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ORIGINAL ARTICLE

Roflumilast in Asian patients with COPD: A randomized placebo-controlled trial

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ABSTRACT

Background and objective: **Roflumilast, an oral, selective phosphodiesterase 4 inhibitor, has been shown to reduce exacerbations and improve pulmonary function in patients with COPD. This study examined the efficacy, safety and tolerability of roflumilast in Asian patients with COPD.**

Methods: **Patients with COPD were randomized 1:1 to enter a 12-week treatment period and receive either oral roflumilast, 500 μg once daily, or placebo, following a single-blind, 4-week baseline period in which all patients received placebo. The primary end point was mean change in FEV_1 from baseline to each postrandomization visit during the treatment period. Other spirometric lung function measurements were evaluated as secondary end points. COPD exacerbations were monitored. Safety was assessed from clinical laboratory tests, vital signs, physical examination (including electrocardiogram) and monitoring of adverse events (AEs).**

Results: **Of 551 patients recruited, 410 were randomized and received at least one dose of study medication (roflumilast, $n = 203$; placebo, $n = 207$). Superiority of roflumilast over placebo was demonstrated by a statistically significant difference in postbronchodilator FEV_1 (79 mL, $P < 0.0001$). Other spirometry end points, including prebronchodilator FEV_1, pre-and postbronchodilator FEV_6, forced vital capacity and peak expiratory flow significantly favoured roflumilast over placebo. AEs were more common with roflumilast than with placebo, but were comparable with those reported in previous studies.**

Conclusions: **Roflumilast, 500 μg once daily, improves pulmonary function in Asian patients with COPD. The safety and tolerability of roflumilast in this population was similar to that in a Caucasian population.**

SUMMARY AT A GLANCE

Roflumilast (500 μg once daily for 12 weeks vs placebo) significantly improved lung function in Asian patients with moderate to severe COPD. Treatment was well tolerated, and no safety/tolerability issues specific to ethnicity were raised. These clinical findings add to those from previous studies of roflumilast in Caucasian patients.

Key words: Asia, chronic obstructive pulmonary disease, phosphodiesterase 4 inhibitor, roflumilast.

INTRODUCTION

COPD represents a major healthcare burden, and is predicted to become the third leading cause of death worldwide in 2030.[1] Several large epidemiological

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studies have been conducted in China, Hong Kong, Taiwan, Japan, Korea and Thailand, and have reported a COPD prevalence of 2.5–10.9%.[2–7] In general, men are affected more than women. Given the high prevalence of tobacco smoking, exposure to aerial pollutants and the aging population in many Asian countries, the burden of COPD is estimated to be several folds higher than in Western countries.[8] Current treatment for COPD usually encompasses pharmacologic therapy, such as long-acting inhaled bronchodilators, coupled with smoking cessation. In Asian countries, oral bronchodilators are commonly used—a reflection of general patient preference for oral over inhaled therapies.[8] Current treatment options are far from ideal, however, and there are continuing efforts to improve treatment strategies, either by developing new therapies or by investigating more closely the subgroups of patients with COPD who might benefit from targeted treatment regimens.[9–11]

Phosphodiesterase 4 (PDE4), a member of the PDE enzyme superfamily that inactivates cyclic adenosine monophosphate and cyclic guanosine monophosphate, is the main PDE isoenzyme occurring in cells involved in inflammatory airway disease.[12] Roflumilast is an oral, potent and selective inhibitor of PDE4, and has a half-life compatible with once-daily dosing.[13] Preclinical studies have shown that roflumilast inhibits the release of mediators from activated inflammatory cells,[14,15] and a clinical study found a significant reduction in the absolute number of neutrophils and eosinophils in induced sputum compared with placebo.[16]

In two early phase III studies, roflumilast was associated with significant improvements in lung function and quality of life in patients with moderate to severe[17] and severe COPD,[18] when compared with placebo. Recently, two 12-month, phase III studies of patients with severe or very severe COPD, and a history of exacerbations and chronic bronchitis, demonstrated that roflumilast significantly improved lung function and significantly reduced the exacerbation rate.[10] In addition, two 6-month, phase III studies reported improved lung function and reduced exacerbation frequency with roflumilast in patients with moderate to severe COPD also receiving long-acting β_2 agonists or long-acting inhaled anti-muscarinic agents.[11]

This placebo-controlled study investigated the effect of roflumilast, 500 μg once daily, on pulmonary function in patients with COPD recruited at centres in the Asia-Pacific region. The safety and tolerability of roflumilast were also assessed.

