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Bronchodilator responsiveness and onset of effect with budesonide/formoterol pMDI in COPD

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KEYWORDS
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Onset of effect;
Treatment

Summary
Background: Chronic obstructive pulmonary disease (COPD) patients are thought to have limited bronchodilator response, determined by changes in forced expiratory volume in 1 s (FEV_1). In this study, we assessed bronchodilator response in patients with COPD using not only FEV_1 but also changes in lung volume expressed as forced vital capacity (FVC) and inspiratory capacity (IC). We also evaluated the speed of onset of bronchodilation.
Methods: Data were from 2 randomized, double-blind, placebo-controlled studies (6-months [NCT00206154]; 12-months [NCT00206167]) in patients with moderate to very severe COPD. Treatments: twice daily budesonide/formoterol pressurized metered-dose inhaler (pMDI) 320/9 μg, budesonide/formoterol pMDI 160/9 μg, formoterol dry powder inhaler (DPI) 9 μg, placebo.
Results: The percentage of patients with FEV_1 improvement (≥12% and ≥200 mL; American Thoracic Society [ATS] criterion) was 34—39% post-albuterol (screening). On day of randomization (DOR), a larger proportion receiving formoterol-containing treatment exhibited reversibility within 60 min: FEV_1 (57—59%). Similar results were seen for IC (50—61%) and FVC (57—67%) using the same improvement criteria. The time to ≥15% FEV_1 improvement on DOR was 5.0, 4.8, and 7.3 min for budesonide/formoterol 320/9, budesonide/formoterol 160/9, and formoterol, respectively. Time to ≥15% FEV_1 improvement was better maintained with budesonide/formoterol than formoterol at treatment end (6 and 12 months).

Abbreviations: ATS, American Thoracic Society; BUD, budesonide; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FM, formoterol; FVC, forced vital capacity; IC, inspiratory capacity; ICS, inhaled corticosteroid; LABA, long-acting β_2-adrenergic agonist; PBO, placebo; pMDI, pressurized metered-dose inhaler; TLC, total lung capacity; TORCH, Towards a Revolution in COPD Health; UPLIFT, Understanding Potential Long-Term Impacts on Function with Tiotropium trial.

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Conclusions: Most patients with moderate to very severe COPD exhibit ATS-defined bronchodilator reversibility based on flow and lung volume measures after budesonide/formoterol pMDI or formoterol treatment. Budesonide/formoterol pMDI also has a rapid (within 5 min) onset of bronchodilation that is maintained over time compared with formoterol alone.

Introduction

Chronic obstructive pulmonary disease (COPD) is a treatable and preventable disease with airflow obstruction that is not fully reversible.[1,2] Characterization of bronchodilator responsiveness is complex in patients with COPD since several factors may influence the results of reversibility testing, including daily variation in initial airway caliber and forced expiratory volume in 1 second (FEV_1).[1,3] In addition, poor short-term bronchodilator response does not preclude a long-term response to maintenance bronchodilator therapy.[4,5] Thus, current COPD guidelines recommend against using reversibility testing to predict a patient's clinical response to long-term bronchodilator therapy.[1,3]

Patients with COPD are thought to have a limited response to bronchodilators. However, Tashkin et al. reported that over half of the patients with moderate to very severe COPD in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial demonstrated reversibility to 2 short-acting bronchodilators combined (ipratropium bromide 80 $\mu g \times 4$ inhalations followed by albuterol 400 $\mu g \times 4$ inhalations) based on a $\geq$12% and $\geq$200 mL improvement in FEV_1.[6] In that study, a smaller proportion of patients with more severe obstruction (Global initiative for chronic Obstructive Lung Disease [GOLD] stages III and IV) manifested a significant FEV_1 response compared with patients with milder obstruction (GOLD stage II).[6] Although not sufficiently emphasized in the article, a review of the data from that study showed that a large proportion of the GOLD stage III—IV patients had a response in terms of lung volume as measure by forced vital capacity (FVC).[6] In addition, inspiratory capacity (IC) was not reported in that study.[6] Clinical benefits of maintenance therapy with a long-acting β_2-adrenergic agonist (LABA) administered alone or in combination with an inhaled corticosteroid (ICS) also have been demonstrated in patients with COPD across COPD severity categories.[7—11]

Treatment with the combination of the ICS budesonide and the LABA formoterol administered in one dry powder inhaler (DPI; Symbicort™ Turbuhaler™, AstraZeneca, Lund, Sweden) has been shown to improve pulmonary function, health-related quality of life, and symptoms in patients with COPD and to reduce the rate of exacerbations compared with placebo.[8,10] Two small studies ($n = 20$ randomized[12] and $n = 90$ randomized[13]) showed that patients with COPD treated with budesonide/formoterol experienced a greater bronchodilator response compared with formoterol alone[12] and a faster onset of effect compared with formoterol alone[12] or fluticasone propionate/salmeterol.[13]

We hypothesized that compared with albuterol or formoterol, the combination of budesonide/formoterol would provide a larger bronchodilator response, measured not only by FEV_1 but also in terms of lung volumes. In addition, we tested whether the speed of bronchodilator response is faster for the combination of budesonide/formoterol compared with either monocomponent. To test these hypotheses, we used pooled data from 2 active- and placebo-controlled phase III clinical studies (6 months and 12 months, respectively) of more than 3500 patients with moderate to very severe COPD.[14,15] From these 2 studies, we evaluated the magnitude and onset of bronchodilation in the subset ($n = 1109$) of patients for whom sequential lung function studies were performed.

Methods

Patients

Details of the studies have been reported previously.[14,15] In brief, the populations consisted of patients $\geq$40 years of age with moderate to very severe COPD, representative of those patients with COPD likely to be treated with an ICS/LABA combination.

Study design and treatments

Both studies were randomized, double-blind, double-dummy, parallel-group, multicenter trials (NCT00206167 and NCT00206154). Clinic visits occurred at screening, randomization, and months 1, 2, 4, and 6 in the 6-month study and at the same time points and months 9 and 12 in the 12-month study. Patients previously receiving ICS or ICS/LABA therapy before study enrollment received ICS monotherapy, and patients previously receiving anticholinergic therapy received ipratropium bromide at a stable dose during a 2-week run-in period. ICS therapy was discontinued at randomization; ipratropium therapy was allowed to continue during the randomized treatment period. Albuterol rescue medication was permitted throughout the study. After the run-in period, patients who met the eligibility criteria were randomized in each trial to one of the treatments shown in Fig. 1. The study protocols were approved by the human studies review board committee at each site, and written informed consent was obtained from patients. The studies conformed with the Declaration of Helsinki.

