Relative Bioavailability of Budesonide/Glycopyrrolate/Formoterol Fumarate Metered Dose Inhaler Administered With and Without a Spacer: Results of a Phase I, Randomized, Crossover Trial in Healthy Adults

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ABSTRACT

Purpose: The triple combination therapy budesonide/glycopyrrolate/formoterol fumarate in a metered dose inhaler (BGF MDI), formulated by using innovative co-suspension delivery technology, is a new inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist fixed-dose combination for the maintenance treatment of COPD. For some patients, the use of an MDI may be optimized with a spacer. This Phase I study assessed the effect of a spacer on lung exposure, total systemic exposure, and safety of BGF MDI 320/36/9.6 μg in healthy subjects.

Methods: : This randomized, open-label, crossover study assessed the pharmacokinetic and safety profiles of BGF MDI in healthy adult subjects who received a single dose of BGF MDI 320/36/9.6 μg (administered as 2 inhalations with 160/18/4.8 μg per actuation) in 4 regimens: without spacer and no charcoal; with spacer and no charcoal; without spacer and with charcoal; and with spacer and with charcoal. Primary objectives were to assess total systemic exposure (without charcoal) and lung exposure (with charcoal) of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer. Safety was also assessed.

Findings: In total, 56 subjects were randomized (mean age, 29.9 years; 60.7% male, 17.9% former smokers). For systemic exposure (without charcoal), the spacer/without spacer ratio, expressed as a percentage (intrasubject %CV) of C_{max} and $AUC_{0-tlast}$, respectively, was 152.0 (47.5) and 132.8 (43.6) for budesonide, 240.6 (80.2) and 154.7 (73.4) for glycopyrronium, and 165.6 (50.7) and 98.6 (53.8) for formoterol. For lung exposure (with charcoal), the spacer/without spacer ratio percentage (%CV) of C_{max} and $AUC_{0-tlast}$, respectively, was 183.6 (65.9) and 198.4 (71.5) for budesonide, 262.0 (91.8) and 373.9 (120.7) for glycopyrronium, and 222.9 (56.3) and 385.2 (147.0) for formoterol. Subjects who were judged to have suboptimal inhalation technique without a spacer (those in the lowest drug exposure quartile based on $AUC_{0-tlast}$) had the greatest increase in both total systemic and lung exposure when a spacer was used versus no spacer. Subjects in the highest quartile had a minimal change in both total systemic and lung exposure when the spacer was used. Treatment-emergent adverse events (TEAEs) (all mild/moderate) reported by >1 subject per regimen were headache, cough, and dizziness. One subject withdrew because of TEAEs of headache and presyncope (neither considered treatment-related).

Implications: Drug delivery can be improved for subjects with suboptimal MDI inhalation technique when using a spacer device with BGF MDI triple therapy. ClinicalTrials.gov identifier: NCT03311373. (*Clin Ther*. 2020;42:634–648) © 2020 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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Key words: chronic obstructive pulmonary disease, BGF, healthy volunteers, ICS/LAMA/LABA, pharmacokinetics, spacer device.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitations[1] and is a leading cause of mortality worldwide.[2] In 2017, COPD had a global prevalence of ~300 million cases,[3] was associated with ~3.2 million deaths,[2] and was ranked seventh as a leading cause of disability worldwide.

Treatment of COPD aims to improve symptoms and health status, and reduce the risk of COPD exacerbations.[4] For symptomatic patients requiring maintenance treatment of COPD, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommends initial therapy with long-acting muscarinic antagonists (LAMAs) and long-acting β_2-agonists (LABAs), as monotherapy or in combination (dual therapy).[4] For patients who remain symptomatic or who experience exacerbations despite treatment with dual therapy, maintenance treatment with triple combination therapy (an inhaled corticosteroid [ICS] plus an LAMA and LABA) is recommended.

To deliver inhaled therapy, most patients can use, or can be taught to use, an inhaler correctly; however, incorrect use can reduce the clinical benefit of treatment and may affect adherence to treatment.[5,6] With respect to metered dose inhalers (MDIs), facilitation of optimal use may require use of a valved holding chamber (spacer), a reservoir with a one-way valve allowing only airflow into a patient's mouth.[6] Use of spacers can also reduce the amount of drug that is deposited in the oropharynx and may improve lung deposition and bioavailability in patients who do not have optimal inhalation technique with an MDI alone.[6]

Budesonide/glycopyrrolate/formoterol fumarate MDI (BGF MDI) 320/18/9.6 μg is an ICS/LAMA/LABA triple fixed-dose combination formulated by using innovative co-suspension delivery technology. A recent Phase III, parallel-group, double-blind study (KRONOS) evaluated the efficacy and safety of triple therapy with BGF MDI in subjects with moderate-to-very severe COPD. Results showed that BGF MDI was well tolerated, improved lung function, and reduced COPD exacerbations compared with dual therapies (glycopyrrolate/formoterol fumarate [GFF] MDI and budesonide/formoterol fumarate MDI).[7] In the KRONOS study, BGF MDI was administered without the use of a spacer device, and subjects requiring use of a spacer were excluded from the study.

Pharmacokinetic (PK) parameters of BGF MDI have previously been characterized in healthy individuals, including Chinese and Japanese subjects.[8–11] However, in these prior studies, BGF MDI was administered without a spacer device. Given that use of a spacer can improve lung deposition, in addition to reducing oral deposition and therefore systemic bioavailability,[6] the objective of this Phase I study was to assess the effect of a spacer device on lung exposure, total systemic exposure, and safety of BGF MDI in healthy adult subjects.

SUBJECTS AND METHODS

Study Design

This Phase I, randomized, open-label, single-dose, crossover study was conducted at a single center in the United States between November 6, 2017, and December 15, 2017. The goal was to assess the PK and safety profiles of BGF MDI in healthy adult subjects with or without a spacer, and with or without oral charcoal (ClinicalTrials.gov: NCT03311373).

The study was conducted according to the ethical principles originating in the Declaration of Helsinki and compliance with the International Council for Harmonisation, Good Clinical Practice Guideline, and local regulatory requirements. The final study protocol and informed consent forms were reviewed and approved by the Institutional Review Board. All subjects provided written informed consent before entry into the study.

