Roflumilast and dyspnea in patients with moderate to very severe chronic obstructive pulmonary disease: a pooled analysis of four clinical trials

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Purpose: Breathlessness is a predominant symptom of chronic obstructive pulmonary disease (COPD), making it a valuable outcome in addition to lung function to assess treatment benefit. The phosphodiesterase-4 inhibitor roflumilast has been shown to provide small but significant improvements in dyspnea, as measured by the transition dyspnea index (TDI), in two 1-year studies in patients with severe to very severe COPD.

Patients and methods: To provide a more comprehensive assessment of the impact of roflumilast on dyspnea, post hoc analyses of four 1-year roflumilast studies (M2-111, M2-112, M2-124, and M2-125) in patients with moderate to very severe COPD were conducted.

Results: In this pooled analysis (N=5,595), roflumilast significantly improved TDI focal scores versus placebo at week 52 (treatment difference, 0.327; P<0.0001). Roflumilast was associated with significantly greater TDI responders and significantly fewer TDI deteriorators (≥1-unit increase or decrease from baseline, respectively) versus placebo at week 52 (P<0.01, both); these significant differences were apparent by week 8 and maintained until study end (P<0.05, all). At study end, the postbronchodilator forced expiratory volume in 1 second improvement in TDI responders was significantly greater with roflumilast versus placebo (P<0.05). Similar to the overall population, improvements in TDI focal scores at week 52 were small but consistently significant over placebo in patients with chronic bronchitis, regardless of exacerbation history, concomitant treatment with short-acting muscarinic antagonists or long-acting β2-agonists, or pretreatment with inhaled corticosteroids.

Conclusion: This analysis shows that patients treated with roflumilast to reduce exacerbation risk may also experience small but significant improvements in dyspnea, with accompanying improvements in lung function.

Keywords: phosphodiesterase-4 inhibitor, breathlessness, lung function, subgroup analyses

Introduction

Current recommended treatment goals for chronic obstructive pulmonary disease (COPD) include reduction of breathlessness, improvement of exercise capacity and health status, and prevention of exacerbations.1 As dyspnea is a predominant symptom of COPD, an appreciation of impaired lung function and breathlessness severity may better reflect the impact of treatment.1 While treatment guidelines recommend a relatively simple approach to evaluating dyspnea (ie, modified Medical Research Council Scale1), more sophisticated tools exist to assess breathlessness in more detail.2,3 One example is the transition dyspnea index (TDI),4 a validated tool that assesses the impact of a patient’s daily activities on breathlessness.5 It has been shown to reliably denote distinct changes in breathing difficulty due to therapeutic intervention.6–10
The phosphodiesterase-4 inhibitor roflumilast, approved to reduce the risk of exacerbations in patients with severe COPD associated with chronic bronchitis and a history of exacerbations, has been shown to reduce markers of inflammation in COPD patient airways. As breathlessness is thought to arise primarily from mechanical limitation of inspiratory effort, we wondered whether an agent with potential anti-inflammatory activities like roflumilast would impact dyspnea. Small but significant improvements in dyspnea, measured by the TDI, have been previously reported with 1 year of roflumilast treatment compared with placebo in two studies in COPD patients; however, these data have not been examined in detail, nor was the sample size in previously reported studies large enough to explore relevant clinical associations. In addition, significant lung function improvements with roflumilast treatment have also been reported in placebo-controlled studies in patients with COPD, but have not yet been evaluated with regard to dyspnea-related outcomes. Thus, to more comprehensively evaluate the impact of roflumilast on breathlessness, including any potential relationship with lung function improvement, individual and pooled analyses of four 1-year clinical studies with roflumilast are presented here. Results from this analysis may have potential implications in the pharmacological management of COPD with regard to the current recommended treatment goals of reduction of COPD symptoms and prevention of exacerbations.

Material and methods
Study design and patients
Data were pooled from four 1-year placebo-controlled, double-blind, multicenter, Phase 3 clinical trials (M2-111, M2-112, M2-124, and M2-125) with once-daily roflumilast 500 µg, which were designed to enroll patients with forced expiratory volume in 1 second (FEV₁) <50% predicted. Patients in M2-124 and M2-125, but not M2-111 and M2-112, were required to have chronic bronchitis and a history of exacerbations. Full details of methodology and patient selection have been reported elsewhere. All four studies were approved by local ethical review committees and performed in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines.

