

Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials



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Summary

Background The phosphodiesterase-4 inhibitor roflumilast can improve lung function and prevent exacerbations in certain patients with chronic obstructive pulmonary disease (COPD). We therefore investigated whether roflumilast would reduce the frequency of exacerbations requiring corticosteroids in patients with COPD.

Methods In two placebo-controlled, double-blind, multicentre trials (M2-124 and M2-125) with identical design that were done in two different populations in an outpatient setting, patients with COPD older than 40 years, with severe airflow limitation, bronchitic symptoms, and a history of exacerbations were randomly assigned to oral roflumilast (500 µg once per day) or placebo for 52 weeks. Primary endpoints were change in prebronchodilator forced expiratory volume in 1 s (FEV₁) and the rate of exacerbations that were moderate (glucocorticosteroid-treated) or severe. Analysis was by intention to treat. The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Findings Patients were assigned to treatment, stratified according to smoking status and treatment with longacting β₂ agonists, and given roflumilast (n=1537) or placebo (n=1554). In both studies, the prespecified primary endpoints were achieved and were similar in magnitude. In a pooled analysis, prebronchodilator FEV₁ increased by 48 mL with roflumilast compared with placebo (p<0·0001). The rate of exacerbations that were moderate or severe per patient per year was 1·14 with roflumilast and 1·37 with placebo (reduction 17% [95% CI 8–25], p<0·0003). Adverse events were more common with roflumilast (1040 [67%]) than with placebo (963 [62%]); 219 (14%) patients in the roflumilast group and 177 (12%) in the placebo group discontinued because of adverse events. In the pooled analysis, the difference in weight change during the study between the roflumilast and placebo groups was –2·17 kg.

Interpretation Since different subsets of patients exist within the broad spectrum of COPD, targeted specific therapies could improve disease management. This possibility should be explored further in prospective studies.

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Introduction

Chronic obstructive pulmonary disease (COPD) is increasing in prevalence; it is associated with periodic exacerbations, resulting in patient anxiety,¹ worsening health status, lung function decline, and increase in mortality rate.^{2–4} Effective management involves pharmacological and non-pharmacological treatments.⁵ Longacting inhaled bronchodilator drugs (β₂ agonists and anticholinergic drugs) can improve health status and reduce the frequency of exacerbations, effects that are greater when longacting β₂ agonists are used in combination with inhaled corticosteroids.^{6–9} However, there is a need for further improvement of COPD therapy.

Phosphodiesterase-4 (PDE4) inhibition provides a novel approach to the treatment of COPD. Drugs that inhibit PDE4 have a wide range of anti-inflammatory actions in vitro and in vivo.^{10–12} Roflumilast, a new PDE4 inhibitor, reduces airway inflammation in COPD, as assessed with sputum neutrophil and eosinophil counts.¹³ However, although roflumilast improved lung function, it did not significantly reduce the frequency of exacerbations in unselected patients with severe COPD.¹⁴ The results of a post-hoc analysis of this study suggested that roflumilast

reduced the rate of exacerbations in patients with severe airflow obstruction, frequent exacerbations, and those requiring oral steroids.¹³

To find out whether PDE4 inhibitors can have any effect on clinical outcomes in COPD, we tested the hypothesis that roflumilast reduces the rate of exacerbations requiring systemic corticosteroids in specific subsets of patients with COPD.

Methods

Setting

Study M2-124 was done in 246 centres in ten countries, and study M2-125 was done in 221 centres in eight countries (webappendix p 12).

Patients

For both studies, we recruited participants from an outpatient setting if they met inclusion criteria—ie, were former smokers or current smokers with at least a 20 pack-year history, older than 40 years, and had a clinical diagnosis of COPD (confirmed with a postbronchodilator [albuterol 400 µg] forced expiratory volume in 1 s [FEV₁]/forced vital capacity [FVC] ratio ≤70%) and chronic

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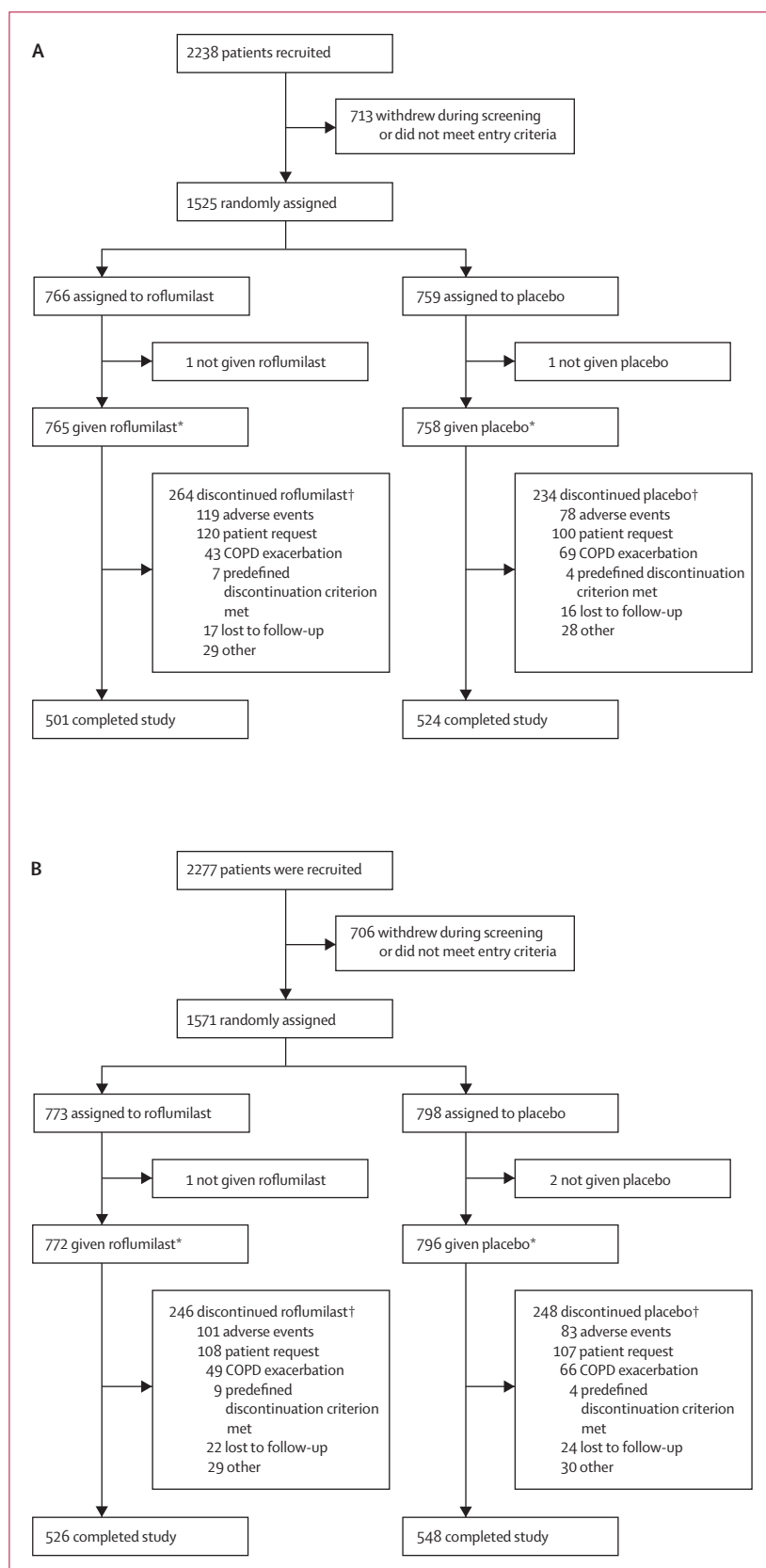
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See Online for webappendix



