

Effect of Roflumilast and Inhaled Corticosteroid/Long-Acting β_2 -Agonist on Chronic Obstructive Pulmonary Disease Exacerbations (RE²SPOND) A Randomized Clinical Trial

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Abstract

Rationale: Moderate and severe exacerbations are incompletely prevented by maximal inhalation therapy in patients with severe chronic obstructive pulmonary disease.

Objectives: To determine whether roflumilast reduces moderate and/or severe chronic obstructive pulmonary disease exacerbations in patients at risk for exacerbations despite treatment with inhaled corticosteroid/long-acting β_2 -agonist with or without a long-acting muscarinic antagonist (LAMA).

Methods: In this 52-week, phase 4, double-blind, placebo-controlled RE²SPOND (Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy) trial (NCT01443845), participants aged 40 years or older with severe/very severe chronic obstructive pulmonary disease, chronic bronchitis, two or more exacerbations and/or hospitalizations in the previous year, and receiving inhaled corticosteroid/long-acting β_2 -agonist with or without LAMA daily for 3 or more months were equally randomized to once-daily roflumilast, 500 μ g ($n = 1,178$), or placebo ($n = 1,176$). Stratification was based on LAMA use.

Measurements and Main Results: Although rate of moderate or severe exacerbations per patient per year (primary endpoint) was reduced by 8.5% with roflumilast versus placebo, the between-group difference was not statistically significant (rate ratio, 0.92; 95% confidence interval, 0.81–1.04; $P = 0.163$). However, roflumilast improved lung function, and in a *post hoc* analysis roflumilast significantly reduced the rate of moderate or severe exacerbations in participants with a history of more than three exacerbations and/or one or more hospitalizations in the prior year. Adverse event–related discontinuations occurred in 11.7% roflumilast-treated and 5.4% placebo-treated participants. Deaths occurred in 2.5% roflumilast and 2.1% placebo participants.

Conclusions: Roflumilast failed to statistically significantly reduce moderate and/or severe exacerbations in the overall population. Roflumilast improved lung function and reduced exacerbations in participants with frequent exacerbations and/or hospitalization history. The safety profile of roflumilast was consistent with that of previous studies.

Clinical trial registered with www.clinicaltrials.gov (NCT01443845).

Keywords: phosphodiesterase-4 inhibitor; hospitalization; bronchodilators; clinical trial

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At a Glance Commentary

Scientific Knowledge on the

Subject: For individuals at high risk of chronic obstructive pulmonary disease (COPD) exacerbations, the recommended first choice treatment is the combination of an inhaled corticosteroid plus a long-acting β_2 -agonist and/or long-acting anticholinergic. The previously published REACT (Roflumilast and Exacerbations in Patients Receiving Appropriate Combination Therapy) study demonstrated the efficacy of roflumilast when added to inhaled corticosteroid/long-acting β_2 -agonist combination therapy, with or without a long-acting muscarinic antagonist, in patients with severe to very severe COPD with chronic bronchitis and a history of two or more exacerbations.

What This Study Adds to the

Field: The RE²SPOND (Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy) study builds on the evidence from the REACT study in a similar patient population; evidence from this study provides additional information on the patient subgroups that are likely to benefit most from roflumilast add-on therapy. Our study suggests that COPD-related hospitalization history and frequency of prior COPD exacerbations may play a role in defining the patients most likely to experience a reduction in moderate to severe exacerbation rates with roflumilast. This highlights the importance of identifying phenotypic subsets of participants with COPD who may respond differently to currently recommended treatments.

Exacerbations in chronic obstructive pulmonary disease (COPD) are acute events characterized by worsening of respiratory symptoms outside the normal, diurnal variations (1). These events typically require a change in medication, often the addition of systemic steroids and/or antibiotics to the overall treatment regimen, and also may require hospitalization (1, 2). Hospitalizations for COPD exacerbations are associated with

poor prognosis and survival (3). In fact, COPD exacerbations are the root cause of frequent hospitalizations (3), decreased quality of life (4), and increased mortality risk (3, 5). Because of their serious nature, the treatment of COPD should include reducing the risk of exacerbations (1).

Roflumilast is the only Food and Drug Administration (FDA)-approved, orally administered selective phosphodiesterase-4 inhibitor that reduces the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of COPD exacerbations (6). Roflumilast may play a role in the reduction of pulmonary inflammation through increased intracellular cAMP in epithelial airway cells and in inflammatory cells (7–9). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends long-term treatment with inhaled corticosteroids (ICS) plus long-acting bronchodilators for patients at high risk for exacerbations. GOLD also recommends the addition of roflumilast to long-acting bronchodilator therapy (with or without ICS) for patients with FEV₁ less than 50% of predicted, chronic bronchitis, and frequent exacerbations (1).

Two 52-week multinational randomized placebo-controlled post-marketing commitment trials have been conducted to evaluate roflumilast when added to ICS/long-acting β_2 -agonist (LABA) with or without long-acting muscarinic antagonist (LAMA) in patients with severe to very severe COPD and chronic bronchitis: REACT (Roflumilast and Exacerbations in Patients Receiving Appropriate Combination Therapy) (which evaluated the European Medicines Agency–approved enteric film-coated formulation) and RE²SPOND (Roflumilast Effect on Exacerbations in Patients on Dual [LABA/ICS] Therapy) (which evaluated the U.S. FDA-approved uncoated formulation). REACT demonstrated the efficacy of roflumilast in reducing moderate to severe COPD exacerbations and hospitalizations when added to ICS/LABA fixed-dose combination (FDC) therapy, with or without tiotropium, in participants with severe to very severe COPD and chronic bronchitis (10). The results of the recently completed RE²SPOND study are reported here. Also presented are the results of subgroup and exploratory analyses conducted to identify the patient populations that may benefit most from roflumilast add-on therapy.

