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Pulmonary deposition of budesonide/glycopyrronium/formoterol fumarate dihydrate metered dose inhaler formulated using co-suspension delivery technology in healthy male subjects

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ABSTRACT

This gamma scintigraphy imaging study assessed pulmonary, extrathoracic and regional lung deposition patterns of a radiolabelled inhaled corticosteroid/long-acting muscarinic antagonist/long-acting β_2-agonist triple fixed-dose combination budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF 320/14.4/10 μg), delivered by pressurised metered dose inhaler (pMDI) using innovative co-suspension delivery technology (Aerosphere™). In this Phase I, randomised, single-centre, single-dose, two-period, crossover study (NCT03740373), 10 healthy male adults received two actuations of BGF MDI (160/7.2/4.8 μg per actuation) radiolabelled with ^{99m}Tc, not exceeding 5 MBq per actuation. Immediately following each inhalation, subjects performed a 10- or 3-second breath-hold, then exhaled into an exhalation filter. The primary objective was to assess the pulmonary deposition of BGF MDI following the 10-second breath-hold. The secondary objectives were to assess deposition after the 3-second breath-hold and lung regional and extrathoracic deposition after each breath-hold length. Imaging of the lungs, stomach, head and neck was recorded by gamma scintigraphy immediately after exhalation. The mean BGF MDI emitted dose deposited in the lungs was 37.7% for the 10-second breath-hold and 34.5% for the 3-second breath-hold. Emitted dose detected in the exhalation filter was ≤0.4% for both breath-hold lengths. The mean normalised peripheral/central ratio was 0.65 and 0.75 for the 10- and 3-second breath-holds, respectively, while the standardised central/peripheral ratios were 1.79 and 1.40, respectively. There were no new or unexpected safety findings. In conclusion, BGF MDI was efficiently deposited in the central and the peripheral regions of the lungs, with similar regional deposition patterns following a 10- and 3-second breath-hold.

1. Introduction

Inhaled bronchodilators and inhaled corticosteroids (ICS) are the cornerstones of current treatment for chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease, 2019). For an inhaled treatment to be optimally effective in patients with COPD, drug particles must be deposited consistently throughout the airways (De Backer et al., 2010).

Lung deposition of inhaled therapies can be assessed by several different methods, including pharmacokinetic analysis, functional respiratory imaging (FRI) and gamma scintigraphy. Pharmacokinetic analysis – assessing concentrations of drug in plasma or urine – can determine general lung deposition, but not specific patterns of distribution within the lung (Newman, 2000). FRI uses three-dimensional models from computerised tomography scans combined with computational fluid dynamics incorporating drug delivery parameters to calculate aerosol airway deposition and distribution patterns (Van Holsbeke et al., 2018). Gamma scintigraphy allows assessment of

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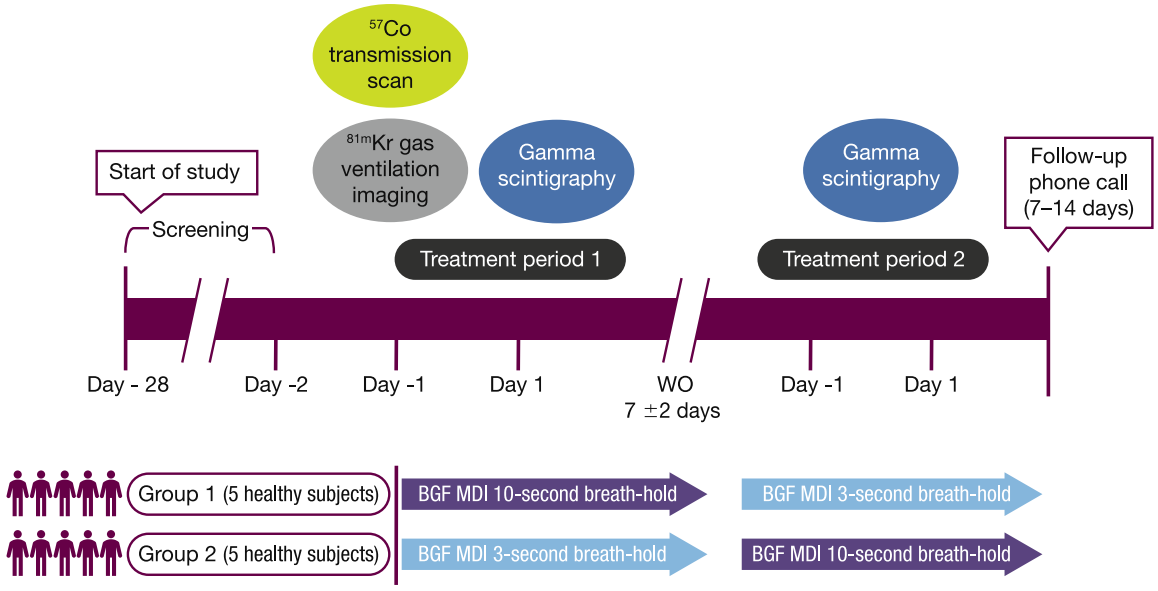

Fig. 1. Study design.
BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; MDI, metered dose inhaler; WO, washout.

the total lung deposition, regional distribution and extrathoracic (oropharyngeal and stomach) deposition of inhaled drugs (Chrystyn, 2000; Darquenne et al., 2016; Newman et al., 2012). Both the total lung deposition and the regional distribution pattern in central and peripheral regions of the lung are important determinants of the effectiveness of inhaled drugs (Biddiscombe et al., 2011; Darquenne et al., 2016; Devadason et al., 2012). It is acknowledged that there is a high prevalence of peripheral lung dysfunction in patients with COPD (Crisafulli et al., 2017) and asthma (Usmani et al., 2016) and that the peripheral airways are the major site of airflow limitation, suggesting inhaled therapies should be optimised to target drugs to this region (Usmani and Barnes, 2012).