Inclusion and Exclusion Criteria

For inclusion in the study, male or female subjects were 18–40 years of age and were required to be in good general health as determined by a thorough medical history, physical examination, ECG, vital signs, and clinical laboratory evaluation. Results of screening laboratory tests must have been within the normal range or determined not to be clinically significant by the investigator. Subjects had to have

normal renal function as evidenced by an estimated glomerular filtration rate ≥90 mL/min, calculated by using the Chronic Kidney Disease Epidemiology Collaboration Equation.[12] Subjects must also have demonstrated correct MDI inhalation technique at screening.

Key exclusion criteria included: a history of smoking or the use of nicotine-containing products (self-reported) within 3 months of screening; any clinically significant medical illness that would have interfered with participation in this study; clinically significant anemia; a clinically significant abnormal 12-lead ECG at screening; treatment with any prescription or nonprescription drugs for 28 days or 5 half-lives before study drug use (whichever was longer); a positive alcohol breathalyzer or urine drug screen for drugs of abuse at screening, or at the beginning of each treatment period; any flu-like syndrome or other respiratory infections within 2 weeks of drug administration; or vaccination with an attenuated live virus within 4 weeks of drug administration.

Study Treatment

All eligible subjects were to receive a single dose of BGF MDI 320/36/9.6 μg (equivalent to budesonide/glycopyrronium/formoterol fumarate dihydrate 320/28.8/10 μg), administered as two inhalations of BGF MDI 160/18/4.8 μg, using four different regimens: regimen A, BGF MDI without spacer and no charcoal; regimen B, BGF MDI with the AeroChamber Plus Flow-Vu spacer (Forest Pharmaceuticals, Inc, St. Louis, MO, USA) and no charcoal; regimen C, BGF MDI without spacer and with charcoal; regimen D, BGF MDI with the AeroChamber Plus Flow-Vu spacer and with charcoal. The glycopyrrolate dose was higher than the dosage in clinical development (BGF MDI 320/18/9.6 μg) to ensure glycopyrronium blood concentrations were above the limit of quantitation.

For regimens C and D, activated charcoal in oral suspension form was given immediately before and after study drug dosing, and at 1 and 2 h postdose. At each time point, subjects received ~48 mL of the oral suspension (10 g) for mouth-rinsing and swallowing, followed by 30–60 mL of water for mouth-rinsing and swallowing.

Subjects were randomized to 1 of 8 regimen sequences (ABCD, ABDC, BACD, BADC, CDAB, CDBA, DCAB, or DCBA) on day 1 of treatment periods 1 to 4 (Figure 1) so that subjects received all four regimens (one regimen per treatment period). Randomization codes were assigned to subjects sequentially in ascending order.

Device training (pressurized MDI and, where applicable, spacer) was conducted during screening, on admission to each treatment period, and before dosing on day 1 of each treatment period. Study drug was administered in the morning at approximately the same time of day (±30 min) in each treatment period.

Subjects were required to fast for ≥6 h before treatment and until after the 4-h post-dose blood draw. A washout period of 5–14 days was included between each treatment period. A follow-up telephone call was conducted 5–7 days after treatment period 4 dosing or after the last dose of study drug (whichever was first) (Figure 1).

No concomitant medication (including herbal remedies, vitamin supplements, and over-the-counter products) was permitted, except paracetamol, acetaminophen, hormone replacement therapy, and systemic contraceptives.

Outcomes

PK Variables

The primary objectives of this study were to assess the total systemic exposure (without charcoal) and the lung exposure (with charcoal) of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer device, as determined by $AUC_{0-tlast}$ and the C_{max}.

The secondary objectives of this study were to characterize the PK profiles of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer device, and with and without oral charcoal. The following PK parameters were characterized: T_{max}, $AUC_{0-\infty}$, time to last measurable plasma concentration (t_{last}), termination elimination rate constant (λ_z), apparent terminal $t_{½}$, CL/F, and V_d/F.

Blood samples (~10 mL) for PK analysis were collected within 60 min before study drug dosing and then at 2, 6, 20, and 40 min and 1, 2, 4, 8, 12, and 24 h after dosing. Budesonide, glycopyrronium, and formoterol plasma concentrations were determined as previously described.[9]

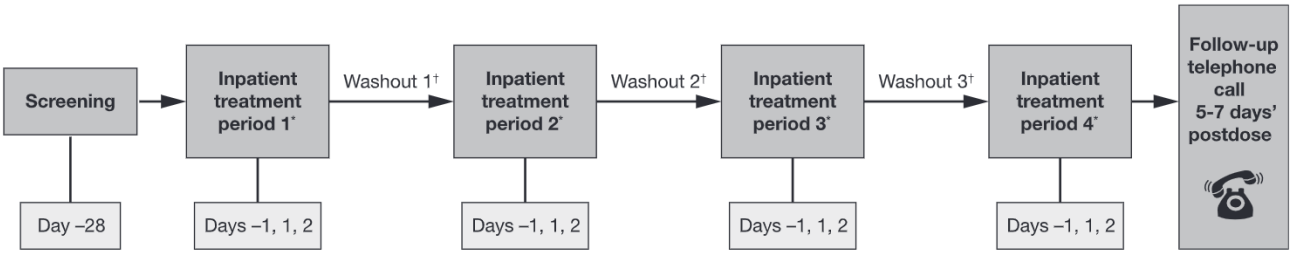

Figure 1. Study design. *Budesonide/glycopyrrolate/formoterol fumarate metered dose inhaler was administered in each treatment period with or without spacer, and with or without charcoal (4 regimens; 8 possible regimen sequences). †Five to 14 days between each treatment period.

Safety Profile

A secondary objective of this study was to assess the safety of single doses of BGF MDI. Assessments included treatment-emergent adverse events (TEAEs), physical examinations, vital signs, 12-lead ECGs, and clinical laboratory tests. Adverse events (AEs) were coded according to the Medical Dictionary for Regulatory Activities, version 20.1.

