Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial

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Summary

Background Roflumilast reduces exacerbations in patients with severe chronic obstructive pulmonary disease. Its effect in patients using fixed combinations of inhaled corticosteroids and longacting β_2 agonists is unknown. We postulated that roflumilast would reduce exacerbations in patients with severe chronic obstructive pulmonary disease at risk for exacerbations, even in combination with inhaled corticosteroid and longacting β_2 agonist treatment.

Methods For this 1-year double-blind, placebo-controlled, parallel group, multicentre, phase 3–4 trial, the Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy (REACT) study, we enrolled patients with severe chronic obstructive pulmonary disease from 203 centres (outpatient clinics, hospitals, specialised pulmonologists, and family doctors) in 21 countries. Eligible patients were 40 years of age or older with a smoking history of at least 20 pack-years and a diagnosis of chronic obstructive pulmonary disease with severe airflow limitation, symptoms of chronic bronchitis, and at least two exacerbations in the previous year. We used a computerised central randomisation system to randomly assign patients in a 1:1 ratio to the two treatment groups: roflumilast 500 μg or placebo given orally once daily together with a fixed inhaled corticosteroid and longacting β_2 agonist combination. Background tiotropium treatment was allowed. All patients and investigators were masked to group assignment. The primary outcome was the rate of moderate to severe chronic obstructive pulmonary disease exacerbations per patient per year, analysed by intention to treat. This study is registered with ClinicalTrials.gov, number NCT01329029.

Findings Between April 3, 2011, and May 27, 2014, we enrolled 1945 eligible participants and randomly assigned 973 to the roflumilast group and 972 to the placebo group. The rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations was 13·2% lower in the roflumilast group than in the placebo group according to a Poisson regression analysis (roflumilast 0·805 *vs* placebo 0·927; rate ratio [RR] 0·868 [95% CI 0·753–1·002], p=0·0529), and 14·2% lower according to a predefined sensitivity analysis using negative binomial regression (0·823 *vs* 0·959; 0·858 [0·740–0·995], p=0·0424). Adverse events were reported by 648 (67%) of 968 patients receiving roflumilast and by 572 (59%) of 967 patients in the placebo group; adverse event-associated patient withdrawal from the study was also more common in the roflumilast group (104/968 [11%]) than in the placebo group (52/967 [5%]). The most frequently reported serious adverse events were chronic obstructive pulmonary disease exacerbations and pneumonia, and 17 (1·8%) deaths occurred in the roflumilast group compared with 18 (1·9%) in the placebo group.

Interpretation Our findings suggest that roflumilast reduces exacerbations and hospital admissions in patients with severe chronic obstructive pulmonary disease and chronic bronchitis who are at risk of frequent and severe exacerbations despite inhaled corticosteroid and longacting β_2 agonist therapy, even in combination with tiotropium.

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Introduction

Severe chronic obstructive pulmonary disease is associated with periodic exacerbations of respiratory symptoms that need aggressive treatment and often necessitate hospital admission.[1,2] These exacerbations worsen patient health status, accelerate decline in lung function, and increase mortality.[1,2] The two alternative recommended pharmacological treatments to prevent exacerbations are either an inhaled longacting muscarinic antagonist alone, a fixed combination of an inhaled corticosteroid and longacting β_2 agonist, or these two treatments combined.[1] These therapies significantly reduce, but do not eliminate, chronic obstructive pulmonary disease exacerbations, especially those necessitating hospital admission, which is problematic for patients at risk of frequent or severe events.[3–5] To increase the doses of longacting bronchodilators[6] and inhaled corticosteroids is not a practical option because of the flat dose–response curve and raised risk of side-effects, especially pneumonia with inhaled corticosteroids.[7,8]

Alternative approaches to prevent chronic obstructive pulmonary disease exacerbations have been investigated,

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See **Online** for appendix

Research in context

Evidence before this study

We searched Medline for articles published in any language up until Jan 8, 2015, with the search terms "roflumilast" and "chronic obstructive pulmonary disease" but not "asthma" or "randomised trial". Our final search was done on Jan 8, 2015. We identified 19 articles reporting randomised controlled trials. However, only five trials compared 1-year treatment with roflumilast versus placebo in more than 1000 patients with moderate-to-very-severe chronic obstructive pulmonary disease and included the assessment of lung function, symptoms, quality of life, and exacerbations. These five trials were reported in three original reports. Two replicate positive randomised clinical trials and the pooled analysis of two negative clinical trials showed a significant effect of roflumilast on moderate-to-severe exacerbations and lung function, especially in patients with severe-to-very-severe chronic obstructive pulmonary disease, symptoms of chronic bronchitis, and a risk of exacerbations. However, none of these trials included patients at high risk of exacerbations (>2 per year) while receiving the standard of care, ie inhaled corticosteroid–longacting β_2 agonist combinations.

Added value of this study

Our findings show that roflumilast reduces moderate-to-severe exacerbations, especially those that lead to hospital admissions, and improves lung function in patients with severe chronic

obstructive pulmonary disease with chronic bronchitis at risk of frequent exacerbations, even those receiving an inhaled corticosteroid–longacting β_2 agonist combination or triple therapy with an inhaled corticosteroid–longacting β_2 agonist combination plus tiotropium. To identify publications reporting the effects of any other drug in patients with severe to very severe chronic obstructive pulmonary disease, chronic bronchitis, and a high risk of exacerbations while being treated with an inhaled corticosteroid–longacting β_2 agonist combination, we also searched Medline using the search terms "cilomilast", "phosphodiesterase IV inhibitors", "beclomethasone", "fluticasone", "budesonide", "salmeterol", "formoterol", "theophylline", "aminophylline", "antibiotics", "macrolides", "infliximab", "benralizumab", "chronic bronchitis", "emphysema", and "randomised trial". We did not find any studies that had been done in patients with these characteristics.