Assessments
Dyspnea was measured at baseline using the baseline dyspnea index (BDI) total score and during treatment (weeks 4, 8, 12, 20, 28, 36, 44, and 52) using the TDI focal score, which evaluates changes from the baseline measurement. BDI total score ranges from 0 (no dyspnea) to 12 (severe dyspnea); TDI focal score ranges from −9 (major deterioration) to 9 (major improvement).

TDI responders were defined as patients who experienced a clinically meaningful improvement (change of ≥1 unit from baseline) in TDI focal score; TDI deteriorators were patients who experienced a ≥1 unit deterioration from baseline. TDI nonresponders and non-deteriorators were those patients not meeting these thresholds. Outcomes assessed in TDI responders/nonresponders were TDI focal score at week 52, change from baseline to week 52 in post-bronchodilator FEV₁, and percentage of patients achieving a clinically meaningful improvement in FEV₁ (≥100 mL) from baseline to week 52.

Statistical analysis
Data were pooled for all randomized patients who took ≥1 dose of study medication in each study. Data analysis was performed post hoc for the overall patient population from the four studies, as well as for the following six subpopulations of patients with: 1) concomitant inhaled corticosteroid (ICS) treatment (M2-111 and M2-112); 2) chronic bronchitis (M2-111, M2-112, M2-124, and M2-125); 3) chronic bronchitis and concomitant short-acting muscarinic antagonist (SAMA) treatment (M2-111, M2-112, M2-124, and M2-125); 4) chronic bronchitis and a history of exacerbations (M2-111, M2-124, and M2-125); 5) chronic bronchitis, a history of exacerbations, and concomitant long-acting β₂-agonists (LABA) treatment (M2-124 and M2-125); and 6) chronic bronchitis, a history of exacerbations, and ICS pretreatment (M2-124 and M2-125). Patients included in the subpopulation analyses were required to have non-missing baseline BDI and post-baseline TDI assessments.

Treatment comparisons on continuous variables were performed at week 52 (last observation carried forward [LOCF]) using analysis of covariance with terms for treatment group, BDI, age, smoking status, sex, ICS pretreatment, country/region, and study. Treatment comparisons on dichotomous/categorical variables were performed using a Cochran–Mantel–Haenszel test (pooled data were stratified by study) at week 52 (LOCF) and weeks 4, 8, 12, 20, 28, 36, 44, and 52 (observed cases). Statistical significance was assessed using an alpha level of 0.05.

Results
In M2-124 and M2-125, the proportion of patients pretreated with ICS was equal in both the roflumilast and placebo groups (42%); the proportions of patients who received concomitant
ICS or LABA were also similar in both roflumilast (21% and 49%, respectively) and placebo (23% and 51%, respectively) groups. Similarly, in M2-111 and M2-112, the proportions of patients who received concomitant ICS or LABA were comparable in both roflumilast (61% and 8%, respectively) and placebo (60% and 9%, respectively) groups. For the overall pooled population, patient demographic and clinical characteristics were similar between treatment arms (Table 1).

Of randomized patients who took ≥1 dose of study medication, 1,921/2,864 (67.1%) and 2,083/2,913 (71.5%) patients completed the trials in the roflumilast and placebo groups, respectively.

At week 52, roflumilast significantly improved mean TDI focal score versus placebo (roflumilast, 0.368; placebo, 0.041; difference [95% confidence interval {CI}], 0.327 [0.166–0.488]; P<0.0001). Between-group differences in TDI focal score for the pooled population were similar to those in the individual studies (Figure 1A) and generally favored roflumilast. Significantly higher percentages of roflumilast-treated patients achieved clinically meaningful improvements in TDI focal score (TDI responders) versus placebo after 52 weeks of treatment (LOCF; 39.0% versus 33.9%, respectively; P=0.0001) (Figure 2A).

Furthermore, the significantly higher percentage of TDI responders observed at week 52 was apparent by week 8 and maintained until study end (all, P<0.01) (Figure 2A). At week 52, roflumilast-treated patients were more likely to demonstrate clinically meaningful improvements in TDI than placebo-treated patients (Figure 1B); generally similar results were observed in the individual trials. Values of P for both analyses in Figure 1 were 0, indicating lack of observed statistical heterogeneity.17 Overall, 20 patients need to be treated with roflumilast to have one additional patient with clinically meaningful improvements in TDI focal score over 1 year (crude number needed to treat, 19.9; 95% CI, 13.3–40.0).