Outcome variables

Spirometry was performed according to American Thoracic Society (ATS) recommendations.[16] In the subset of patients who were willing and able to undergo serial spirometry, FEV_1 was measured predose and 5, 15, 30, 60, 120, 180, 240, 360, 480, 600, and 720 min after study medication on the day of randomization and at the end of months 2 and 6 in the 6-month study and on the day of randomization and at the end of months 6 and 12 in the 12-month study. On

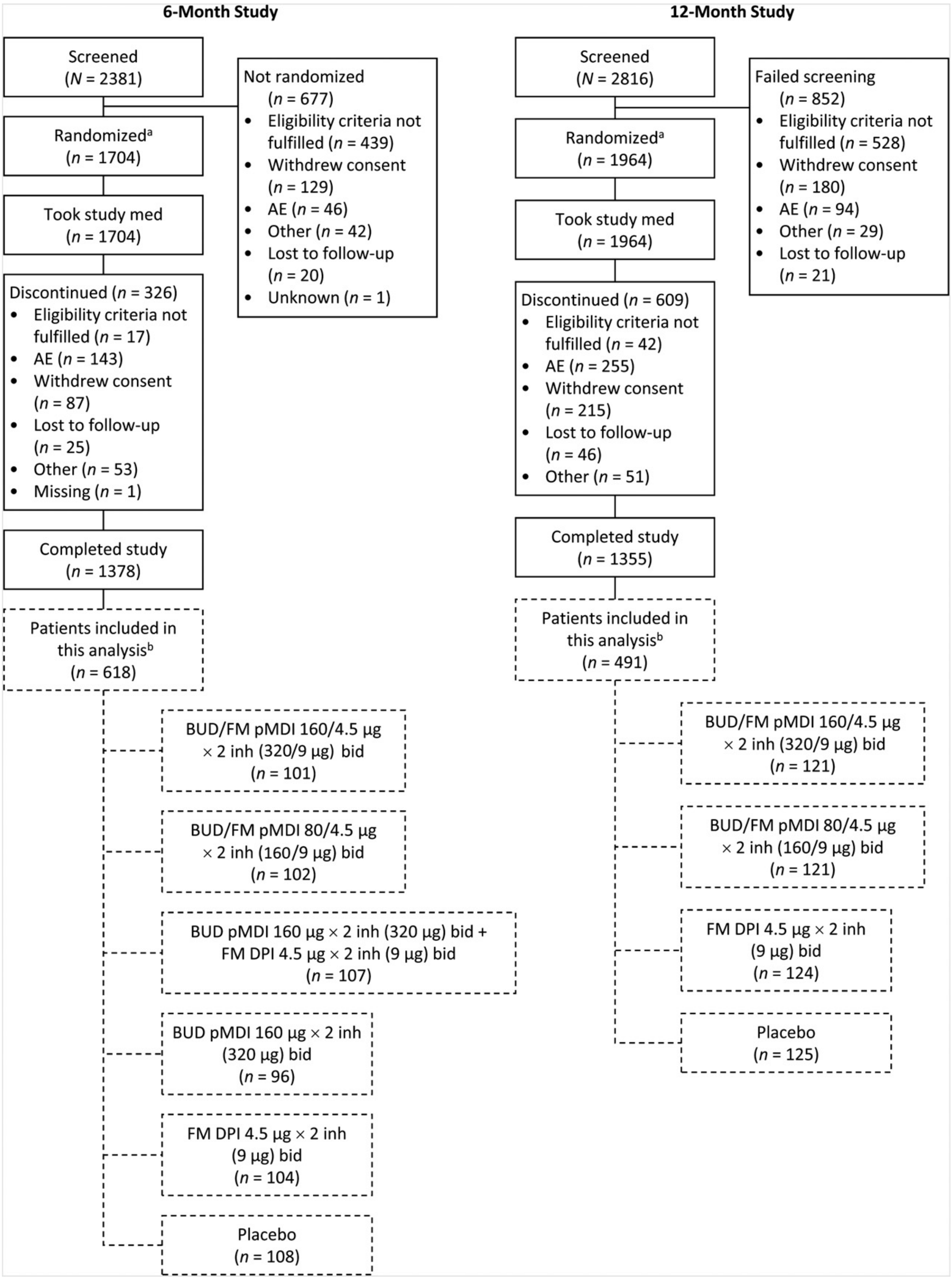


Figure 1 Patient disposition in the 6-month and 12-month trials. AE, adverse event; bid, twice daily; BUD, budesonide; DPI, dry powder inhaler; FM, formoterol; inh, inhalation; PBO, placebo; pMDI, pressurized metered-dose inhaler. [a] Demographic and baseline characteristics of the overall population were presented previously[14,15]; [b] this analysis comprises patients included in the serial spirometry analysis set.

the day of screening, FEV_1 was measured predose and 15–30 minutes after albuterol 90 μg × 2 inhalations. FEV_1 data from the screening and randomization visits were used in the present analysis.

IC was assessed predose and 1-h postdose at randomization and months 2 and 6 in the 6-month study[14] and at randomization and months 6 and 12 in the 12-month study[15] in patients with serial spirometry data. The larger of 2 full inspirations after stabilization of the basal end-expiratory volume was accepted for analysis at each time point. Forced vital capacity (FVC) was assessed predose and 1-hour postdose for all patients at all clinic visits. IC and FVC data from the randomization visit were used in the present analysis.

Patients were instructed to refrain from bronchodilator use before the screening and study visits for at least 6 h for albuterol, 8 h for ipratropium, and 48 h for long-acting bronchodilators.

Data analyses

The serial spirometry analysis included all patients who received ≥1 dose of study medication and had a baseline predose FEV_1 value and ≥1 postdose FEV_1 value.

Bronchodilator responsiveness

Reversibility to albuterol was assessed as the percentage of patients achieving an improvement in FEV_1 of ≥12% and ≥200 mL (ATS criteria[17]) 15–30 min postdose on the screening day. Assessment of reversibility during study treatment was based on the percentage of patients who achieved improvements in FEV_1 of ≥12% and ≥200 mL from the predose value within 30 min or 60 min after administration of medication on the day of randomization. Analysis of change in reversibility to formoterol-containing treatment over time was based on the percentage of patients who achieved ATS-defined FEV_1 reversibility[17] on the day of randomization and at the end of treatment. The volume response was assessed as the percentage of patients who achieved improvements in IC and FVC of ≥12% and ≥200 mL from the respective predose values 1 h after administration of study medication on the day of randomization. Mean changes from baseline (last predose value before the first dose of randomized treatment) in 1-h postdose FEV_1, 1-h postdose IC, and 1-h postdose FVC also were calculated on the day of randomization.

In these analyses, data obtained from all patients have been restricted to the serial spirometry population for comparison with data collected only from this subset. FEV_1 reversibility at randomization was censored at 30 min after administration of study medication to obtain a relevant comparison with data obtained at screening. To obtain relevant comparisons with IC and FVC data, FEV_1 reversibility at randomization visits also was assessed based on either 1-h postdose measurements or sequential serial measurements censored at 60 min.

Data were pooled for treatment groups common to both studies (budesonide/formoterol pMDI 320/9 μg, budesonide/formoterol pMDI 160/9 μg, formoterol 9 μg DPI, and placebo). These data were compared between treatment groups for the population as a whole and for each COPD GOLD severity category based on postbronchodilator FEV_1 screening values (moderate, ≥50–<80%; severe, ≥30–<50%; very severe, <30%).[1] These data were presented using descriptive statistics, with no formal hypothesis testing performed.

