STUDY PROTOCOL

STUDY TITLE: A Phase I, Single-Dose, Gamma Scintigraphy Study to Assess the Pulmonary Deposition of Technetium-99m Radiolabelled Budesonide, Glycopyrronium and Formoterol Fumarate MDI Following a Maximal Breath-Hold of up to 10 seconds in Patients with Moderate to Severe/Very Severe Chronic Obstructive Pulmonary Disease.

STUDY NUMBER: RD708/34000

D5980C00020

EudraCT NUMBER: 2018-004453-25

IRAS ID 259684

INVESTIGATIONAL PRODUCT(s): **Test IP:** Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (BGF MDI; PT010)

PLANNED STUDY DOSE: ^{99m}Tc Radiolabelled BGF MDI
320/14.4/9.6 µg ex-actuator (dosed via two inhalations)

CHIEF INVESTIGATOR: [redacted]
Simbec Research Limited
Merthyr Tydfil
CF48 4DR, UK

STUDY SPONSOR: AstraZeneca

PROTOCOL FINALISATION STATEMENT

This protocol is not considered final unless accompanied by an approval letter from the Research Ethics Committees and Notice of Acceptance from the relevant Competent Authority.

Protocol Prepared by: [redacted]

1 SIGNATURE PAGE

I declare that I have read and understood this study protocol. I agree to abide by this protocol (subject to any amendments agreed in writing between the sponsor and Chief Investigator). Any changes in procedure will only be made if necessary to protect the safety, rights or welfare of the patients.

STUDY SPONSOR:

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Date: 05 March 2019

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Date: 05 March 2019

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Signature: [redacted]

Date: 05 Mar 2019

2 SYNOPSIS

NAME OF COMPANY: AstraZeneca
NAME OF INVESTIGATIONAL PRODUCT (IP): Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (BGF MDI; PT010), radiolabelled with ^{99m}Tc, containing 160/7.2/4.8µg and ≯5 megabecquerel (MBq) per actuation.
NAME OF ACTIVE INGREDIENT: Budesonide, Glycopyrronium and Formoterol Fumarate.
TITLE OF STUDY: A Phase I, Single-Dose, Gamma Scintigraphy Study to Assess the Pulmonary Deposition of Technetium-99m Radiolabelled Budesonide, Glycopyrronium and Formoterol Fumarate MDI Following a Maximal Breath-Hold of up to 10 seconds in patients with Moderate to Severe/Very Severe Chronic Obstructive Pulmonary Disease.
CHIEF INVESTIGATOR:
STUDY CENTRE: Simbec Research Ltd (Simbec) Merthyr Tydfil, CF48 4DR, UK Screening procedures may be performed at selected National Health Service (NHS) study centres. All procedures conducted as part of the treatment period and follow up (including all scintigraphy procedures) will be performed at Simbec.
CLINICAL PHASE: I
OBJECTIVES: **Primary:** • To assess the pulmonary deposition of radiolabelled BGF MDI in patients with moderate to severe/very severe Chronic Obstructive Pulmonary Disease (COPD) following a maximal breath-hold of up to 10 seconds (s). **Secondary:** • To assess the regional airway deposition patterns of radiolabelled BGF MDI in the lungs in patients with moderate to severe/very severe COPD following a maximal breath-hold of up to 10 s. • To assess the deposited dose of radiolabelled BGF MDI in the oropharyngeal and stomach regions in patients with moderate to severe/very severe COPD following a maximal breath-hold of up to 10 s. • To assess the deposited dose of radiolabelled BGF MDI detected on the actuator and exhalation filter in patients with moderate to severe/very severe COPD following a maximal breath-hold of up to 10 s. **Safety Objectives:** • To assess the safety of radiolabelled BGF MDI in patients with moderate to severe/very severe COPD based on adverse events (AEs).
METHODOLOGY: This will be a single-dose study to assess the pulmonary deposition of Radiolabelled BGF MDI following administration in male and female patients with moderate to severe/very severe COPD. Serious Adverse Events (SAEs) will be recorded from the time of signing of informed consent form to Post-study Follow-up phone call. Non-serious AEs will be collected from the first dose on Day 1 to Post-study Follow-up phone call. Study drug will be administered by inhalation. The study will comprise of a Screening Visit, followed by a single Treatment Period and a Post-study Follow-up phone call.

Screening (Day -28 to Day -1): Screening assessments will be carried out within 28 days before administration of IP. Eligible patients will be asked to return for the Treatment Period. Continued eligibility will be assessed on Day -1 and prior to IP dosing.

Treatment Period (Day -1 to Day 1): Eligible patients will receive a single-dose of IP followed by a maximal breath-hold of up to 10 s.

The Treatment Period will be from the afternoon before (Day -1) until 4 hours (h) post-dose (Day 1). Patients will arrive at the Clinical Unit on Day -1. Patients will withhold their regular COPD medication in the morning of Day 1 and instead be given short-acting Ventolin HFA and Atrovent HFA which may be used up to (but not within) 6 h prior to IP dosing. IP will be administered on the afternoon of Day 1 fasted (after a fast of at least 2 h) and patients will be discharged 4 h post dose (Day 1), provided there are no ongoing safety concerns. During the treatment period, patients will also undergo a Krypton-81m (^{81m}Kr) gas ventilation imaging scan and a Cobalt-57 (^{57}Co) transmission scan. SAEs will be evaluated from the time of signing the informed consent form and up to the Post-study Follow-up phone call, non-serious AEs will be evaluated from Day 1 following IP dose and up to the Post-study Follow-up phone call.

Study assessments will be conducted periodically throughout the in-house period as per Table 9.6.1

Post-study: Post-study Follow-up phone call will be conducted 7-14 days after IP dose.

NUMBER OF PATIENTS:

Approximately 20 patients (10 per cohort) will be enrolled for at least 16 to complete the study:

- Approximately 10 patients with moderate COPD (Forced Expiratory Volume in 1 Second (FEV_1) ≥50-<80% of predicted normal), for at least 8 completed patients.
- Approximately 10 patients with severe/very severe COPD (FEV_1 <50% of predicted normal), for at least 8 completed patients.

INCLUSION CRITERIA:

To be confirmed at screening:

1. Males and females at least 40 years of age and no older than 80 years.
2. Patients with diagnosis of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [1].
   - Post bronchodilator (BD) FEV_1 / Forced Vital Capacity (FVC) ratio must be < 0.70.
   - Post BD FEV_1 must be < 80% predicted.
3. Patients with no clinically significant history of previous allergy/sensitivity to Ventolin hydrofluoroalkane (HFA), Atrovent HFA, Budesonide, Glycopyrronium and Formoterol Fumarate or any of the excipients contained within the IP.
4. Patients with a Body Mass Index (BMI) between 18 and 33 kg/m^2 extremes inclusive.
   BMI = body weight (kg) / [height (m)]^2.
5. All patients must be receiving 1 or more inhaled maintenance therapies, including at least 1 long-acting bronchodilator, for the management of their COPD for at least 4 weeks prior to the Screening Visit.
6. Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g. 20 cigarettes per day for 10 years or 10 cigarettes per day for 20 years represent 10 pack-years)].
7. Female patients of child bearing potential with negative pregnancy test at screening and willing to use 2 effective methods of contraception, i.e., established method of contraception + condom, if applicable

(unless of non-childbearing potential or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the patient) from first dose until 3 months after last dose of IP.

8. Female patients of non-child bearing potential with negative pregnancy test at the Screening Visit. For purposes of this protocol, menopausal women are defined as women ≥ 50 years old who are amenorrheic for 12 consecutive months or more following cessation of all exogenous hormonal treatment. *Menopausal status will be confirmed by demonstrating at screening that levels of follicle stimulating hormone (FSH) fall within the respective pathology reference range. In the event a patient's menopause status has been clearly established (for example, the patient indicates she has been amenorrheic for 10 years), but FSH levels are not consistent with a post-menopausal condition, determination of patient eligibility will be at Investigator's discretion following consultation with the sponsor.*
9. Male patients willing to use 2 effective methods of contraception, i.e., established method of contraception + condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the patient) from first dose until 3 months after last dose of IP.
10. Patients with no clinically significant abnormal serum biochemistry and haematology values within 28 days before the first dose of IP as judged by the Investigator.
11. Patients with a negative urinary drugs of abuse at screening, determined within 28 days before the first dose of IP (a positive result may be repeated at Investigator's discretion).
12. Patients with no clinically significant abnormalities in 12-lead ECG determined within 28 days before the first dose of IP as judged by the Investigator.
13. Patients with no clinically significant abnormalities in vital signs (e.g., systolic/diastolic blood pressure, pulse rate, oral body temperature) determined within 28 days before first dose of IP.
14. Patients must be available to complete the study (including Post-study Follow-up phone call) and comply with study restrictions.
15. Patients must be able to perform reliable, reproducible pulmonary function test manoeuvres per ATS/ERS guidelines[1].
16. Patients must be able to demonstrate proper oral MDI inhalation technique.
17. Patients must satisfy the Investigator about their fitness to participate in the study.
18. Patients must provide written informed consent to participate in the study.

To be re-confirmed on day -1 / prior to IP dosing:

- Patient continues to meet all screening inclusion criteria.
- Patient with a negative urinary drugs of abuse screen (including alcohol).
- Female patient with negative pregnancy test.
- Patient continues to demonstrate proper oral MDI inhalation technique.

EXCLUSION CRITERIA:

To be confirmed at screening:

1. Any significant disease or disorder (e.g. including but not limited to gastrointestinal, hepatic, renal/urinary tract, haematological, neurological, musculoskeletal, endocrine, metabolic, eye, psychiatric which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results of the study.
2. Respiratory:
    a. Current diagnosis of asthma, in the opinion of the Investigator.
    b. COPD due to α1-Antitrypsin Deficiency.

c. Sleep apnoea that, in the opinion of the Investigator, is uncontrolled.
d. Other Respiratory Disorders: known active tuberculosis, lung cancer, cystic fibrosis, significant bronchiectasis (high resolution computerised tomography [CT] evidence of bronchiectasis that causes repeated acute exacerbations), immune deficiency disorders, severe neurological disorders affecting control of the upper airway, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or pulmonary thromboembolic disease. Note: allergic rhinitis is not exclusionary.
e. A moderate or severe exacerbation of COPD ending within 6 weeks prior to dosing (Day 1). The end date of an exacerbation is the last day of treatment with systemic corticosteroids or antibiotics.
f. Prior pulmonary resection or Lung Volume Reduction Surgery [i.e., lobectomy, bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants)].

3. Cardiovascular

   Patients with significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure (including significant cor pulmonale), uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator.
4. Current cancer diagnosis requiring treatment.
5. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days (or 5 half-lives (whichever is longer) prior to the first dose of IP that, in the opinion of the Investigator, may interfere with patient safety or the objectives of the study (see Section 9.4.3).
6. A clinically significant history of drug or alcohol abuse.
7. Female patients who are pregnant or lactating, or are planned to become pregnant during the course of the study
8. Hypersensitivity to β2-agonists, muscarinic antagonists or corticosteroids or any component of the IP.
9. Participation in a new chemical entity clinical study within the previous 3 months or treatment with investigational study drug (or device) in another clinical study within the last 30 days or 5 half-lives, whichever is longer. Note: Observational studies (i.e. studies not requiring change to medication or additional intervention) are allowed (Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study).
10. Inability to communicate well with Investigators (i.e., language problem, poor mental development or impaired cerebral function).
11. Donation of 450 mL or more blood within 3 months before the first dose of IP.

To be re-confirmed at day -1 / prior to IP dosing:

- Development of any exclusion criteria since the Screening Visit.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements since screening, unless in the opinion of the Investigator and sponsor's Responsible Physician the medication will not interfere with the study procedures or compromise patient safety.
- Participation in a clinical study since the Screening Visit.
- Donation of 450 mL or more blood since the Screening Visit.

IP ADMINISTRATION:

Each patient will receive the following IP over a single Treatment Period (1 dose), followed by up to a 10 s breath-hold:

- **Test IP**: a single-dose of Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (BGF MDI; PT010), radiolabelled with ^{99m}Tc, containing 160/7.2/4.8µg and ≯5MBq per actuation, 2 oral inhalations (total dose of 320/14.4/9.6 µg).

STUDY SPECIFIC ASSESSMENTS:

Patients will be trained during their Screening Visit by site trained staff on the correct MDI dosing procedure using a commercially available MDI Aerosol Inhalation Monitor (AIM, Vitalograph UK) with placebo i.e. HFA propellant only, canisters. The Vitalograph AIM will be used in order to confirm that the patient is achieving an appropriate inspiratory flow rate following the training provided. Patients who are not able to use the device correctly will not be eligible for enrolment to the study.