cough and sputum production. Their postbronchodilator FEV₁ was 50% or less than the predicted value. All patients had at least one recorded COPD exacerbation requiring systemic glucocorticosteroids or treatment in hospital, or both, in the previous year. Exclusion criteria are shown in the webappendix (p 11); use of theophylline was not allowed from the start of the run-in period.

The studies were approved by local ethical review committees and done in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. All patients provided written informed consent.

Interventions

Each trial had an initial 4-week run-in, during which patients took a placebo tablet once a day in the morning, and recorded their use of shortacting bronchodilator drugs, and production of cough and sputum on their daily diary cards (webappendix p 23). In this initial study phase, patients, but not investigators, were unaware of the treatment they were assigned to. Patients were then randomly assigned to oral roflumilast 500 µg once a day or placebo, taken in the morning for the subsequent 52 weeks, provided that the total of their cough and sputum scores was greater than 14 in the week before randomisation, the haemocult (guaiac) test during the baseline period was negative, at least 80% of prescribed placebo tablets were taken, and patients were clinically stable. Patients could use shortacting β₂ agonists as needed and could continue treatment with longacting or shortacting anticholinergic drugs at stable doses. However, inhaled corticosteroids and longacting anticholinergic drugs were not allowed during the study. Eligible patients were stratified according to their use of longacting β₂ agonists and smoking status.

Randomisation and masking

The sponsor generated a randomisation list of patient random numbers using a pseudorandom number generator. The investigator used an automated, interactive voice response system to randomly assign patients. In the double-blind treatment phase, all individuals involved in the studies were unaware of treatment assignment—tablets were identical in appearance. The investigator or anyone at the study site was prevented from knowing the allocation sequence with code labelling. The sponsor and clinical research associate were notified if there was a clinical reason for an individual's treatment to be unmasked by the investigator with the interactive voice recognition system.

Figure 1: Trial profiles of M2-124 (A) and M2-125 (B)

COPD=chronic obstructive pulmonary disease. *In the M2-124 study, one patient was randomly assigned twice and given study medication twice. The first patient number was included in the intention-to-treat and safety analyses, whereas the second patient number was only included in the safety analysis. Four patients assigned to placebo were given roflumilast instead (at least once) and were included in the roflumilast group for safety analyses. In the M2-125 study, six patients randomly assigned to placebo were given roflumilast instead (at least once) and were included in the roflumilast group for safety analyses. †Patients might have provided more than one reason for discontinuation.

	M2-124		M2-125		M2-124 and M2-125	
	Roflumilast (n=765)	Placebo (n=758)	Roflumilast (n=772)	Placebo (n=796)	Roflumilast (n=1537)	Placebo (n=1554)
Age (years)*	64 (10)	63 (9)	64 (9)	64 (9)	64 (9)	64 (9)
Men	540 (71%)	538 (71%)	610 (79%)	648 (81%)	1150 (75%)	1186 (76%)
Cigarette pack-year*†	48 (24)	46 (23)	49 (26)	47 (24)	48 (25)	47 (23)
Smoking status*						
Current smoker	365 (48%)	361 (48%)	270 (35%)	282 (35%)	635 (41%)	643 (41%)
Former smoker	400 (52%)	397 (52%)	502 (65%)	514 (65%)	902 (59%)	911 (59%)
Prebronchodilator FEV ₁ (L)‡	1.07 (0.4)	1.06 (0.4)	0.95 (0.3)	0.98 (0.4)	1.01 (0.4)	1.02 (0.4)
Postbronchodilator FEV ₁ (L)‡	1.16 (0.4)	1.15 (0.4)	1.05 (0.4)	1.07 (0.4)	1.10 (0.4)	1.11 (0.4)
Prebronchodilator FEV ₁ (% of predicted)‡	34.7 (10.2)	34.6 (10.3)	31.4 (10.1)	32.2 (10.8)	33.0 (10.3)	33.4 (10.6)
Postbronchodilator FEV ₁ (% of predicted)‡	37.6 (10.7)	37.5 (10.4)	34.6 (10.3)	35.3 (10.9)	36.1 (10.6)	36.4 (10.7)
Postbronchodilator FEV ₁ /FVC (%)‡	43.3 (11.6)	42.7 (11.0)	41.2 (10.7)	41.3 (10.8)	42.3 (11.2)	42.0 (10.9)
COPD severity*§¶						
Severe	486 (64%)	510 (67%)	457 (59%)	479 (60%)	943 (61%)	989 (64%)
Very severe	199 (26%)	184 (24%)	264 (34%)	256 (32%)	463 (30%)	440 (28%)
Body-mass index (kg/m ²)‡	26.4 (5.5)	26.0 (5.5)	25.2 (6.2)	25.4 (5.9)	25.8 (5.9)	25.7 (5.7)
C-reactive protein (mg/L)*	8.1 (14.0)	7.2 (12.5)	8.3 (14.6)	9.2 (17.6)	8.2 (14.3)	8.2 (15.4)
Concomitant treatment with longacting β ₂ agonists	378 (49%)	385 (51%)	371 (48%)	408 (51%)	749 (49%)	793 (51%)
Concomitant treatment with shortacting anticholinergics	240 (31%)	245 (32%)	297 (38%)	324 (41%)	537 (35%)	569 (37%)
Concomitant treatment with shortacting β ₂ agonists	761 (99%)	753 (99%)	769 (100%)	791 (99%)	1530 (100%)	1544 (99%)
Pretreatment with inhaled corticosteroids**	338 (44%)	335 (44%)	312 (40%)	322 (40%)	650 (42%)	657 (42%)
Ethnic origin						
Asian	1 (<1%)	1 (<1%)	174 (23%)	179 (22%)	175 (11%)	180 (12%)
Native American	0	1 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)	2 (<1%)
Black	11 (1%)	15 (2%)	8 (1%)	14 (2%)	19 (1%)	29 (2%)
White	737 (96%)	732 (97%)	559 (72%)	568 (71%)	1296 (84%)	1300 (84%)
Other	16 (2%)	9 (1%)	29 (4%)	34 (4%)	45 (3%)	43 (3%)

