Clinical Study Protocol	
Drug Substance	Budesonide/Glycopyrronium/Formoterol Fumarate (BGF)
Study Code	D5980C00019
Version	3.0
Date	05 July 2019

A Randomized, Double-blind, Two Treatment, Two Period, Chronic dosing (4 weeks), Cross-over, Multi-center Pilot study to evaluate the effects of Budesonide/Glycopyrronium/Formoterol Fumarate and Glycopyrronium/Formoterol Fumarate on Specific Image based Airway Volumes and Resistance in Subjects with Moderate to Severe Chronic Obstructive Pulmonary Disease

Sponsor: AstraZeneca AB, 151 85 Södertälje, Sweden

Regulatory Agency Identifying Number(s):

IND Number: 118313

EudraCT Number: 2018-001704-10

VERSION HISTORY

Version 3.0, 05 July 2019 -Protocol Amendment 02

Section 1.1 Schedule of Assessments (SoA):

- Moved and revised footnote "n" from "Adverse Event" to "Demography and Medical/Surgical History" since COPD exacerbation history will be collected as respiratory disease history per revised footnote.

  Updated footnote "f" and added separate row to clarify Visit 1 through Visit 3 prohibited medication washouts and use of maintenance and rescue medications per Table 6, and Section 6.2.2.2.

Section 1.2 Synopsis and Section 3 Objectives and Endpoints:

- Objectives and Endpoints: secondary endpoint variable updated to include the timepoint for "Forced expiratory volume in one second (Post-dose FEV_1)", so as to clarify whether the pre-dose or post-dose FEV1 was to be used as the secondary endpoint

Section 6.2.2.2 Atrovent HFA (Ipratropium Bromide) and Section 8.1.7 Subject Diary Data Collection:

- Added the following text to Section 6.2.2.2 to clarify Atrovent dispensation and start date, "Atrovent is expected to be dispensed at Visit 1; the first dose should be taken in the morning of Visit 2, before the visit procedures will be performed."

- Added "starting at Visit 2" to Section 8.1.7 to ensure collection of Atrovent HFA four times daily in diary

Section 6.5.1 Prohibited COPD Medications:

- add clarification regarding the discontinuation of all prohibited medications as noted in this section and specifications on the start of Atrovent and rescue medication at visit 2 to align with section 6.2.2.2.

Section 7.4 Study and Site Closure:

- Additional information for the study and site closure has been added. The rationale for this change is to specify the conditions for closure of sites during and after study completion

Section 8.1.5 Inhalation Profile with Body Plethysmography:

- Title revised to "Inhalation Profile" to align with the Fluidda Manual

Section 8.1.11 COPD Exacerbations:

- section has been revised to record those exacerbations that are required for safety reporting

Section 8.1.2.2 Stability Criteria:

- Clarified wording based on Section 8.1.2 revisions for pre-dose spirometry timepoints at Visit 3 and Visit 5.

Section 8.3.2 Time Period and Frequency for collecting AE and SAE information

- Collection of SAE time period included

Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's law:

- The appendix has been updated including addition of section E6 in conjunction with sponsor's routine pharmacovigilance activities/processes.

Other administrative changes to correct and/or clarify protocol language were also addressed. These changes included edits for consistency, grammar, and typographical errors, which are not summarized in this table

Version 2.0, 26 October 2018-Protocol Amendment 01

Section 1.1 and 8.1.1: HRCT scans revised to include 7 scans -2 predose ($TLC_{(PRE)}$ and $FRC_{(PRE)}$) at Visit 3 and 2 post dose ($TLC_{(POST)}$ and $FRC_{(POST)}$) at the end of each treatment period. During visit 3 an additional scan of the upper airway (UA) will be taken.

Section 9.1 (Statistical hypotheses): The section was updated to provide additional detail and clarity regarding the statistical hypotheses for the two primary endpoints of this study.

Section 9.2 (Sample size determination): The section was updated to provide an indication of the effect size which could be detected with the 20 planned subjects.

Section 9.3 (Populations for analyses): The terminology for two of the listed populations was updated to be aligned with terminology used in the previous FRI studies. The "Full analysis set" was changed to the "Intent-to-Treat (ITT) analysis set" and the "Evaluable

analysis set" was changed to the "Modified Intent-to-Treat (mITT) analysis set". Also clarified the definition for the mITT analysis set and included how the various analysis sets would be utilized to summarize the data. Section 9.4.1 (General principles): Section was added for clarity. Section 9.4.2 (Efficacy analyses): The section was updated to provide additional detail and clarity regarding the planned efficacy analyses. In addition, the methodology has been updated to reflect the change in collection of the HRCT scans for the efficacy endpoints. Section 9.4.4 (Methods for multiplicity control): Section added to clarify how the analysis of the two primary endpoints for this study would be addressed.
Version 1.0, 26 June 2018 -Original Protocol

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and/or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

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1 PROTOCOL SUMMARY

1.1 Schedule of Activities (SoA)

Table 1 Study Assessments

	Screening		Treatment Period 1 [k]			Treatment Period 2 [k]				Follow-up		
Visit	*1*	*2*	*3[k]*	Telephone Call[q]	*4[k]*	*5[k]*	Telephone Call[q]	*6[k]*	*Discontinuation*	Telephone Call	UNS	*Details in CSP section or Appendix*
Day	**-21**	**-14 or -7[a]**	**1[a]**	**28**	**29**	**53**	**79**	**80**		**87-90**	**N/A**	
Visit window	**±3**	**-3**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**			**N/A**	
Informed consent	X											Section 5.1
Review of Inclusion /Exclusion criteria	X	X	X									Section 5.1 and 5.2
Chest X-ray[e]	X											Section 5.1 and 5.2
Routine Safety Measurements												
Demography and Medical/Surgical History[n]	X											Section 8.2.2
Physical examination[d]	X										X	Section 8.2.2
Vital signs	X		X			X			X		X	Section 8.2.3
Smoking Status	X	X	X		X	X		X	X	X	X	Section 5.3.3
Prior/Concomitant medication[b]	X	X	X		X	X		X	X	X	X	Section 6.5
COPD Washout Medications[f]		X	X		X	X						Section 6.5.1
COPD Maintenance medications[f]	X	X	X		X	X		X	X			
Adverse events		X	X	X	X	X	X	X	X	X	X	Section 8.3
12-lead ECG	X											

	Screening		Treatment Period 1 [k]			Treatment Period 2 [k]				*Follow-up*		
Visit	***1***	***2***	***3[k]***	Telephone Call[q]	***4[k]***	***5[k]***	Telephone Call[q]	***6[k]***	***Discontinuation***	Telephone Call	UNS	***Details in CSP section or Appendix***
Day	**-21**	**-14 or -7[a]**	**1[a]**	**28**	**29**	**53**	**79**	**80**		**87-90**	**N/A**	
Visit window	**±3**	**-3**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**			**N/A**	
Pregnancy test[m]	X		X					X	X			Section 8.4.2
Clinical Laboratory Testing	X											Section 8.2.1
Efficacy Assessments												
Recording of Inhalation Profile with Respiration Belt[l]			X			X						Section 8.1.5
HRCT scan[o]			X		X			X				Section 8.1.1
Spirometry[c]	X	X	X		X	X		X				Section 8.1.2
Reversibility	X											Section 8.1.2.1
COPD Assessment Test (CAT)	X											Section 8.1.10.1
MMRC	X											Section 8.1.10.2
Diffusion Capacity	X											Section 8.1.4
Body Plethysmography			X		X	X		X				Section 8.1.3
Study Treatment Administration												
Randomisation			X									Section 6.3
Study Drug Dispensing/Collection[h]			X		X	X		X	X			Section 6
Study Drug Administration[i]			X		X	X		X				Section 6.1

	Screening		Treatment Period 1 [k]			Treatment Period 2 [k]				Follow-up		
Visit	*1*	*2*	*3[k]*	Telephone Call[q]	*4[k]*	*5[k]*	Telephone Call[q]	*6[k]*	*Discontinuation*	Telephone Call	UNS	*Details in CSP section or Appendix*
Day	**-21**	**-14 or -7[a]**	**1[a]**	**28**	**29**	**53**	**79**	**80**		**87-90**	**N/A**	
Visit window	**±3**	**-3**	**0**	**±3**	**±3**	**±3**	**±3**	**±3**			**N/A**	
Review/Record Study Drug Dose Indicator Reading[j]			X		X	X		X				Section 8.1.9
Review/Record Ventolin Dose Indicator Reading	X	X	X		X	X		X				Section 8.1.8
Inhalation Device Training[g]		X										Section 6.2
Inhalation Profile			X			X						Section 8.8
Diary Training	X	X										Section 8.1.7
Compliance Diary		X	X		X	X		X				Section 8.1.7
Review of Diary			X[p]		X	X		X				Section 8.1.7
Telephone Contact				X			X			X		

Abbreviations: CAT=COPD assessment test; MMRC= Modified Medical Research Council; ECG=electrocardiogram; COPD=Chronic obstructive pulmonary disease; HRCT=High-resolution computed tomography; ICS=inhaled corticosteroids; MDI=metered dose inhaler; FRC= functional residual capacity; TLC=total lung capacity; UNS=unscheduled visit

[a] Scheduling visits: If subject is on a BID COPD maintenance medication(s) return in ~7 days (day -14) and QD COPD maintenance medication(s) return in ~14 days (day -7).

[b] At all visits beyond Visit 2 (Screening), note the time of last dose of COPD medications, including rescue medication (if <6 hours, visit should be rescheduled)

[c] Refer to Section 8.1.2 for spirometry assessments and specific timepoints to be performed at each treatment visit.

[d] Includes evaluation of height and weight at Visit 1.

[e] Obtain a new chest x-ray if the chest x-ray or CT scan performed within 6 months of Visit 1 (Screening) is not available.

[f] After informed consent is obtained, COPD maintenance and rescue medications will be withheld 6 hours before study visits. Prohibited COPD medications will be stopped prior to Visit 1 for ICS and ICS/LABA containing medications and all other prohibited medications will be stopped prior to Visit 3 per Table 6 to be able to start study provided Atrovent HFA QID at Visit 2 as COPD maintenance medication per protocol section 6.2.2.2. At the end of Visit 6, return subject to pre-study or other appropriate inhaled maintenance COPD medications. Additionally, check and instruct on inclusion criteria #8 for no ICS use and exclusion criteria #3m, #3n and #10 through #15 for prohibited medications.

[g] Site should use the sponsor provided placebo MDI to train subjects on the use of MDIs. Additional inhalation training tools (e.g. AIM device) may be used to help ensure the subjects are able to use the MDI device correctly

[h] Sponsor provided Atrovent HFA or Ventolin HFA should be dispensed only after a subject is determined to be eligible to proceed to Visit 3 (Day 1) (i.e., only if a subject meets the definition of COPD following spirometry assessments at Screening).

[i] In-clinic dosing time is recorded as time of the second puff/inhalation.

[j] Refer to Section 8.1.9 for details and instructions on recording dose indicator readings.

[k] Visit windows during each Treatment Period are relative to Day 1 of that Treatment Period. Washout period between Visit 4 and Visits 5 is a minimum of 21 days to a maximum of 28 days.

[l] The inhalation profile with the use of the respiration belt will be measured simultaneously with the drug administration.

[m] Only in female of childbearing potential.

[n] The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Visit 1 (Screening) will be collected as respiratory disease history.

[o] At Visit 3 two breathing levels: $TLC_{(PRE)}$ and $FRC_{(PRE)}$. During Visit 3 an additional scan of the UA will be taken. At Visit 4 (post dose) and 6 (post dose) two breathing level: $TLC_{(POST)}$ and $FRC_{(POST)}$.

[p] Subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding the Randomization Visit (Visit 3) must be retrained. When retraining is required due to noncompliance the Randomization Visit (Visit 3) must be rescheduled.

[q] Prior to Visit 4 and Visit 6 site staff should call the subject to remind them to take the last dose of study medication the day before their following visit.

1.2 Synopsis

Protocol Title:

A randomized, double-blind, two treatment, two period, chronic dosing (4 weeks), cross-over, multi-center study to evaluate the effects of Budesonide/Glycopyrronium/Formoterol Fumarate (BGF) and Glycopyrronium/Formoterol Fumarate (GFF) on specific image based airway volumes and resistance in subjects with moderate to severe Chronic Obstructive Pulmonary Disease (D5980C00019)

Short Title: Phase IIIB mechanistic study using FRI

Rationale:

This imaging methodology will allow an assessment of the extent of airway changes using a triple combination of BGF and the dual combination GFF. Previous studies demonstrated that looking directly at airway volumes and resistance is a more sensitive measure than FEV_1 to evaluate the acute bronchodilating effect of inhaled LABA and/or LAMA (De Backer et al 2011; De Backer et al 2012; Vos et al 2013).

