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Roflumilast with long-acting β_2 agonists for COPD: influence of exacerbation history

E.D. Bateman[1], K.F. Rabe[2], P.M.A. Calverley[3], U.M. Goehring[4], M. Brose[5], D. Bredenbröker[4] and L. Fabbri[6]

[1] Department of Medicine, Pulmonology Division, University of Cape Town, Cape Town, South Africa
[2] University Kiel, Department of Medicine, Germany and Krankenhaus Grosshansdorf, Center for Pulmonology and Thoracic Surgery, Grosshansdorf, Germany
[3] School of Clinical Sciences, University Hospital Aintree, Liverpool, UK
[4] Respiratory Medicine, Nycomed GmbH, Konstanz, Germany
[5] Data Science, Nycomed GmbH, Konstanz, Germany
[6] Department of Oncology, Haematology and Respiratory Diseases, University of Modena & Reggio Emilia, Modena, Italy.

Address for correspondence: Eric D Bateman, University of Cape Town Lung Institute, George Street, Mowbray 7700, Cape Town, South Africa. Tel: +27 21 406-6901. Fax: +27 21 406 6902. Email: Eric.Bateman@uct.ac.za

Running head: Roflumilast with LABA for COPD

ABSTRACT

The oral, selective phosphodiesterase 4 inhibitor roflumilast reduces exacerbations and improves lung function in patients with severe-to-very-severe chronic obstructive pulmonary disease (COPD).

We investigated the efficacy and safety of roflumilast used concomitantly with long-acting β_2 agonists (LABAs) to reduce exacerbations, and the influence of exacerbation history. Pooled data were analysed from two 12-month, placebo-controlled roflumilast (500 μg once daily) studies involving 3091 patients with severe-to-very-severe COPD.

Approximately half of patients used concomitant LABAs; 39% used concomitant short-acting muscarinic antagonists (SAMA); 27% were frequent exacerbators (≥2 exacerbations/year). Roflumilast reduced the rate of moderate or severe exacerbations, with LABA (rate ratio [RR] 0.79 [95%CI: 0.69, 0.91]; p=0.001) or without LABA (RR 0.85 [95%CI: 0.74, 0.99]; p=0.039) and prolonged time both to first (p=0.035, p=0.300) and second (p=0.018, p=0.049) exacerbations. Frequent exacerbators experienced a reduction in moderate or severe exacerbations (RR 0.78 [95%CI: 0.66, 0.91]; p=0.002). Similarly, roflumilast remained effective with concomitant SAMA. No differences arose in adverse events between these subgroups.

Roflumilast may be used to reduce exacerbations, improving dyspnoea and lung function, without increasing adverse events in COPD patients receiving concomitant LABAs.

KEYWORDS: bronchodilators, chronic obstructive pulmonary disease, dyspnoea, exacerbation, lung function, roflumilast

INTRODUCTION

In patients with severe chronic obstructive pulmonary disease (COPD), exacerbations are significant events leading to loss of quality of life [1-3]. When severe or frequent, exacerbations are associated with accelerated decline in lung function and health status, increased mortality and escalating healthcare costs, making their prevention and early treatment a logical focus for management strategies and research [4]. A number of interventions have been shown to reduce COPD exacerbations, including influenza vaccination, smoking cessation, and the regular use of long-acting β_2 agonists (LABAs), long-acting anti-cholinergics and inhaled corticosteroids (ICS), given either alone or in combination [5-9].

The potential role of phosphodiesterase 4 inhibitors in airway diseases has been suggested following studies in both animals and humans [10, 11], but results with early molecules administered by either oral or inhaled routes were inconsistent [12, 13]. However, experience with roflumilast, which like earlier molecules has anti-inflammatory properties [14, 15], has been shown to be effective in improving lung function when given once daily to patients with moderate-to-very severe COPD [16, 17]. More recently, in two 6-month studies in patients with moderate-to-severe COPD receiving either salmeterol or tiotropium, the addition of roflumilast produced significant additional improvements in lung function [18]; however, improvements in secondary endpoints, including patient-related outcomes and exacerbations, were inconsistent and the studies were considered too short and insufficiently powered to provide confident estimates of the efficacy of roflumilast in reducing exacerbations on the background of concomitant long-acting bronchodilators. By contrast, improvements in lung function, COPD symptoms and rate of exacerbations were observed with roflumilast in two larger 12-month trials in patients with severe-to-very-severe COPD, who were allowed to receive short-acting β_2 agonists (SABAs) as needed and who continued their regular treatment with either short-acting muscarinic antagonists (SAMAs) or LABAs but not with ICS [19]. These studies selected patients at greater risk of COPD exacerbations by requiring, at enrolment, that patients had a chronic productive cough.

We report here further results of a pre-specified, additional, pooled analysis of the latter two 12-month trials, addressing clinically relevant questions in patients with severe-to-very-severe COPD. First, whether the reduction in exacerbation rates and the other benefits are influenced by the concomitant use of LABAs (in use by almost half of the patients recruited); and second, whether the reduction in COPD exacerbations seen with roflumilast is in patients at greatest risk — those with a history of repeated episodes in the previous year. Other objectives were to assess the influence of a history of prior ICS use on the efficacy of roflumilast, and to assess its safety in these treatment categories.

