Aerosol in pressurised metered dose inhaler (pMDI), 100 μg/actuation

Duration of treatment

A 2-week run-in period followed by a 52-week treatment period

Statistical methods

All randomised patients who had received at least one dose of Symbicort Turbuhaler or standard COPD treatment for each treatment group, respectively, and for whom any safety data after randomisation were available were included in the safety population. Results from laboratory test values, vital signs and ECG were analysed primarily by means of the descriptive statistics and graphical illustrations. The AE profile of the safety variables were analysed by means of qualitative analysis. All randomised patients who had received at least one dose of Symbicort Turbuhaler or standard COPD treatment for each treatment group, respectively, and for whom any efficacy data after randomisation were available were included in the efficacy population. FEV_1 and Diary variables were presented descriptively as the change from baseline (values collected at Visit 3 and mean values in the run-in period respectively) to the average of the values during the whole treatment period.

Subject population

In total, 328 patients were enrolled, of whom 260 patients were randomised to either of the two treatment groups, ie, the 160/4.5 μg 2 inhalations bid group (hereafter referred to as the Symbicort Turbuhaler group) or the standard COPD treatment group. Of the 260 randomised patients, 222 patients completed 52-week treatment in this study and 38 patients discontinued study treatment. The number of analysed patients was 260 in the safety analysis set and 260 in the efficacy analysis set. The treatment groups were well-balanced with regards to demography and subject baseline characteristics (Table S2).

Table S2 Patient population and disposition [all randomised patients]

		Symbicort 160/4.5 µg 2 inhalations bid	Standard COPD treatment	Total
Population				
Number of patients randomised		130	130	260
Demographic characteristics and disease history				
Age (years)	Mean (SD)	70.1 (8.4)	71.5 (7.0)	70.8 (7.7)
	Range	40 to 87	54 to 85	40 to 87
Sex	Male	125 (96.2%)	126 (96.9%)	251 (96.5%)
	Female	5 (3.8%)	4 (3.1%)	9 (3.5%)
Smoking pack years	Median	60.0	59.5	60.0
	Range	10 to 300	12 to 174	10 to 300
Duration of COPD (years)	Mean (SD)	4.9 (4.6)	4.6 (4.5)	4.8 (4.6)
	Range	0 to 24	0 to 22	0 to 24
Baseline characteristics related to lung function at entry				
FEV_1 (L)	Mean (SD)	1.049 (0.299)	1.051 (0.329)	1.050 (0.314)
	Range	0.53 to 1.90	0.38 to 2.16	0.38 to 2.16
FVC (L)	Mean (SD)	2.722 (0.669)	2.652 (0.694)	2.687 (0.681)
	Range	1.13 to 4.26	1.03 to 4.47	1.03 to 4.47
FEV_1/FVC (%)	Mean (SD)	39.41 (9.40)	40.18 (9.70)	39.79 (9.55)
	Range	18.6 to 62.6	21.2 to 67.2	18.6 to 67.2
FEV_1% of predicted normal (%)	Mean (SD)	34.15 (8.51)	34.86 (9.53)	34.50 (9.03)
	Range	15.6 to 49.7	16.2 to 50.4	15.6 to 50.4
FEV_1% reversibility (%)	Mean (SD)	14.5 (11.6)	15.2 (14.7)	14.8 (13.2)
	Range	-40 to 65	-20 to 93	-40 to 93
Disposition				
Number of patients who completed 52-week treatment		110	112	222
Number of patients who discontinued prior to 52 weeks		20	18	38
Number of patients in safety analysis set		130	130	260
Number of patients in efficacy analysis set		130	130	260

Lung function variables are at post bronchodilator.

Summary of efficacy results

The Symbicort Turbuhaler group had an increase in FEV_1 of 4.25% and the standard COPD treatment group had a decrease of 1.57%. As for FVC, the Symbicort Turbuhaler group showed an increase of 2.51% and the standard COPD treatment group showed an increase of 0.04% (Table S3).

