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Open-Label, Crossover Study to Determine the Pharmacokinetics of Fluticasone Furoate and Batefenterol When Administered Alone, in Combination, or Concurrently

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Abstract

The study aim was to investigate the pharmacokinetics of single high doses and repeated therapeutic doses of fluticasone furoate (FF) and batefenterol (BAT; a bifunctional muscarinic antagonist and β_2-agonist) administered in combination (BAT/FF) or as monotherapy. In this open-label, 6-period, crossover study of 48 subjects, the treatment sequences were (1) single high-dose BAT/FF 900/300 μg followed by repeated therapeutic doses of BAT/FF 300/100 μg (once daily for 7 days); (2) single high-dose BAT 900 μg administered concurrently with FF 300 μg; (3) single high-dose BAT 900 μg followed by repeated therapeutic-dose BAT 300 μg; (4) single high-dose FF 300 μg followed by repeated therapeutic-dose FF 100 μg; (5) single high-dose FF 300 μg (magnesium stearate); and (6) single high-dose FF/vilanterol 300/75 μg. Plasma FF area under the plasma drug concentration-time curve (AUC) was reduced after single high-dose BAT/FF versus FF alone (ratio of geometric least squares means: 0.79; 90% confidence interval: 0.75-0.83). After repeat dosing, FF AUC at the lower therapeutic dosage was similar for BAT/FF and FF (primary endpoint; AUC geometric least squares means: 1.03). Adverse events were minor, the most common being cough. These data support the feasibility of developing BAT/inhaled corticosteroid triple therapy in a single inhaler.

Keywords

batefenterol, bronchodilator, bifunctional molecule, fluticasone furoate, triple therapy

Inhaled bronchodilator therapy with long-acting β_2-adrenergic agonists (LABAs) and long-acting muscarinic antagonists (LAMAs) is central to the maintenance treatment of chronic obstructive pulmonary disease (COPD).[1] The combination of a LAMA and a LABA has been shown to improve lung function and symptoms compared with either monotherapy,[2–6] and the addition of an inhaled corticosteroid (ICS) to LABA can also improve outcomes, particularly in patients with moderate to very severe COPD who continue to experience exacerbations while receiving bronchodilator monotherapy.[7,8] Given the benefits of combination therapies, there has been increasing interest in triple therapy (LABA/LAMA/ICS) for patients with COPD whose symptoms are not adequately controlled with dual combination therapy.[8,9]

Batefenterol (BAT) is a bifunctional molecule with both muscarinic (M_2 and M_3 receptor) antagonist

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and β_2-adrenoceptor agonist pharmacology (termed a muscarinic antagonist β_2 agonist [MABA]), and is in development as maintenance treatment for COPD.[10,11] The MABA approach provides several advantages over combination therapy, including delivery of a fixed ratio of muscarinic antagonist to β_2-agonist at the cellular level,[11] which has the potential for improved efficacy in controlling COPD symptoms. In addition, a MABA formulation may allow for a simplified triple therapy compared with the combination of individual LABA, LAMA, and ICS molecules.

The triple therapy of BAT with the ICS fluticasone furoate (FF) is being evaluated. Pharmacokinetic (PK) studies of FF have indicated that oral bioavailability is very low and is limited by absorption and first-pass metabolism.[12] FF is extensively metabolized; the major route of metabolism is ester hydrolysis, leading to formation of a 17β-carboxylic acid metabolite.[12] Both BAT and FF are substrates of cytochrome P450 3A4 (CYP3A4) and of the transporter P-glycoprotein (P-gp) (unpublished data). Higher systemic exposure of BAT or FF may result from coadministration with strong CYP3A4 or P-gp inhibitors.

A recent study examined the PK of BAT in combination with once-daily ICS FF administered in one inhaler at relatively high doses (BAT 900-1200 μg; FF 300 μg).[13] In that study, FF exposure following single-dose administration of BAT combined with FF (BAT/FF) was reduced compared with administration of FF alone.[13] However, it had not been established whether this reduction was also present with BAT/FF administration at lower, clinically therapeutic doses (eg, BAT 300 μg; FF 100 μg).

Following on from the high-dose BAT/FF PK study,[13] the present study aimed to validate the previous findings and to determine whether the administration of lower, clinically relevant, repeat doses of BAT/FF resulted in similar PK outcomes. In this study, the PK of BAT/FF 300/100 μg administered via Dry Powder Inhaler-ELLIPTA (DPI-E, owned by or licensed to the GlaxoSmithKline group of companies)[13] was compared with that of BAT or FF monotherapy. In addition, the study included single high doses of BAT (900 μg) and FF (300 μg) alone, in combination, and concurrently (one taken immediately after the other via separate inhalers) to provide a bridge between previously reported high-dose data and data for the proposed therapeutic doses.[13] Finally, single high doses of FF/vilanterol (VI; 300/75 μg) and FF (300 μg) formulated with magnesium stearate (MgSt) were included to provide within-study comparisons of PK data with other FF formulations. In particular, FF/VI was included because it has been authorized for use in both asthma and COPD and provides a benchmark for the range of FF lung delivery and systemic concentrations that are known to be clinically efficacious and have an established systemic safety profile.