METHODS

Patients and study design

This phase III, randomized, double-blind, placebo-controlled, parallel-group trial (M2-119, ClinicalTrials.gov identifier NCT00242320) was performed in 32 outpatient centres in Hong Kong, Malaysia, the Philippines, South Korea and Taiwan. The study was approved by the Institutional Review Board or Independent Ethics Committee according to local arrangements (see Supporting Information Table S1 in the online supporting information for a list of committee names and approval numbers), and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The study population comprised adults aged 40 years or older with a history of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[19] Key inclusion and exclusion criteria are shown in Table 1.

A single-blind, 4-week run-in period was followed by a double-blind, 12-week treatment period, which included study visits at 4, 8 and 12 weeks, plus an additional safety follow-up when necessary. Disallowed medications (Table 1) were withdrawn on study entry. At the end of the run-in period, patients were entered into the treatment period if they had not experienced any moderate or severe COPD exacerbations during this period and were in compliance with medication treatment (defined as ≥80% and ≤125%). Patients were stratified according to smoking status (i.e. current smokers/former smokers) and then assigned randomly 1:1 to receive oral roflumilast, 500 μg once daily or placebo once daily, using a computer-generated randomization list.

Lung function tests

Pre-and postbronchodilator lung function tests were performed at the start of the run-in period to determine eligibility, and repeated at baseline and during the treatment period at 4, 8 and 12 weeks. The variables measured were FEV_1, FEV_6, FVC, FEV_1/FVC, mean $FEF_{25–75\%}$ and PEF. Lung function testing was performed according to guidelines set out by the American Thoracic Society.[20]

Other investigations and monitoring

Other assessments included medication history, routine physical examination, chest radiograph, resting 12-lead ECG, standard laboratory investigations (Hb and blood biochemistry, pregnancy test where appropriate, and urinalysis), vital signs, and smoking status.

If a patient experienced a severe exacerbation or two moderate exacerbations during the treatment period, the patient was withdrawn from the study.

Patients who completed the study with reported ongoing adverse events (AEs) returned to the study centre for one or more follow-up visit(s).

Study end points

The primary end point was the mean (least-squares mean adjusted for covariates (LSMean)) change in postbronchodilator FEV_1 from baseline to each post-randomization visit during the treatment period.

Table 1 Inclusion and main exclusion criteria

Inclusion criteria (for baseline period)	Exclusion criteria
• Age ≥ 40 years • History of COPD as defined by the GOLD criteria[19] • Postbronchodilator FEV_1/FVC ratio ≤ 70% • Postbronchodilator FEV_1, 30–80% predicted • Fixed airway obstruction (i.e. FEV_1 increase of ≤15% and/or ≤200 mL after receiving salbutamol, 400 μg) • Current smoker or former smoker with at least 10-pack-year history • Clinically stable COPD within 4 weeks prior to baseline visit V0 Medication allowed: • Salbutamol supplied by sponsor as rescue medication according to the patient's individual needs • Short-acting anticholinergics at a constant daily dosage as concomitant medication if already taken on a regular basis at a constant dosage for at least 4 weeks prior to the study • Other drugs for the treatment of concurrent diseases (with consistent dosage throughout study) • Vaccination	• COPD exacerbation indicated by treatment with systemic glucocorticosteroids not stopped, or lower respiratory tract infection not resolved, 4 weeks prior to the baseline visit V0 • Diagnosis of asthma and/or other relevant lung disease except COPD • Known α_1-antitrypsin deficiency • Need for long-term oxygen therapy (≥16 h/day) • Clinically relevant abnormal laboratory values, known infection with HIV, active hepatitis and/or liver insufficiency, diagnosis or history of cancer or clinically significant cardiopulmonary abnormalities not related to COPD • Pregnancy or breast feeding • Female patients of childbearing potential unwilling to use effective contraception • Participation in another study within 30 days of study start • Alcohol or drug abuse, or use of the following: theophylline; inhaled glucocorticosteroids; any short-acting β_2-agonist (with exception of salbutamol as supplied); inhaled long-acting β_2-agonists or oral β_2-agonists; inhaled long-acting anticholinergics; combination of anticholinergics with short-acting β_2-agonists; lipoxygenase inhibitors, leukotriene antagonists; inhaled and oral cromones; systemic glucocorticosteroids (with an exception for a moderate exacerbation between baseline and week 12) • Suspected hypersensitivity to study or rescue medication

GOLD, Global Initiative for Chronic Obstructive Lung Disease.