Table S3 Descriptive statistics in FEV_1 (L) and FVC (L) [Efficacy analysis set]

Variable	Treatment	Period	n	G-mean	CV	Range
FEV_1 (L)	Symbicort 160/4.5 µg 2 inhalations bid	Baseline	130	0.977	31.479	0.30 to 1.90
		Mean over Visits 4-10	129	1.020	30.641	0.46 to 1.93
		Ratio to baseline (%)	129	104.25	15.07	60.8 to 182.9
	Standard COPD treatment	Baseline	130	0.968	37.276	0.40 to 2.49
		Mean over Visits 4-10	129	0.953	35.883	0.37 to 2.13
		Ratio to baseline (%)	129	98.43	15.70	35.8 to 168.2
FVC (L)	Symbicort 160/4.5 µg 2 inhalations bid	Baseline	130	2.611	27.369	0.84 to 4.22
		Mean over Visits 4-10	129	2.684	26.711	1.04 to 4.40
		Ratio to baseline (%)	129	102.51	10.02	77.8 to 141.5
	Standard COPD treatment	Baseline	130	2.468	30.010	0.88 to 4.50
		Mean over Visits 4-10	129	2.467	30.734	0.81 to 4.50
		Ratio to baseline (%)	129	100.04	11.03	67.6 to 158.2

Baseline: Visit 3. The values with imputation are summarised except for the mean over Visits 4-10.

The mean changes in mPEF from run-in period to the whole treatment period up to 52 weeks were 5.9 L/min in the Symbicort Turbuhaler group and 5.7 L/min in the standard COPD treatment group. The mean changes in ePEF from run-in period to the whole treatment period up to 52 weeks were 2.7 L/min in the Symbicort Turbuhaler group and 5.2 L/min in the standard COPD treatment group.

The total COPD symptom score decreased from run-in period to the whole treatment period up to 52 weeks in both of the two treatment groups. The use of SABA (salbutamol) as reliever medication decreased from the run-in period level in the Symbicort Turbuhaler group but was unchanged in the standard treatment group (Table S4).

Table S4 Descriptive statistics in COPD total symptom score and frequency of SABA [Efficacy analysis set]

Variable	Treatment	n	Run-in period[1] Mean±SD	n	Whole treatment period[2] Mean±SD	n	Change from run-in period[1] Mean±SD
Total COPD symptom score	Symbicort 160/4.5 µg 2 inhalations bid	130	2.4±1.8	130	2.0±2.0	130	-0.4±1.3
	Standard COPD treatment	130	2.4±1.8	130	2.0±1.7	130	-0.3±1.2
Frequency of SABA (times/day)	Symbicort 160/4.5 µg 2 inhalations bid	130	1.0±1.6	130	0.8±1.3	130	-0.2±1.0
	Standard COPD treatment	130	1.1±1.9	130	1.1±2.2	130	0.0±1.4

1) Mean over the last 10 days of the run-in period
2) Mean recorded from the next day of Visit 3 to the last treatment date.

The COPD exacerbation rate per patient-year in the Symbicort Turbuhaler group (0.35) was lower than that in the standard group (0.88) (Table S5).

Table S5 Descriptive statistics in COPD exacerbations [Efficacy analysis set]

Treatment	Symbicort 160/4.5 µg 2 inhalations bid	Standard COPD treatment
No. of patients with at least one event	26 (20.0)	41 (31.5)
Total no. of any exacerbations	41	105
Exacerbation rate (exacerbations/patient-year)	0.35	0.88

( ): %
Exacerbation rate = (N of exacerbations/Total N of days) x 365.25 where the total number of days was the time from randomisation to last assessment of exacerbation status.

The mean changes of SGRQ total score from baseline to the whole treatment period up to 52 weeks (mean over Visits 4-10) were -2.03 in the Symbicort Turbuhaler group and -0.42 and the standard COPD treatment group. The improvement rates at 52 weeks were 39.2% in the Symbicort Turbuhaler group and 35.4% in the standard group.

Summary of safety results

After randomisation, 404 AEs were reported for 123 (94.6%) of the 130 patients in the Symbicort Turbuhaler group and 367 AEs were reported for 112 (86.2%) of the 130 patients in the Standard COPD treatment group (Table S6). No death was reported in the whole treatment period. SAEs were reported by 25 patients (19.2%) in the Symbicort Turbuhaler group and 34 patients (26.2%) in the Standard COPD treatment group. DAEs were reported by 13 patients (10.0%) in the Symbicort Turbuhaler group. The majority of AEs were of mild

or moderate intensity in the two treatment groups. The frequency of AEs was higher in the Symbicort Turbuhaler group than in the Standard COPD treatment group, while the frequency of SAEs was higher in the Standard COPD treatment group (26.2%) than in the Symbicort Turbuhaler group (19.2%). There was no OAE identified in this study. In total, AEs assessed as causally related to Symbicort Turbuhaler by the investigator were reported by 33 patients (25.4%).