METHODS

Data were pooled from two studies (M2-124 and M2-125; ClinicalTrials.gov identifiers NCT00297102 and NCT00297115). The main findings have been reported previously [19]. The participating countries were Australia, Austria, Canada, France, Germany, Hungary, India, Italy, New Zealand, Poland, Romania, Russia, South Africa, Spain, the UK and the USA (see supplementary table 1 for distribution of patients).

Patients

The studies enrolled patients aged ≥40 yrs with a clinical diagnosis of severe-to-very-severe COPD (confirmed by a post-bronchodilator forced expiratory volume in 1 second [FEV_1]/forced vital capacity ratio ≤0.70 and a post-bronchodilator FEV_1 ≤50% of the predicted value) and a chronic productive cough.

All participants were current or former smokers, with a minimum smoking history of at least 20 pack-yrs, who had reported at least one COPD exacerbation in the previous year that required systemic corticosteroid treatment and/or hospital admission. Details of bronchodilator tests and exclusion criteria have been reported previously [19]. The studies were approved by local ethics committees and performed according to Good Clinical Practice guidelines and the Declaration of Helsinki.

Interventions

The study design, treatment details and randomisation procedures have been reported previously [19]. Briefly, following an initial 4-wk, single-blind run-in during which patients received a placebo tablet once daily and maintained a diary card, participants were randomly assigned to receive oral roflumilast 500 μg or placebo once daily for 52 wks. SABAs were used as needed and short-acting anticholinergic drugs were allowed at stable doses for participants not receiving LABAs during the studies. Long-acting anticholinergic drugs and ICS were not allowed during either study. Concomitant use of both LABAs and SAMAs on a regular basis was not allowed during the treatment period.

Patients were stratified according to smoking status and LABA use (salmeterol or formoterol), with the intention of randomising approximately equal proportions of those receiving and not receiving LABAs. Assessments were made at 4-wk intervals for 12 wks and every 8 wks thereafter. At each visit, spirometry was performed before and 15–45 min after administration of inhaled albuterol 400 μg. Details of exacerbations, adverse events, body weight, adherence to treatment, completeness of daily diary card recordings, rescue SABA use and other endpoints were recorded.

Study endpoints

The primary efficacy endpoints in both studies were mean change from baseline in pre-bronchodilator FEV_1 and reduction in the rate of moderate or severe exacerbations. Exacerbations were defined as moderate if they required oral or parenteral corticosteroids, and severe if they were associated with hospital admission or death. A full description of secondary endpoints, which included mean change in post-bronchodilator FEV_1 and mean transitional dyspnoea index (TDI) focal score during the treatment period, is provided in the previous report [19]. The assessment of COPD exacerbations in the previous year was based on documentation in patients' files. To ensure correct treatment and documentation of exacerbations during the study, the investigator regularly monitored the patient's well-being by telephone contact; in addition, all patients received a paper diary to track and report their daily COPD symptoms. Details of all exacerbations were captured in the source notes.

Statistical analysis

All reported efficacy analyses were performed in the intention-to-treat (ITT) population, with the exception of the investigation of adverse events. Data are presented as mean and standard deviation, unless otherwise stated. Results are based on pre-specified and additional post-hoc analyses of pooled data from both trials. Pre-specified analyses included mean rate of exacerbations, pre- and post-bronchodilator FEV_1, and overall results of TDI. Post-hoc analyses were subgroup analyses relating to exacerbation history, time to events, including the onset of a third exacerbation, and subgroup analyses involving TDI and adverse events by LABA subgroup.

We analysed the rate of moderate or severe exacerbations using a Poisson regression model with a correction for over-dispersion, which accounts additionally for the variability in exacerbation rates between patients. A Cox proportional hazard model was used to test for differences in time-to-event data. Changes from baseline in pre- and post-bronchodilator FEV_1 as well as the TDI focal score were analysed using a repeated-measures analysis of covariance with all data available for patients during the 52-wk treatment [20].

For the regression models (Poisson, Cox and analysis of covariance), the covariates included treatment, age, sex, smoking status (current or former) and treatment with LABAs. In the Cox regression analysis, country pool and study were included as strata to allow for individual baseline hazards for each country pool and study. In the Poisson regression analysis, baseline post-bronchodilator FEV_1 (% of predicted value) was also included as a covariate. Adverse events were analysed using descriptive statistics.

The pooled data of both trials were analysed for all patients as well as for the following subgroups: concomitant LABA use, concomitant SAMA use, previous ICS use, and exacerbation history. For the analysis by previous exacerbations, patients were grouped according to the number of moderate or severe COPD exacerbations they had experienced in the previous year: frequent exacerbators were defined as those experiencing ≥2 exacerbations, infrequent exacerbators had <2 exacerbations.

RESULTS

Patients

The profile of patients recruited for the M2-124 and M2-125 studies is provided in the primary publication [19]. A total of 3091 patients were randomly assigned and treated (ITT population) and 2099 completed the studies. Baseline demographics and patient characteristics stratified by LABA use and exacerbation history are shown in table 1 (see supplementary table 2 for the other subgroups). Approximately half of the patients reported concomitant treatment with LABAs at baseline (roflumilast, 49%; placebo, 51%); 27% (both roflumilast and placebo) had ≥2 exacerbations (i.e. were frequent exacerbators) in the previous year; more than one third of patients reported use of SAMAs (roflumilast, 38%; placebo, 40%) and 42% (>60% in the LABA group and 23% in those not taking LABAs) had been previously treated with ICS. Patients receiving LABAs had similar pre-bronchodilator FEV_1 values to those not receiving LABAs, but had a smaller increase after administration of

a SABA. A slightly greater number of frequent exacerbators were receiving LABAs and/or ICS at enrolment compared with infrequent exacerbators (table 1).