The key secondary efficacy end point was the LSMean change in prebronchodilator FEV_1 from baseline to each postrandomization visit. Other secondary end points included change in other lung function measures (pre- and postbronchodilator), time to COPD exacerbation (a moderate exacerbation was defined as one requiring an oral glucocorticosteroid (e.g. prednisolone ≤ 40 mg/day, over 7–10 days) and/or antibiotics; a severe exacerbation was one requiring hospitalization), the proportion of patients experiencing an exacerbation, and time to study withdrawal.

The safety end points were AEs, clinical laboratory investigations, vital signs and physical examinations (including ECG).

Statistical analysis

Primary, key secondary and other secondary end points were analysed using repeated-measures analysis of covariance (ANCOVA) for all visits from baseline to the final scheduled visit at week 12. Additionally, supportive analyses were performed using an ANCOVA model with the last observation carried forward (LOCF). All statistical analyses were carried out using SAS for Windows XP, Release 9.1.3 (SAS Institute, Cary, NC, USA) or PROC StatXact (for nonparametric analyses) for SAS (Version 6.2).

Primary and key secondary end points were tested in an a priori order, such that superiority of roflumilast over placebo was first demonstrated for postbronchodilator FEV_1 before prebronchodilator FEV_1. The intention-to-treat (ITT) analyses were the primary analyses. The ITT population comprised patients who received at least one dose of treatment after randomization. The per-protocol (PP) analyses were used to assess the robustness of the results; the PP population comprised patients in the ITT population who had no documented major study protocol violations.

Determination of sample size

The primary analysis model used was the repeated-measures ANCOVA, with a one-sided significance level of 2.5%, a sample size of 195 patients per treatment group, and 96% power. The following assumptions were made: compound symmetry structure with equal variance (common SD = 230 mL) for all time points and both treatments, equal correlation of 0.6 between all pairs of time points for each patient, and changes from baseline normally distributed. The estimate of the treatment effect was based on clinical considerations, whereas data from previous clinical studies on roflumilast were used for estimating SD

and correlation. The sample size calculation for the repeated-measures ANCOVA model was performed according to Chow *et al.*[21]

RESULTS

Patients

The study was undertaken between 31 August 2005 and 13 March 2007. Altogether, 551 patients were recruited; 411 were randomized to receive roflumilast 500 μg once daily, or placebo. A total of 410 patients received at least one dose of the study medication (roflumilast, $n = 203$; placebo, $n = 207$), and were included in the ITT analyses. Of these, 352 patients completed the study (Fig. 1). Major protocol violations occurred more commonly in the group receiving roflumilast (21.6%, 44/204) compared with the placebo group (14.5%, 30/207).

Baseline and demographic characteristics of the patients were similar between groups (Table 2). Randomized patients were all of Asian origin, aged 41–91 years (median 67 years), with a history of