Materials and Methods

Study Design and Procedures

This was an open-label, 6-period, crossover, single- and repeat-dose PK study in healthy subjects (GlaxoSmithKline study number 201958; www.clinicaltrials.gov registration number NCT02666287) performed between January 2016 and June 2016 at the GlaxoSmithKline investigational site, Hammersmith Medicines Research, Cumberland Avenue, London, UK, NW10 7EW. The study protocol was reviewed and approved by the ethics committee/institutional review board at HSC Business Services Organisation Office for Research Ethics Committees Northern Ireland in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice. All subjects provided written informed consent prior to participation in the study.

Subjects

Healthy male and female subjects 18-64 years of age, with a body mass index 18.5-30 kg/m^2 were enrolled in the study. Subjects were excluded if they had abnormal liver function tests (alanine aminotransferase or bilirubin $>1.5\times$ upper limit of normal); current or chronic history of liver disease; QT interval >450 msec (corrected by Fridericia formula); supine blood pressure $\geq$140/90 mm Hg; heart rate outside 40-90 beats per minute; any pre-existing condition that could interfere with absorption, distribution, metabolism, or elimination of the study drugs; or a history of respiratory disease in the previous 10 years. Further exclusion criteria, as well as a list of medications prohibited during the study, are provided in Supplementary Table 1.

Treatments

Treatments administered in each of the 9 dosing regimens are presented in Table 1. Subjects were allocated to 1 of the 6 treatment sequences shown in Supplementary Table 2. All treatments were administered via DPI-E.

Briefly, BAT/FF 900/300 μg (single high dose; day 1) was administered as 3 inhalations of BAT/FF 300/100 μg (via a 2-strip single inhaler), followed by 1 inhalation of BAT/FF 300/100 μg once daily for 7 days (days 2-8; sequence 1); BAT + FF 900/300 μg (single high dose; day 1) was administered as 3 inhalations of BAT 300 μg and 3 inhalations of FF 100 μg (via separate 2-strip inhalers, each with a lactose second strip), followed by a 7-day washout period

Table 1. Dosing Regimens Used in the Study

Regimen	Regimen Code	Day 1 (Single High Dose)	Regimen Code	Days 2-8 (Repeat Therapeutic Dosing)
BAT/FF	A	BAT/FF 900/300 μg (3 inhalations of BAT 300 μg and FF 100 μg in the same inhaler)	G	BAT/FF 300/100 μg once daily
BAT + FF	B	BAT 900 μg + FF 300 μg (3 inhalations of BAT 300 μg and 3 inhalations of FF 100 μg from separate inhalers)		Washout
BAT	C	BAT 900 μg (3 inhalations of BAT 300 μg)	H	BAT 300 μg once daily
FF	D	FF 300 μg (3 inhalations of FF 100 μg)	I	FF 100 μg once daily
FF MgSt	E	FF 300 μg/MgSt (3 inhalations of FF 100 μg; MgSt administered in the same inhaler from a separate strip[a])		Washout
FF/VI	F	FF/VI 300/75 μg (3 inhalations of FF 100 μg and VI 25 μg[b] in the same inhaler)		Washout

BAT, batefenterol; FF, fluticasone furoate; MgSt, magnesium stearate; VI, vilanterol.
Lactose was used as an inactive carrier for BAT and FF. All inhalers used a double-strip configuration; when only 1 active ingredient was present the second strip had blisters containing lactose only.
[a]MgSt was added to lactose.
[b]VI was blended with lactose and MgSt.

(sequence 2); BAT 900 μg (single high dose; day 1) was administered as 3 inhalations of BAT 300 μg (via 2-strip inhaler with a lactose second strip), followed by 1 inhalation of BAT 300 μg once daily for 7 days (sequence 3); FF 300 μg (single high dose; day 1) was administered as 3 inhalations of FF 100 μg (via a 2-strip inhaler with a lactose second strip), followed by 1 inhalation of FF 100 μg once daily for 7 days (sequence 4); FF 300 μg/MgSt (single high dose; day 1) was administered as 3 inhalations of FF 100 μg (via a 2-strip single inhaler with a MgSt/lactose second strip), followed by a 7-day washout period (sequence 5); FF/VI 300/75 μg (single high dose; day 1) was administered as 3 inhalations of FF/VI 100/25 μg (via a 2-strip single inhaler), followed by a 7-day washout period (sequence 6). For sequences 1-4, the 7-day repeat dosing served as an active washout period for the preceding single high dose.