Exacerbations

The mean rate of moderate or severe exacerbations per patient per year was significantly lower in patients receiving roflumilast than in those receiving placebo across all patients (rate ratio [RR]: 0.83; 95% confidence interval [CI]: 0.75, 0.92; p=0.0003) and regardless of concomitant use of LABAs (RR: 0.79; 95% CI: 0.69, 0.91; p=0.0011) (figure 1). The relative reduction in moderate or severe exacerbation rates in patients treated with LABAs was 20.7% (absolute rate reduction: 0.322 exacerbations per patient per year), and this was unaffected by pre-treatment with LABA before the study began (supplementary table 3). The corresponding number needed to treat with roflumilast to prevent one moderate or severe exacerbation per year was 3.2. The time to onset of the first, second and third moderate or severe COPD exacerbation was significantly delayed across all patients and in the subgroup using LABAs (p=0.0349, p=0.0179 and p=0.0075; roflumilast vs placebo, respectively); in the subgroup not receiving LABAs, only the time to onset of the second exacerbation was significantly delayed (figure 2 and table 2).

In both frequent and infrequent exacerbators, roflumilast significantly reduced the mean rate of moderate or severe exacerbations (RR: 0.78; 95% CI: 0.66, 0.91; p=0.0017 and RR: 0.84; 95% CI: 0.73, 0.95; p=0.0062, respectively) (figure 3). Time to onset for second (p=0.0107) and third (p=0.0074) exacerbation was delayed with roflumilast in frequent exacerbators; time to onset for second (p=0.0245) exacerbation was delayed with roflumilast in infrequent exacerbators.

The mean rate of exacerbations was also significantly lower with roflumilast compared with placebo, regardless of SAMA use or previous treatment with ICS (supplementary table 4). In the subgroup not receiving SAMAs and the previous ICS subgroup, the time to second and third exacerbations was significantly delayed; in the SAMA and no previous ICS subgroups, only the time to second exacerbation was significantly delayed (supplementary table 5).

TDI focal score

The TDI focal score was significantly reduced in patients receiving roflumilast compared with those receiving placebo, regardless of concomitant treatment with LABAs; the difference between roflumilast and placebo was significantly reduced in frequent exacerbators (table 3 and supplementary table 6).

Lung function

Both pre- and post-bronchodilator FEV_1 significantly improved with roflumilast compared with placebo, irrespective of concomitant treatment with LABAs, SAMAs or previous ICS use and by previous exacerbation frequency (supplementary tables 7 and 8).

Safety

The overall pattern of adverse events in patients with or without concomitant LABAs (table 4) was similar to that reported across all patients [19]. An imbalance was observed for episodes of influenza and upper respiratory tract infection, with lower rates in patients who received concomitant LABAs; however, these patients reported a higher number of COPD-related events compared with those not receiving LABAs. There was no indication that roflumilast increased LABA-related adverse events such as tachycardia or cardiovascular events, and concomitant LABA use did not increase the frequency of events associated with roflumilast treatment alone.

DISCUSSION

Roflumilast has been shown to reduce exacerbations in patients at risk of these episodes, but whether this occurs on top of the effect of other therapy has been less clear. In this pre-specified combined analysis of data from two large randomised clinical trials, roflumilast decreased the rate of COPD exacerbations and improved lung function (pre- and post-bronchodilator FEV_1) despite concomitant treatment with LABAs. In addition, the time to onset of the first, second and third moderate or severe exacerbation was reduced by roflumilast regardless of concomitant LABA use, while the frequency of adverse events associated with roflumilast treatment was not different in those with or without LABAs. The relative reduction in moderate or severe exacerbation rates in patients treated with LABAs was 20.7% and the corresponding number needed to treat with roflumilast to prevent one moderate or severe exacerbation per year was low (3.2).

Although the treatment effect of roflumilast together with concomitant long-acting bronchodilators has been reported in two 6-month studies in patients with moderate-to-severe COPD receiving either salmeterol or tiotropium [18], these studies were powered on lung function and not on patient-related outcomes or exacerbations. The addition of roflumilast to salmeterol achieved a similar improvement in mean pre-bronchodilator FEV_1 (49 mL; $p<0.0001$ vs placebo) to that reported in the two 12-month studies, reduced some respiratory symptoms and reduced the proportion of patients experiencing an exacerbation of any severity (28% vs 34%; $p=0.0419$). Taken together, the results of these four studies support the concomitant use of roflumilast with long-acting bronchodilators for three major endpoints: lung function, symptoms of COPD and exacerbations.

Additional post-hoc analyses showed that the reduction in exacerbation rates was statistically significant in frequent exacerbators (patients with a history of ≥2 exacerbations in the previous year). Recently published data found a prior history of exacerbations to be a very strong predictor of future frequent exacerbations (defined as ≥2 exacerbations in a year) and the category ‘frequent exacerbators’ was suggested as a distinct subgroup (or phenotype) of patients who could be easily identified based on patient recall and targeted with specific exacerbation prevention strategies [21]. Other significant findings are that previous use of ICS and concomitant SAMA treatment had no bearing on the results observed with roflumilast. Taken together, these results confirm and extend the findings of the primary analysis, which showed that roflumilast improves lung function and reduces exacerbations in patients with severe-to-very-severe COPD and a chronic productive cough [19].