Data are number (%) or mean (SD). FEV₁=forced expiratory volume in 1 s. FVC=forced vital capacity. COPD=chronic obstructive pulmonary disease. *Measurements were taken at the beginning of the run-in period. †1 pack-year=20 cigarettes per day for 1 year. ‡Measurements were taken at baseline. §Based on the criteria of the Global initiative for chronic Obstructive Lung Disease. ¶Percentages do not add up to 100% because patients with mild or moderate COPD are not shown. ||Based on whether the patient had used medications at least once within the start and up to the end of the treatment period inclusive. **Based on whether the patient had used inhaled corticosteroids at least once within the period starting the day after the first visit until the day before randomisation, inclusive.

Table 1: Demographics and baseline characteristics of the intention-to-treat populations in the M2-124 and M2-125 trials

After randomisation, patients were assessed every 4 weeks up to week 12 and every 8 weeks thereafter. At each visit, spirometric measurements were recorded before and 15–45 min after administration of bronchodilator (inhaled albuterol 400 µg). Additionally, we recorded any new exacerbations or adverse events, the patient's bodyweight, adherence to tablets, completeness of the daily diary records, use of shortacting β₂ agonists, and investigator-administered transition dyspnoea index (TDI),¹⁵ and dispensed study medication.

Study endpoints

The primary endpoints were the change in pre-bronchodilator FEV₁ during treatment and the rate of COPD exacerbations, defined as moderate if they required oral or parenteral corticosteroids, or severe if

they were associated with admission or death. Key secondary outcomes included the postbronchodilator FEV₁ (change from baseline during treatment), time to death from any cause, natural log-transformed C-reactive protein concentration (a possible marker of systemic inflammation in COPD;¹⁶ change from baseline to study end) and TDI focal score (during treatment). A change of one unit in the TDI focal score was considered clinically significant. Additionally, data for the total number of COPD exacerbations (as defined above together with episodes treated with antibiotics alone) and a range of spirometric outcomes were gathered. As part of a planned health economic analysis (data for subsequent presentation), patients completed the Euroqol 5-dimension (EQ-5D) questionnaire, a measure of health utility, at each visit.¹⁷

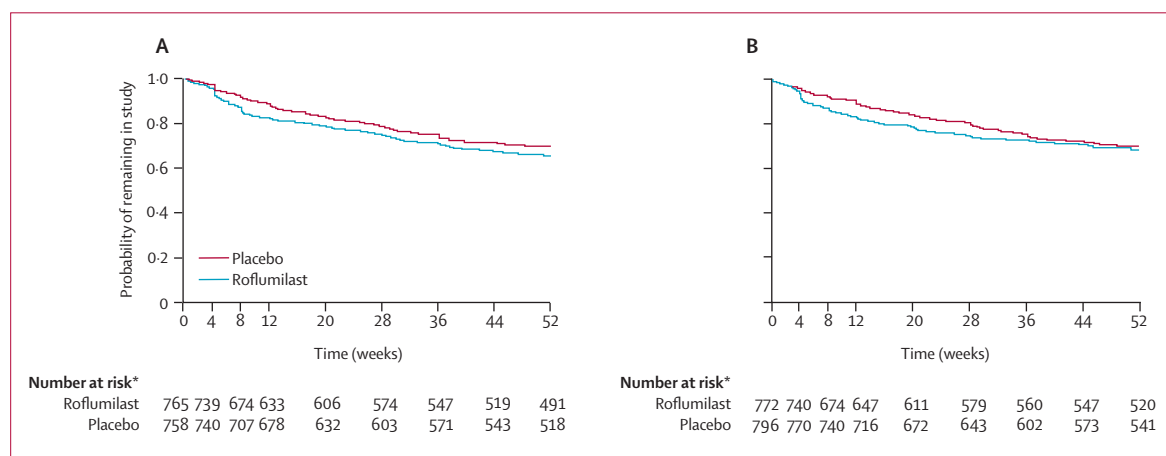


Figure 2: Probability of treatment discontinuation in roflumilast and placebo groups in trials M2-124 (A) and M2-125 (B)

*Number of patients still at risk at the beginning of the respective week; number at risk might be different from the number completing the study because the protocol allowed patients to finish the study up to 7 days before the end of week 52.

Bodyweight was measured with the same scales at each visit, height was measured with a stadiometer, and body-mass index (BMI) was calculated. At weeks 28 and 52 after randomisation, blood samples were taken for routine haematology and biochemistry tests, and an electrocardiogram (ECG) was done. In study M2-125, 24-h Holter monitoring was undertaken at 19 sites to identify any arrhythmias.

Statistical analysis

With the exception of the post-hoc investigation of adverse events and bodyweight, all reported efficacy analyses were prespecified in the intention-to-treat population. Data are presented as mean and SD, unless otherwise indicated. On the basis of an assumption of a mean exacerbation rate of 1.25 per patient per year in the placebo group and 1.00 in the roflumilast group, and using a Poisson regression model, with a correction for overdispersion of 2 based on previous data,¹⁴ we estimated that 750 patients per treatment group in each trial would provide 90% power to detect a significant difference between treatments with a two-sided α level of 0.05. A negative binomial regression analysis was done to assess the robustness of the results against the distributional assumptions.

Data were analysed in the two studies separately and in a pooled analysis. We analysed changes from baseline in prebronchodilator and postbronchodilator FEV₁ using a repeated-measures analysis of covariance with all data available for patients during the 52-week treatment.¹⁸ A Cox proportional hazard model was used to test for differences in time-to-event data. For analysis of the concentrations of C-reactive protein, an analysis of covariance model was used, with the method of the last observation carried forward for the log-transformed data for concentrations.

For the regression models (analysis of covariance, Cox, and Poisson), the covariates included treatment,

age, sex, smoking status (current or former smoker), country, and treatment with longacting β_2 agonists. In the Cox analysis, country was included as a stratum. In the Poisson regression analysis, baseline post-bronchodilator FEV₁ (% of predicted value) was also included as a covariate. To address the issue of multiple comparisons, a hierarchical hypothesis-testing approach was adopted. If the primary outcomes were positive, the key secondary outcomes were tested in the order above. If a significant difference between treatments was not obtained for the primary or key secondary outcomes, all subsequent analyses were considered exploratory. No interim analyses were done in either study before unmasking. However, several statistical analyses were preplanned and done to assess the robustness of the results with respect to the effect of differential dropouts and missing data. Adverse events were analysed with descriptive statistics and 95% CIs for the differences between treatments.