On Day -1 and Day 1 pre-dose, patients will use the sponsor's placebo MDI to confirm that the patient is capable of using the 'test' MDI correctly; the placebo MDI is manufactured by AstraZeneca in the image of the active test product, with no active moieties. Patients will have an opportunity to practice using the sponsor placebo MDI (provided by study personnel and under the direct supervision of study personnel) at any time in the study. At any point during the study, site staff should re-train the patient using the AIM device if it is felt that the patient is not performing the inhalation correctly.

At the time of dosing, patients will be required to perform 2 inhalations (after priming) under the supervision of an Investigator. Immediately following each inhalation, patients will perform a maximal breath-hold, up to 10 s, prior to exhaling into an exhalation filter. Once the second breath hold and exhalation has been performed, patients will rinse their mouth with water and expel the washings for collection. Patients will then swallow bread and water.

Thereafter, posterior and anterior views of the lungs and stomach, and a lateral head and neck view will be recorded using a gamma camera. All images will be of a maximum of 200 s in duration. Images will also be acquired of the exhalation filter and collected mouth washings. Mass balance calculations will be undertaken to determine the fraction of the emitted dose delivered to the lungs of the patients. The distribution pattern of radiolabel within the lungs will be described in terms of a ratio of radioactive counts in different lung regions, after accounting for differences in regional lung volumes.

SAEs will be evaluated from the time of signing the informed consent form and up to the Post-study Follow-up phone call, non-serious AEs will be evaluated from Day 1 following IP dose and up to the Post-study Follow-up phone call.

Test IP: The study product is summarised in the table below:

Product Name & Dose	**Product Strength**	**Dosage Form/ Fill Count**	**Administration**
Radiolabelled BGF MDI (PT010)	160/7.2/4.8 µg per actuation (≥5MBq per actuation)	MDI/ 120 inhalations	Taken as 2 oral inhalations[a]

[a] Single dose, dosed via oral inhalation.

Placebo and Training Device: The placebo and training devices are summarised in the table below:

Placebo and Training Devices	Product Strength	Dosage Form/ Fill Count	Administration
Placebo MDI (PT000)	Formulation does not contain active ingredient	MDI/ 120 inhalations	Inhaled orally as needed for training purposes[a]
Placebo MDI for use with commercially available aerosol inhalation monitor (AIM) device for training purposes at Screening Visit, Day -1 and Day 1 pre-dose[b]	Formulation does not contain active ingredient	N/A	Inhaled orally as needed for training purposes

[a] Placebo will be used for training purposes on Day-1 and Day 1 pre-dose.
[b] If it is felt that the patient is not performing the inhalation correctly the patient will be re-trained using the AIM device.

CRITERIA FOR EVALUATION:

Scintigraphy:

Primary endpoint:

- The percentage (%) emitted dose of radiolabelled BGF MDI deposited in the lungs following a maximal breath-hold of up to 10 s.

Secondary endpoints:

- The regional airway deposition ratios including the non-normalized parameters outer to inner (O/I) and central to peripheral (C/P) regions and the normalized parameters Penetration Index (PI) and standardized C/P ratio (sC/P) of the radiolabelled BGF MDI following a maximal breath-hold of up to 10 s.
- The fraction of the dose of radiolabelled BGF MDI deposited in the oropharyngeal and stomach regions (expressed as % emitted dose) following a maximal breath-hold of up to 10 s.
- The fraction of the dose of radiolabelled BGF MDI deposited on the actuator (expressed as % ex-valve dose) and exhalation filter (expressed as % emitted dose) following a maximal breath-hold of up to 10 s.

Safety:

- Adverse Events

STATISTICAL METHODS: All statistical analysis will be performed using Statistical Analysis Software (SAS)® version 9.3 or higher.

Scintigraphy Data:

The dose to the lung and the oropharynx (including mouth washings and stomach deposition) will be quantified and summarised. This will be achieved by expressing the detected activity as a percentage of the dose emitted from each treatment following appropriate corrections for regional attenuation, background activity, and radioisotope decay. The distribution of radioactivity in different lung regions will be quantified by determining regional radioactive counts after correction for differences in regional lung volume using analysis from the ^{81m}Kr gas scan. The "outer" and "inner" together with "central" and "peripheral" lung regions will be analysed.

Derived scintigraphy deposition variables will be listed and summarised by cohort and overall. Additionally, as supportive information, differences between the cohorts will be estimated using analysis of variance

(ANOVA) and relationships between the deposition endpoints, COPD severity and breath-hold time will be investigated.

Demographic and Background Data: All demographic and background data will be listed. Demographic data will include respiratory demographic data collected in relation to the inclusion criteria i.e. years since COPD diagnosis, number of pack-years smoked, current smoker (yes/no), FEV_1, FEV_1 % predicted normal (%pn), FEV_1/FVC, current COPD maintenance medication. Demographic data will be summarised descriptively (age, height, weight, BMI and respiratory demographics) and by frequency (race and gender) for each cohort and overall. Patient disposition and analysis sets (all enrolled safety and per protocol [PP]) will also be listed and summarised by frequency for each cohort and overall.

Sample Size:

No formal sample size calculation has been performed since this is an investigational study to quantify lung deposition without reference to any marketed formulation. However, a sample size of approximately 20 (10 per patient cohort) will allow an estimate of lung deposition from these formulations to be made within each cohort. 20 patients will be enrolled to ensure that at least 16 patients complete the study. In other investigational scintigraphy studies, sample sizes between 5 and 15 have typically been reported[2-9].

Safety:

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that is current at the time of database lock. All AE's will be listed and the incidence of Treatment Emergent-AEs (TEAEs) will be summarised by organ system, preferred term, severity and relationship to study drug.

DURATION OF STUDY:

Approximately 6 weeks for each individual (from Screening Visit to Post-study Follow-up phone call).

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4 ABBREVIATIONS USED IN THE TEXT

- ABPI Association of the British Pharmaceutical Industry
- AE(s) adverse event(s)
- AIM aerosol inhalation monitor
- ALB albumin
- ALKP alkaline phosphatase
- ALT alanine transaminase
- ANOVA analysis of variance
- AST aspartate transaminase
- BASO basophils
- BD bronchodilator
- BGF Budesonide, Glycopyrronium and Formerol Fumerate
- BIL-D direct bilirubin
- BIL-T total bilirubin
- BLQ below the limit of quantification
- BMI body mass index
- CA calcium
- CKD-EPI Chronic Kidney Disease Epidemiology Collaboration
- CL chloride
- COPD chronic obstructive pulmonary disease
- CSP clinical study protocol
- C/P central to peripheral
- BUN blood urea nitrogen
- CREA creatinine
- CRF case report form
- CSR clinical study report
- CTA Clinical Trial Authorisation
- CV% coefficient of variation
- DPS disintegration per second
- DUS disease under study
- EC European Commission
- ECG electrocardiogram
- ED effective dose
- EMA European Medicines Agency
- EOS eosinophils
- FDA Food and Drug Administration
- FEV forced expiratory volume
- FSH follicle stimulating hormone
- FVC forced vital capacity
- GCP Good Clinical Practice
- GGT gamma glutamyl transferase
- GLU glucose
- GM geometric mean
- GMP Good Manufacturing Practice
- h hour(s)
- HCT haematocrit
- HFA hydrofluoroalkane
- HGB haemoglobin
- HPLC high-performance liquid chromatography
- ICH International Conference on Harmonisation
- ICRP International Commission on Radiological Protection
- ICS inhaled corticosteroid
- IP investigational product
- K potassium
- LABA long acting beta agonist
- LAMA long acting muscarinic antagonist
- Ltd Limited
- LYMP lymphocytes
- MBq megabecquerel
- MCV mean cell volume
- MCH mean cell haemoglobin
- MCHC mean cell haemoglobin concentration
- MDI metered dose inhaler
- MedDRA Medical Dictionary for Regulatory Activities
- MG magnesium
- MHRA Medicines and Healthcare

products Regulatory Agency
- min(s) minute(s)
- MONO monocytes
- N number of patients in the analysis population
- n number of patients with non-missing observations
- NA sodium
- NEUT neutrophils
- NHS National Health Service
- O/I outer to inner
- PD pharmacodynamic
- PFT pulmonary function test
- PHOS phosphate
- PI penetration index
- PLT platelets
- PN predicted normal
- PP per protocol
- PR interval time the electrical impulse takes to travel from the sinus node through the AV node and entering the ventricles; measured from the beginning of the P wave to the beginning of the QRS complex
- PRN *pro re nata*
- PT preferred term
- QA quality assurance
- QID *quater in die*
- QP qualified person
- QRS QRS complex represents ventricular depolarisation
- QT interval the time for both ventricular depolarisation and repolarisation to occur, and therefore roughly estimates the duration of an average ventricular action potential.
- QTcB corrected QT interval using Bazett's formula
- QTcF corrected QT interval using Fridericia's formula
- RBC red blood cells
- REC Research Ethics Committee
- ROI region of interest
- s seconds
- SAE serious adverse event
- SAP statistical analysis plan
- SAS statistical analysis software by SAS Institute Inc., USA
- sCP standardized C/P ratio
- SD standard deviation
- SOC system organ class
- SOP standard operating procedure
- SUSAR serious, unexpected suspected adverse reaction
- Sv sieverts
- TEAE treatment emergent adverse event
- TMF trial master file
- TP total protein
- UK United Kingdom
- UV ultraviolet
- US United States
- WBC white blood cells
- ^{57}Co Cobalt-57
- ^{81m}Kr Krypton-81m
- ^{99m}TC Technetium-99m
- β-hCG β-human chorionic gonadotropin.

5 ETHICS

5.1 Research Ethics Committee

This study protocol will be submitted to the Research Ethics Committee (REC) for review and approval. The approval of the REC must be obtained before commencement of any study procedures.

The favourable opinion is conditional upon the sponsor registering the clinical trial in a publicly accessible database, within 6 weeks of the first participant recruited.

All substantial protocol amendments must be approved by the REC responsible for the study. Non-substantial amendments will not require prior approval by the REC.

If the study is stopped due to AEs it will not be recommenced without reference to the REC responsible for the study.

The outcome of the study (e.g. completed) will be reported to the REC responsible for the study within 90 days of completion of the last patient's final study procedures. In the event of the study being prematurely terminated a summary safety report will be submitted to the REC responsible for the study within 15 days.

A summary of the Clinical Study Report will be submitted to the REC responsible for the study within 1 year of completion of the last patient's final study procedures.

The REC will be informed that Simbec is a commercial organisation and that the study is funded by AstraZeneca. The patients who take part in the clinical study will be paid for their inconvenience and have been informed that there will be no benefits gained by their participation. All potential conflicts of interest will be declared by the Investigators.

5.2 Ethical Conduct of the Study

The Chief Investigator shall be responsible for ensuring that the clinical study is performed in accordance with the following:

- Declaration of Helsinki (Brazil, 2013) (See Appendix 2)[10].
- Association of the British Pharmaceutical Industry (ABPI) Guidelines for Phase 1 Trials (2018)[11].
- ICH (International Council on Harmonisation) Guideline for Good Clinical Practice (GCP) E6 (R2) (CPMP/ICH/135/95) 1996[12].
- The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) and subsequent amendments[13].
- Applicable local standard operating procedures (SOPs).

This clinical study has been registered in the EudraCT database and a Clinical Trials Authorisation (CTA) will be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA) prior to the start of the study in accordance with Part 3, Regulation 12 of the United Kingdom (UK) Statutory Instrument.

5.3 Patient Information and Consent

Potential patients who volunteer for participation in the study will be informed of the aims, methods, anticipated benefits and potential hazards of the study and any possible discomfort it may entail. Information will be given in both oral and written form and in the manner deemed appropriate by the Clinical Unit SOPs. Each patient will also be informed of his/her right to withdraw from the study at any time, for any reason.

A written explanation (participant information sheet) and informed consent form will be provided and the patient will be allowed sufficient time to consider the study information. Prior to signing the informed consent form, the patient will be given an opportunity to discuss any issues concerning the study with an Investigator who has suitable knowledge of the study and will have all questions answered openly and honestly.

If the patient is willing to participate in the study, the informed consent form will be signed and personally dated by the patient and the person taking consent. The patient will receive a copy of the informed consent form together with the participant information sheet and the original signed informed consent form will be retained with the study records at the Investigator site. In addition, the actions and completion of the consenting process will be recorded in the patient's medical record (i.e., source document).

