AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Formoterol
Study Code	D5122C00001
Edition Number	1.0
Date	3 August 2009

A 12-week, randomised, double-blind, placebo-controlled, parallel-group, multi-national, phase III, efficacy and safety study of inhaled formoterol 4.5 µg and 9 µg twice daily in Japanese and European patients with chronic obstructive pulmonary disease (COPD)

Study dates: First patient enrolled : 15 December 2007
Last patient completed : 1 April 2009

Phase of development: Therapeutic confirmatory (III)

Study centre(s)

This study was conducted in 65 centres from 4 countries: Romania (11 centres), Russia (11 centres), Ukraine (9 centres) and Japan (34 centres). The first patient was enrolled on 15 December 2007 and the last subject completed the study on 1 April 2009.

Publications

None at the time of writing this report.

Objectives

The primary objective of this study was to show that formoterol 4.5 µg and 9 µg twice daily were superior to placebo in Japanese and European COPD patients treated for 12 weeks by evaluation of FEV_1 60 minutes post-dose as the primary outcome variable.

Secondary variables related to this objective were:

- Spirometry: FVC and IC 60 minutes post-dose, and FEV_1, FVC and IC pre-dose
- Diary: morning PEF, evening PEF, COPD symptoms scores (night-time awakenings due to symptoms, breathlessness and cough) and use of salbutamol as reliever medication
- HRQL: St George's Respiratory Questionnaire (SGRQ)

The secondary objectives of this study were to:

1. Evaluate the onset of action of formoterol 4.5 µg and 9 µg using placebo as a control, by evaluation of FEV_1 5 minutes post-dose at Visit 3 as the primary variable
2. Compare the effect of formoterol 4.5 µg twice daily with that of formoterol 9 µg twice daily by evaluation of the same primary and secondary variables as for the primary objective.
3. Evaluate the safety of formoterol 4.5 µg and 9 µg twice daily for 12 weeks in terms of adverse events, laboratory variables, 12-lead ECG, blood pressure and pulse rate.

Study design

This was a 12-week randomised, double-blind, parallel-group, multi-national phase III study comparing inhaled formoterol 4.5 µg and 9 µg twice daily to placebo in patients with moderate to severe COPD.

Target population and sample size

Patients aged ≥40 years men and women who had a clinical diagnosis of COPD with current COPD symptoms and a current or previous smoking history of 10 or more pack years, and whose post- postbronchodilator FEV_1 and FEV_1/FVC were < 80% of the predicted normal and <70%, respectively.

A total of 540 patients including 320 patients in Japan and 220 patients in Europe were to be randomised.

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

Investigational product

- Formoterol 4.5 µg: Inhalation powder in Turbuhaler® (Batch number: H 1976-01-01-01)
- Placebo for formoterol: Inhalation powder in Turbuhaler® (Batch number: H 1866-01-01-02)

Patients of each dose group took the investigational product twice daily for 12 weeks.

Additional drug: dosage, mode of administration and batch numbers

Salbutamol 100 µg/actuation: Reliever medication inhaled from pressurised metered dose inhaler (pMDI) (Batch number: 4521 and 4931 in Japan, and H 1978-01-01-01 in Europe)

Duration of treatment

A 1-week enrolment period followed by a 2-week run-in period and a 12-week treatment period.

Criteria for evaluation - efficacy (main variables)

- Primary outcome variable:
  - Change from baseline to treatment period in FEV_1 60 minutes post-dose.
- Secondary outcome variables:
  - Change from baseline to treatment period in
    - FVC and IC 60 minutes post-dose
    - Pre-dose FEV_1, FVC and IC
    - PEF (morning, evening)

  - COPD symptoms scores (Night-time awakenings due to symptoms, breathlessness, cough)
  - Use of salbutamol as reliever medication
- Change from pre-dose to 5 minutes post-dose at Visit 3 in FEV_1, FVC and IC
- Patient reported outcomes (PROs): Change from baseline to end of treatment in overall score and within each domain in St George's Respiratory Questionnaire (SGRQ)

Criteria for evaluation - safety (main variables)

- Adverse events
- Clinical laboratory variables
- 12-lead ECG
- Blood pressure and pulse rate