Table S6 Number of patients who had any adverse events and number of adverse events in any category by treatment group [Safety analysis set]

Category	Symbicort 160/4.5 µg 2 inhalations bid (n=130)	Standard COPD treatment (n=130)
Number of patients with AEs in each category (%)		
Any AE	123 (94.6)	112 (86.2)
Deaths	0 (0)	0 (0)
Serious AEs other than death	25 (19.2)	34 (26.2)
Discontinuations of IP due to AEs	13 [1)] (10.0)	NA
Study withdrawal due to AEs	13 [1)] (10.0)	9 (6.9)
Other significant AEs	0 (0)	0 (0)
Drug-related AEs	33 (25.4)	NA
Number of events in each category		
Any AE	404	367
AEs with mild intensity	316	290
AEs with moderate intensity	79	56
AEs with severe intensity	9	21
Deaths	0	0
Serious AEs other than death	32	49
Discontinuations of IP due to AEs	13	NA
Study withdrawal due to AEs	13	9
Other significant AEs	0	0
Drug-related AEs	45	NA

( ): %
1) One (1) patient with discontinuation of study due to AEs, which started prior to randomisation, is not included.
Adverse events which occurred from the date of Visit 3 onwards are summarised.
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.
Drug-related: The causality was assessed in 2 categories as "related" or "unrelated" by the investigator. AEs judged as "related" are regarded as AEs with a possible causal relationship.

The most commonly reported AE in the study was NASOPHARYNGITIS (Symbicort Turbuhaler group: 42.3%, Standard COPD treatment group: 39.2%). The pattern of AEs in both of the treatment groups was generally reflecting commonly occurring health problems in a COPD population. Overall, the AE profile was similar between the two treatment groups. The frequency of DYSPHONIA was higher in the Symbicort Turbuhaler group than in the Standard COPD treatment group (Symbicort Turbuhaler group: 5.4% [7/130], Standard COPD treatment group 0.8% [1/130]); the event is well known to be associated with budesonide treatment (Table S7).

Table S7 **Number (%) of patients with the most commonly reported adverse events (≥2% in either of the groups) with and without a possible causal relationship, as assessed by the investigator by PT [Safety analysis set]**

	AEs irrespective of causality		**AEs with a possible causal relationship**	
	Symbicort 160/4.5 µg 2 inhalations bid	**Standard COPD treatment**	**Symbicort 160/4.5 µg 2 inhalations bid**	**Standard COPD treatment**
Preferred Term	**n=130**	**n=130**	**n=130**	**n=130**
NASOPHARYNGITIS	55 (42.3)	51 (39.2)	0 (0)	NA
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	14 (10.8)	25 (19.2)	3 (2.3)	NA
BRONCHITIS	15 (11.5)	15 (11.5)	0 (0)	NA
CONSTIPATION	10 (7.7)	13 (10.0)	0 (0)	NA
PNEUMONIA	14 (10.8)	8 (6.2)	5 (3.8)	NA
BACK PAIN	6 (4.6)	10 (7.7)	0 (0)	NA
PHARYNGITIS	9 (6.9)	3 (2.3)	1 (0.8)	NA
PNEUMONIA BACTERIAL	4 (3.1)	8 (6.2)	1 (0.8)	NA
DIARRHOEA	4 (3.1)	6 (4.6)	0 (0)	NA
BENIGN PROSTATIC HYPERPLASIA	5 (3.8)	4 (3.1)	0 (0)	NA
CATARACT	3 (2.3)	6 (4.6)	0 (0)	NA
ECZEMA	5 (3.8)	4 (3.1)	0 (0)	NA
INSOMNIA	2 (1.5)	7 (5.4)	0 (0)	NA
DYSPHONIA	7 (5.4)	1 (0.8)	5 (3.8)	NA
VIRAL UPPER RESPIRATORY TRACT INFECTION	3 (2.3)	5 (3.8)	0 (0)	NA
CONTUSION	6 (4.6)	2 (1.5)	0 (0)	NA

Table S7 **Number (%) of patients with the most commonly reported adverse events (≥2% in either of the groups) with and without a possible causal relationship, as assessed by the investigator by PT [Safety analysis set]**