The study hypothesis states that ICS may change airway caliber via its effect on airway inflammation, edema, and secretions. ICS may also enhance the LABA/LAMA effect and could create beneficial synergies leading to a better regional exposure, a larger bronchodilation, and a reduced inflammation in more peripheral lung regions.

It is believed that the additional effect of ICS on top of LABA/LAMA will reduce hyperinflation and air trapping, resulting in lower lung and lobar volumes. At the same time, the specific airway volume (i.e. airway volumes that are corrected for lung volumes) are expected to increase. The primary goal of this study is to describe the effect on airway volume with the addition of ICS. This goal builds on the results of a lung function study (KRONOS), where we studied the effect on FEV_1 when ICS was added to LAMA/LABA and was recently published [Ferguson, 2018]. As illustrated in Figure 2 of this publication, the addition of budesonide to glycopyrrolate/formoterol, resulted in clinically meaningful improvements of trough FEV1, and of FEV1 AUC 0-4 hours post-dose, in COPD patients.

However, while FEV_1 is a well-established lung function parameter, it is still rather crude and does not make a good representation of the function of smaller airways. Thus, the purpose of the present study is to further characterize the lung function benefit by a more sensitive method. FRI is a well-established method to achieve a more regional characterization of the respiratory system. By simultaneously looking at the airway resistance and internal airflow distribution, functional respiratory imaging will be able to infer physiological changes in the peripheral lung regions.

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Objectives and Endpoints	
Primary objective:	**Endpoint/variable:**
To assess the effects of BGF and GFF on specific image-based airway volumes and resistance in subjects with moderate to severe COPD following chronic twice-daily (BID) dosing after approximately four weeks of treatment	• Specific airway volume ($_{si}V_{aw}$) • Specific airway resistance ($_{si}R_{aw}$)
Secondary objective:	**Endpoint/variable:**
To assess the effects of BGF and GFF on various Functional Respiratory Imaging (FRI) parameters	• Airway volume ($_{i}V_{aw}$) • Airway resistance ($_{i}R_{aw}$)
To assess the effects of BGF and GFF on lung function parameters	Forced expiratory volume in one second (Post-dose FEV_1)
To assess the effects of BGF and GFF on body plethysmography parameters	Functional Residual Capacity (FRC)
Safety objective:	**Endpoint/variable:**
To assess the safety of BGF and GFF	Adverse events (AEs), serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs)
Exploratory	**Endpoint/variable:**
To assess the effects of BGF and GFF on other FRI parameters	• Lobe volumes ($_{i}V_{lobes}$) • Air Trapping (AT) • Internal lobar airflow distribution (IAD) • Low attenuation or emphysema score (LAS) • Blood Vessel density or fibrosis score ($_{i}V_{by}$) • Airway Wall Thickness ($_{i}V_{aww}$) • Mass of deposited particles per defined airway section
To assess the effects of BGF and GFF on other lung function parameters	• Forced vital capacity (FVC) • Tiffeneau index (FEV_1/FVC ratio) • Forced expiratory flow 25%-75% (FEF_{25-75}) • Inspiratory capacity (IC)

Objectives and Endpoints	
To assess the effects of BGF and GFF on other body plethysmography parameters	• Residual volume (RV) • Total Lung Capacity (TLC) • Airway resistance (Raw) • Specific airway resistance (sRaw) • Specific airway conductance (sGaw)

Overall design:

This is a phase IIIb randomised, controlled, two period cross-over, 4 weeks chronic dosing, study to evaluate the effects of Budesonide/Glycopyrronium/Formoterol Fumarate (BGF), 320/14.4/9.6 µg (160/7.2/4.8 µg per actuation), MDI 2 oral inhalations BID, morning* and evening and Glycopyrronium/Formoterol Fumarate (GFF), 14.4/9.6 µg (7.2/4.8 µg per actuation), MDI 2 oral inhalations BID, morning* and evening on specific image based airway volumes and resistance in subjects with moderate to severe Chronic Obstructive Pulmonary Disease. In this study, airway dimension parameters will be calculated for each of the active compounds.

Computed Tomography (CT)-scans during study: On Day 1 of Treatment Period 1(Visit 3) pre-dose baseline measurement inspiratory scans (total lung capacity [$TLC_{(PRE)}$] scan) and expiratory scan (functional residual capacity [$FRC_{(PRE)}$] scan) will be conducted. During Visit 3 an additional scan of the upper airway (UA) will be taken. Post dose measurement inspiratory scan (total lung capacity [$TLC_{(POST)}$] scan) and expiratory scan (functional residual capacity [$FRC_{(POST)}$] scan) will be taken after approximately 4 weeks of each treatment with BGF MDI or GFF MDI on Day 29 ±3 days (Visit 4 and Visit 6). Post dose activities should be started 1 hour after dosing on Visit 4 and Visit 6 and should be concluded within 2.5 hours after dosing. Between the Treatment Periods there will be a washout period of approximately 21-28 days with treatment of Atrovent HFA.

Study is planned to be conducted in one country, approximately three centres.

Study Period:

Estimated date of first patient enrolled 21 December 2018

Estimated date of last patient completed 17 September 2019

Number of Subjects:

A total of approximately 20 patients with moderate to severe COPD will be randomized in a 1:1 scheme of BGF:GFF treatment sequences.

Treatments and treatment duration:

2 cross-over treatments of approximately 28 days each with:

BGF: Budesonide/Glycopyrronium/Formoterol Fumarate, 320/14.4/9.6 µg (160/7.2/4.8 µg per actuation), MDI (current phase III device) 2 oral inhalations in the morning* and 2 oral inhalations in the evening.

GFF: Glycopyrronium/Formoterol Fumarate, 14.4/9.6 µg (7.2/4.8 µg per actuation), MDI (current phase III device) 2 oral inhalations in the morning* and 2 oral inhalations in the evening.

Each treatment will be separated by a washout period of approximately 21-28 days where treatment with Atrovent HFA will be administered.

*Dosing of IP in the clinic should be planned to occur at approximately the same time the patient prefers to administer IP in the mornings between the visits. The patient should then be advised that subsequent morning IP administration should happen at approximately this time, and that evening dosing should occur as close as possible to +12 hours from the morning time. It is recommended that dosing in the clinic occurs before approximately 10:00 AM. If it is unavoidable that IP administration in the clinic is at a later time of day than the patient normally administers IP at home (for example due to the travelling time to site), then patients should be strongly advised that on the day prior to the next clinic visit, the time of IP administration should be adjusted to be approximately 24 hours and 12 hours prior to the planned dosing at the clinic. Sites should make every effort to ensure that dosing in the clinic occurs as close as possible to 24 and 12 hours after the patient's IP intake the previous day.

Table 2 Study Medication and Products

Product Name and Total Dose	Product Strength	Dose Form/Fill Count	Administration route
Blinded Study Medications			
BGF MDI 320/14.4/9.6 µg ex-actuator	BGF MDI 160/7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken BID as two oral inhalations in the morning and two oral inhalations in the evening
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken BID as two oral inhalations in the morning and two oral inhalations in the evening
Open-label Products			
Ventolin (albuterol sulfate) HFA inhalation aerosol 90 µg ex-actuator	Ventolin (albuterol sulfate) HFA inhalation aerosol will be the supplied product Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as needed (PRN)

Atrovent (ipratropium bromide) HFA inhalation aerosol 34 µg ex-actuator	Atrovent (ipratropium bromide) HFA will be the supplied product Each inhalation contains 17 µg ex-actuator per actuation	1 MDI 200 actuations	Taken as two oral inhalations QID during run-in period and washout period

Abbreviations: BGF MDI=Budesonide/Glycopyrronium/Formoterol Fumarate Inhalation Aerosol; GFF MDI= Glycopyrronium/Formoterol Fumarate Inhalation Aerosol; MDI=Metered Dose Inhaler; PRN=as needed; BID= two times daily; QID=four times daily

Note: All study drugs will be administered by oral inhalation.

Note: Glycopyrronium 14.4 µg in GP MDI is equivalent to 18 µg of glycopyrronium bromide.

Data Monitoring Committee: Not Applicable.

Statistical methods

The focus of this study is on estimation of the individual effects of treatment with BGF and GFF. For the primary analyses, the individual ("within-treatment") effects of both BGF and GFF will be assessed. This effect is defined as the change from baseline to Day 29 for BGF treatment and the change from baseline to Day 29 for GFF treatment. Baseline for both treatment groups will be defined as the pre-dose FRI value taken at Visit 3.

The effect will be evaluated for each treatment and for each primary endpoint using a t□test. Mean values and 95% confidence intervals will be calculated for each treatment. The other FRI, spirometry, and body plethysmography parameters listed among the secondary efficacy endpoints will be analysed similarly. Though FEV_1 is measured pre- and post-dose at different visits, the secondary endpoint of change in FEV_1 value will be based on post-dose evaluation of FEV_1.

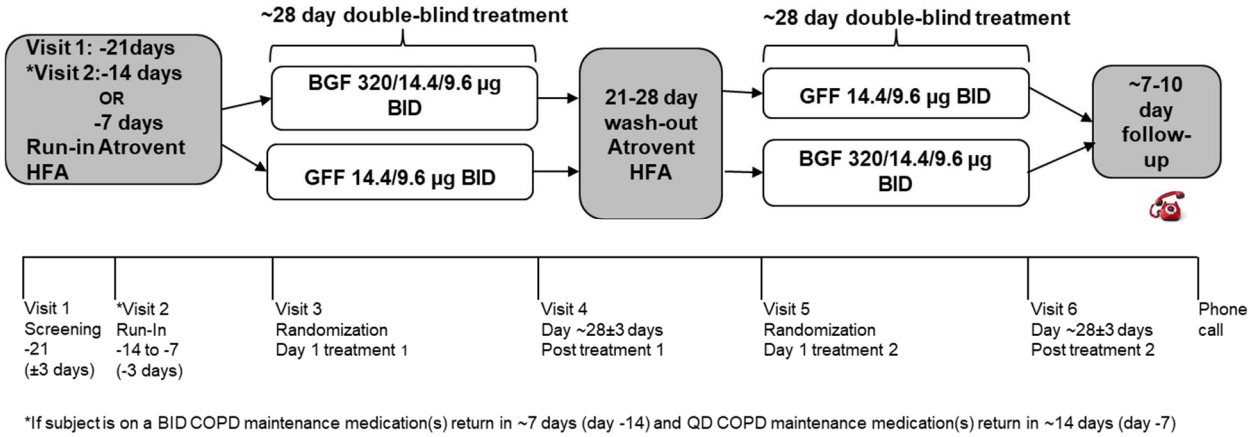
Additional, supportive analyses will compare the distribution of regional effects between the two treatments for the different FRI endpoints. A linear mixed model approach will be chosen for this analysis and specified fully in the statistical analysis plan. These treatment comparisons will not be considered as formal hypothesis testing, but as estimation and investigation of regional treatment effects.

A total of approximately 20 subjects will be randomized. No formal sample size calculation has been done. The proposed sample size is based on previous experience, which included two previously conducted FRI studies with FLUIDDA (PT003018 and PT003019). Each of these studies included approximately 20 subjects. It can be assumed that sufficient precision will be obtained when including approximately 20 subjects.

1.3 Schema

The general study design is summarised in Figure 1.

Figure 1 Study design



*If subject is on a BID COPD maintenance medication(s) return in ~7 days (day -14) and QD COPD maintenance medication(s) return in ~14 days (day -7)

R Randomisation; TC Telephone contact

2 INTRODUCTION

2.1 Study rationale

This imaging methodology will allow an assessment of the extent of airway changes using a triple combination of BGF and the dual combination GFF. Previous studies demonstrated that looking directly at airway volumes and resistance is a more sensitive measure than FEV_1 to evaluate the acute bronchodilating effect of inhaled LABA and/or LAMA (De Backer et al 2011; De Backer et al 2012; Vos et al 2013).

The study hypothesis states that ICS may change airway caliber via its effect on airway inflammation, edema, and secretions. ICS may also enhance the LABA/LAMA effect and could create beneficial synergies leading to a better regional exposure, a larger bronchodilation, and a reduced inflammation in more peripheral lung regions.