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The study will be performed at Simbec Research Limited (Ltd.). Screening and follow-up procedures may be performed at selected NHS centres. The overall responsibility for the study will rest with the Chief Investigator, The Project Manager will act on behalf of the Chief Investigator to ensure the smooth and efficient running of all aspects of the study.

6.1 Study Personnel

Simbec Research Ltd (Simbec)

Chief Investigator:

Project Manager (Main Contact):

Project Manager Deputy:

Statistics:

Seirian Laboratories Central Laboratory:

The Chief Investigator will delegate study related activities according to staff responsibilities and job descriptions. This will be documented in a study specific delegation of responsibilities form.

Cardiff Scintigraphics Ltd.:

Sponsor: AstraZeneca

Project Manager (Main Contact):

Sponsor's Responsible Physician:

Monitor: ORION Clinical Services Ltd

Pharmacovigilance (PV): AstraZeneca (refer to safety plan)

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6.2 Indemnity Arrangements

The sponsor and Simbec carry insurance to pay compensation for injury, accident, ill health or death caused by participation in this study without regard to proof of negligence in accordance with the insurance and compensation in the event of injury in phase I clinical trials 2012[14], guidance issued by the ABPI, the BioIndustry Association and the Clinical Contract Research Association in consultation with the Department of Health and the National Research Ethics Service.

7 INTRODUCTION AND STUDY RATIONALE

AstraZeneca is developing Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) Inhalation Aerosol Metered Dose Inhaler (MDI) for the treatment of COPD. Budesonide, glycopyrronium, and formoterol fumarate are components (alone or in combination) of approved inhalation products for treatment of patients with COPD and their safety and efficacy are well characterised.

BGF MDI is formulated as a suspension with micronized budesonide, micronized glycopyrronium bromide, and micronized formoterol fumarate crystals co-suspended with spray-dried porous particles in a HFA propellant.

The sponsor is developing BGF MDI for the treatment of COPD. COPD is a common preventable and treatable disease characterised by persistent limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. COPD is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. COPD exacerbations are characterised by worsening respiratory symptoms beyond normal day-to-day variations, which leads to a change in medication. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations and improve health status and exercise tolerance [15,16].

Budesonide is a well-established corticosteroid approved worldwide in both intranasal and orally inhaled formulations. Inflammation is a component in the pathogenesis of COPD. The predominant inflammatory cells in COPD include neutrophils, CD8+ T-lymphocytes, and macrophages. The effects of ICS on pulmonary and systemic inflammation in patients with COPD are controversial and their role in the management of stable COPD is limited to specific indications. Regular treatment with ICS has been shown to improve symptoms, lung function and quality of life and reduce the frequency of exacerbations in COPD patients with a FEV_1<60% of predicted [15].

Glycopyrronium is a long acting muscarinic agonist (LAMA) which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including COPD.

Formoterol fumarate is a potent and selective long acting beta agonist (LABA) approved in the US and worldwide for COPD and for asthma. Formoterol fumarate is also approved in the US and worldwide in combination with budesonide for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β2 adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

The lung deposition of BGF in healthy volunteers is being evaluated in an ongoing study (D5980C00007). The purpose of the present study is to evaluate the lung deposition of BGF in COPD patients.

The safety of BGF has been monitored in phase I healthy volunteer studies as well as long-term phase III studies in COPD patients with no significant safety findings observed. Further details of the non-clinical studies and a summary of the known and potential risks and benefits (to patients with COPD) of BGF MDI can be found in the Investigator's brochure[17].

8 STUDY OBJECTIVES

8.1 Primary Study Objective

- To assess the pulmonary deposition of Radiolabelled BGF MDI in patients with moderate to severe/very severe Chronic Obstructive Pulmonary Disease (COPD) following a maximal breath-hold of up to 10 s.

8.2 Secondary Study Objective

- To assess the regional airway deposition patterns of Radiolabelled BGF MDI in the lungs in patients with moderate to severe/very severe COPD following a maximal breath-hold of up to 10 s.
- To assess the deposited dose of Radiolabelled BGF MDI in the oropharyngeal and stomach regions in patients with moderate to severe/very severe COPD following a maximal breath-hold of up to 10 s.
- To assess the deposited dose of Radiolabelled BGF MDI detected on the actuator and exhalation filter in patients with moderate to severe/very severe COPD following a maximal breath-hold of up to 10 s.

8.3 Safety Objective

- To assess the safety of radiolabelled BGF MDI in patients with moderate to severe/very severe COPD based on AEs.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This will be an open-label study to assess the pulmonary deposition of radiolabelled BGF MDI (PT010) following single dose administration in male and female patients with moderate to severe/very severe COPD. Safety will be assessed throughout the study and to Post-study Follow-up phone call. The study drug will be administered by oral inhalation.

The study will comprise of a Screening Visit, followed by a single Treatment Period and a Post-study Follow-up phone call.

Screening (Day -28 to Day -2): Screening assessments will be carried out within 28 days before administration of IP. Eligible patients will be asked to return for the Treatment Period. Continued eligibility will be confirmed pre-dose during the Treatment Period.

Treatment Periods (Day -1 to Day 1): During the Treatment Period, eligible patients will receive a single-dose of IP followed by a maximal breath-hold of up to 10 s.

- **Test IP**: a single-dose of Budesonide, Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler (BGF MDI; PT010), radiolabelled with ^{99m}Tc, containing 160/7.2/4.8µg and ≯5MBq per actuation, 2 inhalations (total dose of 320/14.4/9.6 µg).

The Treatment Period will be from the afternoon before (Day -1) until 4 h post-dose (Day 1). Patients will arrive at the Clinical Unit on Day -1, IP will be administered on the afternoon of Day 1 fasted (following a fast of at least 2 h) and patients will be discharged 4 h post-dose (Day 1), provided there are no ongoing safety concerns. During the Treatment Period, patients will also undergo a Krypton-81m (81mKr) gas ventilation imaging scan and a Cobalt-57 (57Co) transmission scan. SAEs will be evaluated from the time of signing the informed consent form and up to the Post-study Follow-up phone call, non-serious adverse events will be evaluated from first dose and up to the Post-study Follow-up phone call.

Post-study: Post-study Follow-up phone call will be conducted 7 to 14 days after dosing. If following the Post-study Follow-up phone-call, the Investigator determines that the patient requires additional follow-up, then this may be performed at the discretion of the Investigator

The conclusion of the study is defined as last patient last visit.

The study will take place in the [redacted] under full medical and nursing supervision, with the exception of some screening and follow-up procedures, which may be undertaken at selected NHS sites.

A schedule of all study assessments is provided in Table 9.6.1.

9.2 Study Stopping Criteria

The study will be discontinued if any unacceptable safety findings are identified. This decision will be made jointly by the Chief Investigator (or deputy) and the sponsor. A written document signed by the Chief Investigator (or deputy) and sponsor will be produced ratifying the decision.

Please see Section 9.3.3 for possible reasons for discontinuation of an individual patient.

9.3 Selection of Study Population

Approximately 20 patients will be enrolled for 16 to complete the study.

The study is to be conducted in patients with moderate to severe/very severe COPD. Patients will receive a single dose and are therefore not expected to derive any therapeutic benefit from taking part. A patient population with carefully considered inclusion/exclusion criteria will avoid the potential for interaction of BGF MDI (PT010) with any underlying disease state or concomitant medication that it may be necessary for patients to take, while ensuring that patients are fit and well enough for participation in the study.

The following eligibility criteria are designed to select patients for whom protocol treatment and procedures are considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient.

9.3.1 Inclusion Criteria

To be confirmed at screening (Please see criteria below to be re-confirmed on day -1 / prior to IP dosing):

1. Males and females of at least 40 years of age and no older than 80 years.
2. Patients with diagnosis of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) [1].
    - Post BD FEV_1/FVC ratio must be < 0.70.
    - Post BD FEV_1 must be < 80% predicted.
3. Patients with no clinically significant history of previous allergy/sensitivity to Ventolin HFA, Atrovent HFA, Budesonide, Glycopyrronium and Formoterol Fumarate or any of the excipients contained within the IP.
4. Patients with a Body Mass Index (BMI) between 18 and 33 kg/m^2 extremes inclusive. BMI = body weight (kg)/ $[height (m)]^2$.
5. All patients must be receiving 1 or more inhaled maintenance therapies, including at least 1 long-acting bronchodilator, for the management of their COPD for at least 4 weeks prior to screening.
6. Current or former smokers with a history of at least 10 pack-years of cigarette smoking. [Number of pack-years = (number of cigarettes per day/20) x number of years smoked (e.g. 20 cigarettes per day for 10 years or10 cigarettes per day for 20 years represent 10 pack-years)].
7. Female patients of child bearing potential with a negative pregnancy test at screening and willing to use 2 effective methods of contraception, i.e., established method of contraception + condom, if applicable (unless of non-childbearing potential or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the patient) from first dose until 3 months after last dose of IP.
8. Female patients of non-child bearing potential with negative pregnancy test at the screening. For purposes of this protocol, menopausal women are defined as women ≥ 50 years old who are amenorrheic for 12 consecutive months or more following

cessation of all exogenous hormonal treatment. *Menopausal status will be confirmed by demonstrating at screening that levels of follicle stimulating hormone (FSH) fall within the respective pathology reference range. In the event a patient's menopause status has been clearly established (for example, the patient indicates she has been amenorrheic for 10 years), but FSH levels are not consistent with a post-menopausal condition, determination of patient eligibility will be at Investigator's discretion following consultation with the sponsor.*

9. Male patients willing to use 2 effective methods of contraception, i.e., established method of contraception + condom, if applicable (unless anatomically sterile or where abstaining from sexual intercourse is in line with the preferred and usual lifestyle of the patient) from first dose until 3 months after last dose of IP.
10. Patients with no clinically significant abnormal serum biochemistry and haematology values within 28 days before the first dose of IP as judged by the Investigator.
11. Patients with a negative urinary drugs of abuse screening, determined within 28 days before the first dose of IP (a positive result may be repeated at Investigator's discretion).
12. Patients with no clinically significant abnormalities in 12-lead ECG determined within 28 days before the first dose of IP as judged by the Investigator.
13. Patients with no clinically significant abnormalities in vital signs (e.g., systolic/diastolic blood pressure, pulse rate, oral body temperature) determined within 28 days before first dose of IP.
14. Patients must be available to complete the study (including Post-study Follow-up phone call) and comply with study restrictions.
15. Patients must be able to perform reliable, reproducible pulmonary function test manoeuvres per ATS/ERS guidelines[1].
16. Patients must be able to demonstrate proper oral MDI inhalation technique.
17. Patients must satisfy the Investigator about their fitness to participate in the study.
18. Patients must provide written informed consent to participate in the study.

To be re-confirmed on day -1 / prior to IP dosing:

- Patient continues to meet all screening inclusion criteria.
- Patient with a negative urinary drugs of abuse screen (including alcohol).
- Female patient with negative pregnancy test.
- Patient continues to demonstrate proper oral MDI inhalation technique.

9.3.2 Exclusion Criteria

To be confirmed at screening (Please see criteria below to be re-confirmed on day -1 / prior to IP dosing)::

1. Any significant disease or disorder (including but not limited to gastrointestinal, hepatic, renal/urinary tract, haematological, neurological, musculoskeletal, endocrine, metabolic, eye, psychiatric which, in the opinion of the Investigator, may either put the patient at risk because of participation in the study, or influence the results of the study.
2. Respiratory
    a. Current diagnosis of asthma, in the opinion of the Investigator.
    b. COPD due to α1-Antitrypsin Deficiency.
    c. Sleep apnea that, in the opinion of the Investigator, is uncontrolled.
    d. Other Respiratory Disorders: known active tuberculosis, lung cancer, cystic fibrosis, significant bronchiectasis (high resolution CT evidence of bronchiectasis that causes repeated acute exacerbations), immune deficiency disorders, severe neurological disorders affecting control of the upper airway, sarcoidosis, idiopathic interstitial pulmonary fibrosis, primary pulmonary hypertension, or pulmonary thromboembolic disease. Note: allergic rhinitis is not exclusionary.
    e. A moderate or severe exacerbation of COPD ending within 6 weeks prior to dosing (Day 1). The end date of an exacerbation is the last day of treatment with systemic corticosteroids or antibiotics.
    f. Prior pulmonary resection or Lung Volume Reduction Surgery [i.e., lobectomy, bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants)].
3. Cardiovascular

    Patients with significant or unstable ischemic heart disease, arrhythmia, cardiomyopathy, heart failure (including significant cor pulmonale), uncontrolled hypertension as defined by the Investigator, or any other relevant cardiovascular disorder as judged by the Investigator.
4. Current cancer diagnosis requiring treatment.
5. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements within 28 days (or 5 half-lives (whichever is longer) prior to the first dose of IP that, in the opinion of the Investigator, may interfere with patient safety or the objectives of the study (see Section 9.4.3).
6. A clinically significant history of drug or alcohol abuse.
7. Female patients who are pregnant or lactating, or are planned to become pregnant during the course of the study.
8. Hypersensitivity to β2-agonists, muscarinic antagonists or corticosteroids, or any component of the IP.