Implications of all the available evidence

Roflumilast is the only available oral anti-inflammatory drug that provides additional, clinically relevant benefits without unacceptable side-effects. Our findings should help to inform treatment choices for patients with severe to very severe chronic obstructive pulmonary disease and chronic bronchitis who are at risk of severe exacerbations even when they are already taking maximum doses of existing inhalation treatments.

including long-term macrolide therapy, which is effective but associated with the risks of side-effects and antibiotic resistance;[9] statins, which are ineffective;[10] and theophylline[11] and acetylcysteine,[12,13] which produce inconsistent results. None of these studies have investigated whether or not treatment reduced exacerbations in severe chronic obstructive pulmonary disease not adequately controlled with the best available inhalation therapy with inhaled corticosteroid–longacting β_2 agonist combinations or triple longacting muscarinic antagonist–inhaled corticosteroid–longacting β_2 agonist therapy.

Roflumilast is an oral phosphodiesterase-4 inhibitor with anti-inflammatory actions both in vitro and in vivo.[14] It consistently improves lung function and reduces the frequency of exacerbations in patients with severe chronic obstructive pulmonary disease, symptoms of chronic bronchitis, and a history of frequent exacerbations.[15–17] The effect on exacerbations is maintained in patients treated with longacting β_2 agonists, and is more pronounced in patients with frequent exacerbations.[18] However, whether or not roflumilast can effectively reduce exacerbations when patients with chronic obstructive pulmonary disease use inhaled corticosteroid–longacting β_2 agonist combinations as their maintenance therapy, which is the regimen recommended at present by evidence-based guidelines,[1,2] is not known.

We postulated that roflumilast would be effective in patients with severe chronic obstructive pulmonary disease who are at risk for exacerbations and whose disease is not adequately controlled with inhaled corticosteroid–longacting β_2 agonist combinations or triple longacting muscarinic antagonist–inhaled corticosteroid–longacting β_2 agonist therapy. Additionally, we wanted to understand the adverse event profile in this subset of patients to help establish the risk:benefit balance of treatment. To achieve these aims, we undertook the REACT (Roflumilast and Exacerbations in patients receiving Appropriate Combination Therapy) study.[19]

Methods

Patients

REACT was a 1-year, double-blind, placebo-controlled, parallel-group, multicentre study. Patients were recruited from 203 centres (outpatient clinics, hospitals, specialised pulmonologists, and family doctors) in 21 countries worldwide (appendix pp 3–5). Eligible patients were 40 years of age or older with a smoking history of at least 20 pack-years and a diagnosis of chronic obstructive pulmonary disease with severe airflow limitation (confirmed by a post-bronchodilator forced expiratory volume in 1 s [FEV_1]/forced vital capacity [FVC] ratio <0·70 and a post-bronchodilator FEV_1 of ≤50% predicted), symptoms of chronic bronchitis, and a history of at least

two exacerbations in the previous year. Patients must have been taking an inhaled corticosteroid–longacting β_2 agonist combination for 12 months before the study and a constant dose of an inhaled corticosteroid–longacting β_2 agonist fixed combination for at least 3 months before enrolment, with placebo tablet compliance of 80–125% during the 4-week baseline observation period and with a total cough and sputum score of 14 or higher (in which the score was a sum of daily scores on 4-point scales for cough and sputum) recorded in a daily diary during the week preceding the randomisation visit (appendix p 9). Patients were excluded if they had a chronic obstructive pulmonary disease exacerbation that was ongoing during the baseline period, or had a diagnosis of asthma or other major lung disease.

All patients used a fixed-dose inhaled corticosteroid–longacting β_2 agonist combination during the baseline and treatment period. If a patient had an exacerbation that needed additional treatment during the study, the investigator could give them up to 40 mg prednisolone, administered systemically, per day for 7–14 days. In the case of purulent sputum or suspected bacterial infection, additional antibiotic therapy was allowed. A follow-up visit within 10 days after the initial exacerbation was recommended. The use of the following treatments was not allowed: oral and parenteral glucocorticosteroids (except to treat acute exacerbations), longacting β_2 agonist or inhaled corticosteroid monotherapy, shortacting muscarinic antagonists, and any shortacting β_2 agonists (with the exception of salbutamol) or oral β_2 agonists. Patients already taking inhaled tiotropium bromide (a longacting muscarinic antagonist) were allowed to continue this treatment. Appendix p 12 provides a full list of exclusion criteria.

The study protocol was approved by each respective institutional review board and followed established good clinical practice guidelines. All patients gave written informed consent to participate in the study.

Procedures

The study consisted of a single-blind, 4 week run-in period during which all patients received a placebo tablet in addition to their inhaled corticosteroid–longacting β_2 agonist treatment, and, if relevant, tiotropium. Run-in was followed by a 52-week treatment period during which patients were randomly assigned to receive either once-daily roflumilast 500 µg or placebo (appendix p 9). All tablets were taken orally with water in the morning after breakfast. Visits were scheduled at weeks 4, 12, 20, 28, 40, and 52. One additional visit was scheduled between weeks 4 and 12 for pharmacokinetic and pharmacodynamic blood sampling in 986 patients participating in a substudy; these results will be reported separately. A final follow-up visit 12 weeks after treatment ended was scheduled to take place during week 64. During the baseline and treatment periods, patients recorded their daily chronic obstructive pulmonary disease symptoms and use of allowed rescue medication in a diary. At each visit, pulmonary function tests were done, bodyweight was recorded, and any exacerbations and adverse events were reported. The number of tablets taken was documented in the case report form to monitor drug compliance.