Time to onset of bronchodilation

Time to onset of bronchodilation was assessed as the first time point at which an increase in FEV_1 of 15% from baseline was reached within 60 min after dosing on the day of randomization. A similar assessment was performed at the end of treatment (end of 6 and 12 months, respectively). The percentages of patients who achieved improvements in FEV_1 of ≥15% from the predose value within 60 min after administration of medication on the day of randomization and at the end of treatment also were reported. Time to onset of bronchodilation was described using a Kaplan–Meier plot and compared between treatment groups using a log-rank test. The median time to onset of bronchodilation, defined as the point at which ≥50% of patients achieved a ≥15% improvement in FEV_1 within 60 min after dosing on the day of randomization, was calculated for each treatment group within each study and pooled across the studies. A similar calculation was performed at the end of treatment for the individual studies. For all assessments of time to onset of bronchodilation, the data were censored at 60 min.

Factors associated with achievement of ATS-defined reversibility[17] and time to onset of bronchodilation (based on ATS criteria[17]) (data censored at 60 min for both) on the day of randomization were investigated. Factors analyzed were treatment (formoterol-containing vs non–formoterol-containing), sex, age, smoking status (current vs ex-smoker), smoking history (number of pack-years), use of rescue medication (inhalations/day), mean total symptom score (0–4) on the Breathlessness, Cough, and Sputum Scale, medications used during the run-in period (ICS, oxygen, or xanthine), and history of comorbidities (coronary artery disease, diabetes, or hypertension). Multivariate logistic regression analysis and a Cox proportional hazards model were used to assess the relationship between these factors (independent variables) and the dependent variables of ATS-defined reversibility[17] and time to onset of bronchodilation (based on ATS criteria[17]), respectively.

Results

Patients

Of the randomized patients, a subset of 618 patients of 1704 in the 6-month trial and 491 patients of 1964 in the 12-month trial underwent serial spirometry testing and were included in the present analysis (Fig. 1). The baseline characteristics of the population (Table 1) were similar to those of the overall populations in each study.[14,15] At screening, the percentage of patients with reversibility to albuterol was greatest in patients with moderate COPD (Table 1). About one-third fewer patients in the very severe than in the severe group demonstrated albuterol reversibility.

Table 1 Patient demographics and baseline clinical characteristics by COPD severity (serial spirometry population).

Variable	Moderate ($n = 236$)	Severe ($n = 598$)	Very severe ($n = 272$)	Total ($n = 1109$)[a]
Sex, n (%)				
Female	124 (52.5)	212 (35.5)	86 (31.6)	423 (38.1)
Male	112 (47.5)	386 (64.5)	186 (68.4)	686 (61.9)
Age (years)				
Mean (SD)	62.5 (10.0)	64.0 (9.0)	63.6 (8.9)	63.6 (9.2)
Range	40–90	41–88	42–84	40–90
Smoking history, median pack-years	45	42	48	45
Predose FEV_1 at screening (visit 1)				
Liters, mean (SD)	1.3 (0.3)	1.1 (0.3)	0.7 (0.2)	1.0 (0.4)[c]
% Predicted, mean (SD)	45.2 (5.2)	35.2 (6.3)	21.9 (4.6)	34.1 (9.8)[c]
Predose FEV_1 at randomization (visit 2)				
Liters, mean (SD)	1.4 (0.4)	1.0 (0.3)	0.7 (0.2)	1.0 (0.4)
% Reversibility[b] at screening $\geq$12% + change in FEV_1 $\geq$200 mL, n (%)	168 (71.2)	196 (32.8)	38 (14.0)	402 (36.2)
% Reversibility[b] at screening $\geq$15% FEV_1 improvement, n (%)	170 (72.0)	283 (47.3)	126 (46.3)	579 (52.2)

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; SD, standard deviation.
[a] Includes 3 patients with missing data for whom baseline data by severity were not calculated.
[b] Reversibility was assessed based on improvements in FEV_1 from the prebronchodilator value to the postbronchodilator value 15–30 min after administration of 2 inhalations of albuterol pressurized metered-dose inhaler (total dose 180–200 μg).
[c] $n = 1108$.

Bronchodilator responsiveness

FEV_1 and lung volume responsiveness

The percentage of patients who demonstrated ATS-defined reversibility[17] within 30 min was 51–54% after administration of formoterol-containing treatments on the day of randomization. By comparison, only 34–39% of patients in the same population had shown reversibility to albuterol. The percentage of patients who demonstrated reversibility based on FEV_1 within 60 min was 57–59% after administration of formoterol-containing treatments on the day of randomization (Fig. 2, Panel A [all severity categories combined]). The percentage of patients in all severity categories who demonstrated ATS-defined reversibility at the end of treatment after being classified as reversible on the day of randomization was greater in the budesonide/formoterol pMDI 320/9-μg group (82/108; 75.9%) compared with the budesonide/formoterol 160/9-μg (57/99; 57.6%) and formoterol (56/98; 57.1%) groups. Additionally, the percentage of patients who remained reversible using ATS-defined criteria was greater in the formoterol-containing treatment groups compared with the placebo group (11/22; 50%). Improvements in IC and FVC of $\geq$12% and $\geq$200 mL were achieved by 50–61% and 57–67% of patients, respectively, receiving formoterol-containing treatment (Fig. 2, Panels B and C).

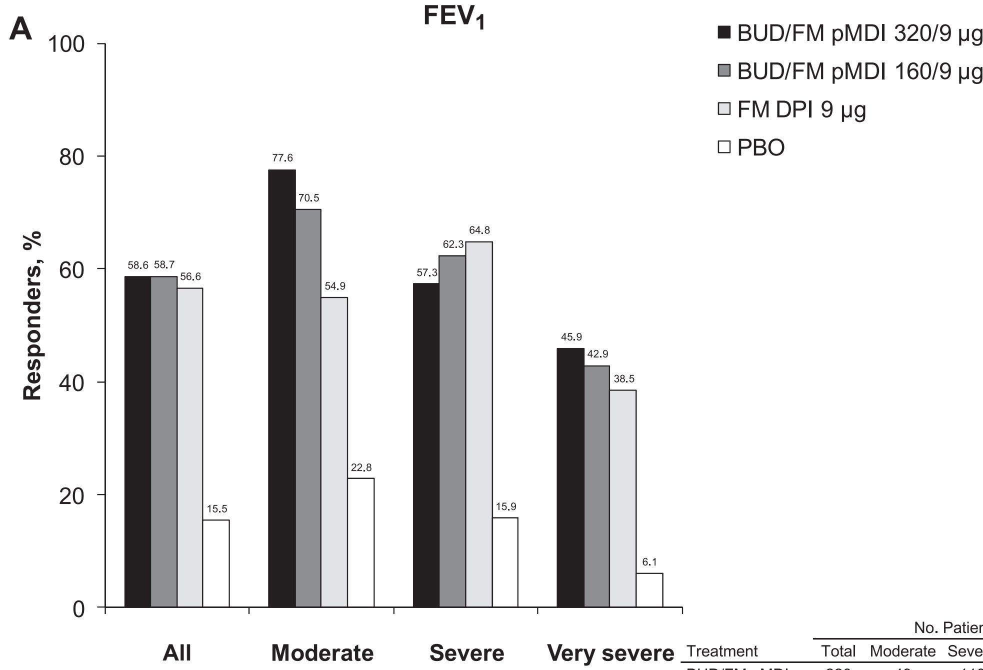
Responsiveness by disease severity

The proportion of patients with moderate COPD (GOLD stage II) who exhibited FEV_1 reversibility within 30 min after budesonide/formoterol pMDI treatment (66–69%) on the day of randomization was greater than that observed within 30 min after formoterol treatment (47%) on the day of randomization and similar to that observed after albuterol treatment (71%; Table 1) on the screening day. The percentage of patients with severe COPD (GOLD stage III) exhibiting FEV_1 reversibility was lower after albuterol at screening (33%) compared to the percentage showing FEV_1 reversibility within 30 min after budesonide/formoterol pMDI (53–56%) or formoterol (62%) treatment on the day of randomization. Similar results were observed in the very severe COPD category (GOLD stage IV), where only 14% of patients had a response to albuterol on the screening day, while 36–41% and 31% showed FEV_1 reversibility to budesonide/formoterol pMDI or formoterol, respectively, within 30 min of treatment on the day of randomization.