The trials are registered with ClinicalTrials.gov, number NCT00297102 for M2-124, and NCT00297115 for M2-125.

Role of the funding source

All authors (academic investigators [PMAC, KFR, LMF, and FJM] and employees of the sponsor [U-MG and SK]) had full access to and interpreted the data, and were responsible for the decision to publish the report. The sponsor did not place any restrictions on the academic authors about the statements made in the final report.

Results

Patient recruitment began in February, 2006, and the studies ended in July, 2008. In the M2-124 study, 1523 patients were randomly assigned and treated (figure 1A). In M2-125, 1568 patients were randomly assigned and treated (figure 1B). Four patients in M2-124 and six in M2-125 were given roflumilast rather than placebo and are included in the treated group for

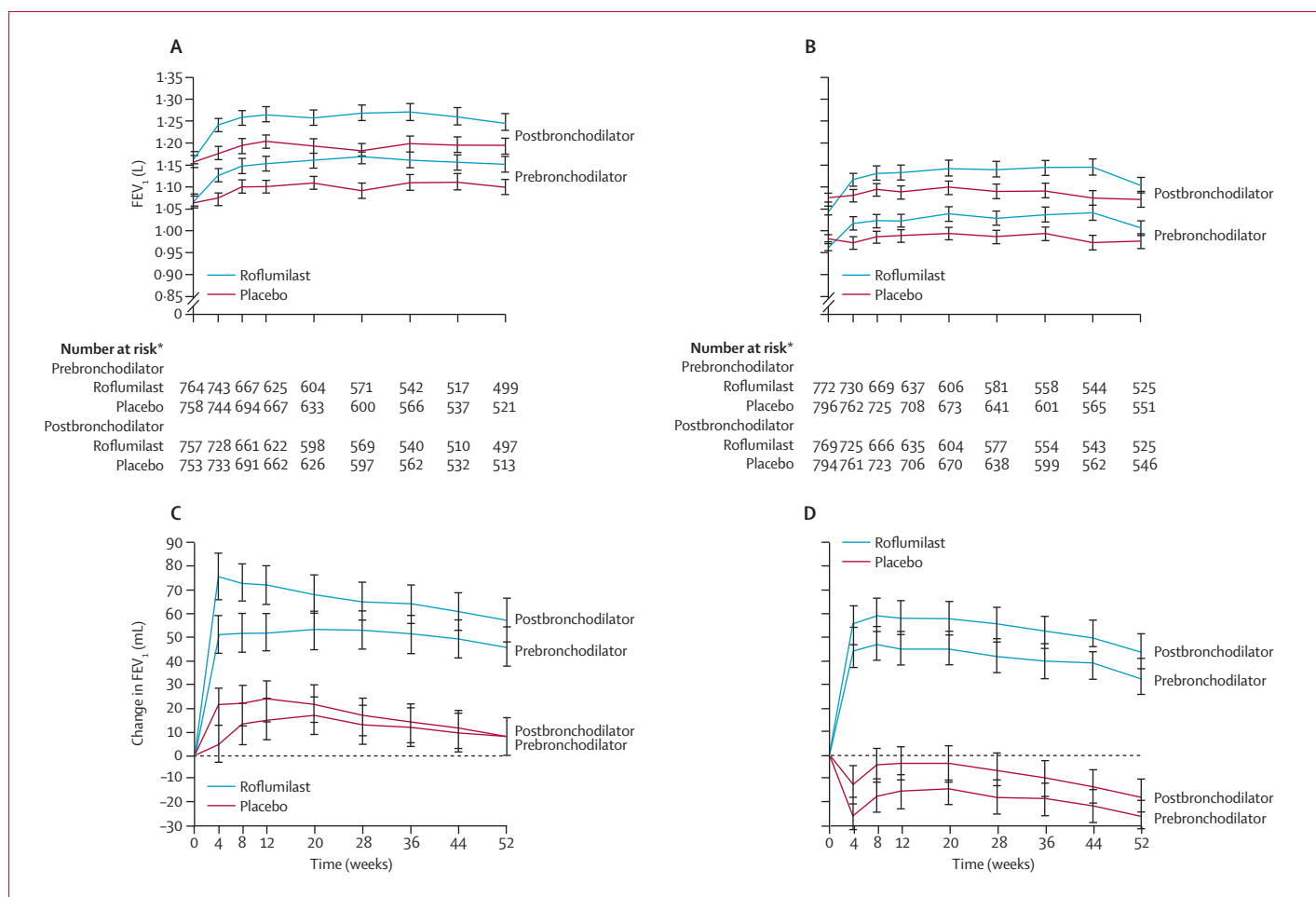


Figure 3: Prebronchodilator and postbronchodilator forced expiratory volumes in 1 s (FEV₁) over 52 weeks in patients in roflumilast and placebo groups in trials M2-124 (A) and M2-125 (B), and changes in prebronchodilator and postbronchodilator FEV₁ over 52 weeks in patients in roflumilast and placebo groups in trials M2-124 (C) and M2-125 (D)

The changes from baseline that could be calculated from the crude means shown in (A) and (B) are different from the changes from baseline (based on adjusted means) shown in (C) and (D): adjusted means are based on a repeated-measures analysis of covariance, including factors and covariables that might have an effect on the crude means. Error bars are SE. Number of patients at risk for the baseline value (week 0) is not equal to the number of patients in the intention-to-treat population (table 1) because some patients did not have a baseline value according to the definition from the statistical analysis plan. Two patients in the roflumilast group left the study during the last visit but were classified as non-completers because they did not undergo all investigations; hence the number of patients with FEV₁ measurements at the last visit is greater than the number of completers in figure 1B. *Number of patients with data available; number of patients reported here differs from the number at risk in figure 2 because some patients did not have their lung function measured at the end of the study, whereas others who did not complete the study had their lung function measured at week 52.

the safety analysis. Table 1 shows the demographic and baseline characteristics of the patients who took at least one dose of study medication. The only difference between the trials was the proportion of Asian patients. The mean prebronchodilator FEV₁ was between 31% and 35% of predicted value in the different study subgroups; 40–44% had used inhaled corticosteroids previously, whereas about 50% used longacting β_2 agonists during the trials (table 1).