AEs were collected from the time of administration of the first dose of study drug to the time of the follow-up telephone call, study termination, or study exit. A full physical examination was conducted at screening and on day 2 of treatment period 4; a brief examination was also performed on day –1 of each treatment period. Vital signs, ECG, and clinical laboratory tests were obtained during screening, on day –1 (vital signs) and day 1 of each treatment period, and day 2 of treatment period 4.

Statistical Analysis

The sample size of the study was selected as it was estimated that ~56 enrolled subjects (47 study completers) would provide the precision to demonstrate a 1-sided 95% lower confidence bound for the geometric mean ratio (regimen D [BGF MDI with the spacer and with charcoal]/regimen C [BGF MDI without spacer and with charcoal]) >80% and a 1-sided 95% upper confidence bound for the geometric mean ratio (regimen B [BGF MDI with the spacer and no charcoal]/regimen A [BGF MDI without spacer and no charcoal]) <150%.

All subjects randomized to treatment who received ≥1 dose of BGF MDI were included in the safety population. The PK population included all subjects in the safety population for whom ≥1 primary PK parameter for a given analyte could be calculated and who had no important protocol deviations that may affect the analysis of the PK data.

PK parameters were calculated by using noncompartmental analysis of plasma concentration–time data. The $AUC_{0-tlast}$ and $AUC_{0-\infty}$ parameters were calculated by using a linear-up log-down trapezoidal method. $AUC_{0-\infty}$ was calculated as: $AUC_{0-\infty} = AUC_{last}$ + (last temporal quantifiable plasma concentration corresponding to t_{last} [C_{last}]/λ_z). The percentage of the AUC extrapolated was also calculated; for subjects for whom the extrapolated area was >20%, $AUC_{0-\infty}$ and parameter estimates dependent on $AUC_{0-\infty}$ (CL/F and Vd/F) were considered unreliable estimates and excluded from descriptive summaries. C_{max} and T_{max} were obtained from the observed values. Where feasible, λ_z was estimated for each subject by linear regression analysis, calculated from the slope of the terminal portion of the ln (drug concentration) versus time curve. The $t_{½}$ was calculated as $\ln 2/\lambda_z$. The CL/F was calculated as dose/$AUC_{0-\infty}$. Descriptive statistics for PK parameters of budesonide, glycopyrronium, and formoterol were summarized according to regimen and included: number of observations, mean %CV, SD, median, minimum, maximum, geometric mean, and geometric CV. For T_{max} and t_{last}, only the number of observations, mean, median, minimum, and maximum were provided. The treatment ratios of each test formulation (regimen B or regimen D) were compared with the reference formulations (regimen A or regimen C) for budesonide, glycopyrronium, and formoterol. Statistical analyses for total systemic

exposure (regimen B vs regimen A) and lung exposure (regimen D vs regimen C) were conducted separately.

Treatment comparisons of prespecified primary PK parameters were assessed on the difference of log-transformed C_{max}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$ of budesonide, glycopyrronium, and formoterol by using a 2-sided 90% CI approach based on an ANOVA model including period, sequence, regimen, and subject within sequence as fixed effects. Estimated geometric least squares means (LSM) ratios with 90% CIs were provided. To investigate the effect of the spacer on $AUC_{0-tlast}$ and C_{max}, summaries of the budesonide, glycopyrronium, and formoterol $AUC_{0-tlast}$ and C_{max} parameters according to exposure quartiles were presented. The quartile analysis was conducted by dividing the subjects into quartiles based on $AUC_{0-tlast}$ during no spacer treatment; $AUC_{0-tlast}$ and C_{max} values and the ratios for with:without spacer were summarized for each quartile. The assumption was that when BGF MDI was used without a spacer, subjects with low exposure (ie, quartiles 3 and 4) were likely to have suboptimal inhalation technique, while subjects with high exposure (ie, quartiles 1 and 2) were likely to have good inhalation technique. Safety and tolerability analyses were based on descriptive statistics for vital signs, laboratory measurements, frequencies of AEs (including any AEs based on ECG findings), and the number and proportion of subjects with AEs.

RESULTS

Subjects

In total, 158 subjects were screened, and 56 subjects were randomized to treatment. All randomized subjects received ≥1 dose of study drug and were included in the PK and safety populations. Overall, 47 (83.9%) subjects completed the study, and 9 subjects (16.1%) withdrew from the study. Reasons for study withdrawal were subject discretion (n = 3), protocol-specified withdrawal criteria (n = 3; all owing to a positive drug screen), AE, investigator decision, and subject lost to follow-up (n = 1 each). Subject disposition across treatment regimens is shown in Figure 2.

The mean age of subjects was 29.9 years, and the majority were male (60.7%) and black or African American (83.9%) (Table I). Overall, 17.9% were

