

The effect of COPD severity and study duration on exacerbation outcome in randomized controlled trials

Göran Eriksson¹
 Peter M Calverley²
 Christine R Jenkins^{3,4}
 Antonio R Anzueto⁵
 Barry J Make⁶
 Magnus Lindberg⁷
 Malin Fagerås⁷
 Dirkje S Postma⁸

¹Department of Respiratory Medicine and Allergology, University Hospital, Lund, Sweden; ²Pulmonary and Rehabilitation Research Group, University Hospital Aintree, Liverpool, UK; ³Concord Clinical School, University of Sydney, ⁴The George Institute for Global Health, Sydney, Australia; ⁵Department of Pulmonary Medicine and Critical Care, University of Texas Health Sciences Center and South Texas Veterans' Health Care System, San Antonio, Texas; ⁶Division of Pulmonary Sciences and Critical Care Medicine, National Jewish Health, University of Colorado, Denver, Colorado, USA; ⁷AstraZeneca R&D, Mölndal, Sweden; ⁸Department of Pulmonary Medicine and Tuberculosis, University Medical Center Groningen, GRIAC Research Institute, University of Groningen, Groningen, the Netherlands

Correspondence: Göran Eriksson
 Department of Respiratory Medicine and Allergology, Skane University Hospital, Klinikgatan 18, 222 42 Lund, Sweden
 Tel +46 73 329 9929
 Email goran.eriksson@med.lu.se

Background: When discontinuation in COPD randomized controlled trials (RCTs) is unevenly distributed between treatments (differential dropout), the capacity to demonstrate treatment effects may be reduced. We investigated the impact of the time of differential dropout on exacerbation outcomes in RCTs, in relation to study duration and COPD severity.

Methods: A post hoc analysis of 2,345 patients from three RCTs of 6- and 12-month duration was performed to compare budesonide/formoterol and formoterol in moderate, severe, and very severe COPD. Outcomes were exacerbation rate, time-to-first exacerbation, or discontinuation; patients were stratified by disease severity. Outcomes were studied by censoring data monthly from 1 to 12 months.

Results: In patients treated with budesonide/formoterol, annualized exacerbation rates (AERs) were comparable for each study duration (rate ratio [RR] =0.6). With formoterol, the AER decreased with study duration (RR =1.20 at 1 month to RR =0.86 at 12 months). There was a treatment-related difference in exacerbation rates of 45%–48% for shorter study durations (≤ 4 months) and 27% for 12-month duration. This treatment-related difference in exacerbation rates was comparable for the three disease severities in studies ≤ 4 months (range: 39%–51%), but this difference decreased with longer study durations, especially in more severe groups (22% and 29% at 12 months). There were fewer discontinuations with budesonide/formoterol; the treatment-related difference in time-to-first discontinuation decreased by study duration (35%, 30%, 26%, and 22% at 3, 6, 9, and 12 months, respectively). Numbers of differential dropouts increased with increasing disease severity, being greatest during second, third, and fourth months.

Conclusions: COPD severity and study duration impact exacerbation as an outcome in double-blind RCTs. This effect is most obvious in patients with severe/very severe COPD and in studies that are longer than 4 months. Early differential dropout particularly impacts study outcome, producing a “healthy survivor effect,” which reduces estimations of treatment impact on exacerbations.

Keywords: healthy survivor effect, exacerbation outcomes, early differential dropout, RCT, disease severity

Background

In patients with COPD, double-blind, randomized controlled trials (RCTs) conducted over 6–12 months are regarded as the most rigorous way to evaluate the efficacy of treatments for symptomatic benefit and/or prevention of future risks, such as exacerbations.¹ These trials often show significant treatment effects compared with placebo, but differences between active treatment arms may only be seen when data are pooled or larger studies conducted.^{2–4} A consistent finding in RCTs in COPD patients is a high

rate of discontinuation, ranging from 27% to 53%,⁵ especially among those with more severe disease. Furthermore, discontinuation occurs early in a trial^{6,7} and correlates with disease severity.⁸ This should not cause a major problem when interpreting RCTs, provided that discontinuation is a random phenomenon between the interventions studied. However, the power calculation for the primary variable needs to compensate for this effect, as the loss of information over time may impact the ability of the study to confidently identify or exclude a treatment effect. A particular problem arises when differential dropout between study arms occurs on top of evenly distributed random discontinuations. The net effect can lead to potential bias in favor of a weaker treatment, if the sicker people in that arm are lost during follow-up.⁹

In this report, we investigate the impact of both disease severity and study duration on COPD exacerbations in double-blind RCTs. A secondary objective was to better understand the impact of premature discontinuations, on exacerbation frequency and treatment effect in relation to disease severity and study duration. A large data set from three RCTs^{10–12} was interrogated as the basis for these analyses.

Methods

Study design and patient population

We analyzed data from three double-blind, randomized, double-dummy, parallel-group, placebo-controlled, multicenter clinical trials of 6 (NCT00206154¹²) and 12 months duration (NCT00206167¹⁰ and NCT00419744¹¹). The efficacy of budesonide/formoterol 320/9 µg and formoterol 9 µg (two inhalations twice daily) (AstraZeneca, Mölndal, Sweden) was compared in patients with COPD. Salbutamol (albuterol) was allowed as reliever medication during screening, run-in, and throughout all studies. All studies were conducted in accordance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable regulatory requirements; all patients gave written, informed consent. These previously published trials were conducted in 237 sites in the USA, Europe, and Mexico;¹⁰ 180 sites in the USA, Central and South America, and South Africa;¹¹ and 194 centers in the USA, Czech Republic, the Netherlands, Poland, and South Africa.¹² Ethical approval was provided in all countries by local Independent Ethics Committees at the time when the studies were first conducted, and details have previously been published.^{10–12}

The study inclusion criteria were similar: smokers or ex-smokers with a smoking history of ≥ 10 pack-years; pre-bronchodilator forced expiratory volume in 1 second (FEV_1) $\leq 50\%$ predicted; pre-bronchodilator FEV_1 /forced

vital capacity (FVC) ratio $< 70\%$; age ≥ 40 years; COPD with a history of ≥ 1 COPD exacerbation requiring treatment with a course of systemic corticosteroids, antibiotics, or both 1–12 months prior to screening; and a modified Medical Research Council dyspnea score of ≥ 2 .

COPD severity and study duration

The impact of disease severity on exacerbation and dropout was assessed by stratifying patients by lung function – moderate, severe, and very severe – according to GOLD recommended criteria.¹³ Study duration was evaluated by censoring data after 1, 2, 3 months, etc., up to 12 months, thereby generating 12 subanalyses of increasing duration.

Exacerbation as an endpoint

Our primary outcome was the impact of study duration and disease severity on exacerbations. A COPD exacerbation was defined as a worsening of COPD symptoms requiring treatment with oral corticosteroids and/or hospitalization. Exacerbations were recorded by patients in diary cards and confirmed at a clinic visit by study investigators/coordinators.