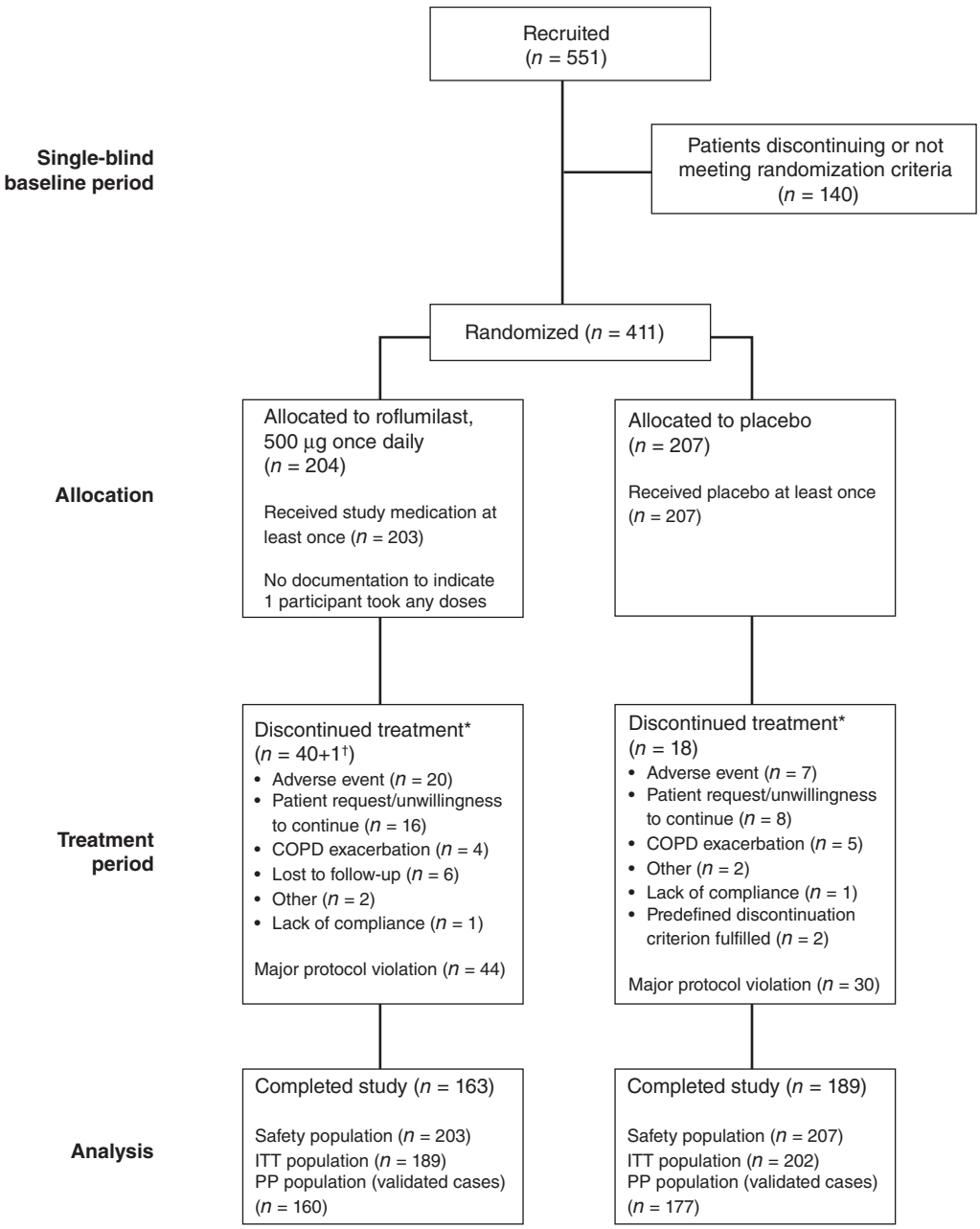

Figure 1 Patient numbers at different stages of the study. *Some patients had more than one reason reported for discontinuing treatment. Discontinuation reasons are given as specified at the termination of the study. †The numbers reported for each reason include the one patient lost to follow-up immediately after randomization.

Table 2 Demographics and baseline characteristics (full analysis set)

Variable†	Roflumilast (*N* = 203)	Placebo (*N* = 207)
Age (years): median (range)	68 (41–91)	67 (41–84)
Height (cm): mean (SD)	163 (8)	163 (7)
Weight (kg): mean (SD)	60 (12)	59 (10)
Body mass index (kg/m^2): mean (SD)	22.39 (3.7)	22.14 (3.4)
Gender, *n* (%)‡		
Male	188 (92.6)	195 (94.2)
Female	15 (7.4)	12 (5.8)
Asian race, *n* (%)‡	203 (100.0)	207 (100.0)
COPD severity, *n* (%)‡		
Very severe	12 (5.9)	14 (6.8)
Severe	75 (36.9)	73 (35.3)
Moderate	106 (52.2)	104 (50.2)
Mild	10 (4.9)	16 (7.7)
Smoking status, *n* (%)‡		
Current	69 (34.0)	69 (33.3)
Former	134 (66.0)	138 (66.7)
Pack-years§: mean (SD)	42 (22.1)	45 (28.9)
Prebronchodilator FEV_1 (L): mean (SD)	1.29 (0.4)	1.28 (0.5)
Postbronchodilator FEV_1 (L): mean (SD)	1.41 (0.5)	1.40 (0.5)
Prebronchodilator FEV_1 (% of predicted): mean (SD)	50.6 (16.3)	50.3 (16.3)
Postbronchodilator FEV_1 (% of predicted): mean (SD)	55.1 (16.5)	54.9 (16.8)
FEV_1 reversibility (mL): mean (SD)	119.21 (131.3)	119.28 (135.1)
FEV_1 reversibility (% increase): mean (SD)	10.3 (11.8)	10.8 (13.9)
Postbronchodilator FEV_1/FVC (% increase): mean (SD)	50.5 (11.8)	49.3 (11.2)