Patient withdrawal was similar in the roflumilast and placebo groups (35% and 31%, respectively, in M2-124, and 32% and 31%, respectively, in M2-125; figure 1). However, more patients in the roflumilast group than in the placebo group withdrew in the first 12 weeks after randomisation (figure 2A and 2B). Adherence to treatment was similar in all groups: mean compliance

was 93% (SD 25) in the roflumilast group and 95% (14) in the placebo group in the M2-124 study, and 93% (16) in the roflumilast group and 96% (15) in the placebo group in the M2-125 study.

The primary endpoints were achieved in both studies. Figure 3 (A to D) shows the FEV₁ data during the studies; table 2 shows the summary results. In the pooled analysis, prebronchodilator FEV₁ increased from baseline in the roflumilast group and decreased in the placebo group (table 2). The postbronchodilator FEV₁, a secondary outcome variable, increased significantly from baseline with roflumilast compared with placebo in both studies and in the pooled analysis (table 2). Prebronchodilator FVC was significantly greater with roflumilast than with placebo in both studies (table 2). Similar significant improvements were seen in postbronchodilator FVC and

	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo
Lung function*									
Change in prebronchodilator FEV ₁ (mL)	46 (8); n=745	8 (8); n=745	Difference 39 (18 to 60); p=0.0003	33 (7); n=730	-25 (7); n=766	Difference 58 (41 to 75); p<0.0001	40 (6); n=1475	-9 (5); n=1511	Difference 48 (35 to 62); p<0.0001
Change in postbronchodilator FEV ₁ (mL)	57 (9); n=729	8 (8); n=736	Difference 49 (26 to 71); p<0.0001	44 (7); n=724	-17 (7); n=764	Difference 61 (44 to 79); p<0.0001	50 (6); n=1453	-4 (6); n=1500	Difference 55 (41 to 69); p<0.0001
Change in prebronchodilator FVC (mL)	68 (15); n=745	-21 (15); n=745	Difference 89 (51 to 127); p<0.0001	60 (14); n=730	-48 (14); n=766	Difference 108 (75 to 141); p<0.0001	64 (10); n=1475	-34 (10); n=1511	Difference 98 (73 to 123); p<0.0001
Change in postbronchodilator FVC (mL)	76 (15); n=729	-25 (15); n=736	Difference 101 (63 to 139); p<0.0001	58 (13); n=724	-45 (13); n=764	Difference 103 (72 to 134); p<0.0001	67 (10); n=1453	-35 (10); n=1500	Difference 101 (77 to 126); p<0.0001
Change in prebronchodilator FEV ₁ /FVC (%)	0.314 (0.223); n=745	0.001 (0.219); n=745	Difference 0.312 (-0.262 to 0.886); p=0.2858	0.200 (0.190); n=730	-0.309 (0.186); n=766	Difference 0.510 (0.061 to 0.958); p=0.0261	0.247 (0.147); n=1475	-0.146 (0.1439); n=1511	Difference 0.393 (0.028 to 0.758); p=0.0350
Change in postbronchodilator FEV ₁ /FVC (%)	0.488 (0.211); n=729	0.286 (0.208); n=736	Difference 0.202 (-0.343 to 0.747); p=0.4674	0.552 (0.186); n=724	-0.115 (0.182); n=764	Difference 0.668 (0.226 to 1.109); p=0.0031	0.517 (0.141); n=1453	0.090 (0.138); n=1500	Difference 0.426 (0.077 to 0.776); p=0.0169
Change in prebronchodilator FEF ₂₅₋₇₅ (mL/s)	19 (5); n=745	2 (5); n=745	Difference 17 (3 to 30); p=0.0152	15 (5); n=730	-10 (5); n=765	Difference 25 (13 to 36); p<0.0001	16 (4); n=1475	-4 (4); n=1510	Difference 20 (12 to 29); p<0.0001
Change in postbronchodilator FEF ₂₅₋₇₅ (mL/s)	22 (6); n=729	12 (6); n=736	Difference 11 (-5 to -27); p=0.1809	21 (5); n=724	-8 (5); n=763	Difference 29 (18 to 40); p<0.0001	21 (4); n=1453	2 (4); n=1499	Difference 19 (10 to 29); p<0.0001
Change in prebronchodilator PEF (L/min)	6.65 (1.45); n=745	3.58 (1.43); n=745	Difference 3.07 (-0.66 to 6.81); p=0.1063	0.75 (1.45); n=730	-3.09 (1.41); n=766	Difference 3.85 (0.46 to 7.23); p=0.0261	3.69 (1.02); n=1475	0.17 (0.99); n=1511	Difference 3.53 (1.01 to 6.04); p=0.0060
Change in postbronchodilator PEF (L/min)	8.08 (1.50); n=729	3.87 (1.48); n=736	Difference 4.21 (0.34 to 8.07); p=0.0328	1.93 (1.49); n=724	-3.14 (1.45); n=764	Difference 5.07 (1.60 to 8.53); p=0.0042	4.93 (1.05); n=1453	0.22 (1.02); n=1500	Difference 4.72 (2.13 to 7.30); p=0.0004
Exacerbations†‡									
Moderate or severe (mean rate, per patient per year [95% CI])	1.08 (0.96-1.21); n=344	1.27 (1.14-1.40); n=389	RR 0.85 (0.74 to 0.98); p=0.0278	1.21 (1.07-1.36); n=373	1.49 (1.33-1.66); n=432	RR 0.82 (0.71 to 0.94); p=0.0035	1.14 (1.05-1.24); n=717	1.37 (1.28-1.48); n=821	RR 0.83 (0.75 to 0.92); p=0.0003
Severe (mean rate, per patient per year [95% CI])	0.11 (0.07-0.15); n=69	0.12 (0.09-0.16); n=81	RR 0.89 (0.61 to 1.29); p=0.5273	0.14 (0.10-0.20); n=88	0.18 (0.13-0.25); n=117	RR 0.77 (0.53 to 1.11); p=0.1656	0.12 (0.10-0.16); n=157	0.15 (0.12-0.19); n=198	RR 0.82 (0.63 to 1.06); p=0.1334
Moderate (mean rate, per patient per year [95% CI])	0.94 (0.83-1.06); n=299	1.11 (1.00-1.25); n=343	RR 0.84 (0.72 to 0.99); p=0.0325	1.04 (0.92-1.18); n=325	1.27 (1.13-1.42); n=380	RR 0.82 (0.71 to 0.95); p=0.0075	0.99 (0.91-1.08); n=624	1.19 (1.10-1.29); n=723	RR 0.83 (0.75 to 0.92); p=0.0007
Treated with systemic corticosteroids, antibiotics, or both (mean rate, per patient per year [95% CI])	1.10 (0.98-1.23); n=336	1.30 (1.17-1.43); n=382	RR 0.85 (0.74 to 0.98); p=0.0240	1.17 (1.04-1.31); n=364	1.41 (1.27-1.57); n=416	RR 0.83 (0.72 to 0.95); p=0.0055	1.13 (1.04-1.23); n=700	1.35 (1.26-1.46); n=798	RR 0.84 (0.76 to 0.92); p=0.0003
Median time to first exacerbation (moderate or severe; days [IQR])	85.0 (29.5-185.5)	71.0 (29.0-152.0)	HR 0.88 (0.76 to 1.02); p=0.0859	73.0 (26.0-195.0)	69.5 (27.0-169.5)	HR 0.89 (0.78 to 1.03); p=0.1132	80.0 (28.0-190.0)	71.0 (28.0-160.0)	HR 0.89 (0.80 to 0.98); p=0.0185
Median time to second exacerbation (moderate or severe; days [IQR])	172.0 (102.0-253.0)	159.0 (97.0-229.0)	HR 0.79 (0.64 to 0.98); p=0.0290	188.0 (84.0-281.0)	144.0 (81.0-239.0)	HR 0.79 (0.65 to 0.97); p=0.0214	177.0 (92.0-262.0)	148.0 (85.0-236.0)	HR 0.79 (0.69 to 0.91); p=0.0014