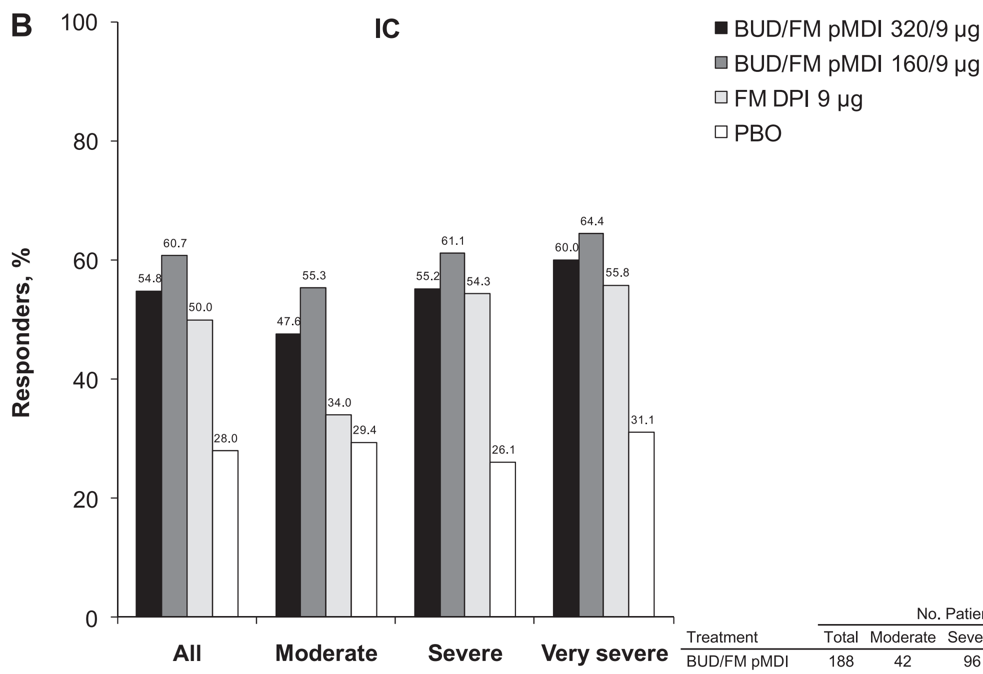
The percentage of patients demonstrating FEV_1 reversibility within 60 min was greater in all formoterol-containing treatment groups compared with placebo in all COPD severity categories and in both budesonide/formoterol pMDI groups compared with formoterol in the moderate and very severe COPD categories (Fig. 2, Panel A). In all COPD severity categories, the proportion of patients with reversibility of IC or FVC was greater in the budesonide/formoterol pMDI and formoterol treatment groups compared with placebo (Fig. 2, Panels B and C).

Magnitude of responsiveness

In the moderate COPD group, patients receiving budesonide/formoterol pMDI had numerically greater mean improvements in FEV_1, IC, and FVC compared with those receiving formoterol alone (Fig 3, Panels A–C). For the whole cohort, the mean absolute improvements from baseline in postdose FEV_1 were greater in the formoterol-containing treatment groups (180–230 mL) compared with placebo (50 mL) (Fig. 3, Panel A). Similarly, mean absolute improvements from baseline in postdose IC and FVC were greater in the formoterol-containing treatment groups (250–330 mL and

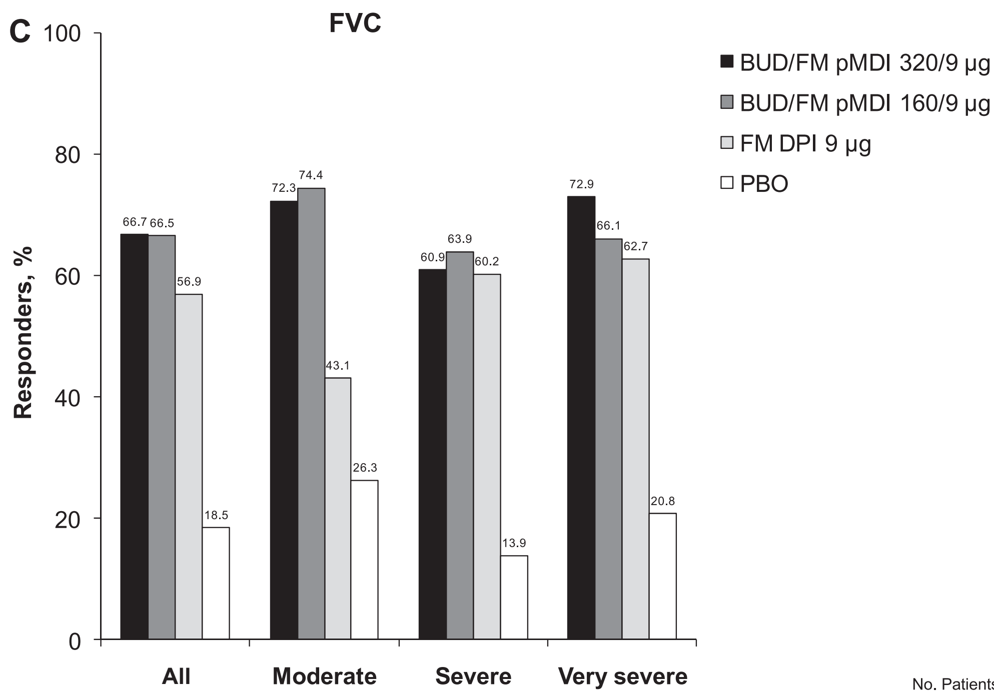


Treatment	No. Patients			
	Total	Moderate	Severe	Very Severe
BUD/FM pMDI 320/9 µg	220	49	110	61
BUD/FM pMDI 160/9 µg	223	44	122	56
FM 9 µg	228	51	125	52
PBO	233	57	126	49



Treatment	No. Patients			
	Total	Moderate	Severe	Very Severe
BUD/FM pMDI 320/9 µg	188	42	96	50
BUD/FM pMDI 160/9 µg	196	38	113	45
FM 9 µg	206	47	116	43
PBO	207	51	111	45

Figure 2 Percentage of patients demonstrating reversibility by study treatment and COPD severity in both studies (pooled data) on the day of randomization based on FEV_1 (A), IC (B), and FVC (C) improvement threshold of $\geq$12% and $\geq$200 mL. BUD, budesonide; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FM, formoterol; FVC, forced vital capacity; IC, inspiratory capacity; PBO, placebo; pMDI, pressurized metered-dose inhaler.



