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ORIGINAL RESEARCH

Efficacy, safety, and pharmacokinetics of budesonide/formoterol fumarate delivered via metered dose inhaler using innovative co-suspension delivery technology in patients with moderate-to-severe COPD

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Purpose: This study investigated the efficacy, safety, and pharmacokinetics of the inhaled corticosteroid/long-acting β_2-agonist fixed-dose combination budesonide/formoterol fumarate (BFF) metered dose inhaler (MDI), compared with the monocomponents budesonide (BD) MDI and formoterol fumarate (FF) MDI, in patients with moderate-to-severe COPD.

Materials and methods: In this Phase IIb, randomized, double-blind, four-period, five-treatment, incomplete-block, crossover study (NCT02196077), all patients received BFF MDI 320/9.6 µg and FF MDI 9.6 µg, and two of either BFF MDI 160/9.6 µg, BFF MDI 80/9.6 µg, or BD MDI 320 µg twice daily for 28 days. The primary efficacy endpoint was forced expiratory volume in 1 second area under the curve from 0 to 12 hours on Day 29. Secondary efficacy endpoints included additional lung function assessments, and evaluation of dyspnea and rescue medication use. Safety was monitored throughout. The systemic exposure to budesonide and formoterol was assessed on Day 29.

Results: Overall, 180 patients were randomized. For forced expiratory volume in 1 second area under the curve from 0 to 12 hours on Day 29, all BFF MDI doses showed significant improvements versus BD MDI 320 µg (least squares mean differences 186–221 mL; all $p<0.0001$), and BFF MDI 320/9.6 µg demonstrated a significant improvement versus FF MDI 9.6 µg (least squares mean difference 56 mL; $p=0.0013$). Furthermore, all BFF MDI doses showed significant improvements versus BD MDI 320 µg for all lung function, dyspnea, and rescue medication use secondary efficacy endpoints. All BFF MDI doses were well tolerated, and the safety profile was not substantially different from the monocomponents. There was no evidence of clinically meaningful pharmacokinetic interactions when budesonide and formoterol were formulated together in BFF MDI.

Conclusion: The findings presented here confirm that BFF MDI 320/9.6 µg is an appropriate dose to take forward into Phase III studies in patients with COPD.

Keywords: BFF MDI, COPD, fixed-dose combination, inhaled corticosteroid, long-acting β_2-agonist, single-inhaler triple therapy

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Introduction

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) report defines COPD as a common, preventable, and treatable disease, which is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[1] Pharmacologic treatments for COPD can reduce the symptoms and the frequency and severity of exacerbations, as well as increase the overall health and exercise tolerance of patients.[1]

Triple therapy with an inhaled corticosteroid (ICS), a long-acting muscarinic antagonist (LAMA), and a long-acting β_2-agonist (LABA) is recommended for the treatment of symptomatic patients with a history of exacerbations (GOLD group D) who experience further exacerbations or persistent symptoms on dual LABA/LAMA or ICS/LABA therapies.[1] Compared with dual ICS/LABA therapy[2–5] or LAMA monotherapy,[6] triple ICS+LAMA+LABA therapy has been shown to improve the lung function and health status and reduce the frequency of moderate-to-severe exacerbations in patients with COPD. Being able to deliver multiple drugs as a fixed-dose combination in a single inhaler may help to improve treatment adherence and clinical outcomes compared with the use of separate inhalers for each drug[7,8] and prevent the selective use or discontinuation of one or more of the compounds.

BGF MDI, an ICS/LAMA/LABA fixed-dose combination of budesonide/glycopyrrolate/formoterol fumarate formulated using co-suspension delivery technology for administration via metered dose inhaler (MDI), is in clinical development for the treatment of COPD. The co-suspension delivery technology provides consistent drug delivery with similar in vitro aerosol performance, regardless of whether a drug is administered alone or in combination with one or more other drugs.[9–11] This study (NCT02196077) investigated the efficacy of the dual fixed-dose combination budesonide/formoterol fumarate (BFF) MDI compared with the monocomponents budesonide (BD) MDI and formoterol fumarate (FF) MDI, and the dose response of budesonide in BFF MDI in patients with moderate-to-severe COPD, to further characterize the optimum dose of budesonide to be used in the co-suspension delivery technology dual and triple fixed-dose combinations and also to assess evidence for a potential pharmacokinetic (PK) interaction when budesonide and formoterol fumarate are formulated together in a single inhaler.

Materials and methods

Study population

The study population comprised male and female current or former smokers (40–80 years of age), with a history of at least 10 pack-years of cigarette smoking. Patients were required to have an established clinical history of COPD as defined by American Thoracic Society (ATS)/European Respiratory Society guidelines,[12] with a pre- and post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio of <0.70 and post-bronchodilator FEV_1 $<80\%$ and $\geq 30\%$ of predicted normal at screening, and a pre-bronchodilator FEV_1/FVC ratio of <0.70 at randomization.

For inclusion in this study, the results of clinical laboratory tests and an electrocardiogram at screening, and a chest X-ray or computerized tomography scan within 6 months prior to screening had to be deemed acceptable by the investigator, based on their medical judgment.

Patients were excluded from this study if they had any clinically significant medical conditions other than COPD, which, in the opinion of the investigator, may have impacted on the patient and/or the study. Those with a primary diagnosis of asthma were excluded, but patients with a prior history of asthma were eligible if COPD was currently their primary diagnosis. Patients with poorly controlled COPD (acute worsening of COPD that required treatment with oral corticosteroids or antibiotics within 6 weeks, or hospitalization within 3 months, prior to or during screening) or who had a lower respiratory tract infection that required antibiotics within 6 weeks prior to or during screening were excluded. Patients who were receiving long-term or nocturnal oxygen therapy for >12 hours per day and those who required the use of a spacer device to compensate for poor hand-to-breath coordination with an MDI were also not eligible for this study.

Patients could be discontinued from the study early at the discretion of the investigator if (on two consecutive assessments ~15 minutes apart) they had a corrected QT interval using Fridericia's correction factor >500 msec with a prolongation increase >60 msec from test day baseline at any time after treatment, a heart rate >120 bpm with an increase >40 bpm from test day baseline at any time within 12 hours after treatment, a systolic blood pressure >180 mmHg with an increase >40 mmHg from test day baseline within 12 hours after treatment, or paradoxical bronchospasm. Patients were also withdrawn from the study if they had a moderate or severe COPD exacerbation. If patients experienced a $\geq 30\%$ decrease in pre-dose FEV_1 from the pre-dose value obtained on Day 1 of Treatment Period 1 at any visit, the investigator or designee determined if they were experiencing a COPD exacerbation and made a decision on their suitability to continue with the study.

