A Randomized, Single blind, 3-Period, 3-Treatment, Single-dose, Crossover Study to Assess the Relative Bioavailability of BGF MDI CCI and BGF MDI CCI Compared with BGF MDI HFA in Healthy Subjects

ClinicalTrials.gov Identifier: NCT04600505

Protocol Amendment No. 2: Final 3.0, 05 March 2021
Clinical Study Protocol

A Randomized, Single blind, 3-Period, 3-Treatment, Single-dose, Crossover Study to Assess the Relative Bioavailability of BGF MDI CCI and BGF MDI CCI Compared with BGF MDI HFA in Healthy Subjects

Parexel Study No.:	PXL245780
Sponsor Study Code:	D5985C00001
IND No./Eudra CT No:	118313
Study Type:	Pharmacokinetics (PK)/Bioavailability
Test Product:	Budesonide/glycopyrronium/formoterol (BGF) metered dose inhaler (MDI) formulated with 2 different propellants Treatment A: CCI Treatment B: CCI
Reference Product:	Budesonide/glycopyrronium/formoterol (BGF) metered dose inhaler (MDI) formulated with reference propellant Treatment C: HFA (HFA propellant)
Therapeutic Indication:	COPD
Pharmacological Class:	Corticosteroid/long-acting muscarinic antagonist/Long-acting beta agonist
Development Phase:	Phase 1

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Study Center:	Parexel Early Phase Clinical Unit Los Angeles PPD Glendale, CA 91206 United States of America
Date of Protocol:	Final 1.0, 01 July 2020
Protocol Amendment No. 1	Final 2.0, 01 October 2020
Protocol Amendment No. 2	Final 3.0, 05 March 2021

This clinical study will be conducted according to the protocol and in compliance with Good Clinical Practice, with the Declaration of Helsinki and with other applicable regulatory requirements.

PROTOCOL AMENDMENTS

Protocol Amendment No. 2, dated 05 March 2021

The following changes were made to the Clinical Study Protocol Amendment No. 1, dated 01 October 2020 (Final 2.0) resulting in the Clinical Study Protocol Amendment No. 2, dated 05 March 2021 (Final 3.0):

! Section 5.1.2 Exclusion criterion 33 added:
Receipt of COVID-19 vaccine (regardless of vaccine delivery platform, eg, vector, lipid nanoparticle) less than 7 days prior to the date of randomization (from last vaccination or booster dose).

! Section 5.3 Replacement of Subjects, updated to ensure a minimum of 20 evaluable subjects for PK. This is due to the dose administration procedures in the original subjects that were inconsistent to the protocol.

! Section 7.7 Concomitant and Post-study Treatments, added details of COVID-19 vaccine restrictions relative to randomization.

! Section 10.3.1 clarified that the Safety Analysis Set includes all original and replacement subjects where the 'at least 1 inhalation' criterion is met.

! Section 10.9.3 Statistical Analysis of Pharmacokinetic Data, added plan for pairwise statistical models to exclude data from the treatment that is not relevant for the comparison in question.

! Section 10.10 Analysis of Safety Data, clarified that safety data for replacement subjects may also be presented separately from the original subjects.

! Number of subjects planned updated from 24 to 48 throughout the protocol to account for replacement subjects. Estimated date of last subject completed updated to Second Quarter 2021.

Protocol Amendment No. 1, dated 01 October 2020

The following substantial changes were made to the Clinical Study Protocol (Version: Final 1.0, dated 01 July 2020) resulting in the Clinical Study Protocol Amendment No. 1, dated 01 October 2020 (Final 2.0):

! Section 3.1 Background Information was updated to include that BGF MDI is being developed for the treatment of both COPD **and asthma** and that it has **recently been approved for the treatment of COPD**.

! Section 3.2.3 Adverse Events, Contraindications and Warnings have been updated according the Investigators Brochure [1] to reflect that, to date, the clinical development program has evaluated over **15000** patients with COPD and BGF MDI was found to be well-tolerated with a safety profile commensurate with the individual components and the medication class.

! Exclusion criterion 18 was updated from:

∀ Has received another new chemical entity (defined as a compound which has not been approved for marketing) within **3 months of the first administration of IMP** in this study. The period of exclusion begins 1 month, or 5 half-lives (whichever is longer), after the final dose.

Note: subjects consented and screened but not randomized in this study or a previous Phase I study, are not excluded.

To read as follows:

∀ Receipt of any investigational drug within **30 days or 5 half-lives (whichever is longer) prior to randomization**.

Note: subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

! Exclusion criterion 31 was updated from:

∀ Subjects who cannot use an inhaler appropriately.

To read as follows:

∀ Subjects who cannot use an inhaler appropriately **and do not demonstrate proper inhalation technique**.

! Section 8.4.3 Vital Signs was updated to reflect that **body temperature will be measured in °C** and not in °F.

! Section 8.4.6 was updated to provide clarity on the **spirometry driven parameters** to be measured as well as **the device(s) to be used**.

! Section 8.4.7.2 was updated to clarify that **free** T4 will be collected.

! Spelling/grammatical/formatting errors were corrected throughout the document.