9. Participation in a new chemical entity clinical study within the previous 3 months or treatment with investigational study drug (or device) in another clinical study within the last 30 days or 5 half-lives, whichever is longer. **Note:** Observational studies (i.e. studies not requiring change to medication or additional intervention) are allowed. (*Washout period between studies is defined as the period of time elapsed between the last dose of the previous study and the first dose of the next study*).
10. Inability to communicate well with Investigators (i.e., language problem, poor mental development or impaired cerebral function).
11. Donation of 450 mL or more blood within 3 months before the first dose of IP.

To be re-confirmed at day -1 / prior to IP dosing:

- Development of any exclusion criteria since the Screening Visit.
- Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements since screening, unless in the opinion of the Investigator and sponsor's Responsible Physician the medication will not interfere with the study procedures or compromise patient safety.
- Participation in a clinical study since the Screening Visit.
- Donation of 450 mL or more blood since the Screening Visit.

9.3.3 Removal of Patients from Therapy or Assessment

Each patient will be informed of their right to withdraw from the study at any time and for any reason.

An Investigator will withdraw a patient from the study at any time for any of the following reasons:

- If a patient experiences a serious or intolerable AE, that prevents them from continuing.
- If a patient incurs a significant protocol violation which impacts on their safety or the scientific integrity of the study (this will be discussed on a case-by-case basis with the sponsor).
- If a patient cannot comply with study procedures.
- At the request of the sponsor.
- If it is considered that the patient's health is compromised by remaining in the study or the patient is not sufficiently cooperative.
- If a patient is lost to follow-up.

The reasons for any patient withdrawal will be recorded on the study completion form of the case report form (CRF).

If a patient is withdrawn or chooses to withdraw from the study for any reason, every possible effort will be made to perform the evaluations described for the Post-study Follow-up (see Table 9.6.1). The data collected from withdrawn patients will be included in the CSR.

In the event of any abnormalities considered to be clinically significant, patients will be followed up with appropriate medical management until values are considered to be clinically acceptable. Referral or collaborative care will be organised if considered necessary.

Sixteen (16) patients are required to complete the study. Patients who withdraw from the study before receiving any study medication will be replaced. Patients who are withdrawn from the study due to significant drug-related AEs will not be replaced. Replacement of all other patients withdrawn from the study after receiving study medication will be decided on a case-by-case basis by the Chief Investigator (or deputy) and sponsor.

9.4 Additional Advice for Study Population

9.4.1 Contraception

To prevent pregnancy female patients of child bearing potential and male patients and their female partner must use 2 reliable forms of contraception, i.e.,

- Condom + Established use of oral, injected or implanted hormonal contraceptive.
- Condom + Intrauterine device.
- Condom + Diaphragm with spermicide.
- True abstinence, when this is in line with the preferred and usual lifestyle of the patient. *[Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception]*.

To prevent exposure of any partner (male or female) during non-vaginal intercourse to the semen from a male patient who has been exposed to the IP the following contraception must be used:

- Condom.

The chosen contraception method(s) must be followed from the first dose until at least 3 months after the last dose of IP.

Male patients must not have unprotected sexual intercourse with a female who is pregnant or breastfeeding during the study.

9.4.2 Sperm Donation

Patients must not donate sperm from the first dose and for at least 3 months after the last dose of IP.

9.4.3 Diet and Fluid Restrictions

9.4.3.1 Meal Times/Fasts

On the day of dosing, patients will receive a light breakfast, a light lunch and an evening meal. Food should not be consumed from 2 h prior to dosing, apart from that given during the dose administration. Fluids should not be consumed from 1 hour prior to dosing to 1 hour post-dose, apart from any given during the dose administration.

On all non-dosing study days, whilst resident in the Clinical Unit, meals will be served at standard times.

Patients will choose meals from a standard menu while resident at the Clinical Unit.

9.4.3.2 Fluid Intake

No fluids (apart from water taken with dose) are allowed from 1 h prior to dosing until 1 h afterwards. Water is then allowed ad libitum. Decaffeinated tea and coffee as well as squash/cordial are allowed from 4 h post-dose.

9.4.3.3 Alcohol Intake

The consumption of alcohol will be limited to a maximum of 2 units per day from 7 days prior to Day 1. Alcohol will be avoided completely for a period of not less than 2 days prior to Day 1 and throughout the study period. Any deviation outside this alcohol intake restriction will be assessed on a case-by-case basis at Investigator's discretion (provided the patient's alcohol intake will not impact in the safety aspects and objectives of the study and the patient has a negative alcohol screen prior to dosing).

9.4.3.4 Caffeine

Food or drink containing caffeine, including coffee, tea, cola, energy drinks or chocolates will be avoided completely for 2 days prior to Day 1 and whilst the patients are resident in the Clinical Unit.

9.4.3.5 Poppy and Sesame Seeds

Patients must not eat food containing poppy or sesame seeds for 3 days before attending the Clinical Unit (or selected NHS study centres for screening procedures). The consumption of poppy or sesame seeds can lead to a positive opiate result in the drugs of abuse test.

9.4.3.6 Grapefruit Juice and Other Restrictions

No food or drink containing grapefruit, cranberry, or Seville oranges (including marmalade and fruit juices), and/or food or drink, sweets, candies or other confectionary containing liquorice will be allowed from 7 days before Day 1 until the final study visit.

9.4.4 Other Life-Style Restrictions

9.4.4.1 Smoking

Smoking must be avoided during the Treatment Period until all procedures are completed.

9.4.4.2 Strenuous Exercise

Strenuous exercise must be avoided completely from 3 days before Day 1.

9.4.4.3 Blood Donation

Patients will be advised that they should not donate blood for at least 3 months after Day 1.

9.5 Investigational Product

9.5.1 Identity

The identity of the IP is detailed in Table 9.5.1.

Table 9.5.1 Identity of Investigational Medicinal Products

Product Name	Strength	Presentation/Form	Route
Radiolabelled BGF (PT010)	160/7.2/4.8 µg per actuation (≯5MBq per actuation)	MDI/ 120 inhalations	Taken as 2 oral inhalations[a]

[a] Single dose, dosed via oral inhalation.

Table 9.5.2 Identity of Placebo and Training Devices

Placebo and Training Devices	Strength	Presentation/Form	Route
Placebo MDI (PT000)	Formulation does not contain active ingredient	MDI/ 120 inhalations	Inhaled orally as needed for training purposes[a]
Placebo MDI for use with commercially available aerosol inhalation monitor (AIM) device for training purposes at screening, Day -1 and Day 1 pre-dose[b]	Formulation does not contain active ingredient	N/A	Inhaled orally as needed for training purposes.

[a] Placebo will be used for training purposed on D-1 and Day 1 pre-dose

[b] If it is felt that the patient is not performing the inhalation correctly the patient will be re-trained using the AIM device

The documentation supplied will make it possible to retrace the composition and pharmaceutical quality of the product.

9.5.2 Receipt and Storage

The test IP (BGF MDI; PT010) and Placebo MDI will be supplied by the sponsor.

The sponsor must notify the Chief Investigator, or the Project Manager, prior to dispatch of the IP supplies, and of the anticipated date of their arrival. IP should arrive at the study site at least 7 days before the first dosing day. The sponsor shall address all supplies to:

The Production Manager

[redacted]
Simbec Research Ltd
[redacted]
Merthyr Tydfil
CF48 4DR

Upon receipt, supplies will be dealt with as per Simbec SOP SR-IMP 053. Data from temperature monitors included with shipments will be downloaded. The sponsor will confirm that the transportation conditions are acceptable.

The IP will be stored under quarantine in a segregated, study-specific area, at 15-25ºC in a secure, temperature-controlled pharmacy. The shipping documentation and bulk product Qualified Person (QP) certification will be reviewed and the supplies will subsequently be removed from quarantine and approved for use.

9.5.3 Assembly and Release

Each study drug will be radiolabelled with ^{99m}Tc-pertechnetate at Simbec Research Ltd (by Cardiff Scintigraphics Ltd) according to Good Manufacturing Practice (GMP). The IP will be labelled as specified in Annex 13 (manufacture of IMP) of the European Commission (EC) guide to GMP[18].

The finished IP will be certified by Simbec's QP according to Simbec SOP BD/324/13/29.

9.5.4 Radiolabelling procedure

BGF (PT010) will be radiolabelled with ^{99m}Tc-pertechnetate at Simbec Research Ltd (by Cardiff Scintigraphics Ltd) according to GMP. Prior to radiolabelling, the MDI canister should be actuated 64 times, per the Actuation cycle as indicated below. This will be performed by hand. There will be a rest time of one minute between actuations. By decreasing the number of actuations in the canisters the total amount of radioactivity required to achieve the target specific activity i.e. ≯5MBq per actuation, is reduced. The radiolabelling process will follow established methods and will meet the industry standards as outlined in Newman *et al.* (2002)[19]. A solution of the gamma-emitting radiopharmaceutical ^{99m}Tc-pertechnetate (radioisotope t½ = 6 h) in a small volume of absolute ethanol i.e. < 10 µL, will be added to each MDI product using a cold transfer process.

The Actuation Cycle
1) **SHAKE** the inhaler for 5 seconds

– Keep the inhaler in the valve-down orientation at all time – Use a calibrated timer to determine the shaking duration – Shake the inhaler in an up-down orientation using only the elbow (i.e. avoid flicking the wrist to minimize potential for ergonomic injury) – Shake the inhaler using a stroke length of ~6 inches and a frequency of ~3 shakes/second (i.e. 15 shakes in 5 seconds) – The thumb should be positioned above the canister without making contact
2) **FIRE** the inhaler into a waste station (priming and seating) or NGI (aerosol collection) – Ensure that the canister is perpendicular to bench – Completely stop any motion of the inhaler before firing – Quickly depress the canister with the thumb using a firm, straight actuation – The delay between completion of shaking and firing the MDI should not exceed 2 seconds
3) **HOLD** the inhaler in the actuated position for 1 second – Use a calibrated timer to determine the hold duration
4) **RELEASE** the canister – Quickly and completely remove the thumb from the canister to release the actuation
5) **REST** the inhaler for 1 minute – Use a calibrated timer to determine the rest duration – During collection, the actuator should remain in the NGI during the rest period
6) **REPEAT** the actuation cycle (if necessary)

The ^{99m}Tc radioactivity in each administered dose i.e. two actuations of the MDI will not exceed 10 MBq.

Prior to the clinical study, the integrity of the surrogate radiolabel was tested *in vitro* using appropriate assays (e.g. high-performance liquid chromatography (HPLC) / ultraviolet (UV) for the actives and gamma camera for ^{99m}Tc). The emitted dose and particle size distribution of the aerosols *in vitro* was evaluated for each delivery system to ascertain that the radiolabel follows the drug substances with high fidelity. In addition, confirmatory experiments were conducted to demonstrate that the quantity and quality of the emitted actives are the same for the radiolabelled and non-radiolabelled formulations. Following *in vitro* radiolabelling validation studies, Master Batch Records were created to detail the method for admixture of ^{99m}Tc-pertechnetate with the MDI formulations at Simbec on each dosing day.

9.5.5 Radiation Dosimetry

The maximum radiation dose received by the patients will be 0.23 milli-Sieverts (mSv) for aerosol exposure and the ^{81m}Kr inhalation, this is equivalent to approximately 1.0 months background radiation exposure. The radiation exposure to the patients is expressed in terms of the effective dose (ED). This is a single figure specifying a hypothetical uniform whole body dose equivalent that would involve the same risk as the actual (non-uniform) dose distribution.

The dose equivalent is expressed in units of Sieverts (Sv) and is a measure of the energy absorbed by biological tissues (i.e., Jkg^{-1} (Gray)) and also takes into account a quality factor.