Current understanding of the pathogenesis and natural history of COPD recognises it as a disease with a variety of manifestations and co-morbidities, demanding an individualised approach based on the presence of factors known to be associated with disease progression and worsening treatment outcomes [22]. These factors include continued smoking, the presence of chronic bronchitis, airway hyper-responsiveness, severity of disease and conditions that increase the risk of COPD exacerbations [23]. Indeed, frequent exacerbations are associated with accelerated loss of lung function, decline in health status and increased mortality, and may be a genuine marker of disease severity [1, 24, 25]. Thus, current guidelines for the management of COPD recommend escalation of maintenance treatment with increasing severity of disease, beginning with the addition of one or more long-acting bronchodilators. The major effects of long-acting bronchodilators are seen in their effect on symptoms and lung function, but they may serve to identify the 'frequent exacerbator' phenotype, who in spite of this treatment, continue to exacerbate. Currently, guidelines recommend the addition of regular ICS in such patients [4, 26]. Our analysis supports the efficacy of roflumilast at this stage in the treatment algorithm, both in patients who have a history of frequent exacerbations and in those who have previously taken ICS. Based on the demographic data, patients previously receiving ICS tended to have more severe disease, and might be more prone to exacerbations [21]. Similarly, patients receiving LABAs and SAMAs appeared to have more severe disease (see supplementary table 2).

Like other phosphodiesterase 4 inhibitors, roflumilast does not have direct bronchodilating effects [27, 28] and, unlike LABAs and LAMAs, only small improvements in lung function are observed with this treatment; together with evidence from preclinical studies, this suggests that it is likely that roflumilast's mode of action is via anti-inflammatory mechanisms [14, 15]. In addition, improvements in lung function with roflumilast are of similar magnitude whether it is administered before or after other bronchodilators [18, 19]. It is reassuring that the effect of roflumilast on exacerbations is not a one-off phenomenon, but persists and influences the frequency and time to both second and subsequent exacerbations.

The present analysis has some limitations. Firstly, the history of exacerbations over the previous year relied on outpatient records, which may have been incomplete, particularly if exacerbations did not require hospital admission; this could have resulted in underreporting of COPD exacerbations due to lack of written proof and confirmation of the diagnosis. However, such underreporting was likely to be similar in both treatment arms. Secondly, while the analyses of time to onset of the first and second COPD exacerbations were pre-specified, several subgroup analyses were not. In addition, within the Cox proportional hazard model the assumption of proportionality does not fully hold for the analysis of the time to the second and third exacerbations.

In conclusion, this pooled analysis of two large 12-month studies confirms that roflumilast 500 µg once daily improves lung function, reduces COPD symptoms and the rate of moderate or severe exacerbations, and increases time to onset of moderate or severe exacerbations in patients with severe-to-very-severe COPD receiving concomitant LABAs. It was effective in those who had previously been receiving ICS, who tended to have more severe disease and a history of frequent exacerbations (≥2 exacerbations per year) subgroup. In addition, there was no indication that roflumilast increased LABA-related adverse events and concomitant treatment with LABAs did not increase the frequency of adverse events associated with roflumilast treatment alone. These results support the recommendation that roflumilast be used concomitantly with long-acting bronchodilators in patients with severe-to-very-severe COPD and symptoms of chronic bronchitis.

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TABLE 1 Baseline characteristics by concomitant treatment with a long-acting β_2 agonist (LABA) and frequency of previous exacerbations[a]. Intention-to-treat analysis