Discontinuation as an endpoint

All discontinuations, irrespective of the reason, were summarized by treatment. Individual reasons for discontinuations were also assessed for each treatment: failure to fulfill eligibility criteria, adverse event, withdrawal of consent (voluntary discontinuation by patient), lost to follow-up, and others.

Exploratory endpoints

We investigated at which month(s) of follow-up the differential dropout peaked by conditional probability of dropout (CPDo), that is, the number of discontinuations in a month divided by the number of patients entering the defined month. A composite of exacerbation and discontinuation (ExDo) was created to evaluate whether early discontinuation could compensate for the loss of treatment effect on exacerbations over time due to early differential dropout.

Statistical analyses

Analyses were performed for the overall patient population and the COPD severity subgroups – moderate, severe, and very severe. The impact of study duration was analyzed cumulatively for 0–1, 0–2, 0–3, etc., up to 0–12 months of duration, that is, data after the defined study duration were censored. As one trial¹² had shorter study duration, these data were censored at 6 months. Differences in rates were analyzed using Poisson regression with study as a factor. Time-to-first events (exacerbation, discontinuations, and ExDo) were analyzed

using Cox-regression analysis with study as a factor. Rate ratios (RRs) and hazard ratios (HRs) with 95% confidence intervals and *P*-values were provided. Treatment-related differences (RR and HR) were expressed as percentage reduction in exacerbations. CPDo was summarized descriptively up to 6 months. Analyses used standard statistical software (SAS v9.2; SAS Institute, Inc., Cary, NC, USA).

Results

Demographics and baseline characteristics

Overall, 2,345 COPD patients (mean age: 63 years; 63% male) were included in the analysis. Demographics and baseline characteristics for all patients, according to disease severity, are shown in Table 1. Studies included (mean) 17% moderate, 57% severe, and 26% very severe COPD patients according to GOLD FEV₁ severity stage (Table 1).

Effect of study duration and disease severity on exacerbation

Exacerbations in all patients

Exacerbation rates per treatment were higher with longer study duration and more so with formoterol (RR =0.86 at 12 months) than with budesonide/formoterol (RR =0.63 at 12 months) (Figure 1A).

Annualized exacerbation rates (AERs) per treatment

In patients treated with budesonide/formoterol, the AERs for each study duration period were comparable irrespective of study duration (RR ≈0.6 exacerbation per patient and year). In the formoterol arm, the AER decreased from RR =1.20 to RR =0.86 (a 28% reduction) over the 12-month period (Figure 1B; Table S1).

Relative treatment difference in exacerbation rate

The differences between treatments in the exacerbation rates decreased with longer study duration. The reduction in favor of budesonide/formoterol was 45%–48% for shorter study durations (≤4 months) and 27% for a study duration of 12 months (Figure 1C; Table S2).

Relative treatment difference in time-to-first exacerbation

The reductions in the risk of a first exacerbation between treatments were 40%–47% for shorter study durations (≤4 months). Thereafter, the difference between treatments in time-to-first exacerbation decreased to 21% at 12 months (Figure 1D; Table S3).

Exacerbations in moderate, severe, and very severe COPD

Exacerbation rates per treatment were higher in more severe patients and more so with formoterol (RR =0.64, RR =0.81, and RR =1.17 exacerbations per patient and 12 months for moderate, severe, and very severe, respectively) than with budesonide/formoterol (RR =0.39, RR =0.57, and RR =0.91, respectively) (Figure S1).

AERs per treatment

In patients treated with budesonide/formoterol, the AERs did not change over time for the three severity groups, though the RR levels differed with disease severity (RR ≈0.45, RR ≈0.55, and RR ≈0.90 exacerbations per patient and year for moderate, severe, and very severe, respectively). In patients treated with formoterol, the AERs decreased over time and more so for more severe disease. The RRs for decrease in AERs from 1–12 months were 0.84–0.64

Table 1 Demographic and baseline characteristics for all patients, stratified according to COPD disease severity group, treated with budesonide/formoterol or formoterol^{10–12}

Characteristics	All patients, n=2,345	COPD disease severity		
		Moderate, n=408	Severe, n=1,325	Very severe, n=612
Age, years	63.2 (9.22)	61.6 (9.82)	63.6 (9.21)	63.4 (8.71)
Male, n (%)	1,487 (63)	206 (50)	833 (63)	448 (73)
FEV ₁ pre-BD, L	1.01 (0.41)	1.38 (0.43)	1.05 (0.33)	0.69 (0.26)
FEV ₁ post-BD, % predicted ^a (range)	38.4 (10.0–103.1)	55.2 (50.0–103.1)	39.8 (30.0–50.0)	24.9 (10.0–30.0)
FEV ₁ /FVC, ratio ^a (range)	0.47 (0.15–0.97)	0.56 (0.28–0.91)	0.47 (0.19–0.98)	0.38 (0.15–0.93)
Pack-years ^a (range)	42.0 (10.0–258.0)	40.0 (10.0–168.0)	41.0 (10.0–258.0)	45.0 (10.0–184.0)
SGRQ total score	55.8 (16.9)	52.7 (16.8)	55.2 (17.3)	59.4 (15.6)
Reliever use, inhalations/day	4.5 (4.0)	3.6 (3.2)	4.2 (3.7)	5.8 (4.7)

Notes: Data are presented as arithmetic mean (SD) unless otherwise stated. ^aThere were two patients with moderate COPD and one with severe COPD, who did not have an FEV₁/FVC <70% at run-in or randomization. Data from Rennard et al;¹⁰ Sharafkhaneh et al;¹¹ Tashkin et al.¹²

Abbreviations: BD, bronchodilator; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation; SGRQ, St George's Respiratory Questionnaire.