PROTOCOL SYNOPSIS

Title of the Study
A randomized, single blind, 3-period, 3-treatment, single-dose, crossover study to assess the relative bioavailability of BGF MDI CCI and BGF MDI CCI compared with BGF MDI HFA in healthy subjects

Principal Investigator (PI)
Dr David Han

Study Center
This study will be conducted at a single study center.

Parexel Early Phase Clinical Unit Los Angeles

PPD

Glendale, CA 91206
United States of America

Study Rationale
The study is intended to assess the relative bioavailability and tolerability of fixed dose combinations (FDCs) of budesonide, glycopyrronium, and formoterol (BGF) metered dose inhaler (MDI) "test" formulations compared to the reference formulation to contribute data to the selection of the next generation propellants (NGPs).

Number of Subjects Planned
Approximately 48 healthy subjects will be randomized to ensure at least 20 evaluable subjects at the end of the last treatment period.

Study Period
Estimated date of first subject enrolled: Last Quarter 2020 (signing of informed consent)
Estimated date of last subject completed: Second Quarter 2021

Study Objectives
Primary Objective:

! To evaluate the relative bioavailability between the test formulations and the reference formulation for FDCs of budesonide, glycopyrronium, and formoterol when delivered as BGF MDI with 3 different propellants.

Secondary Objectives:

! To determine the pharmacokinetic (PK) parameters of budesonide, glycopyrronium, and formoterol when administered as 3 different propellant formulations.

! To assess the safety and tolerability of a combination of budesonide, glycopyrronium, and formoterol when administered as single doses in 3 different propellant formulations in healthy subjects.

Exploratory Objective:

! Not applicable.

Study Design

This study will be a randomized, single blind, 3-period, 3-treatment, single-dose, single-center, crossover study. The study will include the assessment of BGF MDI formulated with 3 different propellants: CCI (Treatment A [test]), CCI (Treatment B [test]) and HFA (Treatment C [reference]).

The study will comprise:

! Screening period: up to 28 days prior to first dosing;

! Three treatment periods of maximum 3 days each: subjects will be resident from the morning of the day before the first dosing with BGF MDI (Day -1) in Treatment Period 1, throughout all treatment and washout periods up to discharge on Day 2 of Treatment Period 3; and

! Follow-up: within 3 to 7 days after the last administration of BGF MDI.

There will be a washout period of 3 to 7 days between each dose.

Each subject will receive 3 single-dose treatments of BGF MDI, following an overnight fast of at least 8 hours.

Expected Duration of the Study

Each subject will be involved in the study for up to 53 days.

Targeted Study Population

This study will be conducted in healthy male subjects, 18 to 60 years of age

Investigational Medicinal Product

BGF MDI formulated with 3 different propellants: Treatment A (CCI propellant [test]), Treatment B (CCI propellant [test]) and Treatment C (HFA propellant [reference]).

Outcome Endpoints

Pharmacokinetic Endpoints:

Where possible, PK parameters will be assessed for budesonide, glycopyrronium, and formoterol from plasma concentrations.

! Primary PK parameters: Cmax, AUCinf, and AUClast for test and reference treatment

! Secondary PK parameters: tmax, t½λz, MRT, λz, CL/F, Vz/F, TRCmax, TRAUCinf, and TRAUClast

Additional PK parameters may be determined where appropriate.

Safety and Tolerability Endpoints:

Safety and tolerability variables will include

! Adverse events (AEs)/Serious adverse events (SAEs)

! Vital signs (systolic and diastolic blood pressure, pulse rate, body temperature,oxygen saturation, and respiratory rate)

! 12-lead safety and digital electrocardiograms (ECGs) as well as cardiac telemetry

! Physical examination

! Laboratory assessments (Hematology, clinical chemistry and urinalysis)

! Spirometry

! Taste assessment

Viral serology and drugs of abuse, alcohol and cotinine will be assessed for eligibility. Use of concomitant medication will also be assessed and reported.

Exploratory Endpoints:

! Not applicable

Statistical Methods

Presentation and Analysis of Pharmacokinetic Data:

All PK concentrations, parameter summaries and statistical analyses will be presented for the PK Analysis Set, unless otherwise specified. The PK concentration and parameter listings will be presented for the Safety Analysis Set and will include all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK Analysis Set or excluded from the descriptive summary tables, figures and/or inferential statistical analyses will be included in the listings and flagged with an appropriate footnote.

The test treatments will be compared to the reference treatment separately (Treatment A vs Treatment C and Treatment B vs Treatment C) and also separately for each analyte. The statistical analyses will be performed using a linear mixed effects analysis of variance model, using the natural logarithm of AUCinf, AUClast, and Cmax as the response variables, with sequence, period, treatment as fixed effects and subject nested within sequence as random effect. Transformed back from the logarithmic scale, geometric means together with and the intra-subject coefficient of variation confidence intervals (CIs) (2 sided 95%) for AUCinf, AUClast, and Cmax will be estimated and presented. In addition, ratios of geometric means together with CIs (2 sided 90%) will be estimated and presented. The 90% CI of the geometric mean ratios of the PK parameters will be evaluated against the standard bioequivalence range of 80.00% to 125.00%.