Baseline characteristic	Concomitant treatment				Exacerbations in the previous year[i]			
	With LABA		Without LABA		Infrequent (<2 per year)		Frequent (≥2 per year)	
	Roflumilast (n=749)	Placebo (n=793)	Roflumilast (n=788)	Placebo (n=761)	Roflumilast (n=1124)	Placebo (n=1137)	Roflumilast (n=413)	Placebo (n=417)
Age (years)[b]	64.2 (9.3)	64.7 (9.0)	63.3 (9.4)	63.0 (9.2)	63.7 (9.2)	64.0 (9.1)	63.8 (9.8)	63.4 (9.3)
Men, n (%)	558 (74.5)	591 (74.5)	592 (75.1)	595 (78.2)	853 (75.9)	877 (77.1)	297 (71.9)	309 (74.1)
Cigarette pack-yr[b,c]	48.9 (24.9)	47.6 (23.9)	47.8 (25.5)	46.1 (22.6)	49.0 (25.0)	47.0 (23.4)	46.6 (25.8)	46.6 (23.1)
Current smoker, n (%)[b]	286 (38.2)	294 (37.1)	349 (44.3)	349 (45.9)	470 (41.8)	467 (41.1)	165 (40.0)	176 (42.2)
Pre-bronchodilator FEV_1 (l)[d]	1.0 (0.4)	1.0 (0.3)	1.0 (0.4)	1.0 (0.4)	1.0 (0.4)	1.03 (0.4)	1.0 (0.4)	0.97 (0.3)
Post-bronchodilator FEV_1 (l)[d]	1.1 (0.4)	1.1 (0.3)	1.1 (0.4)	1.1 (0.4)	1.1 (0.4)	1.13 (0.4)	1.1 (0.4)	1.1 (0.4)
Pre-bronchodilator FEV_1 (% predicted)[d]	33.2 (10.1)	33.4 (9.5)	32.9 (10.5)	33.3 (11.6)	32.7 (10.3)	33.8 (10.3)	33.9 (10.4)	32.1 (11.1)
Post-bronchodilator FEV_1 (% predicted)[d]	35.7 (10.5)	35.9 (9.7)	36.5 (10.7)	36.8 (11.7)	35.9 (10.5)	37.0 (10.7)	36.7 (10.9)	34.6 (10.7)
FEV_1 reversibility increase (%)[d]	8.5 (12.5)	8.6 (15.0)	12.8 (16.3)	12.6 (16.3)	11.1 (14.5)	10.9 (14.9)	9.5 (15.3)	9.7 (17.9)
Post-bronchodilator FEV_1/FVC (%)[d]	42.1 (11.0)	41.4 (10.5)	42.5 (11.4)	42.6 (11.3)	41.8 (11.0)	42.1 (10.8)	43.5 (11.6)	41.6 (11.2)
Body mass index (kg/m^2)[d]	26.8 (5.5)	26.3 (5.4)	24.9 (6.1)	25.0 (5.8)	25.6 (5.9)	25.7 (5.7)	26.2 (5.7)	25.7 (5.7)
COPD severity, n (%)[b,e,f]								
Severe	452 (60.3)	529 (66.7)	491 (62.3)	460 (60.4)	697 (62.0)	750 (66.0)	246 (59.6)	239 (57.3)
Very severe	239 (31.9)	218 (27.5)	224 (28.4)	222 (29.2)	336 (29.9)	289 (25.4)	127 (30.8)	151 (36.2)
Concomitant LABA, n	–	–	–	–	523 (46.5)	546 (48.0)	226 (54.7)	247 (59.2)

(%)[g]								
Concomitant SAMA, n (%)[g]	162 (21.6)	178 (22.4)	426 (54.1)	438 (57.6)	443 (39.4)	448 (39.4)	145 (35.1)	168 (40.3)
Prior ICS[h], n (%)	469 (62.6)	476 (60.0)	181 (23.0)	181 (23.8)	460 (40.9)	462 (40.6)	190 (46.0)	195 (46.8)

Data shown are mean (SD) values (unless otherwise stated).

[a]COPD exacerbations in the previous year (based on patient recall); [b]Measurements were taken at the beginning of run-in period; [c]Pack-yr = duration of smoking history (years) × average number of cigarettes per day/20; [d]Measurements were taken at baseline; [e]Based on the criteria of the Global Initiative for Chronic Obstructive Lung Disease; [f]Percentages do not add up to 100% as patients with mild or moderate COPD are not shown; [g]Based on whether the patient had used medication at least once within the start and up to the end of the treatment period inclusive; [h]Based on whether the patient had used inhaled corticosteroid therapy at least once within the period starting the day after the first visit until the day before randomization, inclusive; [i]post-hoc analyses.

COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC, forced vital capacity; SAMA: short-acting muscarinic antagonist; SD: standard deviation.

TABLE 2 Time to onset of first, second or third moderate or severe COPD exacerbation[a] in patient groups receiving concomitant treatment with a long-acting β_2 agonist (LABA) and by previous exacerbations[b]. Intention-to-treat analysis

	Patients with event, n (%)		Median (68% range) [days]		Hazard ratio (95% CI)	2-sided p-value
	Roflumilast	Placebo	Roflumilast	Placebo		
All patients						
First	717 (46.6)	821 (52.8)	80.0 (18.0–245.0)	71.0 (19.0–200.0)	0.886 (0.802–0.980)	0.0185
Second	329 (21.4)	430 (27.7)	177.0 (72.0–307.0)	148.0 (71.0–267.0)	0.791 (0.685–0.914)	0.0014
Third[c]	152 (9.9)	218 (14.0)	224.5 (123.0–328.0)	197.0 (114.0–308.0)	0.730 (0.593–0.899)	0.0031
With LABA[c]						
First	376 (50.2)	463 (58.4)	74.5 (17.0–220.0)	67.0 (17.0–198.0)	0.863 (0.753–0.990)	0.0349
Second	180 (24.0)	250 (31.5)	160.5 (71.0–301.0)	148.0 (71.0–252.0)	0.792 (0.653–0.961)	0.0179
Third	82 (10.9)	133 (16.8)	222.5 (129.0–312.0)	201.0 (112.0–304.0)	0.684 (0.518–0.903)	0.0075
Without LABA[c]						
First	341 (43.3)	358 (47.0)	85.0 (20.0–266.0)	74.0 (21.0–212.0)	0.924 (0.796–1.073)	0.3002
Second	149 (18.9)	180 (23.7)	194.0 (75.0–316.0)	151.0 (75.0–289.0)	0.803 (0.646–0.999)	0.0493
Third	70 (8.9)	85 (11.2)	226.5 (119.0–332.0)	189.0 (114.0–309.0)	0.792 (0.576–1.090)	0.1530
Infrequent exacerbators[c]						
First	470 (41.8)	545 (47.9)	85.0 (21.0–255.0)	76.0 (20.0–216.0)	0.885 (0.781–1.001)	0.0523
Second	197 (17.5)	260 (22.9)	188.0 (79.0–312.0)	155.0 (75.0–277.0)	0.808 (0.671–0.973)	0.0245
Third	85 (7.6)	118 (10.4)	224.0 (129.0–312.0)	198.5 (114.0–312.0)	0.776 (0.586–1.027)	0.0765
Frequent exacerbators[c]						
First	247 (59.8)	276 (66.2)	69.0 (14.0–215.0)	59.0 (17.0–182.0)	0.895 (0.752–1.065)	0.2101
Second	132 (32.0)	170 (40.8)	155.0 (60.0–289.0)	141.0 (71.0–246.0)	0.740 (0.588–0.932)	0.0107
Third	67 (16.2)	100 (24.0)	227.0 (122.0–332.0)	194.0 (113.5–289.0)	0.653 (0.478–0.892)	0.0074