Statistical methods

The comparison of formoterol 4.5 µg and 9 µg twice daily with placebo was performed on the primary variable, mean change from baseline value in FEV_1 60 minutes post-dose, using an Analysis of Covariance model (ANCOVA) including country and treatment as fixed factors, and the baseline value as a covariate. A two-sided 5% significance level was used. The multiplicity of statistical tests was adjusted by a "closed testing procedure". 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 1. In total, 766 patients were enrolled and 613 patients were randomised to either of the three treatment groups at Visit 3. Of the 613 randomised patients, 563 patients completed the study and 50 patients discontinued study treatment. The number of analysed patients was 613 in the FAS and safety analysis set, 609 in the PPS. The compliance was generally good and the observed levels of compliance appeared similar between treatment groups. The treatment groups were well-balanced with regards to demography and other baseline characteristics.

Table S 1 Patient population and disposition (all randomised patients)

			Formoterol		
		Placebo	4.5 µg bid	9 µg bid	Total
Population					
Number of randomised (Number of planned)		208 (180)	206 (180)	199 (180)	613 (540)
Demographic characteristics					
Age (years)	Mean (SD)	66.3 (9.7)	66.7 (9.4)	67.2 (9.2)	66.7 (9.4)
	Range	(40 to 86)	(41 to 85)	(44 to 88)	(40 to 88)
Sex	Male	186 (89.4%)	183 (88.8%)	170 (85.4%)	539 (87.9%)
	Female	22 (10.6%)	23 (11.2%)	29 (14.6%)	74 (12.1%)
Race	White	98 (47.1%)	100 (48.5%)	91 (45.7%)	289 (47.1%)
	Asian	110 (52.9%)	106 (51.5%)	108 (54.3%)	324 (52.9%)
Smoking pack years	Mean (SD)	47.4 (27.1)	46.1 (24.2)	46.5 (23.4)	46.7 (24.9)
	Range	(10 to 152)	(10 to 150)	(11 to 175)	(10 to 175)
Duration of disease	Mean (SD)	4.3 (5.0)	4.2 (5.0)	4.9 (5.8)	4.5 (5.3)
(years)	Range	(0 to 25)	(0 to 39)	(0 to 34)	(0 to 39)
Baseline characteristics					
FEV_1 (L) [1]	Mean (SD)	1.369 (0.533)	1.303 (0.497)	1.304 (0.524)	1.326 (0.518)
	Range	(0.48 to 3.17)	(0.48 to 3.10)	(0.25 to 2.72)	(0.25 to 3.17)
FVC (L) [1]	Mean (SD)	2.990 (0.873)	2.897 (0.772)	2.805 (0.796)	2.899 (0.817)
	Range	(1.01 to 6.12)	(1.07 to 5.65)	(0.40 to 5.31)	(0.40 to 6.12)
FEV_1/FVC (%)[1]	Mean (SD)	45.63 (10.85)	44.64 (10.16)	46.53 (12.30)	45.59 (11.13)
	Range	(20.5 to 68.8)	(23.0 to 70.4)	(18.1 to 77.2)	(18.1 to 77.2)
IC (L) [1, 2]	Mean (SD)	1.866 (0.669)	1.790 (0.666)	1.735 (0.618)	1.798 (0.653)
	Range	(0.04 to 4.21)	(0.04 to 3.84)	(0.02 to 4.00)	(0.02 to 4.21)
FEV_1 % of predicted	Mean (SD)	52.46 (15.67)	50.36 (14.52)	51.45 (14.73)	51.42 (14.99)
normal (%)[1]	Range	(16.6 to 83.7)	(22.0 to 79.4)	(9.3 to 79.5)	(9.3 to 83.7)
FEV_1 %	Mean (SD)	11.28 (11.44)	10.47 (11.12)	10.67 (12.17)	10.81 (11.57)
reversibility (%)	Range	(-30.3 to 67.2)	(-17.9 to 61.6)	(-57.4 to 63.6)	(-57.4 to 67.2)
Disposition					
Number (%) of patients who Completed		186	195	182	563
Number (%) of patients who discontinued		22	11	17	50
Number of analysed patients for safety		208	206	199	613
Number of analysed patients for FAS		208	206	199	613
Number of analysed patients for PPS		205	205	199	609