At screening, patients who met all entry criteria but were using a short-acting β_2-agonist, short-acting muscarinic antagonist, short-acting β_2-agonist/short-acting muscarinic antagonist fixed-dose combination, LABA, LAMA, LAMA/LABA, phosphodiesterase-4 inhibitor, or theophylline >400 mg/day were switched to sponsor-provided ipratropium bromide MDI 17 µg/inhalation (Atrovent® HFA; Boehringer Ingelheim Pharmaceuticals, Inc., Ridgefield, CT, USA), two inhalations administered four times daily, and sponsor-provided albuterol sulfate MDI 90 µg/inhalation (Ventolin® HFA; GlaxoSmithKline, Research Triangle Park, NC, USA), two inhalations as needed for the screening and washout periods. Patients receiving ICS/LABA maintenance therapy at screening were switched to sponsor-provided budesonide dry powder inhaler (DPI) 180 µg (Pulmicort Flexhaler®; AstraZeneca LP, Wilmington, DE, USA), two inhalations twice daily (BID), and ipratropium MDI four times daily and albuterol MDI as needed during the screening and washout periods, while patients taking an ICS maintenance treatment were switched to sponsor-provided budesonide DPI during the screening and washout periods. Patients who were receiving ICS alone, or as part of a combination therapy, must have been on a stable dose of the ICS component for at least 4 weeks prior to screening.

Study design

This was a Phase IIb, chronic-dosing (28 days), randomized, double-blind, four-period, five-treatment, incomplete-block, crossover study in patients with moderate-to-severe COPD, conducted across 20 sites in the USA. A subset of patients participated in a PK sub-study to assess the systemic exposure of budesonide and formoterol on Day 29 of each treatment period.

Randomization to one of 12 treatment sequences was performed using an Interactive Web Response System, and was stratified by whether or not a patient was participating in the PK sub-study. Patients were still eligible for inclusion in the study if they did not want to participate in the PK sub-study or did not meet the PK sub-study criteria, but met overall study entry criteria.

Each treatment sequence contained BFF MDI 320/9.6 µg (160/4.8 µg per actuation; 9.6 µg FF is equivalent to 10 µg FF dihydrate) and FF MDI 9.6 µg (4.8 µg per actuation), and two of the three remaining treatments (BFF MDI 160/9.6 µg [80/4.8 µg per actuation], BFF MDI 80/9.6 µg [40/4.8 µg per actuation], or BD MDI 320 µg [160 µg per actuation]). All doses represent ex-actuator amounts, which were delivered as two actuations BID. Each of the four treatments was administered for 28 days with a washout period of 14–21 days in between treatments. For each treatment period, patients reported to the clinic on Days 1 and 15 and on the last day of treatment (Day 29), and remained until all scheduled assessments on that day were completed. A telephone follow-up was performed 7–14 days following the last visit of Treatment Period 4. Patients were permitted to use rescue albuterol MDI as needed throughout the study and ipratropium MDI during the washout periods; those who were switched to sponsor-provided budesonide DPI during the screening period could also use this during the washout periods. Patients had to withhold from all COPD medications (including rescue medication) for at least 6 hours prior to any procedures being performed at the start of each treatment period. Prior to dose administration on Day 1 of Treatment Periods 2, 3, and 4, a patient's baseline FEV_1 was required to be within ±20% or 200 mL of the pre-dose FEV_1 on Day 1 of Treatment Period 1.

Patients were not allowed to consume grapefruit or grapefruit juice throughout the study and were not allowed xanthine-containing foods and beverages (such as coffee, tea, chocolate, or cola) for at least 6 hours prior to, and for the duration of, each clinic visit. They were also required to refrain from smoking for at least 4 hours prior to, and throughout the duration of, each clinic visit, although nicotine replacement treatments (such as chewing gum and patches) were permitted as needed, in accordance with recommendations from the investigator.

The study was conducted in accordance with Good Clinical Practice, including the International Conference on Harmonization Guidelines and the Declaration of Helsinki, and registered on the US National Institutes of Health ClinicalTrials.gov website (https://ClinicalTrials.gov/ct2/show/NCT02196077). The study protocol and informed consent form were approved by an institutional review board (Schulman Associates IRB, Cincinnati, OH, USA) and all patients provided written informed consent prior to screening.

Efficacy endpoints

The primary efficacy endpoint was FEV_1 area under the curve from 0 to 12 hours ($AUC_{0–12}$) on Day 29. Secondary efficacy endpoints were the change from baseline in morning pre-dose trough FEV_1 over 28 days, peak change from baseline in FEV_1 on Day 1, peak change from baseline in FEV_1 over 28 days (evaluated using the peak change from baseline on Days 15 and 29), FVC $AUC_{0–12}$ on Day 29, self-administered computerized (SAC) Transition Dyspnea Index (TDI) focal score on Day 29, and the change from baseline in average daily number of puffs of rescue medication over the last week of treatment.

Efficacy assessments

All pulmonary function tests, including FEV_1 and FVC, were performed in accordance with the ATS criteria[13] with a spirometer that met or exceeded minimum ATS performance recommendations. All sites were provided with identical spirometry systems (KoKo® Spirometer; nSpire Health, Inc., Longmont, CO, USA), and the study staff responsible for performing pulmonary function tests received standardized training. On Days 1, 15 and 29 of each treatment period, spirometry was performed 30 and 60 minutes pre-dose, and 15 and 30 minutes and 1 and 2 hours post-dose. In addition to these time points, on Day 29 of each treatment period, spirometry assessments were performed at 4, 6, 8, 10, 11.5, and 12 hours post-dose. The average of the two pre-dose spirometry assessments was used to establish test day baseline FEV_1 and FVC values.

Patients maintained a record of their rescue medication use (total number of "puffs" per day) BID in an eDiary that they were provided with at screening for the duration of the study. The SAC Baseline Dyspnea Index questionnaire was completed pre-dose on Day 1 of Treatment Period 1, and the SAC TDI questionnaire was completed pre-dose on Day 29 of each treatment period.