Hazard ratio, 95% CI and p-values are based on Cox proportional hazards model with the following factors and covariates: treatment, age, sex, smoking status and strata: study and country pool. For all groups apart from LABA usage, concomitant treatment with a LABA was also included as a factor.
[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death; [b]COPD exacerbations in the previous year (based on patient recall). Defined as infrequent if <2 and frequent if ≥2 exacerbations per year; [c]Post-hoc analyses.
CI: confidence interval; COPD: chronic obstructive pulmonary disease.

TABLE 3 Mean change (improvement) in transitional dyspnoea index (TDI) focal score according to concomitant treatment with a long-acting β_2 agonist (LABA) use and frequency of previous exacerbations[a]. Intention-to-treat analysis. TDI is graded from 0 to 4, where 0 is most severe; a change in TDI score of 1.0 unit is considered clinically relevant

	Roflumilast	**Placebo**	**Difference (score, [95% CI])**	**2-sided p-value**
All patients	0.662 n=1470	0.409 n=1514	0.253 (0.104–0.402)	0.0009
LABA use[b]				
With LABA	0.448 n=718	0.159 n=775	0.289 (0.081–0.497)	0.0066
Without LABA	0.904 n=752	0.680 n=739	0.224 (0.002–0.446)	0.0477
Previous exacerbations[b]				
Infrequent	0.604 n=1070	0.451 n=1105	0.153 (–0.026–0.332)	0.0948
Frequent	0.698 n=400	0.201 n=409	0.497 (0.207–0.786)	0.0008

Least square means, 95% CI and p-values are based on a repeated measurements analysis of covariance model with the following factors and covariates: treatment, baseline value, age, sex, smoking status, time, treatment-by-time interaction, study and country pool (only for the overall population). For all groups apart from LABA usage, concomitant treatment with LABA was also included as a factor.

[a]COPD exacerbations in the previous year (based on patient recall). Defined as infrequent if <2 and frequent if ≥2 exacerbations per year; [b]Post-hoc analyses.

CI: confidence interval.

TABLE 4 Most common adverse events (≥2.5% of patients in any treatment group) by concomitant treatment with a long-acting β_2 agonist (LABA)

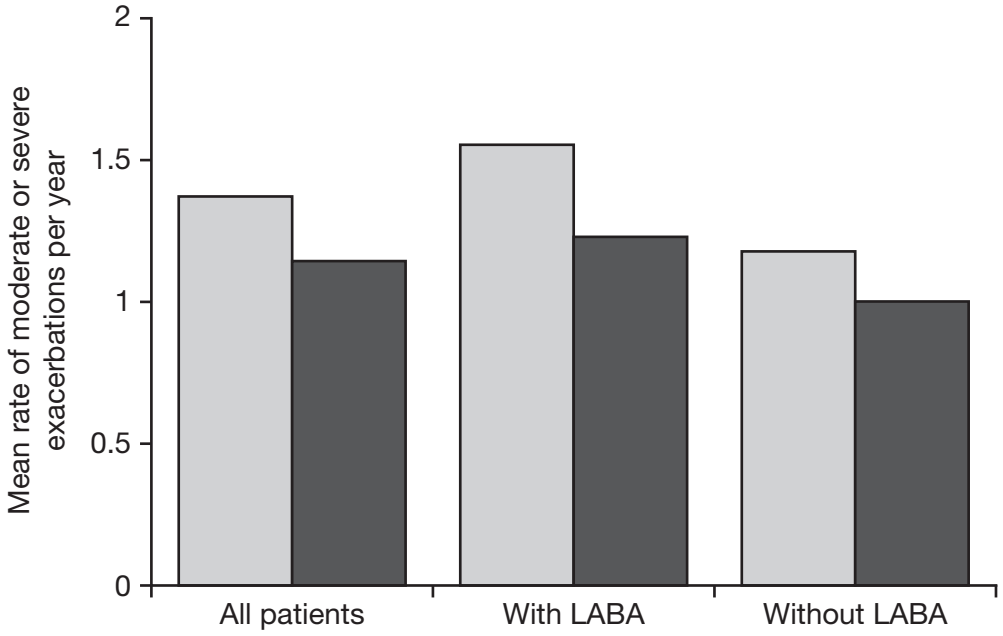
	With LABA[b]		Without LABA[b]	
Adverse events	**Roflumilast[a] (n=753)**	**Placebo (n=789)**	**Roflumilast (n=794)**	**Placebo (n=756)**
COPD	101 (13.4)	130 (16.5)	56 (7.1)	74 (9.8)
Weight decrease	77 (10.2)	24 (3.0)	80 (10.1)	20 (2.6)
Diarrhoea	58 (7.7)	20 (2.5)	72 (9.1)	29 (3.8)
Nasopharyngitis	42 (5.6)	48 (6.1)	50 (6.3)	49 (6.5)
Bronchitis	28 (3.7)	38 (4.8)	28 (3.5)	26 (3.4)
Pneumonia	28 (3.7)	20 (2.5)	14 (1.8)	11 (1.5)
Back pain	25 (3.3)	20 (2.5)	25 (3.1)	15 (2.0)
Nausea	24 (3.2)	11 (1.4)	38 (4.8)	19 (2.5)
Headache	22 (2.9)	15 (1.9)	29 (3.7)	10 (1.3)
Hypertension	21 (2.8)	22 (2.8)	17 (2.1)	26 (3.4)
Insomnia	16 (2.1)	7 (0.9)	21 (2.6)	13 (1.7)
Upper respiratory tract infection	14 (1.9)	22 (2.8)	35 (4.4)	37 (4.9)
Dizziness	10 (1.3)	7 (0.9)	20 (2.5)	9 (1.2)
Influenza	9 (1.2)	11 (1.4)	30 (3.8)	27 (3.6)
Urinary tract infection	9 (1.2)	6 (0.8)	21 (2.6)	6 (0.8)
Gamma-glutamyltransferase increased	1 (0.1)	11 (1.4)	10 (1.3)	19 (2.5)