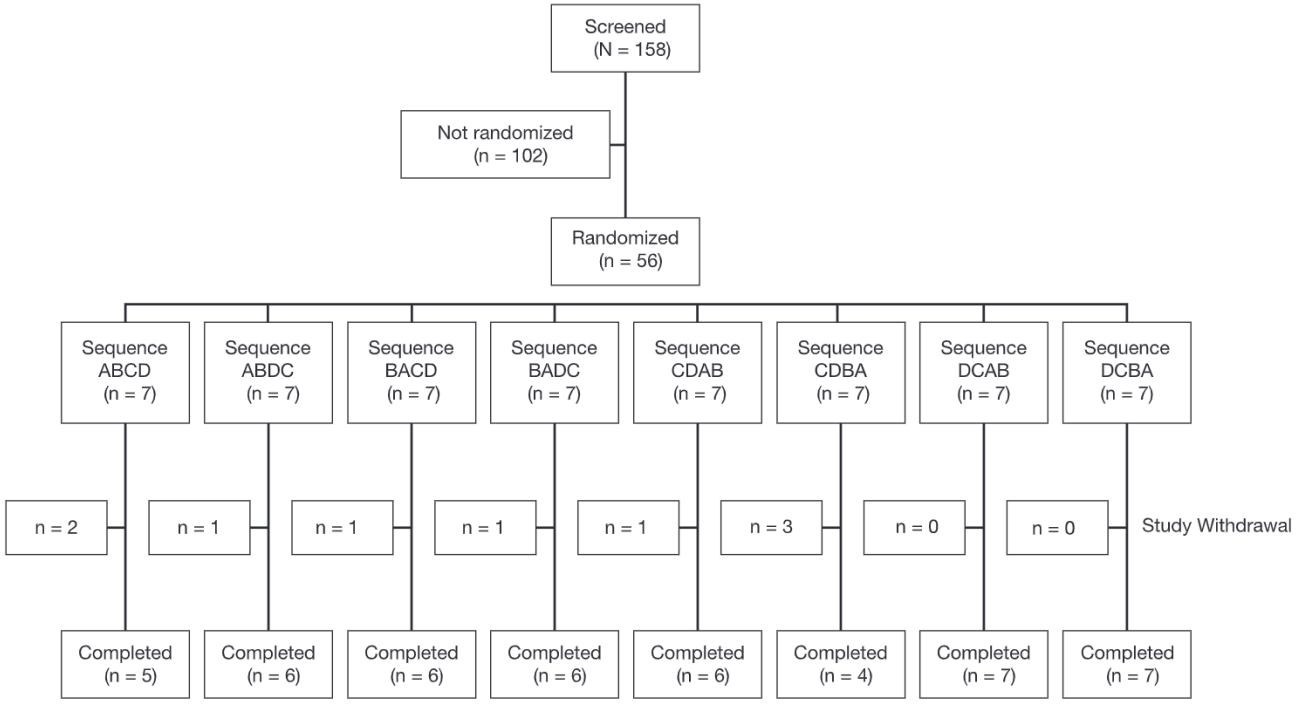

Figure 2. Subject distribution.

former smokers, with an average smoking history of 11.5 years. The mean body mass index was 27.8 kg/m^2.

PK Variables

Plasma Concentration—Time Profiles

Plasma concentrations of budesonide, glycopyrronium, and formoterol after single-dose administration of BGF MDI with and without a spacer, and with and without charcoal, increased quickly after inhalation (Figure 3). T_{max} was 0.33, 0.03, and 0.10 h for budesonide, glycopyrronium, and formoterol, respectively, (Figure 3) and was the same for each regimen (with and without a spacer, and with and without charcoal) (Table II). Plasma concentrations declined quickly for glycopyrronium and formoterol compared with budesonide (Figure 3). Other PK parameters are summarized in Table II.

Effect of the Spacer Device on Systemic Exposure (Without Charcoal)

A statistical comparison of PK parameters with and without a spacer device, and with and without charcoal, is provided in Table III. After BGF MDI treatment, budesonide geometric LSM for C_{max}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$were ~1.3- to 1.5-fold higher with a spacer device versus without a spacer device. Glycopyrronium geometric LSM for C_{max} and $AUC_{0-tlast}$ were 2.4- and 1.5-fold higher, respectively, with a spacer device versus without a spacer device. Formoterol systemic exposure was comparable with and without a spacer for $AUC_{0-tlast}$ and $AUC_{0-\infty}$, and 1.7-fold higher for C_{max} with a spacer.

Table I. Demographic characteristics (safety population).

Parameter	All Subjects (N = 56)
Age, mean (SD) [min, max], y	29.9 (5.3) [20, 40]
Male sex	34 (60.7%)
Race	
Black/African American	47 (83.9%)
White	7 (12.5%)
Asian/other	2 (3.6%)
Smoking status	
Nonsmoker	46 (82.1%)
Former smoker	10 (17.9%)
No. of years smoked, mean (SD)*	11.50 (7.04)
BMI, mean (SD) [min, max], kg/m^2	27.8 (4.3) [19.9, 38.8]

BMI = body mass index; max = maximum; min = minimum.
* Former smokers only.

Effect of the Spacer Device on Lung Exposure (With Charcoal)

Budesonide lung exposure (determined by geometric LSM for C_{max}, $AUC_{0-tlast}$, and $AUC_{0-\infty}$) was ~2-fold higher after treatment with BGF MDI with a spacer versus without a spacer device (Table III). For glycopyrronium, lung exposure was 2.6- to 3.7-fold higher for C_{max} and $AUC_{0-tlast}$, respectively, with a spacer device versus without a spacer device. Formoterol lung exposure was higher with a spacer device versus without a spacer device (2.2-fold higher for C_{max} and 3.9-fold higher for $AUC_{0-tlast}$).

PK by Exposure Quartile

Median C_{max} and $AUC_{0-tlast}$ parameters were analyzed according to total systemic and lung exposure quartiles based on $AUC_{0-tlast}$ during no spacer treatment (Figure 4). For subjects with high exposure to budesonide (quartiles 1 and 2) without the use of a spacer, there was a minimal change in total systemic exposure with a spacer. For subjects with low exposure (quartiles 3 and 4), a more considerable increase in total systemic exposure was noted with a spacer versus without a spacer. Quartile analysis of budesonide lung exposure followed a pattern similar to budesonide systemic exposure, with C_{max} and $AUC_{0-tlast}$ values showing the greatest increases with a spacer in subjects with low exposure without a spacer (quartiles 3 and 4).

For glycopyrronium, the use of a spacer was associated with minimal changes in total systemic and lung exposure for subjects in quartiles 1 and 2. Subjects with low exposure without a spacer (quartiles 3 and 4) had a greater increase in total systemic and lung exposure when a spacer was used compared with those in quartile 1.