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prebronchodilator midexpiratory flow. These changes in lung function were similar with and without treatment with longacting β_2 agonist (mean prebronchodilator FEV₁ increase with longacting β_2 agonist, 46 mL [p<0.0001] and without longacting β_2 agonist, 50 mL [p<0.0001]).

In the pooled analysis, the estimated rate of exacerbations per patient per year that were moderate or severe was 17% lower in the roflumilast group than in the placebo group (table 2). These findings were supported by the negative binomial regression analysis (data not shown). The difference in rates between

treatments was independent of concomitant longacting β_2 agonist use (p=0.5382, treatment by concomitant treatment with longacting β_2 agonist interaction). The total number of exacerbations (excluding severe events) requiring treatment with systemic corticosteroids or antibiotics, or both, was also lower in the roflumilast group than in the placebo group (reduction 16%) in the pooled analysis (table 2). The times to the first and second episodes of exacerbations that were moderate or severe were significantly prolonged (table 2). When the analysis was restricted to patients who completed the

	M2-124			M2-125			M2-124 and M2-125		
	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo	Roflumilast	Placebo	Roflumilast vs placebo
(Continued from previous page)									
Further prespecified secondary analyses									
TDI focal score*	0.7 (0.1); n=741	0.4 (0.1); n=745	Difference 0.2 (0.0 to 0.4); p=0.0356	0.7 (0.1); n=729	0.4 (0.1); n=769	Difference 0.3 (0.1 to 0.5); p=0.0059	0.7 (0.1); n=1470	0.4 (0.1); n=1514	Difference 0.3 (0.1 to 0.4); p=0.0009
Change in C-reactive protein from baseline to last postrandomisation visit (mg/L)*	1.0; n=691	1.1; n=694	Difference 1.0 (0.8 to 1.1); p=0.4089	1.1; n=680	1.0; n=696	Difference 1.1 (0.9 to 1.2); p=0.3627	1.1; n=1371	1.1; n=1390	Difference 1.0 (0.9 to 1.1); p=0.8670
Time to mortality (days; mean, SD)	213.8 (118.9); n=765	207.5 (108.5); n=758	HR 1.0 (0.5 to 2.0); p=0.9212	201.0 (116.9); n=772	214.6 (137.3); n=796	HR 1.2 (0.7 to 2.1); p=0.5028	206.1 (116.4); n=1537	211.7 (125.1); n=1554	HR 1.1 (0.7 to 1.8); p=0.5452
Health utility assessment									
EQ-5D total score*	0.0049 (0.0058); n=743	0.0097 (0.0057); n=740	Difference -0.0047 (-0.0196 to 0.0101); p=0.5331	0.0100 (0.0065); n=727	-0.0006 (0.0063); n=764	Difference 0.0106 (-0.0046 to 0.0257); p=0.1715	0.0072 (0.0043); n=1470	0.0049 (0.0042); n=1504	Difference 0.0023 (-0.0083 to 0.0129); p=0.6712
Data are mean (SE), mean difference (95% CI), or point estimate (95% CI), unless otherwise indicated. n=number of patients with data available (or, for exacerbations, number of patients with at least one exacerbation). FEV ₁ =forced expiratory volume in 1 s. FVC=forced vital capacity. FEF=forced expiratory flow. PEF=peak expiratory flow. RR=rate ratio. HR=hazard ratio. TDI=transition dyspnoea index. EQ-5D=Euroqol 5-dimension. *Least squares means (SE). †Estimated exacerbation rates were based on a Poisson regression model and HRs were based on a Cox proportional hazards model. ‡Since patients might have had more than one type of exacerbation, the total of moderate and severe exacerbations is different from the total of exacerbations that were moderate or severe.									
Table 2: Lung function variables, exacerbations, and other clinical outcomes									

trials, similar differences in exacerbation rates were seen between the groups, although these were not significant (webappendix p 13).

The preplanned sensitivity analyses confirmed the robustness of results for the primary endpoints with respect to the effect of dropouts and missing data (data not shown).

A total of 84 patients died during the studies. The mortality rates per year did not differ in the roflumilast and placebo groups in the M2-124 study (17 [2%] vs 17 [2%]), and in the roflumilast and placebo groups in the M2-125 study (25 [3%] vs 25 [3%]; hazard ratio for time to death from any cause was >1 in both studies; table 2). Baseline concentrations of C-reactive protein varied widely and did not change significantly during the study or with treatment. A small improvement was noted in TDI focal score from baseline with roflumilast compared with placebo but there were no differences in total EQ-5D scores (table 2).

Adverse events in the pooled study population were reported by 1040 (67%) patients in the roflumilast group and 963 (62%) in the placebo group; serious adverse events were reported by 301 (19%) and 336 (22%) patients, respectively. Discontinuations associated with adverse events were more common in the pooled roflumilast groups than in the pooled placebo groups (219 [14%] vs 177 [11%]). With the exception of COPD, the most frequent adverse events leading to discontinuation were diarrhoea, nausea, and headache in the pooled analysis (data not shown). The probability of withdrawal due to adverse events in the first 12 weeks was higher in roflumilast-treated patients (8% in both studies) than in

placebo-treated patients (3% in both studies). The subsequent probability of withdrawal because of adverse events was similar between treatments (9% of roflumilast-treated patients in both studies, and 9% of placebo-treated patients in both studies).