There can be considerable variations in the overall lung deposition and regional deposition patterns of inhaled products depending on the device types for delivery, such as pMDIs versus dry powder inhalers (DPIs). Variation in lung deposition patterns can also occur across different devices of the same type (Newman, 1995). To ensure optimum deposition in the lungs, pMDI devices with a hydrofluoroalkane (HFA) propellant generally require a slow and long inhalation versus the hard and fast inhalation required of DPI use (Bonini and Usmani, 2015). Differences within optimal inhalation technique between different device types can lead to confusion in patients using mixed device types (Barrons et al., 2011; Khassawneh et al., 2008; Vincken et al., 2010) and can impact delivery of drug particles to the lungs, including large and small airways (De Backer et al., 2010). While fine particles can reach the lower airways, deposition may still occur in the upper airways as demonstrated in other studies. Most pMDIs suspend drug particles in a propellant, commonly, which has poor colloidal stability that can lead to agglomeration of the drug crystals and poor dosing consistency despite agitation prior to use. This is improved when using co-suspension delivery technology, which provides consistent dosing, colloidal stability through phospholipid particle use, and also decreases agglomeration of particles and, therefore, the amount of deposition that occurs in the upper airway (De Backer et al., 2010; Lavorini et al., 2017; Vehring et al., 2012).

Triple therapy with an ICS, a long-acting muscarinic antagonist (LAMA) and a long-acting β_2-agonist (LABA) is recommended as a step-up treatment for patients with COPD who remain symptomatic and/or experience exacerbations despite treatment with LAMA/LABA, or ICS/LABA (Global Initiative for Chronic Obstructive Lung Disease, 2019). Glycopyrronium/formoterol fumarate dihydrate 14.4/10 μg MDI (GFF MDI; Bevespi Aerosphere®) was the first LAMA/LABA fixed-dose combination delivered via pMDI formulated using innovative co-suspension delivery technology. Co-suspension delivery technology allows the consistent delivery of drugs over the lifetime of the inhaler, even when variations in flow rate, simulated patient-handling errors, reduced shake energy or increased delay between shaking and actuation were implemented (Doty et al., 2018). A gamma scintigraphy imaging study showed that GFF MDI was efficiently and uniformly deposited in the lungs, after a 10-second breath-hold (Taylor et al., 2018).

The budesonide/glycopyrronium/formoterol fumarate dihydrate (BGF) MDI triple fixed-dose combination therapy (BGF MDI 320/14.4/10 μg; Breztri Aerosphere™), equivalent to budesonide/glycopyrrolate/formoterol fumarate 320/18/9.6 μg, is an ICS/LAMA/LABA triple fixed-dose combination delivered via pMDI using the same co-suspension delivery technology as GFF MDI (Ferguson et al., 2018a). BGF MDI has recently been approved for the treatment of COPD in Japan (AstraZeneca, 2019), and has been shown to improve lung function and symptoms compared with the corresponding ICS/LABA and LAMA/LABA fixed-dose combination therapies (using the same delivery technology) and significantly reduce the rate of moderate or severe COPD exacerbations compared with GFF MDI (Ferguson et al., 2018b).

Lung deposition data for BGF MDI are currently not available. Therefore, this gamma scintigraphy study was designed to evaluate the lung deposition of BGF MDI following a standard 10-second breath-hold after inhalation. However, since some patients may be unable to maintain a breath-hold for this length of time due to the severity of their underlying lung disease (Pleasants and Hess, 2018; Self and Ellingson, 2017), the current study also evaluated the effect of a 3-second breath-hold on lung deposition.

2. Methods

2.1. Study design and treatment

This was a Phase I, randomised, two-period, single-dose, crossover gamma scintigraphy imaging study (NCT03740373) in healthy male subjects (Fig. 1). Subjects attended a screening visit within 28 days of

treatment period 1, which included inhalation training. Each of the two treatment periods was approximately 1 day long (from the afternoon before dosing until 4 hours post-dose), with a minimum washout period of 5 days (7 ± 2 days). A post-study follow-up phone call was conducted 7–14 days after the last dose.

During treatment period 1, a Krypton-81 m (^{81m}Kr) gas ventilation imaging scan was performed to define the ventilated area of the lungs, and a single Cobalt-57 (^{57}Co) transmission scan was conducted to evaluate the regional tissue attenuation of deposited radioactivity.

In each treatment period, 10 subjects received one dose of radiolabelled BGF MDI 320/14.4/10 μg, which was administered as two actuations of 160/7.2/4.8 μg per actuation and radiolabelled with ^{99m}Tc (not exceeding 5 MBq per actuation). BGF MDI was formulated as a suspension with micronised budesonide, micronised glycopyrronium bromide and micronised formoterol fumarate crystals co-suspended with spray-dried porous particles in an HFA propellant (co-suspension delivery technology).