For formoterol, subjects with the highest exposure without a spacer (quartile 1) had a decrease in total systemic exposure and lung exposure in terms of

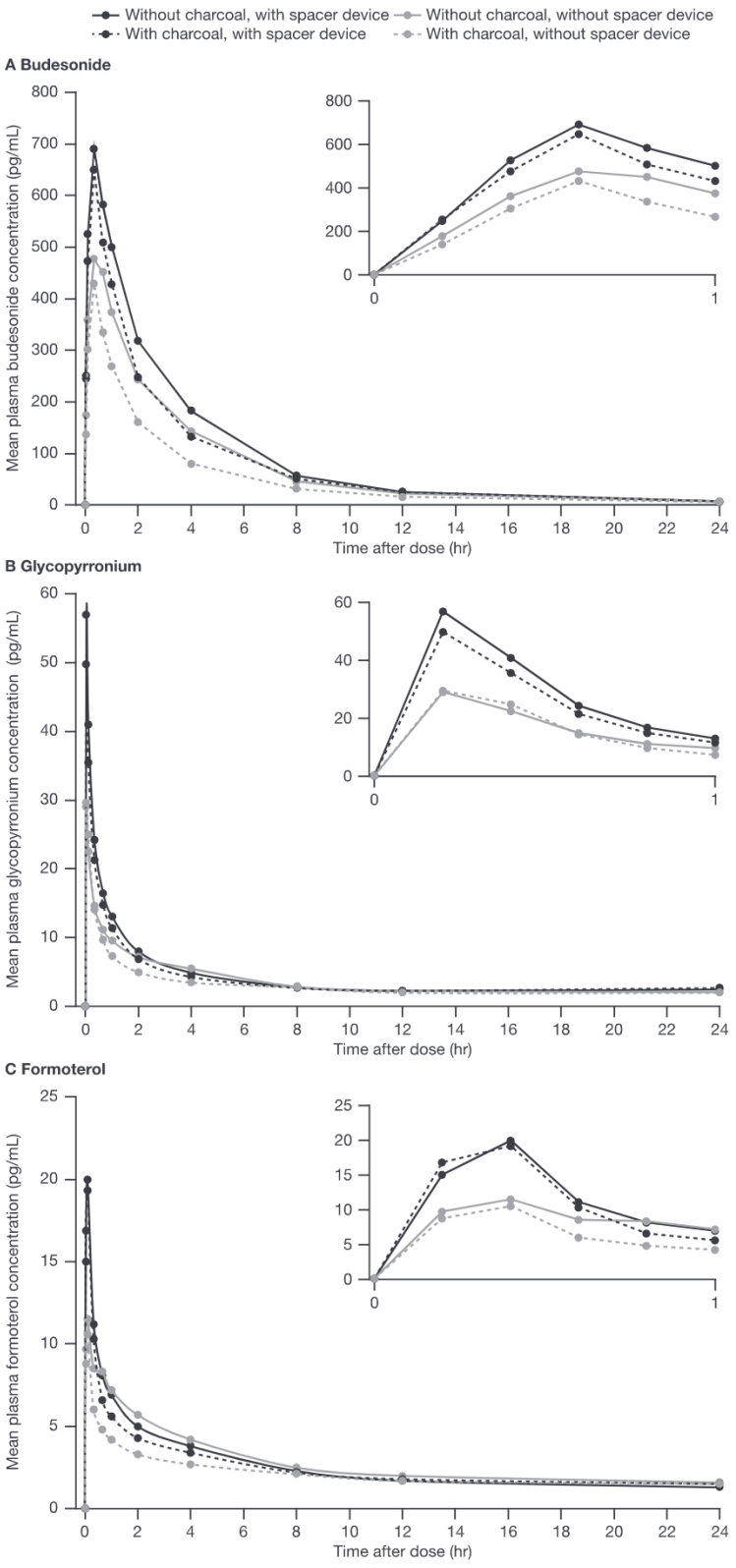

Figure 3. Mean plasma concentration–time profile after single-dose administration of (A) budesonide, (B) glycopyrronium, and (C) formoterol (linear-linear scale; pharmacokinetic population).

$AUC_{0-tlast}$ when the spacer was used, with similar C_{max} values. For subjects in quartile 2, systemic exposure was relatively unchanged; however, there was a modest increase in lung exposure with the use of a spacer. For subjects with low exposure without a spacer (quartiles 3 and 4), increases in total systemic exposure and lung exposure were observed when a spacer was used.

Safety Profile

Overall, the incidence of TEAEs was higher in subjects receiving charcoal-containing regimens (13.5% with spacer and 9.6% without spacer) than in subjects receiving non-charcoal-containing regimens (7.5% with spacer and 7.7% without spacer) (Table IV). TEAEs according to preferred term, which were reported by >1 subject per regimen, were headache, cough, and dizziness. All reported TEAEs were mild or moderate in intensity. Events of headache (4 events), dizziness (3 events), nausea (2 events), and cough (1 event) were considered by the investigator to be related to study treatment. No deaths or other serious AEs were reported. One subject had TEAEs of headache and presyncope that led to withdrawal from the study but they were considered unrelated to study treatment. No clinically meaningful changes were observed in laboratory parameters, vital signs, or ECGs.

DISCUSSION

This Phase I, randomized, open-label, crossover study was conducted in healthy adult subjects. The aim was to characterize the PK and safety profiles of BGF MDI 320/36/9.6 μg (administered as two actuations of 160/18/4.8 μg) after single administration with and without a spacer device, and with and without concomitant activated oral charcoal, to estimate lung and total systemic exposure, respectively.

The PK parameters of BGF MDI administered without a spacer device have previously been characterized in healthy adult subjects.[8–11] The findings of the present study suggest that, in healthy adults, administration of BGF MDI 320/36/9.6 μg with an AeroChamber Plus Flow-Vu spacer device results in greater total systemic exposure of budesonide and glycopyrronium and greater lung exposure of budesonide, glycopyrronium, and formoterol compared with administration of BGF MDI without a spacer device. Lower exposures of budesonide, glycopyrronium, and formoterol were observed with the use of charcoal versus no charcoal, which indicated that gastrointestinal absorption contributed to systemic bioavailability of each component.

Importantly, the results of the quartile analysis showed that subjects with the lowest drug exposure without a spacer had the greatest increases in both total systemic and lung exposure when a spacer was used. Although not specifically assessed, the low drug exposure without a spacer was likely due to suboptimal inhalation technique.

Also, with a spacer, the increase in lung exposure, which reflects increased lung delivery, was greater than total systemic exposure, which is consistent with an increase in lung delivery and a decrease in oral absorption with the use of a spacer. Formoterol has the highest oral availability of the 3 drugs,[8] and use of the spacer will prevent a large proportion of the particles being deposited both orally and in the gastrointestinal tract when inhalation technique is suboptimal, reducing the variability seen in systemic exposure $AUC_{0-tlast}$. When the MDI was used with the spacer, inhalation into the lungs was optimized. Together, these results suggest that use of a spacer device reduced the oral absorption of BGF MDI in favor of improved lung delivery in subjects with suboptimal inhalation technique.