Safety evaluations

The safety profile of the study treatments was determined from vital sign measurements (including blood pressure, heart rate, and temperature), clinical laboratory tests (including hematology and clinical chemistry), and electrocardiograms, which were conducted from 60 minutes pre-dose, up to 2 hours post-dose on Days 1 and 15 and up to 12 hours post-dose on Day 29 (except the clinical laboratory tests, which were performed up to 2 hours post-dose on Day 29). All adverse events (AEs) and serious AEs observed during the study were reported. Paradoxical bronchospasm, which may occur following inhalation from an MDI, was an AE of interest.

PK assessments

Blood samples were collected on Day 1 (30 minutes pre-dose) and Day 29 (30 minutes pre-dose and 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10, and 12 hours post-dose) of each treatment period. Plasma levels of budesonide and formoterol were determined using a validated high-performance liquid chromatography tandem mass spectrometry method.

Statistical analyses

The intent-to-treat (ITT) population and the safety population both included all patients who were randomized to treatment and received at least one dose of study medication. However, the ITT population was analyzed according to the treatment assigned, whereas the safety population was analyzed based on the treatment received. The modified intent-to-treat (mITT) population, which was the primary population for the efficacy analyses, included patients who received treatment and had posttreatment efficacy data from at least two treatment periods. Data impacted by major protocol deviations (determined before unblinding) were excluded from the analysis of the mITT population. The PK population included all randomized and treated patients in the PK sub-study who had sufficient data to reliably calculate at least one PK parameter, and who had no major protocol deviations that could affect the collection and interpretation of their PK data.

The primary analyses (FEV_1 $AUC_{0–12}$ on Day 29) involved comparisons of the three BFF MDI treatments (BFF MDI 320/9.6 µg, BFF MDI 160/9.6 µg, and BFF MDI 80/9.6 µg) with BD MDI 320 µg first and then each of the BFF MDI doses with FF MDI 9.6 µg (secondary efficacy analyses). These comparisons were performed with a repeated measures mixed-effects model. This model with FEV_1 $AUC_{0–12}$ as the dependent variable had the following factors in the model: baseline FEV_1, screening percent reversibility, period, and treatment as fixed factors and subject (sequence) as a random factor. Treatment sequence was also included if it explained significant variability ($p<0.10$). The baseline used as the covariate was defined as the mean of the pre-dose values for treatment across all treatment periods. All covariates in the model were categorical, except for baseline FEV_1 and screening percent reversibility to albuterol MDI, which were continuous. Categorical covariates were unordered covariates. The family-wise Type I error was controlled sequentially by testing the higher dose of BFF MDI compared with BD MDI 320 µg first before testing the middle and then the lower dose compared with BD MDI 320 µg, using a two-sided alpha of 0.05. The same sequential approach was then applied when comparing the BFF MDI doses to FF MDI 9.6 µg for the secondary efficacy analyses. There was no additional control of Type I error prespecified, and *p*-values for the secondary efficacy analyses were interpreted nominally by comparing the two-sided alpha of 0.05. The secondary efficacy endpoints were analyzed using similar models as those for the primary efficacy endpoint.

The PK parameters were estimated from the budesonide and formoterol plasma concentration–time data where feasible by non-compartmental analysis using the software Phoenix® WinNonlin® (Certara USA, Inc., Princeton, NJ, USA).

For PK parameter estimation, any samples that were below the limit of quantification were set to missing in the non-compartmental analysis. For all descriptive statistics, any values below the lower limit of quantification were assigned a value of ½ lower limit of quantification, with the exception of Day 1 pre-dose results, which were assigned a value of zero. AUC_{0-12} was calculated using the linear-log trapezoidal method. Maximum observed plasma concentration (C_{max}) was obtained from the observed values. For the analysis of relative bioavailability, a mixed model with treatment, period, and sequence as fixed effects and subject as a random effect was used. A lack of a drug–drug interaction was concluded if the ratios of systemic exposure were within predefined criteria of the point estimate being within 80%–125%, and the 90% CI contained within 75%–133%.

Based on the properties of the primary efficacy endpoint, the assumption of a composite within-subject SD of 130 mL and a total SD of 184 mL, and the assumption that 20% of patients could drop out and that a two-sided alpha level of 0.05 was used, a sample size of 160 randomized patients was planned in order to provide ~99% power to demonstrate a difference in FEV_1 AUC_{0-12} on Day 29 of 100 mL for each dose of BFF MDI compared with BD MDI 320 µg, ~90% power to demonstrate a difference of 50 mL for BFF MDI 320/9.6 µg compared with FF MDI 9.6 µg, and ~54% power to demonstrate a difference of 50 mL for BFF MDI 160/9.6 µg and BFF MDI 80/9.6 µg compared with FF MDI 9.6 µg.

Results

Study population

A total of 218 patients were screened and 180 (82.6%) were randomized to receive study treatment (Figure 1). All of the randomized patients (100.0%) were included in the overall ITT and safety populations, and 161 patients (89.4%) were included in the overall mITT population. The main reason that patients were excluded from the mITT population was them not having posttreatment efficacy data from at least two treatment periods (n=17). There were 128 patients (71.1%) who completed all four treatment periods.

Patients in the overall ITT population had a mean age of 62.2 years, 46.7% were male, 90.0% were Caucasian, and 61.1% were current smokers (Table 1). The overall mean duration of COPD was 8.2 years, while COPD severity was moderate in 57.2% and severe in 42.8% of patients (Table 1). Overall, 33 patients (18.3%) had previously received dual ICS/LABA therapy. Baseline demographics and clinical characteristics in this crossover study were similar across treatments. The mITT demographic data were similar to the data for the ITT population.