Additionally, the median difference in untransformed tmax between the test treatments and the reference treatment for each analyte and the 90% CIs for the median differences will be calculated using the non-parametric Hodges Lehmann method.

Presentation and Analysis of Safety and Eligibility Data:

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, standard deviation, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment, if applicable. The analysis of the safety variables will be based on the Safety Analysis Set.

Adverse events will be summarized by Preferred Term and System Organ Class using Medical Dictionary for Regulatory Activities vocabulary. Furthermore, listings of SAEs and AEs that led to withdrawal will be made and the number of subjects who had any AEs, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized. Adverse events that occur before dosing will be reported separately.

Tabulations and listings of data for vital signs, clinical laboratory tests, digital ECGs and 12-lead safety ECGs (listings only), telemetry (listings only) and spirometry will be presented. Results from the taste assessment will be presented separately in listings only. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from the baseline when baseline is defined. Clinical laboratory data will be reported in the units provided by the clinical laboratory for the Safety Review Committee meeting, and in Système International units in the Clinical Study Report.

Out-of-range values for safety laboratory assessments will be flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AstraZeneca, program, or laboratory ranges).

Determination of Sample Size

This is a pilot PK study to determine the relative bioavailability between 2 test formulations of BGF MDI with NGPs compared with the current formulation with HFA propellant. Therefore, no sample size calculation has been performed.

It is expected that 48 healthy subjects will be randomized to a 6-sequence Williams design for 3 periods and 3 treatments: ABC, BCA, CAB, ACB, BAC, CBA, in order to ensure at least 20 evaluable subjects at the end of the last treatment period.

Subjects are considered evaluable if they have an evaluable PK profile, ie, (1) receive active treatment, (2) do not significantly violate protocol inclusion or exclusion criteria, or deviate significantly from the protocol, and (3) do not have unavailable or incomplete data which may influence the PK analysis.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation or special term	Explanation
AE	Adverse event (see definition in Section 11.1.1)
AIM	Aerosol inhalation monitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATS	American Thoracic Society
AUC	Area under the concentration-time curve
AV	Atrioventricular
AZ	AstraZeneca
AZRand	AstraZeneca randomization system

BGF	Budesonide, glycopyrronium and formoterol
BID	Twice per day
BLQ	Below limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
ClinBase™	Parexel's electronic source data capturing and information management system
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus disease of 2019
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
CS	Clinically significant
CSP	Clinical study protocol
CSR	Clinical study report
CV	Coefficient of variation
CYP	Cytochrome P450
DAE	Adverse event leading to the discontinuation of IMP
dECG	Digital electrocardiogram
DILI	Drug-induced liver injury
DMP	Data management plan
DSPC	Phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine
DVS	Data validation specification

Abbreviation or special term	**Explanation**
ECG	Electrocardiogram
EClysis©	User-interactive, modular computer-based system for dECG data processing, analysis and measurement of ECG intervals and wave amplitudes, exports and reports, used by the AstraZeneca ECG Center
eCRF	Electronic Case report form

ERS	European Respiratory Society
FDA	Food and Drug Administration
FDC	Fixed dose combination
FEF	Forced exploratory flow
FEV1	Forced expiratory volume in one second
FEV1 %	Forced expiratory volume in one second percentage
FVC	Forced vital capacity
FVC %	Forced vital capacity percentage
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
gmean	Geometric mean
GMP	Good Manufacturing Practice
GWP	Global Warming Potential
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HFA	Hydrofluoroalkane
CCI	CCI
CCI	CCI
HIV	Human immunodeficiency virus
HR	Heart Rate
IATA	International Airline Transportation Association
ICF	Informed consent form
ICH	International Council for Harmonization
IMP	Investigational medicinal product
IRB	Institutional Review Board
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation or special term	Explanation
MRT	Mean residence time in the systemic circulation extrapolated to infinity
n	Number of subjects
NA	Not applicable
NCS	Not clinically significant
NGP	Next generation propellant
NHANES	National Health and Nutrition Examination Survey
NOAEL	No-observed-adverse-effect-level
NQ	Non-quantifiable
OAE	Other significant adverse events
OTC	Over-the-counter
PDS	Protocol Deviation Specification (document)
PHL	Potential Hy's Law
PI	Principal Investigator
PK	Pharmacokinetics
PR (PQ)	ECG interval measured from the onset of the P wave to the onset of the QRS complex
QRS	ECG interval measured from the onset of the QRS complex to the J point
QT	ECG interval measured from the onset of the QRS complex to the end of the T-wave
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
R&D	Research and Development
RBC	Red blood cell
RR	The time between corresponding points on 2 consecutive R waves on ECG
RT-PCR	Reverse transcription polymerase chain reaction
SAE	Serious adverse event (see definition in Section 11.1.2).
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SAS	Statistical Analysis Software
SD	Standard deviation

SOC	System Organ Class
SOP	Standard Operating Procedure
SpO_2	Oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
TBL	Total bilirubin
TCA	Tricyclic anti-depressant
TCS	Tata Consultancy Services – an AstraZeneca partner who conduct data entry onto Sapphire

Abbreviation or special term	**Explanation**
TFL	Tables, figures, listings
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
USA	United States of America
WAD	Windows Allowance Document
WBC	White blood cell

1. ETHICAL AND REGULATORY REQUIREMENTS

1.1. Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH GCP and the AstraZeneca policy on Bioethics and Human Biological Samples.