It is believed that the additional effect of ICS on top of LABA/LAMA will reduce hyperinflation and air trapping, resulting in lower lung and lobar volumes. At the same time, the specific airway volume (i.e. airway volumes that are corrected for lung volumes) are expected to increase. The primary goal of this study is to describe the effect on airway volume with the addition of ICS. This goal builds on the results of a lung function study (KRONOS), where we studied the effect on FEV1 when ICS was added to LAMA/LABA and was recently published [Ferguson, 2018]. As illustrated in Figure 2 of this publication, the addition of budesonide to glycopyrrolate/formoterol, resulted in clinically meaningful improvements of trough FEV1, and of FEV1 AUC 0-4 hours post-dose, in COPD patients.
However, while FEV1 is a well-established lung function parameter, it is still rather crude and does not make a good representation of the function of smaller airways. Thus, the purpose of the present study is to further characterize the lung function benefit by a more sensitive method. FRI is a well-established method to achieve a more regional characterization of the respiratory system. By simultaneously looking at the airway resistance and internal airflow distribution, functional respiratory imaging will be able to infer physiological changes in the peripheral lung regions

2.2 Background

A detailed description of the chemistry, pharmacology, efficacy, and safety of BGF is provided in the Investigator's Brochure for BGF MDI, BFF MDI and GFF is provided in the Investigator's Brochure for GFF MDI.

2.3 Benefit/risk assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BGF and GFF may be found in the respective Investigator Brochures.

3 OBJECTIVES AND ENDPOINTS

Table 3 Study objectives

Primary objective:	**Endpoint/variable:**
To assess the effects of BGF and GFF on specific image-based airway volumes and resistance in subjects with moderate to severe COPD following chronic twice-daily (BID) dosing after approximately four weeks of treatment	• Specific airway volume ($_{si}V_{aw}$) • Specific airway resistance ($_{si}R_{aw}$)
Secondary objective:	**Endpoint/variable:**
To assess the effects of BGF and GFF on various Functional Respiratory Imaging (FRI) parameters	• Airway volume ($_{i}V_{aw}$) • Airway resistance ($_{i}R_{aw}$)
To assess the effects of BGF and GFF on lung function parameters	Forced expiratory volume in one second (Post-dose FEV_1)
To assess the effects of BGF and GFF on body plethysmography parameters	Functional Residual Capacity (FRC)
Safety objective:	**Endpoint/variable:**
To assess the safety of BGF and GFF	Adverse events (AEs), serious adverse events (SAEs), adverse events leading to treatment discontinuation (DAEs)
Exploratory	**Endpoint/variable:**
To assess the effects of BGF and GFF on other FRI parameters	• Lobe volumes ($_{i}V_{lobes}$) • Air Trapping (AT) • Internal lobar airflow distribution (IAD) • Low attenuation or emphysema score (LAS) • Blood Vessel density or fibrosis score ($_{i}V_{by}$) • Airway Wall Thickness ($_{i}V_{aww}$) • Mass of deposited particles per defined airway section

To assess the effects of BGF and GFF on other lung function parameters	• Forced vital capacity (FVC) • Tiffeneau index (FEV_1/FVC ratio) • Forced expiratory flow 25%-75% (FEF_{25-75}) • Inspiratory capacity (IC)
To assess the effects of BGF and GFF on other body plethysmography parameters	• Residual volume (RV) • Total Lung Capacity (TLC) • Airway resistance (Raw) • Specific airway resistance (sRaw) • Specific airway conductance (sGaw)

4 STUDY DESIGN

4.1 Overall design

For an overview of the study design see Figure 1, Section 1.3. For details on treatments given during the study, see Section 6.1 Treatments administered.

For details on what is included in the efficacy and safety endpoints, see Section 3 Objectives and Endpoints.

4.2 Scientific rationale for study design

This study will recruit patients with moderate to severe COPD; therefore, spirometry entry requirements are set according to the thresholds defined by GOLD guidelines (GOLD 2018). These requirements are in line with the inclusion criteria used in the pivotal study programmes of both GFF and BGF. In patients meeting these criteria, with severe or persistent breathlessness, treatment with at least dual bronchodilator therapy is recommended (GOLD 2018).

Randomisation and blinding will minimise any potential for selection bias, or bias in the assessment of study endpoints or the management of patients. Patients will also continue to use short-acting rescue medication when necessary (albuterol/salbutamol MDI inhaler).

4.3 Justification for dose

GFF is an approved therapy for COPD in the USA and Canada currently. GFF treatment will be given in accordance with the labelled dosing regimens. BGF treatment is currently in phase III development and a pivotal study has been completed using the 320mcg BID regimen [Ferguson, 2018].

4.4 End of study definition

The end of study is defined as the last expected visit/contact of the last subject undergoing the study.

A subject is considered to have completed the study when he/she has completed the follow-up telephone contact post last treatment

See Appendix A 5 for guidelines for the dissemination of study results.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrolment criteria, also known as protocol waivers or exemptions, is not permitted.

Each subject should meet all of the inclusion criteria and none of the exclusion criteria for this study in order to assigned/randomised to a study intervention. Under no circumstances can there be exceptions to this rule. Subjects who do not meet the entry requirements are screen failures, refer to section 5.4

For procedures for withdrawal of incorrectly enrolled subjects see Section 7.3.

5.1 Inclusion criteria

Subjects are eligible to be included in the study only if all of the following inclusion criteria and none of the exclusion criteria apply:

Informed consent

1. Give their signed written informed consent to participate.

- Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.
- Provision of signed and dated, written informed consent form prior to any mandatory study specific procedures, sampling, and analyses.

The ICF process is described in Appendix A 3.

Age

2 Subject must be 40 years to ≤80 years of age inclusive, at the time of signing the informed consent form at Visit 1.

Type of subject and disease characteristics

3 Subjects with an established clinical history of COPD as defined by the American Thoracic Society (ATS)/European Respiratory Society (ERS) (Celli, 2004) or by locally applicable guidelines e.g., JRS Guidelines (JRS, 2013) characterized by:

- Airflow limitation that is not fully reversible. Progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

4 Tobacco Use: Current or former smokers with a history of at least 10 pack-years of 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]).

5 Severity of Disease: Subjects with an established clinical history of COPD and severity defined as:

- At Visit 1 pre-bronchodilator FEV1 must be >30% and <80% predicted normal value, calculated using The Third National Health and Nutrition Examination Survey (NHANES III) reference equations.
- At Visit 2 post-bronchodilator FEV1/FVC ratio of <0.70.
- At Visit 2 post-bronchodilator FEV1 must be >30% and <80% predicted normal value, calculated using The Third National Health and Nutrition Examination Survey (NHANES III) reference equations.

6 Stability criteria: At Visit 5 if the pre-dose -60 minute FEV1 value is outside of the ±20% range compared to the average (-30 and -60 minute) pre-dose FEV1 value of Visit 3, the visit may be rescheduled at the Investigator's discretion, or the subject may be discontinued.

7 Blood eosinophil count > 150 cells per μL at Visit 1

8 Patients should be on scheduled maintenance treatment with one or more inhaled bronchodilator therapies, since at least 1 month prior to visit 1. LAMA, LABA, or regular scheduled maintenance with SAMA or SABA would qualify. Note: Inhaled corticosteroids are not allowed for 3 months prior to Visit 1.

9 Chest x-ray or computed tomography (CT) scan of the chest/lungs within 12 months prior to Visit 1 must be acceptable to the Investigator. Subjects who have a chest x-ray that reveals clinically significant abnormalities not believed to be due to the presence of COPD should not be included.

10 Screening clinical laboratory tests must be acceptable to the Investigator.

11 Screening ECG must be acceptable to the Investigator.

12 Individual is willing and, in the opinion of the Investigator, able to adjust current COPD therapy as required by the protocol.

13 Compliance: Subjects must be willing to remain at the study center as required per protocol to complete all visit assessments.

Sex

14 Male or female

Reproduction

15 Negative pregnancy test (urine or serum) for female subjects of childbearing potential.

16 Female subjects must be 1 year post-menopausal, surgically sterile, or using an acceptable method of contraception (an acceptable method of contraception is defined as a barrier method in conjunction with a spermicide) for the duration of the study (from the time they sign consent) and for 1 month after the last dose of study medication to prevent pregnancy. In addition, oral contraceptives, approved contraceptive implant, long-term

injectable contraception, intrauterine device, or tubal ligation are allowed. Oral contraception alone is not acceptable; additional barrier methods in conjunction with spermicide must be used.

5.2 Exclusion criteria

Medical conditions

1 As judged by the investigator, any evidence of significant diseases other than COPD, i.e., disease or condition which, in the investigator's opinion makes it undesirable for the subject to participate in the trial.

2 Respiratory:

a. Asthma: Subjects, who in the opinion of the Investigator, have a current or recent (i.e., within the past 10 years) diagnosis of asthma.

b. Alpha-1 Antitrypsin Deficiency: Subjects who have alpha-1 antitrypsin deficiency as the cause of COPD.

c. Other Respiratory Disorders: Subjects who have other active pulmonary disease such as active tuberculosis, lung cancer, bronchiectasis (High Resolution Computed Tomography (HRCT) evidence of bronchiectasis that causes repeated acute exacerbations), sarcoidosis, idiopathic interstitial pulmonary fibrosis (IPF), WHO group 1 or primary pulmonary hypertension, or uncontrolled sleep apnea (i.e., in the opinion of the Investigator severity of the disorder would impact the conduct of the study).

   Note: Allergic rhinitis is not exclusionary.

d. Lung Volume Reduction: Subjects who have undergone lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction (endobronchial blockers, airway bypass, endobronchial valves, thermal vapor ablation, biological sealants, and airway implants) within 1 year of Visit 1.

e. Hospitalization: Subjects who have been hospitalized due to poorly controlled COPD within 3 months prior to Visit 1 (Screening) or during the run-in period (Visit 1 to Visit 3).

f. Poorly Controlled COPD: Subjects who have poorly controlled COPD, defined as acute worsening of COPD that requires treatment with oral corticosteroids or antibiotics within 3 months prior to Visit 1 (Screening) or during the run-in period (Visit 1 to Visit 3).

g. Lower Respiratory Tract Infection: Subjects who had lower respiratory tract infections that required antibiotics and/or oral steroids within 6 weeks prior to Visit 1 (Screening) or during the run-in period (Visit 1 to Visit 3).

h. Spirometry Performance:

1) Acceptability: Subjects who cannot perform acceptable spirometry, i.e., meet ATS/ERS acceptability criteria.

2) Repeatability: Subjects who cannot perform technically acceptable spirometry with at least three acceptable flow-volume curves with two or more meeting ATS repeatability criteria for FEV_1 during the pre-bronchodilator assessments at Visit 1 and at the post-bronchodilator assessment at Visit 1.

i. Oxygen: Subjects receiving long-term-oxygen therapy (LTOT).

Note: PRN oxygen use is not exclusionary.

j. Subject use of any non-invasive positive pressure ventilation device (NIPPV).

Note: Subjects using continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) for Sleep Apnea Syndrome are allowed in the study.

k. Change in smoking status (i.e., start or stop smoking,) or initiation of a smoking cessation program within 6 weeks of Visit 1 and throughout the run-in period (Visit 1 to Visit 3).

l. Pulmonary Rehabilitation: Subjects who have participated in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1 (Screening) or who will enter the acute phase of a pulmonary rehabilitation program during the study. Subjects who are in the maintenance phase of a pulmonary rehabilitation program are not to be excluded.

m. Subjects who are steroid dependent and maintained on inhaled corticosteroids, either as mono products or as part of fixed combination products, or on oral /systemic corticosteroids, are not eligible.

n. Subjects who have initiated or altered the dose regimen of intranasal corticosteroids, intranasal antihistamines, or a combination thereof within 7 days prior to Visit 1 or during the run-in period (Visit 1 to Visit 3)

o. Risk factors for pneumonia: immune suppression (HIV) severe neurological disorders affecting control of the upper airway or other risk factors that in the opinion of the Investigator would put the subject at substantial risk of pneumonia

p. Pneumonia not clinically resolved within 1 month of Visit 1.

3 Cancer: Subjects who have cancer that has not been in complete remission for at least five years.

Note: Subjects with squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or localized prostate cancer are eligible, if in the opinion of the Investigator, the condition

has been adequately evaluated, is clinically controlled and the subject's participation in the study would not represent a safety concern.

4 Glaucoma: Subjects with a diagnosis of narrow-angle glaucoma that, in the opinion of the Investigator, has not been adequately treated. All medications approved for control of intraocular pressures are allowed including topical ophthalmic non-selective beta-blockers (such as betaxolol, carteolol, levobunolol, metipranolol, timolol) and prostaglandin analogues.

5 Substance Abuse: Subjects, who in the opinion of the Investigator, significantly abuse alcohol or drugs (refer to Exclusion Criterion 1).

6 Liver: Subjects with abnormal liver function tests defined as Alanine aminotransferase (ALT), Aspartate aminotransferase (AST), or total bilirubin ≥1.5 times upper limit of normal at Visit 1.