Randomisation and masking

Enrolled patients were randomly assigned in a 1:1 ratio, with a block size of 4, by a computerised central randomisation system, the Interactive Voice Response System–Interactive Web Response System (PPD Global Limited, Cambridge, UK). At each dispensing visit, the system assigned either roflumilast or placebo from the stock available at the site for each patient. Roflumilast and placebo were supplied as identical yellow triangular tablets in wallet cards containing 40 tablets. During the single-blind baseline period, the sponsor and investigator were aware that patients received placebo; during double-blind treatment and until end of follow-up, all parties involved in the study were masked to treatment assignment.
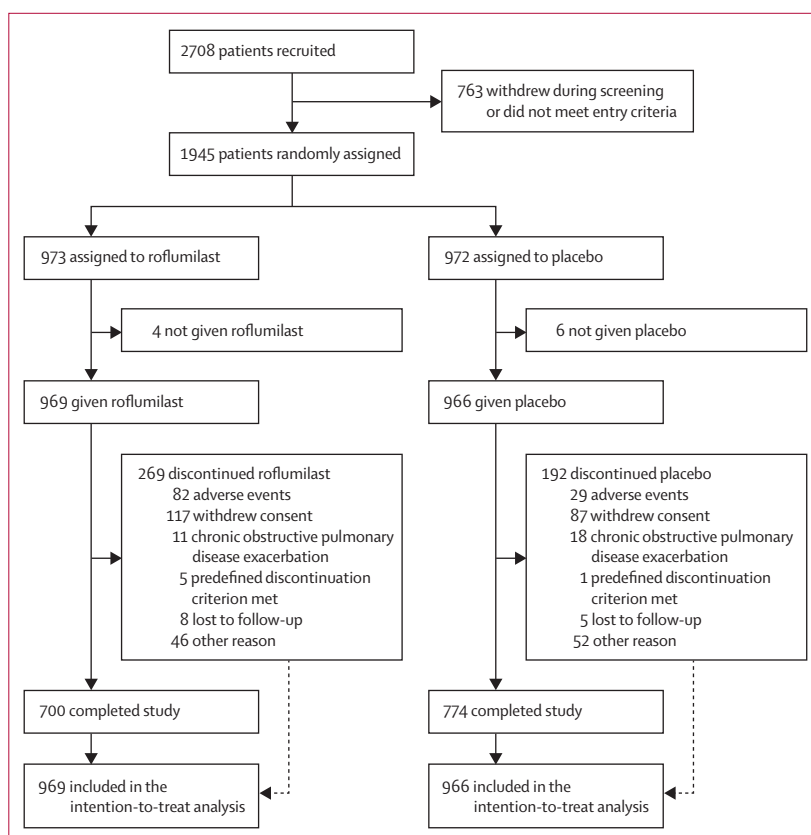

Figure 1: Trial profile
Ten patients were randomly assigned in error or did not receive any dose of double-blind study medication. These patients were excluded from the safety, full analysis, and valid cases set. One patient assigned to roflumilast received placebo during the entire study and was therefore included in the placebo group for the safety analysis. 657 patients in the roflumilast group and 737 patients in the placebo group of the study were followed up for a further 3 months. 37 patients who received roflumilast during double-blind treatment continued to receive the drug for a further 3 months; 50 patients who received placebo also received roflumilast during the 3-month follow-up period.

	Roflumilast group (n=969)	Placebo group (n=966)
Age (years)	65 (8·4)	65 (8·4)
Male sex	718 (74%)	725 (75%)
Body-mass index (kg/m²)	26·5 (5·47)	26·6 (5·36)
Cigarette pack-years	48 (24·6)	48 (23·6)
Smoking status		
Current smoker	411 (42%)	432 (45%)
Former smoker	558 (58%)	534 (55%)
Pre-bronchodilator FEV_1 (L)	1·0 (0·31)	1·0 (0·32)
Post-bronchodilator FEV_1 (L)	1·1 (0·33)	1·1 (0·32)
% of predicted pre-bronchodilator FEV_1	33·3% (9·08)	33·6% (9·00)
% of predicted post-bronchodilator FEV_1	35·4% (9·25)	35·5% (8·76)
Post-bronchodilator FEV_1/FVC	40·2% (10·81)	40·1% (10·26)
Chronic obstructive pulmonary disease severity		
Mild	2 (<1%)	0
Moderate	18 (2%)	16 (2%)
Severe	658 (68%)	677 (70%)
Very severe	291 (30%)	273 (28%)
Concomitant treatment with LAMA*	677 (70%)	669 (69%)
CAT score	20·4 (7·22)	19·8 (6·88)
Medical Research Council score	2·2 (0·97)	2·1 (0·94)
Number of exacerbations in the past year†		
<2 exacerbations	6 (<1%)	4 (<1%)
2 exacerbations	855 (88%)	859 (89%)
>2 exacerbations	103 (11%)	100 (10%)
History of cardiovascular disease	414 (43%)	440 (46%)

Data are n (%) or mean (SD). FEV_1=forced expiratory volume in 1 s. FVC=forced vital capacity. LAMA=longacting muscarinic antagonist. CAT=Chronic Obstructive Pulmonary Disease Assessment Test. MRC=Medical Research Council. *Patients were classified as receiving concomitant treatment with a LAMA if they used this therapy during baseline and at least 80% of the duration of the treatment period. †Historical exacerbations were counted as the number of exacerbations in the past year that led to hospital admission and/or needed treatment with systemic glucocorticosteroids in the year before baseline visit; percentages do not add up to 100% in this section because of missing data.