Conversely, roflumilast treatment was associated with significantly fewer TDI deteriorators versus placebo after 52 weeks (LOCF; 20.4% versus 23.7%, respectively; P=0.0022) (Figure 2B). This significant between-group difference was also apparent by week 8 and maintained for the remainder of the study (all, P<0.05).

To explore the potential association of breathlessness with improved lung function, clinically meaningful improvements in TDI focal score and FEV₁ were evaluated. In the overall population, the proportion of patients who achieved the minimum clinically important difference (MCID) of 100 mL in FEV₁ (ie, FEV₁ responders) was significantly greater with roflumilast versus placebo by week 4, which was maintained until study end (all, P<0.0001) (Figure 3).

Among TDI responders, roflumilast led to significantly higher percentages of patients who achieved MCID in FEV₁ (36%) versus placebo (29%; P<0.01) at study end. Furthermore, the magnitude of FEV₁ improvement was significantly greater with roflumilast versus placebo in both TDI responders (P<0.05) and nonresponders (P<0.0001) (Figure 4). Consistent with this observed treatment effect in the magnitude of FEV₁ improvement with roflumilast in both TDI responders and nonresponders, a greater proportion of patients treated with roflumilast versus placebo demonstrated improvements from baseline in FEV₁, a treatment effect (ie, shift to the right in favor of roflumilast) also observed in both TDI responders and nonresponders (Figure 5). In addition, as the roflumilast curve is generally above that of placebo across the positive x-axis in both TDI responders and nonresponders, there was also a greater percentage of roflumilast-treated patients than placebo-treated patients for most levels of positive FEV₁ change from baseline.

Further analysis of the pooled ITT population revealed that particular baseline characteristics were associated with a
These characteristics included being a former smoker (versus current), no concomitant use of LABAs or SAMAs (versus with), and no concomitant or pre-ICS use (versus with). To further analyze whether patient characteristics such as chronic bronchitis, history of exacerbations, or concomitant medications had an effect on TDI response, six subpopulations were examined (Figure 6). In COPD patients with chronic bronchitis, roflumilast significantly improved TDI focal scores versus placebo (P<0.05) regardless of exacerbation history, concomitant treatment with SAMA or LABA, or pretreatment with ICS (Table 3). In the patient subpopulation treated with concomitant ICS, roflumilast was associated with significantly less deterioration in TDI focal score versus placebo (P=0.0114). TDI responders and deteriorators for each subpopulation are presented in Figures S1–S6. In all subpopulations, treatment with roflumilast was associated with more TDI responders and fewer TDI deteriorators versus placebo at all treatment weeks; however, differences were not statistically significant at all treatment weeks.

**Discussion**

As breathlessness in COPD patients worsens gradually over time and is related to lung function, physical activity, and quality of life, dyspnea has been considered a surrogate marker for disease progression. Moderate improvements in breathlessness with roflumilast have previously been reported in patients with severe to very severe COPD. To further characterize the effect of roflumilast on dyspnea, data from four 1-year roflumilast studies were pooled for those patients with or without clinically meaningful responses in TDI. In addition, evaluation of the corresponding FEV₁ improvements among TDI responders explored the relationship between breathlessness and lung function.

The results from the current analysis confirm previous findings that roflumilast significantly improves breathlessness compared with placebo, as measured by TDI, in patients with severe to very severe COPD. Furthermore, these results show that a significantly greater percentage of roflumilast-treated patients (40%) experienced clinically meaningful improvements in TDI focal score versus placebo (36%) starting at week 8 (P=0.001); this 4% between-group difference was maintained to 1 year (LOCF; week 52; roflumilast, 39%; placebo, 34%; P<0.01 for all). Conversely, significantly fewer roflumilast-treated patients experienced clinically meaningful deteriorations in dyspnea compared with placebo-treated patients.

In patients with COPD, improvements in lung function have been reported to occur with decreased breathlessness. Patients with COPD in several 1-year studies of various inhaled bronchodilators exhibited improvements in trough FEV₁ over placebo (range, 108–160 mL) at study endpoint, which were accompanied by improvements in TDI focal scores (range, 0.6–1.1 units). As roflumilast is an anti-inflammatory agent, and its effects on lung function in the individual studies pooled here (ie, between-treatment change in prebronchodilator FEV₁, range, 36–58 mL) are lower than those seen for bronchodilators, it is not surprising that the effect of roflumilast on dyspnea reported in this pooled analysis (0.327 units) is lower in magnitude versus those of bronchodilators. However, consistent with studies demonstrating correlations between dyspnea and lung function

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**Figure 1** Improvements in dyspnea in patients treated with roflumilast or placebo at week 52. (A) Differences and 95% CIs between roflumilast- and placebo-treated patients for TDI focal score and (B) odds ratios and 95% CIs for TDI responders in the roflumilast and placebo groups at week 52 (last observation carried forward) for the four pooled studies and for each individual study.