Subjects were randomly assigned to one of two treatment sequences: (i) Radiolabelled BGF MDI with a 10-second breath-hold per inhalation during treatment period 1 and a 3-second breath-hold during treatment period 2 and (ii) Radiolabelled BGF MDI with a 3-second breath-hold per inhalation during treatment period 1 and a 10-second breath-hold during treatment period 2.

The study was conducted at a single centre (Simbec Research Ltd, Merthyr Tydfil, UK) between 4 September 2018 and 11 October 2018. The study was performed in accordance with the Declaration of Helsinki and is consistent with the International Council for Harmonisation/Good Clinical Practice guidelines. The clinical study protocol, together with subject information and consent documents, were reviewed and approved by an independent Research Ethics Committee (Wales Research Ethics Committee 1, Cardiff, Wales, UK). Subjects gave written informed consent prior to screening.

2.2. Subjects

Subjects were eligible for participation if they were healthy males (restricted to males due to radiolabel focus of the study), 28–50 years of age, with a bodyweight of ≥50 kg and a body mass index (BMI) of 18–30 kg/m^2 at screening, who had test results in the normal range for serum biochemistry, haematology and urine within 28 days before the first dose of study drug. Subjects had negative hepatitis B, hepatitis C and HIV results, no significant abnormalities in 12-lead electrocardiogram or vital signs, and no prior allergy/sensitivity to BGF MDI. Subjects agreed to use a highly effective, medically acceptable form of contraception from the first dose to at least 3 months after the last dose of study drug.

The main exclusion criteria were clinically significant medical illnesses that would have interfered with participation in this study or participation in any study in which radioisotopes were administered within 1 year prior to the study. Also excluded were subjects with a forced expiratory volume in 1 second (FEV_1) <80% of predicted value and/or an FEV_1/forced vital capacity ratio <0.7 at screening, or those unable to perform reliably reproducible pulmonary function test manoeuvres. Subjects were excluded if they had abnormal findings in a previous chest X-ray or computerised tomography scan, were unable to demonstrate acceptable use of the pMDI device (including sufficient inspiratory flow rate) and exhalation filter after training, or had any abnormal findings on the ^{81m}Kr ventilation scan.

2.2.1. Inhaler training

Inhaler training was provided by trained site staff for all subjects at screening, using the pMDI training simulator Vitalograph® Aerosol Inhalation Monitor™ (AIM™) (Garbe, 2013), with propellant-only pMDI. The AIM™ device uses a red/green traffic light system to indicate the correct co-ordination of actuation and inhalation, breath-hold and flow rate. On Day 1 pre-dose, subjects used non-radiolabelled placebo pMDI to confirm that they were capable of using the device correctly; if a subject was not performing the inhalation correctly at any point during the study (Garbe, 2013), the subject received additional training by the site staff, including additional use of the AIM device with propellant-only pMDI canisters. Subjects were also trained on how to use the exhalation filter.

2.3. Dosing procedure

Subjects took 2 inhalations from the pMDI. Immediately following each inhalation, subjects performed a 10- or 3-second breath-hold, then exhaled into an exhalation filter. After the second exhalation, subjects rinsed their mouth with approximately 20 ml of water and expelled the washings for collection. Subjects then swallowed approximately a quarter of a slice of bread and approximately 100 ml of water to minimise interference on the gamma scintigraphy images from any radiation that may have been present in the mouth and throat following inhalation.

2.4. Gamma scintigraphy imaging

Gamma scintigraphy imaging was conducted immediately following completion of the dosing procedures described above. Posterior and anterior views of the lungs and stomach, and a lateral head and neck view, were recorded using a gamma camera (Axis Dual Head, Philips Medical Systems Limited) and a commercially available nuclear medicine software package (Odyssey V9.4B, Philips Medical Systems Limited). Images were also acquired of the pMDI before and after use and of the collected mouth washings and exhalation filter. All images were a maximum of 200 seconds in duration.

The radiolabelling procedures for BGF MDI were validated prior to the study. *In vitro* tests were conducted to demonstrate that the aerodynamic particle size distribution of the radiolabel was the same as that for the micronised drug particles, as determined by *in vitro* Next Generation Impactor tests (data not shown). The validation also showed that the radiolabelling process did not change the performance of the radiolabelled pressurised MDIs relative to that of the control, non-radiolabelled devices. On each dosing day prior to treatment administration, *in vitro* characterisation of the radiolabelled pMDI product was performed to ensure it complied with predefined release specifications. Details of validation methods and data are presented in Supplementary Information 1, Supplementary Table 1 and Supplementary Fig. 1.

2.5. Outcome variables

The primary objective was to assess the pulmonary deposition of radiolabelled BGF MDI following a breath-hold period of 10 seconds. Secondary objectives included assessment of the pulmonary deposition following a breath-hold period of 3 seconds, as well as assessments of the regional (central/peripheral) airway deposition patterns in the lungs, the deposited dose in the oropharyngeal and stomach regions and the deposited dose detected on the actuator and exhalation filter, all after a 3- and 10-second breath-hold. Pulmonary deposition was expressed as the percentage emitted dose of radiolabelled BGF MDI that was deposited in the lungs.