Lung function

BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg all significantly improved FEV_1 AUC_{0-12} on Day 29 (primary endpoint) compared with BD MDI 320 µg (least squares mean [LSM] differences 221, 186, and 194 mL, respectively; all $p<0.0001$; Figure 2). BFF MDI 320/9.6 µg also

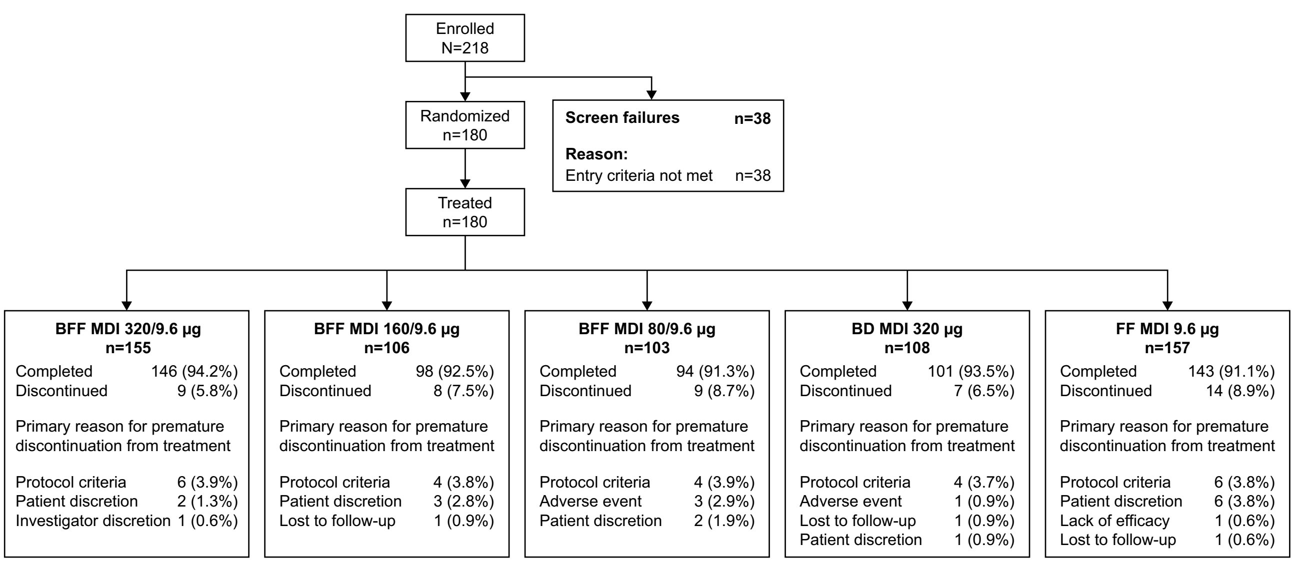

Figure 1 Patient disposition.

Note: All patients who discontinued treatment early due to protocol criteria had a moderate or severe COPD exacerbation (n=18), an acute exacerbation of chronic bronchitis (n=1), or they did not meet baseline FEV_1 stability criteria (n=5).

Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; MDI, metered dose inhaler.

Table 1 Baseline demographics and clinical characteristics (safety/ITT population)

Parameter	BFF MDI 320/9.6 µg, n=155	BFF MDI 160/9.6 µg, n=106	BFF MDI 80/9.6 µg, n=103	BD MDI 320 µg, n=108	FF MDI 9.6 µg, n=157	All patients, N=180
Mean age, years (SD)	61.7 (8.5)	61.8 (8.0)	61.7 (8.7)	62.3 (8.2)	62.4 (8.6)	62.2 (8.4)
Mean BMI, kg/m^2 (SD)	28.4 (6.5)	27.4 (5.7)	28.5 (6.4)	28.4 (6.4)	28.3 (6.2)	28.3 (6.4)
Gender, % male	45.2	49.1	44.7	45.4	46.5	46.7
Race, %						
Caucasian	89.0	90.6	88.3	90.7	88.5	90.0
Black or African-American	11.0	9.4	11.7	9.3	11.5	10.0
Smoking status, % current	63.9	66.0	60.2	63.0	62.4	61.1
Mean smoking history, pack-years (SD)	49.5 (23.0)	50.5 (23.6)	48.6 (22.4)	51.3 (23.1)	50.7 (23.1)	50.8 (23.2)
COPD severity,[a] % severe[b]	40.6	47.2	38.8	39.8	42.0	42.8
Mean duration of COPD, years (SD)	8.1 (5.3)	8.3 (4.9)	7.5 (5.4)	8.2 (5.3)	8.2 (5.2)	8.2 (5.2)
Prior medication use,[c] n (%)						
LAMA	14 (9.0)	10 (9.4)	10 (9.7)	7 (6.5)	16 (10.2)	18 (10.0)
ICS	10 (6.5)	7 (6.6)	7 (6.8)	7 (6.5)	11 (7.0)	11 (6.1)
LAMA/LABA FDC	1 (0.6)	1 (0.9)	1 (1.0)	0	1 (0.6)	1 (0.6)
ICS+LABA[d]	27 (17.4)	17 (16.0)	19 (18.4)	22 (20.4)	26 (16.6)	33 (18.3)
ICS+LAMA[e]	2 (1.3)	2 (1.9)	1 (1.0)	1 (0.9)	2 (1.3)	2 (1.1)
ICS+LAMA+LABA[e]	16 (10.3)	11 (10.4)	11 (10.7)	10 (9.3)	18 (11.5)	22 (12.2)
Exacerbation history,[f] n (%) [number of events]						
Moderate[g]	16 (10.3) [24]	12 (11.3) [13]	9 (8.7) [15]	12 (11.1) [19]	15 (9.6) [21]	18 (10.0) [26]
Severe[h]	2 (1.3) [5]	1 (0.9) [1]	2 (1.9) [5]	1 (0.9) [4]	2 (1.3) [5]	2 (1.1) [5]
Mean SAC BDI score[i] (SD)	7.0 (2.1)	6.9 (2.1)	7.2 (2.2)	6.9 (2.0)	7.0 (2.2)	7.0 (2.0)
Mean baseline daily puffs of albuterol[j] (SD)	2.7 (3.3)	3.1 (3.7)	2.5 (2.7)	2.9 (3.5)	2.7 (3.2)	2.8 (3.3)
Mean screening FEV_1, % predicted (SD)						
Pre-bronchodilator	46.4 (12.6)	45.0 (12.7)	47.5 (12.4)	46.4 (12.5)	46.3 (12.4)	46.2 (12.3)
Post-bronchodilator	53.1 (12.6)	51.5 (12.3)	53.6 (12.6)	53.4 (12.8)	52.9 (12.5)	52.7 (12.3)
Mean screening FEV_1, L (SD)						
Pre-bronchodilator	1.318 (0.456)	1.312 (0.497)	1.350 (0.424)	1.306 (0.430)	1.305 (0.440)	1.318 (0.456)
Post-bronchodilator	1.512 (0.490)	1.502 (0.523)	1.528 (0.458)	1.506 (0.467)	1.496 (0.474)	1.506 (0.488)
Mean reversibility,[k] % (SD)	16.3 (13.1)	16.6 (13.9)	14.1 (11.2)	16.8 (13.4)	16.1 (13.4)	15.8 (13.0)

Notes: [a]Severity of COPD was based on the non-missing post-bronchodilator assessment at screening. [b]30%≤FEV_1<50% predicted (GOLD 3).[1] [c]During the 2-week period prior to Visit 1. If a patient was on an FDC therapy and monotherapy component of the combination during the period of interest, the patient was categorized as being on the combination. Only data for long-acting therapies are shown. [d]Delivered as an FDC or via separate inhalers. [e]Delivered via separate inhalers. [f]Within the past 12 months of the screening visit. [g]Treated with systemic (oral or intravenous) corticosteroids and/or antibiotics. [h]Resulted in hospital admission or emergency room treatment. [i]ITT population: n=152, n=100, n=99, n=103, n=148, n=171. [j]Obtained using the non-missing values from the last 7 days prior to randomization. [k]Defined as ([the change from pre-bronchodilator to post-bronchodilator FEV_1]/pre-bronchodilator FEV_1)×100.