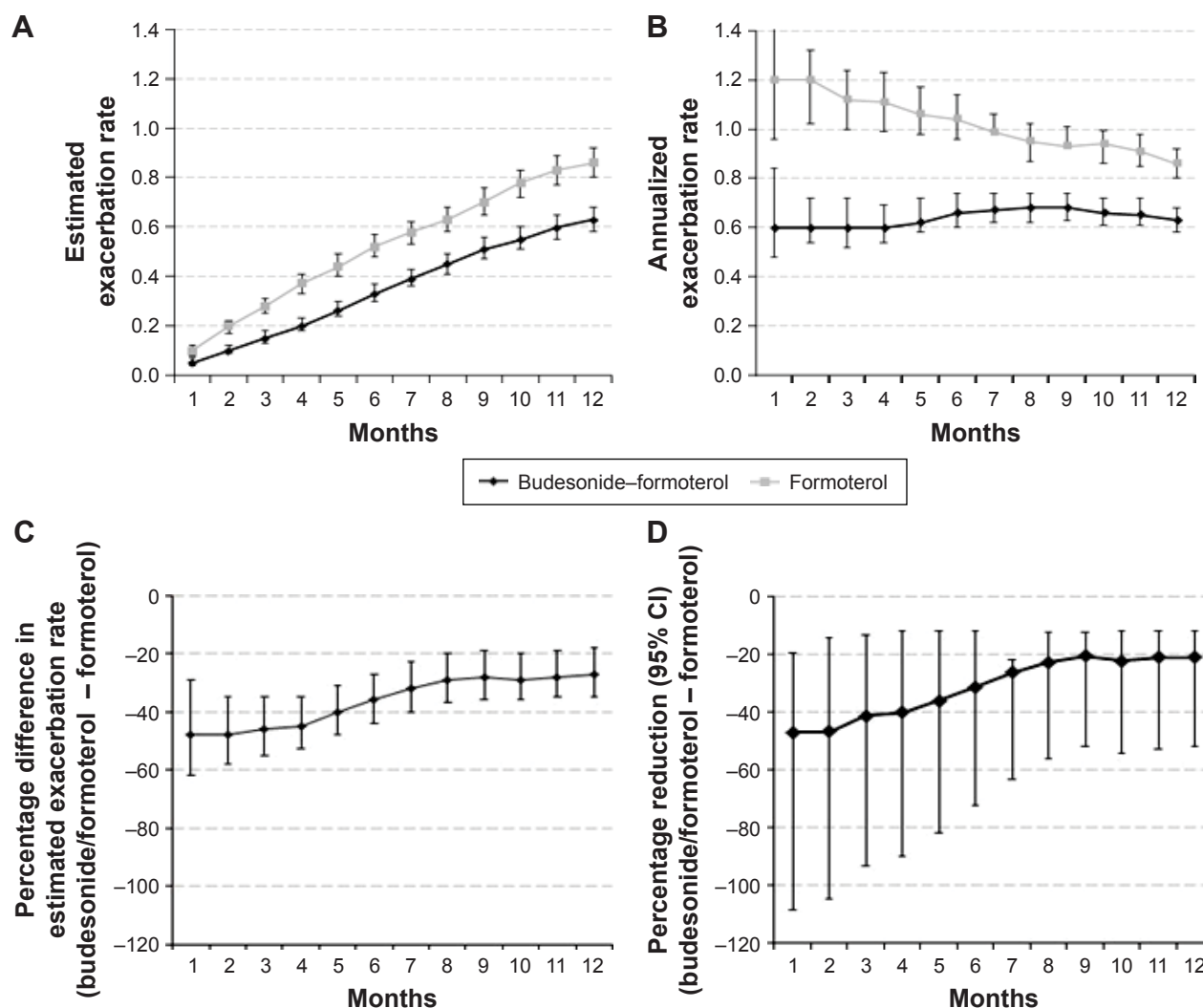


Figure 1 Exacerbations in all patients: (A) exacerbation rates for budesonide/formoterol and formoterol; (B) annualized exacerbation rates for budesonide/formoterol and formoterol; (C) percentage reduction in the exacerbation rates; (D) percentage reduction in time-to-first exacerbation.

Notes: Data in (A) and (B) are presented as estimated exacerbation rates with 95% confidence intervals. Data in (C) and (D) are presented as difference in estimated exacerbation rates with 95% confidence intervals in percentage.

Abbreviation: CI, confidence interval.

(reduction of 23.8%), 1.10–0.81 (26.4%), and 1.68–1.17 (30.4%) for moderate, severe, and very severe COPD, respectively (Table 2).

Relative treatment difference in exacerbation rate

The exacerbation rate reduction of budesonide/formoterol versus formoterol over the first 4 months was similar across studies in moderate, severe, and very severe patients, ranging between 39% and 51% (Figure 2A; Table S2). In patients with moderate COPD, the initial difference in exacerbation rates (39%–50%) was generally maintained for all study durations up to 12 months. However, in the severe and very severe COPD groups, the initial effect (ranging between 41% and 51%) decreased to 29% and 22% at 12 months, respectively.

Relative treatment difference in time-to-first exacerbation

Differences in time-to-first exacerbation between treatments were similar for moderate, severe, and very severe disease when study duration was short (≤ 4 months), ranging from 38% to 49% (Figure 2B). Thereafter, the differences decreased for all three disease severities, with a trend for greater decrease in difference with increasing disease severity (-25% [$P=0.14$], -23% [$P<0.01$], and -18% [$P=0.12$]) for moderate, severe, and very severe, respectively (Table S3).

Discontinuation and differential dropout

All discontinuations per study and treatment

The percentage of discontinuations was lower for budesonide/formoterol than for formoterol alone. The difference in favor

Table 2 Annualized exacerbation rates for budesonide/formoterol and formoterol according to COPD disease severity group

Study month	Annualized exacerbation rates											
	Disease severity											
	Moderate, n=408				Severe, n=1,325				Very severe, n=612			
	BUD/ FOR	95% CI	FOR	95% CI	BUD/ FOR	95% CI	FOR	95% CI	BUD/ FOR	95% CI	FOR	95% CI
1	0.48	0.24–0.84	0.84	0.48–1.44	0.60	0.39–0.72	1.08	0.84–1.32	0.96	0.6–1.32	1.68	1.2–2.28
2	0.48	0.30–0.78	0.78	0.54–1.08	0.54	0.42–0.66	1.08	0.90–1.26	0.90	0.66–1.2	1.74	1.38–2.16
3	0.44	0.32–0.68	0.84	0.60–1.12	0.52	0.44–0.64	1.04	0.92–1.24	0.88	0.68–1.12	1.48	1.20–1.76
4	0.45	0.33–0.66	0.84	0.63–1.08	0.54	0.45–0.66	0.99	0.87–1.14	0.84	0.66–1.05	1.53	1.29–1.80
5	0.43	0.31–0.60	0.82	0.65–1.06	0.60	0.50–0.70	0.98	0.86–1.10	0.86	0.72–1.06	1.44	1.22–1.68
6	0.44	0.34–0.62	0.78	0.78–0.98	0.60	0.52–0.70	0.96	0.86–1.08	0.96	0.82–1.14	1.44	1.24–1.66
7	0.43	0.32–0.58	0.74	0.58–0.91	0.62	0.53–0.70	0.93	0.82–1.03	0.98	0.84–1.15	1.34	1.33–1.52
8	0.42	0.33–0.57	0.71	0.57–0.87	0.62	0.54–0.69	0.89	0.80–0.99	0.98	0.84–1.13	1.26	1.10–1.44
9	0.43	0.32–0.56	0.69	0.57–0.85	0.63	0.55–0.70	0.88	0.80–0.98	0.97	0.84–1.12	1.24	1.09–1.41
10	0.41	0.31–0.53	0.72	0.59–0.88	0.61	0.54–0.68	0.86	0.80–0.96	0.95	0.83–1.1	1.24	1.08–1.40
11	0.40	0.30–0.52	0.64	0.57–0.84	0.66	0.55–0.68	0.84	0.83–0.93	0.93	0.81–1.07	1.21	1.07–1.37
12	0.39	0.30–0.50	0.64	0.53–0.78	0.57	0.51–0.64	0.81	0.73–0.89	0.91	0.80–1.04	1.17	1.03–1.32

Note: Data are presented as annualized exacerbation rates with 95% confidence intervals.