1) Pre-bronchodilator
2) Formoterol 4.5 µg bid: n=205, Total: n=612

Summary of efficacy results

The descriptive statistics of FEV_1 at 60 minutes post-dose as primary variable in FAS, and the results of comparison between treatment groups using ANCOVA are presented in Table S 2 and Table S 3, respectively. The increases in FEV_1 at 60 minutes post-dose were statistically significantly greater in formoterol 4.5 µg and 9 µg bid than in placebo (ANCOVA: $p<0.0001$ in each comparison). There was no statistically significant difference in change in FEV_1 at 60 minutes post-dose between formoterol 4.5 µg and 9 µg bid (ANCOVA: $p=0.6429$).

Table S 2 Descriptive statistics in FEV_1 (L) at 60 minutes post-dose (FAS)

Treatment	Period	n	G-mean	CV	Min	Median	Max
Placebo	Baseline	208	1.232	42.974	0.41	1.255	3.22
	Mean over Visit 4-6	208	1.247	42.297	0.42	1.237	3.55
	Ratio to baseline (%)	208	101.28	14.71	58.3	100.35	189.1
Formoterol 4.5 µg bid	Baseline	206	1.180	39.901	0.46	1.160	3.07
	Mean over Visit 4-6	206	1.329	37.838	0.49	1.310	3.25
	Ratio to baseline (%)	206	112.59	14.83	75.1	110.72	177.0
Formoterol 9 µg bid	Baseline	199	1.160	41.414	0.43	1.150	2.84
	Mean over Visit 4-6	199	1.314	39.838	0.43	1.300	3.16
	Ratio to baseline (%)	199	113.36	14.76	66.2	112.89	184.0

Baseline: Pre-dose at Visit 3
The values with imputation were summarised.

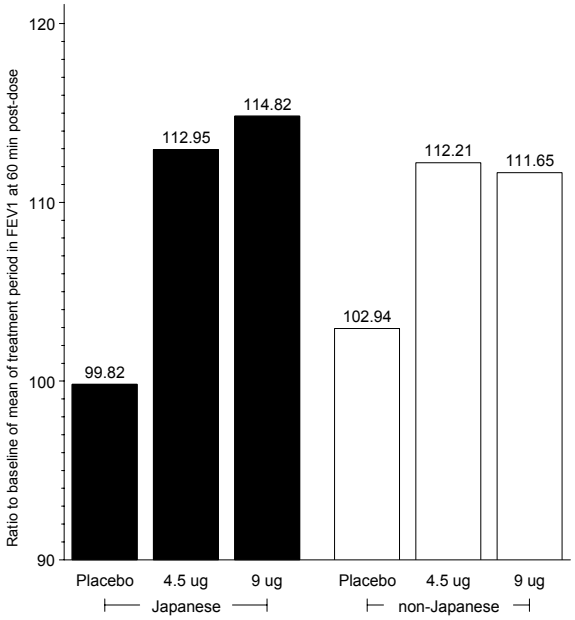
Table S 3 Comparison between treatment groups for the change from baseline to the mean of treatment period in FEV_1 (L) at 60 minutes post-dose using ANCOVA (FAS)

		95% confidence interval		
Comparison	**Adjusted ratio**	**Lower**	**Upper**	**p-value**
Formoterol 9 µg bid vs Placebo	1.114	1.083	1.145	<0.0001
Formoterol 4.5 µg bid vs Placebo	1.106	1.077	1.137	<0.0001
Formoterol 9 µg bid vs 4.5 µg bid	1.007	0.979	1.035	0.6429

Baseline: Pre-dose at Visit 3
ANCOVA: Multiplicative model including country and treatment as fixed factors, and log (baseline value) as covariate

The G-mean of ratio to baseline of the mean of treatment period in FEV_1 at 60 minutes post-dose by population (Japanese/non-Japanese) is shown in Figure S 1. Treatment differences were not apparently observed between Japanese and non-Japanese population.