Treatment	No. Patients			
	Total	Moderate	Severe	Very Severe
BUD/FM pMDI 320/9 μg	216	47	110	59
BUD/FM pMDI 160/9 μg	218	43	119	56
FM 9 μg	225	51	123	51
PBO	227	57	122	48

Figure 2 (*Continued*)

350–410 mL, respectively) compared with placebo (100 mL for both variables) (Fig. 3, Panels B and C). Assessment by COPD severity showed greater mean absolute improvements from baseline in postdose FEV_1 with formoterol-containing treatment in the moderate (200–340 mL) and severe (200–210 mL) COPD groups compared with the very severe (110–170 mL) COPD group (Fig. 3, Panel A). In contrast, improvements in IC and FVC generally were similar across all severity groups with formoterol-containing treatment (Fig. 3, Panels B and C).

Time to onset of bronchodilation

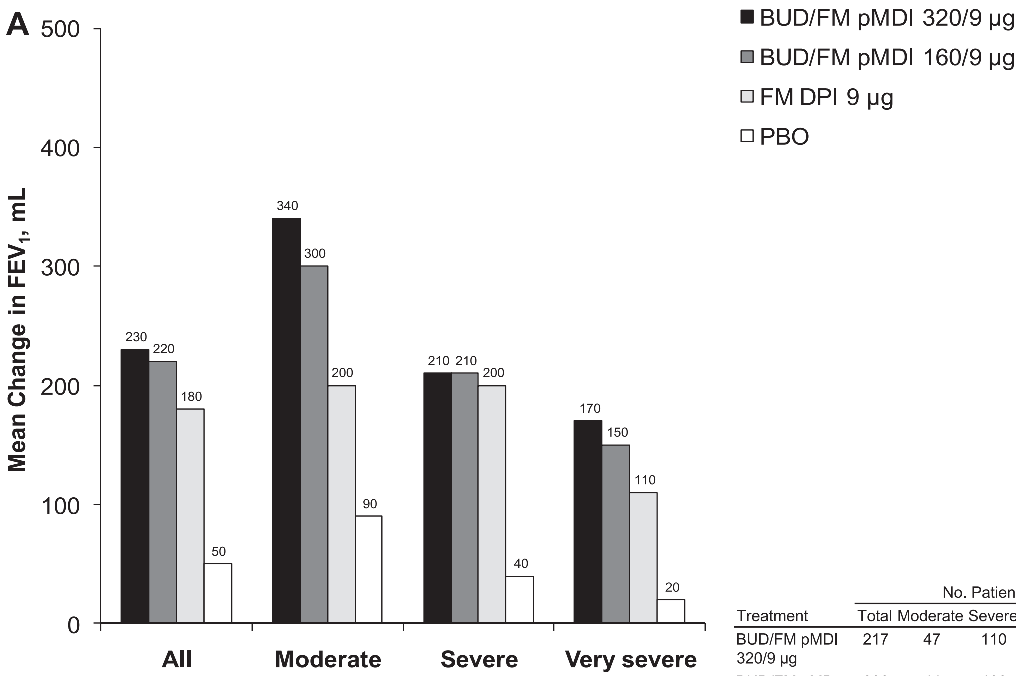
The time to onset of bronchodilation on the day of randomization and at end of treatment for each study, is shown in Table 2 and Fig. 4. As shown in Fig. 4, Panel A, on the day of randomization, the time to achieve a 15% improvement in FEV_1 was significantly shorter with both doses of budesonide/formoterol pMDI compared with budesonide pMDI and placebo and with formoterol DPI compared with placebo in the 6-month study ($p < 0.001$). In the 12-month study, the time to 15% improvement was significantly shorter with both doses of budesonide/formoterol pMDI and formoterol DPI compared with placebo ($p < 0.001$). When data from both studies were combined, the median time to onset of 15% improvement in FEV_1 was 5.0, 4.8, and 7.3 min for the budesonide/formoterol pMDI 320/9-μg, budesonide/formoterol pMDI 160/9-μg, and formoterol DPI groups, respectively. Because fewer than 50% of patients achieved a 15% improvement within the first 60 min after dosing of study medication in the placebo group, the median time to 15% improvement could not be estimated. Compared with the day of randomization, the time to achieve a 15% improvement in FEV_1 at the end of treatment (6 months [study 1]; 12 months [study 2]) generally was maintained with both budesonide/formoterol pMDI doses but was prolonged with formoterol DPI (Fig. 4, Panel B).

Predictors of ATS-defined bronchodilator reversibility and time to onset of bronchodilation

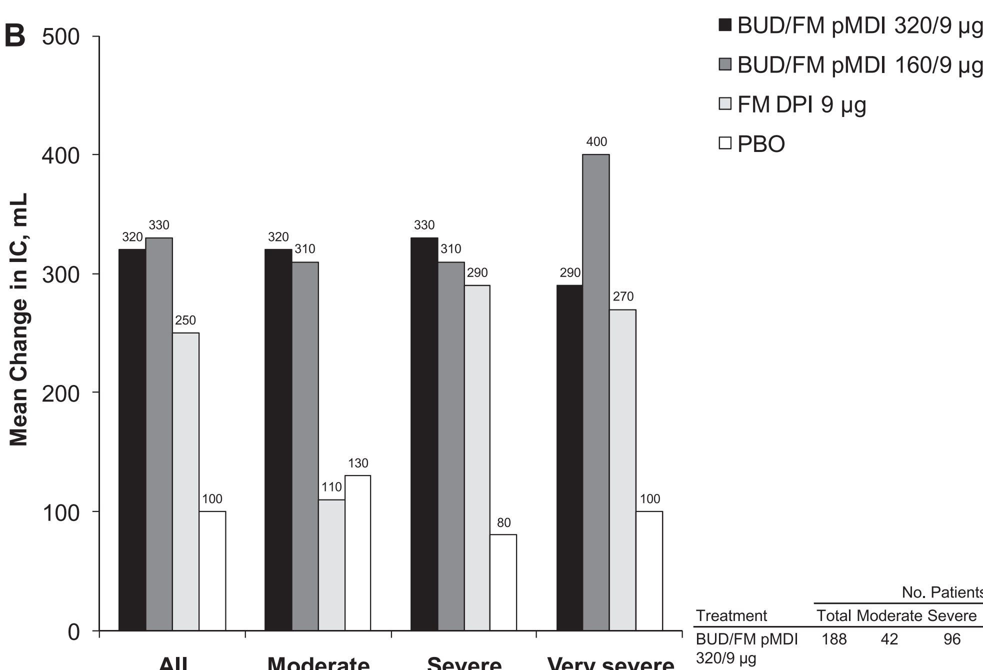
Formoterol-containing treatment was the most important predictor of achieving ATS-defined[17] reversibility (odds ratio [OR]: 7.48; 95% confidence interval [CI]: 5.34, 10.48; $p < 0.0001$) and a faster time to onset of bronchodilation (hazard ratio [HR]: 5.02; 95% CI: 3.76, 6.70; $p < 0.0001$). Additionally, men and younger patients were significantly ($p < 0.0001$) more likely than women and older patients to achieve ATS-defined reversibility[17] (OR: 1.87; 95% CI: 1.41, 2.47 and OR: 0.97; 95% CI: 0.95, 0.98, respectively) and a faster time to onset of bronchodilation (HR: 1.59; 95% CI: 1.31, 1.94; HR: 0.98; 95% CI: 0.97, 0.99, respectively). No significant associations were observed for other factors assessed (comorbidities, smoking status, number of pack-years, baseline symptoms, baseline rescue medication use, or medications used during run-in [ICS, oxygen, or xanthine]) ($p \geq 0.071$).