7 Renal

a. Subjects with symptomatic prostatic hypertrophy that is clinically significant in the opinion of the Investigator. Subjects with a trans-urethral resection of prostate (TURP) or full resection of the prostate within 6 months prior to Visit 1 are excluded from the study.
b. Subjects with bladder neck obstruction or urinary retention that is clinically significant in the opinion of the Investigator.
c. Subjects with a calculated creatinine clearance ≤30 mL/minute using Chronic Kidney Disease Epidemiology Collaboration. (CKD-EPI) formula (Levey et al 2009) at Visit 1 and on repeat testing prior to Visit 3.
Note: Subjects with overactive bladder syndrome treated with oral anticholinergics that have been on treatment for at least one month are allowed in the Study.

8 Cardiac disease

a. Subjects who have unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of Screening (Visit 1). Subjects with a recent history of acute coronary syndrome, or who have undergone percutaneous coronary intervention or coronary artery bypass graft within the past 3 months are to be excluded.
b. Subjects with congestive heart failure (CHF) The New York Heart Association (NYHA) Class III/IV).
c. Clinically significant abnormal ECG: A clinically significant abnormal ECG is defined as (but not limited to) any of the following:
    - Clinically significant conduction abnormalities [e.g., left bundle branch block, Wolff-Parkinson-White syndrome or evidence of second degree (Mobitz Type II) or third degree atrioventricular block (unless pacemaker or defibrillator has been inserted)].

- QT interval corrected for heart rate (using Fridericia's formula; QTcF) ≥500 milliseconds (msec) in patients with QRS <120 msec and QTcF ≥530 msec in patients with QRS ≥120 msec.

9 Clinically Uncontrolled Hypertension: Subjects who have clinically significant uncontrolled hypertension.

Prior/concomitant therapy

10 Any concomitant medications known to be associated with Torsades de Pointes or potent inducers of cytochrome P450 3A4 (CYP3A4).

11 Medication prior to spirometry: Subjects who are medically unable to withhold their short-acting bronchodilators for the 6-hour period required prior to spirometry testing at each study visit will be excluded.

12 Prohibited Medications: Subjects who, in the opinion of the Investigator, would be unable to abstain from protocol-defined prohibited medications during the Screening Period and treatment phases of this study.

13 Subjects using any herbal inhalation and nebulizer products within 2 weeks prior to Visit 1 (Screening) and do not agree to stop using them during the study drug treatment.

Note: Nebulized albuterol is acceptable, but requires a minimum 6 hours washout prior to Visit 1 and must be discontinued at Visit 1 and throughout the study.

Prior/concurrent clinical study experience

14 Participation in another clinical study with an investigational product administered in the last 30 days or five half-lives prior to Visit 1 (Screening), whichever is longer.

Note: Subject participation in observational studies (i.e., studies that do not require change to medication or an additional intervention) is not exclusionary.

15 Drug Allergy: Subjects who have a history of hypersensitivity to β2 agonists, budesonide or any other corticosteroid components, glycopyrronium or other muscarinic anticholinergics, or any component of the MDI.

Other exclusions

16 Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site).

17 Affiliations with Investigator site: Study Investigators, sub-Investigators, study coordinators, employees of a participating Investigator or immediate family members of the aforementioned are excluded from participation in this study.

18 Questionable Validity of Consent: Subjects with a history of psychiatric disease, intellectual deficiency, poor motivation, substance abuse (including drug and alcohol), or other conditions that will limit the validity of informed consent to participate in the study.

19 Hand-to-Breath Coordination: Subjects who requires the use of a spacer device to compensate for poor hand-to-breath coordination with a MDI.

Note: Use of a nebulizer to deliver COPD medications is prohibited throughout the trial.

20 Judgment by the investigator that the subject should not participate in the study if the subject is unlikely to comply with study procedures, restrictions and requirements.

21 Previous enrolment in the present study.

22 For women only - currently pregnant (confirmed with positive pregnancy test) or breast-feeding.

5.3 Lifestyle restrictions

5.3.1 Meals and dietary restrictions

Subjects are encouraged to refrain from consuming grapefruits or grapefruit juice throughout the study. Subjects must not ingest xanthine (i.e., caffeine)-containing foods and beverages for at least 6 hours prior to each study visit and for the duration of each study visit. Examples of such products include coffee, tea, chocolate, and cola. Decaffeinated beverages are acceptable.

5.3.2 Illicit Drug and or Drugs of Abuse

Illicit drugs or drugs of abuse will not be allowed from the start of Screening (Visit 1) to the end of Visit 5 or to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented, and the subject will be discontinued. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption.

5.3.3 Smoking Status

Changes in a subject's smoking status (i.e., stopping or re-starting smoking) may have an impact on the efficacy outcome measures. At all visits the subject will be asked about any recent change in their smoking status (i.e., whether a subject's status has changed from smoker to non-smoker or vice versa). Any change in smoking status during the run-in period (Visit 1 to Visit 2) will result in a screen failure. Smoking status changes during the 4-week treatment periods will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects will be required to refrain from smoking (including medical marijuana and electronic cigarettes) for at least 4 hours prior to each study visit and throughout the duration of each study visit. Study participants may utilize various nicotine replacement treatments such as chewing gum, inhaler and patches (PRN), in accordance with recommendations from the Investigator during the entire study visit.

Note: For this study, the use of electronic cigarettes will be treated in the same manner as cigarette smoking except for the calculation of pack-years to determine cigarette smoking history.

5.4 Screen failures

Screen failures are defined as subjects who signed the informed consent form to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened.

These subjects should have the reason for study withdrawal recorded in eCRF.

6 STUDY TREATMENTS

Study treatment is defined as any investigational product(s) (including marketed product comparator and placebo) or medical device(s) intended to be administered to a study participant according to the study protocol. Study treatment in this study refers to blinded treatment and open label products (Ventolin and Atrovent).

6.1 Treatments administered

6.1.1 Investigational products

Table 4 Investigational Products

Product Name and Dosage	Product Strength	Dose Form/Fill Count	Administration Route
Blinded Study Medications			
BGF MDI 320/14.4/9.6 µg ex-actuator	BGF MDI 160/7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken BID as two oral inhalations in the morning and two oral inhalations in the evening*
GFF MDI 14.4/9.6 µg ex-actuator	GFF MDI 7.2/4.8 µg per actuation	1 MDI 120 inhalations	Taken BID as two oral inhalations in the morning and two oral inhalations in the evening*
Open-label Products			
Ventolin (albuterol sulfate) HFA inhalation aerosol 90 µg ex-actuator	Ventolin (albuterol sulfate) HFA inhalation aerosol will be the supplied product Each inhalation contains 108 µg corresponding to 90 µg albuterol base per actuation	1 MDI 60 or 200 actuations	Taken as needed (PRN)
Atrovent (ipratropium bromide) HFA inhalation aerosol 34 µg ex-actuator	Atrovent (ipratropium bromide) HFA will be the supplied product Each inhalation contains 17 µg ex-actuator per actuation	1 MDI 200 actuations	Taken as two inhalations QID during run-in period and washout period

Abbreviations: BGF MDI=Budesonide/Glycopyrronium/Formoterol Fumarate Inhalation Aerosol; GFF MDI= Glycopyrronium/Formoterol Fumarate Inhalation Aerosol; MDI=Metered Dose Inhaler; PRN=as needed; BID= two times daily; QID=four times daily

* approximately 12 hours apart

Note: All study drugs will be administered by oral inhalations.

6.1.2 Medical devices

The sponsor manufactured medical devices provided for use in this study are BGF MDI and GFF MDI.

Other medical devices (not manufactured by or for sponsor) provided for use in this study are Ventolin HFA, and Atrovent HFA.

Instructions for medical device use are provided in Section 6.2.2.

Medical device incidents, including those resulting from malfunctions of the device, must be detected, documented, and reported by the investigator throughout the study (see Section 8.4.4)

6.1.3 Primary Packaging and Labelling Information

Investigational materials will be packaged by the sponsor/designee. Atrovent HFA and Ventolin HFA supplies will be supplied as open-label MDIs.

Blinded Supplies: Each MDI will be labeled with a single label. The MDI actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

Open-label Supplies: Open-label Atrovent HFA and Ventolin HFA will be provided as individually labeled MDIs. Each MDI will contain a single label. The MDI actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

Both single and two-part labels will be printed with black ink and may include the following text:

Packaging Lot Trace ID #	Dosing Instructions
Space for entry of screening #	Storage Conditions
Component ID #	Compound ID - Protocol #
Space for entry of randomization #	Country regulatory requirements
Fill Count & Dosage Form	Sponsor address (If applicable)
Space for entry of Interval ID (Visit # only)	Translation Key (If applicable)
Re-evaluation/Expiration date (if applicable)	

Abbreviation: ID=identification

6.1.4 Secondary Packaging and Labelling Information (Box)

Blinded investigational drug and open-label (Atrovent HFA and Ventolin HFA) supplies will be packaged in individual boxes as outlined in Table 5. Box configuration is subject to change as a result of packaging constraints.

Table 5 Description of Boxes

Drug supplies	Individual box contents
Blinded	1 MDI
Atrovent HFA	1 MDI
Ventolin HFA	1 MDI

Each box will be labeled with a two-part label printed with black ink and may include the following text:

Packaging Lot ID #	Dosing Instructions (if applicable)
Space for entry of screening #	Storage Conditions
Component ID #	Compound ID - Protocol #
Space for entry of randomization #	Country regulatory requirements
Kit Contents (1 MDI)	Sponsor address (If applicable)
Space for entry of Interval ID	Translation Key (If applicable)
Re-evaluation/Expiration date (if applicable)	

Abbreviation: ID=identification

6.2 Preparation/handling/storage/accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

Only subjects enrolled in the study may receive study treatment and only authorised site staff may supply or administer study treatment. All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labelled storage conditions with access limited to the investigator and authorised site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in section 6.2.3.

6.2.1 Storage Requirements

Blinded supplies: Store below 25° C (77° F) in a dry place. Excursions permitted up to 30° C (86° F).

Ventolin HFA supplies: Store between 20° and 25°C (68° and 77°F); excursions permitted to 15°-30°C (59°□86°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw into a fire or incinerator.

Atrovent HFA supplies: Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). For optimal results, the canister should be at room temperature before use. Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 49°C (120°F) may cause bursting. Never throw the inhaler into a fire or incinerator.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in this protocol or in the product label. Documentation of temperature monitoring should be maintained.

6.2.2 Instructions for Preparation of Treatments for Administration and Dispensing

6.2.2.1 BGF MDI and GFF MDI

Individual BGF MDI and GFF MDI will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component identification number. Confirm that the identifier given by the randomization lists and the component identification number written on the label are the same. The visit treatment box is labelled with a two-part label. Write the subject number and treatment visit number on each of the two-part labels. The ‘tear-off’ part of the label is to be placed onto the subject’s worksheets.

All MDIs must be primed before the first use. Priming involves releasing 4 sprays into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use.

The MDI must be primed in a separate room from the subject treatment area. Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until subject returns to the clinic. The MDI should be

stored upright at room temperature by the subject, avoiding temperature extremes, and storage in direct sunlight.

6.2.2.2 Atrovent HFA (Ipratropium Bromide)

Open-label Atrovent HFA will be provided by Sponsor and stored in a secured location within the clinic or pharmacy facilities.

Atrovent HFA is a solution aerosol that does not require shaking. However, as with any other MDI, some coordination is required between actuating the canister and inhaling the medication. Atrovent HFA should be primed per manufacturer's instructions prior to dispensing to subject (i.e., "prime" or actuate Atrovent HFA before using for the first time by releasing 2 test sprays into the air away from the face). In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Subjects should avoid spraying Atrovent HFA into their eyes.

Subjects will be dispensed the Atrovent HFA for COPD maintenance therapy during the run-in period (between Visit 2 and 3) and during the washout period (between Visit 4 and 5) per the manufacturer's instruction, 2 puffs with each administration four times a day, divided over the daytime. Atrovent is expected to be dispensed at Visit 1; the first dose should be taken starting at Visit 2, after the visit 2 procedures are performed after ensuring the washout of prohibited medications prior to Visit 3 have been achieved per Table 6 in section 6.5.1. The MDI should be stored at room temperature by the subject, avoiding temperature extremes and storage in direct sunlight.

6.2.2.3 Ventolin HFA (Albuterol Sulfate)

Open-label Ventolin HFA will be provided by Sponsor and stored in a secured location within the clinic or pharmacy facilities. Ventolin HFA should be stored at room temperature by the subject. Ventolin HFA should be primed per manufacturer's instructions prior to dispensing to subject. Study personnel will record number on the dose counter at the time of dispensing (following priming and characterization of reversibility) and upon return.