1.2. Subject Data Protection

The ICF will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

All clinical study findings and documents will be regarded as confidential. The PI and members of his research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating subjects must be maintained. Subjects will be specified in outputs and other documents containing subject data by their subject number, not by name. Documents that identify the subject (eg, signed ICF) will be maintained in confidence by the PI.

Study data will be stored in accordance with local and global data protection laws.

1.3. Ethics and Regulatory Review

The study will be submitted to the national regulatory agency (FDA) for review and approval, by AstraZeneca in accordance with local regulatory procedures.

The study will be submitted to the IRB for ethical review and approval by the PI in accordance with local procedures.

Parexel will provide the IRB and PI with safety updates/reports according to local requirements, including SUSARs, where relevant.

AstraZeneca will provide the regulatory authority with safety updates/reports according to local requirements, including SUSARs, where relevant.

The PI is also responsible for providing the IRB with reports of any serious and/or unexpected adverse drug reactions from any other study conducted with the IMP. AstraZeneca will provide this information to the PI, so he can meet these reporting requirements.

Compensation will be reasonable and related to the nature and degree of inconvenience and discomfort as a result of participation in the study. Information on how participants will be compensated is contained in the ICF.

1.4. Insurance

The Sponsor has covered this clinical study by means of an insurance of the clinical study according to national requirements. The name and address of the relevant insurance company, the certificate of insurance, the policy number and the sum insured are provided in the Investigator's Site File.

1.5. Informed Consent

The subjects shall be informed of the nature, significance, implications and risks of the trial, and informed consent will be freely given and evidenced in writing, dated and signed, or otherwise marked, by the subject as evidence to indicate his free informed consent, prior to the start of the study.

The nature of the informed consent will comply with the Declaration of Helsinki, the current requirements of GCP (CPMP/ICH/135/95) and local regulation which ever offers the greater subject protection.

1.6. Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the PI and AstraZeneca.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

If a protocol amendment requires a change to the ICF the IRB should approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by the IRB.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	PPD AstraZeneca R&D BioPharmaceuticals PPD Gaithersburg, MD 20878 United States of America Tel: PPD Email: PPD
Sponsor's Biostatistician:	PPD AstraZeneca PPD Gaithersburg, MD 20878 United States of America Email: PPD
Sponsor's Clinical Pharmacologist:	PPD AstraZeneca PPD Gaithersburg, MD 20878 United States of America Email: PPD
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Clinical Laboratory:	GenX Laboratories Inc. PPD Los Angeles, CA 90065 United States of America Phone: PPD

	Fax: PPD Email: PPD
Analytical Laboratory: PK sample analysis)	Covance Laboratories, Inc. PPD Salt Lake City, UT 84124 USA Contact: PPD PPD
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services Fax: PPD Email: PPD

A list and contact details of investigators and other key study team members are provided in the Project Plan in the electronic Investigator's Site File. A list of all participating investigators will be provided in the CSR.

3. INTRODUCTION

3.1. Background Information

Pressurized MDIs are frequently used in the application of therapeutic delivery for the treatment of pulmonary diseases, such as COPD and/or asthma. Their formulations are generally comprised of a therapeutic material, a propellant, co-solvents, and surfactants to prevent drug-aerosol coagulation and to lubricate moving parts of the metering valve. Historically these propellants were ozone-depleting chlorofluorocarbons, which prompted the search for more environmentally friendly alternatives [1].

The current HFA propellant (reference treatment) is known to have a relatively high GWP compared with some alternative propellants and contributes substantially to the Sponsor, AstraZeneca's carbon footprint. The reformulation of AstraZeneca's MDI products with a NGP that has much lower GWP will allow patients to continue to use MDI type treatments while contributing to AstraZeneca's sustainability efforts.

AstraZeneca is developing a Budesonide, Glycopyrronium, and Formoterol Fumarate MDI, hereinafter referred to as BGF MDI, for the treatment of COPD and asthma. The use of BGF MDI has recently been approved for the treatment of COPD. This drug product is a MDI formulated as a suspension with micronized active pharmaceutical ingredients and Co-Suspension™ Delivery Technology.

The Co-Suspension™ Delivery Technology consists of spray-dried porous particles comprised of the phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine and calcium chloride (DSPC)

suspended in a HFA propellant. When used in combination MDI products, these particles form strong non-specific associations with the active pharmaceutical ingredients, preventing the drugs from interacting with each other in the suspension and providing reproducible drug delivery and long-term stability.

The formulations to be evaluated in this study are MDIs containing a fixed-dose triple combination of budesonide, an inhaled corticosteroid, glycopyrronium, a long-acting muscarinic antagonist, and formoterol fumarate, a long-acting β_2-agonist that utilize either the current propellant (HFA [Treatment C]) or one of two NGPs with lower GWP (CCI [Treatment A] and CCI [Treatment B]). This will be the first study of BGF MDI formulated with the NGPs and will determine the relative bioavailability of the new formulations compared with the current formulation.