Abbreviations: BD, budesonide; BDI, Baseline Dyspnea Index; BFF, budesonide/formoterol fumarate; BMI, body mass index; FDC, fixed-dose combination; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; ITT, intent-to-treat; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; MDI, metered dose inhaler; SAC, self-administered computerized.

demonstrated a statistically significant improvement versus FF MDI 9.6 µg in FEV_1 AUC_{0-12} on Day 29 (LSM difference 56 mL; p=0.0013; Figure 2), whereas BFF MDI 160/9.6 µg and BFF MDI 80/9.6 µg showed numerical improvements versus FF MDI 9.6 µg. No significant differences in FEV_1 AUC_{0-12} on Day 29 were observed between the doses of BFF MDI.

All three doses of BFF MDI resulted in statistically significant improvements versus BD MDI 320 µg in change from baseline in morning pre-dose trough FEV_1 over 28 days, with a dose-related numerical increase observed from the low to high doses of BFF MDI (LSM difference range 88–115 mL; all $p<0.0001$; Table 2). Both BFF MDI 320/9.6 µg and 160/9.6 µg significantly improved the change from baseline in morning pre-dose trough FEV_1 over 28 days versus FF MDI 9.6 µg, with a numerical increase shown for BFF MDI 80/9.6 µg relative to FF MDI 9.6 µg (Table 2). On Days 1, 15, and 29, as well as over 28 days, all BFF MDI doses resulted in significant improvements in the peak change from baseline in FEV_1 versus BD MDI 320 µg (LSM difference range over 28 days 212–248 mL; all $p<0.0001$; Figure 3). BFF MDI 320/9.6 µg and BFF MDI 160/9.6 µg both significantly increased the peak change from baseline in FEV_1 over 28 days compared with FF MDI 9.6 µg (LSM differences 68 mL; $p<0.0001$ and 40 mL; p=0.0288, respectively; Figure 3). Treatment with any of the doses of BFF MDI significantly improved FVC AUC_{0-12} on Day 29 versus BD MDI 320 µg (LSM difference range 244–303 mL; all $p<0.0001$), but not compared with FF MDI 9.6 µg (Table 2).

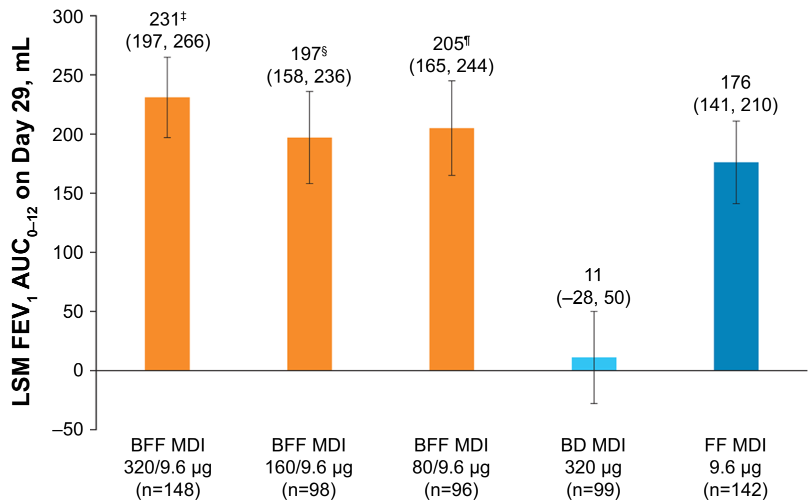

Figure 2 FEV_1 $AUC_{0–12}$ on Day 29 (mITT population).
Notes: ‡$p<0.0001$ versus BD MDI; $p=0.0013$ versus FF MDI; §$p<0.0001$ versus BD MDI; $p=0.2827$ versus FF MDI; ¶$p<0.0001$ versus BD MDI; $p=0.1436$ versus FF MDI. Error bars represent 95% CI.
Abbreviations: $AUC_{0–12}$, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat.

Table 2 Summary of secondary efficacy endpoints (mITT population)

Parameter	LSM	LSM differences between treatments	
		BD MDI 320 μg	FF MDI 9.6 μg
Change from baseline in morning pre-dose trough FEV_1 over 28 days, mL			
BFF MDI 320/9.6 μg, n=151		n=102	n=147
LSM (95% CI)	138 (111, 165)	115‡ (81, 150)	55*** (24, 86)
BFF MDI 160/9.6 μg, n=100			
LSM (95% CI)	121 (89, 153)	99‡ (60, 137)	38* (3, 73)
BFF MDI 80/9.6 μg, n=97			
LSM (95% CI)	110 (78, 142)	88‡ (49, 127)	27 (–8, 63)
FVC $AUC_{0–12}$ on Day 29, mL			
BFF MDI 320/9.6 μg, n=148		n=99	n=142
LSM (95% CI)	305 (244, 365)	303‡ (229, 376)	52 (–13, 117)
BFF MDI 160/9.6 μg, n=98			
LSM (95% CI)	245 (176, 315)	244‡ (161, 327)	–7 (–82, 68)
BFF MDI 80/9.6 μg, n=96			
LSM (95% CI)	267 (196, 337)	265‡ (182, 348)	14 (–60, 89)
SAC TDI focal score on Day 29			
BFF MDI 320/9.6 μg, n=149		n=100	n=142
LSM (95% CI)	0.598 (0.298, 0.899)	0.707** (0.285, 1.130)	0.339 (–0.039, 0.717)
BFF MDI 160/9.6 μg, n=97			
LSM (95% CI)	0.882 (0.518, 1.246)	0.992‡ (0.516, 1.467)	0.623** (0.190, 1.056)
BFF MDI 80/9.6 μg, n=96			
LSM (95% CI)	0.459 (0.093, 0.825)	0.568* (0.091, 1.045)	0.200 (–0.233, 0.632)
Change from baseline in mean daily number of puffs of rescue medication over the last week of treatment			
BFF MDI 320/9.6 μg, n=152		n=104	n=149
LSM (95% CI)	0.05 (–0.34, 0.43)	–0.92‡ (–1.29, –0.54)	–0.40* (–0.73, –0.07)
BFF MDI 160/9.6 μg, n=101			
LSM (95% CI)	0.16 (–0.27, 0.58)	–0.81*** (–1.23, –0.39)	–0.29 (–0.67, 0.09)
BFF MDI 80/9.6 μg, n=98			
LSM (95% CI)	0.24 (–0.19, 0.67)	–0.73*** (–1.15, –0.30)	–0.21 (–0.59, 0.17)