Regional deposition ratios included the outer/inner (O/I) and central/peripheral (C/P) ratios and the normalised O/I ([nO/I] equivalent to penetration index [PI]) (Newman et al., 2012) and standardised C/P ratio (sC/P) (Biddiscombe et al., 2011). The deposited doses in the oropharyngeal and stomach regions and on the exhalation filter were expressed as percentage emitted dose, and the deposition on the actuator was expressed as percentage of the ex-valve dose. For both O/I

and C/P, regional lung volumes were normalised by comparison to the ^{81m}Kr ventilation scan in each subject.

All adverse events were to be listed and coded using the Medical Dictionary for Regulatory Activities (MedDRA), version 21.0. The incidence of treatment-emergent adverse events was to be summarised by organ system, preferred term, severity and relationship to investigational study drug. Laboratory data, vital signs, physical examination, 12-lead electrocardiogram and lung function data were listed with out-of-range values to be flagged.

2.6. Statistical analysis

No formal sample size calculation was performed as this was an investigational study to quantify lung deposition; however, a sample size of 8 was deemed adequate to enable a direct estimate of lung deposition. As such, 10 subjects were enroled to ensure that at least 8 subjects completed the study. Two analysis sets were used to analyse the data: the per protocol (PP) statistical analysis set and the safety analysis set. The PP statistical analysis set included all subjects who received a dose of the investigational product, had fully evaluable scintigraphy data and who did not violate the protocol. The analysis was performed on the randomised treatment received. The statistical comparison of the two treatments (10- second and 3-second breath-hold) were carried out only for subjects who were in the PP set in both treatment periods. All subjects who received at least one dose of the investigational product were included in the safety analysis set. Subjects were analysed according to the length of breath-hold during the study. The primary analysis comprised descriptive statistics and analysis based on statistical models for the primary and secondary endpoints using the PP analysis set. Analyses were performed on the safety analysis set and were considered supportive of the primary analysis.

The derived BGF MDI deposition variables: percentage emitted dose in lungs, in oropharyngeal and stomach regions, on the exhalation filter, percentage ex-valve dose on actuator and the regional airway deposition ratios including O/I, C/P, nO/I and sC/P, were tabulated using descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum). This analysis was not powered to detect statistical significance.

For the comparison of the deposition of BGF MDI following a 10-second breath-hold to that following a 3-second breath-hold, statistical analysis used a mixed-effects analysis of variance (ANOVA) model. The model included fixed effects for treatment, study period and sequence of administration and a random effect of subject nested within the sequence. Point estimates and 95% confidence intervals (CI) for the differences between the two treatments (10- vs 3-second breath-hold) were constructed using the residual mean square error obtained from the ANOVA statistical model described above.

3. Results

3.1. Subjects

Of the 26 subjects screened, 10 were randomised and dosed (Fig. 2). All 10 subjects were included in the safety analysis set. In the PP analysis, all 10 subjects were included for the 10-second breath-hold. However, for the 3-second breath-hold, one subject was excluded due to poor inhalation technique and non-evaluable scintigraphy data (Fig. 2). All subjects were male and white, with a mean (SD) age of 35.0 (7.8) years, a weight of 79.7 kg (12.4) and a mean BMI of 25.4 (3.1) kg/m^2. The demographic and baseline characteristics were the same for the PP and safety analysis set.

3.2. Lung deposition

Gamma scintigraphy images for the ^{81m}Kr gas ventilation, BGF MDI for a 10-second breath-hold and BGF MDI for a 3-second breath-hold are shown in Fig. 3. Data for the PP analysis set are presented in this section, data for the safety analysis set are presented in the Supplementary Material (Supplementary Table 2; Supplementary Fig. 2). The mean percentage of BGF MDI emitted dose deposited in the lungs for the 10-second breath-hold (primary outcome) was 37.7% in the PP analysis set (Table 1; Fig. 4).

The mean percentage of BGF MDI emitted dose deposited in the lungs for the 3-second breath-hold was 34.5% (Table 1; Fig. 4). There was a wide variation in the mean lung deposition values for both the 10-second breath-hold (20.3–68.3%) and 3-second breath-hold (17.3–52.7%; Table 1). The least-squares mean difference between the 10- and 3-second breath-hold was 5.5% (95% CI –3.8, 14.8; Table 2).

The mean percentage of the emitted dose deposited in the oropharyngeal and stomach regions was 62.0% for the 10-second breath-hold and 65.1% for the 3-second breath-hold (Table 1). A low percentage ($\leq$0.4%) of the emitted dose was detected in the exhalation filter for radiolabelled BGF MDI for the 10- and 3-second breath-hold, and the mean percentage of the metered dose detected in the actuator after inhalation was 10.3% and 10.0% with the 10- and 3-second breath-hold, respectively. The mean regional airway deposition ratio O/I was 1.25 for the 10-second breath-hold and 1.45 for the 3-second breath-hold (Table 2), while the mean nO/I regional airway deposition ratio was 0.65 and 0.75 for the 10- and 3-second breath-hold, respectively. The mean regional airway deposition ratio C/P was 0.72 and 0.56 for the 10- and 3-second breath-hold, respectively, and the sC/P was 1.79 and 1.40 for the 10- and 3-second breath-hold, respectively (Fig. 4). The least squares mean difference in C/P (95% CI) following a 10- vs 3-second breath-hold was 0.17 ($-$0.01, 0.35) and the least squares mean difference in sC/P was 0.40 ($-$0.03, 0.84) (Table 2).