Treatments were administered via the DPI-E device on the morning of each day following an overnight fast. Subjects received training on the correct use of the inhalation device, and practiced its use the day before and on the morning of the first dose. Subjects attended a follow-up visit 7-14 days after the last dose (up to 15 weeks on study for each subject).

PK Assessments

The primary endpoints were the area under the plasma drug concentration-time curve (AUC) and the maximum observed plasma concentration (C_{max}) for FF following repeat therapeutic dosing (BAT/FF or FF alone). Secondary endpoints were AUC and C_{max} for FF following single high dose (BAT/FF, BAT + FF, or FF alone); AUC and C_{max} following repeat therapeutic dosing (BAT/FF or BAT alone) and following single high dose (BAT alone); AUC and C_{max} for FF following single high doses of other FF formulations (FF/VI or FF MgSt).

Serial blood samples for PK analysis were collected before dosing and at 0.25, 0.5, 0.75, 1, 2, 3, 4, 6, 8, 12, and 24 hours after the single dose (day 1) and the last repeated dose (day 8). Upon collection, blood samples were centrifuged; plasma samples were then harvested and frozen within 2 hours and stored at −20°C or below until they were sent for analysis (Aptuit Srl, Verona, Italy, for BAT concentration; York Bioanalytical Solutions Ltd, York, UK, for FF concentration). The lower limit of quantification (LLQ) for the BAT concentration analysis was 5 pg/mL. This limit was lower than that used in the previous study (25 pg/mL),[13] as the bioanalytical methodology was re-developed to obtain adequate PK data at the therapeutic dose of BAT (300 μg). Details of the FF assay have been reported previously.[13] Further details of the analytical methodologies for the FF and BAT assays are provided in the Online Supplement.

Safety Assessments

Safety assessments included the monitoring of adverse events (AEs), 12-lead ECG, vital signs, and standard hematology and clinical chemistry laboratory parameters. Incidents of inhaler malfunctions during the study were to be reported by the investigators. Forced expiratory volume in 1 second and forced vital capacity were also measured.

Table 2. Comparison of BAT/FF Versus Other Regimens Following Single and Repeat Administration: Ratios of Geometric Means for FF PK Parameters (PK Population)

		Single High Dose					
		Arithmetic Mean (SD)		Geometric LSM			
Parameter	Comparison	BAT/FF	Comparator	BAT/FF	Comparator	Ratio (90%CI)	CVw (%)
$AUC_{(0\text{-}t')}$ (pg ·h/mL)	BAT/FF (n = 35) vs FF (n = 47)	440 (159)	570 (211)	415	526	0.79 (0.75–0.83)	13.3
	BAT/FF (n = 35) vs BAT + FF (n = 43)	440 (159)	539 (207)	415	493	0.84 (0.80–0.89)	–
	BAT/FF (n = 35) vs FF/VI (n = 44)	440 (159)	534 (188)	415	493	0.84 (0.80–0.88)	–
	BAT/FF (n = 35) vs FF MgSt (n = 46)	440 (159)	591 (222)	415	548	0.76 (0.72–0.80)	–
$AUC_{(0\text{-}t)}$ (pg ·h/mL)	BAT/FF (n = 35) vs FF (n = 47)	476 (145)	625 (184)	455	591	0.77 (0.71–0.83)	20.5
	BAT/FF (n = 35) vs BAT + FF (n = 43)	476 (145)	597 (185)	455	561	0.81 (0.75–0.88)	–
	BAT/FF (n = 35) vs FF/VI (n = 44)	476 (145)	581 (175)	455	551	0.83 (0.76–0.89)	–
	BAT/FF (n = 35) vs FF MgSt (n = 46)	476 (145)	642 (207)	455	603	0.75 (0.70–0.81)	–
C_{max} (pg/mL)	BAT/FF (n = 35) vs FF (n = 47)	61.3 (17.4)	83.8 (24.1)	58.8	80.1	0.73 (0.68–0.80)	21.7
	BAT/FF (n = 35) vs BAT + FF (n = 43)	61.3 (17.4)	81.2 (27.0)	58.8	75.7	0.78 (0.72–0.84)	–
	BAT/FF (n = 35) vs FF/VI (n = 44)	61.3 (17.4)	64.5 (16.0)	58.8	62.2	0.95 (0.87–1.03)	–
	BAT/FF (n = 35) vs FF MgSt (n = 46)	61.3 (17.4)	84.8 (22.8)	58.8	81.5	0.72 (0.67–0.78)	–
		Repeat Therapeutic Dose					
$AUC_{(0\text{-}t')}$ (pg ·h/mL)	BAT/FF (n = 35) vs FF (n = 47)	275 (158)	306 (176)	243	236	1.03 (0.97–1.09)	13.9
$AUC_{(0\text{-}t)}$ (pg ·h/mL)	BAT/FF (n = 35) vs FF (n = 47)	312 (150)	319 (174)	288	247	1.16 (0.93–1.45)	60.5
$AUC_{(0\text{-}t)}$[a] (pg ·h/mL)	BAT/FF (n = 35) vs FF (n = 46)	–	–	294	270	1.09 (0.95–1.25)	35.0
C_{max} (pg/mL)	BAT/FF (n = 35) vs FF (n = 47)	34.1 (7.9)	36.8 (11.2)	33.4	35.3	0.95 (0.88–1.02)	19.5