† FEV_1 measurements were taken at baseline; all other measurements were recorded at the beginning of the run-in period.

‡ Percentages are based on the number of patients in the respective treatment group.

§ Pack-years = duration of smoking history (years) × average number of cigarettes per day/20.

N, number of patients in the respective treatment group; *n*, number of patients in the respective category; SD, standard deviation.

smoking. The patients were predominantly male (93%). All patients had COPD, which was mostly moderate (51%) or severe (36%).

During the treatment period, compliance was high in both treatment groups: mean compliance was 92.3% for roflumilast and 96.9% for placebo (ITT populations).

Primary end point

The LSMean postbronchodilator FEV_1 increased at the final scheduled visit by 52 mL for patients receiving roflumilast but decreased by 27 mL for placebo (Table 3). A statistically significant between-treatment difference of 79 mL demonstrated the superiority of roflumilast for improving postbronchodilator FEV_1 in patients with COPD ($P < 0.0001$). Similar analyses of data from the PP population (between-treatment difference of 68 mL, $P < 0.0001$) and including the LOCF method confirmed the superiority of roflumilast over placebo. Differences in postbronchodilator FEV_1 between roflumilast- and placebo-treated patients were observed after 4 weeks of treatment and remained to the end of the study (Fig. 2a). The difference from baseline in LSMean FEV_1 between roflumilast and placebo groups was 81 mL (95% confidence interval (CI): 48–114 mL; $P < 0.0001$) at week 4, 61 mL (95% CI: 24–99 mL; $P < 0.0007$) at week 8, and 97 mL (95% CI: 55–138 mL; $P < 0.0001$) at the final scheduled visit.

Exploratory subgroup analyses indicated that the improvements were independent of concomitant short-acting cholinergic treatment, COPD severity or smoking status.

Secondary spirometry end points

The LSMean prebronchodilator FEV_1 increased from baseline by 54 mL for roflumilast but decreased by 42 mL for placebo (Table 3). A statistically significant between-treatment difference of 95 mL demonstrated the superiority of roflumilast over placebo ($P < 0.0001$) in the ITT population; this was confirmed by PP analysis. Differences in prebronchodilator FEV_1 between roflumilast- and placebo-treated patients were also observed after 4 weeks of treatment and remained to the end of the study (Fig. 2b). The difference from baseline in LSMean FEV_1 between roflumilast and placebo groups was 88 mL (95% CI: 51–124 mL; $P < 0.0001$) at week 4, 85 mL (95% CI: 47–123 mL;

Table 3 Within- and between-treatment differences in expiratory variables from baseline to the final scheduled visit (repeated-measurements analyses; ITT population)