3.2. Investigational Medicinal Product Information

3.2.1. Description of Investigational Medicinal Products

The study will include the assessment of BGF MDI formulated with 3 different propellants: CCI (Treatment A [test]), CCI (Treatment B [test]) and HFA (Treatment C [reference]). Each

subject will receive 3 single-dose treatments of BGF MDI, following an overnight fast of at least 8 hours:

- Treatment A: 2 inhalations of CCI of BGF MDI (CCI propellant) - test formulation.
- Treatment B: 2 inhalations of CCI of BGF MDI (CCI propellant) - test formulation.
- Treatment C: 2 inhalations of CCI of BGF MDI (HFA propellant) - reference formulation.

No fluids will be allowed apart from water which can be given until 1 hour prior to administration of the investigational products and then from 2 hours after administration of the investigational products. A meal will be given 4 hours after administration of the investigational products.

There will be a 3 to 7-days washout between each treatment period. Subjects will be resident from the morning of the day before dosing with BGF MDI in Treatment Period 1 until 24 hours following dosing in Treatment Period 3.

3.2.2. Clinical Pharmacokinetics

Budesonide, glycopyrronium, and formoterol fumarate are components (alone or in combination) of approved inhalation products (HFA propellant based) for treatment of patients with COPD and their safety and efficacy are well characterized. Specific nonclinical absorption, distribution, metabolism, and excretion studies for the combination have not been conducted as it has been extensively investigated and is available in marketed products. General PK/toxicokinetic parameters were assessed in rats and dogs in (or in parallel to) the toxicity studies on the FDC and each active substance individually and showed no significant PK interactions. The Sponsor has completed 13 clinical studies in support of the clinical development program for BGF MDI. In addition, the Sponsor has completed 3 PK studies (Phase 1) and 1 clinical (Phase 2) study in support of the clinical development program for BGF MDI to assist in dose selection for budesonide [1].

Budesonide

The plasma protein binding of budesonide is moderate with an unbound fraction of 8 to 15% in human and nonclinical species plasma. Budesonide is a high clearance compound with the elimination being solely dependent on metabolic clearance. Two major metabolites, formed via CYP3A4 catalyzed biotransformation, have been identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these metabolites is less than 1% of that of the parent compound. Data indicates little potential for budesonide to be involved in drug-drug interactions. Budesonide is a substrate of P-glycoprotein and did not show any inhibition toward any of the transporters tested. In addition, budesonide did not inhibit or induce

any CYP enzymes with the exception of a moderate inhibition of CYP3A4 at a relatively high concentration [1].

Glycopyrronium

The free fraction of glycopyrronium in plasma is approximately 60% to 80% in nonclinical species and approximately 50% in human. In vitro, hepatocytes from nonclinical species and man showed the main metabolic pathways in most species were mono-oxygenation, di-oxygenation and mono-oxygenation in combination with desaturation. No turnover was seen in lung microsomes. CYP2D6 was found to be the predominant CYP isoform involved in the metabolism of glycopyrronium. However, in vivo metabolism data in animals showed that unchanged glycopyrronium accounted for the major part of drug-related material in plasma and urine following intravenous administration whereas an acidic metabolite (formed by hydrolysis of glycopyrronium) was the major metabolite in plasma following oral administration. Glycopyrronium shows some drug transporter interactions at high concentrations, but the potential for drug interaction is considered to be low from comparison to relevant plasma concentrations at a therapeutic dose [1].

Formoterol Fumarate

The free fraction of formoterol in plasma is approximately 50% in both human and nonclinical species. The primary metabolism of formoterol is by direct glucuronidation and by O-demethylation followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation. The CYP enzymes involved in the O-demethylation are CYP2D6 and CYP2C. Possible interaction of formoterol with other substrates metabolized by CYP enzymes was also studied. Results indicated that drug-drug interactions do not seem likely except possibly for CYP2D6; however, low concentrations of formoterol with therapeutic dosing makes any interaction unlikely [1].

Next Generation Propellants

Refer to [2] and [3] for information on the NGPs.

3.2.3. Adverse Events, Contraindications and Warnings

As the IMP contains budesonide, glycopyrroniumand formoterol, the type and severityof adverse reactions associated with each of these components may be expected.

To date, the clinical development program has evaluated over 15000 patients with COPD and BGF MDI was found to be well-tolerated with a safety profile commensurate with the individual components and the medication class. The following AEs may be associated with BGF MDI: oral candidiasis, pneumonia, hyperglycemia, anxiety, insomnia, headache, palpitations, dysphonia, coughing, nausea, urinary tract infections, and muscle spasms – common frequency; hypersensitivity, depression, agitation, restlessness, nervousness, tremor, dizziness, angina pectoris, tachycardia, cardiac arrhythmias, throat irritation, bronchospasms, dry mouth, bruising, urinary retention, chest pain, endocrine and psychiatric disorders -

uncommon frequency. The IMP is contraindicated in subjects who exhibit hypersensitivity to any of the excipients or to drugs which are chemically similar to BGF. No formal drug interaction studies have been

performed, therefore co-administration with other anticholinergic and/or long-acting β_2-agonist containing medicinal product is not recommended [1].