Figure S 1 G-mean of ratio to baseline of the mean of treatment period in FEV_1 at 60 minutes post-dose by population (Japanese/non-Japanese) (FAS)



The results of comparison between treatment groups in secondary lung function variables using ANCOVA are presented in Table S 4. Formoterol 4.5 µg and 9 µg twice daily improved lung function as measured by 60 minutes post-dose FVC and pre-dose FEV_1, compared to placebo. Formoterol 4.5 µg and 9 µg twice daily improved lung function 5 minutes post-dose as compared to placebo, demonstrating fast onset of effect on both FEV_1 and FVC.

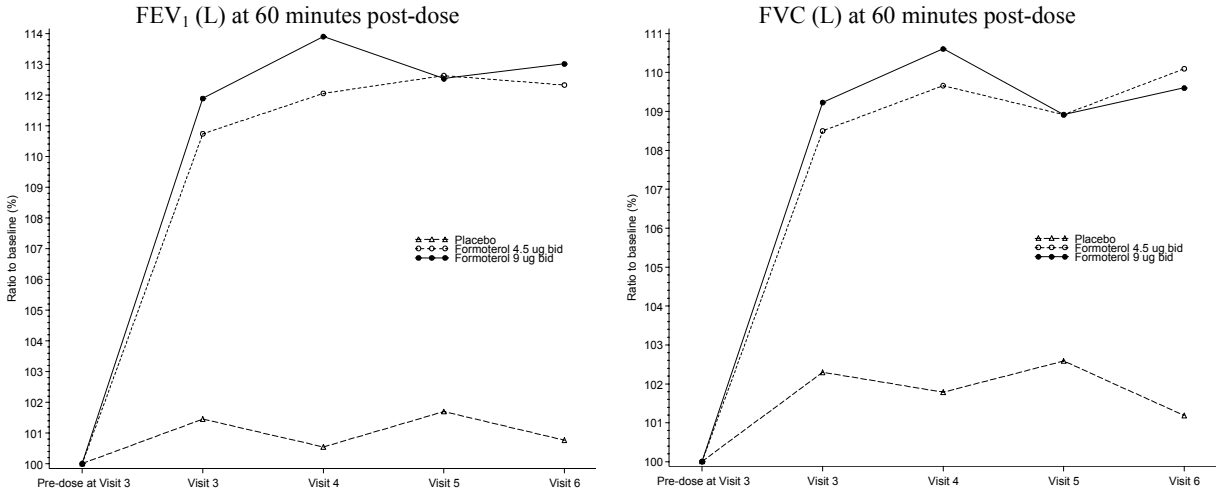
Table S 4 Comparison between treatment groups for the change from baseline to the mean of treatment period in secondary lung function variables using ANCOVA (FAS)

Variable		Comparison	Adjusted ratio	95% CI Lower	Upper	p-value
FEV_1 (L)	Pre-dose	Formoterol 9 µg bid vs Placebo	1.044	1.017	1.072	0.0015
		Formoterol 4.5 µg bid vs Placebo	1.043	1.016	1.071	0.0016
		Formoterol 9 µg bid vs 4.5 µg bid	1.001	0.975	1.028	0.9547
	5 minutes post-dose at Visit 3	Formoterol 9 µg bid vs Placebo	1.086	1.069	1.103	<0.0001
		Formoterol 4.5 µg bid vs Placebo	1.086	1.069	1.103	<0.0001
		Formoterol 9 µg bid vs 4.5 µg bid	1.000	0.984	1.016	0.9840
FVC (L)	60 minutes post-dose	Formoterol 9 µg bid vs Placebo	1.066	1.041	1.092	<0.0001
		Formoterol 4.5 µg bid vs Placebo	1.072	1.047	1.098	<0.0001
		Formoterol 9 µg bid vs 4.5 µg bid	0.994	0.971	1.018	0.6420
	Pre-dose	Formoterol 9 µg bid vs Placebo	1.018	0.995	1.042	0.1345
		Formoterol 4.5 µg bid vs Placebo	1.026	1.003	1.050	0.0259
		Formoterol 9 µg bid vs 4.5 µg bid	0.992	0.969	1.015	0.4829
	5 minutes post-dose at Visit 3	Formoterol 9 µg bid vs Placebo	1.067	1.049	1.084	<0.0001
		Formoterol 4.5 µg bid vs Placebo	1.067	1.050	1.084	<0.0001
		Formoterol 9 µg bid vs 4.5 µg bid	1.000	0.984	1.016	0.9820