Lung deposition results for the safety analysis set (including the subject excluded from the 3-second breath-hold data in the PP analysis) were similar to those for the PP analysis (Supplementary Tables 2 and 3; Supplementary Fig. 2).

3.3. Safety

No adverse events were reported.

4. Discussion

This Phase I gamma scintigraphy imaging study was the first to evaluate the lung deposition and regional distribution patterns of BGF MDI, an ICS/LAMA/LABA fixed-dose combination formulated using co-suspension delivery technology. The mean total lung deposition for BGF MDI following a 10-second breath-hold observed in this study (37.7%) was similar to that observed in another study for the LAMA/LABA fixed-dose combination GFF MDI (38.4%), which was also formulated using co-suspension delivery technology (Taylor et al., 2018). The nO/I and sC/P ratios for BGF MDI following a 10-second breath-hold (0.65 and 1.79, respectively) were also similar to those previously described for GFF MDI (0.57 and 1.85, respectively) (Taylor et al., 2018). This supports the conclusion that regardless of the formulation, co-suspension delivery technology enables consistent drug delivery to the lungs and consistent regional deposition patterns. The nO/I and sC/P ratios showed that BGF MDI distributed the aerosol particles to all regions of the lungs. The inner lung deposition was higher than the peripheral lung deposition, as indicated by the fact that the nO/I was <1 and the sC/P was >1, but drug deposition was evident in both regions.

It is generally recommended for patients to hold their breath for as long as is comfortable, up to 10 seconds, following inhalation with a

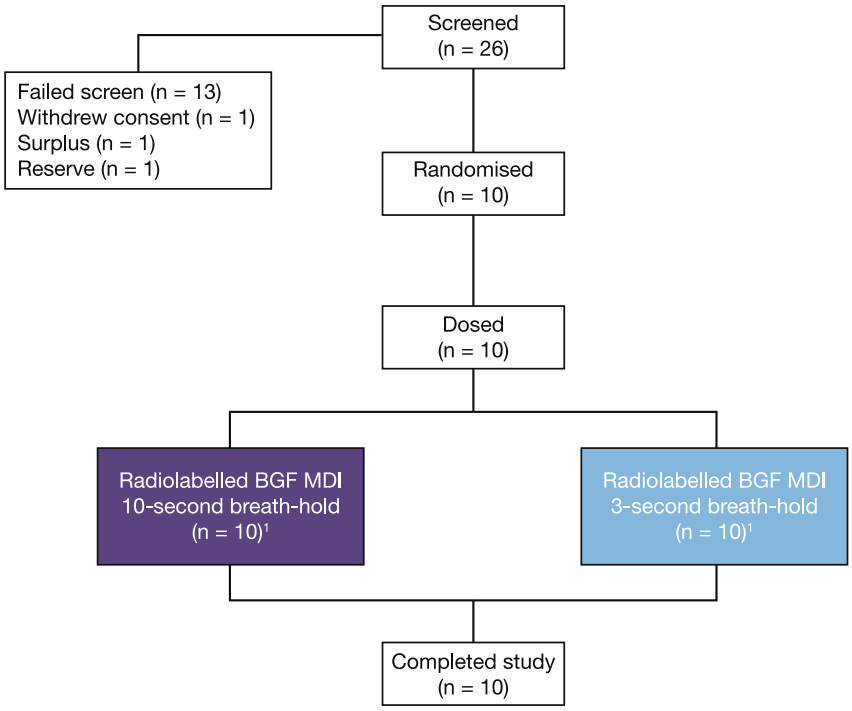

Fig. 2. Subject disposition.
[1]Treatment sequence AB (n = 5); treatment sequence BA (n = 5). A = Radiolabelled BGF pMDI 3-second breath-hold; B = Radiolabelled BGF pMDI 10-second breath-holdy.
One subject was excluded from the PP analysis set for the 3-second breath-hold for poor dose inhalation and non-evaluable scintigraphy data. Therefore, for the 10-second breath-hold n = 10 and 3-second breath-hold n = 9.
BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; pMDI, pressurised metered dose inhaler; PP, per protocol.

pMDI (Pleasants and Hess, 2018). However, patients with significant lung function impairment may be unable to hold their breath for this length of time. For such patients, a breath-hold of 3–5 seconds may be more achievable (Self and Ellingson, 2017). Additionally, many patients who can hold their breath for 10 seconds frequently do not. In fact, a systematic review of MDI technique in patients with COPD or asthma showed that 46% of patients studied had no post-inhalation breath-hold (Sanchis et al., 2016).

Although lung deposition is an important determinant of the efficacy of inhaled drugs, (Usmani et al., 2005) there is a paucity of data assessing the impact of a shorter breath-hold times on overall lung deposition of inhaled products administered by pMDIs. A previous study of a now obsolete chlorofluorocarbon-propelled MDI had compared 4- and 10-second breath-holds, showing that the greatest whole lung, tracheobronchial and alveolar deposition was found with a 10-second breath-hold (Newman et al., 1982). However, due to the difference in propellants, these data are not directly comparable to current HFA devices, and as such highlight the requirement for a greater understanding of the lung deposition impact of breath-hold time for current MDI therapies and formulations.