In the case of gamma radiation, the quality factor is 1. Thus, the dose equivalent is equal to the absorbed dose. The effective dose equivalent is the sum of the weighted organ dose equivalents. The weighting factors reflect the different radio sensitivity of various organs and tissues[20]

In the current study, the calculations of ED are based upon data in the Notes for Guidance on the Administration of Radioactive Substances to Persons for Purposes of Diagnosis, Treatment or Research and the Annals of the International Commission on Radiological Protection (ICRP) Publication 80 (1998)[21]. These documents provide information concerning the ED arising from a given maximum administered dose by a particular route of administration. The administered dose is defined in terms of MBq (i.e., 1 Becquerel = 1 disintegration per second (DPS), 1 MBq = 106 DPS). Thus, the ^{81m}Kr ventilation image ED (0.04 mSv) was derived from specific data relating to this diagnostic procedure. The ED for the ^{99m}Tc administration was extrapolated from data relating to both inhalation of ^{99m}Tc-pertechnetate and oral administration to account for the oropharyngeal deposition during the administration.

For comparison, the ED associated with common diagnostic x-ray and nuclear medicine procedures are as follows[22]:

Radiographic Test	**ED (mSv)**	**Equivalent Period of Natural Background Radiation (Months)***
Barium enema	2.2	9.78
Barium meal	1.3	5.78
Thoracic spine	0.38	1.69
Skull	0.068	0.30
Chest	0.014	0.06
CT Chest	6.6	29.33
Nuclear Medicine Test	**ED (mSv)**	
Bone scan	2.15-3.83	12-24
Lung perfusion/Liver scan	0.92 - 1.22	6-7
Current Study	**ED (mSv)**	
Radiolabel Deposition	0.23	1.0

* Assuming the average annual radiation dose in the UK from naturally occurring and artificial radiation sources is 2.7 mSv[23].

9.5.6 Metered Dose Inhaler Priming (IP)

A new inhaler with the radiolabeled study drug will be primed four times into a waste container by a study site team member who is an experienced MDI analyst. A new clean actuator will be fitted to the radiolabelled canister prior to each patient dosing. To ensure the canister is correctly seated in the new clean actuator two actuations will be fired to waste prior to patient dosing. This process will be performed by a study site team member who is an experienced MDI analyst.

9.5.7 IP Administration

Patients will be trained during their Screening Visit by site trained staff on the correct MDI dosing procedure using a commercially available MDI Aerosol Inhalation Monitor (AIM, Vitalograph UK) with placebo i.e. HFA propellant only, canisters. The AIM device will be used in order to confirm that the patient is achieving an appropriate inspiratory flow rate following the training provided. Patients who are not able to use the device correctly will not be eligible for enrolment to the study.

On Day-1 and Day 1 pre-dose, patients will use the sponsor's placebo MDI to confirm that the patient is capable of using the 'test' MDI correctly; the placebo MDI is manufactured by AstraZeneca in the image of the active test product, with no active moieties. Patients will have an opportunity to practice using the sponsor placebo MDI (provided by study personnel and under the direct supervision of study personnel) at any time in the study. At any point during the study, site staff should re-train the patient using the AIM device if it is felt that the patient is not performing the inhalation correctly. Patients will also receive training on how to exhale into the exhalation filter. The treatment will be administered to the patients under the supervision of the investigator, or an individual to whom the investigator has delegated this responsibility.

At the time of dosing, patients will be required to perform 2 inhalations (after priming) under the supervision of an Investigator. Immediately following each inhalation, patients will perform a maximal breath-hold of up to 10 s, prior to exhaling into an exhalation filter. The site will keep a record of each subject's breath hold time, in seconds, for each inhalation.

After the second breath hold and exhalation has been performed, patients will rinse their mouth with water (approximately 20 mL) and expel the washings for collection. Patients will then swallow bread (approximately quarter of a slice of bread) and water (approximately 100 mL).

Any patient who does not take the study drug as required will be withdrawn from the study. Patients will be dosed in close proximity to the gamma camera to allow rapid alignment between the detectors after the dose is administered (the required alignment of the patient between the detectors will be determined prior to dosing).

9.5.8 Return/Destruction

Unused, non-radiolabelled IP and IP containers will be held under quarantine in the Simbec Pharmacy pending return/destruction.

Radiolabelled IP will be placed in a secure area until the radiolabel has decayed sufficiently that it becomes safe to handle normally. It will then be treated in the same manner as non-radiolabelled IP.

The sponsor must provide approval for return/destruction of all remaining IP within 8 weeks of study completion. After this period, a charge for storage will be incurred.

9.5.9 Method of Numbering Patients

Patients will be numbered sequentially from 001 (i.e. 001, 002 etc.). Replacement patients will be assigned the same numbering as the patient they are replacing, however, 100 will be added to the number (i.e., 101 would replace 001 etc.).

9.5.10 Selection and Timing of Dose for Each Patient

Doses will be administered on Day 1 of the Treatment Period. Patients will be required to fast for at least 2 h prior to each dose (see Section 9.4.3.1).

9.5.11 Blinding

Not applicable.

9.5.12 Prior and Concomitant Therapy

Prior Medication: Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken within 28 days (or 5 half-lives (whichever is longer) prior to the first dose of IP, unless in the opinion of the Investigator and sponsor's Responsible Physician the medication will not interfere with the study procedures or compromise patient safety.

Medication which is considered necessary for the patient's safety and wellbeing (other than those listed in Section 9.5.13), may be given at the discretion of the Investigator.

All prescription or non-prescription drugs, including vitamins, herbal and dietary supplements taken during the 28 days before dosing will be noted in the patient's CRF along with:

- Dose and dose regimen
- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Inclusion of patients who have taken prior medication will be reviewed on a case-by-case basis in relation to the safety aspects and objectives of this study.

Concomitant Medication: Prescription or non-prescription drugs, including vitamins, herbal and dietary supplements should not be taken throughout the duration of the study, except for medication which is considered necessary for the patient's safety and wellbeing (other than those listed in Section 9.5.13), which may be given at the discretion of the Investigator.

If intake of ***ANY*** prior or concomitant medication is necessary during the study, this will be recorded on the patient's CRF along with:

- Dose and dose regimen
- Reason for use
- Dates of administration including start and end dates

- Dosage information including dose and frequency

Adjustment of COPD Medications: Patients who meet all entry criteria will continue their regular maintenance medication through Day -1. In the morning of Day 1, patients will withhold their regular maintenance medications, to be resumed after discharge from the Clinical Unit, and be provided Atrovent HFA and/or Ventolin HFA which may be used up to (but not within) 6 h before dosing.

Rescue Medication: The study site will supply Ventolin HFA and Atrovent HFA rescue medication. Although the use of rescue medications is allowable at any time during the study, the use of rescue medications should be delayed, if possible, for at least 4 h following the administration of Study treatment (regular medications me be resumed following discharge). The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

9.5.13 Other prohibited Medications

Patient using the below listed medications are prohibited from participating in this study. Patients who recently discontinued use of these medications may be considered for study enrollment provided they have not received these medications for a minimum of 4 weeks before the Screening Visit. These medications are prohibited throughout the course of the study.

Prohibited Medications

- Any drug with potential to significantly prolong the QT interval (e.g., quinidine, bepridil, sotalol, amiodarone, chlorpromazine, erythromycin, etc.)
- Non-selective beta-adrenergic antagonists
- Cardiac antiarrhythmics Class Ia, III
- Any drug that causes significant tachycardia (pseudoephedrine, appetite suppressants, etc.)
- Other investigational drugs
- CYP3A4 inhibitors, including amiodarone, diltiazem, cimetidine, erythromycin, itraconazole, norfloxacin, ciprofloxacin, fluconazole, ketoconazole, clarithromycin, fluvoxamine, mifepristone, nefazodone, and troleandomycin
- CYP3A4 inducers including barbiturates (e.g., phenobarbital), carbamazepine, phenytoin, and rifampin
- Anticonvulsants (barbiturates, hydantoins, and carbamazepine) for the treatment of seizure disorder
- Tricyclic antidepressants
- Antipsychotic drugs (phenothiazines)
- Monoamine oxidase inhibitors
- Anti-tumor necrosis factor α antibodies (e.g., infliximab and any other members of this class of drugs)
- Monoclonal antibodies
- Systemic calcineurin inhibitors

- Protease inhibitors
- Systemic anticholinergics
- Chinese complementary and alternative bronchodilatory medicines, ie, herbal therapies (e.g., *Astragalus membranaceus* [huáng qí], *Panax ginseng* [ginseng products], *Cordyceps sinensis*, and *A. membranaceus* [ghost moth caterpillar fungus])

9.5.14 Treatment Compliance

The dose of IP will be taken under supervision. The exact dosing time for each patient will be recorded on the patient's CRF.

9.6 Efficacy and Safety Variables

9.6.1 Efficacy and Safety Measurements Assessed and Flow Chart

A schedule of study assessments is provided in Table 9.6.1.

Simbec personnel (and personnel at selected NHS study centres) who have been appropriately trained will carry out study procedures.

Where more than 1 procedure is scheduled for the same time-point, the following order of priority will apply:

1. All baseline assessments may be performed within 1 h before dosing
2. ^{81m}Kr Ventilation Scan and ^{57}Co Transmission Scan may be performed at any time during the Treatment Period

Table 9.6.1 Study Flow Chart

Procedure	Screening	Treatment Period		Follow-up phone call
Study Day	**-28 to -2**	**Day-1**	**Day 1**	**7-14 days after dose**
Informed Consent	X			
Medical History	X			
Demographics	X			
Physical Examination	X			
Height, Weight and BMI	X			
Vital Signs (BP, Temperature, HR, Respiratory Rate)	X			
Eligibility Review	X	X	X	
12-lead ECG	X			
Clinical Laboratory Testing	X			
Lung Function Testing[a]	X			
Adverse Events	X	X	X	X
Concomitant Medications	X	X	X	X
Urine Drug Screen (including alcohol and cotinine)	X	X		
β-hCG pregnancy test (females only)	X(serum)	X(urine)		
FSH (females only)[b]	X			
^{81m}Kr Ventilation/^{57}Co Transmission Scan[c]		X	X	
Training on Inhaler Use (Use AIM device)[d]	X	X	X	
Training on Placebo MDI[e]			X	
Administer Radiolabelled BGF MDI			X	
Gamma Scintigraphy Imaging			X	

Study Flow Chart Footnotes:

a. Lung function testing will be performed pre and post BD. The post BD assessment will be used to confirm eligibility.

b. To be performed on females of non-child bearing potential only.

c. To be performed once during the Treatment Period. If logistical issues are encountered when performing the ^{57}Co Transmission Scan, the procedure may be performed at a separate visit.

d. At screening, a commercially available MDI aerosol inhalation monitor with placebo canisters (AIM device) will be used for inhalation device training. This device may also be used on Day-1 and Day 1 pre-dose if additional training is required.

e. The sponsor's placebo MDI will be used for inhalation device training.

f. If following the Post-study Follow-up hone-call, the Investigator determines that the patient requires additional follow-up, then this may be performed at the discretion of the Investigator

9.6.1.1 Demographic and Background Assessments

The following demographic and background assessments will be performed during the study at the time-points specified in Table 9.6.1.

9.6.1.1.1 Demographics and Baseline Characteristics

Demographic data: age, date of birth, gender, race, height, weight, BMI and respiratory demographic data (i.e. years since COPD diagnosis, number of pack-years smoked, current smoker (yes/no), FEV_1, FEV_1 %pn, FEV/FVC, current COPD maintenance medication).

Height in metres (to the nearest cm) and weight in kg (to the nearest 0.1 kg) in indoor clothing and without shoes will be measured. BMI = body weight (kg) / [height (m)]^2 will be calculated.

9.6.1.1.2 Medical History and Concurrent Conditions

Relevant medical history and current conditions will be recorded in the CRF.

9.6.1.1.3 Drugs of Abuse and Alcohol

Urine alcohol and drugs of abuse screen: Cannabinoids, amphetamines, cocaine, benzodiazepines, opiates cotinine and barbiturates.

A mid-stream urine sample will be collected into a 20 mL Sterilin tube.

Drugs of abuse and alcohol samples will be analysed by Seirian Laboratories, Simbec using the Roche Cobas c6000 analyser series comprising of c501 and e601 modules.

9.6.1.1.4 Pregnancy Test, Menstrual and Obstetric History

Pregnancy tests will be performed on all female patients regardless of post-menopausal or sterilised status. Pregnancy tests will be performed by Seirian Laboratories, Simbec. Serum pregnancy tests will be performed using the Roche Cobas c6000 analyser series comprising of c501 and e601 modules. Urine pregnancy analysis will be performed manually using appropriate kits.