Abbreviations: BUD, budesonide; FOR, formoterol; CI, confidence interval.

of the budesonide/formoterol was 4.2% and 4.7% units in the two 12-month studies and 7.4% units in the 6-month study (Table 3).

Reason for discontinuations per treatment

Adverse event and withdrawal of consent were the two dominating reasons for discontinuations and differential dropout.

More patients discontinued on formoterol than budesonide/formoterol due to adverse events (2.4% units) and withdrawal of consent (2.0% units) (Table 4).

CPDo

Discontinuations were higher for formoterol-treated patients than for budesonide/formoterol-treated patients

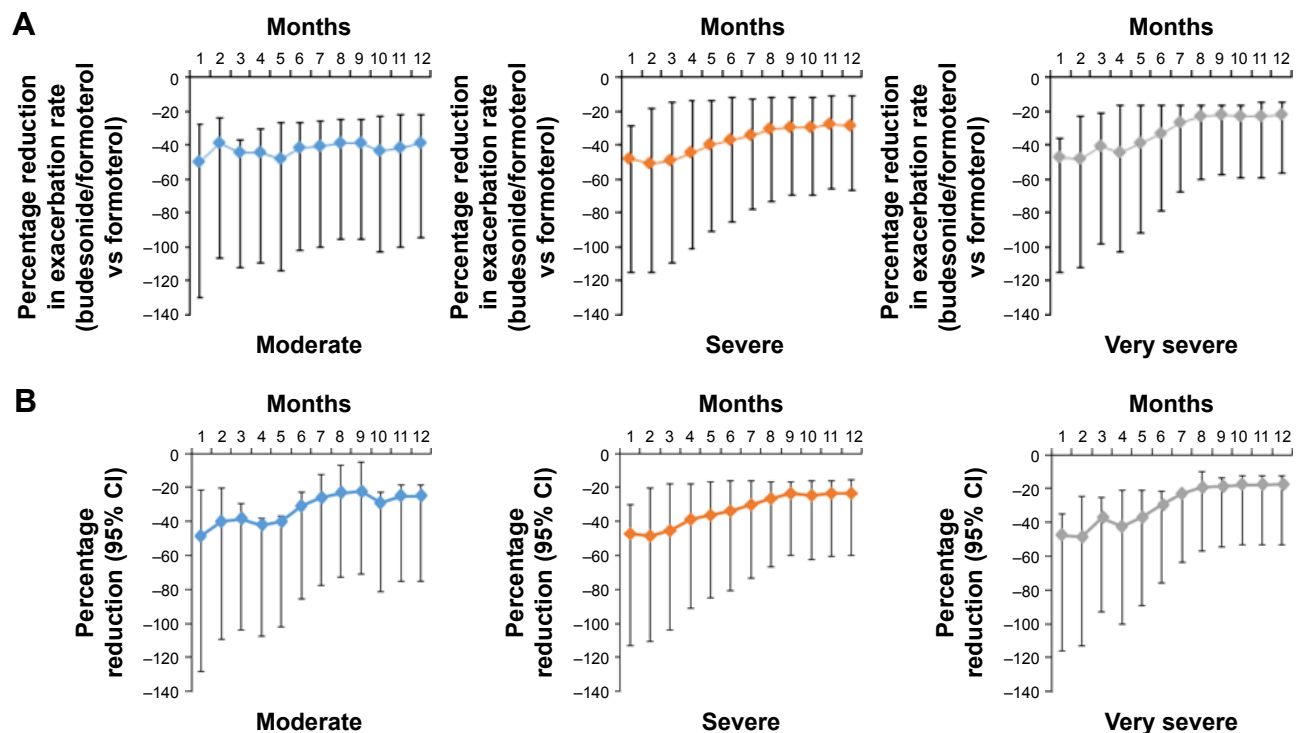


Figure 2 Exacerbations over time in patients with moderate, severe, and very severe COPD: (A) treatment effect on exacerbation rate (% change in favor of budesonide/formoterol over formoterol only) for different study durations; (B) risk reduction of time-to-first exacerbation (percentage change in favor of budesonide/formoterol over formoterol only) for different study durations.

Note: Data are presented with 95% confidence intervals.

Abbreviation: CI, confidence interval.

Table 3 All discontinuations and differential dropouts by study and treatment arm

Treatment	Randomized (N)	Discontinuations (N)	Discontinuations/randomized (%)
BUD/FOR ^a	494	134	27.1
BUD/FOR ^b	407	117	28.7
BUD/FOR ^{c,d}	277	39	14.1
FOR ^a	495	157	31.7
FOR ^b	404	133	32.9
FOR ^{c,d}	284	61	21.5

Notes: Data from ^aRennard et al;¹⁰ ^bSharafkhaneh et al;¹¹ ^cTashkin et al;¹² ^d6-month study.

Abbreviations: BUD, budesonide; FOR, formoterol.

at months 2, 3, and 4, and increased with disease severity (Figure 3). The pattern in moderate disease was not clear, since the number of discontinuations was the lowest and the cohort was the smallest.

Overall, this descriptive analysis indicated that the highest differential dropout occurred at months 2, 3, and 4.

Discontinuations

In all patients, the time-to-discontinuation was significantly shorter with formoterol than with budesonide/formoterol from 2 to 12 months. This treatment difference decreased with study duration (35%, 30%, 26%, and 22% at 3, 6, 9, and 12 months, respectively). We observed a similar pattern with moderate and severe COPD, moving from treatment differences of 32% and 34% at 3 months to 15% at 12 months. In patients with moderate disease, no significant difference between treatments could be detected, whereas in patients with severe COPD, there was a statistically significant difference in time-to-first discontinuation at 3-, 4-, 5-, and 6-month study durations in favor of the budesonide/formoterol group. The very severe group showed, however, significant treatment difference from 3 to 12 months. This treatment difference was high over the whole study duration (34%–38% from 3 to 12 months) (Figure 4; Table S4).

Table 4 Reasons for discontinuations per treatment arm

Reason for discontinuation	BUD/FOR (N)	BUD/FOR, reason/randomized (%)	FOR (N)	FOR, reason/randomized (%)	ΔBUD/FOR–FOR (%)
Adverse events	120	10.2	149	12.6	–2.4
Consent withdrawn	92	7.8	116	9.8	–2.0
Others	40	3.4	41	3.5	–0.1
Eligibility	17	1.4	26	2.2	–0.8
Lost to follow-up	21	1.8	19	1.6	+0.2
Total	290	24.6	351	29.7	–5.1

Note: ΔBUD/FOR–FOR, percentage unit difference for BUD/FOR–FOR.