Discussion

This manuscript presents a large-scale analysis of bronchodilator responsiveness using not only degree of airflow obstruction change (FEV_1) but also lung volume response (IC and FVC). In addition, the time to onset of bronchodilation in

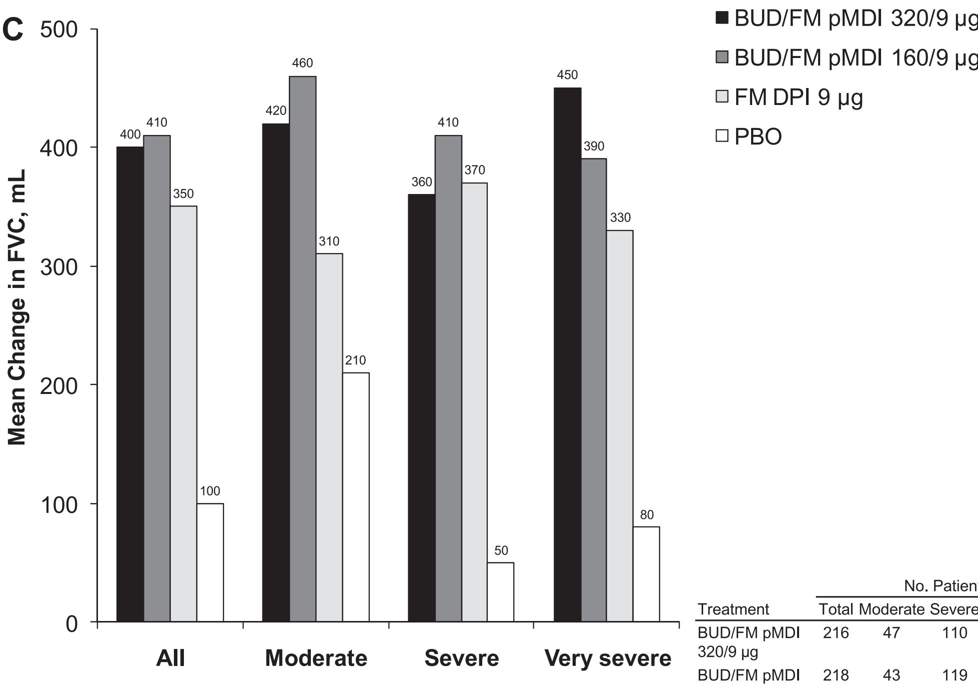


Treatment	No. Patients Total	Moderate	Severe	Very Severe
BUD/FM pMDI 320/9 µg	217	47	110	60
BUD/FM pMDI 160/9 µg	222	44	122	56
FM 9 µg	227	51	125	51
PBO	230	57	125	48



Treatment	No. Patients Total	Moderate	Severe	Very Severe
BUD/FM pMDI 320/9 µg	188	42	96	50
BUD/FM pMDI 160/9 µg	196	38	113	45
FM 9 µg	206	47	116	43
PBO	207	51	111	45

Figure 3 Mean change from predose to 1-h postdose FEV_1 (A), IC (B), and FVC (C) on the day of randomization by study treatment and COPD severity in both studies (pooled data). BUD, budesonide; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 s; FM, formoterol; FVC, forced vital capacity; IC, inspiratory capacity; PBO, placebo; pMDI, pressurized metered-dose inhaler.



Treatment	No. Patients Total	Moderate	Severe	Very Severe
BUD/FM pMDI 320/9 μg	216	47	110	59
BUD/FM pMDI 160/9 μg	218	43	119	56
FM 9 μg	225	51	123	51
PBO	227	57	122	48

Figure 3 (*Continued*)

patients with COPD was analyzed. The proportion of patients with moderate (stage II) COPD who exhibited FEV_1 reversibility was similar after albuterol treatment at screening and after budesonide/formoterol pMDI treatment on the day of randomization. The proportion of patients with more severe COPD (stages III and IV) who showed FEV_1 reversibility was greater with budesonide/formoterol pMDI or formoterol treatment than with albuterol alone. Improvements in lung volumes (IC and FVC) also were observed with budesonide/formoterol pMDI and formoterol, and these improvements in

Table 2 Bronchodilation and estimated time to onset of bronchodilation based on a 15% improvement in FEV_1 from baseline within 60 minutes of study drug administration at randomization and end of treatment.

	BUD/FM 320/9 μg	BUD/FM 160/9 μg	BUD 320 μg + FM 9 μg	BUD 320 μg	FM 9 μg	PBO
Predose FEV_1 (L), mean (SD)						
6-Month study	1.00 (0.41)	1.00 (0.35)	0.98 (0.36)	1.01 (0.39)	1.06 (0.40)	1.08 (0.35)
12-Month study	1.02 (0.40)	0.97 (0.40)	—	—	1.00 (0.38)	1.02 (0.43)
≥15% Improvement in FEV_1 randomization						
6-Month study						
Number (%) of responders	74 (74.7)	71 (69.6)	74 (69.2)	29 (30.2)	72 (69.2)	28 (25.9)
Median time (minutes)	6.8	4.9	6.2	NA	9.0	NA
12-Month study						
Number (%) of responders	98 (81.0)	97 (80.2)	—	—	90 (72.6)	31 (24.8)
Median time (minutes)	4.2	4.8	—	—	6.0	NA
End of treatment						
6-Month study						
Number (%) of responders	68 (67.3)	58 (56.9)	66 (61.7)	33 (34.4)	56 (53.8)	32 (29.6)
Median time (minutes)	4.3	6.2	10.8	NA	18.6	NA
12-Month study						
Number (%) of responders	88 (72.7)	87 (72.5)	—	—	74 (59.7)	32 (25.6)
Median time (minutes)	4.5	4.3	—	—	16.3	NA

BUD, budesonide; FEV_1, forced expiratory volume in 1 s; FM, formoterol; NA, not available because <50% of patients achieved a 15% improvement within the first 60 min after dosing; PBO, placebo.