Measurement	Within-treatment difference (L) LSMean (SE) (95% CI)	Between-treatment difference LSMean (SE) (95% CI)	*P*-value[†]
Prebronchodilator			
FEV_1 (mL)			
Roflumilast ($n = 189$)	54 (21) (13, 94)	95 (16) (63, 127)	<0.0001
Placebo ($n = 201$)	−42 (21) (−82, −1)		
FEV_6 (mL)			
Roflumilast ($n = 189$)	59 (30) (0, 117)	148 (22) (104, 192)	<0.0001
Placebo ($n = 201$)	−89 (29) (−147, −32)		
FVC (mL)			
Roflumilast ($n = 189$)	51 (35) (−17, 120)	151 (26) (101, 202)	<0.0001
Placebo ($n = 202$)	−100 (34) (−168, −33)		
$FEF_{25–75\%}$ (mL/s)			
Roflumilast ($n = 189$)	−71 (40) (−150, 7)	54 (31) (−7, 116)	0.0837
Placebo ($n = 202$)	−126 (40) (−204, −47)		
PEF (mL/min)			
Roflumilast ($n = 189$)	3060 (4490) (−11 880, 5760)	10,130 (3450) (3340, 16,920)	0.0036
Placebo ($n = 202$)	−13,190 (4480) (−21 990, −4380)		
Postbronchodilator			
FEV_1 (mL)			
Roflumilast ($n = 189$)	52 (20) (13, 91)	79 ± 16 (48, 110)	<0.0001
Placebo ($n = 202$)	−27 (20) (−66, 12)		
FEV_6 (mL)			
Roflumilast ($n = 188$)	32 (27) (−22, 85)	111 (20) (71, 151)	<0.0001
Placebo ($n = 201$)	−79 (27) (−133, −26)		
FVC (mL)			
Roflumilast ($n = 189$)	24 (32) (−141, −19)	104 (23) (59, 149)	<0.0001
Placebo ($n = 202$)	−80 (31) (−141, −19)		
$FEF_{25–75\%}$ (mL/s)			
Roflumilast ($n = 189$)	44 (18) (8, 80)	44 (14) (15, 72)	0.0026
Placebo ($n = 202$)	0 (18) (−36, 36)		
PEF (mL/min)			
Roflumilast ($n = 189$)	−530 (5080) (−10 500, 9450)	9360 (3910) (1680, 17,040)	0.0170
Placebo ($n = 202$)	−9890 (5060) (−19 840, 50)		

[†] Statistical significance taken as $P < 0.05$ for the two-sided test.
ITT, intention-to-treat; LSMean, least-squares mean adjusted for covariates.

$P < 0.0001$) at week 8, and 116 mL (95% CI: 74–157 mL; $P < 0.0001$) at the final scheduled visit.

In the roflumilast group, a within-treatment improvement was observed for all pre- and postbronchodilator expiratory lung-function secondary variables except for prebronchodilator $FEF_{25–75\%}$ and pre- and postbronchodilator PEF (Table 3). In the placebo group, a within-treatment decrease was observed for all pre- and postbronchodilator variables assessed, with the exception of postbronchodilator $FEF_{25–75\%}$, which remained unchanged. Statistically significant between-treatment differences that favoured roflumilast over placebo were observed for all pre- and postbronchodilator secondary variables, with the exception of prebronchodilator $FEF_{25–75\%}$.

COPD exacerbations

Ten (4.9%) patients in the roflumilast group and 15 (7.2%) patients in the placebo group experienced at least one moderate exacerbation. Four (2.0%) patients in the roflumilast group and 3 (1.4%) patients in the placebo group experienced at least one severe exacerbation. Mean (SD) time to onset of the first moderate or severe exacerbation was 32.7 (23.2) days for roflumilast ($n = 14$) and 37.9 (25.7) days for placebo ($n = 17$).

Time to discontinuation of study

The numbers of patients discontinuing the study are shown in Figure 1. Overall, the number of patients discontinuing the study was relatively low. The risk for early study discontinuation was higher for patients in the roflumilast group compared with placebo; Cox proportional hazards regression analysis showed a hazard ratio of 2.35 (95% CI: 1.32–4.18). The risk of early study discontinuation because of one or more AEs was also higher for patients in the roflumilast