Abbreviations: BUD, budesonide; FOR, formoterol.

Composite of ExDo

ExDo, the composite of exacerbations and discontinuations, increased the number of events over that of exacerbations alone, both in all patients and in all three severity groups. ExDo also showed more consistent results in more severe COPD, where the differential dropout was more prominent. For example, the relative treatment difference in time-to-exacerbation was 18%–19% and not significant in analyses of 7- to 12-month study durations, whereas relative treatment difference in time-to-ExDo was significant for all these study durations with a 21%–23% difference in favor of budesonide/formoterol (Table 5).

Discussion

Our results demonstrate that both disease severity and study duration influence exacerbation outcomes in double-blind RCTs in COPD. This effect is particularly apparent in patients with severe/very severe COPD and in studies that are longer than 4 months' duration, where early differential dropout resulted in a "healthy survivor effect". This effect changed the composition of the study groups and tended to reduce the effect of therapy over time.

The impact of differential dropout on long-term efficacy outcomes in COPD has been recognized as a potential source of bias, and several studies have highlighted this problem.^{7,8,14,15} These studies had all a follow-up of 3–4 years. However, the consequences for shorter term studies (≤12 months), a commonly used study design in phases II–III and for regulatory purposes, has not been formally investigated. This retrospective analysis of moderate-to-very-severe COPD in three RCTs^{10–12} of 6–12 months' duration showed over time a marked loss in exacerbation difference between the two treatments: budesonide/formoterol and formoterol. This loss of treatment difference was increased by study duration and in more severe COPD, but these effects were almost negligible in moderate COPD. Of importance, the time-to-first exacerbation was more impacted than exacerbation rates,

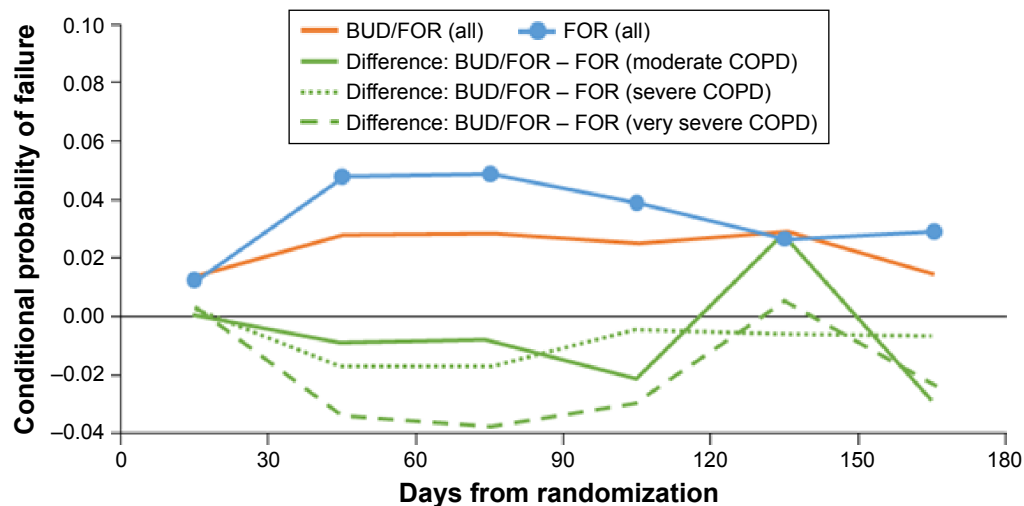


Figure 3 Discontinuations for budesonide/formoterol and formoterol in all patients, and difference in discontinuations for budesonide/formoterol versus formoterol in patients with moderate, severe, and very severe COPD.

Note: No data are presented after 6 months as the number of patients that drop out (one study 6 months) and the number of discontinuations per month decrease.

Abbreviations: BUD/FOR, budesonide/formoterol; FOR, formoterol.

and the differential dropout preceded the loss of treatment effect on exacerbations. We believe these results will further raise the awareness of how important study methodology, selection of patients, and calculation of sample size are in exacerbation studies.

In the budesonide/formoterol treatment arm, the AERs were similar for shorter and longer study durations, whereas

they decreased over time with monotherapy formoterol, indicating differential effects of these treatments. Our shorter term data support those of Vestbo et al,⁷ reporting that differential withdrawal over a 3-year period resulted in a reduction in AERs from 6.8 to 0.9 in placebo and from 3.0 to 0.8 with salmeterol/fluticasone. These data together, showing a decrease in AERs over time, indicate that weaker treatments may lose more patients over time, who are more exacerbation prone than those in the more active comparator arm. We demonstrate that this effect can already be seen during the first 6 months in very severe patients.

The analyses of the relative treatment difference in exacerbation rate also demonstrate this time-dependent effect. In the whole population, this was already evident after >4 months' study duration. A 45%–48% difference in studies of short duration was reduced to 27%–29% in the studies over 9–12 months. The time-to-first exacerbation analyses showed similar results, with a treatment difference being 40%–47% in the first 3 months, decreasing to 21%–22% in months 9–12. The most likely explanation for the decrease in relative treatment difference is that the more severe patients randomized to formoterol are more vulnerable to early discontinuation than similarly severe patients in the budesonide/formoterol arm. These data may also explain why a 3-month study by Welte et al¹⁶ could show a 60% treatment difference between budesonide/formoterol and placebo and importantly with no differential dropout.

The impact of COPD severity on exacerbation outcomes has been investigated in many studies, but two studies specifically addressed the moderate, severe, and very

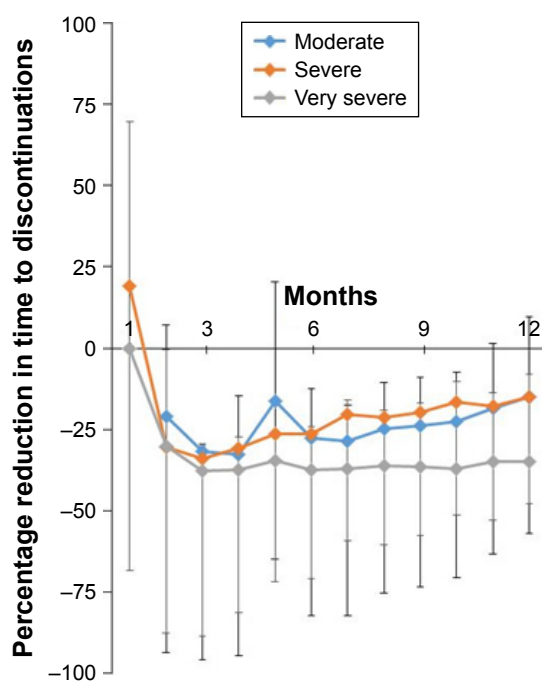


Figure 4 Percentage reduction in time to discontinuation for budesonide/formoterol compared with formoterol according to COPD disease severity.

