Pharmacokinetics and Tolerability of Budesonide/Glycopyrronium/Formoterol Fumarate Dihydrate and Glycopyrronium/Formoterol Fumarate Dihydrate Metered Dose Inhalers in Healthy Chinese Adults: A Randomized, Double-blind, Parallel-group Study

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ABSTRACT

Purpose: The objective of this study was to assess pharmacokinetic (PK) and safety profiles of 2 fixed-dose combinations in development for the treatment of chronic obstructive pulmonary disease (COPD): budesonide/glycopyrronium/formoterol fumarate dihydrate metered-dose inhaler (BGF MDI; triple combination) and glycopyrronium/formoterol fumarate dihydrate (GFF MDI; dual combination). The PK and safety profiles of BGF MDI and GFF MDI were assessed for the first time in healthy Chinese adults after single and repeated (7-day) dosing.

Methods: This Phase I, randomized, double-blind, parallel-group study was conducted at a single site in Shanghai, China. Male or female Chinese subjects, 18−45 years of age and in good general health, were randomized 1:1:1 to receive BGF MDI 320/14.4/10 μg, BGF MDI 160/14.4/10 μg, or GFF MDI 14.4/10 μg. PK parameters were assessed after a single dose (day 1) and at steady state (day 8), and included AUC_{0-12}, C_{max}, and T_{max}. Tolerability was assessed using physical examination findings, adverse events reporting, 12-lead ECG, vital signs, and clinical laboratory values.

Findings: Ninety-six subjects (mean age, 25.6 years; 83.3% male) were randomized and received treatment. All randomized subjects were included in the safety and PK populations. After single and repeated dosing, budesonide AUC_{0-12} and C_{max} were increased dose proportionally from BGF MDI 160/14.4/10 μg to BGF MDI 320/14.4/10 μg, respectively (single dose: AUC_{0-12}, 811.8 vs 1748 h · pg/mL; C_{max}, 224.3 vs 459.3 pg/mL; repeated dosing: AUC_{0-12}, 1250 vs 2510 h · pg/mL; C_{max}, 315.4 vs 626.4 pg/mL). After single and repeated dosing, glycopyrronium AUC_{0-12} and C_{max} were similar across all treatments (single dose: AUC_{0-12}, 27.20−29.40 h · pg/mL; C_{max}, 4.884−5.674 pg/mL; repeated dosing: AUC_{0-12}, 69.49−77.08 h · pg/mL; C_{max}, 11.30−13.12 pg/mL) and formoterol (single dose: AUC_{0-12}, 46.49−53.58 h · pg/mL; C_{max} 9.651−10.62 pg/mL; repeated dosing: AUC_{0-12}, 81.94−85.32 h · pg/mL; C_{max}, 16.13−17.71 pg/mL), suggesting that the addition of budesonide did not appreciably alter the PK properties of GFF MDI. All treatment-emergent adverse events were mild in severity and rates were similar across groups (range, 50.0%−56.3%). There were no new or unexpected findings on tolerability.

Implications: Overall, all treatments were well tolerated and PK parameters were generally comparable to those previously reported in Western and Japanese healthy subjects, suggesting that the doses of BGF MDI and GFF MDI in development globally for COPD are also appropriate for Chinese patients with COPD. ClinicalTrials.gov identifier: NCT03075267. (*Clin Ther*. 2019;41:897−909)

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Key words: budesonide, chronic obstructive pulmonary disease, co-suspension delivery technology, formoterol fumarate, glycopyrrolate, pharmacokinetics.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) represents an important public health challenge worldwide. [1] In China, COPD affected an estimated 99.9 million people (corresponding to 8.6% of adults aged 20 years or older) in 2015. [2] The prevalence was higher (almost 14%) in adults aged ≥40 years. [2,3] COPD is the fifth leading cause of death in China (2016 data), [4] and Chinese patients account for approximately one third of deaths worldwide from the disease (2013 data). [5] However, data from a cross-sectional survey in 2014–2015 showed that only a small percentage (11.7%) of Chinese patients with COPD were receiving treatment. [3].

Recommended treatments for COPD are based on symptom burden and exacerbation history, and include bronchodilators (long-acting muscarinic antagonists [LAMAs] and long-acting β_2 agonists [LABAs]) and inhaled corticosteroids (ICSs). Dual combination therapies (ICS/LABA or LAMA/LABA) are important treatment options in patients with high symptom burden or exacerbation history. [6] In symptomatic patients with a high exacerbation risk who experience further exacerbations on a LAMA/LABA combination, or further exacerbations or symptoms on a ICS/LABA combination, the use of ICS/LAMA/LABA triple therapy is recommended and may provide additional benefit over dual therapies in improving lung function and patient-reported outcomes, and/or in reducing exacerbations in these patients. [6–8].

The dual LAMA/LABA glycopyrronium/formoterol fumarate dihydrate 14.4/10 μg metered-dose inhaler (GFF MDI*), formulated using co-suspension delivery technology, is the first LAMA/LABA fixed-dose combination delivered via MDI, and has been shown to be efficacious and well tolerated in patients with COPD in pivotal Phase III studies. [9–11] Budesonide/glycopyrronium/formoterol fumarate dihydrate triple fixed-dose combination therapy (BGF MDI), an ICS/LAMA/LABA delivered via MDI using the same co-suspension delivery technology, is currently in clinical development globally for the treatment of COPD, with 1 pivotal Phase III study completed. [7] BGF MDI was reported to improve lung function compared with the corresponding ICS/LABA and LAMA/LABA (GFF MDI) therapies and significantly reduce exacerbations compared with GFF MDI. [7].