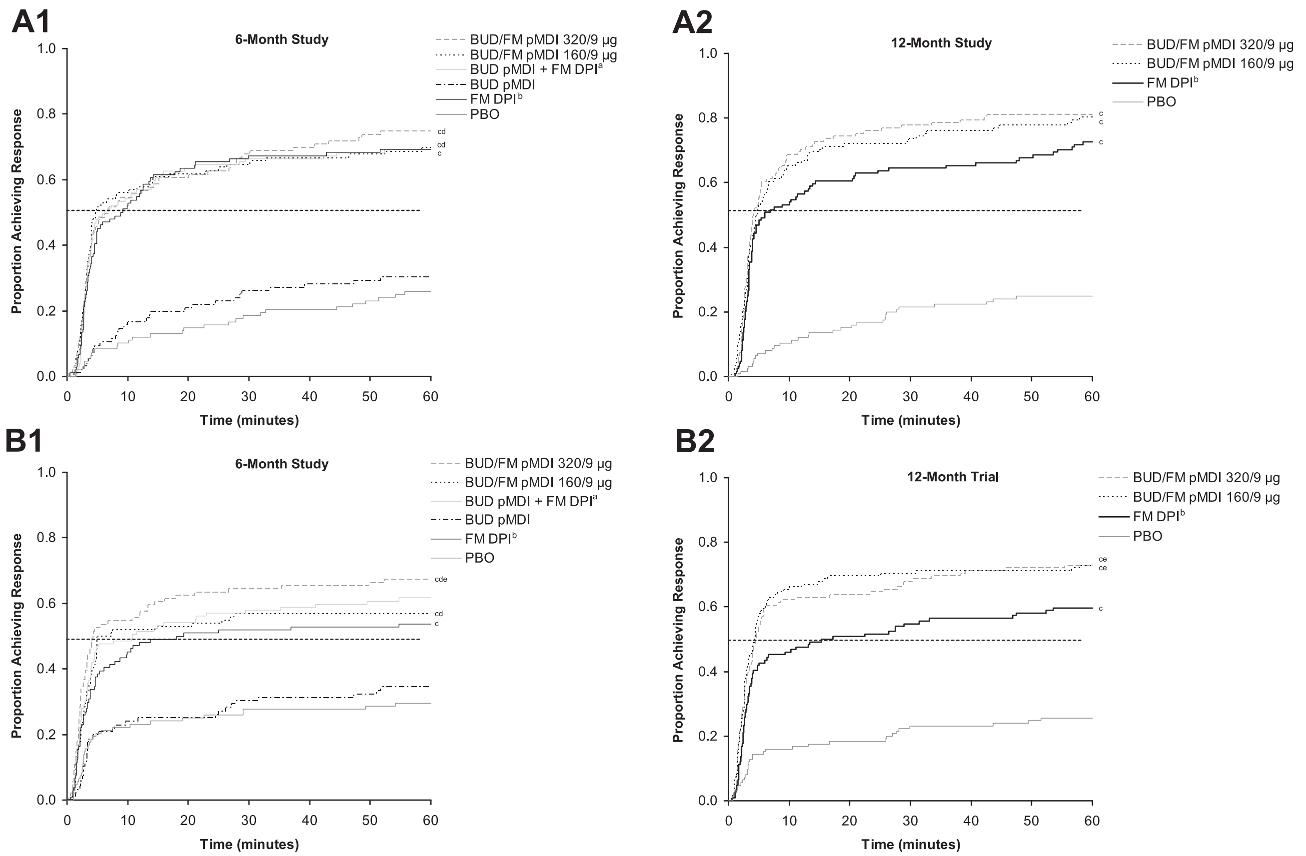


Figure 4 Kaplan–Meier probability curves for the estimated time to 15% improvement in FEV_1 during the first 60 min after administration of study medication on the day of randomization (A) and end of treatment (B) in the 6-month and 12-month trials. [a]Statistical comparison performed for BUD pMDI 320 μg + FM DPI 9 μg vs BUD/FM pMDI 320/9 μg only; [b]statistical comparison for FM DPI 9 μg vs BUD pMDI 320 μg not performed; [c]$p < 0.001$ vs PBO; [d]$p < 0.001$ vs BUD pMDI; [e]$p < 0.05$ vs FM DPI. BUD, budesonide; DPI, dry powder inhaler; FEV_1, forced expiratory volume in 1 second; FM, formoterol; PBO, placebo; pMDI, pressurized metered-dose inhaler.

lung volumes, in contrast to those in FEV_1, were comparable across the spectrum of disease severity. The onset of bronchodilation is rapid (within 5 min) after budesonide/formoterol pMDI treatment and this effect is sustained through 6 and 12 months of treatment.

Currently, there is no consensus regarding a preferred method of evaluating bronchodilator responsiveness in patients with COPD. It has been suggested that including a measure of absolute improvement from baseline in FEV_1 may provide an assessment with some degree of independence from the baseline value.[18] As such, an improvement of $\geq$12% + $\geq$200 mL in FEV_1 and/or FVC is recommended by the ATS guidelines for assessing bronchodilator responsiveness.[19] However, the use of this combined threshold has limitations. Notably, an improvement in FEV_1 of 100–140 mL is considered clinically meaningful in patients with COPD.[20] Thus, patients with severe or very severe COPD, who tend to have lower baseline FEV_1 values,[20] may not meet the combined $\geq$12% + $\geq$200 mL criteria, but they could still have a clinically meaningful improvement. In addition, the minimal important differences for FVC and IC have not been determined. However, because the combined $\geq$12% + $\geq$200 mL ATS threshold is commonly accepted for assessing and defining bronchodilator responsiveness in clinical trials,[4,6,21,22] its use is valuable for cross-comparison of results.

Using the combined improvement threshold, a substantial percentage of patients in the present analysis demonstrated FEV_1 reversibility within 30 min to budesonide/formoterol pMDI (52–54%) on the day of randomization. These results are consistent with those reported by Tashkin et al., who observed that 54% of patients with COPD demonstrated FEV_1 reversibility after bronchodilator (80 μg ipratropium and 400 μg albuterol) administration.[6] The magnitude of improvement in FEV_1 after formoterol-containing treatment (180–230 mL) also was similar to that reported by Tashkin et al. after bronchodilator treatment (229 mL).[6]

The present study also assessed whether patients who were initially classified as reversible using the combined improvement threshold remained so at the end of treatment. Findings from a previous study showed substantial intra-individual variation in reversibility status over time after treatment with ipratropium bromide and albuterol in patients with moderate to severe COPD.[23] In contrast, the present results showed that most patients remained reversible to formoterol-containing treatment, with a greater proportion of patients treated with budesonide/formoterol pMDI 320/9 μg maintaining reversibility versus those treated with the lower dose of combination therapy or formoterol alone. This effect may be related to the potentially protective effect of budesonide against β_2-adrenergic tachyphylaxis; however, these studies were not designed to assess tachyphylaxis. Corticosteroids have been shown to increase transcription of the β_2-receptor gene; however, studies suggesting that corticosteroids protect against β_2-adrenergic tachyphylaxis have been inconsistent.[24,25]

Notably, in the present analysis, the proportion of patients demonstrating reversibility within 30 min to budesonide/formoterol pMDI (52–54%) at randomization was different from the proportion of patients who demonstrated reversibility to albuterol (34–39%) at screening using the same combined threshold. The reason for this difference is not clear but could be due, in part, to possible differences in adherence to the instructions for withholding previously prescribed bronchodilator therapy at the screening visit versus the randomization visit or to differences in the timing of spirometry after albuterol administration at screening (15–30 min) compared with sequential serial assessments up to the 30-min time point after study medication administration on the day of randomization. This observation also could be related to differences in beta agonist activity between albuterol and formoterol, with albuterol acting as a partial agonist and formoterol as a full agonist. We acknowledge that comparisons of bronchodilator effects on different days and time points may not provide absolute accuracy. However, the results suggest that a patient's response to budesonide/formoterol pMDI treatment may not be inferred from the results of standard albuterol testing.