The increase in bioavailability of budesonide, glycopyrronium, and formoterol with a spacer may be partly due to greater lung delivery and less oropharyngeal delivery with the spacer device; this may be particularly important for those with suboptimal inhalation technique. It is important to note that the resulting exposure levels with the use of a spacer were within the range of levels observed in subjects with the highest exposure (ie, those considered to have good inhalation technique without a spacer); this indicates that use of a spacer device may increase drug delivery in subjects with suboptimal inhalation technique without resulting in any safety concerns because exposure levels did not exceed those seen in subjects who used the device optimally without a spacer.

The results of this study also reinforce the need for ongoing education on the correct use of inhalation devices. Results of a systematic literature review showed that educational interventions have a positive effect on inhaler technique (regardless of device type)

Table II. Budesonide, glycopyrronium, and formoterol pharmacokinetic parameters according to regimen (pharmacokinetic population). Data shown are geometric mean (%CV) except for T_{max} and time to last measurable plasma concentration (t_{last}), which are median (minimum, maximum).

Variable	Total Systemic Exposure (Without Charcoal)		Lung Exposure (With Charcoal)	
	With Spacer	Without Spacer	With Spacer	Without Spacer
Budesonide				
n	52	52	52	52
$AUC_{0-tlast}$, h · pg/mL	1934 (54.9)	1453 (66.0)	1619 (74.9)	823.9 (121.2)
C_{max}, pg/mL	702.3 (46.4)	452.6 (74.6)	612.0 (74.0)	340.0 (117.1)
T_{max}, h	0.33 (0.10, 1.00)	0.33 (0.10, 2.00)	0.33 (0.10, 1.00)	0.33 (0.10, 2.00)
$AUC_{0-\infty}$, h · pg/mL	2132 (40.9)*	1492 (64.4)†	1806 (39.1)*	955.2 (88.5)‡
t_{last}, h	24.00 (1.00, 24.18)	24.00 (8.00, 24.17)	24.00 (4.00, 24.10)	12.00 (4.00, 24.17)
λ_z, 1/h	0.16 (31.9)*	0.16 (35.6)†	0.16 (33.6)§	0.19 (33.4)‡
$t_{½}$, h	4.2 (31.9)*	4.3 (35.6)†	4.3 (33.6)§	3.6 (33.4)‡
CL/F, L/h	150.1 (40.9)*	214.5 (64.4)†	177.2 (39.1)*	335.0 (88.5)‡
Vd/F, L	918.5 (45.7)*	1325 (58.1)†	1103 (39.6)*	1758 (68.4)‡
Glycopyrronium				
n	52	52	51	51
$AUC_{0-tlast}$, h · pg/mL	74.3 (96.4)	48.1 (122.4)	69.2 (85.2)	19.8 (325.0)
C_{max}, pg/mL	47.7 (73.3)	19.0 (131.0)	42.1 (65.4)	17.1 (181.7)
T_{max}, h	0.03 (0.03, 0.67)	0.03 (0.03, 4.00)	0.03 (0.03, 0.10)	0.03 (0.03, 0.67)
$AUC_{0-\infty}$, h · pg/mL	40.4 (49.6)‖	65.9 (44.7)¶	39.2 (96.5)#	15.2 (54.5)#
t_{last}, h	24.00 (1.00, 24.18)	24.00 (4.00, 24.17)	24.00 (2.00, 24.12)	4.03 (0.67, 24.17)
λ_z, 1/h	0.35 (102.2)#	0.15 (93.4)**	0.25 (99.7)††	0.45 (146.3)‡‡
$t_{½}$, h	2.0 (102.2)#	4.7 (93.4)**	2.7 (99.6)††	1.5 (146.3)‡‡
CL/F, L/h	712.9 (49.6)‖	436.9 (44.7)¶	734.7 (96.5)#	1889 (54.5)#
Vd/F, L	3028 (19.8)‖	2380 (46.6)¶	3510 (28.7)#	3561 (28.8)#
Formoterol				
n	52	52	51	51
$AUC_{0-tlast}$, h · pg/mL	35.9 (97.5)	37.0 (88.7)	33.1 (71.3)	8.9 (471.8)
C_{max}, pg/mL	18.1 (58.4)	10.8 (66.3)	17.9 (48.1)	8.3 (98.6)
T_{max}, h	0.10 (0.03, 0.67)	0.10 (0.03, 4.00)	0.10 (0.03, 0.33)	0.10 (0.03, 0.67)
$AUC_{0-\infty}$, h · pg/mL	63.2 (37.1)§§	62.7 (62.2)‖‖	62.0 (42.2)¶¶	62.6 (55.0)¶
t_{last}, h	12.00 (0.33, 24.07)	12.00 (2.00, 24.02)	12.00 (4.00, 24.10)	4.02 (0.10, 24.05)
λ_z, 1/h	0.12 (33.6)‡	0.13 (53.0)##	0.12 (37.9)##	0.15 (111.0)***

Table II. (*Continued*)

Variable	Total Systemic Exposure (Without Charcoal)		Lung Exposure (With Charcoal)	
	With Spacer	Without Spacer	With Spacer	Without Spacer
$t_{½}$, h	5.8 (33.6)[‡]	5.2 (53.0)[##]	5.6 (37.9)[##]	4.5 (111.0)[***]
CL/F, L/h	152.0 (37.1)[§§]	153.1 (62.2)[‖‖]	154.9 (42.2)[¶¶]	153.3 (55.0)[¶]
Vd/F, L	1137 (30.5)[§§]	1033 (23.5)[‖‖]	1195 (31.8)[¶¶]	1357 (22.4)[¶]

*n = 49.
†n = 51.
‡n = 48.
§n = 50.
‖n = 5.
¶n = 4.
#n = 7.
**n = 15.
††n = 9.
‡‡n = 22.
§§n = 20.
‖‖n = 18.
¶¶n = 11.
##n = 41.
***n = 31.