The efficacy of inhaled COPD treatments is associated with the presence of the drug in the lungs [12]; however, absorption into the systemic circulation may elicit additional pharmacologic effects that could influence the safety and tolerability profile of the drug. [13] Previous studies have found that the pharmacokinetic (PK) profiles of BGF MDI and GFF MDI were comparable between Western and Japanese healthy adults. [14–17] However, to date, the PK profiles of these medications have not been assessed in Chinese subjects. Thus, the aim of this study was to examine the PK profiles and the tolerability of 2 doses of BGF MDI and 1 dose of GFF MDI in healthy Chinese adults after single and repeated (7-day) dosing.

SUBJECTS AND METHODS

Subjects

Subjects were male or female Chinese adults aged 18–45 years, who had a weight of ≥50 kg and a body mass index of 19–24 kg/m^2 at screening. Eligible subjects were in good general health as determined by medical history, physical examination, ECG, vital signs, and clinical laboratory evaluation. Complete blood cell count, serum creatinine, electrolytes, serum glucose, aspartate aminotransferase, alanine aminotransferase, and total bilirubin were required to be within normal ranges or deemed to be not clinically significant by the Investigator or medically qualified designee.

Exclusion criteria included a clinically significant medical illness that would interfere with study participation, a chronic medical condition that required ongoing treatment with medication, and clinically significant chest X-ray or ECG abnormalities. Major surgical interventions were not permitted within 4 weeks of treatment day 1, and minor surgical interventions were not permitted within 2 weeks of treatment day 1. Subjects must not

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have smoked, or used electronic cigarettes or nicotine-containing products, within 3 months prior to screening. Subjects who had a history of substance-related disorders, those who had used an illicit drug within 1 year prior to screening, and those who had an alcohol breathalyzer or urine screen positive for an illicit drug at screening or at inpatient admission were excluded.

Study Design

This Phase I, double-blind, parallel-group study (ClinicalTrials.gov identifier: NCT03075267) was conducted at a single site in Shanghai, China. Following the screening period from days −28 to −2, subjects were admitted as inpatients on day −1. On day 1, subjects were randomized, in a 1:1:1 ratio using an envelope-based randomization system, to receive BGF MDI 320/14.4/10 μg, BGF MDI 160/14.4/10 μg, or GFF MDI 14.4/10 μg (equivalent to glycopyrrolate/formoterol fumarate 18/9.6 μg). The study staff, subjects, and investigators were blinded to the treatment allocation. BGF MDI and GFF MDI were identical in form and function and indistinguishable from each other.

Subjects were required to fast for at least 8 hours prior to the scheduled blood draws at screening, inpatient admission, and 24 hours postdose on treatment day 8. Standardized meals were provided at specific times, but no restrictions were placed on clear fluid intake. Subjects were not permitted to consume grapefruit or grapefruit juice during the study, or xanthine-containing foods, beverages, or medications for at least 6 hours prior to and for the duration of each study visit. Smoking or the use of illicit drugs was prohibited during the study. Use of medications within 30 days or 5 half-lives prior to screening (for investigational therapies) or prior to day 1 of treatment (for any other prescription or nonprescription medications) was prohibited. Permitted exceptions were acetaminophen at a dose of ≤2 g/d, if deemed necessary by the Investigator, and oral/implanted contraceptives. Other medication deemed necessary for the safety and well-being of the subjects could be administered at the discretion of the investigator.

Subjects received treatment as a single dose on the morning of day 1, twice-daily doses (morning and evening, ~12 hours apart) on days 2−7, and a single dose on the morning of day 8, administered as 2 inhalations per dose at approximately the same times each day. At screening, admission, and before study medication dosing on days 1 and 8, subjects were instructed on the proper use of an MDI and were required to demonstrate the ability to use the device correctly. To prevent possible cross-contamination, all MDIs were primed in a separate room, away from the subject treatment area; only 1 subject was permitted in the inhalation room at any given time; and blood sampling for the study of drug inhalation took place in a separate room. Cannulation sites were covered with bandages while subjects were in the inhalation room. Both subjects and study personnel were required to wear gloves while handling the inhalers, and subjects were also required to wear a surgical mask for ~30 minutes before and after dosing in order to prevent spread of study drug to the blood collection equipment via skin contact or exhalation of study drug. Subjects were discharged on the morning of day 9. A follow-up phone call was carried out 5−7 days following the final dose of study treatment.

This study was conducted in accordance with the ethics principles that have their origin in the Declaration of Helsinki and that are consistent with International Conference on Harmonisation/Good Clinical Practice guidelines, and applicable regulatory requirements. The Ethics Committee of Shanghai Xuhui District Central Hospital approved the protocol and informed consent form (approval number 2016-34). Subjects provided written informed consent prior to the start of the study.

Pharmacokinetic Assessments

The primary objective of this study was to assess the budesonide, glycopyrronium, and formoterol PK profiles of BGF MDI 320/14.4/10 μg and BGF MDI 160/14.4/10 μg, and the glycopyrronium and formoterol PK profiles of GFF MDI 14.4/10 μg, in healthy Chinese subjects. On treatment day 1 (single dose) and day 8 (steady state), ~6 mL of whole blood was collected within 60 minutes predose, and at 2, 6, 20, and 40 minutes and 1, 2, 4, 8, 10, 12, and 24 hours postdose. Blood samples were collected into vacuum collection tubes containing EDTA tripotassium. Plasma concentrations of budesonide, glycopyrronium, and formoterol were measured using LC-MS/MS assays (see Supplemental Material in the online version at https://doi.org/10.1016/j.clinthera.2019.03.007). PK parameters assessed included

AUC_{0-12}, $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, T_{max}, $t_{1/2}$, and the AUC_{0-12} and C_{max} accumulation ratios.

Tolerability Assessments

The secondary objective of this study was to examine the tolerability of BGF MDI and GFF MDI in healthy Chinese subjects. Tolerability was assessed using physical examination findings, spontaneous reporting of adverse events (AEs) including serious AEs, 12-lead ECG, vital signs, and clinical laboratory values.