Table 1: **Baseline characteristics of the intention-to-treat population**

Outcomes

The primary endpoint was the rate of moderate-to-severe chronic obstructive pulmonary disease exacerbations per patient per year. Moderate exacerbations were defined as those that needed treatment with oral or parenteral glucocorticosteroids (with or without antibiotics), and severe exacerbations were defined as those that needed hospital admission, led to death, or both. Key secondary endpoints were post-bronchodilator FEV_1 (change from randomisation during treatment) and the rate of severe chronic obstructive pulmonary disease exacerbations per patient per year. Data about the number of chronic obstructive pulmonary disease exacerbations treated with antibiotics and on a range of spirometric outcomes were also collected and were included as other secondary outcomes.

Safety was monitored by recording changes in laboratory values, vital signs, physical examination findings, changes in bodyweight and body-mass index (BMI), and reported adverse events. The occurrence of major adverse cardiovascular events—a composite endpoint consisting of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke—was assessed according to criteria predefined by the Major Adverse Cardiovascular Event Adjudication Committee (appendix p 7). Quality of life was assessed with the Chronic Obstructive Pulmonary Disease Assessment Test (CAT; GlaxoSmithKline, Middlesex, UK), and was measured as change from randomisation during treatment.[20] Mortality was assessed as deaths that occurred from any cause, from a chronic obstructive pulmonary disease exacerbation, or from an adverse event during active study participation.

Statistical analysis

All reported efficacy analyses were predefined. Data are expressed as mean (95% CI) unless otherwise stated, and a p value less than 0·05 was judged significant. We analysed the primary endpoint using a Poisson regression model that included a correction for overdispersion. The number of exacerbations per patient was used as the dependent variable. The model included an offset variable that represented how long a patient remained in the study. Treatment was included as an independent variable in the model. We also did a predefined negative binomial regression analysis, analogous to the Poisson regression, to assess the robustness of the results against the distributional assumptions.

We assessed the rate of severe chronic obstructive pulmonary disease exacerbations per patient per year using a negative binomial regression analysis because this approach is judged to be more appropriate than Poisson regression, especially for low event rates.[21] We analysed change in post-bronchodilator FEV_1 with a repeated measurements model. The dependent variable was change from randomisation at each scheduled post-randomisation visit.

To address the issue of multiple comparisons, we used a hierarchical hypothesis-testing approach. If the primary outcome was positive, we tested the key secondary outcomes in the predefined order described in the Outcomes section (ie, post-bronchodilator FEV_1 first, then rate of severe chronic obstructive pulmonary disease exacerbations per patient per year). If a significant difference between treatments was not recorded for the primary or key secondary outcomes, we regarded all subsequent analyses as exploratory. Safety analyses were done descriptively.

With the assumption of a mean exacerbation rate of 1·25 per patient per year in the placebo group and a reduction in exacerbations of 20% with roflumilast 500 µg, and with the use of a Poisson regression model with a correction for overdispersion, we estimated that 967 patients per treatment group would provide 90% power to detect a significant difference between treatments for the primary endpoint with a two-sided α level of 0·05. The correction for overdispersion and mean exposure time was estimated from previously published roflumilast data.[16]

The scientific oversight of the study was provided by a steering committee responsible for providing scientific advice about the study design, execution, interpretation, and publication of results. A major adverse cardiovascular event adjudication committee, comprising independent cardiologists, adjudicated all cardiovascular events in a masked manner (appendix p 6). As sponsor of this study, Takeda (Takeda Development Centre Europe Ltd, London, UK) was responsible for study oversight and overall project management. PPD Global Ltd (Cambridge, UK) managed the administration, coordination, and monitoring of the study, including data management, statistical analysis, and the Interactive Voice Response System–Interactive Web Response System. SAS version 9.1.3 was used for all statistical analyses.

This study is registered with ClinicalTrials.gov, number NCT01329029.

Role of the funding source

The study was funded by Takeda. The steering committee, consisting of four academic investigators (PMAC, KFR, LMF, and FJM) and two employees of Takeda (U-MG and MB), developed the design and concept of the studies, approved the statistical plans, had full access to and interpreted the data, wrote the report, and had responsibility for the decision to publish the report. Data collection was coordinated by the two employees of Takeda (U-MG and MB). An academic author (FJM) wrote a draft of the report and an employee of Takeda (MB) did the statistical analysis. All authors vouch for the accuracy and completeness of the data and the analyses. Takeda did not place any restrictions on the academic authors regarding statements made in the final report. The corresponding author had full access to all the data in the study and final responsibility to submit for publication.

Results

Patient recruitment began on April 3, 2011, and the study ended on May 27, 2014. Of 2708 patients recruited, 1945 were randomly assigned and 1935 actually received treatment (969 in the roflumilast group and 966 in the placebo group; figure 1). Table 1 shows the demographic and baseline characteristics of the randomly assigned patients who received at least one dose of study medication. The mean pre-bronchodilator FEV_1 was 1·0 L (SD 0·32) and the mean post-bronchodilator FEV_1 was 1·1 L (SD 0·33). As anticipated in view of the inclusion criteria, 1900 (98%) of 1935 patients were using a combination of inhaled corticosteroid–longacting β_2 agonist according to the protocol. 1346 (70%) of 1935 patients were also using a longacting muscarinic antagonist during the course of the study, with similar numbers in each study group. Despite the use of these inhaled therapies, study participants had a history of frequent exacerbations and impaired health status.