FSH will be analysed from the biochemistry screen for females of non-child bearing potential only**.** FSH will be measured at Seirian Laboratories, Simbec or Prince Charles Hospital, Merthyr Tydfil.

9.6.1.2 Compliance with Inclusion/Exclusion Criteria

An Investigator will assess all participants against the study inclusion and exclusion criteria at screening and Day -1/prior to IP dosing. Compliance will be re-confirmed Day -1 / prior to dosing on Day 1.

9.6.1.3 Study Specific Assessments

9.6.1.3.1 Gamma Scintigraphy Imaging

On Day 1, patients will be prepared for scintigraphic imaging by attaching two external markers containing approximately 0.1 MBq ^{99m}Tc, anteriorly in an appropriate anatomical location. Markers may be applied to the patients to help with the alignment of subsequent gamma camera images.

Immediately following completion of dosing and exhalation into the exhalation filter, patients will rinse their mouths with water (approximately 20 mL), expel the washings for collection, and swallow a small piece of bread (approximately quarter of a slice of bread) and water (approximately 100 mL). Immediately thereafter, patients will be imaged using a gamma camera (Axis Dual Head, Philips Medicals Systems Limited) to obtain simultaneous anterior and posterior views of their lungs and stomach followed by a lateral view of their head and neck. All images will be of a maximum of 200 seconds in duration. Images will also be acquired of the MDI before and after use and the collected mouth washings. Calculations will be undertaken to determine the fraction of the emitted dose delivered to the lungs of the patients. The regional distribution pattern of radiolabel within the lungs will be described in terms of ratios of radioactive counts in outer/inner and central/peripheral lung regions, after accounting for differences in regional lung volumes.

9.6.1.3.2 ^{81m}Kr Ventilation and ^{57}Co Transmission Scans

Patients will undergo ^{81m}Kr gas ventilation imaging procedure during the Treatment Period. Patients with any abnormal findings in the ventilation scan that are not compatible with a COPD diagnosis, where a degree of abnormality is to be expected, will be excluded from further participation in the study.

The inhalation of an appropriate radioactive gas, such as ^{81m}Kr, is regarded as the 'gold standard' for definition of the ventilated regions of the lung. The ^{81m}Kr gas imaging procedure is conducted to allow accurate definition of the ventilated area of the lungs. The margins of the lungs, so defined, will be used as a template to permit accurate determination of the intrapulmonary deposition of radiolabelled drug. ^{81m}Kr gas will be supplied by an approved supplier.

For the ventilation scan, anterior and posterior views will be acquired while the patient inhales the ^{81m}Kr gas until a reading of 200,000 counts has been reached.

Patients will also undergo a ^{57}Co transmission scan on a single occasion. This will be performed during the Treatment Period, followed by a 30 minute washout before any of the aerosol dosing procedures, or if there are logistical issues, the procedure may be performed at a separate visit. A flood source of ^{57}Co will be used to generate a uniform count rate across the field of view of the gamma camera collimators. Patients will be positioned in front of the collimator to obtain an anterior image (up to 240 s duration) and a lateral head/neck image (up to 120 s duration).

The ^{57}Co transmission scans are performed to enable the regional tissue attenuation of the deposited radioactivity to be determined. These measurements are necessary due to the different attenuation of radioactivity deposited in the various anatomical regions. Upon inhalation, radioactivity will be deposited in the lungs, also in the mouth and subsequently swallowed, and a portion will remain in the oral cavity. The overlying tissues in each of these anatomical regions will reduce the proportion of detected radioactivity by varying degrees. Regions of interest (ROIs) equating to the various anatomical areas (e.g., thorax, abdomen, head and neck), will be drawn on the ^{57}Co transmission images and the attenuation of the detected radiation in each ROI will be determined.

9.6.1.3.3 Efficacy Assessments

Not applicable.

9.6.1.3.4 Safety Assessments

The following safety assessments will be performed at the time-points specified in Table 9.6.1.

9.7 Collection of Adverse Events

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section. The definitions of an AE or SAE can be found in Appendix 3.

AE will be reported by the patient (or, when appropriate, by a caregiver, surrogate, or the patient's legally authorized representative).

The investigator and any designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. For information on how to follow/up AEs see Section 9.7.3.

9.7.1 Method of detecting AEs and SAEs

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the patient is the preferred method to inquire about AE occurrences.

9.7.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from Day 1 following IP dose, throughout the Treatment Period and including the Post-study Follow-up phone call.
SAEs will be recorded from the time of signing of informed consent form.

All SAEs will be recorded and reported to the sponsor or designee within 24 h, as indicated in Appendix 3. The investigator will submit any updated SAE data to the sponsor within 24 h of it being available.

Investigators are not obligated to actively seek AE or SAE in former study patients. However, if the investigator learns of any SAE, including a death, at any time after a patient’s last visit

and he/she considers the event to be reasonably related to the Study treatment or study participation, the investigator may notify the sponsor.

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3.

9.7.3 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each patient at subsequent visits/contacts. All AE/SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the patient is lost to follow-up.

Any AEs that are unresolved at the Post-study Follow-up phone call will be followed up by the Investigator for as long as medically indicated, but without further recording in the CRF. AstraZeneca retains the right to request additional information for any patient with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

9.7.4 Adverse event data collection

The following variables will be collect for each AE;

- AE (verbatim)
- The date when the AE started and stopped
- Maximum intensity of AE (Refer to Appendix 3 A6 Intensity rating scale)
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- AE caused patient's withdrawal from study (yes or no)
- Outcome.

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to
- Date of hospitalisation
- Date of discharge

- Probable cause of death
- Date of death
- Autopsy performed
- Causality assessment in relation to Study procedure(s)
- Causality assessment to other medication.

9.7.5 Causality collection

The Investigator will assess causal relationship between Investigational Medicinal Product and each Adverse Event, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational medicinal product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures and/or AZ Medical device. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes'.

A guide to the interpretation of the causality question is found in Appendix 3 of the Clinical Study Protocol.

9.7.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study site staff: '*Have you had any health problems since you were last asked?'*, or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred (when possible) to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

9.7.7 Adverse events based on examinations and tests

The results from the Clinical Study Protocol mandated laboratory tests and vital signs will be summarised in the CSR.

No safety parameters are to be measured as standard during the study and only examined at the Screening Visit. Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs should therefore only be reported as AEs if they fulfil any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value/vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result/vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anaemia versus low haemoglobin value). In

the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

9.7.8 Hy's law

Not applicable.

9.7.9 Disease-under study (DUS)

Symptoms of DUS are those which might be expected to occur as a direct result of COPD. Events which are unequivocally due to disease under study should not be reported as an AE during the study unless they meet SAE criteria or lead to discontinuation of the IP.

9.7.10 Disease progression

Not applicable.

9.8 Safety Reporting and Medical Management

9.8.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational medicinal product, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then Investigators or other site personnel inform the appropriate AstraZeneca representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening adverse events where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform AstraZeneca representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

For further guidance on the definition of a SAE, see Appendix 3.

9.8.2 Maternal exposure

If a patient becomes pregnant during the course of the study, BGF MDI (PT010) should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as

SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality) should be followed up and documented even if the patient was discontinued from the study.

If any pregnancy occurs during the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

9.8.3 Paternal exposure

Please see Section 9.4.1 and Section 9.4.2.

Pregnancy outcomes must be collected for the female partners of any males who took the IP. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

9.8.4 Overdose

For this study, any dose of BGF (PT010) greater than 320/14.4/9.6 µg ex-actuator (dosed via two inhalations) will be considered an overdose.

If an overdose of an AstraZeneca study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site.

For overdoses associated with a SAE, the standard reporting timelines apply, see Section 9.7.2. For other overdoses, reporting must occur within 30 days.

9.8.5 Medication Error

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

The designated AstraZeneca representative works with the Investigator to ensure that all relevant information is completed within 1 (Initial Fatal/Life-Threatening or follow-up Fatal/Life-Threatening) or 5 (other serious initial and follow-up) calendar days if there is an

SAE associated with the medication error (see Section 9.7.2) and within 30 days for all other medication errors.

The definition of a Medication Error can be found in Appendix 3.

9.8.6 Laboratory Safety

All assessments will be performed at the time-points specified in Table 9.6.1.

9.8.7 Laboratory Eligibility Testing

Routine laboratory safety screen samples will be analysed by Seirian Laboratories, Simbec. Printed reports will include normal reference ranges. The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at centre as source data for laboratory variables. Clinically significant abnormalities that occur during AE reporting period will be recorded on the AE page. The reference ranges for laboratory parameters will also be filed in the Investigator site file.

Haematology: Haemoglobin (HGB), haematocrit (HCT), mean cell volume (MCV), mean cell haemoglobin (MCH), mean cell haemoglobin concentration (MCHC), red blood cells (RBC), white blood cells (WBC), neutrophils (NEUT), lymphocytes (LYMP), monocytes (MONO), eosinophils (EOS), basophils (BASO) and platelets (PLT).

Samples will be collected into an ethylenediaminetetraacetic acid (EDTA) collection tube* and analysed using the Siemens Advia 2120® or Siemens Advia 120®.

Biochemistry: Total protein (TP), albumin (ALB), alkaline phosphatase (ALKP), total bilirubin (BIL-T), direct bilirubin (BIL-D), alanine transaminase (ALT), aspartate transaminase (AST), gamma glutamyl transferase (GGT), glucose (GLU), sodium (NA), potassium (K), creatinine (CREA), urea (UREA), chloride (CL), magnesium (MG), calcium (CA), inorganic phosphorus (PHOS) and blood urea nitrogen (BUN).

Serum creatinine value will be used to calculate eGFR using CKD-EPI.

At screening, biochemistry samples will be collected into a serum collection tube (not exceeding 4.5 mL). This volume allows sufficient serum for FSH pregnancy test screening. Biochemistry samples will be analysed using the Roche Cobas c6000 analyser series comprising of c501 and e601 modules.

9.8.8 Vital Signs

Vital Signs: Systolic/diastolic blood pressure, pulse rate, oral body temperature.

Blood pressure, pulse and temperature will be measured by the DINAMAP* Compact Vital Signs Monitor (Model TS) or equivalent. Normal ranges for vital signs are presented in Appendix 4.

9.8.9 Physical Examination

A physical examination will be performed by an Investigator. The examination will include ear/nose/throat, ophthalmological, dermatological, cardiovascular, respiratory,

gastrointestinal, central nervous system, lymph nodes and musculoskeletal). An Investigator can examine other body systems if required, at their discretion.

9.8.10 12-Lead ECG

12-lead ECG: Heart rate, PR interval, QRS width, QT interval and QT interval corrected using Bazett's formula (QTcB) and Fridericia's formula (QTcF).

12-lead ECG recordings will be made using a MAC 5500 or equivalent. Each ECG trace should be labelled with the study number, patient number, patient initials and date of birth. An Investigator will provide an interpretation of each tracing. Clinically significant abnormalities will be recorded on the AE page. Normal ranges for 12-lead ECG parameters are presented in Appendix 4.

9.8.11 Concomitant Medication

All prior and concomitant medications taken during the study will be recorded in the patient's CRF (see Section 9.5.12).

9.8.12 Lung Function Testing

All spirometry evaluations should follow the recommendations of the ATS/ERS 2005[24].

The spirometry equipment used during the trial must meet or exceed the minimal ATS/ERS recommendations for diagnostic spirometry equipment as defined in the guideline. Calibration of the spirometry equipment is mandatory and must be performed before the first study measurement. All calibration reports and patient spirometry reports should be stored as source data. All staff conducting the spirometry tests must have received appropriate training that must be documented.

All spirometry manoeuvers should be performed in sitting position whilst wearing nose-clips. At least three acceptable manoeuvers should be performed for each time point, and the results must meet within-test and between-test criteria for acceptability. A maximum of eight manoeuvers should be performed at any time point.

Spirometry assessments will include: FEV_1, FVC and FEV_1/FVC.

To measure post-BD FEV_1 values towards inclusion criterion # 2, the following procedure shall be followed:

- Perform pre-BD pulmonary function test (PFT) (-60 min and -30 min) prior to administration of Ventolin HFA
- Administer 4 puffs of Ventolin HFA
- Perform post-BD PFT 30 min after the administration of Ventolin HFA

Reversibility will be a comparison of the average best FEV_1 effort obtained at -60 min and -30 min pre-bronchodilator to the best FEV_1 effort obtained at 30 minutes post-BD.

Pre-BD FEV_1 and reversibility will be recorded to characterise the study population.

The lung function tests will be performed at the time points specified in Table 9.6.1. of the protocol.

9.8.13 Appropriateness of Measurements

All measurements performed in the study are standard measurements.