$AUC_{(0\text{-}t)}$, area under the plasma drug concentration-time curve from time zero (before dosing) to last time of quantifiable concentration
$AUC_{(0\text{-}t')}$, area under the plasma drug concentration-time curve from time zero (before dosing) to the last common time point with quantifiable concentrations within an analyte, within a dosing day for each subject
BAT/FF, batefenterol and fluticasone furoate given in combination (single inhaler); BAT + FF, batefenterol and fluticasone furoate given concurrently; CI, confidence interval; C_{max}, maximum observed concentration; CVw, coefficient of variation (within subject); FF, fluticasone furoate; LSM, least squares means; MgSt, magnesium stearate; PK, pharmacokinetic; SD, standard deviation; VI, vilanterol.
[a]After removing the outlier in group FF (lactose).

Statistical Methods

A sample size of 40 subjects was chosen based on logistical considerations and to attain a reasonable level of precision for treatment comparisons. Based on this sample size and assuming a within-subject coefficient of variation in log (AUC) for single doses of FF and BAT of 32% and 27%, respectively, the precision for comparisons of single-dose AUC and C_{max} was calculated to be at least 13% of the observed point estimate, with precision expressed as the half-width of the 90% confidence interval (CI).[13,14] Assuming a constant variance for repeat and single doses and achievement of BAT and FF steady state by day 8, the same sample size was considered sufficient for repeat-dose analysis. To ensure that at least 40 subjects completed the dosing and PK assessments, 48 subjects were recruited into the trial.