6.2.2.4 Placebo MDI

At screening, on admission to each Treatment Period (as needed), subjects will be instructed by site staff on how to use the MDI device correctly using placebo MDIs. In addition, MDI training will be supplemented using the Vitalograph AIM Aerosol Inhalation Monitor or an equivalent device.

6.2.3 Drug Accountability/Return of Clinical Supplies

Under no circumstances will the Investigator(s) allow the study drug to be used other than as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated assistants have access. Storage conditions for the clinical supplies should be observed, monitored and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator is responsible for keeping accurate records of the clinical supplies received from Sponsor, the amount dispensed to and returned by the subject, and the amount remaining at the conclusion of the study. The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by Sponsor.

Sites should check with the Sponsor representative for appropriate documentation that needs to be completed for drug accountability.

The Investigator or designated assistant should not open individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Any deviation from this must be discussed with the Clinical Monitor.

For each subject, all used study drug materials will be collected. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Sponsor or designee.

Note: Used study drug will be stored separately from unused study drug.

All product complaints (including device malfunctions) must be reported to the Sponsor or designee using the Product Complaints Form provided in each site's investigator file. Sponsor or designee will contact the site to evaluate the nature of the complaint and determine what further action is needed.

6.3 Measures to minimise bias: randomisation and blinding

Subjects will be randomized to receive one of the treatment sequences BGF-GFF and GFF-BGF in the proportion 1:1 using a fixed block size. Separate randomization lists will be created for each centre. Interactive Voice/Web Response System (IVRS/IWRS) will not be used.

If a subject withdraws from the study, then his/her enrolment/randomisation code cannot be reused. Withdrawn subjects may be replaced.

6.4 Treatment compliance

Any change from the dosing schedule, does interruptions, dose reductions, dose discontinuations should be recorded in eCRF.

The Investigational Product Storage Manager is responsible for managing the IMP from receipt by the study site until the destruction or return of all unused IMP. The Investigator(s) is responsible for ensuring that the subject has returned all unused IMP.

6.5 Concomitant therapy

Any medication or vaccine including over-the-counter or prescription medicines, vitamins, and/or herbal supplements that the subject is receiving at the time of enrolment within 30 days before Visit 1 (Screening) or receives during the study including any additions, deletions, or changes in the dose of these medications while in the study must be recorded along with:

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

6.5.1 Prohibited COPD Medications

The following medications used for the treatment of COPD are not permitted during this study. These medications must be discontinued 6 hours to 24 hours prior to Visit 1 (Screening) and are not permitted during the run-in period. The minimum washout period before Visit 1 and between Visit 1 and Visit 3 are shown in Table 6. The only COPD medications permitted during the study are sponsor-provided Atrovent HFA® for COPD maintenance during the run-in and wash-out period and sponsor-provided Ventolin HFA® for rescue of COPD symptoms during the study.

Table 6 Prohibited COPD Medications and Required Washout Periods Prior to Visit 1 and Visit 3

	Minimum Washout Period Prior to:	
Class of Medication	**Visit 1**	**Visit 3**
LAMAs	24 hours	Tiotropium: 14 days Aclidinium: 7 days Glycopyrronium: 7 days Umeclidinium: 7 days
Short-acting muscarinic antagonists (SAMA)[a]	6 hours	6 hours
LABAs (inhaled)	24 hours	48 hours (Indacaterol: 15 days)
Fixed-combinations of LABA/LAMA	24 hours	7 days (14 days for indacaterol/glycopyrronium and olodaterol/tiotropium)
Fixed-combinations of LABA/ICS	3 months	
Fixed-combinations of SABAs and SAMAs	6 hours	6 hours
SABAs[b]	6 hours	6 hours
Oral β-agonists		2 days
Theophylline (total daily dose >400 mg/day)[c]		7 days
ICS (alone or in combination)	3 months	

Abbreviations: COPD=chronic obstructive pulmonary disease; HFA=hydrofluoroalkane; ICS=inhaled corticosteroid; LABA=long-acting β2-agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β2-agonist

Note: Subjects taking roflumilast are allowed provided they have been on stable dose of therapy for at least 2 months prior to Randomization.

a. Discontinue and use only sponsor-provided Atrovent HFA during run-in and washout period

b. Discontinue and use only sponsor-provided rescue Ventolin HFA throughout the study

c. Theophylline (<400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Randomization.

Subjects that have received depot corticosteroids including, intra-articular or intraocular corticosteroids require a 3 month washout prior to Visit 1. Subjects that have received oral, intravenous or intramuscular corticosteroids for any reason require a 6 week washout prior

to Visit 1. Any subject that requires use of systemic corticosteroids during the run-in period (Visit 1 to Visit 3) will be screen failed.

Note:

- During the TP 1 and 2 (Visit 3 to Visit 4 and Visit 5 to Visit 6), subjects treated with oral corticosteroids and/ or antibiotics for exacerbation should be discontinued from the study.

Subjects who meet all entry criteria but are using one or more of the prohibited COPD medications (previously listed) will have their maintenance therapy for COPD adjusted as follows:

- Subjects taking prohibited inhaled COPD medications (listed in this section) will discontinue these medications as noted above. At Visit 2 after study procedures subjects will be switched to sponsor-provided Atrovent HFA MDI administered QID (during the run-in and wash-out periods only) and sponsor-provided Ventolin HFA to be administered as needed (PRN) throughout the study for control of COPD symptoms.
- Sponsor-provided Atrovent HFA MDI administered QID (during the run-in and wash-out periods only), and sponsor-provided Ventolin HFA to be administered as needed (PRN) throughout the study for control of COPD symptoms.
- All subjects treated with either a LABA (salmeterol, formoterol, indacaterol) or currently marketed LAMA (tiotropium, aclidinium, glycopyrronium, [eg, Seebri]) administered alone or as a loose combination will have these medications discontinued and replaced with sponsor-provided Atrovent HFA MDI administered QID (during the run-in and wash-out periods only), and sponsor-provided Ventolin HFA to be administered as needed (PRN) throughout the study for control of COPD symptoms.

The following respiratory medications are not permitted during this study (Table 7)

Table 7 Other Respiratory/Nasal Medications: Required Washout Periods

Required washout periods prior to Visit 3:	
Class of medication	**Minimum cessation period prior to Visit 3**
Leukotriene antagonists (eg, zafirlukast, montelukast)	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen *	7 days

*Ketotifen eye drops are allowed

6.5.2 Other concomitant treatment

Other medication other than that described above, which is considered necessary for the subject's safety and wellbeing, may be given at the discretion of the Investigator and recorded in the appropriate sections of the Case Report Form.

6.5.3 Rescue medication

The study site will supply Ventolin HFA® rescue medication that will be provided by the sponsor.

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 6 hours following the administration of Study treatment. The date and time of rescue medication administration as well as the name and dosage regimen of the rescue medication must be recorded.

Table 8 Rescue medication

Rescue/Supportive medication/class of drug:	Usage:
Ventolin HFA®	For rescue of COPD symptoms

6.6 Dose modification

N/A

6.7 Treatment after the end of the study

N/A

7 DISCONTINUATION OF TREATMENT AND SUBJECT WITHDRAWAL

7.1 Discontinuation of study treatment

Subjects may be discontinued from investigational product (IP) in the following situations. Note that discontinuation from study treatment is NOT the same thing as a complete withdrawal from the study.

- Subject decision. The subject is at any time free to discontinue treatment, without prejudice to further treatment
- Adverse Event
- Severe non-compliance with the Clinical Study Protocol
- Subjects who require treatment for their COPD symptoms, other than the study or rescue medication during the treatment period will be discontinued from the study.
- If a female subject becomes pregnant during the course of the study, the subject will be discontinued and the pregnancy will be followed full-term through delivery or final outcome (refer to Section 8.4.2).

See the SoA for data to be collected at the time of treatment discontinuation and follow-up and for any further evaluations that need to be completed.

7.1.1 Procedures for discontinuation of study treatment

The investigator should instruct the subject to contact the site before or at the time if study treatment is stopped. A subject that decides to discontinue study treatment will always be asked about the reason(s) and the presence of any AEs. The date of last intake of study treatment should be documented in the electronic CRF. All study treatment should be returned by the subject at their next on-site study visit or unscheduled visit. Subjects permanently discontinuing study treatment should be given locally available standard of care therapy, at the discretion of the Investigator.

7.2 Lost to follow-up

A subject will be considered potentially lost to follow-up if he or she fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject or next of kin by e.g. repeat telephone calls, certified letter to the subject´s last known mailing address or local equivalent

methods. These contact attempts should be documented in the subject's medical record.

- Efforts to reach the subject should continue until the end of the study. Should the subject be unreachable at the end of the study the subject should be considered to be lost to follow up with unknown vital status at end of study and censored at latest follow up contact.

7.3 Withdrawal from the study

A subject may withdraw from the study (eg, withdraw consent), at any time (investigational product **and** assessments) at his/her own request, without prejudice to further treatment.

A subject who considers withdrawing from the study must be informed by the Investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or information from medical records).

If the subject withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken, and the investigator must document this in the site study records.

A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). The Investigator will follow up subjects as medically indicated.

See SoA, Table 1, for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. All Study treatment should be returned by the subject.

7.4 Study and Site Closure

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. The study may be stopped if, in the judgment of AstraZeneca, trial subjects are placed at undue risk because of clinically significant findings that:

- meet individual stopping criteria or are otherwise considered significant
- are assessed as causally related to study drug,
- are not considered to be consistent with continuation of the study

Regardless of the reason for termination, all data available for the subject at the time of discontinuation or follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the subjects' interests

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator

Discontinuation of further study intervention development

8 STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarised in the SoA.

The investigator will ensure that data are recorded on the electronic Case Report Forms.

The investigator ensures the accuracy, completeness, for electronic CRFs include: legibility and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed electronic Case Report Forms. A copy of the completed electronic Case Report Forms will be archived at the study site.

Immediate safety concerns should be discussed with the sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue Study treatment.

Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The investigator will maintain a screening log to record details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.

Procedures conducted as part of the subject's routine clinical management (e.g., blood count) and obtained before signing of the ICF may be utilised for screening or baseline purposes

provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

The maximum amount of blood collected from each subject over the duration of the study, including any extra assessments that may be required, will not exceed 10 mL. Repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

8.1 Efficacy assessments

8.1.1 HRCT scans

Subjects will receive a total of seven HRCT scans. The first will be conducted at baseline, the beginning of treatment period 1 at Visit 3. The pre-dose CT-scan of the thorax will be taken on two breathing levels, $TLC_{(PRE)}$ and $FRC_{(PRE)}$. During Visit 3 an additional scan of the UA will be taken. The post-dose measurement will be performed on two breathing level, $TLC_{(POST)}$ and $FRC_{(POST)}$. The Post dose scans will be taken after approximately 4 weeks of each treatment (treatment 1 and treatment 2) of BGF MDI and GFF MDI on Day 29 (±3 days) (Visit 4 and Visit 6).

On Day 1 of the first TP (Visit 3) the HRCT scans ($TLC_{(PRE)}$ and $FRC_{(PRE)}$) and the UA scan will be taken at least 30 minutes prior to dosing.

Post dose HRCT scans ($TLC_{(POST)}$ and $FRC_{(POST)}$) on Day 29 (±3 days) of each TP (Visit 4 and Visit 6) should be started 90 minutes ± 30 minutes after dosing.

Spirometry followed by body plethysmography will be performed after the HRCT scans but within 150 minutes after dosing.

Between the two TPs there will be a washout period of a minimum of 21 days up to a maximum of 28 days.

Whenever possible the same scanner should be used at all the study visits.

HRCT scan is performed with a low radiation protocol (average exposure of 1.806 mSv * 6 + 1mSV (UA scan) = 11.836 mSv). These images are made to perform Computational fluid dynamics (CFD) in order to obtain more information on regional lung function characteristics.

8.1.2 Spirometry

Forced expiratory spirometry maneuvers for derivation of FEV_1, FVC, FEF_{25-75}, FEV_1/FVC ratio and IC will be assessed using a spirometer that meets or exceeds minimum performance recommendations of the ATS.

Spirometry will be conducted at all visits. At Visit 1, Spirometry will be conducted approximately 60 minutes and 30 minutes prior to bronchodilator administration and approximately 30-60 minutes post-bronchodilator (refer to Section 8.1.2.1).

Note: Spirometry must meet the severity and both acceptability and repeatability criteria.