Methods

Study Design

In this 52-week, multicenter, randomized, double-blind, placebo-controlled, phase 4 trial, the efficacy and safety of roflumilast added to ICS/LABA FDC therapy with or without LAMA was evaluated. Study design and methods were described previously (11). Eligible participants were 40 years of age or older with severe to very severe COPD, chronic bronchitis, two or more exacerbations and/or hospitalizations in the previous year, and were receiving ICS/LABA with or without LAMA daily for 3 months or longer. Participants had to remain on the same COPD maintenance treatment from screening through randomization. Participants were randomized 1:1 to once-daily roflumilast, 500 μ g, or placebo (stratified by LAMA use) for 52 weeks following a 2-week single-blind placebo run-in phase, while maintaining background medications of ICS/LABA FDC (fluticasone propionate/salmeterol, 250/50 μ g [1 inhalation twice a day], or budesonide/formoterol, 160/4.5 μ g [2 inhalations twice a day]) (Figure 1). Participants taking fluticasone propionate/salmeterol, 500/50 μ g, at study entry were required to switch to the lower dosage (250/50 μ g) before entry. Up to 60% of participants were allowed concomitant LAMA (e.g., tiotropium) if administered for 3 or more months before screening, with no dose change.

The study was conducted in accordance with good clinical practice guidelines. The study protocol was approved by the institutional review board at each U.S. study center and by the Independent Ethics Committee at each non-U.S. study center. All participants provided written informed consent.

Outcomes

The primary efficacy measure was rate of moderate or severe COPD exacerbations per patient per year. Moderate COPD exacerbations were defined as those that required oral or parenteral corticosteroid treatment. Severe exacerbations were defined as those that resulted in hospitalization and/or led to death. The stop date of a moderate or severe COPD exacerbation was based on when symptoms or lung function were clinically improved, as determined by the study investigator. Exacerbations that occurred within 10 days of each other were

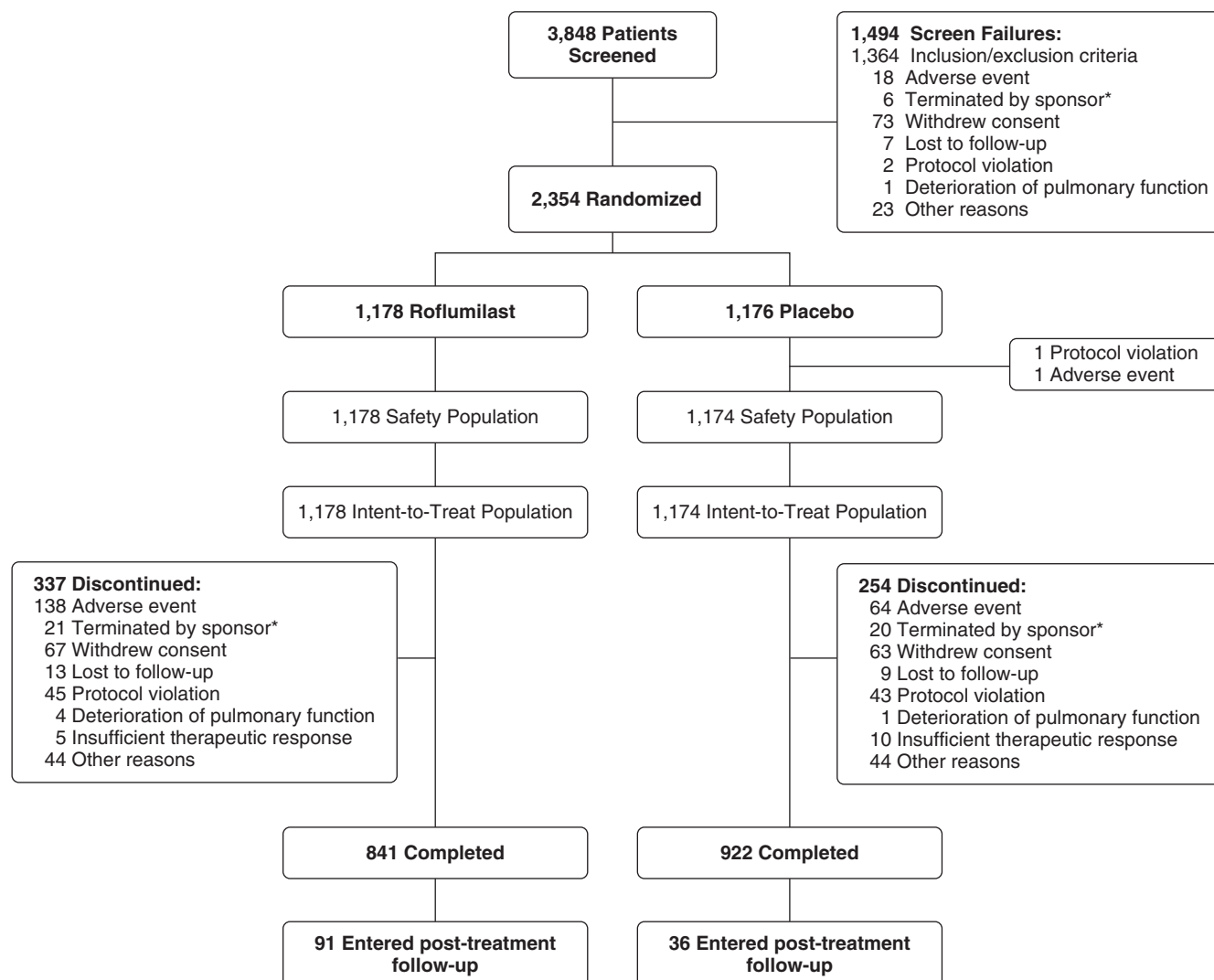


Figure 1. Consort diagram of the study population. *Terminated by sponsor indicates that the study site was shut down.