Statistical Analysis

The *safety population* was defined as all subjects who received at least 1 dose of study treatment, whereas the *PK population* consisted of all subjects in the safety population who had sufficient data to reliably calculate any PK parameters and who did not have a major protocol deviation. Protocol deviations that had the potential to affect membership in an analysis population were considered to be major; all protocol deviations were reviewed during a blinded data review meeting to determine whether they warranted removal of the subject from the study. As a previous study had indicated high variability in glycopyrronium PK parameters (%CV as high as 235%), [14] the sample size of 32 randomized subjects per treatment arm was selected to limit variation in glycopyrronium AUC to 51%, assuming no dropouts on day 1.

Descriptive statistics were used to summarize data on the plasma concentrations of budesonide, formoterol, and glycopyrronium by treatment, visit, and time point. The PK parameters AUC_{0-12}, AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, T_{max}, $t_{1/2}$, terminal elimination rate constant (λ_z), apparent total body clearance (CL/F), and apparent volume of distribution (Vd/F) were estimated from the plasma concentration−time data on budesonide, glycopyrronium, and formoterol from each subject when possible on day 1. On day 8, AUC_{0-12}, C_{max}, and T_{max} values in each subject were estimated. For PK visits in which <3 quantifiable concentrations were above the lower limit of quantification of a reported analyte, only C_{max} and T_{max} were reported. No PK parameters were estimated for PK visits during which all reported concentrations were below the lower limit of quantification. The partial AUC_{0-12} was not estimated if the time of last measurable (positive) concentration was prior to 12 hours postdose and the corresponding λ_z was not estimated in a particular subject profile.

Descriptive statistics for the PK parameters of budesonide, formoterol, and glycopyrronium were summarized by treatment and visit. PK parameters were estimated by noncompartmental analysis using the Phoenix WinNonlin software version 6.4 (Certara, Princeton, New Jersey). AUC parameters were calculated using the linear-log trapezoidal method. Where feasible, λ_z in each subject was estimated by linear regression analysis, calculated from the slope of the terminal portion of the ln (drug concentration) versus time curve. C_{max} and T_{max} were obtained from the observed values, and $t_{1/2}$ was calculated as $\ln 2/\lambda_z$. AUC_{0-12} and C_{max} accumulation ratios were calculated as subject-level ratios of day 8 to day 1 values.

RESULTS

Study Population

From April 17, 2017, to September 5, 2017, 261 subjects were screened, and 96 subjects were randomized and received treatment (Figure 1). All randomized subjects were included in the safety and PK populations. Although 1 subject in the BGF MDI 320/14.4/10 μg treatment arm discontinued early due to a major protocol deviation of smoking during the study (PK samples were not collected on day 8), this subject was included in both analysis populations as the deviation occurred on day 2 of the study and day-1 PK data were not affected.

The baseline demographic characteristics are summarized in Table I; most subjects were male (83.3%), the mean age was 25.6 years, and the mean body mass index was 21.7 kg/m^2. None of the subjects reported use of any concurrent medications during the treatment period.

Pharmacokinetic Parameters

After treatment with BGF MDI 320/14.4/10 μg, BGF MDI 160/14.4/10 μg, and GFF 14.4/10 μg, the plasma concentration−time profiles of all components displayed a similar shape after single versus repeated dosing, with higher plasma concentrations of all components on day 8 compared with day 1 (Figure 2).

The plasma budesonide concentrations were higher after treatment with BGF MDI 320/14.4/10 μg compared with 160/14.4/10 μg on both days 1 and 8