It is commonly thought that prolonged breath-hold can increase the time available for deposition in the peripheral airways. However, given the properties of the porous particle formulation and the low exhaled fraction seen with GFF MDI (≤0.25%) (Taylor et al., 2018) relative to other pMDIs such as beclomethasone dipropionate (BDP)/formoterol MDI (2.8%) (De Backer et al., 2010; de Boer et al., 2015), we hypothesised that differing breath-hold times would not have an appreciable impact on the deposition of BGF MDI. For subjects who had evaluable data for both the 10- and 3-second breath-hold, the difference in total lung deposition was small, with deposition slightly lower for the 3-second breath-hold. The peripheral deposition, based on nO/I, was not adversely affected by the shorter breath-hold, and the sC/P ratio was lower compared with that observed with the 10-second breath-hold (Fig. 4). Consistent with our hypothesis, these data suggest that total lung and peripheral deposition of BGF MDI was not adversely affected by a shorter breath-hold, and that the total lung deposition and regional deposition patterns of BGF MDI were similar to those of the LAMA/LABA therapy formulated using co-suspension technology GFF MDI (Taylor et al., 2018). As such, these data suggest that even patients with COPD who are unable to perform a breath-hold of 10-seconds can derive benefit from BGF MDI with as little as a 3-second breath-hold by virtue of the co-suspension delivery technology. Whether or not this is a property specific to Aerosphere inhaler delivery is unknown, as this has not, to the authors' knowledge, been studied in other MDIs.

The overall lung deposition in this study was broadly similar to the deposition described for other HFA suspension pMDIs (16–58% lung deposition) (De Backer et al., 2010; Hirst et al., 2002; Leach et al., 2012; Leach et al., 2016; Taylor et al., 2018). In particular, lung deposition data presented here for BGF MDI was similar to the 34.1% lung deposition observed following a 10-second breath-hold of extrafine BDP/formoterol (mass median aerodynamic diameter [MMAD] 1.3–1.4 μm) MDI, which is a solution formulation using Modulite® technology (De Backer et al., 2010).

Gamma scintigraphy lung deposition data for other ICS/LAMA/LABA triple fixed-dose combinations have not been published. However, the lung deposition of a beclomethasone dipropionate/formoterol fumarate/glycopyrronium (BDP/FF/G) pMDI has been simulated using functional respiratory imaging and lung computed tomography scans of patients with COPD, where the *in silico* lung deposition of this formulation was 31.0% (Usmani et al., 2018), slightly lower than the lung deposition for BGF MDI in this study. The *in silico* study also showed that the lung deposition of BDP/FF/G was comparable to BDP/FF, and that for BDP/FF *in silico*, lung deposition data were similar to those obtained using gamma scintigraphy (De Backer et al., 2010).

A potential limitation of the current study is the low number of subjects and that it enroled healthy subjects rather than patients with COPD. However, the small study size and the enrolment of healthy subjects are common in gamma scintigraphy studies (Boyd et al., 2004; De Backer et al., 2010; Hirst et al., 2002; Nikander et al., 2010; Taylor et al., 2018; Weers et al., 2009), and gamma scintigraphy studies with BDP/FF showed similar deposition in healthy subjects and in patients with asthma or COPD (De Backer et al., 2010). An additional