Notes: *$p<0.05$, **$p<0.01$, ***$p<0.001$, ‡$p<0.0001$.
Abbreviations: $AUC_{0–12}$, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; FVC, forced vital capacity; LSM, least squares mean; MDI, metered dose inhaler; mITT, modified intent-to-treat; SAC, self-administered computerized; TDI, Transition Dyspnea Index.

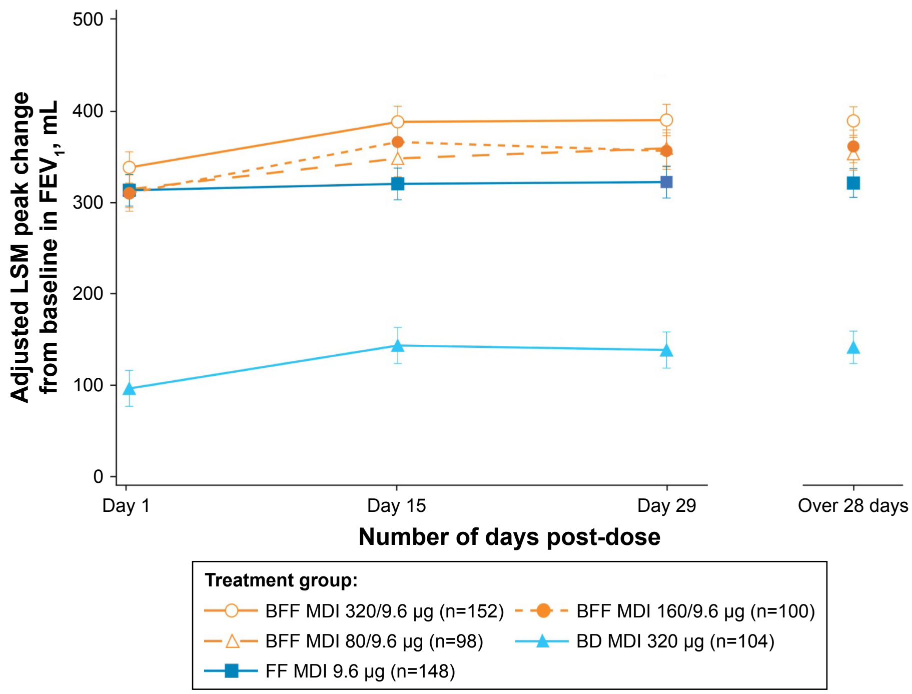

Figure 3 Peak change from baseline in FEV_1 over 28 days (mITT population).

Notes: Error bars represent standard error. The LSM treatment difference between all doses of BFF MDI and BD MDI 320 µg was significant ($p<0.0001$) for all time points and over 28 days. The LSM treatment difference between BFF MDI and FF MDI 9.6 µg was significant ($p<0.05$) for BFF MDI 320/9.6 µg and BFF MDI 160/9.6 µg on Day 15 and over 28 days, and for BFF MDI 320/9.6 µg on Day 29.

Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FEV_1, forced expiratory volume in 1 second; FF, formoterol fumarate; LSM, least squares mean; mITT, modified intent-to-treat; MDI, metered dose inhaler.

Dyspnea

BFF MDI 320/9.6, 160/9.6, and 80/9.6 µg all resulted in statistically significant improvements versus BD MDI 320 µg in SAC TDI focal score on Day 29 (LSM differences 0.707 [$p=0.0011$], 0.992 [$p<0.0001$], and 0.568 [$p=0.0197$], respectively; Table 2). BFF MDI 160/9.6 µg also significantly improved SAC TDI focal score on Day 29 versus FF MDI 9.6 µg (Table 2). BFF MDI 320/9.6 µg and 80/9.6 µg numerically improved SAC TDI focal score relative to FF MDI 9.6 µg (LSM differences 0.339 [$p=0.0786$] and 0.200 [$p=0.3646$], respectively).

Rescue medication use

During treatment with BFF MDI 320/9.6, 160/9.6, or 80/9.6 µg, patients used significantly less rescue medication over the last week of the treatment period than those who received BD MDI 320 µg (LSM differences −0.73 to −0.92 puffs/day; all $p<0.001$; Table 2). Relative to FF MDI 9.6 µg, significantly less rescue medication was used over the last week of treatment by patients treated with BFF MDI 320/9.6 µg but not BFF MDI 160/9.6 µg or 80/9.6 µg (Table 2).

Safety

The percentage of patients who experienced at least one treatment-emergent AE (TEAE) was similar across the treatments, ranging from 18.9% (BFF MDI 160/9.6 µg) to 25.9% (BD MDI 320 µg; Table 3). TEAEs that occurred in ≥2% of patients following any treatment were nasopharyngitis, hypertension, cough, and upper respiratory tract infection (Table 3). No incidences of paradoxical bronchospasm (AE of interest) were reported.

Most TEAEs were mild or moderate in severity. The number of patients with serious TEAEs across treatments ranged from zero (BFF MDI 160/9.6 µg) to three (BFF MDI 80/9.6 µg [2.9%] and BD MDI 320 µg [2.8%]; Table 3). Overall, two patients (1.1%), both following treatment with BFF MDI 80/9.6 µg, experienced serious TEAEs that were considered by the investigator to be possibly related to the study drug and led to discontinuation from the study: acute myocardial infarction (n=1) and angina pectoris (n=1). Six patients (3.3%) discontinued the study early due to TEAEs (BFF MDI 320/9.6 µg, cough [n=1]; BFF MDI 80/9.6 µg, wheezing and dyspnea [n=1], acute myocardial infarction [n=1], and angina pectoris/worsening of COPD [n=1]; BD MDI 320 µg, COPD exacerbation [n=2]). No treatment-emergent deaths were reported for this study.