**Notes:** TDI focal scores for M2-124 and M2-125 reported in (A) are from the prespecified ANCOVA reported in the individual studies. All other data in A and B are based on the ANCOVA model used in the current post hoc analysis, as no prespecified ANCOVA analyses were performed for these outcomes in the individual studies.

**Abbreviations:** ANCOVA, analysis of covariance; CI, confidence interval; TDI, transition dyspnea index.
improvements, the present analysis demonstrates that roflumilast-treated patients with clinically meaningful improvements in dyspnea (TDI responders) had a significantly greater magnitude of improvement in FEV₁ and were more likely to have a clinically meaningful improvement in lung function compared with placebo-treated patients.

Furthermore, the present analysis is consistent with a previous study that reported significant lung function improvements occurring earlier than significant reductions in breathlessness. In the individual 1-year roflumilast studies, small but significant treatment-associated improvements in lung function were demonstrated as early as week 4. In
the current analysis, significantly more patients achieved the FEV₁ MCID with roflumilast treatment versus placebo as early as week 4 and at every study visit thereafter. In comparison, more roflumilast-treated patients achieved the TDI focal score MCID at week 4 compared with placebo; however, this difference did not reach significance until week 8, at which point it was maintained until study end. Together, these time courses suggest that significant lung function improvements may be observed earlier than significant dyspnea improvements. The mechanisms by which roflumilast may lead to improved airflow are not fully defined, but an anti-inflammatory effect has been suggested.11,28

Similar to results in the overall population, improvements in TDI focal scores at study end were small but consistently significant over placebo in patients with chronic bronchitis, regardless of exacerbation history, concomitant SAMA or LABA treatment, or ICS pretreatment. Although greater proportions of TDI responders were observed with roflumilast versus placebo in the subgroups of patients receiving concomitant ICS, LABA, or SAMA treatment throughout the treatment period, these differences were not significant at every study visit. In contrast, significantly greater percentages of TDI responders were consistently observed with roflumilast versus placebo from treatment weeks 8 through 52 in patients with chronic bronchitis, a history of exacerbations, and ICS pretreatment.

Consistent with the results presented here, a 6-month placebo-controlled study examining the effects of roflumilast in patients with moderate to severe COPD and chronic bronchitis who were already being treated with tiotropium demonstrated that significantly more roflumilast+tiotropium patients achieved clinically meaningful improvements in TDI focal score compared with placebo+tiotropium patients, with a between-group difference (0.4 units) that was generally similar to that reported in the current analysis. In addition, compared with placebo, significantly more patients receiving roflumilast+tiotropium in the 6-month study achieved

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**Figure 3** Percentage of patients who achieved a clinically meaningful (≥100 mL) improvement from baseline in postbronchodilator FEV₁ (ie, FEV₁ responders) over time for the overall population.

*Note:* ***P<0.001 versus placebo.

**Abbreviations:** FEV₁, forced expiratory volume in 1 second; LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed.

**Figure 4** Mean change from baseline in postbronchodilator FEV₁ (mL) in TDI responders and nonresponders at week 52.

*Note:* *P<0.05; ***P<0.001 versus placebo.

**Abbreviations:** FEV₁, forced expiratory volume in 1 second; TDI, transition dyspnea index.
clinically meaningful differences in an instrument that assessed dyspnea associated with specific activities of daily living, the University of California, San Diego Shortness of Breath Questionnaire (SOBQ), further demonstrating the positive impact of roflumilast treatment on breathlessness. Numerical improvements in TDI focal scores were also observed with the addition of roflumilast to salmeterol in a separate 6-month study in patients with moderate to severe COPD; however, these differences were not significantly different from patients treated with salmeterol and placebo.
Table 2 Percentage of TDI responders at week 52 (LOCF) according to baseline characteristics in pooled ITT population (N=5,595)