combined for analysis and counted as a single exacerbation; thus, exacerbations separated by more than 10 days were considered discrete exacerbations. Key secondary efficacy endpoints were rate of severe exacerbations, rate of moderate or severe antibiotic-treated COPD exacerbations, and mean change from baseline in predose FEV₁ over 52 weeks. Additional efficacy assessments included the frequency of moderate or severe COPD exacerbations, median time to first moderate or severe exacerbation, mean changes from baseline in predose FVC over 52 weeks, mean changes from baseline over time in the COPD Assessment Test (CAT) (12), and daily symptoms measured via EXacerbation of Chronic Pulmonary Disease Tool–Patient

Reported Outcomes (EXACT-PRO) (13). Safety was assessed based on adverse events (AEs), Columbia-Suicide Severity Rating Scale (14), laboratory parameters, and vital signs. Major adverse cardiac events (MACE) also were assessed.

Statistical Analyses

Details regarding the primary outcome have been published (11) and are described in Table E1 in the online supplement. Description of the prespecified subgroup analyses and exploratory *post hoc* analyses also are provided in the online supplement. Briefly, the rate of moderate or severe COPD exacerbations was analyzed using a negative binomial regression model (15) with number of moderate or severe COPD exacerbations as a dependent variable, and

stratum (LAMA/no LAMA) and treatment as independent variables. Time to first moderate or severe exacerbation was analyzed using a multiple time to event analysis (16).

Rate of moderate or severe exacerbations and predose FEV₁ were analyzed in several subgroups: age (≤ 65 or > 65 yr), sex, race, smoking status, ICS/LABA (fluticasone propionate/salmeterol or budesonide/formoterol), LAMA use, COPD severity (severe, FEV₁ [postbronchodilator] 30–50% of predicted; very severe, FEV₁ [postbronchodilator] $< 30\%$ of predicted). *Post hoc* analyses examined rates of moderate or severe exacerbations in participants with a history of two, three, and more than three exacerbations in the prior year and in those

with a history of zero or one or more severe exacerbations (defined as COPD exacerbations resulting in hospitalization) in the prior year.

Assuming a rate of 1.35 moderate or severe COPD exacerbations per patient per year (primary outcome) in the placebo group, a sample size of 1,150 randomized participants per treatment group had 90% power to detect an 18% reduction in moderate or severe COPD exacerbation rates with roflumilast versus placebo (17). All statistical tests were two-sided ($\alpha = 0.05$); rate ratios (RRs) and corresponding 95% confidence intervals (CIs) were calculated. *P* values less than 0.05 are statistically significant without additional control of type I error. All analyses were performed using SAS version 9.2 (or newer) (SAS Institute, Inc., Cary, NC).

Results

Participants

Participant recruitment began September 30, 2011, and the study ended on January 8, 2016 (based on database lock). A total of 380 study centers in 17 countries (see online supplement for details) screened participants, and 318 centers randomized at least one participant for a total of 2,354 who were randomized ($n = 1,178$ roflumilast, $n = 1,176$ placebo); 2,352 participants were included in the safety and intent-to-treat populations ($n = 1,178$ roflumilast, $n = 1,174$ placebo) (Figure 1). Baseline demographics and clinical characteristics were comparable between treatment groups (Table 1), including similar predose FEV₁ values and mean CAT scores of 18. More participants in the roflumilast group discontinued the study than in the placebo group, mainly because of AEs (Figure 1). Median treatment duration was 363 days. Percentages of participants with a history of cardiac disorders (375 [31.8%] roflumilast vs. 384 [32.7%] placebo) or hypertension (630 [53.5%] vs. 631 [53.7%]) were similar between the two treatment groups.

Efficacy

The rate of moderate or severe COPD exacerbations per patient per year (primary endpoint) was numerically reduced with roflumilast compared with placebo (−8.5%), but this difference did not reach statistical significance ($P = 0.163$) (Figure 2). Compared with the placebo

Table 1. Baseline Participant Demographic and Clinical Characteristics (Safety Population)