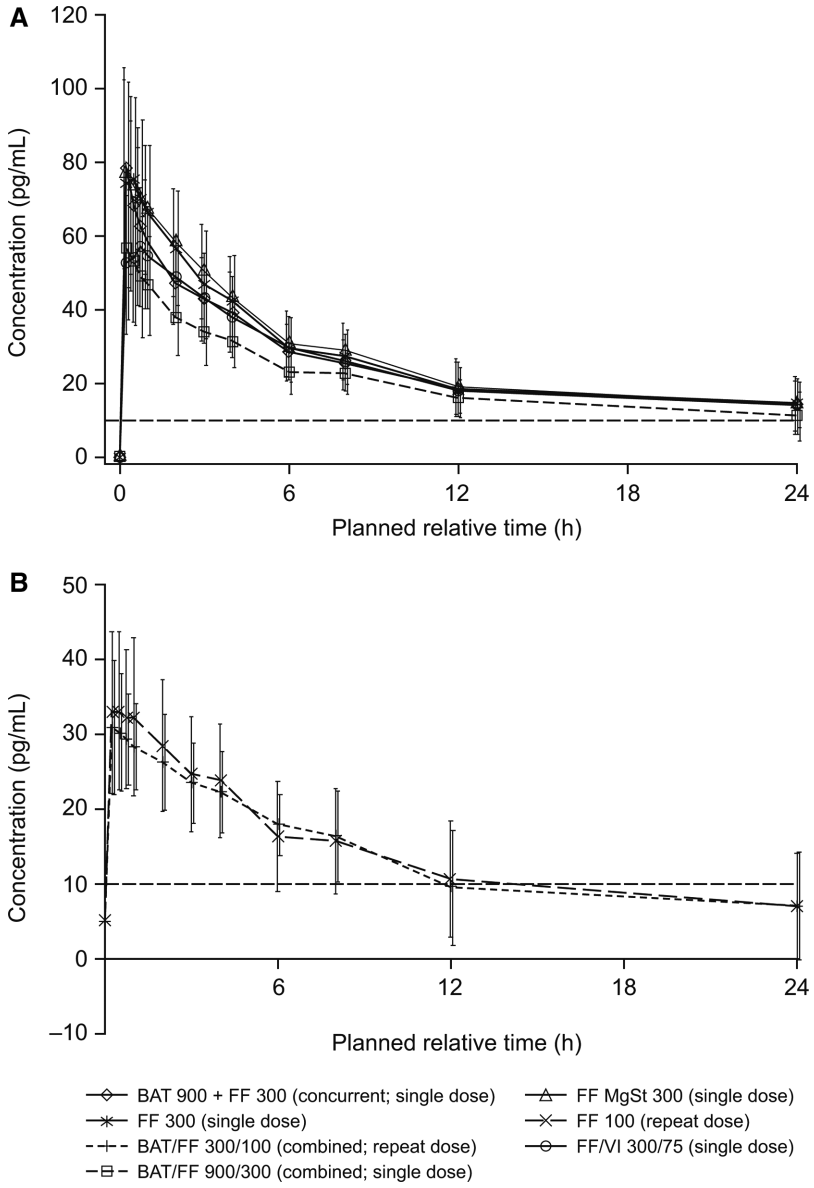

Figure 1. Mean plasma FF concentration-time plots, by treatment regimen following A) single high doses (day 1; PK population) and B) repeat dosing at therapeutic dose (day 8; PK population). BAT, batefenterol; FF, fluticasone furoate; MgSt, magnesium stearate; PK, pharmacokinetic; RD, repeated-dose regimen; SD, single-dose regimen. The dashed horizontal lines refer to the LLQ for each assessment. All plotted data points represent the arithmetic mean. All values below the limit of quantification were added as zero and included within the calculation of means. Error bars represent standard error.

The all-subjects population comprised all enrolled subjects who received at least 1 dose of study medication. Safety was assessed in the all-subjects population. The PK analysis population comprised all subjects who received ≥1 dose of study treatment and for whom at least 1 PK sample was obtained and analyzed.

PK Analyses

Concentration-time data were analyzed using standard noncompartmental analysis (Phoenix WinNonlin Version 6.4, Certara, Princeton, New Jersey). From the concentration-time data, the following PK parameters for BAT and FF were derived: AUC from time zero (before dosing) to the last common time point with quantifiable concentrations within an analyte and within a dosing day for each subject ($AUC_{(0\text{-}t')}$), AUC from time zero (before dosing) to the time of the last quantifiable concentration ($AUC_{(0\text{-}t)}$), C_{max}, time to reach C_{max} (t_{max}), and apparent terminal half-life ($t_{1/2}$).

To evaluate drug exposure following single high doses and repeat therapeutic dosing, $\log_e$-transformed AUC and C_{max} were analyzed separately using a

Table 3. Comparison of BAT/FF Versus Other Regimens Following Single and Repeat Administration: Ratios of Geometric Means for BAT PK Parameters (PK Population)

		Single High Dose					
		Arithmetic Mean (SD)		Geometric LSM			
Parameter	Comparison	BAT/FF	Comparator	BAT/FF	Comparator	Ratio (90%CI)	CVw (%)
$AUC_{(0\text{-}t')}$ (pg ·h/mL)	BAT/FF (n = 35) vs BAT (n = 33)	527 (171)	555 (182)	485	519	0.93 (0.89–0.98)	11.3
	BAT/FF (n = 35) vs BAT + FF (n = 43)	527 (171)	580 (192)	485	541	0.90 (0.86–0.94)	
$AUC_{(0\text{-}t)}$ (pg ·h/mL)	BAT/FF (n = 35) vs BAT (n = 33)	539 (159)	566 (172)	500	533	0.94 (0.89–0.99)	13.0
	BAT/FF (n = 35) vs BAT + FF (n = 43)	539 (159)	590 (181)	500	553	0.90 (0.86–0.95)	
C_{max} (pg/mL)	BAT/FF (n = 35) vs BAT (n = 33)	125.8 (29.3)	126.9 (40.8)	118	118	1.00 (0.94–1.06)	14.2
	BAT/FF (n = 35) vs BAT + FF (n = 43)	125.8 (29.3)	133.2 (37.5)	118	127	0.93 (0.88–0.98)	
		Repeat Therapeutic Dose					
$AUC_{(0\text{-}t')}$ (pg ·h/mL)	BAT/FF (n = 35) vs BAT (n = 33)	426 (139)	452 (145)	395	431	0.91 (0.87–0.96)	11.8
$AUC_{(0\text{-}t)}$ (pg ·h/mL)	BAT/FF (n = 35) vs BAT (n = 33)	431 (133)	453 (143)	405	433	0.93 (0.87–1.01)	16.7
C_{max} (pg/mL)	BAT/FF (n = 35) vs BAT (n = 33)	60.0 (14.8)	60.8 (16.6)	57.8	59.3	0.98 (0.91–1.04)	15.0