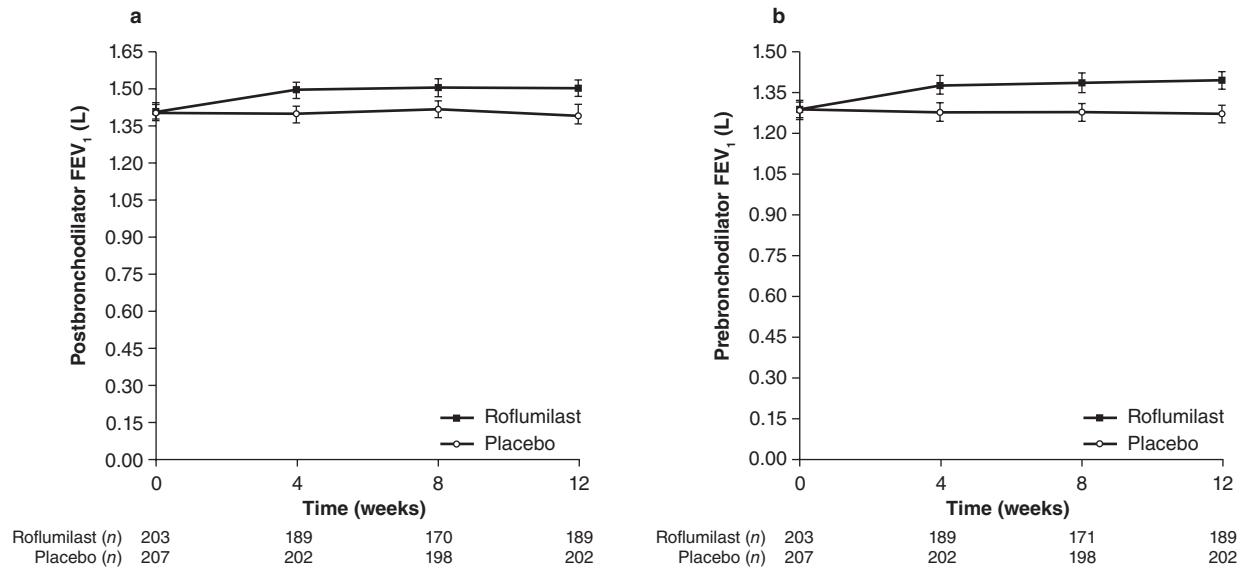

Figure 2 Postbronchodilator (a) and prebronchodilator (b) mean (SE) FEV_1 values from baseline to last visit (last observation carried forward) with roflumilast and placebo.

group compared with placebo (hazard ratio, 3.19 (95% CI: 1.27–8.01)).

Safety analysis

During the treatment period, 310 AEs were reported in 134 (66.0%) patients receiving roflumilast and 147 in 90 (43.5%) patients receiving placebo. Overall, COPD (including exacerbations) was the most frequent treatment-emergent AE in both study groups (Table 4). Upper respiratory tract infections were the most frequent AE in patients receiving roflumilast, followed by diarrhoea and weight decrease. Eleven roflumilast-treated patients reported weight decrease as an AE, although none was severe. With the exception of COPD (including exacerbations), the rates of treatment-emergent AEs were higher for roflumilast than placebo.

Three patients died during the study: one patient died from acute respiratory failure and aggravated COPD during the placebo run-in phase, and two patients receiving roflumilast died during the treatment period, one from pneumonia and one from atrial fibrillation, acute respiratory failure, pneumonia and sepsis. No AE leading to death was considered causally related to study medication by either the investigators or the sponsor. Serious AEs (SAEs) were reported for 18 (8.9%) patients receiving roflumilast and 6 (2.9%) patients receiving placebo (for individual events see footnote to Table 4). The rate of AE-related withdrawals was higher for roflumilast than placebo (18 (8.9%) patients vs 6 (2.9%) patients). The number of patients with treatment-emergent AEs judged to be likely or definitely related to study medication was 47 (23.2%) for roflumilast and 11 (5.3%) for placebo.

The mean decrease in body weight from baseline to final study visit was 1.6 kg for roflumilast versus no change for placebo (LSMean, −1.57 kg; two-sided $P < 0.0001$).

Physical examinations and routine laboratory tests (including ECG) did not reveal any clinically relevant changes associated with administration of the study medication.

DISCUSSION

Our data demonstrate that roflumilast significantly increased postbronchodilator FEV_1 compared with placebo in Asian patients with COPD. Similar improvements occurred with roflumilast in other measures of lung function: prebronchodilator FEV_1, pre- and postbronchodilator FEV_6, FVC and PEF. The effect of roflumilast on pulmonary function reported here is in accordance with findings from other phase III studies.[10,11,17,18] Improved lung function was observed within 4 weeks of roflumilast treatment and these benefits were maintained throughout the study.

More than 90% of patients in both groups completed the 12-week treatment period without experiencing a COPD exacerbation. However, in this study a history of exacerbations was not required for inclusion, and the majority of patients had moderate rather than severe COPD. Taken together with the low number of exacerbations reported, this limits the conclusions that can be drawn from these results. Consequently, the effect of roflumilast on exacerbation rate could not be evaluated in this trial.