	Roflumilast (<i>n</i> = 1,178)	Placebo (<i>n</i> = 1,174)
Age, mean (SD), yr	64.4 (8.8)	64.5 (8.4)
Male, <i>n</i> (%)	821 (70)	794 (68)
White, <i>n</i> (%)	935 (79)	944 (80)
BMI, mean (SD), kg/m ²	26.0 (5.9)	25.7 (5.7)
Smoking status, <i>n</i> (%) [*]		
Current	462 (39)	464 (40)
Former	716 (61)	710 (60)
Total cigarette pack-years, mean (SD)	52.2 (28.8)	53.1 (28.1)
COPD severity, <i>n</i> (%) [†]		
Moderate	1 (<1)	0
Severe	697 (59)	720 (61)
Very severe	474 (40)	446 (38)
COPD duration, mean (SD), yr [‡]	9.2 (6.3)	9.5 (6.3)
Prebronchodilator FEV ₁ , mean (SD), L	0.89 (0.32)	0.88 (0.31)
Post-bronchodilator FEV ₁ , mean (SD), L	0.98 (0.33)	0.97 (0.32)
% Predicted prebronchodilator FEV ₁ , mean (SD), L	29.87 (8.93)	29.96 (8.87)
% Predicted post-bronchodilator FEV ₁ , mean (SD), L	33.00 (9.04)	32.97 (8.88)
Post-bronchodilator FEV ₁ /FVC ratio, mean (SD)	38.49 (10.26)	39.28 (10.47)
No. of moderate or severe exacerbations in previous 12 mo, mean (SD) [§]	2.4 (<1)	2.4 (<1)
No. of moderate or severe exacerbations in previous year, <i>n</i> (%)		
2	874 (74)	876 (75)
3	179 (15)	180 (15)
>3	112 (10)	108 (9)
Prior hospitalizations, <i>n</i> (%)		
0	789 (67)	805 (68)
≥1	381 (32)	364 (31)
CAT score, mean (SD)	18.0 (7.1)	18.1 (6.8)
EXACT-PRO total score, mean (SD)	39.5 (10.6)	39.6 (9.9)
ICS/LABA therapy, <i>n</i> (%)		
Fluticasone propionate/salmeterol FDC	768 (65)	766 (65)
Budesonide/formoterol FDC	410 (35)	408 (35)
LAMA use, <i>n</i> (%)	548 (47)	546 (47)

Definition of abbreviations: BMI = body mass index; CAT = COPD Assessment Test; COPD = chronic obstructive pulmonary disease; EXACT-PRO = EXacerbations of Chronic Pulmonary Disease Tool – Patient-Reported Outcome; FDC = fixed-dose combination; ICS = inhaled corticosteroids; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist.

^{*}Current smoker = the date of last cigarette smoked is ≤ 1 year before the screen visit date; former smoker = the date of last cigarette smoked is > 1 year before the screen visit date.

[†]Moderate = $50\% \leq \text{FEV}_1 < 80\%$ predicted; severe = $30\% \leq \text{FEV}_1 < 50\%$ predicted; very severe = $\text{FEV}_1 < 30\%$ predicted (post-bronchodilator FEV₁).

[‡]Duration = (year of screening visit – year of first COPD diagnosis) + 1.

[§]Placebo, $n = 1,170$; roflumilast, $n = 1,174$.

group, a greater proportion of participants in the roflumilast group had no moderate or severe COPD exacerbations over the 52-week treatment period (54.2% roflumilast vs. 48.5% placebo) (Figure 2). The median time to first moderate or severe exacerbation was 319 and 286 days in the roflumilast and placebo groups, respectively, with no significant difference between the two groups (hazard ratio, 0.9; 95% CI, 0.8–1.1; $P = 0.323$). There were no between-group differences in the rates of severe exacerbations (roflumilast rate: 0.28; 95% CI, 0.23–0.33; placebo: 0.29; 0.25–0.34; RR, 0.95; 95% CI,

0.75–1.19; $P = 0.635$) or moderate or severe or antibiotic-treated exacerbations (roflumilast: 1.31; 1.20–1.43; placebo: 1.45; 1.34–1.57; RR, 0.90; 95% CI, 0.80–1.02; $P = 0.088$).

In a *post hoc* analysis in participants with more than three exacerbations in the prior year, the rate of moderate or severe COPD exacerbations was reduced by 39% with roflumilast ($n = 112$) versus placebo ($n = 108$) (RR, 0.61; 95% CI, 0.39–0.95; $P = 0.030$) (Figure 3A). In participants with one or more prior severe exacerbations, the rate of moderate or severe COPD exacerbations was reduced by 25% with

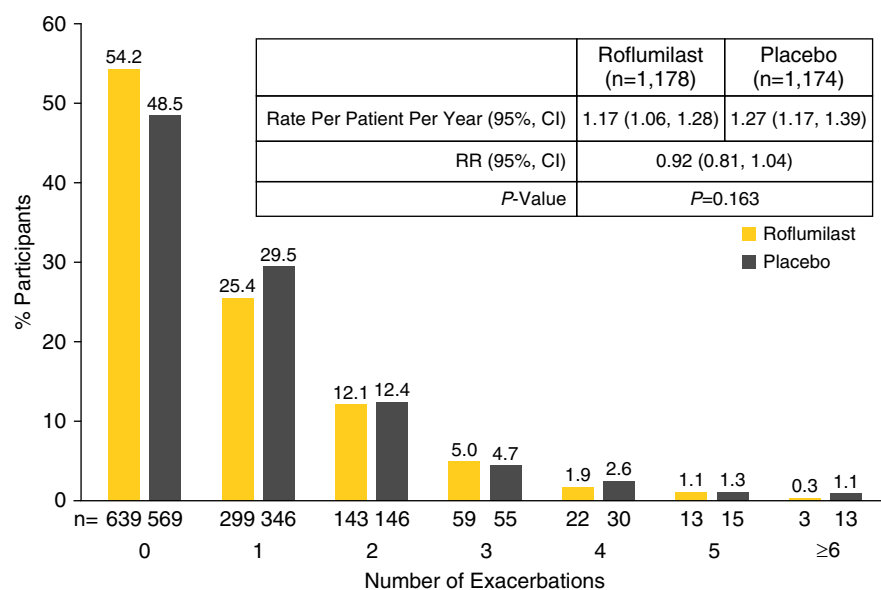


Figure 2. Frequency of moderate or severe chronic obstructive pulmonary disease exacerbations per patient per year at Week 52 (intention-to-treat population). The numbers shown below each of the bars represent the number of patients with exacerbations. CI = confidence interval; RR = rate ratio.