Figure 1 shows patient disposition throughout the study. The patient withdrawal rate was similar in both treatment
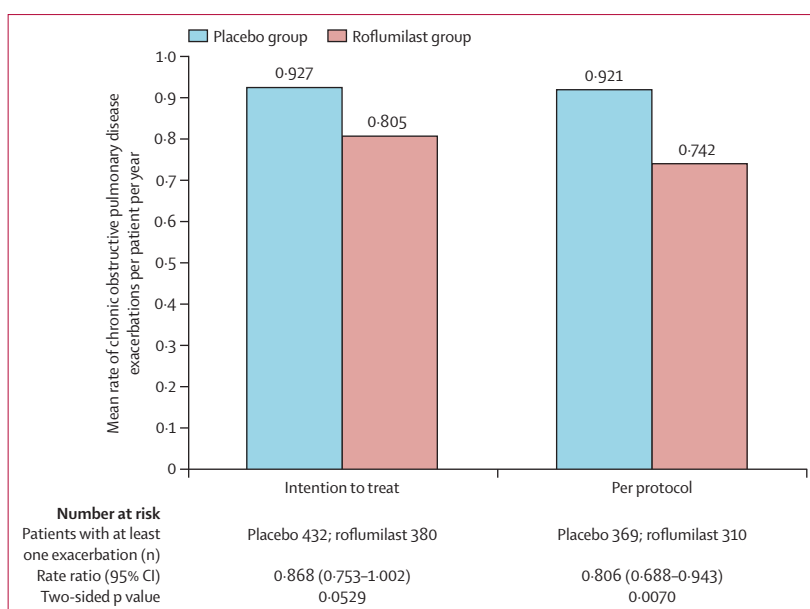

Figure 2: **Mean rate of moderate or severe chronic obstructive pulmonary disease exacerbations per patient per year**
Rate ratios, 95% CIs, and p values are based on a Poisson regression analysis.

groups (269 [28%] of 969 in the roflumilast group *vs* 192 [20%] of 966 in the placebo group). However, more patients withdrew in the first 12 weeks post-randomisation in the roflumilast group than in the placebo group (appendix p 10). Adherence to treatment was very high (99%) in both groups. 312 (16%) of 1935 participants had protocol violations (appendix p 15), which were mainly failures to meet the spirometric entry criteria.

Figure 2 illustrates and table 2 enumerates the effect of roflumilast versus placebo on the rate of moderate-to-severe exacerbations analysed with Poisson regression and negative binomial regression in the intention-to-treat and per-protocol populations. The numerical reductions were similar in both analyses. In the intention-to-treat population, the frequency of moderate-to-severe exacerbations was 13·2% lower in the roflumilast group than in the placebo group in the Poisson regression analysis (rate ratio [RR] 0·868 [95% CI 0·753–1·002], p=0·0529), and was 14·2% lower (0·858 [0·740–0·995], p=0·0424) in the negative binomial regression analysis. The reduction in the moderate-to-severe exacerbation rate was greater in the per-protocol population (analysed with Poisson regression) than in the intention-to-treat population (also analysed with Poisson regression; figure 2). Importantly, the effect of roflumilast was similar irrespective of concomitant treatment with a longacting muscarinic antagonist (appendix p 16). Table 2 also shows the effects of roflumilast treatment according to predefined, alternative definitions for exacerbations.

In view of the small number of anticipated events, we analysed the effect of roflumilast on severe exacerbations and on those necessitating hospital admission using

	Roflumilast (ITT n=969, PP n=810)	Placebo (ITT n=966, PP n=823)	Roflumilast *vs* placebo
Chronic obstructive pulmonary disease exacerbations (mean rate per patient per year [95% CI]; number of patients with at least one exacerbation)			
Moderate to severe			
Poisson regression, ITT*	0·805 (0·724–0·895); n=380	0·927 (0·843–1·020); n=432	RR 0·868 (0·753–1·002); p=0·0529
Poisson regression, PP*	0·742 (0·659–0·836); n=310	0·921 (0·831–1·021); n=369	RR 0·806 (0·688–0·943); p=0·0070
Negative binomial regression, ITT†	0·823 (0·738–0·917); n=380	0·959 (0·867–1·061); n=432	RR 0·858 (0·740–0·995); p=0·0424
Severe			
Negative binomial regression, ITT†	0·239 (0·201–0·283); n=151	0·315 (0·270–0·368); n=192	RR 0·757 (0·601–0·952); p=0·0175
Negative binomial regression, PP†	0·218 (0·180–0·264); n=120	0·326 (0·277–0·385); n=167	RR 0·668 (0·518–0·861); p=0·0018
Leading to hospital admission			
Negative binomial regression, ITT†	0·238 (0·200–0·283); n=150	0·313 (0·268–0·365); n=190	RR 0·761 (0·604–0·960); p=0·0209
Moderate			
Poisson regression, ITT*	0·574 (0·508–0·648); n=287	0·627 (0·561–0·702); n=333	RR 0·914 (0·775–1·078); p=0·2875
Moderate or treated with antibiotics			
Poisson regression, ITT*	0·794 (0·716–0·881); n=370	0·929 (0·847–1·019); n=433	RR 0·854 (0·744–0·982); p=0·0262
Moderate to severe or treated with antibiotics			
Poisson regression, ITT*	1·012 (0·922–1·110); n=448	1·210 (1·115–1·313); n=513	RR 0·837 (0·739–0·947); p=0·0047
Median time (days) to exacerbations (IQR); number of patients with at least one exacerbation			
Time to first moderate to severe exacerbation	103·5 (45·5–195·5); n=380	111·5 (46·5–191·0); n=432	HR 0·918 (0·800–1·054); p=0·2245
Time to second moderate to severe exacerbation	197·0 (135·0–281·0); n=153	190·0 (128·0–271·0); n=206	HR 0·790 (0·641–0·974); p=0·0272
Time to third moderate to severe exacerbation	248·0 (185·0–321·0); n=65	242·0 (174·0–280·0); n=93	HR 0·749 (0·545–1·028); p=0·0735
Lung function (mean change [SE]; number of patients with data available)			
Change from baseline to week 52 in post-bronchodilator FEV$_1$, ITT (mL)	52 (6·4); n=928	–4 (6·2); n=941	Difference 56 (38–73); p<0·0001
Change from baseline to week 52 in post-bronchodilator FVC, ITT (mL)	36 (11·4); n=928	–57 (11·1); n=941	Difference 92 (61–124); p<0·0001
Other outcomes (mean change [SE]; number of patients with data available)			
Change in CAT total score	–1·270 (0·1556); n=924	–0·985 (0·1518); n=940	Difference –0·285 (–0·711 to 0·142); p=0·1909