	AEs irrespective of causality		AEs with a possible causal relationship	
	Symbicort 160/4.5 µg 2 inhalations bid	Standard COPD treatment	Symbicort 160/4.5 µg 2 inhalations bid	Standard COPD treatment
Preferred Term	**n=130**	**n=130**	**n=130**	**n=130**
ARTHRALGIA	2 (1.5)	5 (3.8)	0 (0)	NA
ECZEMA ASTEATOTIC	3 (2.3)	4 (3.1)	0 (0)	NA
HERPES ZOSTER	5 (3.8)	2 (1.5)	0 (0)	NA
INFLUENZA	6 (4.6)	1 (0.8)	0 (0)	NA
ORAL CANDIDIASIS	4 (3.1)	3 (2.3)	3 (2.3)	NA
HEADACHE	5 (3.8)	1 (0.8)	0 (0)	NA
OEDEMA PERIPHERAL	2 (1.5)	4 (3.1)	0 (0)	NA
PYREXIA	4 (3.1)	2 (1.5)	0 (0)	NA
SPINAL OSTEOARTHRITIS	4 (3.1)	2 (1.5)	0 (0)	NA
STOMATITIS	4 (3.1)	2 (1.5)	1 (0.8)	NA
DECREASED APPETITE	1 (0.8)	5 (3.8)	0 (0)	NA
DIZZINESS	3 (2.3)	2 (1.5)	0 (0)	NA
GASTRITIS	3 (2.3)	2 (1.5)	0 (0)	NA
GASTROOESOPHAGEAL REFLUX DISEASE	3 (2.3)	2 (1.5)	0 (0)	NA
GASTROENTERITIS	3 (2.3)	2 (1.5)	0 (0)	NA
HYPERTENSION	5 (3.8)	0 (0)	0 (0)	NA
MUSCLE SPASMS	3 (2.3)	2 (1.5)	2 (1.5)	NA
UPPER RESPIRATORY TRACT INFECTION BACTERIAL	3 (2.3)	2 (1.5)	0 (0)	NA
ABDOMINAL DISCOMFORT	4 (3.1)	0 (0)	0 (0)	NA
ABDOMINAL PAIN UPPER	3 (2.3)	1 (0.8)	0 (0)	NA
ATRIAL FIBRILLATION	0 (0)	4 (3.1)	0 (0)	NA
DRUG ERUPTION	3 (2.3)	1 (0.8)	1 (0.8)	NA
RHINITIS	3 (2.3)	1 (0.8)	0 (0)	NA
VERTIGO	0 (0)	4 (3.1)	0 (0)	NA

Table S7 **Number (%) of patients with the most commonly reported adverse events (≥2% in either of the groups) with and without a possible causal relationship, as assessed by the investigator by PT [Safety analysis set]**

	AEs irrespective of causality		AEs with a possible causal relationship	
	Symbicort 160/4.5 µg 2 inhalations bid	Standard COPD treatment	Symbicort 160/4.5 µg 2 inhalations bid	Standard COPD treatment
Preferred Term	**n=130**	**n=130**	**n=130**	**n=130**
BRONCHITIS BACTERIAL	1 (0.8)	3 (2.3)	0 (0)	NA
OESOPHAGEAL CANDIDIASIS	3 (2.3)	0 (0)	3 (2.3)	NA
PERIODONTITIS	0 (0)	3 (2.3)	0 (0)	NA
SPINAL COMPRESSION FRACTURE	3 (2.3)	0 (0)	0 (0)	NA
UPPER RESPIRATORY TRACT INFECTION	3 (2.3)	0 (0)	2 (1.5)	NA
VENTRICULAR EXTRASYSTOLES	3 (2.3)	0 (0)	2 (1.5)	NA
INTERCOSTAL NEURALGIA	0 (0)	3 (2.3)	0 (0)	NA
INTERVERTEBRAL DISC PROTRUSION	3 (2.3)	0 (0)	0 (0)	NA
MUSCULOSKELETAL CHEST PAIN	3 (2.3)	0 (0)	1 (0.8)	NA
ORAL HERPES	3 (2.3)	0 (0)	0 (0)	NA
OROPHARYNGEAL DISCOMFORT	3 (2.3)	0 (0)	1 (0.8)	NA

MedDRA version 14.1
( ): %
AEs with an incidence of ≥2% in either of the groups are displayed.
Causal relationship: The causality was assessed in 2 categories as "related" or "unrelated" by the investigator. AEs judged as "related" are regarded as AEs with a possible causal relationship.

After randomisation, 32 SAEs were reported for 25 (19.2%) of the 130 patients in the Symbicort Turbuhaler group, and 49 SAEs were reported for 34 (26.2%) of the130 patients in the Standard COPD treatment group. Seven (7) cases of SAEs (3 each of PNEUMONIA and CHRONIC OBSTRUCTIVE PULMONARY DISEASE, and 1 LOSS OF CONSCIOUSNESS) in the Symbicort Turbuhaler group were judged as drug-related by the investigator. Thirteen (13) DAEs were reported for 13 (10.0%) of the 130 patients in the Symbicort Turbuhaler group. Four (4) cases of DAEs (2 PNEUMONIA, 1 each of LOSS OF CONSCIOUSNESS and DRUG ERUPTION) in the Symbicort Turbuhaler group were judged as drug related 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 Symbicort Turbuhaler 160/4.5 µg 2 inhalations bid.