No reproductive and development toxicity studies have been conducted with BGF MDI since each of the individual active substances have been investigated. As with other glucocorticosteroids, budesonide is teratogenic and embryocidal in studies in rats and rabbits. Formoterol has been shown to cause embryofetal toxicity, teratogenicity, and reduced male fertility only at very high doses, and glycopyrronium has shown no significant effects on reproduction at large multiples of the therapeutic dose. Experience with glucocorticosteroids suggests that rodents are more prone to teratogenic effects from glucocorticosteroids than humans. Studies of pregnant women have shown that inhaled budesonide does not increase the risk of abnormality when used during pregnancy. However, there are no adequate and well controlled studies of the use of BGF MDI during pregnancy and lactation, therefore women will not be allowed to participate in this study [1].

There is no previous clinical experience with the NGPs (CCI and CCI), however preclinical data generated indicates an adequate safety profile. For more information on the preclinical data generated, refer to [2] and [3].

3.3. Study Rationale and Justification of Study Design

3.3.1. Study Rationale

The study is intended to assess the relative bioavailability and tolerability of FDCs of BGF MDI "test" formulations compared to the reference formulation to contribute data to the selection of the NGPs.

3.3.2. Overall Study Design

This study will be a randomized, single blind, 3-period, 3-treatment, single-dose, single-center, crossover study. The study will include the assessment of BGF MDI formulated with 3 different propellants: CCI (Treatment A [test]), CCI (Treatment B [test]) and HFA (Treatment C [reference]) described in Section 3.2.1.

The study will comprise:

! Screening period: up to 28 days prior to first dosing;

! Three treatment periods of maximum 3 days each: subjects will be resident from the morning of the day before the first dosing with BGF MDI (Day -1) in Treatment Period 1, throughout all treatment and washout periods up to discharge on Day 2 of Treatment Period 3; and

! Follow-up: within 3 to 7 days after the last administration of BGF MDI.

There will be a washout period of 3 to 7 days between each dose.

Each subject will receive 3 single-dose treatments of BGF MDI (1 dose CCI [Treatment A]; 1 dose CCI [Treatment B] and 1 dose HFA [Treatment C]), following an overnight fast of at least 8 hours.

Approximately 48 healthy male subjects will be randomized in this study to ensure that at least 20 subjects are evaluable.

3.3.2.1. End of Study

The end of study is defined as the last subject's last visit to the Clinical Unit.

3.3.2.2. Expected Duration of the Study

Each subject will be involved in the study for up to 53 days.

Table 3–1 Expected Duration of Each Study Part

Screening	Up to 28 days prior to first dosing

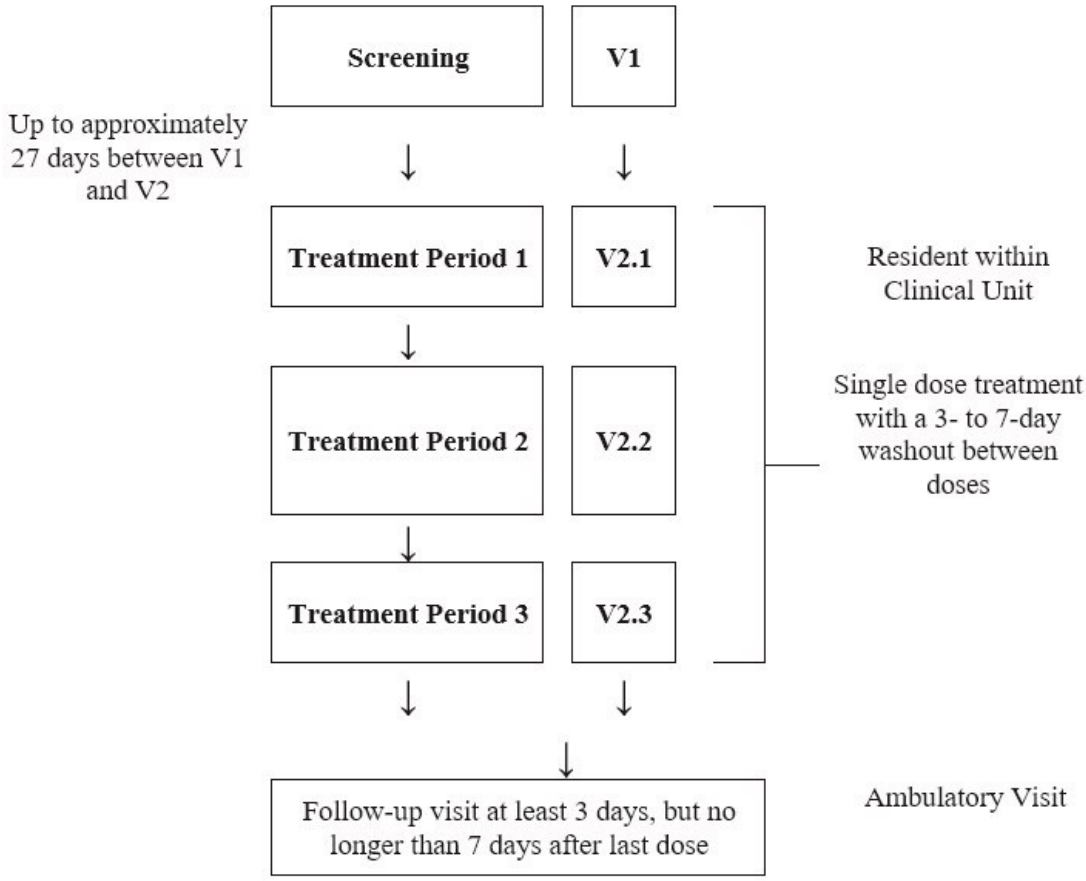
Treatment Periods 1, 2 and 3	Subjects will be resident at the Clinical Unit from the morning of the day before the first dosing with BGF MDI (Day -1) in Treatment Period 1, throughout all treatment and washout periods up to discharge on Day 2 of Treatment Period 3. There will be a 3- to 7-day washout period between each treatment period
Follow-up	Within 3 to 7 days after final dose of BGF MDI in Treatment Period 3
Total Duration	Up to 53 days

