AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Formoterol (OT)
Study Code	D5122C00002
Edition Number	1
Date	2 December 2011

An open phase III, multi-centre 52-week, parallel-group study evaluating the safety and efficacy of formoterol 18 µg daily dose compared with standard COPD treatment, in Japanese patients with chronic obstructive pulmonary disease (COPD)

Study dates:	First subject enrolled: 18 December 2009 Last subject last visit: 20 July 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 30 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 S 1.

Table S 1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
To investigate safety of formoterol and standard COPD (JRS guideline and GOLD) treatment in a Japanese population of moderate to severe COPD patients treated for 52 weeks.	• Adverse events , vital signs, laboratory variables, ECG and physical examination.	Safety
Secondary	**Secondary**	
To investigate efficacy profile of formoterol treatment in patients treated for 52 weeks	• Forced Expiratory Volume in 1 second (FEV_1) • Forced Vital Capacity (FVC) • Peak Expiratory Flow (PEF) (morning, evening) • COPD symptoms scores (0-4) – Registered in the morning: Night-time awakenings – Registered in the evening: Daytime breathlessness Daytime cough • COPD exacerbations: A COPD exacerbation is defined as worsening in COPD symptoms requiring treatment with either a course of systemic steroid (oral or parenteral) or hospitalisation. The COPD sign or symptoms include bronchitis, cough, phlegm, sputum increased, dyspnoea and wheeze. – Number of COPD exacerbations over the treatment period • Use of SABA (salbutamol) as reliever medication • SGRQ	Efficacy

Study design

This was a multicentre, open, randomised, parallel-group study with formoterol 9 µg one inhalation b.i.d, or standard COPD therapy. Standard (reference) COPD treatment arm was the group to refer to when safety results of formoterol arm was evaluated.

Target subject population and sample size

The target patient was to be patients with COPD to whom a treatment with inhaled LABA was recommended, with a reference to the guidelines (JRS and GOLD). Specifically, COPD patients with <80% of FEV_1 predicted normal were selected for the study.

Two hundred forty patients with moderate-to-severe COPD (120 patients in the formoterol-arm and 120 patients on standard COPD therapy) to obtain 100 patients per arm for 1-year treatment.

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

Investigational products

Formoterol 4.5 µg/dose: Inhalation powder in Turbuhaler, 4.5 µg/dose, 60 doses/Turbuhaler (Batch number: 09-002576AZ, 11-000333AZ)

Formoterol 9 µg/dose: Inhalation powder in Turbuhaler, 9 µg/dose, 60 doses/Turbuhaler (Batch number: 09-002583AZ, 10-005107AZ)

Comparator

Standard COPD treatment

Reliever medication

Salbutamol: Aerosol in pressurised metered dose inhaler (pMDI), 100 µg/actuation, Ca 200 actuations/pMDI

Duration of treatment

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

Statistical methods

All randomised subjects who received at least one dose of formoterol or standard COPD treatment for each treatment group respectively and for whom any safety data after randomisation are 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 was analysed by means of qualitative analysis. All randomised subjects who received at least one dose of formoterol 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 last 10 days of the run-in period respectively) to the average of the values during the whole treatment period.

Subject population

The disposition and demographic and key baseline characteristics of the patients in this study are summarised in Table S 2. In total, 251 patients were randomised to either of the two treatment groups at Visit 3. Of the 251 randomised patients, 225 patients completed 52-week treatment in this study and 26 patients discontinued study treatment. The number of analysed patients was 251 in the FAS and safety analysis set. The treatment groups were well-balanced with regards to demography and subject baseline characteristics.