Data are number (%). Adverse events were reported independently of the investigator causality assessments. Patients might have had more than one adverse event.
[a]Incidence of adverse events in the roflumilast with LABA group, in descending order**;** [b]Post-hoc analyses.
COPD: chronic obstructive pulmonary disease.

FIGURE LEGENDS

FIGURE 1. Mean rate of moderate or severe exacerbations[a] per patient per year according to concomitant treatment with a long-acting β_2 agonist (LABA). The mean percentage difference between exacerbation rates for roflumilast-treated and placebo-treated patients across all patients was –16.9% (95% CI, –25, –8), while the percentage difference in patients treated with LABAs was –20.7% (95% CI, –31, –9) and in those not receiving LABAs the difference was –14.6% (95% CI, –26, –1). Intention-to-treat analysis.

Rate ratio, 95% CI and p-values are based on a Poisson regression model with the following factors and covariates: treatment, age, sex, smoking status, baseline post-bronchodilator FEV_1 (% predicted), study and country pool (only for the overall population). For all groups apart from LABA usage, concomitant LABA treatment was also included as a factor.
[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death.
CI: confidence interval; FEV_1: forced expiratory volume in 1 second.



	All patients	With LABA	Without LABA
Placebo	1.374 (n=1554)	1.554 (n=793)	1.17 (n=761)
Roflumilast	1.142 (n=1537)	1.232 (n=749)	0.999 (n=788)
Rate ratio (95% CI)	0.831 (0.75, 0.92)	0.793 (0.69, 0.91)	0.854 (0.74, 0.99)
Two-sided p-value	0.0003	0.0011	0.0387

FIGURE 2. Time to onset of first (A, B), second (C, D) and third (E, F) moderate or severe exacerbation[a], with and without a long-acting β_2 agonist (LABA).

[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death.