Vomiting was reported by 17 (1%) patients in the roflumilast groups and 11 (<1%) in the placebo groups. More patients in the roflumilast than in the placebo groups had weight loss (table 3). The mean weight change was a reduction of 2.09 kg (SD 3.98) with roflumilast after 1 year and an increase of 0.08 kg (3.48) with placebo. The change in weight in the roflumilast group happened in the first 6 months of treatment and was attenuated thereafter. Patients in the roflumilast group reporting diarrhoea, nausea, vomiting, or headache had greater weight loss than did those not reporting these symptoms (2.60 kg [3.72] vs 2.02 kg [4.01]). The largest absolute weight loss with roflumilast occurred in obese patients (BMI>30; webappendix p 14). No differences were noted in the proportion of reported cardiovascular adverse events in the roflumilast and placebo groups (108 [7%] and 120 [8%], respectively). Atrial fibrillation was an infrequent complication reported by 17 (1%) patients in the roflumilast groups and 7 (<1%) of those in the placebo groups. There was no difference between roflumilast and placebo groups in the occurrence of rhythm disturbances in 33 and 22 Holter-monitored recordings, respectively (webappendix p 16). The incidence of pneumonia or other pulmonary infections did not increase during treatment with roflumilast (data not shown).

	M2-124			M2-125*		
	Roflumilast (n=769)†	Placebo (n=755)†	Roflumilast vs placebo (difference, 95% CI)	Roflumilast (n=778)‡	Placebo (n=790)‡	Roflumilast vs placebo (difference, 95% CI)
COPD	70 (9%)	82 (11%)	-1.76% (-4.90 to 1.38)	87 (11%)	122 (15%)	-4.26% (-7.74 to -0.78)
Diarrhoea	63 (8%)	26 (3%)	4.75% (2.28 to 7.21)	67 (9%)	23 (3%)	5.70% (3.28 to 8.12)
Weight loss	92 (12%)	24 (3%)	8.78% (6.04 to 11.53)	65 (8%)	20 (3%)	5.82% (3.46 to 8.18)
Nasopharyngitis	57 (7%)	50 (7%)	0.79% (-1.91 to 3.49)	35 (5%)	47 (6%)	-1.45% (-3.78 to 0.88)
Upper respiratory tract infection	16 (2%)	21 (3%)	-0.70% (-2.38 to 0.98)	33 (4%)	38 (5%)	-0.57% (-2.75 to 1.62)
Headache	26 (3%)	17 (2%)	1.13% (-0.66 to 2.92)	25 (3%)	8 (1%)	2.20% (0.65 to 3.75)
Pneumonia	17 (2%)	15 (2%)	0.22% (-1.35 to 1.79)	25 (3%)	16 (2%)	1.19% (-0.52 to 2.90)
Back pain	27 (4%)	22 (3%)	0.60% (-1.30 to 2.50)	23 (3%)	13 (2%)	1.31% (-0.30 to 2.92)
Acute bronchitis	35 (5%)	40 (5%)	-0.75% (-3.05 to 1.56)	21 (3%)	24 (3%)	-0.34% (-2.12 to 1.44)
Nausea	41 (5%)	15 (2%)	3.34% (1.34 to 5.35)	21 (3%)	15 (2%)	0.80% (-0.81 to 2.41)
Hypertension	20 (3%)	28 (4%)	-1.11% (-2.99 to 0.78)	18 (2%)	20 (3%)	-0.22% (-1.87 to 1.43)
Insomnia	19 (2%)	8 (1%)	1.41% (-0.04 to 2.86)	18 (2%)	12 (2%)	0.79% (-0.69 to 2.28)
Decreased appetite	21 (3%)	2 (<1%)	2.47% (1.13 to 3.81)	15 (2%)	5 (<1%)	1.30% (0.05 to 2.54)
Influenza	27 (4%)	18 (2%)	1.13% (-0.70 to 2.95)	12 (2%)	20 (3%)	-0.99% (-2.51 to 0.53)

Data are number (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. COPD=chronic obstructive pulmonary disease. *Incidence of adverse events in roflumilast-treated patients in study M2-125 is in descending order. †One patient was randomised twice, and included twice in the safety analysis but only once in the efficacy analysis; four patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for the safety analysis; 765 patients in the roflumilast group and 758 in the placebo group were included in the efficacy analysis. ‡Six patients assigned to placebo were given roflumilast instead and were included in the roflumilast group for safety analysis; 772 patients in the roflumilast group and 796 in the placebo group were included in the efficacy analysis.

Table 3: Adverse events occurring in at least 2.5% of patients in one of the treatment groups

Discussion

Roflumilast reduced exacerbation frequency and induced consistent and significant improvements in FEV₁, both before and after bronchodilator use. Similar changes occurred in FVC and midexpiratory flow, suggesting a general improvement in operating lung volume. These changes were independent of the patient's smoking status or use of concomitant medication, such as inhaled longacting β_2 agonists, and were similar to those reported in other patient populations with COPD.^{14,19}

PDE4 inhibition provides a novel approach to the treatment of patients with COPD. However, results from previous studies have shown inconsistent effects of PDE4 inhibitors on clinically relevant outcomes such as acute exacerbation frequency, although results from a post-hoc analysis suggested that roflumilast might be effective in selected patients with COPD.¹³ The results from the M2-124 and M2-125 studies show that carefully defined patient groups that are particularly at risk of exacerbations benefit from treatment with roflumilast.

The effects of roflumilast in our proposed subgroups, which should be easily identified clinically, were tested in these two adequately powered studies with an identical design, undertaken in two geographically different populations. Participants in both studies were preselected for specific characteristics identified from earlier trials.^{7,19} They had substantial airflow limitation (stages III and IV according to the criteria of the Global initiative for chronic Obstructive Lung Disease), documented cough and sputum production as a marker

for persistent airway inflammation,²⁰ and a history of exacerbations treated in the year before entry into the study.

Many clinical trials identify patient subgroups that seem to respond to treatment in a secondary or post-hoc analysis, which is not confirmed in studies that are better powered.²¹ In an earlier study, roflumilast did not reduce overall exacerbation rate but decreased the number of exacerbations requiring oral corticosteroids.¹⁴ Data from our two studies confirmed this finding. Treatment with inhaled corticosteroids has been shown to prevent exacerbations, including those that are subsequently managed with oral corticosteroids.^{7,22} The same holds true for treatment with roflumilast. A direct comparison of the effect of inhaled steroids or roflumilast on reduction of exacerbations cannot be directly assessed with the present data, but is worth investigation in the future. The rate of exacerbations in our placebo-treated patients was higher than in previous studies, with few episodes being treated with antibiotics alone, possibly because of our study design and patient recruitment. As in other 1-year trials in patients with COPD, roflumilast did not have much effect on episodes requiring treatment in hospital,²³⁻²⁵ which were infrequent. In our studies, the number of patients needed to treat with roflumilast to prevent one exacerbation per year that was moderate or severe was 5.29 in the M2-124 study and 3.64 in the M2-125 study, irrespective of concurrent treatment with an inhaled longacting β_2 agonist.