| Baseline characteristic | Subgroup comparisons | % of TDI responders | P-value* |
|-------------------------|----------------------|---------------------|----------|
| Sex                     | Male versus female   | 37% versus 34%      | NS       |
| Age groups              | ≤65 versus >65 years | 37% versus 35%      | NS       |
| Smoking status          | Former versus current smoker | 38% versus 34% | 0.0070 |
| Race                    | Asian versus African-American versus Caucasian | 60% versus 37% versus 35% | <0.0001 |
| COPD severity           | Moderate versus severe versus very severe | 49% versus 37% versus 30% | <0.0001 |
| Concomitant LABA        | Without versus with  | 38% versus 32%      | <0.0001 |
| Concomitant SAMA        | Without versus with  | 38% versus 34%      | 0.0009   |
| Concomitant ICS         | Without versus with  | 39% versus 33%      | <0.0001 |
| ICS pretreatment        | Without versus with  | 38% versus 34%      | 0.0019   |

Note: *P-values are from chi-square tests that were not stratified by study.

Abbreviations: COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroid; ITT, intent to treat; LABA, long-acting β2-agonist; LOCF, last observation carried forward; NS, not significant; SAMA, short-acting muscarinic antagonist; TDI, transition dyspnea index.

Figure 6 Patient subpopulations examined in this analysis.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; SAMA, short-acting muscarinic antagonist.

Table 3 TDI focal scores for subpopulations at week 52 (LOCF)

| Patient group | Placebo n | Mean change from baseline | Roflumilast n | Mean change from baseline | Roflumilast – placebo (P-value) |
|---------------|-----------|----------------------------|---------------|---------------------------|---------------------------------|
| All patients  | 2,835     | 0.041                      | 2,760         | 0.368                     | 0.327 (<0.0001)                 |
| Concomitant ICS | 800 | –0.719                     | 781           | –0.330                    | 0.389 (0.0114)                 |
| Chronic bronchitis | 2,342 | 0.079                      | 2,276         | 0.478                     | 0.398 (<0.0001)                 |
| + Concomitant SAMA | 1,100 | –0.029                     | 1,028         | 0.256                     | 0.285 (0.0421)                 |
| + History of exacerbations | 1,803 | 0.004                      | 1,761         | 0.379                     | 0.375 (0.0003)                 |
| + Concomitant LABA | 771 | –0.268                     | 722           | 0.104                     | 0.371 (0.0241)                 |
| + ICS pretreatment | 643 | –0.377                     | 621           | 0.077                     | 0.454 (0.0125)                 |

Notes: *Includes patients from studies M2-111/112/124/125; +Includes only patients from studies M2-111/112, which permitted concomitant ICS treatment; +Includes patients from studies M2-111/112/124/125, which permitted concomitant SAMA treatment; +Includes only patients from studies M2-111/124/125; +Includes only patients from studies M2-124/125, which permitted concomitant LABA treatment and/or ICS pretreatment.

Abbreviations: ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LOCF, last observation carried forward; n, number of patients with measurements available; SAMA, short-acting muscarinic antagonist; TDI, transition dyspnea index.
analyses presented here were small in magnitude; however, the variation in the magnitude of treatment effect of roflumilast on dyspnea in tiotropium-treated patients versus salmeterol-treated patients may have been due to these differences in patients’ baseline characteristics between the two studies. Inclusion of both of these 6-month roflumilast trials in a recent meta-analysis by Pan et al demonstrated a moderate but significant increase in TDI focal scores with roflumilast (weighted mean difference of 0.30 units; 95% CI, 0.14–0.46), similar to what was reported in the current analysis that focused on 1-year studies alone.

Increased dyspnea is strongly associated with reduced quality of life in COPD patients. In M2-111, the St George's Respiratory Questionnaire (SGRQ), a disease-specific quality of life instrument that assesses causes and impacts of dyspnea, was used to evaluate health status. Compared with placebo at week 52, roflumilast provided moderate but significant improvements in SGRQ total score, and a significantly greater percentage of patients achieved a clinically meaningful improvement in SGRQ with roflumilast (P<0.05 for both). Furthermore, pooled data in patients with chronic bronchitis and/or emphysema (M2-111 and M2-112) demonstrated a significant difference in SGRQ total score improvement versus placebo after 52 weeks of treatment. This suggests that roflumilast may similarly provide clinically meaningful improvements in quality of life in some COPD patients, possibly due to a reduction of breathlessness.