Table 3 Summary of TEAEs overall and by treatment group (safety population)[a]

Parameter, n (%)	BFF MDI 320/9.6 μg, n=155	BFF MDI 160/9.6 μg, n=106	BFF MDI 80/9.6 μg, n=103	BD MDI 320 μg, n=108	FF MDI 9.6 μg, n=157	All patients, N=180
Patients with at least one TEAE	36 (23.2)	20 (18.9)	22 (21.4)	28 (25.9)	31 (19.7)	96 (53.3)
Patients with TEAEs related[b] to study treatment	5 (3.2)	3 (2.8)	4 (3.9)	6 (5.6)	3 (1.9)	19 (10.6)
Patients with serious TEAEs	2 (1.3)	0	3 (2.9)	3 (2.8)	1 (0.6)	9 (5.0)
Patients with serious TEAEs related[b] to study treatment	0	0	2 (1.9)	0	0	2 (1.1)
Patients with TEAEs that led to early discontinuation	1 (0.6)	0	3 (2.9)	2 (1.9)	0	6 (3.3)
TEAEs (preferred term) reported in ≥2% patients in any treatment group						
Nasopharyngitis	5 (3.2)	1 (0.9)	2 (1.9)	2 (1.9)	5 (3.2)	13 (7.2)
Hypertension	2 (1.3)	1 (0.9)	1 (1.0)	3 (2.8)	2 (1.3)	9 (5.0)
Cough	1 (0.6)	0	1 (1.0)	3 (2.8)	1 (0.6)	6 (3.3)
Upper respiratory tract infection	4 (2.6)	0	1 (1.0)	0	0	5 (2.8)

Notes: [a]These data do not include TEAEs with onset during the washout periods. [b]Judged by the investigator to be possibly, probably, or definitely related.
Abbreviations: BD, budesonide; BFF, budesonide/formoterol fumarate; FF, formoterol fumarate; MDI, metered dose inhaler; TEAE, treatment-emergent adverse event.

There were no clinically significant changes from baseline in hematology or kidney function following any treatment. There was no notable evidence of treatment-related effects on vital signs or Fridericia-corrected QT (QTcF), PR, or QRS interval prolongation following any treatment, with the exception of one patient who, in the opinion of the investigator, experienced clinically significant QTcF prolongation values (1 hour post-dose with BFF MDI 80/9.6 μg, QTcF >470 msec and change from baseline >30 msec). This was the same patient who discontinued due to an acute myocardial infarction following treatment with BFF MDI 80/9.6 μg.

Pharmacokinetics

Eighty-two patients participated in the PK sub-study and were included in the PK population. The overall systemic exposure of budesonide on Day 29 following treatment with BFF MDI 320/9.6 μg was similar to BD MDI 320 μg, as measured by AUC_{0-12} (geometric LSM 2,767.45 h*pg/mL and 2,602.30 h* pg/mL, respectively). The C_{max} of budesonide was ~19% higher for BFF MDI 320/9.6 μg compared with BD MDI 320 μg (geometric LSM 742.37 and 623.60 pg/mL, respectively). The formoterol systemic exposure on Day 29 (AUC_{0-12} and C_{max}) was similar across each dose of BFF MDI compared with FF MDI 9.6 μg. The ratio of the AUC_{0-12} and C_{max} geometric LSMs (and the resulting 90% CIs) for each of these treatment comparisons on Day 29 fell within the predefined bounds of 80%–125% (75%–133% for the 90% CIs; Figure 4).

Discussion

This study investigated the efficacy and safety of three doses of BFF MDI (320/9.6, 160/9.6, and 80/9.6 μg) compared with BD MDI 320 μg and FF MDI 9.6 μg (all BID), all formulated using co-suspension delivery technology, in patients with moderate-to-severe COPD. All doses of BFF MDI resulted in statistically significant increases versus BD MDI 320 μg for the primary analysis of FEV_1 AUC_{0-12} at Day 29, and BFF MDI 320/9.6 μg also resulted in significant improvement in FEV_1 AUC_{0-12} at Day 29 versus FF MDI 9.6 μg. Moreover, BFF MDI 320/9.6 μg consistently showed statistically significant improvement over both monocomponent MDIs for lung function and rescue medication use, apart from versus FF MDI 9.6 μg for FVC AUC_{0-12} and SAC TDI focal score, both on Day 29, and for peak change from baseline in FEV_1 on Day 1. The improvement in morning pre-dose trough FEV_1 over 28 days with BFF MDI 320/9.6 μg relative to BD MDI 320 μg exceeded the minimal clinically important difference of 100 mL,[14] which suggested that this treatment difference was clinically relevant.

For the primary and secondary efficacy endpoints, the magnitude of response to BFF MDI 320/9.6 μg was the greatest of the doses examined, with the exception of SAC TDI focal score on Day 29 (greatest magnitude of response with BFF MDI 160/9.6 μg). A numerical dose response from BFF MDI 80/9.6 μg to BFF MDI 320/9.6 μg was observed for the change from baseline in morning pre-dose trough FEV_1 over 28 days, peak FEV_1 over 28 days, and rescue medication use over the last week of treatment.

All BFF MDI doses were well tolerated with no unexpected safety findings. The safety profile of the BFF MDI doses demonstrated no appreciable dose response and no substantial differences compared with BD MDI 320 μg or FF MDI 9.6 μg. The safety findings are in line with previous studies using a different formulation, which showed that budesonide/formoterol fumarate dihydrate (Symbicort®)