3.3.3. Study Flow Chart and Schedule of Assessments

The flow of events is illustrated in Figure 3-1 for all treatments, depending on the subject's assigned randomization (refer to Section 7.9.2).

The Schedule of Assessments displaying assessments/tasks and time points is presented in Table 3–2.

Figure 3-1 Study Flow Chart



Abbreviations: V = Visit

Table 3–2 Schedule of Assessments

		Treatment Periods 1, 2, and 3[a]		
	Screening	**Day -1**	**Day 1 to 2**	**Follow-up/ Early Termination Visit (within 3 to 7 days postfinal dose)**
Informed consent	X			

Assignment of enrolment number	X			
Inclusion/exclusion criteria	X	X (Treatment Period 1)		
Demographic data	X			
Medical history	X			
Urinalysis	X	X (Treatment Period 1)		
Urinary drug/cotinine and serum alcohol screen	X	X (Treatment Period 1)		
Concomitant medication		X	X	X
Serology	X			
COVID-19 testing	X	X (Treatment Period 1)		
Randomization			X (Day 1 of Treatment Period 1)	
Study residency Check-in		X (Morning of Treatment Period 1)		
Check-out			X (Day 2 of Treatment Period 3; after the last study procedure)	
Ambulatory Visit				X
Inhalation Practice Device and inhalation training with placebo and with AIM trainer	X	X	X (prior to dosing)	
IMP administration			Day 1 (0 hours)	
Safety and tolerability Adverse events	X (SAE)	X	X	X
Taste assessment			Immediately post-dose and 30 minutes post-dose	
		Treatment Periods 1, 2, and 3[a]		

	Screening	Day -1	Day 1 to 2	Follow-up/ Early Termination Visit (within 3 to 7 days postfinal dose)
Blood pressure, pulse rate, SpO_2, body temperature and respiratory rate (supine)	X	X	pre-dose, 0.5, 1, 4, 12, and 24 hours post-dose	X
12-lead safety ECG	X	X	pre-dose, 0.5, 1, 2, 4, 8, 12, and 24 hours post-dose	X
12-lead dECG[b]			X	
Cardiac Telemetry[c]		X	X	
Spirometry	X		pre-dose, 0.5, 1, 4, 12, and 24 hours post-dose	X
Clinical laboratory evaluations[d]	X	X	24 hours post-dose	X
Physical examination	X		pre-dose and 24 hours post-dose (brief)	X
Body weight	X			X
Pharmacokinetics				
Plasma for budesonide, glycopyrronium, and formoterol[e]			pre-dose and 2, 5, 10, 20, 30, and 45 minutes post-dose and 1, 2, 4, 8, 12 and 24 hours post-dose	

Abbreviations: AIM = aerosol inhalation monitor; ECG = electrocardiogram; dECG = digital electrocardiogram; IMP = Investigational Medicinal Product; SAE = serious adverse event; SpO_2 = Oxygen saturation [a] There will be a 3 to 7-day washout period between the doses in Treatment Periods 1 and 2 and between Treatment Periods 2 and 3.

[b] 12-lead dECG to be performed as per Table 3–3.

[c] A 12-lead real-time cardiac telemetry ECG will be performed for 4 to 6 hours on the day before dosing days, and from at least 30 minutes pre-dose until 24 hours post-dose on dosing days using the Mortara Surveyor Telemetry 12-leads system.

[d] Refer to Section 8.4.7 for more information on the specific evaluations being performed.

[e] In the event of a delay due to technical or logistical issues with the vital sign assessment, PK blood sampling can take priority to ensure that it is taken within the ± 1-minute window allowed.

Table 3–3 Time Schedule for Digital Electrocardiogram Assessments (Visit 2, Treatment Period 1, 2 and 3)

Treatment Period 1,2,3[f]	ECG Number	Time Point	Start Time hour: minutes[d,e]	Dose	Stop Time	dECG Cont.[a,b,c]	Other
			-01:30		-01:00		Apply the electrodes[b]
			-00:40		-00:30		Rest in bed
	1	Pre-dose	-00:30	Pre-dose	-00:20	10 minutes	
			-00:20		-00:05		Toilet use recommended
			00:00	IMP dosing			
	2	0.5 h	00:20		00:25	5 minutes[c]	
	3	1 h	00:50		00:55	5 minutes[c]	
	4	2 h	01:50		01:55	5 minutes[c]	
	5	4 h	03:50		03:55	5 minutes[c]	
	6	8 h	07:50		07:55	5 minutes[c]	
	7	12 h	11:50		11:55	5 minutes[c]	
	8	24 h	23:50		23:55	5 minutes[c]	

dECG = Digital ECG; ECG = Electrocardiogram; h = hour; IMP = Investigational Medicinal Product; PK: Pharmacokinetics

[a] Subjects must be in the same supine body position (maximum 30 degrees flexion in the hip) at each time point and at all visits. Subjects' feet should not contact the footboard of the bed.