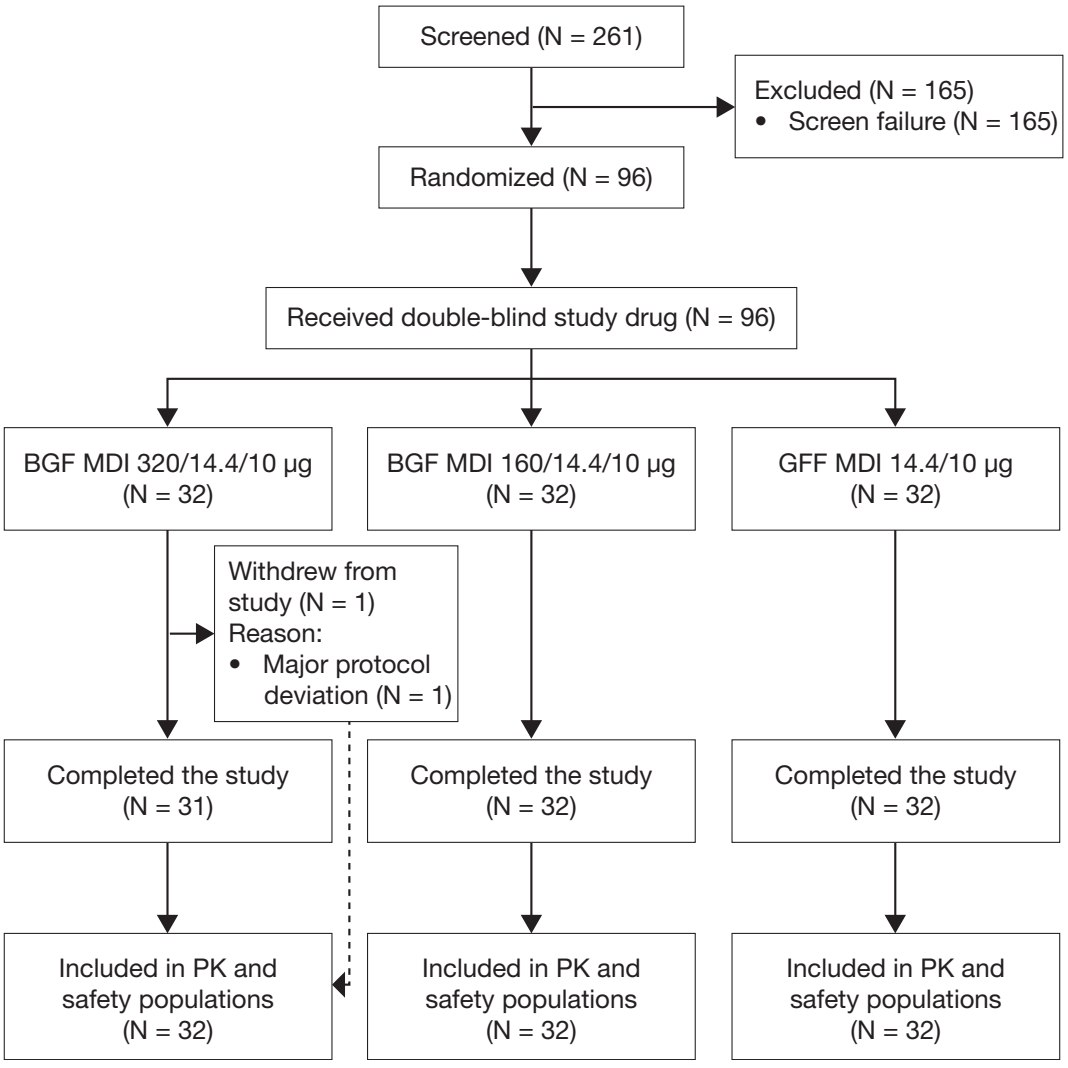

Figure 1. Subject disposition. BGF = budesonide/glycopyrronium/formoterol fumarate dihydrate; GFF = glycopyrronium/formoterol fumarate dihydrate; MDI = metered-dose inhaler; PK = pharmacokinetic.

(Figure 2A). The exposure to budesonide was also dose proportional, with AUC_{0-12} and C_{max} values ~2-fold higher after treatment with BGF MDI 320/14.4/10 µg compared with BGF MDI 160/14.4/10 µg on day 1 (AUC_{0-12}, 1748 vs 811.8 h · pg/mL; C_{max}, 459.3 vs 224.3 pg/mL) and day 8 (AUC_{0-12}, 2510 vs 1250 h · pg/mL; C_{max}, 626.4 vs 315.4 pg/mL) (Table II). Median T_{max} for budesonide occurred at the same time (20 minutes) for both doses of BGF MDI after single and repeated dosing. The budesonide accumulation ratios for AUC_{0-12} (1.5) and C_{max} (1.4) were comparable between BGF MDI 320/14.4/10 µg and BGF MDI 160/14.4/10 µg.

The PK parameters of glycopyrronium were similar across treatment groups, with AUC and C_{max} values generally comparable between BGF MDI 320/14.4/10 µg, BGF MDI 160/14.4/10 µg, and GFF 14.4/10 µg after both single (AUC_{0-12}, 27.20–29.40 h · pg/mL; C_{max}, 4.884–5.674 pg/mL) and repeated dosing (AUC_{0-12}, 69.49–77.08 h · pg/mL; C_{max}, 11.30–13.12 pg/mL) (Table II). The median T_{max} values of glycopyrronium were 6 minutes on day

Table I. Baseline demographics (safety/pharmacokinetics population)

Characteristic	BGF MDI 320/14.4/10 μg (n = 32)	BGF MDI 160/14.4/10 μg (n = 32)	GFF MDI 14.4/10 μg (n = 32)	All Subjects (n = 96)
Age, mean (SD), y	25.1 (3.8)	26.9 (5.1)	24.7 (4.1)	25.6 (4.4)
Male, no. (%)	25 (78.1)	26 (81.3)	29 (90.6)	80 (83.3)
Asian, no. (%)	32 (100.0)	32 (100.0)	32 (100.0)	96 (100.0)
Weight, mean (SD), kg	60.0 (5.3)	60.0 (6.1)	62.8 (5.3)	60.9 (5.7)
BMI, mean (SD), kg/m^2	21.5 (1.4)	21.6 (1.2)	21.9 (1.1)	21.7 (1.2)
Smoking status				
Former smoker, no. (%)	4 (12.5)	3 (9.4)	2 (6.3)	9 (9.4)
Years since last smoked, mean (SD)	0.36 (0.11)	0.34 (0.04)	1.92 (1.52)	0.70 (0.88)
Nonsmoker, no. (%)	28 (87.5)	29 (90.6)	30 (93.8)	87 (90.6)

BGF = budesonide/glycopyrronium/formoterol fumarate dihydrate; BMI = body mass index; GFF = glycopyrronium/formoterol fumarate dihydrate; MDI = metered-dose inhaler.

1 and 20 minutes on day 8 with all 3 treatments. The glycopyrronium accumulation ratios for AUC_{0-12} (3.0−3.3) and C_{max} (2.3−2.4) were similar with both doses of BGF MDI as well as GFF MDI.

Formoterol AUC and C_{max} values were similar with all treatments on both day 1 (AUC_{0-12}, 46.49−53.58 h · pg/mL; C_{max}, 9.651−10.62 pg/mL) and day 8 (AUC_{0-12}, 81.94−85.32 h · pg/mL; C_{max}, 16.13−17.71 pg/mL) (Table II). The median T_{max} of formoterol was 6 minutes with all treatments after single and repeated dosing, with the exception of BGF MDI 320/14.4/10 μg on day 1 (50 minutes). However, the overall distribution of T_{max} values on day 1 was only modestly different across the treatment groups. In the BGF MDI 320/14.4/10 μg group, T_{max} was 6 minutes in <50% of subjects (n = 15), while in the BGF MDI 160/14.4/10 μg and GFF MDI 14.4/10 μg groups, T_{max} was 6 minutes in >50% of subjects (n = 18 and n = 21, respectively), which resulted in the median value with those treatments being 6 minutes on day 1. In 1 subject in each of the BGF MDI groups, T_{max} was 40 minutes, whereas T_{max} was 1.0 or 2.0 hours in 16, 13, and 11 subjects in the BGF MDI 320/14.4/10 μg, BGF MDI 160/14.4/10 μg, and GFF MDI 14.4/10 μg groups, respectively. Formoterol accumulation ratios for AUC_{0-12} (1.6−1.8) and C_{max} (1.7) were similar across all 3 treatments.