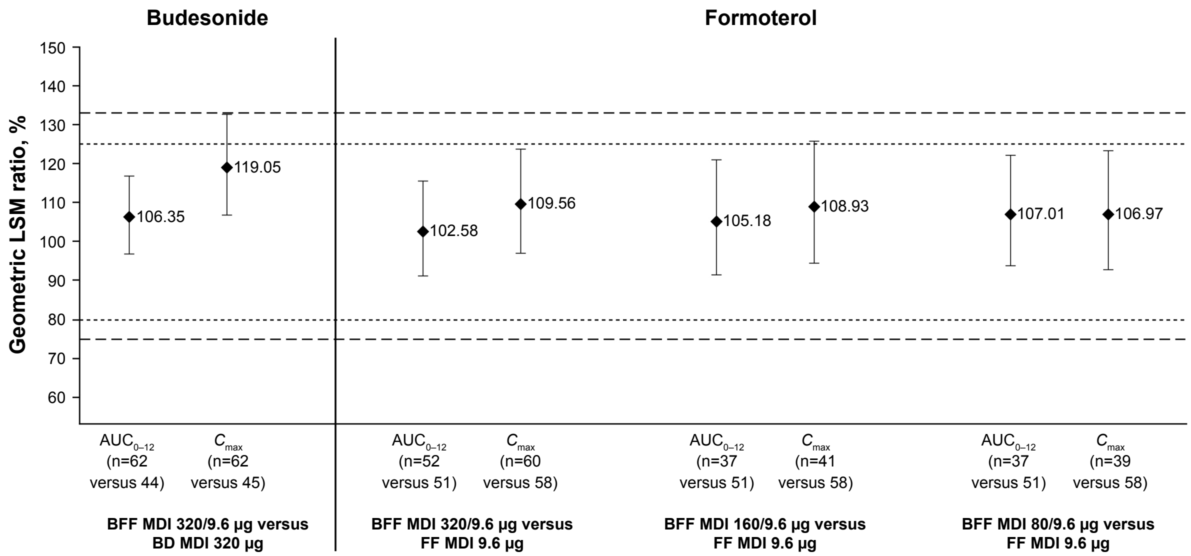

Figure 4 Relative bioavailability of budesonide and formoterol on Day 29 (PK population).

Notes: Vertical bars are 90% CI of the ratio (combination/monocomponent) of geometric LSM. Dashed lines represent the predefined bounds of 80%–125% for the point estimate for the ratio, and 75% and 133% for the 90% CIs.

Abbreviations: AUC_{0-12}, area under the curve from 0 to 12 hours; BD, budesonide; BFF, budesonide/formoterol fumarate; C_{max}, maximum observed plasma concentration; FF, formoterol fumarate; LSM, least squares mean; MDI, metered dose inhaler; PK, pharmacokinetic.

320/9 and 160/9 µg inhaled via MDI were well tolerated over both 6 and 12 months,[15–17] with a safety profile similar to that of the monocomponent MDIs.[16–18]

The PK analysis in this study found that the presence of budesonide in the fixed-dose combination BFF MDI did not alter the systemic exposure of formoterol, that is, the AUC_{0-12} and C_{max} ratios for all three doses of BFF MDI versus FF MDI 9.6 µg fell within the prespecified equivalence criteria for the point ratio and 90% CIs. Similarly, the presence of formoterol in the fixed-dose combination BFF MDI did not markedly alter the systemic exposure of budesonide. Therefore, there was no evidence of a significant PK drug–drug or formulation interaction between budesonide and formoterol when delivered via BFF MDI. These results are consistent with other PK analyses of co-suspension delivery technology formulations for delivery via MDI, which demonstrated a lack of significant drug–drug interactions when formoterol fumarate and the LAMA glycopyrrolate were formulated together.[19]

The crossover design of this study, where an ICS/LABA fixed-dose combination was compared to its individual monocomponents delivered via MDI, is uncommon in studies investigating ICS/LABA fixed-dose combinations. To ensure that the crossover approach was suitable for this study, it was important to check that the patients' baseline FEV_1 was stable and was reflective of their COPD severity prior to dosing at the start of each treatment period. As such, the baseline FEV_1 measurements obtained on Day 1 of Treatment Periods 2, 3, and 4 had to be within 20% or 200 mL of the pre-dose FEV_1 obtained at randomization (Day 1 of Treatment Period 1). Additionally, the screening and washout periods of this study ensured that there was an identical approach to concomitant medications prior to each treatment phase, whereby all medications were washed out before the treatment began.

In other studies, budesonide/formoterol fumarate dihydrate fixed-dose combinations (formulated as DPIs or conventional MDIs without co-suspension delivery technology) have been shown to reduce the risk of exacerbations and improve health-related quality of life compared to treatment with formoterol alone in patients with COPD who have a history of exacerbations.[18,20] Therefore, investigations into the effect of BFF MDI, formulated using co-suspension delivery technology, on exacerbations and health-related quality of life are required.

Limitations of this study include that each treatment period lasted for 4 weeks only. Concomitant background treatment with a LAMA was prohibited, which meant that treatment regimens did not always conform with current treatment paradigms in patients with COPD.[1] Also, the inclusion criteria did not include a requirement for patients to have a history of COPD exacerbations; such patients, based on the GOLD recommendations, are those for whom ICS/LABA is a proposed treatment option (GOLD groups C and D).[1]

Conclusion

The findings of this study confirm BFF MDI 320/9.6 µg as an appropriate dose to progress into Phase III clinical trials in patients with COPD. BFF MDI 320/9.6 µg and BFF MDI 160/9.6 µg formulated using co-suspension delivery technology are currently under investigation in the Phase III studies TELOS (NCT02766608) and SOPHOS (NCT02727660) in patients with moderate-to-very severe COPD.

Data sharing statement

All relevant data analyzed during this study are included in this published article.

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Author contributions

Employees of the sponsor (CR, PD, and ESR) were involved in various aspects of the conception and design of the study, acquisition of data and analysis and interpretation of data, and input into manuscript development. All authors contributed toward the conception and design, data acquisition, or data analysis and interpretation, critically revising and providing final approval of the manuscript, and agree to be accountable for all aspects of the work.

Disclosure

EMK has consulted and participated in scientific advisory boards, speaker panels, or received travel reimbursement from Amphastar, AstraZeneca, Forest, Mylan, Novartis, Oriel, Pearl – a member of the AstraZeneca Group, Sunovion, Teva, and Theravance. TMS has consulted for Sunovion and Vapotherm, participated in speaker bureaus for AstraZeneca, Boehringer Ingelheim, and Sunovion, and received research grants from AstraZeneca, Boehringer Ingelheim, Chiesi, Forest, GlaxoSmithKline, Novartis, Oncocyte, Pearl – a member of the AstraZeneca Group, Proterix, Sunovion, and Theravance. PD and ESR are employees of Pearl – a member of the AstraZeneca Group. CR is Chief Executive Officer of Pearl – a member of the AstraZeneca Group and an employee of AstraZeneca. The authors report no other conflicts of interest in this work.

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