The results of safety assessments are in line with those reported in other roflumilast studies.[10,11,17,18] The AEs frequently reported in roflumilast-treated patients were mainly gastrointestinal: diarrhoea, weight loss, decreased appetite and anorexia. Although COPD exacerbation was the most frequent SAE, similar numbers of patients were affected in both treatment groups ($n = 3$). With the exception of pneumonia and anorexia, all other SAEs occurred only once. Overall, the rates of treatment-emergent

Table 4 Incidence of adverse events affecting at least 3% of patients in a treatment group (safety set)

MedDRA system organ class[†] preferred term	Roflumilast ($N = 203$)		Placebo ($N = 207$)	
	n (%)[‡]	Number of events	*n* (%)[†]	Number of events
Overall incidence of events	134 (66.0)	310	90 (43.5)	147
COPD[§]	22 (10.8)	26	23 (11.1)	27
Upper respiratory tract infection	27 (13.3)	31	15 (7.2)	16
Diarrhoea	23 (11.3)	24	1 (0.5)	1
Weight decreased	11 (5.4)	11	1 (0.5)	1
Nasopharyngitis	7 (3.4)	8	4 (1.9)	5
Decreased appetite	10 (4.9)	10	1 (0.5)	1
Anorexia	10 (4.9)	10	0 (0.0)	0
Dizziness	7 (3.4)	7	3 (1.4)	3
Pneumonia	6 (3.0)	6	3 (1.4)	3
Headache	7 (3.4)	7	1 (0.5)	1
Gastritis	6 (3.0)	6	2 (1.0)	2

[†] Adverse events are listed by decreasing frequency based on the sum of the numbers of patients in both groups in which the adverse event occurred.

[‡] Percentages are based on the number of patients in the respective treatment group.

[§] MedDRA version 10.0 assigns COPD exacerbation to the preferred term 'chronic obstructive pulmonary disease'.

NB: Serious adverse events were reported for 18 (8.9%) patients receiving roflumilast (cerebrovascular accident, congestive cardiac failure, small intestine carcinoma, irritable bowel syndrome, upper respiratory tract infection, acute cholecystitis, benign prostatic hyperplasia, duodenitis, diarrhoea, inguinal hernia, acute myocardial infarction, gastric cancer, nausea, pneumonia ($n = 1$ for each), anorexia ($n = 2$), COPD ($n = 3$)) and 6 (2.9%) patients receiving placebo (intestinal obstruction ($n = 1$), arteriosclerosis ($n = 1$), pneumonia ($n = 2$), COPD ($n = 3$)).

MedDRA, Medicinal Dictionary for Regulatory Activities; *N*, number of patients in the respective treatment group; *n*, number of patients with at least one event in the specified category.

AEs and SAEs were higher for roflumilast than placebo (66.0% vs 43.5% for AEs; 8.9% vs 2.9% for SAEs), Similarly, the number of patients with treatment-emergent AEs judged to be likely or definitely related to study medication was higher for roflumilast (23.2% vs 5.3% for placebo), as was the risk of early study discontinuation due to AEs (hazard ratio = 3.19 compared with placebo). The majority of AEs occurred in the first 4 weeks of roflumilast treatment, in line with longer-term studies of roflumilast.[10]

As previously mentioned, one of the limitations of this study is that it was not powered to evaluate treatment effects on COPD exacerbations. Although previous trials have demonstrated that roflumilast has beneficial effects on exacerbation rates,[10] these findings cannot be confirmed based on the results presented here. Another limitation is that concomitant treatment with long-acting bronchodilators or inhaled corticosteroids was not permitted during the study, meaning that the findings are not directly in context with the GOLD treatment algorithm. However, data from two recent pooled analyses of previous studies have shown that the concomitant use of long-acting bronchodilators or previous ICS use do not alter the beneficial effects of roflumilast or its safety and tolerability profile.[22,23]

In conclusion, roflumilast effectively improved lung function in Asian patients with pre-existing COPD, in the absence of other medication except for salbutamol as rescue therapy or short-acting anticholinergic agents. The safety and tolerability profile of roflumilast was consistent with other clinical studies comprising patients with moderate to severe COPD of wider ethnic distribution, and does not suggest any effects specific to the Asian patient population.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1 List of Independent Review Boards (IRBs)/ Independent Ethics Committees (IECs).

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