Table III. Statistical comparisons of pharmacokinetic (PK) parameters for budesonide, glycopyrronium, and formoterol by regimen with/without a spacer, and with/without charcoal (PK population).

Parameter	Total Systemic Exposure (Without Charcoal)					Lung Exposure (With Charcoal)				
	n	With Spacer, Geometric LSM	Without Spacer, Geometric LSM	With:Without Spacer Ratio (90% CI)*	Intrasubject %CV†	n	With Spacer, Geometric LSM	Without Spacer, Geometric LSM	With:Without Spacer Ratio (90% CI)*	Intrasubject %CV†
Budesonide										
$AUC_{0-tlast}$, h • pg/mL	49	2020	1521	132.8 (115.2–153.1)	43.6	51	1610	811.2	198.4 (160.3–245.7)	71.5
$AUC_{0-\infty}$, h • pg/mL	48	2135	1573	135.8 (119.0–154.9)	39.8	45	1854	952.0	194.8 (165.8–228.8)	47.8
C_{max}, pg/mL	49	714.6	470.3	152.0 (130.3–177.2)	47.5	51	614.8	334.8	183.6 (150.4–224.2)	65.9
Glycopyrronium										
$AUC_{0-tlast}$, h • pg/mL	49	78.73	50.90	154.7 (123.7–193.4)	73.4	49	74.19	19.84	373.9 (271.1–515.8)	120.7
$AUC_{0-\infty}$, h • pg/mL	1	NA	NA	NA	NA	3	NA	NA	NA	NA
C_{max}, pg/mL	49	47.48	19.74	240.6 (189.2–305.9)	80.2	49	44.71	17.07	262.0 (200.9–341.5)	91.8
Formoterol										
$AUC_{0-tlast}$, h • pg/mL	49	37.16	37.69	98.60 (83.05–117.1)	53.8	49	33.35	8.66	385.2 (267.7–554.3)	147.0
$AUC_{0-\infty}$, h • pg/mL	10	73.46	66.29	110.8 (80.75–152.1)	38.6	3	NA	NA	NA	NA
C_{max}, pg/mL	49	18.15	10.96	165.6 (140.7–195.0)	50.7	49	18.55	8.32	222.9 (186.6–266.4)	56.3

LSM = least squares means; NA = not applicable, no estimate obtained given too few data.

* Ratio (expressed as %) of exponentiated mean difference of log-transformed PK parameter. CI from the ANOVA model with period, sequence, regimen, and subject within sequence as fixed effects.

† 100 * sqrt[exp(residual variance) − 1].

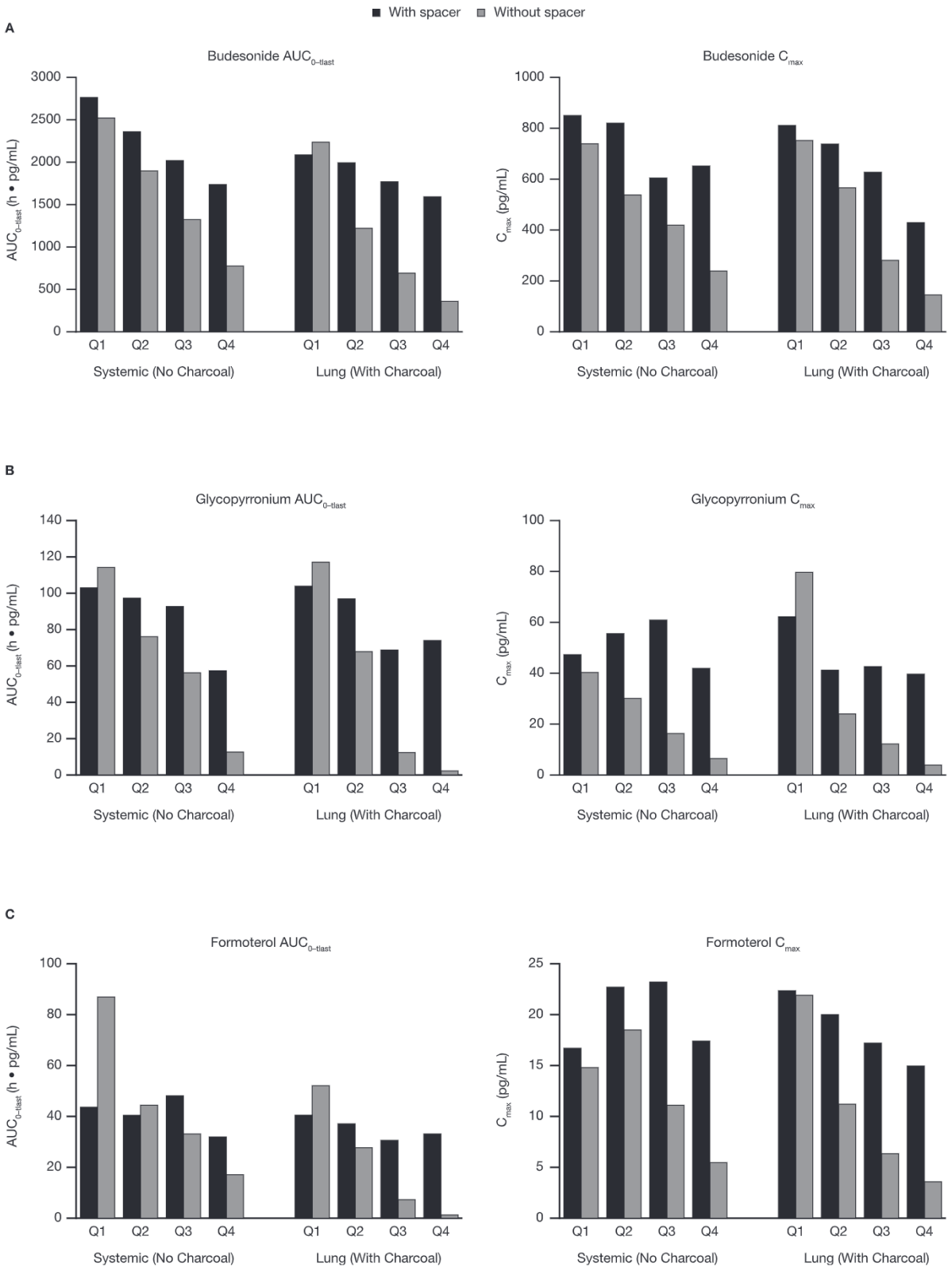

Figure 4. Median pharmacokine1tic parameters by exposure quartile for (A) budesonide, (B) glycopyrronium, and (C) formoterol (pharmacokinetic population). Q1 = quartile 1; Q2 = quartile 2; Q3 = quartile 3; Q4 = quartile 4.