At Visit 3 and Visit 5, spirometry will be obtained at the beginning of the visit. A second spirometry will be obtained before the study drug administration after the pre-dose CT-scans are taken (at Visit 3 only). The -60 minute FEV_1 value obtained at Visit 5 prior to study drug administration will be used to check the stability criteria. At Visit 4 and Visit 6, spirometry will be obtained before the study drug administration, and post-dosing of study drug. Post-dose spirometry assessments will not be conducted before the CT-scan is taken. At Visit 4 and 6 none of the post dose assessments will start before 1 hour after the administration of the study drug. All assessments should be completed within 2.5 hours after dosing.

8.1.2.1 Characterization of Reversibility

Reversibility to Ventolin HFA (SABA) will be evaluated at Visit 1.

The procedure will be, as follows: Reversibility testing to Ventolin HFA:

- Perform pre-bronchodilator PFTs (approximately -60 minutes and -30 minutes) prior to administration of Ventolin HFA (albuterol).
- Administer 4 puffs of Ventolin HFA (albuterol).
- Perform post-bronchodilator PFT 30-60 minutes after the administration of Ventolin HFA.

Reversibility will be a comparison of the average best FEV_1 effort obtained at approximately -60 minutes and -30 minutes pre-bronchodilator to the best FEV_1 effort obtained at approximately 30-60 minutes post-bronchodilator. A subject is determined to be reversible to Ventolin HFA if the improvement in FEV_1 approximately 30-60 minutes following administration of 4 puffs of Ventolin HFA, respectively, is ≥12% and ≥200 ml. Reversibility to Ventolin HFA (obtained at Visit 1) will be used to characterize the population.

8.1.2.2 Stability Criteria

It is important to ensure that the baseline FEV_1 is stable and reflective of the subject's COPD severity prior to continuation in the second TP.

At Visit 3, spirometry will be obtained at the beginning of the visit. A second spirometry will be obtained before the study drug administration after the pre-dose CT scans are taken (at Visit 3 only). The average of the FEV_1 values obtained prior to study drug administration (- 60 min and - 30 min) at Visit 3 will be the baseline value used to compare with the -60 minute FEV_1 value obtained at Visit 5 to check baseline stability.

At Visit 5, if the pre-dose FEV_1 is outside of the ±20% or 200 mL range compared to the average (-30 and -60 minute) pre-dose FEV_1 value of Visit 3, at the investigator's discretion, the visit may be rescheduled or the subject may be discontinued.

8.1.2.3 Inspiratory Capacity

Visit 2 to Visit 6: IC assessments will be conducted with every spirometry. All subjects will be instructed on the performance of the IC manoeuvre. Subjects must be tested in the seated position wearing a nose clip with no air leaks between the mouth and mouthpiece. Subjects should be relaxed with shoulders down and asked to breathe regularly for several breaths until the end-expiratory lung volume is stable (this usually requires at least five tidal manoeuvres). They are then urged to take a deep breath to TLC with no hesitation. From at least three acceptable trials, the two largest IC measurements should agree within 5% or 150 ml, both of these IC values will be captured and analysed.

8.1.2.4 Standardization of IC and Spirometry Collections

All pulmonary function tests including FEV_1, FVC, FEF_{25-75}, FEV_1/FVC ratio, as well as all IC assessments, as defined in ATS/ERS guidelines will be performed in accordance with ATS criteria (Miller et al 2005).

The volume accuracy of the spirometer is to be checked daily using a 3 L syringe across 3 flow ranges (i.e., low, medium and high flows), with temperature and barometric pressure correction. The calibration syringe must meet ATS specifications and must not be used beyond the expiry date. Required accuracy is ± 3% (i.e., 3,09 L to 2,91 L) (ATS/ERS). The results of the calibration factor will be maintained on site, which will be available if the sponsor wants to check for compliance or an audit.

8.1.3 Body plethysmography

Visit 3 to Visit 6: RV, TLC, FRC, R_{aw}, $_sR_{aw}$, $_sG_{aw}$ will be measured using body plethysmography.
On Day 1 of each treatment period (Visit 3 and Visit 5) the body plethysmography measurement will be performed after the CT-scan (at Visit 3 only) however, before the IP administration.
On Day 29 (±3 days) of each treatment period (Visit 4 and Visit 6) the body plethysmography measurement will be performed after the CT-scan and after the post-dose spirometry measurement.

Post dose activities on Day 29 (±3 days) of each treatment period (Visit 4 and Visit 6) will be started 1 hour after dosing on and will be concluded within 2.5 hours after dosing.

8.1.4 Diffusion capacity

The single-breath diffusing capacity of the lungs for carbon monoxide (TCO), alveolar volume (VA) and TCO/VA will be measured at Visit 1. TCO measurement will be used to characterize the subjects enrolled in the trial and will not be used to determine subject eligibility to participate in the study.

8.1.5 Inhalation Profile

Visit 3 and Visit 5: In order to draw an airflow versus time curve, the subject's inhalation profile will be measured. The subject will be asked to inhale and exhale maximally through a mouthpiece without a nose clip. This measurement is performed by a (mobile) pneumotachograph with extraction of all flow data collected during the inhalation profile. At the moment of this measurement the signal from the respiration belt, used for the measurement of the inhalation profile during the study drug administration, will also be logged. The thorax and abdomen expansion will be measured with the Alice PDx diagnostic device.

8.1.6 Inhalation Profile during administration

Visit 3 and Visit 5: During IP administration on Day 1 of both active compounds, the inhalation profile will be recorded while the subject inhales through the device to generate a subject specific inhalation profile by using a respiration belt. The thorax and abdomen expansion will be measured with the Alice PDx diagnostic device.

Sensor cables transmit the appropriate signals to the Alice PDx. The signals are stored on the removable memory card, or if configured to do so, the signals can be displayed from the Alice PDx on a computer running the appropriated software application.

8.1.7 Subject Diary Data Collection

At Visit 1, subjects will be provided with a Diary to be completed twice daily (morning and evening). Study personnel will train subjects on Diary completion and will instruct subjects to return Diary responses to the clinic for all in-clinic study visits.

- At Visit 1, subjects will be instructed to record in the Diary Atrovent HFA four-times daily use (starting at Visit 2) and rescue Ventolin HFA use during the Run-in Period prior to Visit 3.
- At Visit 3, subjects will be instructed to record in the Diary study medication administration during the treatment phase.
- At Visit 4, subjects will be instructed to record in the Diary Atrovent HFA four times daily use and rescue Ventolin HFA) use during the Wash-out Period between Visit 4 and Visit 5.
- At Visit 5, subjects will be instructed to record in the Diary study medication use administration during the treatment phase.

Diary Compliance Requirement: Subject participation may be terminated at any time during the study for the following reason:

Chronic failure, in the judgment of the Investigator, to comply with diary completion, despite documentation at the site of repeated efforts to reinforce compliance. As defined for this study, compliance requires >70% subject completion of diary assessments. The Sponsor may also instruct a site to discontinue a subject based on consistent noncompliance.

Subjects who are unable to meet the compliance requirement (>70% subject completion of diary assessments) in the last 7 days preceding the Randomization Visit (Visit 3) must be retrained. When retraining is required due to non-compliance the Randomization Visit (Visit 3) must be rescheduled.

In-clinic dosing times and dose indicator readings will be documented in the eCRF by the site staff and will not be entered by the subject into their Diary.

During the treatment periods, the subject will record study medication usage.

8.1.8 Rescue Ventolin HFA Use

Subjects requiring more than 8 puffs per day on 3 consecutive days with worsening symptoms should contact the site. The number of "puffs" of rescue Ventolin HFA is the number of actuations of the canister. For example, when rescue Ventolin HFA is required and 2 actuations are inhaled, this should be counted as 2 "puffs." In the event the subject requires 4 actuations, this should be counted as 4 "puffs".

At all study visits the subject will be asked to bring the rescue Ventolin HFA and the site personnel will review the number of actuations of the canister to ensure compliance and subject safety.

8.1.9 Recording of Dose Indicator Reading

The BGF MDI and GFF MDI are fitted with a dose indicator to track use of the MDI.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use.

Site personnel will be instructed to record the dose indicator reading from the MDI after priming (prior to the first dosing Day 1) and after the first dosing Day 1 of both the TPs (Visit 3 and Visit 5).

Prior to dosing at Day 29 (±3 days) of each TP Visit (Visit 4 and Visit 6) or at a Premature Discontinuation Visit, site personnel will observe the dose indicator reading on the study drug returned by the subject and record the dose indicator reading in the source.

Note: The dose indicator reading recorded by the site staff on Day 29 (±3 days) of each TP (Visit 4 and Visit 6) will be the dose indicator reading observed prior to subject dosing.

At Visit 4 and 6, the site staff will compare the dose indicator reading from the prior entered reading of Day 1 (Visit 3 and Visit 5 respectively) of that TP. For major discrepancies (i.e., >20 puff difference), the site staff will review the major discrepancy with the subject and document reason for the major discrepancy in the appropriate study source and eCRF. If appropriate, site staff will retrain the subject on the proper use of the MDI.

8.1.10 Subject Questionnaires

The following subject questionnaires will be completed by subjects at Visit 1: CAT, and MMRC.

8.1.10.1 COPD Assessment Test

The CAT is a self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD. Since the CAT is designed to assess the impact of COPD on the subject by measuring overall impairment, it has moderate correlations with other instruments, such as the MMRC Dyspnea Scale.

Subjects will complete the CAT at Visit 1.

The CAT score will describe the burden and symptomatic impact of COPD in subjects enrolled in the trial and will not be used to determine subject eligibility to participate in the study.

8.1.10.2 Modified Medical Research Council Dyspnea Scale

The MMRC Dyspnea Scale uses a simple grading system to assess a subject's level of dyspnea, shortness of breath.

Table 9 MMRC Dyspnea Scale

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise.
1	I get short of breath when hurrying on level ground or walking up a slight hill.
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace.
3	I stop for breath after walking about 100 meters or after a few minutes on level ground.
4	I am too breathless to leave the house or I am breathless when dressing.

The MMRC scale is a five-point scale published in 1959 that considers certain activities, such as walking or climbing stairs, which provoke breathlessness (Fletcher et al 1959).
In one minute, the subject selects a grade on the MMRC scale that most closely matches his/her severity of dyspnea. The MMRC scale is considered a discriminative instrument that can categorize subjects with COPD in terms of their disability. The MMRC scale is not satisfactory as an evaluative instrument to measure changes in dyspnea, and its broad grades are generally unresponsive to interventions such as pharmacotherapy.

Subjects will complete the MMRC scale at Visit 1, as a description of the symptomatic burden in study subjects. The MMRC scale will not be used to determine subject eligibility to participate in the study.

8.1.11 COPD Exacerbations

COPD exacerbations will only be recorded and summarized if they meet the criteria of being an SAE or if they lead to discontinuation of study drug.

8.2 Safety assessments

Planned time points for all safety assessments are provided in the SoA.

8.2.1 Clinical safety laboratory assessments

See Table 10 for the list of clinical safety laboratory tests to be performed and to the SoA for the timing and frequency. All protocol-required laboratory assessments, as defined in the table, must be conducted in accordance with the laboratory manual and the SoA.

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.

For information on how AEs based on laboratory tests should be recorded and reported, see Section 8.3.7.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The clinically abnormal results (values, units and reference ranges) will be recorded on the appropriate CRF (Medical History if prior to randomization or Adverse Event if after randomization unless serious that may require documentation on the SAE eCRF).

The clinical chemistry, haematology and urinalysis will be performed at a local laboratory at or near to the Investigator site. Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

Table 10 Laboratory safety variables

Haematology/Haemostasis (whole blood)	Clinical Chemistry (serum or plasma)
B-Haemoglobin (Hb)	S/P-Creatinine
B-Leukocyte count	S/P-Bilirubin, total
B-Leukocyte differential count (absolute count)	S/P-Alkaline phosphatase (ALP)
B-Platelet count	S/P-Aspartate transaminase (AST)
Hematocrit	S/P-Alanine transaminase (ALT)
Red Blood Cell Count	S/P-Albumin
B-Glucose	S/P-Potassium
B-Urea Nitrogen (BUN)	S/P-Calcium, total
	S/P-Sodium

NB. In case a subject shows an AST **or** ALT ≥3xULN together with total bilirubin ≥2xULN please refer to Appendix D 'Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law', for further instructions.

8.2.2 Medical/Surgical History and Physical Examination

Medical history, including smoking history details, will be collected at timelines as specified in the SoA. The number of COPD exacerbations requiring oral steroids and/or oral antibiotics, or hospitalization within 12 months of Visit 1 (Screening) will be collected.

A complete physical examination will be performed and include evaluation of relevant body parts, general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed and height will be recorded at Visit 1 (Screening).