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

		Formoterol 9 µg bid	Standard	Total
Population				
Number of patients who was randomised		125	126	251
Demographic characteristics				
Age (years)	Mean (SD)	70.8 (7.8)	70.3 (7.7)	70.6 (7.7)
	Range	(43 to 88)	(50 to 83)	(43 to 88)
Sex	Male	119 (95.2%)	117 (92.9%)	236 (94.0%)
	Female	6 (4.8%)	9 (7.1%)	15 (6.0%)
Smoking pack years	Median	50.0	50.5	50.0
(years)	Range	(15 to 138)	(13 to 168)	(13 to 168)
Duration of COPD	Mean (SD)	3.3 (4.1)	3.5 (3.8)	3.4 (3.9)
disease (years)	Range	(0 to 29)	(0 to16)	(0 to 29)
Baseline characteristics				
FEV_1 (L)	Mean (SD)	1.514 (0.512)	1.440 (0.531)	1.477 (0.522)
	Range	(0.54 to 2.99)	(0.55 to 2.67)	(0.54 to 2.99)
FVC (L)	Mean (SD)	3.116 (0.741)	3.016 (0.758)	3.066 (0.749)
	Range	(1.14 to 4.97)	(1.17 to 4.80)	(1.14 to 4.97)
FEV_1/FVC (%)	Mean (SD)	48.80 (12.11)	47.59 (11.72)	48.19 (11.91)
	Range	(22.5 to 69.3)	(24.4 to 69.2)	(22.5 to 69.3)
FEV_1 % of predicted	Mean (SD)	55.31 (15.96)	52.80 (15.87)	54.05 (15.94)
normal (%)	Range	(23.6 to 79.4)	(22.8 to 79.5)	(22.8 to 79.5)
FEV_1 % reversibility	Mean (SD)	10.8 (10.4)	13.6 (15.2)	12.2 (13.1)
(%)	Range	(-9 to 49)	(-25 to 131)	(-25 to 131)
Disposition				
Number of patients who completed		108	117	225
Number of patients who discontinued		17	9	26
Number of analysed patients for safety		125	126	251
Number of analysed patients for FAS		125	126	251

Summary of efficacy results

The descriptive statistics of FEV_1 and FVC are shown in Table S 3. The changes in mean values of FEV_1 and FVC from baseline were similar between treatment groups.

Table S 3 Descriptive statistics in FEV_1 (L) and FVC (L) (FAS)

Variable	Treatment	Period	n	G-mean	CV	Range
FEV_1 (L)	Formoterol	Baseline	125	1.375	37.523	0.51 to 3.01
	9 µg bid	Mean over Visit 4-10	125	1.395	37.964	0.53 to 3.10
		Ratio to baseline (%)	125	101.46	11.39	68.9 to 139.2
	Standard	Baseline	126	1.307	41.118	0.49 to 3.03
	COPD	Mean over Visit 4-10	126	1.299	40.901	0.51 to 2.82
	treatment	Ratio to baseline (%)	126	99.42	9.68	80.3 to 165.1
FVC (L)	Formoterol	Baseline	125	2.929	26.925	1.17 to 4.84
	9 µg bid	Mean over Visit 4-10	125	2.977	25.229	1.30 to 5.10
		Ratio to baseline (%)	125	101.62	9.78	76.9 to 157.3
	Standard	Baseline	126	2.827	27.705	1.26 to 4.88
	COPD	Mean over Visit 4-10	126	2.802	27.394	1.33 to 4.83
	treatment	Ratio to baseline (%)	126	99.13	10.20	75.3 to 163.0

Baseline: Visit 3 at Week 0, The values with imputation were summarised.

The descriptive statistics of mPEF and ePEF are shown in Table S 4. The changes in mean values of mPEF and ePEF from baseline were similar between treatment groups.

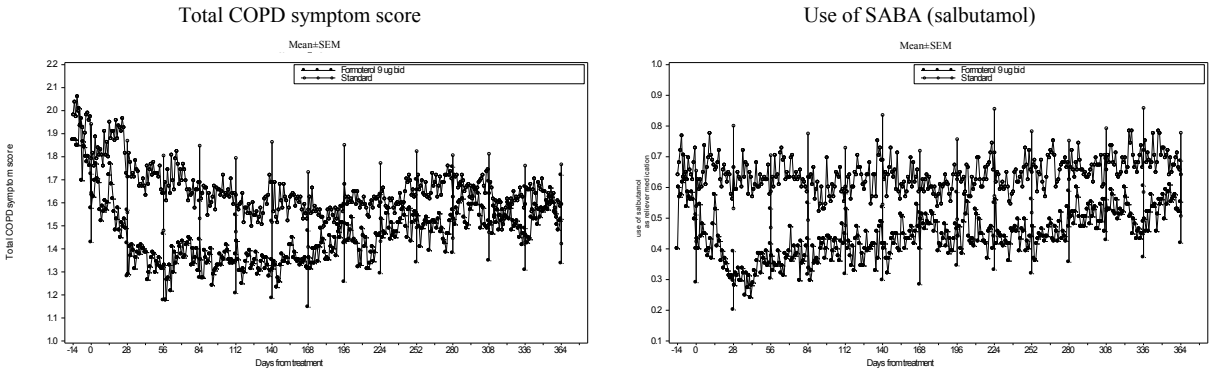
Table S 4 Descriptive statistics in mPEF and ePEF (FAS)

Variable	Treatment	n	Baseline [1)]	Whole treatment period [2)]	Change from baseline
mPEF (L/min)	Formoterol 9 µg bid	125	241.6±88.2	253.7±92.8	12.2±34.9
	Standard COPD treatment	126	223.9±87.0	231.2±91.2	7.3±26.2
ePEF (L/min)	Formoterol 9 µg bid	125	252.4±93.7	261.9±94.6	9.6±34.0
	Standard COPD treatment	126	232.1±91.2	240.0±95.6	7.9±28.2

1) Average over the last 10 days of the run-in period
2) Average during whole treatment period for mPEF and ePEF
The values with imputation were summarised.