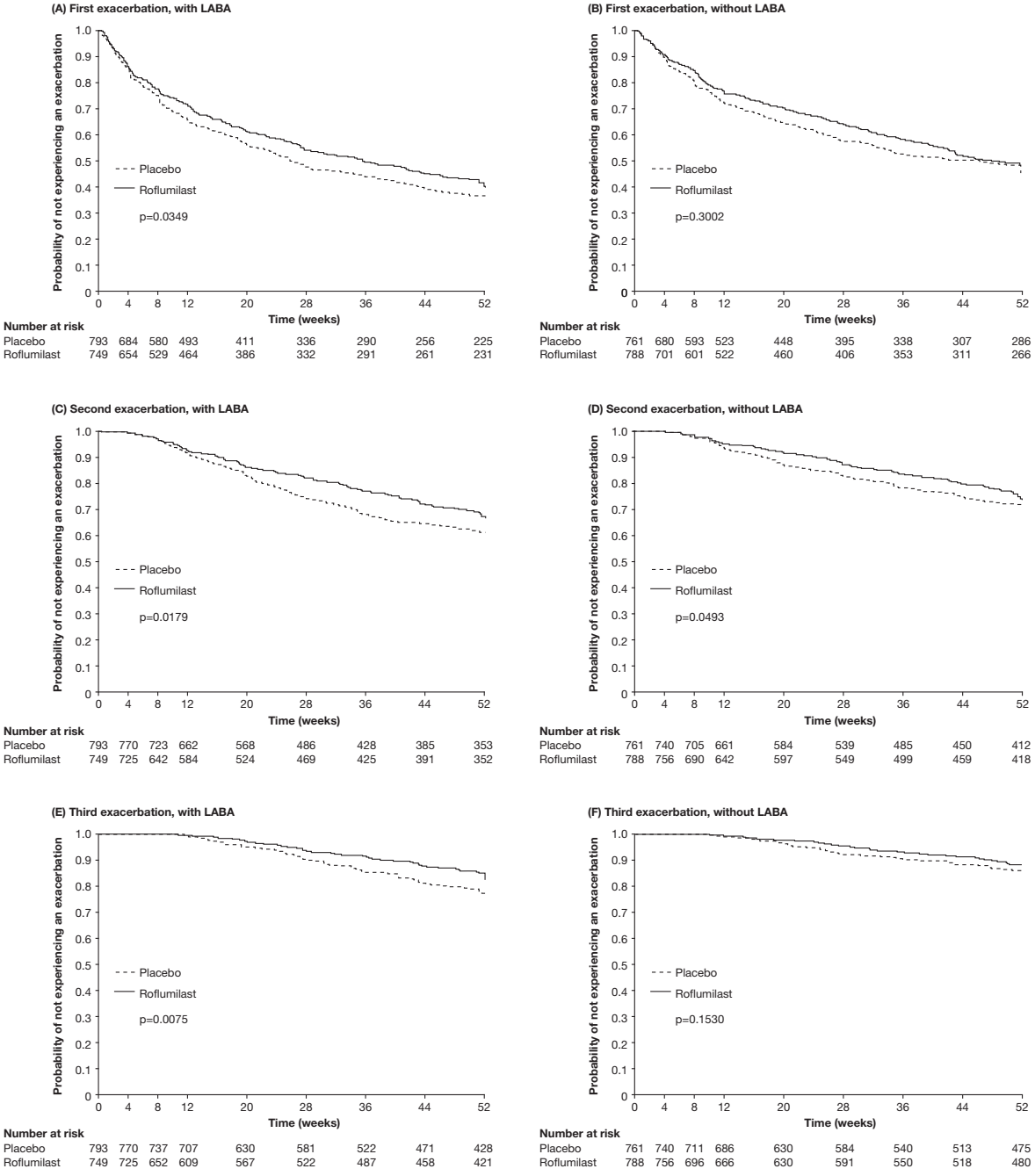
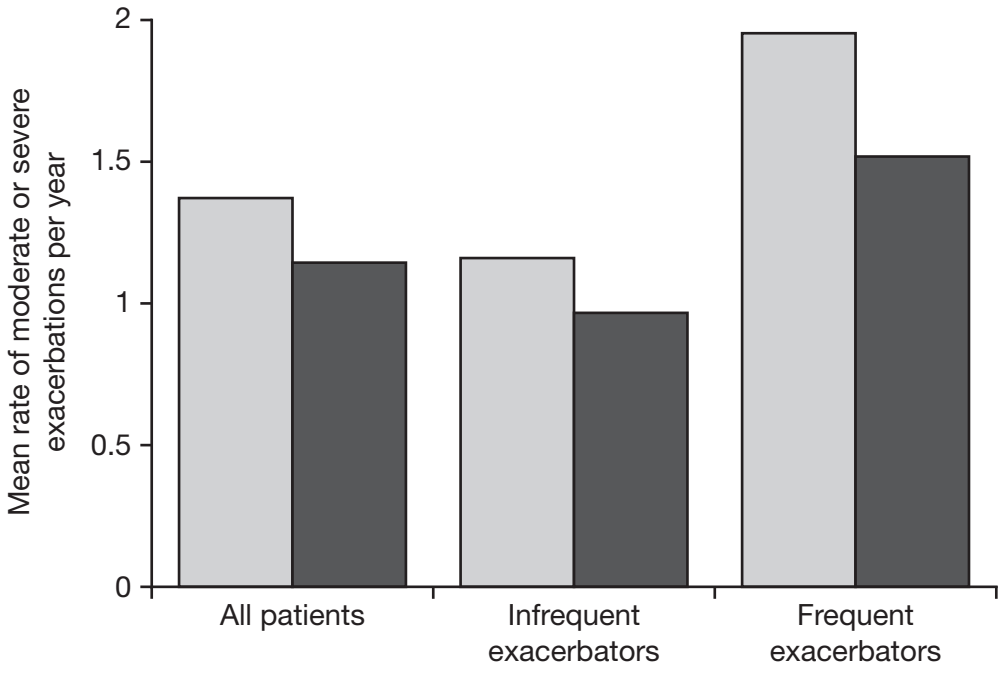


FIGURE 3. Mean rate of moderate or severe exacerbations[a] per patient per year according to exacerbation status[b] in the previous year. The mean percentage difference between exacerbation rates for roflumilast-treated and placebo-treated patients across all patients was –16.9% (95% CI, –25, –8), while the percentage difference in patients who were infrequent exacerbators was –16.5% (95% CI, –27, –5) and in those who were frequent exacerbators the difference was –22.3% (95% CI, –34, –9). Intention-to-treat analysis.

Rate ratio, 95% CI and p-values are based on a Poisson regression model with the following factors and covariates: treatment, age, sex, smoking status, baseline post-bronchodilator FEV_1 (% predicted), concomitant treatment with LABA, study and country pool (only for the overall population).
[a]Exacerbations requiring corticosteroid treatment and/or resulting in hospitalisation or death;
[b]COPD exacerbations in the previous year (based on patient records). Defined as infrequent if <2 and frequent if ≥2 exacerbations per year.
CI: confidence interval; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second.



Placebo	1.374 (n=1554)	1.151 (n=1137)	1.945 (n=417)
Roflumilast	1.142 (n=1537)	0.96 (n=1124)	1.512 (n=413)
Rate ratio (95% CI)	0.831 (0.75, 0.92)	0.835 (0.73, 0.95)	0.777 (0.66, 0.91)
Two-sided p-value	0.0003	0.0062	0.0017