Several limitations of the present analysis should be noted. As all analyses were performed post hoc, and the included component studies were not designed to detect clinically meaningful improvements in dyspnea, these comparisons should be interpreted with caution and used primarily to generate hypotheses for future studies. Findings may not be generalizable to all patients with COPD, as inclusion criteria for each individual study contributing to this pooled analysis may have excluded patients typically seen in clinical practice. The use of LOCF in the current analysis may not have taken into account missing data that were nonrandom (ie, treatment-related discontinuations). The average placebo-adjusted improvements in dyspnea observed in the analyses presented here were small in magnitude; however, patients who improved their TDI focal score by ≥1 unit were observed with roflumilast treatment throughout the studies, suggesting that some patients treated with roflumilast may experience clinically meaningful improvements in breathlessness. Furthermore, the studies included in this analysis were only 1 year in duration. Since worsened breathlessness has been associated with an increased risk for COPD exacerbations, and the effects of roflumilast on dyspnea may be related to a reduction in exacerbation rates, it is possible that longer studies in which more exacerbations would be prevented with roflumilast may enable observation of greater magnitudes of dyspnea improvement. As two of the four studies included in this pooled analysis had a population enriched with patients with a history of exacerbations, it is unclear whether COPD patients with chronic bronchitis who are frequent exacerbators would experience greater improvements in breathlessness compared with non-exacerbators.

Finally, this analysis was based on monotherapy trials that limited concomitant use of medications commonly used to treat COPD, such as fixed-dose ICS/LABA, long-acting muscarinic antagonist, or theophylline. While data derived from subgroups of patients who were pretreated with ICS or who received concomitant SAMA, LABA, or ICS treatment during the studies can be suggestive of potential treatment combinations, this may not be directly applicable to patients who are simultaneously prescribed multiple medications to manage their COPD.

**Conclusion**

In conclusion, these results further explore the effects of roflumilast on breathlessness, demonstrating small but generally consistent improvements in dyspnea with roflumilast treatment over placebo. Furthermore, patients that had reduced breathlessness also experienced accompanying improvements in lung function. Patients being treated with roflumilast to reduce their risk of exacerbations may also experience reduced dyspnea, regardless of patient characteristics such as chronic bronchitis, history of exacerbations, or previous (ICS) or concomitant (SAMA, LABA, or ICS) treatment. The added benefit of reducing breathlessness with roflumilast treatment, although small in magnitude, may provide an added value to consider in the use of this phosphodiesterase-4 inhibitor in the management of COPD.

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Disclosure

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Supplementary materials

Figure S1 TDI responders (A) and deteriorators (B) over time for the subpopulation of patients with chronic bronchitis.

Notes: *P<0.05; **P<0.01; ***P<0.001 versus placebo.

Abbreviations: LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed; TDI, transition dyspnea index.
Figure S2 TDI responders (A) and deteriorators (B) over time for the subpopulation of patients with chronic bronchitis and a history of exacerbations.

Notes: *P<0.05; **P<0.01; ***P<0.001 versus placebo.

Abbreviations: LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed; TDI, transition dyspnea index.
Figure S3 TDI responders (A) and deteriorators (B) over time for the subpopulation of patients with chronic bronchitis, a history of exacerbations, and pretreatment with inhaled corticosteroids.

Notes: *P<0.05; ***P<0.001 versus placebo.

Abbreviations: LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed; TDI, transition dyspnea index.
**Figure S4** TDI responders (A) and deteriorators (B) over time for the subpopulation of patients with chronic bronchitis, a history of exacerbations, and concomitant long-acting β₂-agonist treatment.

Notes: *P<0.05; **P≤0.01; ***P≤0.001 versus placebo.

Abbreviations: LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed; TDI, transition dyspnea index.
Figure S5 TDI responders (A) and deteriorators (B) over time for the subpopulation of patients with chronic bronchitis and concomitant short-acting muscarinic antagonist treatment.

Notes: *P<0.05; **P≤0.01.

Abbreviations: LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed; TDI, transition dyspnea index.
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Figure S6  TDI responders (A) and deteriorators (B) over time for the subpopulation of patients with concomitant inhaled corticosteroid treatment.

Notes: *P<0.05; **P<0.01; ***P≤0.001 versus placebo.

Abbreviations: LOCF, last observation carried forward; n, number of responders; N, number of patients analyzed; TDI, transition dyspnea index.