Data in second and third columns are mean rate per patient per year (95% CI), median (IQR), or mean change (SE); data in final column are RR or HR (95% CI), or mean difference (95% CI) and p values. ITT=intention to treat. PP=per protocol. RR=rate ratio. HR=hazard ratio. FEV$_1$=forced expiratory volume in 1 s. FVC=forced vital capacity. CAT=Chronic Obstructive Pulmonary Disease Assessment Test. *Estimated exacerbation rates based on a Poisson regression model. †Estimated exacerbation rates based on a negative binomial regression model excluding correction for overdispersion.

Table 2: Chronic obstructive pulmonary disease exacerbations, lung function variables, and other outcomes

a pre-planned negative binomial regression in the intention-to-treat population. Compared with placebo, roflumilast treatment led to a 24·3% reduction in severe events (RR 0·757 [95% CI 0·601–0·952], p=0·0175) and 23·9% reduction in exacerbations necessitating hospital admission (0·761 [0·604–0·960], p=0·0209; figure 3, table 2). This difference also remained significant in patients taking concomitant longacting muscarinic antagonist treatment (appendix p 16).

Compared with placebo, roflumilast therapy was associated with significant improvements from baseline in post-bronchodilator FEV$_1$ and FVC (table 2, figure 4). Changes in lung function were similar irrespective of treatment with longacting muscarinic antagonists: the mean post-bronchodilator FEV$_1$ increase with longacting muscarinic antagonist treatment was 59 mL (95% CI 39–79; p<0·0001), compared with 49 mL (15–83; p=0·0045) with no longacting muscarinic antagonist treatment (appendix p 17).

CAT score did not change with roflumilast therapy (table 2). Little consistent effect was recorded on other respiratory symptoms (eg, cough and sputum; appendix

p 18). A modest but significant decrease in rescue medication used was reported with roflumilast therapy (p=0·0027; appendix p 18).

One patient assigned to roflumilast accidentally received placebo during the entire study and was therefore included in the placebo group for the safety analysis. Adverse events were reported by 648 (67%) of 968 patients receiving roflumilast and by 572 (59%) of 967 patients in the placebo group (table 3); serious adverse events were reported by 249 (26%) patients in the roflumilast group and 285 (30%) in the placebo group. The most frequently reported adverse events were chronic obstructive pulmonary disease exacerbations, diarrhoea, and weight loss. Patient withdrawals associated with adverse events were more common in patients who were given roflumilast (104 [11%]) than in those receiving placebo (52 [5%]).

Mortality was a secondary efficacy endpoint in the study. During double-blind treatment, 17 (2%) deaths occurred in the roflumilast group and 18 (2%) in the placebo group (table 4). Additionally, the number of major adverse cardiovascular events did not differ between the two groups (table 4). No increase in the

incidence of pneumonia occurred during treatment with roflumilast (appendix p 19).

Weight loss was self-reported as an adverse event by 88 (9%) of 968 patients who received roflumilast compared with 27 (3%) of 967 in the placebo group. Patients who received roflumilast lost a mean of 2·65 kg (SD 4·37), compared with 0·15 kg (SD 3·69) in the placebo group (table 4). After the double-blind treatment period, patients stopped taking roflumilast or placebo provided by Takeda, but were able to take commercially available roflumilast; this group, which included 657 patients who received roflumilast during the treatment period and 737 patients who received placebo, were followed for another 3 months. During follow-up, 37 (6%) of the 657 patients randomly assigned to roflumilast continued on roflumilast, and 50 (7%) of the 737 patients randomly assigned to placebo received roflumilast. Bodyweight reportedly increased during this 3-month follow-up in roflumilast-treated patients who discontinued roflumilast (appendix p 11).

Discussion

Our findings show that roflumilast prevented moderate and severe exacerbations and improved lung function in patients with severe chronic obstructive pulmonary disease and chronic bronchitis who continued to have exacerbations despite inhaled combination therapy. The number of hospital admissions of patients with severe chronic obstructive pulmonary disease was significantly reduced in patients receiving roflumilast, without a change in symptoms. Additionally, the anticipated side-effects of roflumilast treatment were not increased despite concomitant combination inhaled therapy compared with previous studies with less underlying medication. These data provide important new information relevant to the treatment of these high-risk patients.