Notes: Data are presented with 95% confidence intervals. Four discontinuations (three on formoterol and one on budesonide/formoterol) at 1 month in patients with moderate COPD.

Table 5 Time-to-ExDo analyses for budesonide/formoterol versus formoterol in all patients and according to COPD disease severity group

Study month	Time-to-ExDo				
	All patients, n=2,345		Disease severity		
		P-value	Moderate, n=408	Severe, n=1,325	Very severe, n=612
1	0.570 (0.429, 0.759)	0.0001	0.514 (0.220, 1.202)	0.589 (0.395, 0.879)*	0.558 (0.350, 0.889)*
2	0.571 (0.468, 0.697)	<0.0001	0.690 (0.385, 1.236)	0.552 (0.417, 0.731)***	0.551 (0.398, 0.764)**
3	0.588 (0.497, 0.696)	<0.0001	0.641 (0.411, 0.999)*	0.555 (0.438, 0.704)***	0.606 (0.456, 0.806)**
4	0.610 (0.525, 0.709)	<0.0001	0.623 (0.421, 0.921)*	0.623 (0.504, 0.770)***	0.576 (0.446, 0.743)***
5	0.668 (0.581, 0.768)	<0.0001	0.691 (0.481, 0.993)*	0.670 (0.551, 0.815)***	0.639 (0.503, 0.811)**
6	0.703 (0.617, 0.802)	<0.0001	0.727 (0.518, 1.022)	0.692 (0.576, 0.832)***	0.692 (0.552, 0.867)**
7	0.747 (0.659, 0.848)	<0.0001	0.765 (0.553, 1.059)	0.733 (0.615, 0.875)**	0.743 (0.597, 0.924)*
8	0.773 (0.683, 0.874)	<0.0001	0.774 (0.563, 1.064)	0.756 (0.636, 0.898)**	0.780 (0.630, 0.965)*
9	0.787 (0.698, 0.887)	<0.0001	0.786 (0.576, 1.071)	0.779 (0.660, 0.920)**	0.780 (0.633, 0.959)*
10	0.777 (0.691, 0.874)	<0.0001	0.776 (0.574, 1.051)	0.769 (0.653, 0.904)**	0.773 (0.629, 0.950)*
11	0.788 (0.701, 0.884)	<0.0001	0.789 (0.585, 1.065)	0.776 (0.661, 0.911)**	0.786 (0.641, 0.964)*
12	0.791 (0.705, 0.887)	<0.0001	0.799 (0.593, 1.078)	0.778 (0.664, 0.911)**	0.788 (0.644, 0.964)*

Notes: Data are presented as hazard ratios and 95% confidence intervals. * $P<0.05$; ** $P<0.005$; *** $P<0.0001$. BUD/FOR versus FOR.

Abbreviations: ExDo, exacerbation and discontinuation; BUD, budesonide; FOR, formoterol.

severe COPD subgroups.^{15,17} Our approach extends their work by showing that the impact on exacerbations occurs early (≤ 12 months). In the three severity groups, we found that the AERs for the two treatments were consistent with those from the whole group, that is, budesonide/formoterol showed constant values over time irrespective of severity, whereas formoterol treatment was accompanied by a reduction in annualized exacerbations over time and with increased severity. As a consequence, the treatment differences with respect to the exacerbation rate decreased over time and with severity. These data support the assumption that more severe and unstable patients discontinue earlier in a treatment arm, where efficacy is not sufficient for the severity stage. The severity of COPD had less (or minimal) impact on studies with shorter duration (≤ 4 months), while it was marked in studies beyond 5–6 months, and in studies involving patients with severe and very severe COPD. For these patients, the treatment effect decreased over time, from 41%–51% for shorter durations to 29% and 22%, respectively, at 12 months' duration. However, the treatment difference in moderate disease remained unaffected over time (about 40%–45% difference in favor of budesonide/formoterol). The results from the time-to-first exacerbation in the three severity groups paralleled our findings from the whole group. However, this statistical method seemed to be less powerful and sensitive to disease severity than using exacerbation rates. For example, the moderate severity group showed loss in effect over time for time-to-first exacerbation (but not with exacerbation rate) and the very severe group showed an initial significant difference in effect, whereas the

effect was nonsignificant in study durations of 6–12 months (but not with exacerbation rate). Similar findings with time-to-first exacerbation analyses have been observed in corticosteroid withdrawal studies¹⁸ and may reflect a greater likelihood of frequent exacerbaters to drop out early.

As expected, discontinuations in COPD studies were high, especially as our patients predominantly had severe-to-very-severe COPD. We also found a higher discontinuation in the formoterol group, likely related to more treatment failures and/or more long-acting beta agonist (LABA)-related adverse events in the LABA-only group. As both groups used LABA and general adverse events were similar, it can be speculated that the differential dropout is related to a weaker effect of LABA alone. Two explanations predominated as causes of differential dropout: adverse event and withdrawal of informed consent. Both may be due to disease worsening or perceived lack of benefit. By comparison, reasons such as eligibility for the study, loss to follow-up, and “others” were more comparable between treatments.

To understand the time course of the differential dropout, we performed an exploratory analysis, investigating conditional probability to dropout (CPDo) at a certain month. The all-patient analysis showed that fewer patients discontinued during months 2, 3, and 4 on budesonide/formoterol compared with formoterol alone. In the very severe group, a clear difference in discontinuation frequency was seen during months 2–5. Though the group with moderate COPD also indicated a difference, the lower number of discontinuations due to less severe disease and longer time in the study made interpretation difficult.

The analysis of time-to-first discontinuations showed a large difference between active and less active treatment in study durations of 2–4 months (~35%). Thereafter, the difference between treatments for all patients, moderate and severe COPD decreased with longer study durations (15%–20% for studies ≥ 9 months), indicating a decrease in differential dropout over time. The very severe COPD group showed a different pattern with a high difference between treatments, irrespective of study duration (38%–34%). These analyses support the CPDo data that the differential dropout effects appear early and before the change of treatment differences in exacerbations are noted. In addition, and in line with CPDo, the impact is more pronounced and longer lasting in very severe COPD.

This post hoc analysis has some limitations. Patient numbers across the three severity groups comprised a skewed distribution, due to the original studies not being designed around severities; the limited number of patients in the moderate COPD group ($n=408$) may have affected analysis, especially when compared to the severe COPD group ($n=1,325$); patients included in the original trials had a history of ≥ 1 COPD exacerbation in the previous year so our results are not generalizable to all patients with COPD. The present analysis only investigated the addition of budesonide to formoterol, and our results should, therefore, be validated with other drug classes. Finally, analyses such as the one presented cannot be generalized to differential dropout due to differences in side-effect profiles.