Due to values falling below the lower limit of quantitation, some subjects did not have evaluable data on AUC_{0-12}, $AUC_{0-\infty}$, and $t_{1/2}$ of glycopyrronium on day 1 and on $AUC_{0-\infty}$ of formoterol on day 1. The number of subjects evaluated for each parameter is provided in Table II.

Tolerability

Fifty subjects (52.1%) reported at least 1 treatment-emergent (TE) AE, with 44 subjects (45.8%) reporting TEAEs related to study treatment (Table III). The incidence of TEAEs was similar among the treatments (50.0%−56.3% of subjects), with no evidence of a dose−response relationship in the pattern or frequency of TEAEs between the BGF MDI 160/14.4/10 μg and BGF MDI 320/14.4/10 μg groups. All AEs were mild in severity, and a majority of the TEAEs that occurred in ≥5% of subjects were laboratory abnormalities of blood potassium and blood glucose concentrations (Table III). Of 83 total TEAEs reported, 81 were recovered or resolved; the outcome of the remaining 2 TEAEs was unknown.

Laboratory values were generally similar across treatment groups, with comparable mean changes from baseline. One subject who received BGF MDI 160/14.4/10 μg experienced hyperkalemia (potassium 6.13 mmol/L) at 2 hours postdose on day 1; however, no complaints were recorded, and all subsequent and prior potassium measurements in this subject were ≤6.0 mmol/L. Mean changes in vital sign values were generally small, clinically nonsignificant, and similar

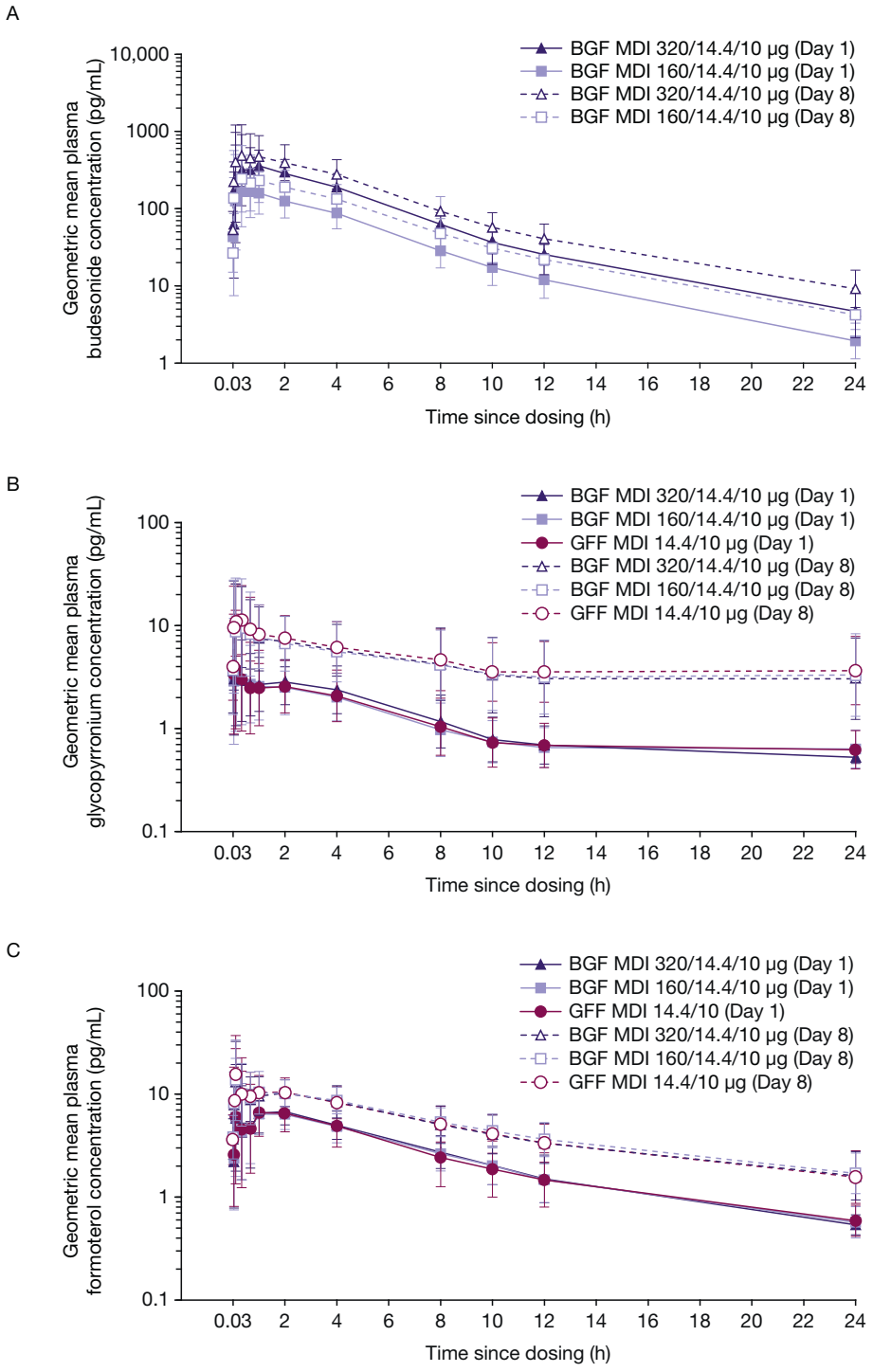

Figure 2. Plasma concentration-time profiles of budesonide (A), glycopyrronium (B), and formoterol (C) after single and chronic dosing (PK population). BGF = budesonide/glycopyrronium/formoterol fumarate dihydrate; GFF = glycopyrronium/formoterol fumarate dihydrate; LLQ = lower limit of quantification; MDI = metered-dose inhaler; PK = pharmacokinetic. Error bars represent the geometric SD. Values below LLQ were set to LLQ/2.