Several secondary outcomes were assessed. Mortality rate during treatment did not differ between treatments

and was similar to other events during treatment in the first year of a large COPD survival trial.⁷ The concentration of C-reactive protein was unaffected by treatment. However, the use of this marker in cardiorespiratory disease has been questioned.²⁶ Small but significant improvements in breathlessness assessed by the investigator-administered TDI occurred in both studies, but did not reach the agreed minimum clinically important difference. Whether this result indicates that the benefit of treatment with roflumilast is predominantly on prevention of exacerbations rather than improvement of exercise performance, or is a result of the selection criteria used will require further study.

Since we allowed patients to continue using inhaled longacting β_2 agonists throughout the study, and inhaled corticosteroids were withdrawn at entry, no conclusions can be drawn about synergy or interaction between roflumilast and other drugs; further studies will be needed to test specifically the effectiveness of inhaled corticosteroids alone or in combination with roflumilast. Whether the effects of roflumilast are additive to longacting inhaled bronchodilators is addressed by Fabbri and colleagues.²⁷ For practical reasons, the effect of roflumilast on breathlessness was tested rather than assessment of the global health status. In general, health status improves when the exacerbation rate falls by the magnitude seen here,^{28,29} but confirmation of this association by means of a disease-specific instrument is needed for roflumilast. Changes in health status were not seen in the previous 1-year roflumilast study and the general health measure EQ-5D did not seem to identify differences in the data.¹⁴ The health-care utilisation definition of exacerbations used in this study cannot precisely define the duration of events and might miss mild episodes.^{30–32} In other studies with daily diary cards, substantially more events have been identified than in our studies, including many events that were not treated with corticosteroids or antibiotics. The results of a previous study have suggested that mild events associated with increased symptoms and use of shortacting β_2 agonists could be prevented with roflumilast;¹⁹ the reduction in use of shortacting β_2 agonists that was noted in our studies supports this finding. Since roflumilast is an anti-inflammatory drug, we focused on its ability to change corticosteroid-treated exacerbations. There were fewer antibiotic-treated episodes than expected, possibly indicating the way investigators interpreted the study protocol. Interpretation of the data has been complicated by the pattern of patient withdrawal in these trials, which differed between treatment groups in the early and late phases. In general, this pattern would tend to result in a minimum biological effect of the active therapy by reducing the statistical power of the study comparisons. In accordance with good clinical trial practice, we focused on recruiting patients likely to adhere to treatment and, thus, caution is needed when generalising these findings to the general clinical population.

No significant neurological or cardiac toxicity was noted with roflumilast. A range of predicted adverse events occur-

red with roflumilast that were centrally mediated (insomnia, nausea, headache, but not vomiting) or gastrointestinal (predominantly diarrhoea). These were most evident in the first 4–12 weeks of treatment when they contributed to the early difference in withdrawal in both studies. Thereafter, no difference was noted between treatment groups in the occurrence of these adverse events and the withdrawals associated with them. Patients reported weight loss more frequently in the roflumilast groups than in the placebo groups, a finding confirmed by objective measurements. The mean weight loss of 2.1 kg (SD 4.0) over the course of the study was greatest in the first 6 months of roflumilast treatment. Patients reporting gastrointestinal or neurological symptoms lost more weight, but weight loss was still seen in patients without these side-effects. The change in bodyweight was similar irrespective of initial BMI and might not be an unwelcome treatment effect in obese patients who showed the largest absolute weight loss. We did not notice the occurrence of more pneumonias among patients in the roflumilast groups than among those in the placebo groups, whereas pneumonia was reported more frequently with inhaled corticosteroids in studies with similar patient-years of treatment exposure to our studies.³³ This increased frequency suggests that pneumonia might relate to local effects of inhaled corticosteroids rather than representing a general outcome of treatment with anti-inflammatory drugs in patients with COPD.

Our results from these clinical trials with identical design that were done in two different populations have shown that roflumilast, a PDE4 inhibitor, improves lung function and reduces the frequency of exacerbations in patients with bronchitic symptoms and severe airflow limitation. It should be noted that this treatment is not suitable for all patients because of the presence of class-related adverse effects that usually arise soon after initiation of treatment. Nonetheless, these results suggest that different subsets of patients exist within the broad range of COPD, and that specific therapies might improve disease management. This possibility should be explored further in prospective studies.

Contributors

All authors were members of the steering committee that developed the design and concept of the studies, approved the statistical plans, interpreted the data, and wrote the report. PMAC wrote the first draft of the report. U-MG and SK coordinated data gathering and SK did the statistical analysis. All authors vouch for the veracity and completeness of the data and the data analysis.

Conflicts of interest

PMAC has served on advisory boards for AstraZeneca, GlaxoSmithKline, Nycomed, and Novartis; received research funding from GlaxoSmithKline, Nycomed, and Boehringer Ingelheim; and spoken at meetings supported by AstraZeneca, GlaxoSmithKline, and Nycomed. KFR has served as a consultant, participated in advisory board meetings, and received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, Pfizer, Novartis, Nycomed, Merck Sharp and Dohme, and GlaxoSmithKline; and received research funding from AltanaPharma, Novartis, AstraZeneca, Boehringer Ingelheim, Roche, and GlaxoSmithKline. LMF has served as a consultant to AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck

Sharp and Dohme, Novartis, Nycomed, Roche, Pfizer, and Sigma-Tau; received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Novartis, Nycomed, Roche, and Pfizer; and received grant support from AstraZeneca, Boehringer Ingelheim, Menarini, Schering-Plough, Chiesi Farmaceutici, GlaxoSmithKline, Merck Sharp and Dohme, Nycomed, Union Chimique Belge, Pfizer, Sigma-Tau, Italian Ministry of Health, and Italian Ministry for University and Research. FJM has been a member of advisory boards for GlaxoSmithKline, Schering-Plough, Novartis, Nycomed, Genzyme, Forest/Almirall, Talecris, and Roche; on the speaker's bureau for Boehringer Ingelheim, GlaxoSmithKline, and AstraZeneca; a member of steering committees for studies supported by Gilead, Actelion, Johnson & Johnson, United BioSource, and the National Institutes of Health; and an investigator in trials supported by Boehringer Ingelheim and Actelion. U-MG and SK are employees of Nycomed.

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