Baseline: Pre-dose at Visit 3
ANCOVA: Multiplicative model including country and treatment as fixed factors, and log (baseline value) as covariate

G-mean of ratio to baseline (%) of FEV_1 and FVC at 60 minutes post-dose is shown in Figure S 2. The G-mean of ratio to baseline of FEV_1 and FVC at 60 minutes post-dose for formoterol 4.5 µg and 9 µg bid showed a larger increase than placebo throughout the treatment period.

Figure S 2 G-mean of ratio to baseline (%) of FEV_1 (L) and FVC (L) at 60 minutes post-dose over time (FAS)

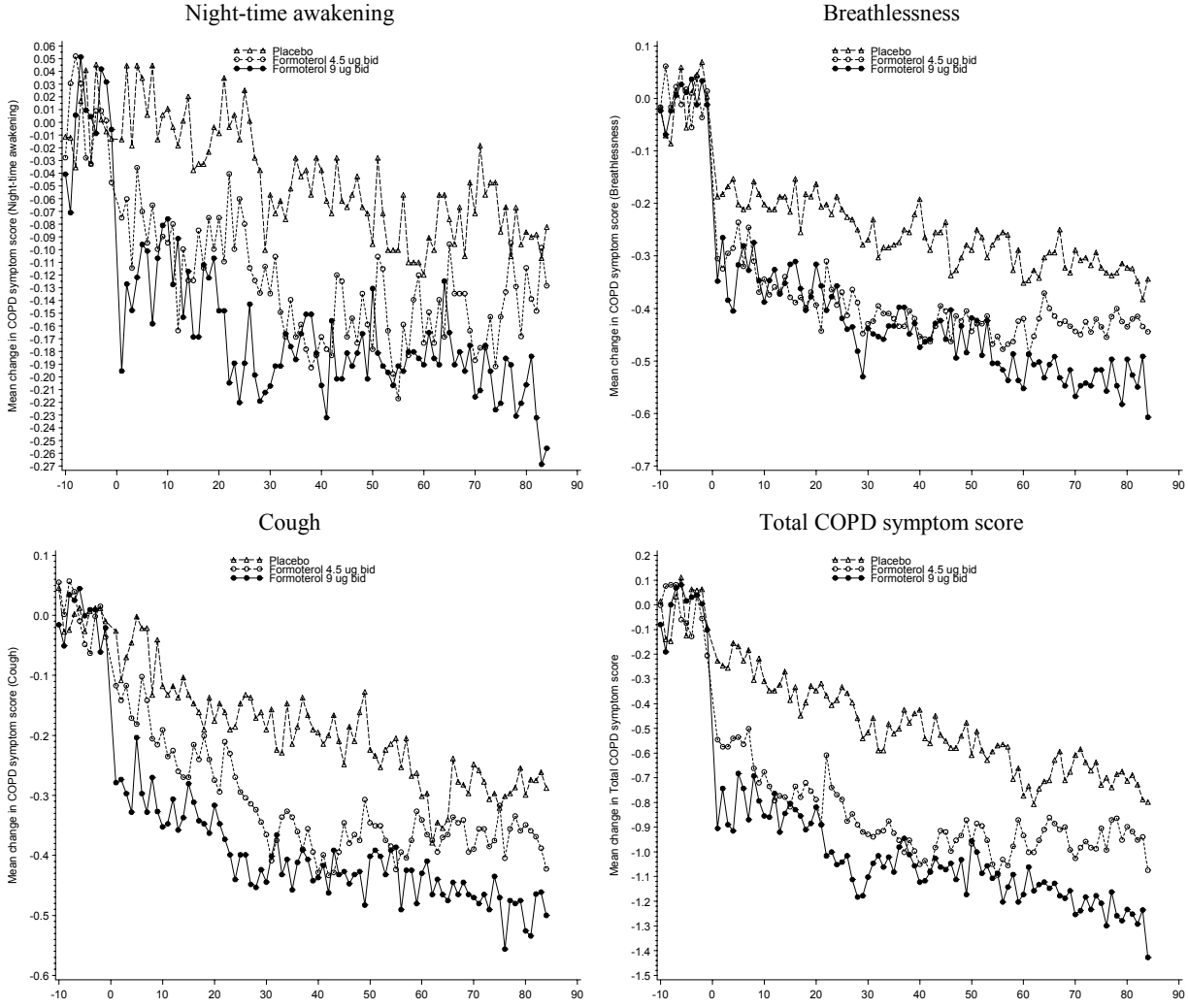


The values with imputation were summarised.

The increases in mPEF and ePEF were statistically significantly greater in formoterol 4.5 µg and 9 µg bid than in placebo. There was no statistically significant difference in changes in mPEF and ePEF between formoterol 4.5 µg and 9 µg bid.

Mean changes in COPD symptom score (night-time awakening, breathlessness, cough and total COPD symptom score) are shown in Figure S 3. The mean changes in COPD symptom score (night-time awakening, breathlessness, cough and total COPD symptom score) for formoterol 4.5 µg and 9 µg bid showed a larger decrease than placebo throughout the treatment period.

Figure S 3 **Mean changes from baseline in COPD symptom score (night-time awakening, breathlessness, cough and total COPD symptom score) over time (FAS)**



The values with imputation were summarised.

The results of comparison between treatment groups in use of salbutamol using ANCOVA are presented in Table S 5. The decreases in use of salbutamol were statistically significantly greater in formoterol 4.5 µg and 9 µg bid than in placebo (ANCOVA: <0.0001 in formoterol 9 µg bid vs placebo, p=0.0268 in formoterol 4.5 µg bid vs placebo). Formoterol 9 µg bid showed statistically significantly greater decrease in use of salbutamol compared to formoterol 4.5 µg bid (ANCOVA: p=0.0293).