Table II. Pharmacokinetic (PK) parameters of budesonide, glycopyrronium, and formoterol after single dosing (day 1) and at steady state (day 8) (PK population). Data are given as geometric mean (%CV) unless otherwise noted

Parameter	Day 1			Day 8		
	BGF MDI 320/14.4/10 μg	BGF MDI 160/14.4/10 μg	GFF MDI 14.4/10 μg	BGF MDI 320/14.4/10 μg	BGF MDI 160/14.4/10 μg	GFF MDI 14.4/10 μg
Budesonide						
AUC_{0-12}, h · pg/mL	(n = 32)	(n = 32)	—	(n = 31)	(n = 32)	—
	1748 (43.5)	811.8 (58.2)	—	2510 (53.4)	1250 (52.0)	—
AUC_{0-t}, h · pg/mL	(n = 32)	(n = 32)	—	—	—	—
	1885 (43.5)	830.0 (61.1)	—	—	—	—
$AUC_{0-\infty,}$* h · pg/mL	(n = 32)	(n = 32)	—	—	—	—
	1936 (42.0)	876.7 (58.8)	—	—	—	—
C_{max}, pg/mL	(n = 32)	(n = 32)	—	(n = 31)	(n = 32)	—
	459.3 (67.6)	224.3 (98.1)	—	626.4 (78.1)	315.4 (80.2)	—
T_{max}	(n = 32)	(n = 32)	—	(n = 31)	(n = 32)	—
Median (range), h	0.333 (0.10—2.00)	0.333 (0.10—2.00)	—	0.333 (0.10—4.00)	0.333 (0.03—4.00)	—
$t_{1/2,}$ h	(n = 32)	(n = 32)	—	—	—	—
	4.572 (25.3)	3.168 (31.9)	—	—	—	—
R_{AC} AUC_{0-12}	—	—	—	(n = 31)	(n = 32)	—
	—	—	—	1.455 (45.9)	1.539 (37.1)	—
R_{AC} C_{max}	—	—	—	(n = 31)	(n = 32)	—
	—	—	—	1.400 (71.4)	1.406 (62.6)	—
Glycopyrronium						
AUC_{0-12}, h · pg/mL	(n = 20)	(n = 19)	(n = 20)	(n = 29)	(n = 28)	(n = 31)
	29.40 (23.5)	27.20 (41.3)	29.00 (42.6)	69.49 (64.8)	77.08 (47.5)	72.64 (57.2)
AUC_{0-t}, h · pg/mL	(n = 31)	(n = 30)	(n = 28)	—	—	—
	17.62 (89.8)	17.71 (111.2)	20.29 (103.3)	—	—	—
$AUC_{0-\infty,}$* h · pg/mL	(n = 5)	(n = 1)	(n = 3)	—	—	—
	35.47 (19.6)	33.01 (NA)	43.54 (18.3)	—	—	—
C_{max}, pg/mL	(n = 32)	(n = 31)	(n = 31)	(n = 31)	(n = 32)	(n = 32)
	4.884 (92.5)	5.286 (120.8)	5.674 (113.4)	11.30 (96.9)	11.75 (103.0)	13.12 (82.3)
T_{max}	(n = 32)	(n = 31)	(n = 31)	(n = 31)	(n = 32)	(n = 32)
Median (range), h	0.100 (0.03—2.00)	0.100 (0.03—4.00)	0.100 (0.03—4.00)	0.333 (0.03—4.00)	0.333 (0.03—4.00)	0.333 (0.03—2.00)

Table II. (*Continued*)

Parameter	Day 1			Day 8		
	BGF MDI 320/14.4/10 μg	BGF MDI 160/14.4/10 μg	GFF MDI 14.4/10 μg	BGF MDI 320/14.4/10 μg	BGF MDI 160/14.4/10 μg	GFF MDI 14.4/10 μg
$t_{1/2}$, h	(n = 20)	(n = 14)	(n = 15)	—	—	—
	5.676 (52.5)	8.539 (161.3)	6.194 (108.2)	—	—	—
R_{AC} AUC_{0-12}	—	—	—	(n = 18)	(n = 18)	(n = 19)
	—	—	—	3.324 (47.5)	3.030 (43.0)	3.189 (31.5)
R_{AC} C_{max}	—	—	—	(n = 31)	(n = 31)	(n = 31)
	—	—	—	2.383 (86.4)	2.319 (90.3)	2.412 (89.7)
Formoterol						
AUC_{0-12}, h · pg/mL	(n = 32)	(n = 32)	(n = 28)	(n = 31)	(n = 32)	(n = 32)
	47.84 (35.0)	46.49 (39.3)	53.58 (38.0)	81.94 (39.5)	85.32 (34.0)	83.50 (37.8)
AUC_{0-t}, h · pg/mL	(n = 32)	(n = 32)	(n = 32)	—	—	—
	48.33 (41.4)	47.41 (48.2)	45.95 (78.1)	—	—	—
$AUC_{0-\infty}$,* h · pg/mL	(n = 21)	(n = 18)	(n = 19)	—	—	—
	61.62 (37.5)	73.12 (40.5)	70.61 (46.0)	—	—	—
C_{max}, pg/mL	(n = 32)	(n = 32)	(n = 32)	(n = 31)	(n = 32)	(n = 32)
	9.651 (55.8)	9.932 (71.9)	10.62 (76.6)	16.13 (59.1)	16.95 (54.5)	17.71 (57.6)
T_{max}	(n = 32)	(n = 32)	(n = 32)	(n = 31)	(n = 32)	(n = 32)
Median (range), h	0.833 (0.10—2.00)	0.100 (0.10—2.00)	0.100 (0.10—2.00)	0.100 (0.10—2.00)	0.100 (0.10—4.00)	0.100 (0.10—4.00)
$t_{1/2}$, h	(n = 31)	(n = 32)	(n = 28)	—	—	—
	5.098 (22.7)	5.657 (38.1)	5.628 (34.2)	—	—	—
R_{AC} AUC_{0-12}	—	—	—	(n = 31)	(n = 32)	(n = 28)
	—	—	—	1.718 (28.7)	1.835 (26.2)	1.620 (27.5)
R_{AC} C_{max}	—	—	—	(n = 31)	(n = 32)	(n = 32)
	—	—	—	1.678 (50.1)	1.706 (42.1)	1.668 (62.2)