roflumilast ($n = 381$) versus placebo ($n = 364$) (RR, 0.75; 95% CI, 0.60–0.93; $P = 0.010$) (Figure 3B). Roflumilast resulted in a statistically significant reduction in moderate exacerbations in those participants with a previous hospitalized exacerbation (RR, 0.78; 95% CI, 0.61–1.00). A reduction in severe exacerbations was numerically similar but not statistically significant (RR, 0.79; 95% CI, 0.56–1.10). In an assessment of overlap between these two more severe COPD subgroups, 152 of 743 (20%) participants with one or more prior severe exacerbations also had very frequent (>3) exacerbations in the prior year, whereas 152 of 219 (69%) participants with more than three prior exacerbations also had one or more severe exacerbations in the prior year.

In prespecified subgroup analyses the rate of moderate or severe COPD exacerbations per participant per year was numerically reduced in roflumilast-treated participants versus placebo-treated participants in most subgroups, with significant reductions for male participants (RR, 0.83; 95% CI, 0.71–0.97; $P = 0.020$) and for those using fluticasone propionate/salmeterol (RR, 0.85; 95% CI, 0.74–0.99; $P = 0.039$) (Figure 4; see Table E2 in the online supplement). When analyzed separately for participants who concomitantly used LAMAs and for those

who did not concomitantly use LAMAs, the rate of moderate or severe exacerbations was similar in the roflumilast and placebo groups (see Table E2).

The difference in mean change from baseline in predose FEV₁ at 52 weeks was significant in favor of roflumilast (least squares mean difference, 0.053 L; 95% CI, 0.040–0.066; $P < 0.0001$). Greater improvements in FVC were observed in the roflumilast group than in the placebo group (least squares mean difference, 0.083 L; 95% CI, 0.055–0.111; $P < 0.0001$). Significant improvements in FEV₁ occurred in all roflumilast-treated participant subgroups ($P < 0.05$, all) (Figure 5). There were no significant differences between the roflumilast and placebo groups on mean change from baseline at 52 weeks in the EXACT-PRO total scores (see Table E3). Mean changes from baseline at 52 weeks in CAT total score were not significantly different between the treatment groups (see Table E4).

Safety

A similar percentage of participants in the roflumilast (68.3%) and placebo (64.6%) groups reported a treatment-emergent AE (TEAE). The most commonly reported TEAEs are shown in Table 2. Most TEAEs were mild to moderate in intensity. Gastrointestinal TEAEs, such as diarrhea,

weight loss, and nausea, were more common with roflumilast than with placebo; all other TEAE rates were similar between treatment groups. Withdrawal from the study because of TEAEs occurred in 11.7% and 5.4% of participants in the roflumilast and placebo groups, respectively. The most commonly reported serious TEAE ($\geq 0.4\%$) was pneumonia (3.0% roflumilast vs. 2.7% placebo). A total of 30 (2.5%) and 25 (2.1%) deaths occurred in the roflumilast and placebo groups, respectively (Table 2); one death was considered treatment-related by the investigator (completed suicide in the roflumilast group). The participant was a 65-year-old man who had a completed suicide on Day 33 of randomized treatment, 1 day after roflumilast discontinuation. There were no other reported relevant TEAEs, medical history of psychiatric disorders, history of suicidal thoughts or behavior, prior treatment with psychoactive medications, history of alcohol or drug use/abuse, or family history of mental disorders for this participant. The participant lost his job 1 week before his death. Incidence of suicidal ideation and suicidal behavior based on the Columbia-Suicide Severity Rating Scale in the overall population is shown in Table 2; more detailed information is included in Table E5.

A composite MACE event (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) occurred in 10 ($<1\%$) roflumilast and eight ($<1\%$) placebo participants. There were no significant differences between the roflumilast and placebo groups on composite or other MACE categories.

Discussion

Reduction in exacerbations of COPD is a key component of the therapeutic paradigm. The REACT and RE²SPOND trials examined the efficacy of roflumilast in reducing moderate to severe COPD exacerbations and hospitalizations when added to ICS/LABA FDC therapy, with or without LAMA (tiotropium), in participants with chronic bronchitis, two or more exacerbations and/or hospitalizations in the prior year, and severe to very severe COPD (10). Although the primary efficacy endpoint in RE²SPOND did not reach statistical significance, treatment with