Table S 5 Comparison between treatment groups for the change from run-in period average to treatment period average in use of salbutamol using ANCOVA (FAS)

Variable	Comparison	Adjusted difference	95% confidence interval Lower	Upper	p-value
Use of salbutamol	Formoterol 9 µg bid vs Placebo	-0.548	-0.794	-0.302	<0.0001
(times/day)	Formoterol 4.5 µg bid vs Placebo	-0.274	-0.516	-0.032	0.0268
	Formoterol 9 µg bid vs 4.5 µg bid	-0.274	-0.520	-0.028	0.0293

Run-in period average was calculated as average recorded over the last 10 days of the run-in period.
ANCOVA: Additive model including country and treatment as fixed factors, and the baseline value as covariate

The distribution of categorised changes in the SGRQ total score and the comparison between treatment groups were shown in Table S 6. Statistical significant differences in total score were observed between formoterol 9 µg bid and placebo (χ^2 test: p= 0.0004), but not observed between formoterol 4.5 µg bid and placebo (χ^2 test: p= 0.0682). Formoterol 4.5 µg and 9 µg bid improved the SGRQ total score compared to placebo with tendency for dose response as there was no statistically significant difference between formoterol 4.5 µg and 9 µg bid (χ^2 test: p= 0.0757).

Table S 6 Comparison between treatment groups for the categorised change in SGRQ total score from baseline to last available score using χ^2 test (FAS)

		Change in score from baseline [1)]			
	Treatment	Improved	Unchanged	Deteriorated	% of Improved
Total score	Placebo	85	57	64	41.3% (85/206)
	Formoterol 4.5 µg	102	64	37	50.2% (102/203)
	Formoterol 9 µg bid	113	46	32	59.2% (113/191)
χ^2 test	9 µg bid vs placebo: p=0.0004, 4.5 µg bid vs placebo: p=0.0682, 9 µg bid vs 4.5 µg: p=0.0757				