Mean changes in total COPD symptom score and use of SABA (salbutamol) are shown in Figure S 1.

Figure S 1 Changes in mean total COPD symptom score and frequency of SABA (salbutamol) over time (FAS)



The values with imputation were summarised.

The descriptive statistics in COPD exacerbation score are shown in Table S 5. The total exacerbation rates were 0.2342 exacerbations/ patient-year in the formoterol treatment group and 0.1579 exacerbations/ patient-year in the standard COPD treatment group. No difference in hospitalization due to exacerbation was found between treatment groups.

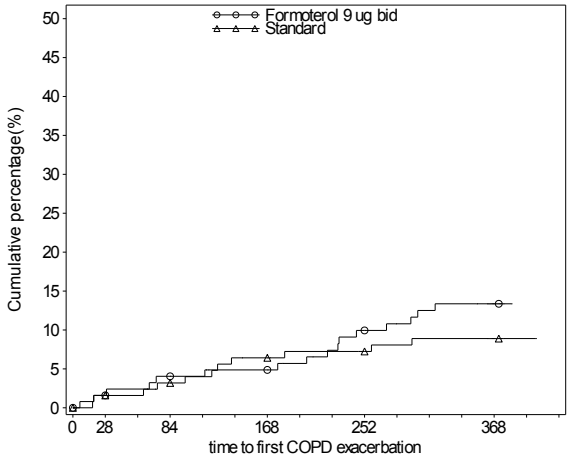
Table S 5 Descriptive statistics in COPD exacerbation score (FAS)

Treatment	Formoterol 9 µg bid	Standard COPD treatment
Any exacerbation (Total No. of events)	27	19
Exacerbation rate	0.2342	0.1579

Exacerbation rate: Total No. of events/Total time from randomisation to last assessment of exacerbation status (day) * 362.25

Kaplan Meier curves for time to first COPD exacerbation are shown in Figure S 2. At the end of the 52 weeks period 12.8% in the formoterol group and 8.7% in the standard group had experienced an exacerbation.

Figure S 2 Kaplan-Meier plot of time to first COPD exacerbation (FAS)



The change in scores from baseline was categorised as improved (decrease of 4 units or more), unchanged or deteriorated (increase of 4 units or more). The distribution of categorised changes in the SGRQ total score and the comparison between treatment groups were shown in Table S 6. A higher percentage of patients in the formoterol group than in the standard treatment group had a clinically meaningful improvement of at least 4 units at week 4, and the advantage for the formoterol treatment was maintained during the 52 week period.

Table S 6 Categorised change in SGRQ total score from baseline (FAS)

Treatment		Change in score from baseline [1)]				
period	**Treatment**	**n**	**Improved**	**Unchanged**	**Deteriorated**	**% of Improved**
Week 4	Formoterol 9 µg bid	123	46	50	27	37.4% (46/123)
	Standard COPD treatment	126	33	63	30	26.2% (33/126)
Week 26	Formoterol 9 µg bid	123	49	46	28	39.8% (49/123)
	Standard COPD treatment	126	44	54	28	34.9% (44/126)
Week 52	Formoterol 9 µg bid	123	45	36	42	36.6% (45/123)
	Standard COPD treatment	126	38	43	45	30.2% (38/126)

Baseline: Visit 3 at Week 0
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 7. After randomisation, 290 AEs were reported for 100 of the 125 patients (80.0%) in the formoterol 9 µg bid and 240 AEs were reported for 96 of the 126 patients (76.2%) in the standard COPD treatment group. The majority of AE were of mild or moderate intensity. The frequency and intensity of AEs were similar between treatment groups. One (1) death was reported in the standard COPD treatment group. SAEs other than death were reported by 20 patients (16.0%) in the formoterol 9 µg bid and 17 patients (13.5%) in the standard COPD treatment group. DAEs

were reported by 9 patients (7.2%) in the formoterol 9 µg bid. By definition, a DAE cannot occur in the standard COPD treatment group since no IP was administrated. However, 5 patients (4.0%) in the standard COPD treatment group withdrew from the study due to AEs. There was no OAE identified in this study.