BGF = budesonide/glycopyrronium/formoterol fumarate dihydrate; GFF = glycopyrronium/formoterol fumarate dihydrate; MDI = metered dose inhaler; R_{AC} = accumulation ratio.

* In subjects with >20% of the $AUC_{0-\infty}$ having been extrapolated, the $AUC_{0-\infty}$ values were excluded.

Table III. Summary of TEAEs (tolerability population). Data are given as number (%) of subjects

Parameter	BGF MDI 320/14.4/10 μg (n = 32)	BGF MDI 160/14.4/10 μg (n = 32)	GFF MDI 14.4/10 μg (n = 32)	All Subjects (n = 96)
At least one TEAE	18 (56.3)	16 (50.0)	16 (50.0)	50 (52.1)
TEAEs related to study treatment*	16 (50.0)	12 (37.5)	16 (50.0)	44 (45.8)
Serious TEAEs	0	0	0	0
TEAEs leading to early withdrawal	0	0	0	0
Deaths	0	0	0	0
TEAEs occurring in ≥5% of all subjects (preferred term)				
Blood glucose increased	4 (12.5)	3 (9.4)	4 (12.5)	11 (11.5)
Dry throat	3 (9.4)	2 (6.3)	4 (12.5)	9 (9.4)
Blood potassium decreased	2 (6.3)	5 (15.6)	2 (6.3)	9 (9.4)
Blood potassium increased	2 (6.3)	1 (3.1)	6 (18.8)	9 (9.4)
Oropharyngeal pain	2 (6.3)	1 (3.1)	2 (6.3)	5 (5.2)
Sensation of foreign body	1 (3.1)	1 (3.1)	3 (9.4)	5 (5.2)

BGF = budesonide/glycopyrronium/formoterol fumarate dihydrate; GFF = glycopyrronium/formoterol fumarate dihydrate; MDI = metered-dose inhaler; TEAE = treatment-emergent adverse event.
* Related to treatment assessed by the Investigator as "yes" or "no."

across treatment groups. Two subjects in the BGF MDI 320/14.4/10 μg group each experienced a single bradycardia event (≤50 bpm and ≥15% decrease from baseline); neither was considered to be a TEAE. No serious AEs, TEAEs leading to early withdrawal, or deaths were reported (Table III).

DISCUSSION

This study was the first to investigate the PK and safety profiles of BGF MDI and GFF MDI in healthy Chinese subjects. Two doses of BGF MDI (320/14.4/10 μg and 160/14.4/10 μg), in addition to GFF MDI 14.4/10 μg, were evaluated after single and repeated (7-day) dosing.

The increase in systemic exposure of budesonide was proportional as the dose was increased from 160 to 320 μg, suggesting dose linearity in this range. This finding is consistent with previous findings with BGF MDI 320/14.4/10 μg and BGF MDI 160/14.4/10 μg in healthy Western and Japanese subjects. [14,15] Furthermore, the systemic exposures to glycopyrronium and formoterol were comparable between the 2 doses of BGF MDI in healthy Chinese subjects, as previously reported in healthy Western and Japanese subjects. [14,15] In the present study, the PK parameters of glycopyrronium and formoterol with both doses of BGF MDI were also similar to those with GFF MDI alone, suggesting no interaction of these compounds with budesonide.

The mean AUC_{0-12} and C_{max} accumulation ratios were similar across treatments in this study for budesonide (1.5 and 1.4, respectively), glycopyrronium (3.0−3.3 and 2.3−2.4, respectively), and formoterol (1.6−1.8 and 1.7, respectively), and were consistent with the known PK properties of the 3 compounds. [15,18,19] These findings were generally comparable with the AUC_{0-12} and C_{max} accumulation ratios of budesonide (1.4−1.5 and 1.2−1.3, respectively), glycopyrronium (3.0−4.1 and 2.0−2.6, respectively), and formoterol (1.4−1.7 and 2.0−2.1, respectively) in a previous study in Japanese healthy subjects treated with BGF MDI 320/14.4/10 μg and BGF MDI 160/14.4/10 μg for 7 days. [15] In a previous study in which the PK profile of GFF MDI 14.4/10 μg was assessed in predominantly white patients with moderate to very severe COPD who received treatment for 12 weeks, accumulation ratios of formoterol were comparable to those in the present study (AUC_{0-12} and C_{max} accumulation ratios, 1.5 and 1.3, respectively), whereas glycopyrronium accumulation ratios were slightly lower (2.3 and 1.4, respectively) compared with those in the present study, [20] which

may be a consequence of the older study population as well as the Phase III study design in which dosing conditions are less controlled.