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 7. After randomisation, 96 AEs were reported for 68 of the 206 patients (33.0%) in formoterol 4.5 µg bid, 83 AEs were reported for 61 of the 199 patients (30.7%) in formoterol 9 µg bid and 98 AEs were reported for 69 of the 208 patients (33.2%) in placebo. Two deaths were reported in formoterol 4.5 µg bid. SAEs other than death were reported 4 patients (1.9%) in formoterol 4.5 µg bid, 7 patients (3.5%) in formoterol 9 µg bid and 4 patients (1.9%) in the placebo group. DAEs were reported 7 patients (3.4%) in formoterol 4.5 µg bid, 9 patients (4.5%) in formoterol 9 µg bid and 11 patients (5.3%) in the placebo group. There was no OAE identified in this study. The 3 treatment groups display a similar pattern and frequency of AEs.

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

			Formoterol			
	Placebo		4.5 µg bid		9 µg bid	
Category	n=208		n=206		n=199	
Number of patients who had an AE in each category [1)]						
Any AEs	69	(33.2%)	68	(33.0%)	61	(30.7%)
AEs with mild intensity	43	(20.7%)	53	(25.7%)	42	(21.1%)
AEs with moderate intensity	23	(11.1%)	11	(5.3%)	15	(7.5%)
AEs with severe intensity	3	(1.4%)	4	(1.9%)	4	(2.0%)
Serious AEs leading to death	0		2	(1.0%)	0	
Serious AEs other than death	4	(1.9%)	4	(1.9%)	7	(3.5%)
Discontinuations of study treatment due to AEs	11	(5.3%)	7	(3.4%)	9	(4.5%)
Other significant AEs	0		0		0	
Drug-related adverse events [3)]	7	(3.4%)	6	(2.9%)	6	(3.0%)
Total number of events [2)]						
Any AEs	98		96		83	
AEs with mild intensity	69		77		55	
AEs with moderate intensity	26		15		23	
AEs with severe intensity	3		4		5	
Death	0		2		0	
Serious AEs other than death	4		4		7	
Discontinuations of study treatment due to AEs	11		8		10	
Other significant AEs	0		0		0	
Drug-related adverse events [3)]	9		8		7	

1) Patients with multiple events in the same category were counted only once in that category. Patients with events in more than one category were counted once in each of those categories.

2) Multiple occurrence of the same event in a subject was counted only once. Multiple events in the same category were counted multiple times in that category. Multiple events belonging to more than one category were counted in each of those categories.
3) The causality was judged by the investigator.

The most commonly reported AEs (those with an incidence 0.5% on PT level in total) in the study are shown in Table S 8. The most commonly reported AEs in the study were Nasopharyngitis (formoterol 4.5 µg bid: 11.7%, formoterol 9 µg bid: 12.6%, placebo: 9.6%) and Chronic obstructive pulmonary disease (formoterol 4.5 µg bid: 4.9%, formoterol 9 µg bid: 4.0%, placebo: 8.2%). The pattern of AEs in the formoterol group was generally reflecting commonly occurring health problems in a COPD population. Overall the AE profile was similar among treatment groups.

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

			Formoterol			
	Placebo		4.5 µg bid		9 µg bid	
Preferred term [1), 2), 3)]	n=208		n=206		n=199	
NASOPHARYNGITIS	20	(9.6%)	24	(11.7%)	25	(12.6%)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	17	(8.2%)	10	(4.9%)	8	(4.0%)
BRONCHITIS	2	(1.0%)	1	(0.5%)	6	(3.0%)
PNEUMONIA	0		2	(1.0%)	3	(1.5%)
ILL-DEFINED DISORDER	2	(1.0%)	2	(1.0%)	1	(0.5%)
BACK PAIN	3	(1.4%)	0		1	(0.5%)
DIZZINESS	1	(0.5%)	2	(1.0%)	1	(0.5%)
GLUCOSE URINE PRESENT	2	(1.0%)	2	(1.0%)	0	

1) This table used a cut-off of 0.5% of patients in total.
2) A patient experiencing more than one AE within a PT was counted once within that PT.
3) MedDRA 11.1
Table was sorted by frequency of group total.

After randomisation, 2 death cases were reported in formoterol 4.5 µg (cardiopulmonary failure and death of unknown cause), however the causal relationships between these events 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 4.5 µg and 9 µg twice daily.