$AUC_{(0\text{-}t)}$, area under the plasma drug concentration-time curve from time zero (before dosing) to last time of quantifiable concentration; $AUC_{(0\text{-}t')}$, area under the plasma drug concentration-time curve from time zero (before dosing) to the last common time point with quantifiable concentrations within an analyte, within a dosing day for each subject; BAT/FF, batefenterol and fluticasone furoate given in combination (single inhaler); BAT + FF, batefenterol and fluticasone furoate given concurrently; CI, confidence interval; C_{max}, maximum observed concentration; CVw, coefficient of variation (within subject); FF, fluticasone furoate; LSM, least squares means; PK, pharmacokinetic; SD, standard deviation.

mixed-effects model with fixed effects terms for period and treatment and a random effects term for subject. Point estimates for treatment ratios and corresponding 90%CIs are presented.

Results

Subject Demographics and Disposition

A total of 48 subjects were enrolled. All 48 subjects received at least 1 dose of study medication and were included in the PK and safety analysis populations. The mean age was 37.1 years (standard deviation [SD]: 10.18), the mean body mass index was 23.9 kg/m^2 (SD: 2.72), and 69% of the population was male. Four (8%) subjects withdrew from the study; 2 due to AEs (1 subject reported nasopharyngitis, 1 reported viral infection) and 2 withdrew consent.

Pharmacokinetics

Single High Dose. Following a single high dose of BAT/FF, FF exposure was reduced by approximately 20% compared with FF alone ($AUC_{(0\text{-}t')}$ ratio of geometric least squares means [GLSM]: 0.79; $AUC_{(0\text{-}t)}$ GLSM: 0.77; Table 2; Figure 1A). BAT + FF, FF/VI, and FF MgSt produced FF PK profiles similar to FF alone (Figure 1A). Following BAT/FF, FF exposure was reduced by 16%-25% compared with concurrent BAT + FF, FF/VI, and FF MgSt ($AUC_{(0\text{-}t')}$ GLSM: 0.76-0.84; $AUC_{(0\text{-}t)}$ GLSM: 0.75-0.83; Table 2). Following BAT/FF, plasma FF C_{max} was reduced compared with that seen with FF alone, BAT + FF, and FF MgSt (GLSM: 0.72-0.78; Table 2), but not with FF/VI (GLSM: 0.95; 90%CI: 0.87-1.03; Table 2).

Systemic exposures of BAT following BAT/FF were within approximately 5% of the exposure following BAT alone (GLSM: 0.93; 90%CI: 0.89-0.98; Table 3) and within approximately 10% of that following BAT + FF (GLSM: 0.90; 90%CI: 0.86-0.94; Table 3). BAT PK profiles were similar following BAT/FF, BAT + FF, or BAT alone (Figure 2A). Plasma C_{max} following treatment with BAT/FF was similar compared with BAT alone (GLSM: 1.00; 90%CI: 0.94-1.06; Table 3) and slightly reduced compared with BAT + FF (GLSM: 0.93; 90%CI: 0.88-0.98; Table 3).

Repeat Therapeutic Dose. FF PK parameters after repeat therapeutic dosing (primary endpoint) were similar for BAT/FF and FF alone ($AUC_{(0\text{-}t')}$ GLSM: 1.03;