No dose reduction of formoterol from 9 µg bid to 4.5 µg bid due to a tolerability reason was reported over the 52 week treatment period.

Table S 7 Number (%) of patients who had any adverse events in any category by treatment group (Safety analysis set)

Category	Formoterol 9 µg bid (n=125)		Standard COPD treatment (n=126)	
Number of patients with AEs in each category [1] (%)				
Any AE	100	(80.0)	96	(76.2)
Deaths	0	(0)	1	(0.8)
Serious AEs other than deaths	20	(16.0)	17	(13.5)
Discontinuations of IP (formoterol) due to AEs [2]	9	(7.2)	N/A	
Study withdrawal due to AEs	9	(7.2)	5	(4.0)
Other significant AEs	0	(0)	0	(0)
Drug-related AEs [3]	7	(5.6)	N/A	
Number of events in each category [4]				
Any AE	290		240	
AEs with mild intensity	253		216	
AEs with moderate intensity	29		15	
AEs with severe intensity	8		9	
Deaths	0		1	
Serious AEs other than deaths	27		22	
Discontinuations of IP (formoterol) due to AEs [2]	9		N/A	
Study withdrawal due to AEs	9		5	
Other significant AEs	0		0	
Drug-related AEs [3]	7		N/A	

1) A patient experiencing more than one AE within the same category was counted once within that category. A patient experiencing AEs in more than one category was counted once in each of those categories.
2) The action taken investigational product was assessed in 4 categories as "none", "dose changed", "temporarily stopped" or "permanently stopped" by the investigator only for the formoterol group. AEs assessed as "permanently stopped" are regarded as "Discontinuations of IP due to AEs". The action taken investigational product for AEs in the standard COPD treatment group was not assessed.
3) The causality was assessed in 2 categories as "related" or "unrelated" by the investigator only for the formoterol group. AEs judged as "related" are regarded as AEs with a possible causal relationship. The causality for AEs in the standard COPD treatment group was not assessed.
4) Multiple occurrence of the same event in a subject are 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 8. The most commonly reported AEs in the study were nasopharyngitis in both treatment groups. The pattern of AEs in the formoterol 9 µg bid groups generally reflected commonly occurring health problems in a COPD population. Overall the AE profile was similar in both treatment groups.

Table S 8 Number (%) of patients with the most commonly reported adverse events by preferred term (Safety analysis set)

Preferred Term [1), 2), 3)]	Formoterol 9 µg bid (n=125)		Standard COPD treatment (n=126)	
NASOPHARYNGITIS	42	(33.6)	53	(42.1)
BACK PAIN	13	(10.4)	2	(1.6)
BRONCHITIS	5	(4.0)	9	(7.1)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	9	(7.2)	5	(4.0)
PHARYNGITIS	7	(5.6)	4	(3.2)
PNEUMONIA	8	(6.4)	3	(2.4)
CONJUNCTIVITIS	5	(4.0)	5	(4.0)
CONSTIPATION	5	(4.0)	4	(3.2)
DIZZINESS	6	(4.8)	2	(1.6)
GASTRITIS	3	(2.4)	5	(4.0)
HYPERTENSION	3	(2.4)	5	(4.0)
INSOMNIA	3	(2.4)	4	(3.2)
RHINITIS	5	(4.0)	2	(1.6)
CONTUSION	4	(3.2)	3	(2.4)
HEADACHE	2	(1.6)	4	(3.2)
UPPER RESPIRATORY TRACT INFECTION	4	(3.2)	2	(1.6)
ECZEMA	4	(3.2)	1	(0.8)
NAUSEA	3	(2.4)	2	(1.6)
PALPITATIONS	3	(2.4)	2	(1.6)
HEPATIC FUNCTION ABNORMAL	1	(0.8)	3	(2.4)
INFLUENZA	1	(0.8)	3	(2.4)
DERMATITIS CONTACT	3	(2.4)	0	(0)
PERIARTHRITIS	3	(2.4)	0	(0)
STOMATITIS	3	(2.4)	0	(0)
URTICARIA	3	(2.4)	0	(0)

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

After randomisation, 1 death case was reported in the standard COPD treatment group (bipolar disorder), however the patient died by suicide and the causal relationships between this event and investigational product were excluded 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 formoterol 9 µg bid.