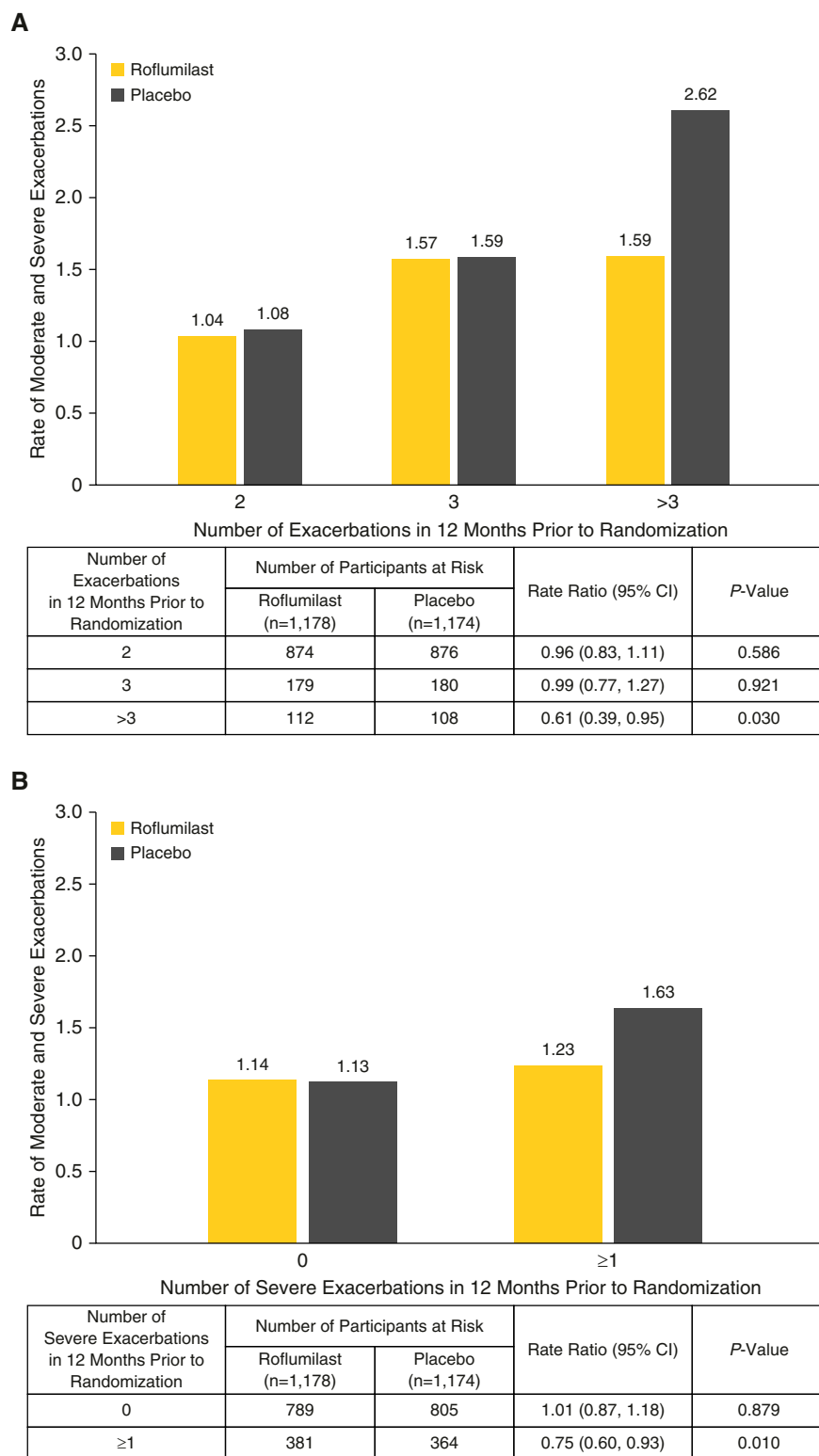


Figure 3. (A) Rate of moderate or severe exacerbations per patient per year at Week 52 by exacerbation history (intention-to-treat population). Fifteen participants (nine roflumilast and six placebo) had fewer than two exacerbations in the 12 months before randomization and were excluded from this analysis. (B) Rate of moderate or severe exacerbations per patient per year by severe exacerbation rate in previous year (intention-to-treat population). CI = confidence interval.

roflumilast numerically reduced the rate of moderate to severe exacerbations and significantly improved lung function versus placebo in the overall population of participants receiving ICS/LABA treatment with or without LAMA. Across numerous predefined subgroups, roflumilast numerically reduced the rate of moderate or severe COPD exacerbations, with statistically significant between-group differences observed in men and in those treated with concomitant fluticasone propionate/salmeterol FDC.

Additional analyses did not reveal a compelling reason for the significant differences in exacerbations rates between men and women and between those treated with fluticasone/salmeterol and budesonide/formoterol (data on file). In *post hoc* analyses, roflumilast decreased the rate of moderate or severe exacerbations in participants with more than three exacerbations in the prior year and in those with at least one prior severe exacerbation. In addition, roflumilast significantly improved lung function across all subgroups, and AEs overall were similar to those seen in other studies of roflumilast in COPD participants, including the pivotal trials and REACT study (6, 10, 18).

The current study did not confirm a statistically significant decrease with roflumilast in the rate of moderate to severe exacerbations in a broad population of participants with severe COPD with chronic bronchitis who are concomitantly treated with multiple inhaled therapies. The efficacy and tolerability of roflumilast to reduce the risk of COPD exacerbations in participants with severe COPD associated with chronic bronchitis and a history of exacerbations was previously demonstrated in pivotal trials (6). In contrast, REACT confirmed significant reductions in the rates of moderate to severe exacerbations (14% reduction) and severe exacerbations (24% reduction) with roflumilast versus placebo when added to inhaled therapy in a similar participant population (10). The greater effect size for the primary efficacy endpoint demonstrated in REACT (RR, 0.86; 0.74–0.99) (10) versus RE²SPOND (RR, 0.92; 0.81–1.04) (*see* Table E1), both using negative binomial analyses, may reflect differences in the participant populations and concomitant therapies. For example, RE²SPOND had 10% more participants with very severe chronic airflow obstruction. Differences also