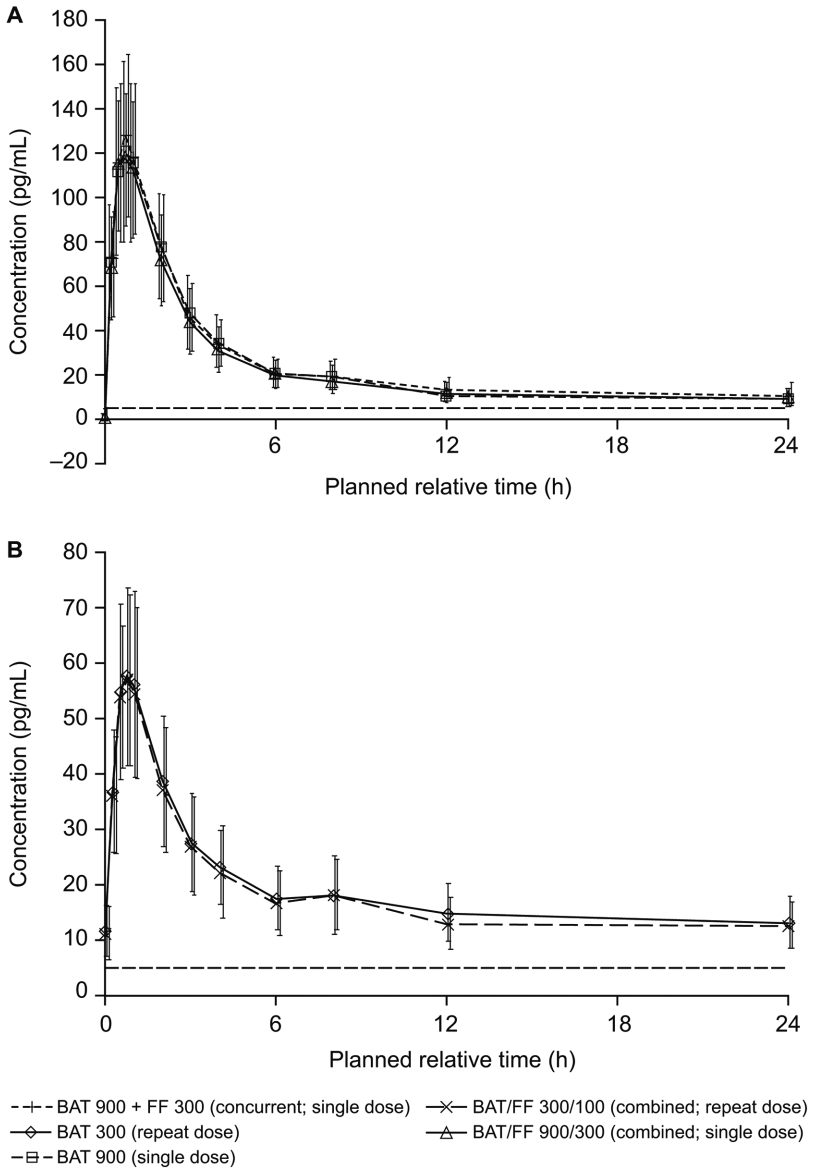

Figure 2. Mean plasma BAT concentration-time plots, by treatment regimen, following (A) single high doses (day 1; PK population) and (B) repeat dosing at anticipated therapeutic doses (day 8; PK population). BAT, batefenterol; FF, fluticasone furoate; MgSt, magnesium stearate; PK, pharmacokinetic; RD, repeated-dose regimen; SD, single-dose regimen. The dashed horizontal lines refer to the LLQ for each assessment. All plotted data points represent the arithmetic mean. All values below the limit of quantification were added as zero and included within the calculation of means. Error bars represent standard error.

$AUC_{(0\text{-}t)}$ GLSM: 1.16; Table 2, Figure 1B). An outlier in the FF alone group was identified due to the low $AUC_{(0\text{-}t)}$ compared with the more typical value for this subject after BAT/FF (2.36 pg ·h/mL vs 131 pg ·h/mL). After removing this outlier, BAT/FF $AUC_{(0\text{-}t)}$ GLSM was closer to unity with FF alone (1.09; Table 2). Plasma C_{max} following repeat dosing with BAT/FF was similar compared with FF alone (GLSM: 0.95; 90%CI: 0.88-1.02; Table 2).

BAT PK parameters were slightly reduced after repeat therapeutic dosing with either BAT/FF or BAT alone (GLSM: 0.91-0.98; Table 3, Figure 2B). However, these comparisons still lay within the bioequivalence limits of 0.8 and 1.25.

Safety

The number of subjects experiencing AEs in each treatment group is summarized in Table 4. Overall, 73% of subjects experienced at least 1 AE during all 6 treatment periods (Table 4). Across treatments, the greatest overall incidence of AEs was reported in the BAT group (66%), followed by the BAT/FF (37%) and BAT + FF treatment groups (35%; Table 4).

Table 4. Summary of AEs, Stratified by Treatment Regimen (All-Subjects Population)

Subjects With AEs, n (%)	BAT/FF[a] (n = 43)	BAT[a] (n = 47)	FF[a] (n = 47)	BAT + FF[b] (n = 46)	FF/VI[b] (n = 44)	FF MgSt[b] (n = 46)	Total (n = 48)
Any AE	16 (37)	31 (66)	13 (28)	16 (35)	10 (23)	9 (20)	35 (73)
Drug-related AE	10 (23)	15 (32)	4 (9)	4 (9)	2 (5)	2 (4)	22 (46)
Most Common Drug-Related AEs (Occurring in ≥2 Subjects Overall)							
Cough	8 (19)	13 (28)	0	3 (7)	0	0	15 (31)
Headache	1 (2)	0	0	0	2 (5)	1 (2)	3 (6)
Tremor	1 (2)	2 (4)	0	1 (2)	0	0	2 (4)
Nausea	1 (2)	0	1 (2)	0	0	0	2 (4)
Fatigue	0	1 (2)	1 (2)	0	0	0	2 (4)

AE, adverse event; BAT/FF, batefenterol and fluticasone furoate given in combination (single inhaler); BAT + FF, batefenterol and fluticasone furoate given concurrently; FF, fluticasone furoate; MgSt, magnesium stearate; VI, vilanterol.
[a]Single high dose followed by repeated therapeutic dose for 7 days.
[b]Single high dose only.