In conclusion, our data indicate that the relative treatment differences in exacerbation rates over a whole study can vary by threefold. As the benefit of an effective intervention may be underestimated in longer studies, this may have implications for drug development. Our data highlight the importance of study design, patient selection, and study duration, and show that subtle differences in these parameters can make comparisons between studies challenging and questionable. Future studies of new agents designed to modify exacerbation outcomes in COPD may benefit from adopting a shorter focused design, which minimizes the effect of differential dropout, an approach already shown to be effective in clinical trials of COPD.¹⁶

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Author contributions

All authors contributed to data interpretation, and conceiving, writing, and revising of the manuscript. All authors approved the final version of the manuscript. ML was responsible for statistical analyses. GE, the corresponding author, had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Disclosure

GE consults for Airsonett, ALK, Almirall, MVIC, and Novartis. He is an ex-employee of AstraZeneca (March 2013).

PMC is a board member for Boehringer Ingelheim, the Department of Health Respiratory Programme Board, GlaxoSmithKline, and Nycomed. He has been a consultant for Novartis and provided expert testimony for Forest. PMC has received honoraria for advising on the conduct and analysis of clinical trial data from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Novartis, and Nycomed. He has also spoken at meetings supported by these companies. Support for travel to meetings has been provided by AstraZeneca.

CRJ is an advisory board member for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Merck Limited, and Novartis, and a consultant for AstraZeneca, GlaxoSmithKline, Pieris, and Chiesi. Educational presentations have been developed for AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis, with honoraria paid to CRJ or her institution. Lectures have been presented on behalf of AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, and Novartis. Support for travel to advisory meetings has been provided by AstraZeneca, Novartis, and Boehringer Ingelheim.

ARA is a consultant and speaker for AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Sunovion Pharma, GlaxoSmithKline, and Pfizer, and has received honoraria from these companies. Educational presentations have been developed for AstraZeneca, Bayer Pharma, Boehringer Ingelheim, Sunovion Pharma, GSK, and Pfizer. University of Texas Health Science Center at San Antonio has received money for research to perform clinical trials. Support for travel to meetings has also been provided by AstraZeneca.

BJM is an advisory board member for Aerocrine, AstraZeneca, Boehringer Ingelheim, CSL Bering, Forest, Novartis, and Theravance, and a consultant for Astellas, Forest, and Chiesi. Clinical trial data have been reviewed for Spiration, with grants received and controlled by National Jewish Health from AstraZeneca, Boehringer Ingelheim,

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ML and MF are employees of AstraZeneca and own stocks within the company.

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Supplementary materials

Table S1 Annualized exacerbation rates for budesonide/formoterol and formoterol for all patients

Study month	Annualized exacerbation rates			
	All patients, n=2,345			
	BUD/FOR	95% CI	FOR	95% CI
1	0.60	0.48–0.84	1.20	0.96–1.44
2	0.60	0.54–0.72	1.20	1.02–1.32
3	0.60	0.52–0.72	1.12	1.0–1.24
4	0.60	0.54–0.69	1.11	0.99–1.23
5	0.62	0.58–0.72	1.06	0.98–1.17
6	0.66	0.60–0.74	1.04	0.96–1.14
7	0.67	0.62–0.74	0.99	0.99–1.06
8	0.68	0.62–0.74	0.95	0.87–1.02
9	0.68	0.63–0.74	0.93	0.93–1.01
10	0.66	0.61–0.72	0.94	0.86–0.996
11	0.65	0.61–0.72	0.91	0.85–0.98
12	0.63	0.58–0.68	0.86	0.80–0.92

Abbreviations: BUD, budesonide; CI, confidential interval; FOR, formoterol.

Table S2 Exacerbation rate ratios for budesonide/formoterol compared with formoterol in all patients and in the three COPD disease severity groups

Study month	Exacerbation rate ratios							
	All patients, n=2,345		Disease severity					
			Moderate COPD, n=408		Severe COPD, n=1,325		Very severe COPD, n=612	
		P-value		P-value		P-value		P-value
1	−0.48 (−0.62, −0.29)	<0.0001	−0.50 (−0.80, 0.22)	0.1266	−0.48 (−0.67, −0.19)	0.0036	−0.47 (−0.68, −0.11)	0.0152
2	−0.48 (−0.58, −0.35)	<0.0001	−0.39 (−0.68, 0.15)	0.1270	−0.51 (−0.64, −0.32)	<0.0001	−0.48 (−0.64, −0.25)	0.0004
3	−0.46 (−0.55, −0.35)	<0.0001	−0.45 (−0.67, −0.08)	0.0231	−0.49 (−0.61, −0.34)	<0.0001	−0.41 (−0.57, −0.20)	0.0008
4	−0.45 (−0.53, −0.35)	<0.0001	−0.45 (−0.65, −0.14)	0.0091	−0.45 (−0.56, −0.31)	<0.0001	−0.45 (−0.58, −0.28)	<0.0001
5	−0.40 (−0.48, −0.31)	<0.0001	−0.48 (−0.66, −0.21)	0.0021	−0.40 (−0.51, −0.26)	<0.0001	−0.39 (−0.53, −0.22)	<0.0001
6	−0.36 (−0.44, −0.27)	<0.0001	−0.42 (−0.60, −0.15)	0.0055	−0.37 (−0.48, −0.25)	<0.0001	−0.33 (−0.46, −0.16)	0.0004
7	−0.32 (−0.40, −0.23)	<0.0001	−0.41 (−0.59, −0.15)	0.0043	−0.34 (−0.44, −0.21)	<0.0001	−0.27 (−0.41, −0.10)	0.0037
8	−0.29 (−0.37, −0.20)	<0.0001	−0.39 (−0.57, −0.14)	0.0055	−0.31 (−0.42, −0.19)	<0.0001	−0.23 (−0.37, −0.06)	0.0121
9	−0.28 (−0.36, −0.19)	<0.0001	−0.39 (−0.57, −0.14)	0.0045	−0.30 (−0.40, −0.18)	<0.0001	−0.22 (−0.36, −0.05)	0.0145
10	−0.29 (−0.36, −0.20)	<0.0001	−0.44 (−0.59, −0.21)	0.0007	−0.30 (−0.40, −0.18)	<0.0001	−0.23 (−0.36, −0.06)	0.0082
11	−0.28 (−0.35, −0.19)	<0.0001	−0.42 (−0.58, −0.20)	0.0009	−0.28 (−0.38, −0.17)	<0.0001	−0.23 (−0.36, −0.08)	0.0052
12	−0.27 (−0.35, −0.19)	<0.0001	−0.39 (−0.56, −0.17)	0.0017	−0.29 (−0.38, −0.18)	<0.0001	−0.22 (−0.35, −0.07)	0.0063

Note: Data are presented as reduction in the exacerbation rate ratio and 95% confidence intervals.