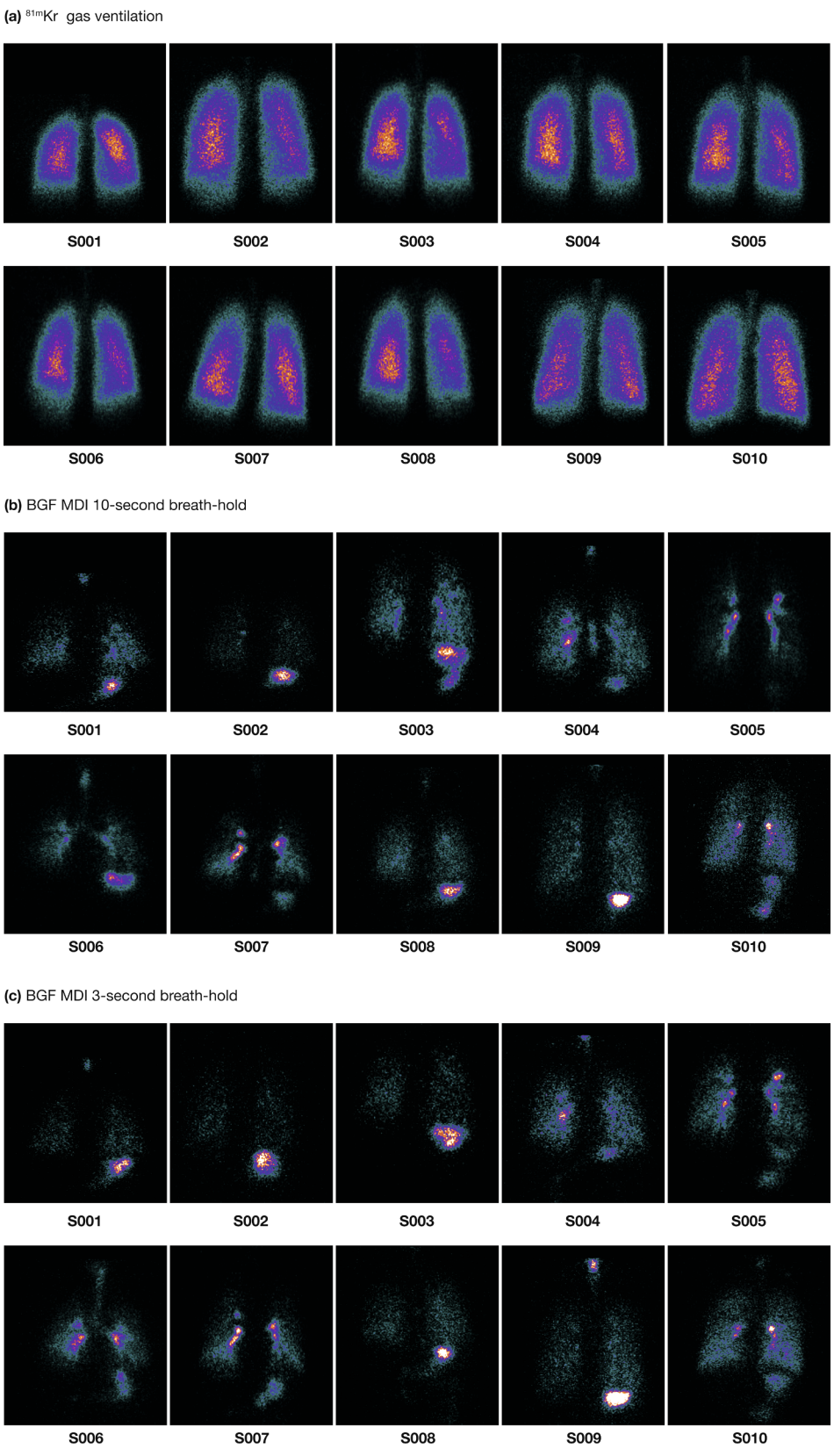

Fig. 3. Gamma scintigraphy posterior view images of (a) Krypton-81 m gas ventilation, and lung deposition of BGF MDI (b) 10- and (c) 3-second breath-hold. Subject 002 was excluded from the PP analysis set for the 3-second breath-hold for poor dose inhalation and non-evaluable scintigraphy data.
BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; MDI, metered dose inhaler; PP, per protocol.

Table 1
Summary of derived deposition data (PP analysis set).

Treatment	Variable	Mean	SD	Median	Min, Max
BGF MDI	% emitted dose in lungs	34.5	14.4	42.8	17.3, 52.7
3-second breath-hold	% emitted dose in oropharyngeal + stomach regions	65.1	14.5	57.1	45.9, 82.3
(N = 9)	% emitted dose in exhalation filter	0.4	0.4	0.3	0.1, 1.4
	% ex-valve dose on actuator	10.0	1.6	9.9	7.7, 12.8
	Regional airway deposition ratio:				
	O/I	1.45	0.46	1.48	0.74, 2.09
	C/P	0.56	0.25	0.45	0.30, 1.05
	nO/I	0.75	0.23	0.79	0.47, 1.11
	sC/P	1.40	0.51	1.27	0.76, 2.19
BGF MDI	% emitted dose in lungs	37.7	15.2	35.5	20.3, 68.3
10-second breath-hold (N = 10)	% emitted dose in oropharyngeal + stomach regions	62.0	15.2	64.3	31.4, 79.5
	% emitted dose in exhalation filter	0.3	0.2	0.2	0.1, 0.7
	% ex-valve dose on actuator	10.3	1.5	10.5	7.5, 13.1
	Regional airway deposition ratio:				
	O/I	1.25	0.40	1.24	0.64, 1.76
	C/P	0.72	0.39	0.76	0.31, 1.62
	nO/I	0.65	0.20	0.61	0.41, 0.94
	sC/P	1.79	0.79	2.00	0.83, 3.19

BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; C/P, central/peripheral ratio; MDI, metered dose inhaler; nO/I, normalised O/I; O/I, outer/inner ratio; PP, per protocol; sC/P, standardised C/P ratio; SD, standard deviation.

scintigraphy study of BGF MDI in patients with moderate to severe COPD (NCT03906045) is currently ongoing (ClinicalTrials.gov, 2019).

In conclusion, these data in healthy male subjects show that BGF MDI, formulated using innovative co-suspension delivery technology, was efficiently deposited in the inner and the peripheral regions of the lungs, with similar regional deposition patterns following a 10- and 3-second breath-hold [Figs. 3b, c; 4], suggesting that a prolonged breath-hold is not needed with this triple combination formulation as adequate deposition occurred in the shorter, 3-second breath-hold. This may be particularly important for patients with COPD who are unable to