The mean systemic exposures to budesonide and formoterol in healthy Chinese subjects were similar to those previously observed after a single dose in healthy Western subjects. [14,16] Modest differences in glycopyrronium systemic exposure were observed between Chinese subjects in the current study and Western subjects in previous studies of BGF MDI (slightly lower C_{max} and slightly higher AUC_{0-12} and AUC_{0-t}). [14,16] A recent study investigating the PK properties of inhaled glycopyrronium 50 μg in healthy Chinese subjects concluded that the glycopyrronium systemic exposure after single and 14-day once-daily dosing could be considered to be consistent across Chinese, Japanese, and white subjects. [19] Given the variability in glycopyrronium PK parameters between subjects and studies, and that higher doses of glycopyrronium than those in BGF MDI have been shown to be well tolerated, [21,22] the differences are not expected to constitute a safety concern. The clinical efficacy and tolerability of BGF MDI in patients with COPD are supported by findings from a Phase III study in patients with COPD that included patients from the United States, Canada, Japan, and China. [7].

The degree of variability in the PK parameters of budesonide, glycopyrronium, and formoterol observed in this study was high, as indicated by the %CV of the individual PK parameters, particularly of glycopyrronium. However, this degree of variability is inherent to inhaled drugs and has also been observed in other published studies assessing the PK parameters of budesonide, glycopyrronium, and formoterol. [14–16,23,24].

Overall, the results of this study, along with results of similar studies of BGF MDI and GFF MDI in healthy Western and Japanese subjects, suggest that any PK differences in the systemic exposures to budesonide, glycopyrronium, or formoterol across different ethnicities were modest and unlikely to be clinically relevant. [14–17] Although the sample of the current study was limited to healthy subjects, PK studies of BGF MDI in Western patients with COPD are ongoing, and findings on GFF MDI have been reported. [20,25] Additionally, the clinical efficacy and tolerability of BGF MDI and GFF MDI have been assessed in global populations with COPD, including patients from China. [7,11].

BGF MDI 320/14.4/10 μg, BGF MDI 160/14.4/10 μg, and GFF MDI 14.4/10 μg were well tolerated in these healthy Chinese subjects, and findings on tolerability were consistent with those from previous studies of BGF MDI in Western and Japanese healthy subjects, [14–16] and with the well-characterized safety profile of GFF MDI in patients with COPD. [9–11] Most of the TEAEs observed in this study were mild laboratory abnormalities, with no evidence of a dose–response relationship between the 2 doses of BGF MDI.

CONCLUSIONS

This study investigating the PK properties of BGF MDI and GFF MDI in healthy Chinese subjects showed that budesonide systemic exposure was increased proportionally between the 2 doses of BGF MDI, and that the PK properties of glycopyrronium and formoterol were comparable between GFF MDI alone and in combination with 160 or 320 μg of budesonide. The PK and safety profiles of BGF MDI and GFF MDI were generally comparable with data reported from studies of these therapies in Western and Japanese populations, suggesting that the doses of BGF MDI and GFF MDI in development globally for the treatment of COPD are also appropriate for Chinese patients with COPD.

CONFLICTS OF INTEREST

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H. Yu, K. Shen, P.N. Assam, M. Gillen, and P Dorinsky are employees of AstraZeneca. The authors have indicated that they have no other conflicts of interest with regard to the content of this article.

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APPENDIX A. SUPPLEMENTARY DATA

The following are the supplementary data to this article:

Bioanalytical Methods

Samples were analyzed using a 500 μL aliquot volume and a solid-phase extraction procedure, followed by liquid chromatography tandem mass spectrometry. Budesonide concentrations were calculated with a $1/x^2$ linear regression over a concentration range of 3.00 to 500 pg/mL using budesonide-d_8 as an internal standard (Toronto Research Chemicals, Inc., Toronto, Ontario, Canada). Glycopyrronium and formoterol concentrations were calculated with a $1/x^2$ linear regression over a concentration range of 1.00 to 200 pg/mL using glycopyrronium-d_3 and formoterol-d_6, respectively, as internal standards (Toronto Research Chemicals, Inc., Toronto, Ontario, Canada). An API 5500 (AB Sciex, Concord, Ontario, Canada) was operated in the selected reaction monitoring (SRM) mode under conditions for detection of sample and internal standard positive ions formed by electrospray ionization. For detection of budesonide, the stationary phase was an Xbridge C8, 50 x 2.1 mm, 5 μm column (Waters, Milford, MA, USA) maintained at 50°C, and the mobile phases were 10 mM ammonium bicarbonate and 50:50 methanol:acetonitrile. Glycopyrronium and formoterol were detected using a Pursuit XRZ Ultra 2.8 Diphenyl 100 x 2.0 mm column (Agilent Technologies, Santa Clara, CA, USA) maintained at 50°C, with 0.1% formic acid in 10 mM ammonium acetate and 100% methanol as the mobile phases. SRM transitions (±0.3 atomic mass units) were m/z 431.3 → 323.2 for budesonide (439.3 → 323.2 for budesonide-d_8), 318.0 → 116.1 for glycopyrronium (321.3 → 118.9 for glycopyrronium-d_3), and 345.0 → 149.1 for formoterol (351.2 → 155.2 for formoterol-d_6). The intra- and inter-assay precision (coefficient of variation %) over the low to high quality-control range was 0.5 to 5.9% and 2.9 to 5.2%, respectively, for budesonide, 1.4 to 3.9% and 2.1 to 3.5%, respectively, for glycopyrronium, and 1.3 to 4.3% and 2.3 to 4.8%, respectively, for formoterol. The lower limit of quantification was 3.00 pg/mL for budesonide, 1.00 pg/mL for glycopyrronium, and 1.00 pg/mL for formoterol.