We aimed to detect a change in the number of moderate-to-severe exacerbations treated with oral corticosteroids. We used Poisson regression to compare our results with previously published data. In keeping with previous studies,[7,14,22,23] exacerbations in patients who received placebo were less frequent than expected, which is the most likely reason that the Poisson regression analysis based on the intention-to-treat population did not reach statistical significance. The negative binomial method used in the sensitivity analysis, which assumes a different exacerbation rate per patient than does the Poisson regression and offers a more precise estimate,[21] confirmed that the treatment differences in reducing moderate-to-severe exacerbations were significant. Additionally, when the analysis was restricted to the per-protocol population, corresponding to the approved indication for this drug, or to severe events leading to hospital admission or death, roflumilast treatment produced statistically significant reductions in exacerbations. This finding gives us confidence that a true reduction in exacerbation frequency occurred. This study is the first time a chronic obstructive pulmonary
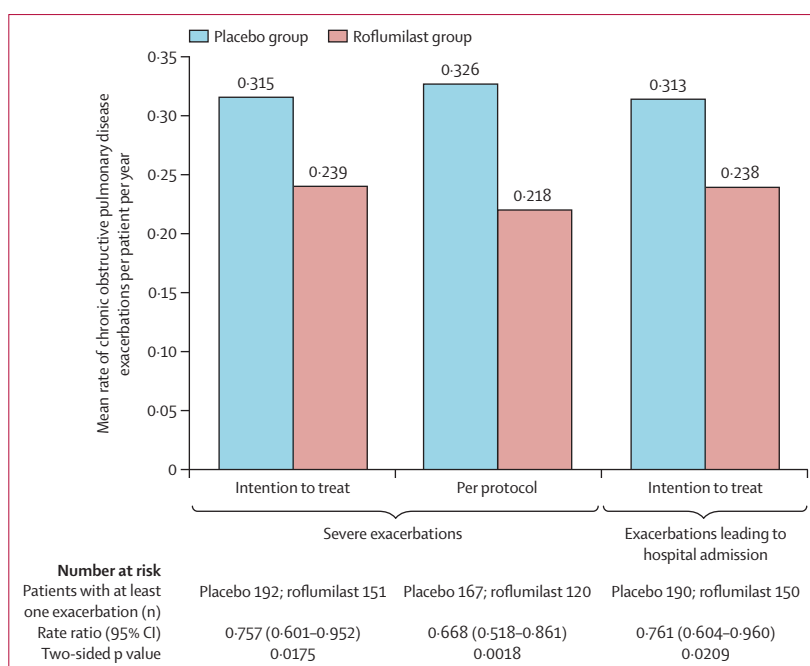

Figure 3: Mean rate of severe exacerbations or exacerbations leading to hospital admission per patient per year
Rate ratios, 95% CIs, and p values are based on a negative binomial regression model excluding a correction for overdispersion.
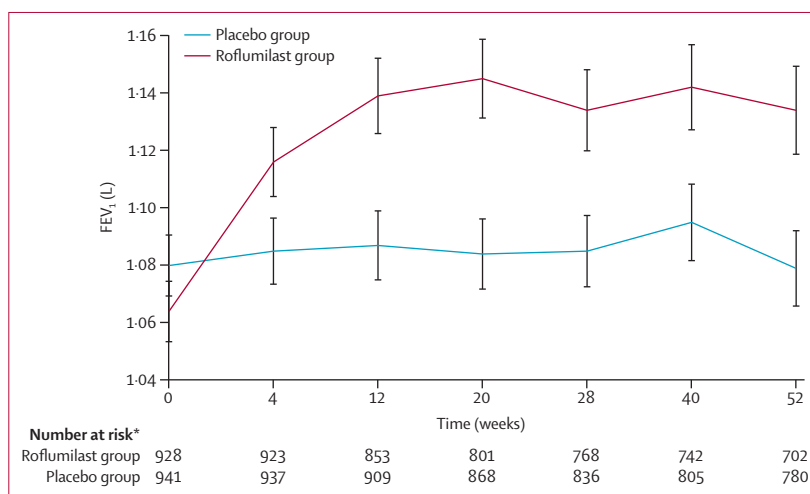

Figure 4: Post-bronchodilator FEV₁ in patients in the roflumilast and placebo groups over 52 weeks
Data are crude means (SE) in the intention-to-treat analysis, including measurements from baseline and at each post-randomisation visit up to the end of the treatment period. Treatment difference in FEV₁ after 52 weeks between the two groups: 56 mL (95% CI 0·038–0·073; p<0·0001). FEV₁=forced expiratory volume in 1 s. *Number of patients with data available.

disease treatment has been shown to reduce hospital admissions in patients receiving several inhaled treatments. Similarly, roflumilast reduced the number of exacerbations (p=0·0047) even when exacerbations treated with antibiotics alone were included with events treated with systemic glucocorticosteroids (moderate exacerbations) or events leading to hospital admission, death, or both (severe exacerbations), suggesting that

	Roflumilast group (n=968)	Placebo group (n=967)	Difference between groups (95% CI)
Chronic obstructive pulmonary disease exacerbation	145 (15%)	185 (19%)	–4·2% (–5·08 to –3·23)
Diarrhoea	99 (10%)	35 (4%)	6·6% (5·50 to 7·71)
Weight decrease	88 (9%)	27 (3%)	6·3% (5·22 to 7·38)
Nausea	55 (6%)	15 (2%)	4·1% (3·24 to 5·02)
Nasopharyngitis	52 (5%)	52 (5%)	0% (–0·04 to 0·03)
Headache	40 (4%)	21 (2%)	2·0% (1·34 to 2·58)
Pneumonia	39 (4%)	45 (5%)	–0·6% (–0·98 to –0·27)
Decreased appetite	36 (4%)	5 (1%)	3·2% (2·42 to 3·99)
Insomnia	29 (3%)	15 (2%)	1·4% (0·91 to 1·98)
Back pain	27 (3%)	14 (1%)	1·3% (0·83 to 1·85)
Upper abdominal pain	25 (3%)	10 (1%)	1·5% (1·00 to 2·10)
Hypertension	24 (3%)	27 (3%)	–0·3% (–0·56 to –0·06)

Data are n (%), unless otherwise indicated. Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event. One patient assigned to roflumilast accidentally received placebo for the entire duration of the study and was therefore included in the placebo group for the safety analysis.