Table S3 Time-to-first exacerbation for budesonide/formoterol and formoterol in all patients and according to COPD disease severity group

Study month	Time-to-first exacerbation				
	All patients, n=2,345		Disease severity		
		P-value	Moderate COPD, n=408	Severe COPD, n=1,325	Very severe COPD, n=612
1	0.528 (0.385, 0.723)	<0.0001	0.513 (0.207, 1.272)	0.531 (0.340, 0.830)*	0.525 (0.316, 0.873)*
2	0.532 (0.420, 0.673)	<0.0001	0.601 (0.303, 1.194)	0.519 (0.373, 0.722)***	0.519 (0.352, 0.765)**
3	0.586 (0.478, 0.718)	<0.0001	0.615 (0.347, 1.089)	0.547 (0.412, 0.726)***	0.625 (0.443, 0.881)*
4	0.599 (0.499, 0.719)	<0.0001	0.578 (0.349, 0.957)*	0.613 (0.476, 0.790)**	0.575 (0.422, 0.782)**
5	0.639 (0.540, 0.758)	<0.0001	0.603 (0.374, 0.974)*	0.641 (0.508, 0.810)**	0.632 (0.474, 0.843)**
6	0.687 (0.586, 0.805)	<0.0001	0.694 (0.447, 1.077)	0.660 (0.531, 0.822)**	0.705 (0.539, 0.923)*
7	0.736 (0.632, 0.857)	<0.0001	0.740 (0.483, 1.134)	0.699 (0.567, 0.862)**	0.770 (0.593, 0.998)*
8	0.772 (0.665, 0.895)	0.0006	0.767 (0.504, 1.165)	0.736 (0.600, 0.903)**	0.806 (0.625, 1.040)
9	0.794 (0.688, 0.917)	0.0017	0.777 (0.516, 1.170)	0.769 (0.632, 0.935)**	0.816 (0.637, 1.046)
10	0.778 (0.676, 0.897)	0.0005	0.710 (0.475, 1.061)	0.754 (0.622, 0.913)**	0.823 (0.643, 1.053)
11	0.788 (0.685, 0.906)	0.0008	0.745 (0.501, 1.107)	0.763 (0.632, 0.921)**	0.823 (0.644, 1.051)
12	0.790 (0.688, 0.907)	0.0008	0.745 (0.501, 1.107)	0.765 (0.635, 0.921)**	0.824 (0.646, 1.050)

Notes: Data are presented as reduction in time-to-first exacerbation and 95% confidence intervals. *P<0.05; **P<0.005; ***P<0.0001.

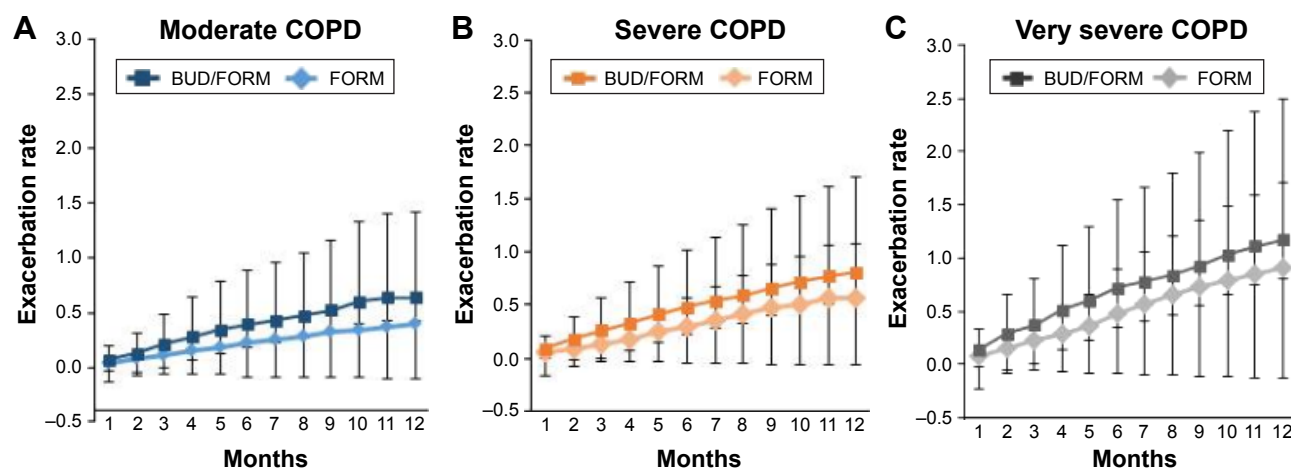


Figure S1 Exacerbation rate for budesonide/formoterol and formoterol over time according to COPD disease severity: (A) moderate COPD, (B) severe COPD, and (C) very severe COPD.

Note: Data are presented as 95% confidence intervals.

Abbreviations: BUD, budesonide; FORM, formoterol.

Table S4 Time-to-discontinuations for budesonide/formoterol versus formoterol in all patients and according to COPD disease severity group

Study month	Time-to-discontinuations		Disease severity		
	All patients n=2,345	P-value	Moderate COPD, n=408	Severe COPD, n=1,325	Very severe COPD, n=612
1	0.998 (0.519, 1.919)	0.9961	0.350 (0.036, 3.369)	1.192 (0.494, 2.876)	1.000 (0.323, 3.101)
2	0.709 (0.503, 0.999)	0.0494	0.791 (0.274, 2.280)	0.695 (0.428, 1.130)	0.700 (0.406, 1.210)
3	0.651 (0.500, 0.846)	0.0013	0.684 (0.357, 1.312)	0.660 (0.454, 0.961)*	0.623 (0.400, 0.972)*
4	0.665 (0.529, 0.836)	0.0005	0.673 (0.383, 1.180)	0.692 (0.497, 0.965)*	0.627 (0.427, 0.921)*
5	0.724 (0.587, 0.892)	0.0024	0.838 (0.514, 1.366)	0.737 (0.545, 0.997)*	0.655 (0.457, 0.939)*
6	0.695 (0.571, 0.847)	0.0003	0.723 (0.454, 1.153)	0.737 (0.556, 0.977)*	0.625 (0.443, 0.882)*
7	0.723 (0.600, 0.871)	0.0007	0.716 (0.463, 1.110)	0.798 (0.611, 1.042)	0.631 (0.456, 0.873)*
8	0.728 (0.609, 0.870)	0.0005	0.752 (0.495, 1.142)	0.788 (0.608, 1.020)	0.639 (0.472, 0.867)**
9	0.735 (0.619, 0.874)	0.0005	0.762 (0.506, 1.147)	0.802 (0.623, 1.031)	0.637 (0.475, 0.855)**
10	0.750 (0.633, 0.887)	0.0008	0.775 (0.521, 1.151)	0.834 (0.654, 1.064)	0.629 (0.471, 0.840)**
11	0.761 (0.646, 0.896)	0.0010	0.815 (0.553, 1.200)	0.822 (0.649, 1.041)	0.652 (0.493, 0.863)**
12	0.779 (0.663, 0.915)	0.0023	0.850 (0.580, 1.246)	0.849 (0.673, 1.071)	0.652 (0.496, 0.857)**

Notes: Data are presented as hazard ratios and 95% confidence intervals. * $P < 0.05$; ** $P < 0.005$.

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