Drug-related AEs were reported in 46% of subjects across all 6 treatment periods; the most commonly reported were cough (31%) and headache (6%). Other drug-related AEs that occurred in >1 patient were tremor, nausea, and fatigue (all 4%; Table 4). Cough was reported only in BAT-containing treatment regimens and all cough AEs were considered related to study treatment. There were no serious AEs, deaths, abnormal vital signs, or abnormal ECG findings reported.

Clinical chemistry and hematology abnormalities of potential clinical importance were reported in 7 and 12 subjects, respectively. None were reported as AEs or resulted in withdrawal from the study.

No inhaler device incidents or malfunctions were reported. No clinically significant spirometry findings were reported during the study.

Discussion

This study was conducted in healthy subjects and was a follow-on investigation from the work of Ambery et al, which examined the PK of BAT and FF administered alone or in combination at single high doses.[13] In the present study, there was no reduction in the systemic exposure of FF with repeated administration of BAT/FF at therapeutic doses. At the same time, this study confirmed the previous findings, in that administration of single high-dose BAT/FF resulted in a reduction of the FF exposure compared with FF alone and FF MgSt.

This effect (reduction) is unlikely to result from a formulation-based interaction owing to differences in the masses of fine particles or arising during aerosolization, as the in vitro emitted doses of fine particles were similar for the formulations tested in the study (GlaxoSmithKline, data on file). Instead, the reduction may result from a molecular interaction due to a pharmacological or physiochemical interaction between BAT and FF in the lung or systemically. A molecular interaction could be associated with (1) the high BAT dose increasing mucociliary clearance of FF particles prior to dissolution and absorption (a known effect of β_2-agonists); (2) an effect of BAT on the dissolution rate of FF particles or absorption rate/extent across the lung epithelium (no known mechanism); or (3) an effect of BAT on the systemic PK of FF (considered not feasible because of the low circulating concentrations of BAT and FF in this study). This molecular interaction hypothesis is supported by the trend observed by Ambery et al, wherein FF exposure was reduced by a greater amount with increasing BAT dose: 27% following combination BAT/FF 900/300 μg and 36% following combination BAT/FF 1200/900 μg.[13] The 23% reduction observed after administration of BAT/FF in the present study is consistent with this trend.

A limitation of the study is that sampling was not performed beyond 24 hours after single-dose administration. However, little benefit would have been gained from continuing sampling beyond this time, as values obtained at the final sampling point were very close to the LLQ.

While an interaction between BAT and FF was indicated with single high-dose administrations, following repeated dosing over 7 days at the anticipated therapeutic doses of BAT/FF, the PK parameters were similar to those following repeated doses of FF alone, implying that a molecular interaction between BAT and FF was not observed at these lower doses. These findings suggest that the FF PK interaction is unlikely to be relevant at therapeutic doses of BAT or under the intended maintenance therapy regimen.

All treatments in the study had a favorable safety profile. The safety profile observed for BAT administered as a single high dose (900 μg) was consistent with that reported in the previous PK study.[13] The most frequently reported drug-related AE in subjects

receiving treatments containing BAT (cough) was also consistent with previous results, though the incidences of cough for repeated doses of BAT/FF and BAT + FF were lower than previously reported for BAT/FF 900/300 μg (19% and 7%, respectively, compared with 48%).[13] Only minor AEs were reported in the BAT-containing treatment arms; no serious AEs were reported. Compared with the previous PK study,[13] no new safety signals were identified in healthy volunteers who received BAT at single doses up to 900 μg and/or a BAT regimen that included 300 μg daily for 7 days.

In summary, following repeated, therapeutic doses of BAT/FF, FF exposure was similar to that seen for FF alone. Consistent with the previous PK study, administration of single high-dose BAT/FF reduced FF exposure compared with FF alone (300 μg). These results support the feasibility of developing triple therapy for COPD by combining MABA pharmacology with a once-daily ICS in a single inhaler.

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Declaration of Conflicting Interests

C.A., G.Y., T.F., A.G., and P.D-Y. are employees of GSK and hold stocks or shares in the company. A.P.'s employer (Hammersmith Medicines Research Ltd) has received funding from GSK for studies outside of this submitted work. D.R.'s employer (Quanticate) supported the analysis and reporting of the current study.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.