Table 3: Adverse events occurring in at least 2·5% of patients in either treatment group

	Roflumilast group	Placebo group
Mortality (n=969 in roflumilast group; n=966 in placebo group)		
Deaths*	17 (2%)	18 (2%)
Primary cause of death*		
Chronic obstructive pulmonary disease exacerbation	7 (1%)	7 (1%)
Adverse event	10 (1%)	11 (1%)
Major adverse cardiovascular events (n=969 in roflumilast group; n=966 in placebo group)		
Composite major adverse cardiovascular events	16 (2%)	16 (2%)
Major adverse cardiovascular event due to cardiovascular death (including death from undetermined cause)	9 (1%)	7 (1%)
Major adverse cardiovascular event due to non-fatal myocardial infarction	3 (<1%)	6 (1%)
Major adverse cardiovascular event due to non-fatal stroke	4 (<1%)	3 (<1%)
Bodyweight changes (n=968 in roflumilast group; n=967 in placebo group)		
Change in bodyweight (kg) during double-blind treatment	–2·65 (4·37); n=938†	–0·15 (3·69); n=944†
Change in bodyweight (kg) post-randomisation to end of follow-up‡		
Roflumilast in post-treatment period	0·28 (1·58); n=36†	–1·62 (2·49); n=48†
No roflumilast in post-treatment period	1·10 (2·61); n=612†	0·11 (2·60); n=679†

Data are n (%) or mean (SD). One patient assigned to roflumilast received placebo for the entire study and was therefore included in the placebo group for the safety analysis. The total numbers of patients for the mortality and major adverse cardiovascular event analyses are based on the full analysis population of patients, whereas bodyweight is based on the safety population. *Analysis includes deaths during the double-blind treatment period only. †The number of patients with bodyweight measurements available. ‡Analysis includes data from the entire observation period.

Table 4: Key safety outcomes

phosphodiesterase 4 inhibition prevents all types of exacerbations in the specific group of patients assessed in the present study—ie, those with severe chronic obstructive pulmonary disease and chronic bronchitis at risk of frequent exacerbations that are inadequately controlled with standard inhaled therapy. Roflumilast did not change the time to first event but did reduce the total number of events and the time to a second event.

Roflumilast produced a sustained improvement in post-bronchodilator FEV_1 of 56 mL compared with placebo—a change similar to that noted previously in patients receiving less background therapy.[17,24,25] The change in lung function, which equated to 5% of the baseline value, is unlikely to have modified the patients' degree of breathlessness,[26] but could have contributed to the reduction in exacerbations. Significant changes in exacerbation frequency have been reported with inhaled corticosteroids without a corresponding change in lung function.[7] In view of the different mechanisms of action and the additional spirometric change following roflumilast treatment versus that due to inhaled corticosteroids, the change in exacerbation rate is likely to have been attributable to an anti-inflammatory effect of roflumilast. Neither the diary card symptom scores nor the CAT scores differed between groups. The CAT score is related to more complex measurements of health status similar to St George's Respiratory Questionnaire[27] and might be expected to improve as exacerbation rates fall.[28] A modest decrease in the use of rescue medication was noted, which may reflect an improvement in symptomatic control or the effect of experiencing fewer exacerbations.

Patients who received roflumilast reported the anticipated range of pharmacologically predictable side-effects. The pattern of withdrawal rates was similar to that in previous studies, and the overall adverse event rate was similar to that reported in less severely affected patients.[24] The magnitude of weight loss was similar to that seen in previous studies. However, bodyweight did not completely return to baseline 3 months after treatment stopped. The mechanism for the weight loss remains to be fully elucidated, although a direct metabolic effect has been recorded in patients with diabetes.[29] We noted no excess occurrence of pneumonia with roflumilast treatment. However, the overall rate of pneumonia (in patients taking roflumilast or placebo) was higher than previously reported, which is indicative of the known risk factors for pneumonia in this population.[30]

Our study did have limitations. Although patients were recruited according to their past history of exacerbations, the observed exacerbation rate was 25% lower than we anticipated. This finding might represent better medical care and treatment adherence than in previous studies, but also draws attention to the difficulty of using exacerbations as an endpoint in view of their known tendency for temporal clustering.[31] Although this study confirmed that no increase of cardiac side-effects occurred in patients treated with roflumilast,[32] we did not observe a reduction of major adverse cardiac events in the current study. The mortality in our patients was low compared with other reports,[3,4] especially in view of the high incidence of hospitalisations we saw, which is an established risk factor for mortality.[33] We recorded in-treatment mortality but did not follow all participants

to the end of the study, which probably led to an underestimation of the true risk of dying. Although we did not seek to exclude patients with concomitant cardiac disease, most patients died from respiratory causes, which is indicative of the disease severity of our patients.

Our results have important clinical implications. The ability of roflumilast to reduce exacerbations and improve lung function in patients with severe chronic obstructive pulmonary disease and chronic bronchitis receiving longacting β_2 agonist and longacting muscarinic antagonist bronchodilators and inhaled corticosteroids suggests that the ceiling of benefit from additional medical treatment in chronic obstructive pulmonary disease has not yet been reached. The reduction in hospital admissions recorded with roflumilast has positive clinical and economic implications and justifies our decision to target at-risk patients with chronic obstructive pulmonary disease. The identification of a specific patient subgroup in whom treatment can be justified is in keeping with existing approaches to personalised care. The REACT data should inform treatment choices for chronic obstructive pulmonary disease patients meeting our study criteria, who are at ongoing risk for exacerbations despite taking the recommended inhaled therapy.

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