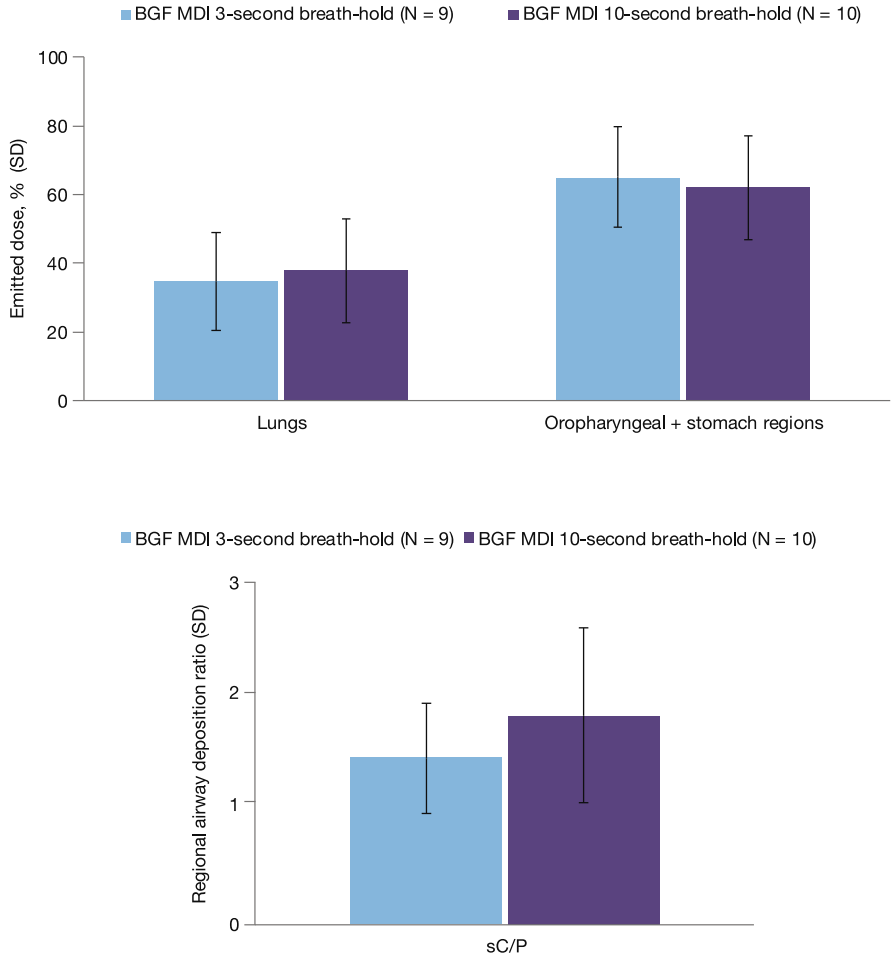

Fig. 4. Derived deposition data for (a) percentage emitted dose in the lungs and oropharyngeal + stomach regions and (b) sC/P (per protocol analysis set).
BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; MDI, metered dose inhaler; sC/P, standardised central/peripheral ratio, SD, standard deviation.

Table 2
Lung deposition and regional airway deposition for the 10- versus 3-second breath-hold (per protocol analysis set).

Variable	3-second breath-hold LSM (SE) (N = 9)	10-second breath-hold LSM (SE) (N = 10)	10- vs 3-second breath-hold Difference in LSM (SE)	95% CI
Emitted dose in lungs, %	34.9 (4.8)	40.3 (4.8)	5.5 (3.9)	–3.8, 14.8
Regional airway deposition ratio:				
O/I	1.42 (0.12)	1.25 (0.12)	–0.17 (0.07)	–0.33, –0.01
C/P	0.57 (0.11)	0.74 (0.11)	0.17 (0.08)	–0.01, 0.35
nO/I	0.73 (0.07)	0.65 (0.07)	–0.09 (0.04)	–0.17, 0.00
sC/P	1.42 (0.23)	1.82 (0.23)	0.40 (0.18)	–0.03, 0.84

PP analysis represents subjects with data for both breath-holds, only.
Results obtained using a mixed-effects ANOVA with fixed effects for the study period, sequence, treatment and a random effect of subject (sequence). One subject was excluded from the PP analysis set for the 3-second breath-hold for poor dose inhalation resulting in non-evaluable scintigraphy data. Only evaluable data from subjects for both treatments were compared, resulting in the reduced number (9) in the comparisons.
ANOVA, Analysis of variance; BGF, budesonide/glycopyrronium/formoterol fumarate dihydrate; CI, confidence interval; C/P, central/peripheral ratio; LSM, least-squares mean; MDI, metered dose inhaler; O/I, outer/inner ratio, nO/I, normalised O/I; PP, per protocol; sC/P, standardised C/P ratio; SE, standard error.

achieve a 10 second breath-hold and for the large number of patients with airway disease who, despite having the ability, do not hold their breath for 10 seconds following inhalation from a pMDI.

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CRediT authorship contribution statement

Samuel Israel: Writing - review & editing, Project administration, Investigation, Resources, Visualization, Conceptualization, Methodology. **Ashish Kumar:** Writing - review & editing, Formal analysis, Software, Validation, Visualization. **Kiernan DeAngelis:** Writing - review & editing, Visualization. **Magnus Aurivillius:** Writing - review & editing, Visualization, Conceptualization. **Paul Dorinsky:** Writing - review & editing, Visualization, Conceptualization, Methodology, Supervision. **Nicolas Roche:** Writing - review & editing, Visualization, Conceptualization. **Omar S. Usmani:** Writing - review & editing, Visualization, Conceptualization.

Declaration of Competing Interest

Samuel Israel has no conflicts to report. Ashish Kumar is an employee of Kelly Services Global LLC. Nicolas Roche reports grants and personal fees from Boehringer Ingelheim, Novartis, Pfizer and personal fees from AstraZeneca, Chiesi, Cipla, GlaxoSmithKline, Mundipharma, Sanofi, Sandoz, Teva, Trudell, Zambon and 3 M. Omar S. Usmani reports academic grants from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline and personal fees from Aerocrine, AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Mundipharma, NAPP, Prosonix, Sandoz, Takeda and Zentiva. Magnus Aurivillius and Paul Dorinsky are employees of AstraZeneca. Kiernan DeAngelis is a former employee of AstraZeneca.

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Supplementary materials

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