The total volume of blood to be collected from each patient during the study (approximately 7.2 mL) is considered acceptable (Table 9.8.1).

Table 9.8.1 Summary of Blood Volume

Procedure	Visit	No. Samples	Blood Volume per Sample (mL)	No. Treatment Periods	Blood Volume (mL)
Biochemistry	Screening[a]	1	4.5	N/A	4.5
Haematology	Screening	1	2.7	N/A	2.7
				Total Blood Volume	7.2

[a] From the screening biochemistry blood samples, the serum pregnancy test and FSH test will be conducted.

9.8.14 Primary Efficacy Variable(s)

Not applicable.

9.8.15 Drug Concentration Measurements

Not applicable.

9.8.16 Pharmacodynamic Assessments

Not applicable.

9.8.17 Other Assessments

Scintigraphy imaging will be performed at the time points specified in Table 9.6.1.

9.9 Data Quality Assurance

At the time the study is initiated, a representative of the sponsor will thoroughly review the final protocol and CRFs with the Chief Investigator and site staff. During the course of the study the Monitor will visit the Clinical Unit (and selected NHS study centres) regularly to check the completeness of the patient records (including the volunteer (patient) master files, laboratory and 12-lead ECG print-outs), the accuracy of entries into the CRFs, the adherence to the final protocol and to ICH GCP[12], the progress of enrolment and also to ensure the storage, handling and accountability of the IP. The Chief Investigator and key study personnel will be available to assist the Monitor during these visits.

The Chief Investigator will give the Monitor, Auditor(s), the REC, and the MHRA direct access to relevant clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave Simbec. The sponsor will maintain the confidentiality of all patient records.

Study data will be fully documented in the CRFs and study log books. Dated signatures will be given to account for all interventions in the study by research staff.

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies).

For the purposes of this study the source data will be recorded as detailed in Table 9.9.1:

Table 9.9.1 Summary of Source Documentation Location

Data	Source Document		
	Volunteer Master File	CRF	Paper Diary
Evidence of healthy patient status/primary disease condition for entry into clinical study	X		
Demographic data		X	
Medical history	X		
Inclusion and exclusion criteria		X	
Informed consent form[a]	X	X	
Patient participation in the clinical study		X	
Patient number in the clinical study		X	
Adverse events		X	
Previous and on-going therapy	X		
Concomitant therapy		X	
Results of study examinations (e.g., 12-lead ECGs, vital signs and laboratory safety tests)[b]		X	
Study visit dates		X	
Administration of study medication		X	
Adherence to maintenance medication		X	X

[a] Copies of the informed consent form should be present in the volunteer master file. The original informed consent forms will be maintained in the study officer file during the clinical phase and will then be transferred to the Project Manager for archiving with the Investigator site file at the end of the study.

[b] The 12-lead ECG trace and laboratory safety test print-out will be stored in the CRF.

The above table indicates where source data will be recorded but for completeness the following information will also be recorded in the volunteer master file:

- Clinical study code.
- Study visit dates (pre-dose; post-dose).
- IP administration (date of last dose).
- Results of any key safety and efficacy measures from the clinical study that in the opinion of an Investigator should be noted.
- Any concomitant medications used to treat the patient during the study that in the opinion of an Investigator should be noted.

The data collected in the CRFs during the study will be subject to quality control checking by clinical staff prior to sign off.

The study will be subject to an independent audit by the Simbec Quality Assurance as outlined in SOP GRP-QA 005.

Independent clinical quality assurance audits may be performed at any time during or following completion of the study by the sponsor, or its authorised agents, and Regulatory Authorities and/or the REC.

9.10 Statistical Methods and Determination of Sample Size

9.10.1 Statistical and Analytical Plan

A statistical analysis plan (SAP) will be written by Simbec and agreed by AstraZeneca prior to the locking of the database and subsequent reporting of the study data.

9.10.1.1 Analysis Sets

All Enrolled Patients: All patients who were enrolled onto the study, including those who did not receive a dose of study drug.

This analysis set will be used for listings containing baseline information.

Safety Analysis Set (Safety): All patients who receive any amount of study drug will be included in the safety analysis.

The Safety Analysis Set will be used for baseline and safety summaries as well as for all non-baseline data listings.

Per Protocol Analysis Set (PP): All patients who receive a dose of study drug, have fully evaluable scintigraphy data and who do not violate the protocol in such a way that may invalidate or bias the results (important protocol deviations) will be included in the PP Analysis Set.

The PP Analysis Set will be used for scintigraphy data summaries.

9.10.1.2 Description of Statistical Methods

All statistical analysis will be performed using SAS® version 9.3 or higher.

9.10.1.2.1 Demographic and Background Data

All demographic and background data will be listed, in addition:

Disposition: Patient disposition will be listed with any withdrawals flagged. Frequencies (number and %) of the total number of patients dosed, completed and prematurely discontinued (including reason for discontinuation) from the study will be summarised by cohort and overall. Additionally, the frequency of patients within each analysis set will be summarised by cohort and overall.

Demographics: Demographic data will be listed. Descriptive statistics (number of patients in the analysis population (N), number of patients with non-missing observations (n), mean, standard deviation (SD), minimum, median and maximum) will be tabulated by cohort and overall for the continuous variables age, height, weight and BMI and frequencies (number and %) for the categorical variables race and gender.

Efficacy Data:

Not applicable.

9.10.1.2.2 Safety Data:

The safety endpoints are:

- AEs.

All safety data will be listed, in addition:

AEs: All AEs will be coded using the MedDRA version that is current at the time of database lock.

All AEs, including those which occurred prior to the first dose of IP, will be listed. Only TEAEs, will be included within the summary tables.

An overall summary of AEs will be produced including the number and % of patients reporting at least 1 TEAE, a TEAE considered related to study drug, TEAEs by intensity, a TEAE with an outcome of death, a serious TEAE and a TEAE leading to withdrawal from the study. A similar table will be produced for the number of TEAEs within each cohort.

The number and % of patients reporting at least 1 TEAE will be tabulated by system organ class (SOC) and preferred term (PT). A patient reporting multiple episodes of a particular AE within the Treatment Period will only contribute 1 count towards the corresponding SOC and PT.

In addition, the number and % of patients reporting TEAEs will be tabulated by maximum intensity and maximum reported causality to IP within a PT. For the summary of TEAEs by maximum intensity, if a patient has multiple events occurring within the same PT, the event with the highest intensity will be counted. Similarly, for TEAEs by study drug causality, if a patient has multiple events occurring within the same PT, the event with the maximum reported causality to IP will be counted.

9.10.1.2.3 Pharmacokinetic Data

Not applicable

9.10.1.2.4 Pharmacodynamic Data

Not applicable.

9.10.1.2.5 Other Data

Scintigraphic Data

For each administration the emitted dose is defined as the sum of corrected activities detected in the lungs and oropharynx (including mouth washings and stomach deposition) and on the exhalation filter.

Lung deposition will be derived from the scintigraphy data as follows: A geometric mean (GM) image of the anterior and posterior ^{81m}Kr ventilation images of each patient will be calculated

using a commercially available nuclear medicine software package (Odyssey V9.4B, Philips Medical Systems Limited). The lung margins of each patient will be defined by drawing a region of interest (ROI) around the geometric mean lung image. For each patient the ROIs determined from the GM ventilation images will be superimposed over the anterior and posterior images acquired following drug treatment. ROIs will also be manually drawn where appropriate around the images of the oropharynx and stomach. The anterior and posterior counts will be used to calculate geometric mean counts for these regions. ROIs will also be drawn around images of the filter used for collection of exhaled radioactivity, mouth washing collection vessel, and around the images of the actuator. The radioactivity within each of the defined ROIs will be calculated.

Corrections for regional tissue attenuation of radioactivity will be calculated by the following method:

An anterior view of the thorax and abdomen and also the head and neck will be acquired in the presence of a flood source of activity; the same view will then be acquired in the absence of the patient. The lung ROI determined from the ^{81m}Kr ventilation procedure will be superimposed over the flood view and a further ROI defining the mediastinum and stomach will be drawn. The counts in these regions in the presence and absence of the patient will be recorded and expressed as a transmittance (T) value:

$$T = \frac{\text{counts in ROI in presence of subject}}{\text{counts in ROI in absence of subject}}$$

The calculated transmittances will be used to determine a value of Perspex thickness equivalent to the whole body in the regions of the lung, stomach, and head and neck, from a previously constructed standard curve[25]. This value will be halved to give the transmittance associated with half body thickness (T') at these locations. The appropriate attenuation factor will be determined from the following relationship:

$$\text{Attenuation Factor} = \frac{1}{T'}$$

The corrected geometric mean (GMc) counts of posterior and anterior images will be calculated as follows:

$$GMc = GM \times \text{Attenuation Factor}$$

This procedure will be used to derive attenuation factors for the lung images; a similar approach will be used for the stomach. The procedure will be repeated for the head and neck view.

If necessary, corrections of the counts for different imaging acquisition times and radioactive decay will also be performed. Calculation of background correction will be conducted as follows:

Throughout each study day at regular intervals, background images (i.e., in the absence of patients), will be acquired for 60 seconds. The total counts in each background image will be

determined and the mean counts over the duration of the study will be calculated. The mean total counts will be divided by the total number of pixels per view and the counts/pixel/second derived. This value will be used, where appropriate, for background radiation correction of images.

The emitted dose will be derived from the sum of corrected radioactivity recovered in the patient, i.e., lungs, stomach, oropharynx, and where appropriate on the exhalation filter and in the mouthwash.

Regional Airway Deposition: The regional airway deposition ratios including outer to inner (O/I) and central to peripheral (C/P) regions of the Radiolabelled BGF MDI in the lungs will be determined after correcting for regional lung volume (using O/I and C/P from the ^{81m}Kr gas scan). These will be calculated for the geometric mean image of the right lung only, since activity associated with the stomach may interfere with the left lung image. The methods described in Biddiscombe et al. 2011 and Newman et al., 2012[26, 19] will be used. The ^{81m}Kr gas geometric mean lung image of each patient will be used to define a rectangle and regions of interest drawn to define outer, inner, central and peripheral areas. Thus ratios of outer to inner counts and central to peripheral counts will be obtained for the ^{81m}Kr gas and these values will be used to account for differences in regional lung volumes.

O/I = O (outer region GM counts)/ I (inner region GM counts)

C/P = C (central region GM counts)/ P (peripheral region GM counts)

A similar calculation will be performed to determine the O/I ratio for ^{99m}Tc inhaled from the study treatments. The ^{81m}Kr gas right lung margin image of each patient will be superimposed over the geometric mean images obtained following treatment dosing.

The penetration index (PI) represents the regional distribution of the aerosol particles normalized for regional lung volume.

PI = (O/I for ^{99m}Tc aerosol)/(O/I for ^{81m}Kr gas)

The standardized C/P ratio (sC/P) is an alternative measure of regional distribution of the aerosol particles normalized for regional lung volume.

sC/P= (C/P for ^{99m}Tc aerosol)/(C/P for ^{81m}Kr gas)

Oropharyngeal Deposition: The fraction of the dose of Radiolabelled BGF MDI deposited in the oropharyngeal and stomach regions will be determined using geometric mean images from regions defining the oropharynx (lateral view) and stomach (frontal view). The fraction of the dose recovered in the mouthwash will be determined using the image from the vessel used to recover the mouth-rinsing from the volunteer. The counts in each of these images will be expressed as % emitted dose, after correction for attenuation, background activity and radioisotope decay, as described in Section 9.10.1.2.5 above. The sum of oropharyngeal, stomach and mouthwash counts will provide the % emitted dose initially impacting in the oropharyngeal region after inhalation of the ^{99m}Tc aerosol treatments.

Actuator Deposition: The fraction of the dose of Radiolabelled BGF MDI deposited on the actuator will be determined using the image of the actuator following its removal from the MDI canister. The counts in this image will be expressed as % ex-valve dose, after correction for attenuation, background activity and radioisotope decay, as described in Section 9.10.1.2.5 above

The following derived deposition endpoints will be listed and summarised by cohort and overall:

- The fraction of the dose of Radiolabelled BGF MDI deposited in the lungs and in the oropharyngeal and stomach regions (expressed as % emitted dose) following a maximal breath-hold of up to 10 s.
- The regional airway deposition ratios including the non-normalized parameters outer to inner (O/I) and central to peripheral (C/P) regions and the normalized parameters Penetration index (PI) and the standardized C/P ratio (sC/P) of the Radiolabelled BGF MDI in the lungs following a maximal breath-hold of up to 10 s.
- The fraction of the dose of Radiolabelled BGF MDI deposited on the actuator (expressed as % ex-valve dose) and exhalation filter (expressed as % emitted dose) following a maximal breath-hold of up to 10 s.