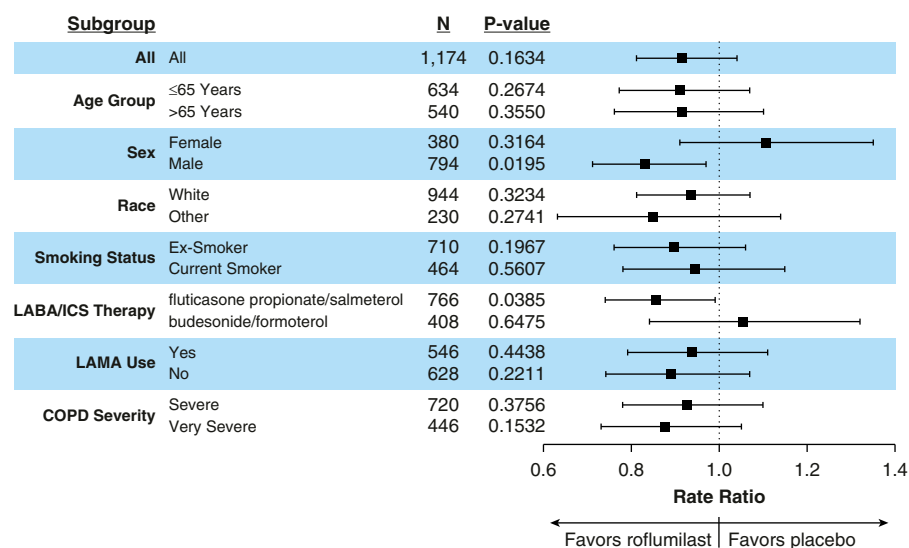


Figure 4. Rates of moderate or severe exacerbations per patient per year by subgroup (intention-to-treat population). COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist.

existed between the study participants in terms of prior exacerbations, with 24–25% of participants in RE²SPOND experiencing more than two exacerbations in the previous year compared with 10–11% in REACT (10).

The method of analyzing exacerbation rates and the exacerbation definitions used could have had an impact on the rate of moderate or severe exacerbation and on the significance of the results, limiting cross-study comparisons. In the REACT study, the primary efficacy analysis employed a

Poisson regression model, which did not find significant differences between the groups; however, a predefined sensitivity analysis using a negative binomial regression showed the effect was statistically significant (10). Only a negative binomial regression model was used in RE²SPOND, and differences between the two treatments for the primary efficacy variable were not significant. In REACT, the primary endpoint of moderate to severe exacerbations, which did not consider antibiotics in the definition, demonstrated

a 13.2% reduction ($P = 0.0529$) in exacerbation rates with roflumilast versus placebo. However, prespecified secondary endpoints (also analyzed using a Poisson regression model) that considered antibiotics in the definitions (moderate or antibiotic-treated exacerbations; moderate to severe or antibiotic-treated exacerbations) did show statistically significant reductions in exacerbation rates with roflumilast versus placebo (14.6% reduction [$P = 0.0262$] and 16.3% reduction [$P = 0.0047$], respectively) (10).

In contrast, in the RE²SPOND study, statistically nonsignificant reductions in the rate of moderate or severe exacerbations (primary variable; 8.5% reduction; $P = 0.163$) and in the rate of moderate, severe, or antibiotic-treated exacerbations (10% reduction; $P = 0.088$) were observed with roflumilast versus placebo when using a binomial regression model. In addition, in both REACT and RE²SPOND, the definition used for a COPD exacerbation relied on physician judgment to determine the end date of the COPD exacerbation, which could result in greater outcome variability when compared with a more objective measure (e.g., duration of prescribed medication). Thus, cross-comparison of study results may benefit from standardized, objective definitions of exacerbations and consistent analytical methodologies.

The REACT and RE²SPOND studies also had several key differences in study methodology, including differences in the highest ICS/LABA dose approved for COPD allowed in each study. The maximum European Medicines Agency-approved dose of fluticasone/salmeterol was allowed for use in REACT (fluticasone/salmeterol, 500/50 μ g [1 inhalation twice daily], not sponsor-provided), whereas the highest FDA-approved dose was allowed for use in RE²SPOND (fluticasone/salmeterol, 250/50 μ g [1 inhalation twice daily], sponsor-provided) (see Table E1). Additionally, the RE²SPOND trial initially excluded participants using LAMA; this criterion was later amended to allow LAMA use, which may have led to participant dissimilarities between the REACT and RE²SPOND studies and perhaps explains the lower percentage of participants on LAMA in the RE²SPOND study. Different formulations of roflumilast (film coated in REACT versus non-film coated in

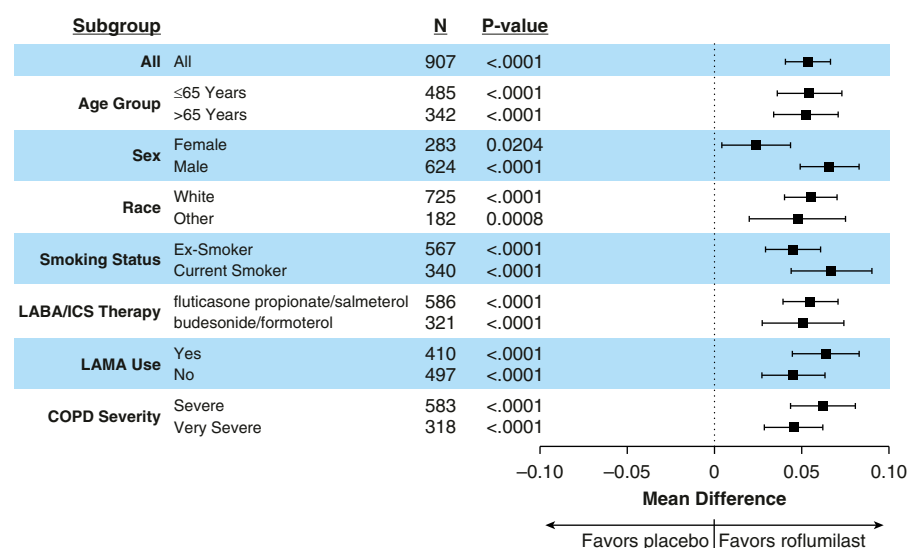


Figure 5. Mean change from baseline to Week 52 in predose FEV₁ by subgroup (intention-to-treat population). COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroids; LABA = long-acting β -agonist; LAMA = long-acting muscarinic antagonist.