At all visits (including the follow-up telephone call [TC]) the subject will be asked about any recent change in their smoking status (i.e., whether a subject's status has changed from smoker to non-smoker or vice versa).

Physical examination will be performed at timelines as specified in the SoA, Investigators should pay special attention to clinical signs related to previous serious illnesses, new or worsening abnormalities may qualify as adverse events, see Section 8.3.7 for details.

8.2.3 Vital Sign Measurements

Heart rate, systolic and diastolic blood pressure, ('vital signs') will be assessed at timelines as specified in the SoA; assessments may be obtained in either the supine or seated position obtained after the subject has been in the supine or seated position for 5 minutes.

If, in the opinion of the Investigator, a clinically significant vital sign change occurs, then the measurement will be repeated at medically appropriate intervals until the value returns to within an acceptable range. Temperature will be collected at Screening (Visit 1) and at pre-dose at all visits and will not be repeated post-dose.

8.2.4 Electrocardiograms

12-lead ECG will be collected for screening purposes only.

Electrocardiogram parameter assessments include: heart rate, QRS duration, QT interval, and QTcF ECG values will be checked by the investigator or designee.

8.3 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 B.

AE will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject'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 8.3.3.

8.3.1 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 subject is the preferred method to inquire about AE occurrences.

8.3.2 Time period and frequency for collecting AE and SAE information

Adverse Events will be collected from visit 2 throughout the treatment period and including the follow-up period telephone call.

SAEs will be reported from when the subject has signed informed consent and will continue throughout the clinical study until the end of any follow-up period. All SAEs will be recorded and reported to the sponsor or designee within 24 hours, as indicated in Appendix B. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE in former study subjects. However, if the investigator learns of any SAE, including a death, at any time after a subject'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 B.

8.3.3 Follow-up of AEs and SAEs

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

Any AEs that are unresolved at the subject's last AE assessment in the study are 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 subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

8.3.4 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
- Whether the AE is serious or not
- Investigator causality rating against the Investigational Product(s) (yes or no)
- Action taken with regard to Investigational Product(s)

- 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'

8.3.5 Causality collection

The Investigator will assess causal relationship between Investigational 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 product?'

For SAEs, causal relationship will also be assessed for other medication and study procedures and 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 B to the Clinical Study Protocol.

8.3.6 Adverse events based on signs and symptoms

All AEs spontaneously reported by the subject or reported in response to the open question from the study site staff: *'Have you had any health problems since the previous visit/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.

8.3.7 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. Deterioration as compared to baseline in protocol-mandated 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 investigational product.

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).

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE unless unequivocally related to the disease under study, see sections 8.3.9 and 8.310.

8.3.8 Hy's law

Cases where subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3xULN together with total bilirubin ≥ 2xULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law

8.3.9 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 investigational product.

8.4 Safety reporting and medical management

8.4.1 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the investigational 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.

Once the Investigators or other site personnel indicate an AE is serious in the EDC system, an automated email alert is sent to the designated AstraZeneca representative.

If the EDC system is not available, then the Investigator or other study site staff reports a SAE to the appropriate AstraZeneca representative by telephone.

The AstraZeneca representative will advise the Investigator/study site staff how to proceed.

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both local authority and other regulatory agencies about the safety of a study intervention under clinical investigation.

The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority. Institutional Review Boards (IRB)/Independent Ethics Committees (IEC) and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receive safety report describing a SAE or other safety information (e.g. summary of listing of SAEs) from the sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC if appropriate according to local requirements.

For further guidance on the definition of a SAE, see Appendix B of the Clinical Study Protocol.

8.4.2 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for:

- If the pregnancy is discovered before the study subject has received any study drug

  If a pregnancy is reported, the investigator should inform the sponsor within 24 hours of learning of the pregnancy.

  Abnormal pregnancy outcomes (eg, spontaneous abortion, foetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

A urine pregnancy test will be performed in women of childbearing potential only, at timelines as specified in the SoA.

If any of these tests are positive, the subject must be discontinued from the study. The pregnancy test should be performed at the beginning of the visit.

8.4.2.1 Maternal exposure

If a subject becomes pregnant during the course of the study, investigational product should be discontinued immediately.

Pregnancy itself is not regarded as an adverse event unless there is a suspicion that the investigational product 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 subject was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the appropriate AstraZeneca representatives within 1day 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 (see Section 9.2.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

8.4.2.2 Paternal exposure

There is no restriction on fathering children or donating sperm during the study.

8.4.3 Overdose

For this study, any dose of study medication greater than the high dose level evaluated in this study as described in Section 6.1 will be considered an overdose.

Sponsor does not recommend specific treatment for an overdose.

- An overdose with associated AEs is recorded as the AE diagnosis/symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.
- An overdose without associated symptoms is only reported on the Overdose CRF module

If an overdose on 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 Time period and frequency for collecting AE and SAE information8.3.2. For other overdoses, reporting must occur within 30 days.

8.4.4 Medical device incidents (including malfunctions)

Medical devices are being provided for use in this study in order to dispense the dose to the patient. In order to fulfil regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of incident or malfunction that occur during the study with such devices.

The definition of a Medical Device Incident can be found in Appendix E

NOTE: Incidents fulfilling the definition of an AE/SAE will also follow the processes outlined in Section 8.3 and Appendix B of the protocol.

8.4.4.1 Time period for detecting medical device incidents

- Medical device incidents or malfunctions of the device that result in an incident will be detected, documented, and reported during all periods of the study in which the medical device is used.
- If the investigator learns of any incident at any time after a subject has been discharged from the study, and such incident is considered reasonably related to a medical device provided for the study, the investigator will promptly notify the sponsor.

The method of documenting Medical Device Incidents is provided in Appendix E.

8.4.4.2 Follow-up of medical device incidents

- All medical device incidents involving an AE will be followed and reported in the same manner as other AEs (see Section 8.3.2). This applies to all subjects, including those who discontinue Study treatment.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the incident.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

8.4.4.3 Reporting of medical device incidents to sponsor

- Medical device incidents will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device incident.
- The Medical Device CRF module will be completed in RAVE.
- The same individual will be the contact for the receipt of medical device reports and SAE.
- If an investigational medical device is used, the Study Representative will send the SAE report to AZ DES within **one calendar day**.

8.4.4.4 Regulatory reporting requirements for medical device incidents

- The investigator will promptly report all incidents occurring with any medical device provided for use in the study in order for the sponsor to fulfil the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (e.g., the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of incidents to the IRB/IEC.

8.4.5 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 8.3.2) and within 30 days for all other medication errors.

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

8.5 Pharmacokinetics

PK parameters are not evaluated in this study.

8.6 Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7 Genetics

Genetic testing is not evaluated in this study.

8.8 Biomarkers

Biomarkers are not evaluated in this study.

8.9 Medical Resource Utilization and Health Economics

Medical Resource Utilization and Health Economics parameters are not evaluated in this study.

9 STATISTICAL CONSIDERATIONS

9.1 Statistical hypotheses

The purpose of this study is to assess the extent of airway changes with each of two treatments (BGF and GFF) over 4 weeks. The first day of treatment in each treatment period is Day 1. Each treatment period is planned to contain 29 (±3 days) calendar days. Therefore, the assessments collected on Day 29 (Visits 4 and 6) will occur following 28 days of treatment.

Denote the FRI value at baseline by $FRI_{(PRE)}$ and the post-treatment FRI value at Day 29 by $FRI_{(POST)}$. The change from baseline for each subject will then be calculated as $FRI_{(CHG)} = FRI_{(POST)} - FRI_{(PRE)}$ and analysed for each treatment. The hypotheses for the respective "within-treatment" comparisons are:

H_0: $FRI_{(CHG)} = 0$, for BGF (no effect of treatment)
H_1: $FRI_{(CHG)} \neq 0$, for BGF

H_0: $FRI_{(CHG)} = 0$, for GFF (no effect of treatment)
H_1: $FRI_{(CHG)} \neq 0$, for GFF

9.2 Sample size determination

A total of approximately 20 subjects will be randomized. No formal sample size calculation has been done. The proposed sample size for this pilot study is based on previous experience, which included two previously conducted FRI studies with FLUIDDA (PT003018 and PT003019). Each of these studies included approximately 20 subjects.

In PT003019, the change (ratio) from baseline observed with glycopyrronium treatment was 1.13 (SD=0.22); leading to an effect size of 0.59. Assuming similar improvements from baseline in airway volume parameters with active treatments in this study, a change of 13% can be observed when 20 subjects are included (power goal 80%, alpha=0.05).

9.3 Populations for analyses

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All subjects who sign the ICF.
Intent-to-Treat (ITT) analysis set	All subjects who were randomized to study treatment.
Modified ITT (mITT) analysis set	All subjects in the ITT analysis set who completed both treatment periods and have FRI data at baseline and after approximately four weeks of treatment. Data judged to be impacted by major protocol deviations will be determined prior to unblinding and excluded.

Safety analysis set	All subjects who were randomized to study treatment and who took at least 1 dose of IMP and for whom any post-dose data are available.

Demographics and subject characteristics will be summarized for the ITT analysis set. Extent of exposure and safety data will be summarized for the safety analysis set. The ITT analysis set will be considered the primary analysis population for efficacy. The mITT analysis set is a subset of the ITT analysis set. If the data contributing to the mITT analyses differs from the data contributing to the ITT analyses, then the mITT analysis set may be used to conduct sensitivity analyses for the two primary endpoints.

9.4 Statistical analyses

All personnel involved with the analysis of the study will remain blinded until database lock and Clinical Study Protocol deviations identified.

Analyses will be performed by AstraZeneca or its representatives. A comprehensive statistical analysis plan will be developed and finalised before database lock and will describe the subject populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints. Any deviations from this plan will be reported in the clinical study report.

9.4.1 General principles

Continuous efficacy variables will be summarized with descriptive statistics (n, mean, standard deviation, median, minimum and maximum). Categorical variables will be summarized with frequency counts and percentages.

It is anticipated that logarithmic transformations may be required for most FRI and body plethysmography endpoints. If this is the case, estimates for the treatment effect will be presented as a ratio.

No imputation for missing values is planned.

9.4.2 Efficacy analyses

The focus of this study is on estimation of the individual effects of treatment with BGF and GFF. For the primary analyses, the individual (“within-treatment”) effects of both BGF and GFF will be assessed. This effect is defined as the change from baseline to Day 29 for BGF treatment and the change from baseline to Day 29 for GFF treatment. Baseline for both treatment groups will be defined as the pre-dose FRI value taken at Visit 3.

The hypothesis that $FRI_{(CHG)} = 0$ will be evaluated for each treatment and for each primary endpoint using a t□test. Mean values and 95% confidence intervals will be calculated for each treatment. The other FRI, spirometry, and body plethysmography parameters listed among the secondary efficacy endpoints will be analysed similarly. The secondary endpoint of change from baseline in FEV_1 will be based on post-dose evaluations of FEV_1.

Additional, supportive analyses will compare the distribution of regional effects between the two treatments for the different FRI endpoints. A linear mixed model approach will be chosen for this analysis and specified fully in the statistical analysis plan. These treatment comparisons will not be considered as formal hypothesis testing, but as estimation and investigation of regional treatment effects.

9.4.3 Safety analyses

Adverse events during each treatment will be summarized by the number of subjects experiencing an event. Tabulations will be broken down by severity, seriousness, AEs leading to discontinuation, and relationship to study drug. No hypothesis tests will be performed. Tables will show the overall incidence of AEs and the incidence for each treatment.

9.4.4 Methods for multiplicity control

For the primary efficacy endpoints, Hochberg's step-up procedure will be used as a multiplicity adjustment to control the type I error within each product at 5%. Specifically, Hochberg’s procedure will be applied once for the siVaw and siRaw endpoints for BGF, and then applied separately again for the same endpoints for GFF. No correction will be performed for the other secondary or exploratory endpoints. P-values outside of the Hochberg procedures will be interpreted at the two-sided 5% level.

9.5 Interim analyses

Not applicable.

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11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

Appendix A Regulatory, ethical and study oversight considerations

A 1 Regulatory and ethical considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
- Applicable ICH Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.

Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
- Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

The study will be performed in accordance with the AstraZeneca policy on Bioethics and Human Biological Samples.

AstraZeneca will provide Regulatory Authorities, Ethics Committees and Principal Investigators with safety updates/reports according to local requirements.

A 2 Financial disclosure

Investigators and sub-investigators will provide the sponsor with sufficient, accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators

are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

A 3 Informed consent process

The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorised representative and answer all questions regarding the study.

Subjects must be informed that their participation is voluntary. Subjects or their legally authorised representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study centre.