9.10.2 Sample Size Calculation

No formal sample size calculation has been performed since this is an investigational study to quantify lung deposition without reference to any marketed formulation. However, a sample size of 16 (8 per cohort) will allow a direct estimate of lung deposition from these formulations to be made within each cohort. Approximately 20 patients will be enrolled to ensure that at least 16 patients complete the study. In other investigational scintigraphy studies, sample sizes between 5 and 15 have typically been reported [2-9].

10 PRACTICAL CONSIDERATIONS

10.1 Storage of Data

The Investigator site file and associated study documentation will be archived for at least 5 years after the end of the study (last patient last visit) as per The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (No. 1928)[13]. The study documentation may be transferred to an offsite storage facility during this period but will remain under the control of Simbec.

10.2 Protocol Amendments

Changes in the study protocol must take the form of written protocol amendments and shall require the approval of all persons responsible for the study (see Section 1).

A protocol amendment is deemed to constitute a substantial protocol amendment if it is considered to be likely to affect to a significant degree either:

a. the safety or physical or mental integrity of the patients of the study.
b. the scientific value of the study.
c. the conduct or management of the study.
d. the quality or safety of any IP used in the study.

Such amendments must be submitted to the REC responsible for the study and the MHRA for approval prior to implementation.

Protocol amendments required for urgent safety reasons may be implemented immediately. However, the REC and MHRA must be notified in writing within 3 days of the measures taken and the reasons for implementation.

All other amendments shall be deemed to be non-substantial and as such do not need the prior approval of the REC and the MHRA.

10.3 Confidentiality

The confidentiality of the study must be maintained at all times and the Chief Investigator must not reveal any information relating to the study without express permission from the study sponsor.

10.4 Study Report and Publication Policy

Simbec will investigate and analyse the data generated with all due speed.

A draft study report will be sent to the sponsor for review. The sponsor will forward any comments on the draft study report to the Project Manager within 30 days of receipt. Upon receipt of these comments a final, QA approved report will be issued with all due speed. A copy of the report will be forwarded to the sponsor.

The Chief Investigator will obtain the sponsor's written permission before any information concerning this study is submitted for publication.

11 REFERENCES

[1] B.R. Celli and W. MacNee. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper , European Respiratory Journal 2004; 23, 932-946.

[2] Boyd B, Noymer P, Liu K, Okikawa J, Hasegawa D, Warren S, Taylor G, Ferguson E, Schuster, J, Farr S, Gonda I, Effect of gender and device mouthpiece shape on bolus insulin aerosol delivery using the AER(x) pulmonary delivery system. Pharmaceut Res 2004; 21: 1776-1782.

[3] Cassidy JP, Amin N, Marino M, Gotfried M, Meyer T, Sommerer K, Insulin lung deposition and clearance following Technosphere(®) insulin inhalation powder administration, Pharm. Res. 2011; 28 : 2157-2164.

[4] Farr SJ, Warren SJ, Lloyd P, Okikawa J, Schuster J, Rowe A, Rubsamen R, Taylor G. Comparison of in vitro and in vivo efficiencies of a novel unit-dose liquid aerosol generator and a pressurized metered dose inhaler. Int J Pharmaceut. 2000; 198; 63-70.

[5] Hirst PH, Pitcairn GR, Weers JG, Tarara TE, Clark AR, Dellamary LA, Hall G, Shorr J, and Newman SP. In Vivo Lung Deposition of Hollow Porous Particles from a Pressurized Metered Dose Inhaler. Pharmaceutical Research 2002; 19 (3) 258 – 264.

[6] Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ, Influence of particle size and patient dosing technique on lung deposition of HFA-beclomethasone from a metered dose inhaler J Aerosol Med 2005; 18: 379-385.

[7] Leach CL, Colice GL, A Pilot Study to Assess Lung Deposition of HFA-Beclomethasone and CFC-Beclomethasone from a Pressurized Metered Dose Inhaler with and without Add-On Spacers and Using Varying Breathhold Times. J Aerosol Medicine 2010; 23:355-361.

[8] Sebti et al 2006, Sebti T, pilcer G, Van Gansbeke B, et al. Pharmacoscintigraphic evaluation of lipid dry powder budesonide formulations for inhalation. Eur J Pharmaceut Biopharmaceut 2006; 64:26-32.

[9] Shrewsbury SB, Armer TA, Newman SP, et al. Breath-synchronized plume-control inhaler for pulmonary delivery of fluticasone propionate Int. J Pharmaceut 2008; 356: 137-143.

[10] World Health Association Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, and 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, 52nd WMA General Assembly, Edinburgh, Scotland,

October 2000, 53rd WMA General Assembly, Washington 2002 (Note of Clarification on Paragraph 29 added), 55th WMA General Assembly, Tokyo 2004 (Note for Clarification on Paragraph 30 added), 59th WMA General Assembly, Seoul, October 2008 and 64th WMA General Assembly, Fortaleza, Brazil, October 2013.

[11] ABPI (The Association of the British Pharmaceutical Industry). Guidelines for Phase 1 Clinical Trials. 2018 edition.

[12] ICH (International Council on Harmonisation) Guideline for Good Clinical Practice (GCP) E6 (R2) (CPMP/ICH/135/95) 1996

[13] The Medicines for Human Use (Clinical Trials) Regulations 2004 (Statutory Instrument 2004 No. 1031) and subsequent amendments.

[14] Insurance and compensation in the event of injury in Phase I clinical trials 2012. Guidance developed by the ABPI the BioIndustry Association and the Clinical Contract Research Association in consultation with the Department of Health and the National Research Ethics Service.

[15] Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of Chronic Obstructive Pulmonary Disease. Updated; 2015:1-117. Available from: http://www.goldcopd.org/uploads/users/files/GOLD_Report_2015_Feb18.pdf.

[16] Japanese Respiratory Society (JRS). Guidelines for the Diagnosis and Treatment of COPD, 4th edition, 2013.

[17] Budesonide, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (BGF MDI); Budesonide and Formoterol Fumarate Inhalation Aerosol (BFF MDI) Investigator's Brochure, version 6.0 19 November 2018.

[18] European Commission. EudraLex The rules governing medicinal products in the European Union – Volume 4: Good Manufacturing Practice Guidelines.

[19] Newman S, Bennett WD, Biddiscombe M, Devadason SG, Dolovich MB, Fleming J, Haeussermann S, Kietzig C, Kuehl PJ, Laube BL, Sommerer K, Taylor G, Usmani OS, and Zeman KL. Standardization of Techniques for Using Planar (2D) Imaging for Aerosol Deposition Assessment of Orally Inhaled Products. Journal of Aerosol Medicine and Pulmonary Drug Delivery 2012; 25, Supplement 1, S10 – 28.

[20] Publications of the International Commission on Radiological Protection (ICRP) (1977) Recommendations of the International Commission on Radiological Protection 26.

[21] Notes for Guidance on the Administration of Radioactive Substances to Persons for Purposes of Diagnosis, Treatment or Research and the Annals of the International Commission on Radiological Protection (ICRP) Publication 80 (1998).

[22] HPA-CRCE-012 Frequency and Collective Dose for Medical and Dental X-ray Examinations in the UK 2008, Hart, D, Wall, BF, Huillier, MC and Shrimpton, PC

[23] Mobbs SF, Muirhead CR. and Harrison JD. Risks from Ionising Radiation. Health Protection Agency-RPD-066, 2010.

[24] Standardisation of spirometry. ATS/ERS Task Force Standardisation of Lung Function Testing: Standardisation of Spirometry (2005).

[25] Colthorpe P, Taylor G, Farr SJ. (1997) A comparison of two non-invasive methods for quantifying aerosol deposition in the lungs of rabbits. J. Aerosol Med.; 10:255.

[26] Biddiscombe MF, Meah SN, Underwood RS, and Usmani OS. Comparing Lung Regions of Interest in Gamma Scintigraphy for Assessing Inhaled Therapeutic Aerosol Deposition. Journal of Aerosol Medicine and Pulmonary Drug Delivery Volume 24, Number 3, 2011, pp 165 – 173.

APPENDIX 1: AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	05 March 2019	2.0	Substantial amendment (REC only)	Change of Chief Investigator Administrative changes.

APPENDIX 2: DECLARATION OF HELSINKI (BRAZIL, 2013)

DECLARATION OF HELSINKI (BRAZIL, 2013)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964
and amended by the:
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
52nd WMA General Assembly, Edinburgh, Scotland, October 2000
53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)
55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)
59th WMA General Assembly, Seoul, Republic of Korea, October 2008
64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

   The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

    Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

    Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

    When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

    All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group. In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

    The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

    In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

    The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific

information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent, preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.

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APPENDIX 3: ADVERSE EVENT DEFINITIONS AND ADDITIONAL SAFETY INFORMATION

3.1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a patient or clinical study patient administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (e.g. an abnormal laboratory finding), symptom (for example nausea, chest pain), or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The term AE is used to include both serious and non-serious AEs and can include a deterioration of a pre-existing medical occurrence. An AE may occur at any time, including run-in or washout periods, even if no Study treatment has been administered.

3.2 Definitions of serious adverse event

A serious adverse event is an AE occurring during any study phase (i.e., run-in, treatment, washout, follow-up phone call), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity.
- Is a congenital abnormality or birth defect
- Is an important medical event that may jeopardise the patient or may require medical treatment to prevent one of the outcomes listed above.

3.3 Life threatening

'Life-threatening' means that the patient was at immediate risk of death from the AE as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

3.4 Hospitalisation

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal oedema). Hospital admissions and/or surgical

operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

3.5 Important medical event or medical treatment

Medical and scientific judgement should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life threatening or result in death, hospitalisation, disability or incapacity but may jeopardize the patient or may require medical treatment to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgement must be used.

- Angioedema not severe enough to require intubation but requiring iv hydrocortisone treatment
- Hepatotoxicity caused by paracetamol (acetaminophen) overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anaemia requiring blood transfusion, etc.) or convulsions that do not result in hospitalisation
- Development of drug dependency or drug abuse

3.6 Intensity rating scale:

- mild (awareness of sign or symptom, but easily tolerated)
- moderate (discomfort sufficient to cause interference with normal activities)
- severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Appendix 3 section 2.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not a SAE unless it meets the criteria shown in Appendix 3 section 2.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be a SAE when it satisfies the criteria shown in Appendix 3 section 2.2.

3.7 A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a ‘reasonable possibility’ that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another aetiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.
Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

3.8 Medication Error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the participant or has the potential to cause harm to the participant.

A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or participant.

Medication error includes situations where an error.

- occurred
- was identified and intercepted before the participant received the drug
- did not occur, but circumstances were recognize that could have led to an error

Examples of events to be reported in clinical studies as medication errors:

- Drug name confusion
- Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the participant
- Drug not administered as indicated, for example, wrong route or wrong site of administration
- Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
- Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
- Wrong participant received the medication
- Wrong drug administered to participant

Examples of events that **do not** require reporting as medication errors in clinical studies:
error

- Participant accidentally missed drug dose(s) e.g. forgot to take medication
- Accidental overdose (will be captured as an overdose)
- Participant failed to return unused medication or empty packaging
- Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AZ product

  Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

APPENDIX 4: NORMAL RANGES FOR VITAL SIGNS AND ECG PARAMETERS

SIMBEC RESEARCH

NORMAL RANGES FOR VITAL SIGNS AND ECG PARAMETERS

Vital Sign Parameters

Parameter	Normal Range	Units
Pulse Rate	40 – 100	Beats per minute (bpm)
Systolic Blood Pressure	90 – 140	mmHg
Diastolic Blood Pressure	50 – 90	mmHg
Respiratory rate	12 – 18	Breaths per minute
Oral Temperature	35.0 – 37.5	Degrees Celsius
Pulse Oximetry	94 – 100%	

ECG Parameters

Parameter	Normal Range	Units
Heart Rate (HR)	40-100	Beats per minute (bpm)
PR Interval	120-220	Millisecond (msec)
QRS Width	70-120	Millisecond (msec)
QT Interval	Not Applicable	Not Applicable
QT_c Interval (Bazett's & Fridericia's formulae)	350-450 (Males) 350-450 (Females)	Millisecond (msec) Millisecond (msec)

[redacted] Date: 31 OCT 17

Date: 31 OCT 2017

Clinic Normal Ranges Vital Signs and ECG version 3.0 31 Oct 2017