Table 2. Key Safety Outcomes (Safety Population)

	Roflumilast (n = 1,178)	Placebo (n = 1,174)
Participants with TEAEs, n (%)	804 (68)	758 (65)
TEAE ≥2.5% of participants (either group), n (%)		
Diarrhea	119 (10)	38 (3)
Weight decreased	91 (8)	28 (2)
Headache	80 (7)	48 (4)
Pneumonia	66 (6)	68 (6)
Upper respiratory tract infection	60 (5)	66 (6)
Nausea	64 (5)	30 (3)
Urinary tract infection	48 (4)	44 (4)
Nasopharyngitis	47 (4)	58 (5)
Insomnia	55 (5)	21 (2)
Influenza	31 (3)	30 (3)
Hypertension	33 (3)	43 (4)
Back pain	33 (3)	27 (2)
Appetite decreased	38 (3)	10 (<1)
Participants with SAEs, n (%)	180 (15)	162 (14)
Suicidal ideation, n (%) [*]	99 (8)	90 (8)
Suicidal behavior, n (%) [*]	29 (3)	20 (2)
Suicidal attempt, n (%) [*]	13 (1)	12 (1)
Deaths, n (%) [†]	30 (3)	25 (2)

Definition of abbreviations: SAE = serious adverse event; TEAE = treatment-emergent adverse event.

^{*}As assessed by the Columbia-Suicide Severity Rating Scale.

[†]One completed suicide was associated with roflumilast treatment.

RE²SPOND) also were used in the two studies; however, the two formulations have demonstrated bioequivalence (data on file) and no differences were observed between the studies in AEs.

Because the population in this study comprised severely ill participants (25% had a history of three or more exacerbations in the 12 months before the study), exploratory analyses were performed to determine the effect of roflumilast on the subset of participants who may be at the greatest risk for recurrent, severe exacerbations. *Post hoc* analyses revealed that roflumilast treatment was particularly beneficial in the most severely ill participants based on exacerbation burden, because roflumilast significantly reduced the rate of moderate to severe exacerbations by 39% and 25% in those with a history of more than three exacerbations and in those who had one or more prior severe exacerbations, respectively. Importantly, a *post hoc* analysis of the REACT study demonstrated a very similar effect with a 34.9% reduction in severe exacerbations in participants with a prior respiratory hospitalization (see Table E1) compared with a 7.6% reduction in those without a prior respiratory hospitalization (19). A *post hoc* analysis on two of the pivotal roflumilast trials showed that roflumilast treatment might stabilize exacerbations

in those participants who experience frequent exacerbations (20). The results from RE²SPOND, in conjunction with the results from REACT, suggest that roflumilast added to background ICS/LABA or ICS/LABA/LAMA could be an important treatment option for a distinct phenotypic group of patients with COPD who experience recurrent COPD exacerbations or have experienced a previous hospitalization.

The current study confirms that roflumilast improves FEV₁ and FVC when added to inhaled therapies. The magnitude of the differences is remarkably consistent with previous studies (see Table E1) (6, 10, 18). In addition, a similar percentage of participants in the roflumilast-treated groups reported a TEAE, as has been noted in other reports. As anticipated, the most commonly reported AEs were mild to moderate in intensity and reflected gastrointestinal intolerance. Few deaths or MACE were noted in the study population, which is similar to the REACT study (10).

Limitations of this study include the possibility that participants were receiving suboptimal therapy based on a lower number of participants receiving LAMA at the start of the study than expected (only 47% of participants were on concomitant LAMAs, whereas the protocol allowed for up to 60% on LAMA). Additionally, LAMA

use was not tracked during either study; therefore, it is unknown whether participants who began the study on LAMA continued this treatment throughout the study. Another potential limitation of the study design is that participants may have been required to reduce their ICS/LABA (fluticasone/salmeterol) dose on study entry for RE²SPOND, whereas in the REACT study, participants remained on the maximum approved dose of ICS/LABA in each country if they were on that dose before study entry. Also, with regard to the *post hoc* analysis of moderate to severe exacerbations by prior exacerbation history, there were a relatively smaller number of participants with a history of more frequent (3 or >3) exacerbations; therefore, the data from that analysis should be interpreted with caution. In addition, any differences in how exacerbations were reported and monitored in the studies could explain the dissimilar placebo rate of moderate or severe exacerbations in REACT (0.93; 95% CI, 0.84–1.02) (10) and RE²SPOND (1.27; 95% CI, 1.17–1.39).

Conclusions

The primary efficacy endpoint in RE²SPOND was not achieved. However, the results of this study suggest that the effectiveness of roflumilast in reducing moderate to severe exacerbation rates is most pronounced in those patients with a history of COPD-related hospitalization and those with more frequent COPD exacerbations. Findings from this trial may have important implications for clinical practice and health care resources utilization because it supports consideration of pharmacotherapeutic options based on distinct phenotypic groups (21). ■

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