Table IV. Summary of treatment-emergent adverse events (AEs) according to regimen with/without a spacer, and with/without charcoal (safety population). Data are given as no. (%).

Variable	Without Charcoal		With Charcoal	
	With Spacer (n = 53)	Without Spacer (n = 52)	With Spacer (n = 52)	Without Spacer (n = 52)
Subjects with ≥1 AE	4 (7.5)	4 (7.7)	7 (13.5)	5 (9.6)
Subjects with treatment-related AEs	3 (5.7)	0	3 (5.8)	1 (1.9)
Subjects with AE leading to early withdrawal	1 (1.9)	0	0	0
Subjects with serious AEs	0	0	0	0
Deaths	0	0	0	0
Headache	3 (5.7)	1 (1.9)	2 (3.8)	2 (3.8)
Cough	0	0	2 (3.8)	2 (3.8)
Dizziness	2 (3.8)	0	0	1 (1.9)
Nausea	1 (1.9)	0	1 (1.9)	0
Abdominal pain upper	0	1 (1.9)	0	0
Diarrhea	1 (1.9)	0	0	0
Epistaxis	0	0	1 (1.9)	0
Feces discolored	0	1 (1.9)	0	0
Hot flush	0	1 (1.9)	0	0
Muscle spasms	0	0	0	1 (1.9)
Oropharyngeal pain	0	0	0	1 (1.9)
Presyncope	1 (1.9)	0	0	0
Somnolence	0	0	1 (1.9)	0
Throat irritation	0	0	1 (1.9)	0

in patients with COPD. Specifically, the effectiveness of educational interventions can be predicted by a patient's initial technique and the time since the intervention but not the inhaler type used,[13] suggesting that ongoing training is important for everyone using inhaler devices.

BGF MDI 320/36/9.6 μg was well tolerated, and no new or unexpected safety signals were observed during the study. All TEAEs were mild or moderate in intensity, and only 1 subject withdrew due to an AE, which was not considered related to study treatment. The use of a spacer device did not appreciably alter the AE profile of BGF MDI relative to its use without a spacer device.

A previous open-label Phase I study evaluated the effect of a spacer on the PK and safety profiles of dual therapy with budesonide/formoterol MDI in healthy subjects.[14] Consistent with this study, the use of a spacer was shown to increase the bioavailability of budesonide/formoterol in subjects with suboptimal inhalation technique to a level similar to those with good inhalation technique without a spacer.[14] Moreover, a previous open-label Phase III study in adult subjects with COPD who were treated with GFF MDI, a dual LAMA/LABA fixed-dose combination that uses the same co-suspension delivery technology as BGF MDI, found that the bronchodilator effects (based on forced expiratory volume in 1 s AUC_{0-12} and other lung function end points) of GFF MDI were similar with and without the AeroChamber Plus Flow-Vu spacer.[15] Overall, across a range of good and suboptimal inhalation techniques, the therapeutic effects of GFF MDI remained consistent and were not enhanced when lung delivery was improved after spacer use.[11]

One limitation of this analysis is the small number of subjects enrolled and the inclusion of healthy subjects rather than patients with COPD; however, this is a standard approach for Phase I studies and enables differences in drug exposure to be evaluated without the potential for confounding effects of airway disease. Such effects can either obscure between-treatment differences or lead to the detection of variations that are artifacts.[16] It may be possible to achieve increased sensitivity to detect between-treatment differences in healthy subjects with normal lung function owing to greater peripheral lung deposition compared with patients with COPD. Moreover, healthy subjects are likely to have had less prior experience using inhaler devices than patients with COPD; this potential limitation is mitigated, however, by the exclusion of subjects who were unable to demonstrate a correct technique. An additional limitation of the study is the use of one type of spacer, which may limit the generalizability of the findings. However, the spacer used in the present study is widely available and commonly used.[15]

CONCLUSIONS

The results of this Phase I randomized study in healthy subjects show that, for subjects who likely had suboptimal inhalation technique, administration of BGF MDI 320/36/9.6 μg with an AeroChamber Plus Flow-Vu spacer device resulted in greater total systemic and lung exposure of budesonide and glycopyrronium and greater lung exposure of formoterol, compared with administration of BGF MDI without a spacer device. For subjects who likely had suboptimal inhalation technique, using the spacer device improved drug exposures so that they were similar to those achieved by subjects who likely had good inhalation technique without the use of a spacer device. These results indicate that BGF MDI can be administered safely and effectively with a spacer device and that use of BGF MDI with a spacer device can improve drug delivery to the lungs in subjects with suboptimal inhalation technique.

DISCLOSURES

Dr. Dorinsky and Mr Gillen are employees of AstraZeneca and hold stock and/or stock options in the company. Ms. Trivedi and Dr. Darken are employees of AstraZeneca. Dr. DeAngelis is a former employee of AstraZeneca and holds stock and/or stock options in the company. Dr. DePetrillo is an employee of Pharmaron CPC.

Employees of AstraZeneca were involved in various aspects of the conception and design of the studies, acquisition of data, analysis and interpretation of data, and input into manuscript development. The sponsor did not place any restrictions on authors about the statements made in the final article.

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at: https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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All authors contributed to the conception and design of the analysis, data acquisition, data analysis, and interpretation. All authors contributed to the drafting of the article, were involved in critically revising the manuscript for important intellectual content, and approved the final version for publication. All authors agree to be accountable for all aspects of the work and ensure that questions related to the accuracy or integrity of the work were investigated appropriately and resolved.

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