The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorised person obtaining the informed consent must also sign the ICF.

Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.

A copy of the ICF(s) must be provided to the subject or the subject's legally authorised representative.

Subjects who are rescreened are required to sign a new ICF.

A 4 Data protection

Each subject will be assigned a unique identifier by the sponsor. Any subject records or data sets transferred to the sponsor will contain only the identifier; subject names or any information which would make the subject identifiable will not be transferred.

The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the subject.

The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

The safety of all AstraZeneca clinical studies is closely monitored on an on-going basis by AstraZeneca representatives in consultation with Patient Safety. Issues identified will be

addressed; for instance, this could involve amendments to the Clinical Study Protocol and letters to Investigators.

A 5 Dissemination of clinical study data

A description of this clinical trial will be available on http://astrazenecaclinicaltrials.com and http://www.clinicaltrials.gov as will the summary of the study results when they are available. The clinical trial and/or summary of study results may also be available on other websites according to the regulations of the countries in which the study is conducted.

A 6 Data quality assurance

All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorised site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of subjects are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

A 7 Source documents

Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data reported on the CRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

A 8 Publication policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicentre studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Appendix B Adverse event definitions and additional safety information

B 1 Definition of adverse events

An adverse event is the development of any untoward medical occurrence in a subject or clinical study subject 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.

B 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), that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-subject 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 subject or may require medical treatment to prevent one of the outcomes listed above.

B 3 Life threatening

'Life-threatening' means that the subject 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 subject'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).

B 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 subject was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

B 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 subject 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

B 6 Intensity rating scale:

1 mild (awareness of sign or symptom, but easily tolerated)

2 moderate (discomfort sufficient to cause interference with normal activities)

3 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 B 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 B 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 B 2.

B 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 subject 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.

B 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:

- 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 C Handling of Human Biological Samples

C 1 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Investigator at each centre keeps full traceability of collected biological samples from the subjects while in storage at the centre until shipment or disposal (where appropriate).

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

AstraZeneca will keep oversight of the entire life cycle through internal procedures, monitoring of study sites, auditing or process checks, and contractual requirements of external laboratory providers

C 2 Withdrawal of Informed Consent for donated biological samples

If a subject withdraws consent to the use of donated biological samples, the samples will be disposed of/destroyed, and the action documented. If samples are already analysed, AstraZeneca is not obliged to destroy the results of this research.

As collection of the biological sample(s) is an optional part of the study, then the subject may continue in the study.

The Investigator:

- Ensures subjects' withdrawal of informed consent to the use of donated samples is notified immediately to AstraZeneca
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented
- Ensures the organization(s) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject and AstraZeneca are informed about the sample disposal.

AstraZeneca ensures the organizations holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed of/destroyed and the action documented and returned to the study site.

C 3 [redacted] Guidance Document

LABELLING AND SHIPMENT OF BIOHAZARD SAMPLES

[redacted] classifies biohazardous agents into 3 categories

[redacted] For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in [redacted] Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and Categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are eg, Ebola, Lassa fever virus:

- are to be packed and shipped in accordance with [redacted]

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are eg, Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- [redacted]
- [redacted]

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under [redacted]
- Clinical trial samples will routinely be packed and transported at ambient
- [redacted]
- **Biological samples transported in dry ice require additional dangerous goods specification for the dry-ice content**
- [redacted] courier and packaging materials should be used for packing and transportation and packing should be done by an [redacted], as applicable
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. [redacted] biological sample containment standards are encouraged wherever possible when road or rail transport is used.

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Appendix D Actions required in cases of increases in liver biochemistry and evaluation of Hy's Law

D 1 Introduction

This Appendix describes the process to be followed in order to identify and appropriately report Potential Hy's Law (PHL) cases and Hy's Law (HL) cases. It is not intended to be a comprehensive guide to the management of elevated liver biochemistries.

<<Specific guidance on managing liver abnormalities can be found in Section XX of the Clinical Study Protocol >>.

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a subject meets potential PHL criteria at any point during the study.

All sources of laboratory data are appropriate for the determination of PHL and HL events; this includes samples taken at scheduled study visits and other visits including central and all local laboratory evaluations even if collected outside of the study visits; for example, PHL criteria could be met by an elevated ALT from a central laboratory and/or elevated TBL from a local laboratory.

The Investigator will also review Adverse Event data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The Investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Medicinal Product (IMP).

The Investigator is responsible for recording data pertaining to PHL/HL cases and for reporting Serious Adverse Events (SAEs) and Adverse Events (AEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

D 2 Definitions

Potential Hy's Law (PHL)

Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) ≥ 3x Upper Limit of Normal (ULN) together with Total Bilirubin (TBL) ≥ 2xULN at any point during the study

following the start of study medication irrespective of an increase in Alkaline Phosphatase (ALP).

Hy's Law (HL)

AST or ALT ≥ 3x ULN together with TBL ≥ 2xULN, where no other reason, other than the IMP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL the elevation in transaminases must precede or be coincident with (i.e. on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

D 3 Identification of potential Hy's Law cases

In order to identify cases of PHL it is important to perform a comprehensive review of laboratory data for any subject who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 × ULN
- AST ≥ 3 × ULN
- TBL ≥ 2 × ULN

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the AstraZeneca representative
- Determine whether the subject meets PHL criteria (see Appendix D 2 for definition) by reviewing laboratory reports from all previous visits
- Promptly enter the laboratory data into the laboratory CRF

D 4 Follow-up

D 4.1 Potential Hy's Law criteria not met

If the subject does not meet PHL criteria the Investigator will:

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

D 4.2 Potential Hy's Law Criteria Met

If the subject does meet PHL criteria the Investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team

- Within 1 day of PHL criteria being met, the Investigator will report the case as an SAE of Potential Hy's Law; serious criteria 'Important medical event' and causality assessment 'yes/related' according to CSP process for SAE reporting.

- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change# in the subject's condition

- The Study Physician contacts the Investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data

- Subsequent to this contact the Investigator will:

    - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the aetiology of the event and perform diagnostic investigations as discussed with the Study Physician. << For studies using a central laboratory add: This includes deciding which the tests available in the Hy's law lab kit should be used>>
    - Complete the three Liver CRF Modules as information becomes available

A 'significant' change in the subject's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or total bilirubin) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the Investigator, this may be in consultation with the Study Physician if there is any uncertainty.

D 5 Review and assessment of potential Hy's Law cases

The instructions in this section should be followed for all cases where PHL criteria are met.

As soon as possible after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IMP, to ensure timely analysis and reporting to health authorities within 15 calendar days from date PHL criteria was met. The AstraZeneca Global Clinical Lead or equivalent and Global Safety Physician will also be involved in this review together with other subject matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

Where there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for a SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF
- If the alternative explanation is an AE/SAE: update the previously submitted Potential Hy's Law SAE and AE CRFs accordingly with the new information (reassessing event term; causality and seriousness criteria) following the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IMP:

- Send updated SAE (report term 'Hy's Law') according to AstraZeneca standard processes.
- The 'Medically Important' serious criterion should be used if no other serious criteria apply
- As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 15 calendar days in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Provides any further update to the previously submitted SAE of Potential Hy's Law, (report term now 'Hy's Law case') ensuring causality assessment is related to IMP and seriousness criteria is medically important, according to CSP process for SAE reporting.

- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are still met. Update the previously submitted PHL SAE report following CSP process for SAE reporting, according to the outcome of the review and amending the reported term if an alternative explanation for the liver biochemistry elevations is determined.

D 6 Laboratory tests

Hy's Law lab kit for laboratories

Additional standard chemistry and coagulation tests	GGT LDH Prothrombin time INR
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA IgG anti-HCV HCV RNA* IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)**
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation

* HCV RNA is only tested when IgG anti-HCV is positive or inconclusive

References

Aithal et al 2011, Clinical Pharmacology and Therapeutics 89(6):806-815.

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'

Appendix E Medical device incidents: definition and procedures for recording, evaluating, follow-up, and reporting

E 1 Definitions of a Medical Device Incident

The detection and documentation procedures described in this protocol apply to all sponsor provided medical devices provided for use in the study (see Section 6.1.2) for the list of sponsor provided medical devices).

Medical Device Incident Definition
• A medical device incident is any malfunction or deterioration in the characteristics and/or performance of a device as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a subject/user/other person or to a serious deterioration in his/her state of health. • Not all incidents lead to death or serious deterioration in health. The non-occurrence of such a result might have been due to other fortunate circumstances or to the treatment of health care personnel.

It is sufficient that:

- An **incident** associated with a device happened.

AND

- The **incident** was such that, if it occurred again, might lead to death or a serious deterioration in health.

A serious deterioration in state of health can include any of the following:

- Life-threatening illness
- Permanent impairment of body function or permanent damage to body structure
- Condition necessitating medical or surgical treatment to prevent one of the above
- Foetal distress, foetal death, or any congenital abnormality or birth defects

Examples of incidents:
• A subject, user, caregiver, or healthcare professional is injured as a result of a medical device failure or its misuse. • A subject's Study treatment is interrupted or compromised by a medical device failure. • A misdiagnosis due to medical device failure leads to inappropriate treatment. A subject's health deteriorates due to medical device failure.

Documenting medical device incidents

Medical device incident documentation
Any medical device incident occurring during the study will be documented in the subject's medical records, in accordance with the investigator's normal clinical practice, and on the appropriate form of the CRF. For incidents fulfilling the definition of an AE or an SAE, the appropriate AE/SAE CRF page will be completed as described in Appendix B. The CRF will be completed as thoroughly as possible and signed by the investigator before transmittal to the sponsor or designee. It is very important that the investigator provides his/her assessment of causality (relationship to the medical device provided by the sponsor) at the time of the initial AE or SAE report and describes any corrective or remedial actions taken to prevent recurrence of the incident. A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of an incident. This includes any amendment to the device design to prevent recurrence.

Appendix F Abbreviations

Abbreviation or special term	Explanation
AE	adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AT	Air Trapping
ATS	American Thoracic Society
BGF	Budesonide/Glycopyrronium/Formoterol Fumarate
BID	twice-daily
BiPAP	bilevel positive airway pressure
CAT	COPD assessment test
CFD	Computational fluid dynamics
CIOMS	Council for International Organizations of Medical Sciences
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CPAP	continuous positive airway pressure
CRF	case report form (electronic/paper)
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CSA	clinical study agreement
CSR	clinical study report
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Event
DAE	discontinuation of investigational product due to adverse event
DES	data entry site
DILI	drug induced liver injury
DNA	deoxyribonucleic acid
DUS	Disease-under study
EC	ethics committee, synonymous to institutional review board (IRB) and independent ethics committee (IEC)
ECG	Electrocardiogram

Abbreviation or special term	Explanation
EDC	electronic data capture
ERS	European Respiratory Society
FAS	full analysis set
FEV_1	Forced expiratory volume in one second
FRI	functional respiratory imaging
FRC	functional residual capacity
FVC	Forced vital capacity
GCP	Good Clinical Practice
GFF	Glycopyrronium/Formoterol Fumarate
GOLD	The Global Initiative for Chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
HIPAA	Health Insurance Portability and Accountability Act
HL	Hy's Law
HRCT	High Resolution Computed Tomography
IAD	Internal lobar airflow distribution
IATA	International Airline Transportation Association
IC	Inspiratory capacity
ICF	informed consent form
ICH	International Conference on Harmonisation
ICS	inhaled corticosteroids
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IPF	interstitial pulmonary fibrosis
IRB	Institutional Review Board
IVRS	interactive voice response system
IWRS	interactive web response system
LABA	long-acting β2-agonist
LAMA	long-acting muscarinic antagonist
LAS	Low attenuation or emphysema score
LSLV	last subject last visit

Abbreviation or special term	Explanation
LIMS	laboratory information management system
LTOT	long-term-oxygen therapy
MDI	metered dose inhaler
MMRC	Modified Medical Research Council
NIPPV	non-invasive positive pressure ventilation
OAE	other significant adverse event
PHL	potential Hy's Law
PI	principal investigator
PRN	as needed
QID	four times daily
RV	Residual volume
SABA	short-acting β2-agonist
SAE	serious adverse event
SAMA	Short acting muscarinic antagonist
SAP	statistical analysis plan
SoA	Schedule of Activities
SUSAR	Serious unexpected suspected adverse reaction
TBL	Total Bilirubin Level
TC	telephone call
TCO	transfer factor for carbon monoxide
TLC	total lung capacity
TP	treatment period
TURP	trans-urethral resection of prostate
UA	upper airway
ULN	upper limit of normal
UNS	unscheduled visit
VA	alveolar volume
WBDC	web based data capture

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