Consistent with the findings reported by Tashkin et al., the percentage of patients with COPD who demonstrated an FEV_1 bronchodilator response decreased as the severity of COPD increased.[6] However, in the present analysis, a larger percentage of patients with very severe COPD still demonstrated reversibility within 30 min to formoterol-containing treatments (31–41%) compared with approximately 20% of very severe COPD patients showing reversibility to ipratropium and albuterol in the analysis by Tashkin et al.[6] This difference between the 2 analyses may be related to differences in baseline patient characteristics or methodologies used. Of interest, in the present analysis and the analysis by Tashkin et al.,[6] the odds of achieving a bronchodilator response based on ATS criteria was greater for men than for women and for younger patients compared with older patients. In the present analysis, the very severe COPD group also had the highest percentage of men (68%) compared with the moderate (48%) and severe (65%) COPD groups.

Lung volume responsiveness in patients with COPD may be demonstrated using measures of IC[1,26] and FVC,[27] and some patients with COPD may show changes in lung volume after bronchodilator administration without meeting one or more thresholds for reversibility based on FEV_1.[6] In addition, these measures provide clinically relevant information since improvements in IC have been correlated with an increase in exercise endurance and tolerance[28] and a decrease in exertional dyspnea,[29,30] and both FVC[1] and the IC/(total lung capacity) ratio[31] have been shown to be predictors of all-cause mortality in patients with COPD. In the present analysis, a substantial percentage of patients receiving budesonide/formoterol pMDI or formoterol treatments demonstrated lung volume response based on IC and FVC improvement with no clear pattern of response observed across COPD severity categories. The magnitude of improvement in postdose FVC from baseline on the day of randomization was lower in the present studies (350–410 mL) compared with the study by Tashkin et al. (471 mL).[6] This difference may be due to the maximal bronchodilation in the Tashkin et al. study, where patients received 4 inhalations of ipratropium (80 μg) followed 60 min later by 4 inhalations of albuterol (400 μg) before postbronchodilator spirometry.[6] In contrast, patients in the present studies who were randomized to a budesonide/formoterol pMDI or formoterol treatment received 9 μg of formoterol before postbronchodilator spirometry.

In the present analysis, a greater proportion of patients with moderate COPD demonstrated bronchodilator responsiveness based on improvements in FEV_1, IC, and FVC with budesonide/formoterol pMDI compared with formoterol. Although it is not clear what role budesonide may play with regard to acute effects on pulmonary function, these results generally are consistent with the results of a post hoc analysis of efficacy data from the TOwards a Revolution in COPD Health (TORCH) study, in which a numerical decrease in the annual rate of exacerbations was observed with salmeterol/fluticasone versus salmeterol alone at early stages of the disease (GOLD stage II [0.57 vs 0.71, respectively]; GOLD stage III [0.91 vs 1.08, respectively]), but not at GOLD stage IV (1.54 vs 1.40, respectively).[11] Taken together, these results suggest that the addition of ICS to LABA therapy may result in clinical benefit at milder stages of the disease.

The time to onset of bronchodilation of budesonide/formoterol pMDI has not been explored previously in patients with COPD. In the current study, the time to onset was rapid (within 5 min) with both budesonide/formoterol pMDI doses and formoterol on the day of randomization. At the end of treatment, the time to onset of bronchodilation was maintained with the budesonide/formoterol treatments but was prolonged with formoterol treatment. Possible explanations for these results may be that the budesonide component of the budesonide/formoterol pMDI product protects against a decrease in responsiveness to formoterol over time or that there is a synergistic effect between the budesonide and formoterol components; however, further studies are needed to investigate these or other possible mechanisms. Rapid onset of bronchodilation may offer clinical benefits in symptom control. The results of a recent survey of 803 patients with COPD indicate that COPD symptoms are particularly severe in the morning.[32] A medication providing rapid relief could be of particular importance to patients with COPD.

In summary, the present findings suggest that a large percentage of patients with moderate to very severe COPD experience the ATS-defined threshold for reversibility after treatment with formoterol, administered alone or in combination with budesonide. The improvements in IC and FVC on the day of randomization provide evidence of rapid improvements in lung volumes with budesonide/formoterol pMDI therapy in patients with COPD. Budesonide/formoterol pMDI also demonstrated a rapid (within 5 min) onset of bronchodilation based on FEV_1 that was maintained through 6 or 12 months of treatment, which may have clinical relevance to symptomatic patients with COPD.

Conflict of interest statement

Bartolome Celli, MD, has received advisory board payments from Aeris, Almirall, Astra Zeneca, Boehringer Ingelheim, Deep Breeze, and GlaxoSmithKline. He has received industry-sponsored grants from Aeris, AstraZeneca, Boehringer Ingelheim, Forrest Medical, and GlaxoSmithKline. Neither Dr. Celli nor his family have shares or interest in any company, and he has not received money nor has stocks in any tobacco-related companies. **Donald P. Tashkin, MD,** has served as a consultant or on advisory boards for AstraZeneca, Boehringer Ingelheim, Merck, Novartis, and Schering-Plough. He has received lecture fees from AstraZeneca, Boehringer Ingelheim, Dey Labs, GlaxoSmithKline, Merck, Pfizer, and TEVA. He has received industry-sponsored grants from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Dey Labs, GlaxoSmithKline, Novartis, Pfizer, Schering-Plough, and Sepracor. **Stephen I. Rennard, MD,** has served as a consultant or on advisory boards for Able Associates, Adelphi Research, Almirall/Prescott, APT Pharma/Britnall, Aradigm, AstraZeneca, Boehringer Ingelheim, Chiesi, CommonHealth, Consult Complete, COPDForum, DataMonitor, Decision Resources, Defined Health, Dey, Dunn Group, Eaton Associates, Equinox, Gerson, GlaxoSmithKline, Infomed, KOL Connection, M. Pankove MedaCorp, MDRx Financial, Mpex, Novartis, Nycomed, Oriel Therapeutics, Otsuka, Pennside Partners, Pfizer (Varenicline), PharmaVentures, Pharmaxis, Price Waterhouse, Propagate, Pulmatrix, Reckner Associates, Recruiting Resources, Roche, Schlesinger Medical, Scimed, Sudler and Hennessey, TargeGen, Theravance, UBC, Uptake Medical, and VantagePoint Management. He has received lecture fees from the American Thoracic Society, AstraZeneca, Boehringer Ingelheim, the California Allergy Society, the Creative Educational Concept, the France Foundation, Information TV, the Network for Continuing Education, Novartis, Pfizer, and SOMA. He has received industry-sponsored grants from AstraZeneca, Biomarck, Centocor, Mpex, Nabi, Novartis, and Otsuka. **Jennifer McElhattan, MS,** and **Ubaldo J. Martin, MD,** are employed by and own stock in AstraZeneca LP.

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