[b] Skin must be cleaned, and electrode positions marked with an indelible pen. Electrodes should be applied at least 30 minutes before first recording.

[c] Subject must rest in bed for at least 10 minutes prior to each ECG time point. [d] Time points for dECG may be adjusted according to emerging PK data.

[e] Times are approximate as dECG and safety ECGs need to be completed before blood sampling. [f] The same time schedule will be applied in each treatment period. For dECG data the treatment periods 1, 2 and 3 will be identified as Visit 2.1, Visit 2.2 and Visit 2.3.

3.3.4. Total Blood Volume

The approximate total amount of blood to be collected from each subject in this study, excluding repeat samples, is summarized in Table 3–4.

Table 3–4 Total Blood Volume

	Volume per Sample	Number of Samples	Total
Hematology	4.0 mL	8	32 mL
Serology	3.5 mL	1	3.5 mL
Clinical chemistry	5.0 mL	8	40 mL
Plasma for budesonide, glycopyrronium, and formoterol	10 mL	39	390 mL
Total			465.5 mL

Repeat blood samples may be collected for safety reasons. The maximum volume to be drawn from each subject must not exceed 500 mL.

3.3.5. Order of Assessments

It is important that PK sampling occurs as close as possible to scheduled time. In order to achieve this, other assessments scheduled at the same time may be initiated prior to the time point. The sequence at a particular time point is:

1 Electrocardiograms.

2 Vital signs (systolic and diastolic BP, pulse rate, SpO_2, body temperature and respiratory rate).

3 Pharmacokinetic blood sampling (will be drawn at the specified time point).

4 Spirometry.

In the event of a delay due to technical or logistical issues with the vital sign assessment, PK blood sampling should be prioritized to ensure that it is taken within the ± 1-minute window allowed.

Pre-dose assessments (except for pre-dose PK assessments) may be performed up to 60 minutes prior to dosing.

3.4. Dose Rationale

The current dosage is 2 inhalations BID and therefore 2 inhalations should be sufficient to reliably estimate PK parameters. The dose of the propellant to which participants will be exposed, is reflective of a 12 hour cycle which is part of the 2 inhalation BID dosage of BGF.

3.5. Risk-benefit Assessment

3.5.1. Risks

See Section 3.2.3 for risks and AEs that may be associated with BGF MDI.

A detailed description of the chemistry, pharmacology, efficacy, safety, known and expected benefits, and potential risks of BGF MDI is provided in the Investigator's Brochure [1]. Overall, BGF MDI is well tolerated, especially considering that this study includes only single-dose administrations.

Since the products to test are reformulations based on a change in the excipient propellant gas:

! The active ingredients are the same

! Treatment is expected to be as safe as it was previously

! Treatment is expected to be as effective as it was previously

! Inhaler device of reformulated drug is same as previous inhaler

! NGPs are not expected to be environmentally damaging

! Trials have been undertaken with the NGP-based products in the past

CCI CCI was negative in a battery of genotoxicity tests. It was also very well tolerated in single-dose (mouse and rat) and repeat dose (rat and dog) studies with the most noteworthy in-life finding being a non-adverse, slight reduction in body weight gain in dogs (up to 3620 mg/kg/day). During an inhaled multigeneration reproductive toxicology study, 10 female rats given 19400 ppm for 6 hours/day (equating to female doses > 20000 mg/kg/day) were found dead or were killed early during the lactation stage (distributed across the F0 and F1 generations). In one F0 animal, the paralysis was associated with brain lesions identified histologically; there were no histological findings to explain the deaths/poor condition of other decedents [2].

In repeat dose studies in rats, microscopic changes were observed in the heart and liver. In repeat dose rat studies, very high gas concentrations were associated with an exacerbation of progressive murine cardiomyopathy, a commonly observed background finding in control animals. The severity of this finding was low and did not progress upon longer term dosing; a NOAEL of 5000 ppm (6 or 4 hours/day) was maintained at 3 and 6 months. It was also generally associated with an increase in plasma AST activity. In a 2 week study, rats given ≥ 20500 ppm showed hepatocyte vacuolation and inflammation with alterations in some associated clinical pathology parameters. This finding was not observed in longer term studies up to 6 months at doses to 15000 ppm. There were no findings in the heart or liver of dogs treated with CCI for up to 3 months (14700 ppm for 2 hour/day [> 3000 mg/kg/day]). The

NOAEL in the 6 month rat study (5180 ppm, 4280 mg/kg/day) provides a safety margin in excess of > 2000 fold, compared with the proposed human single-dose of 1.95 mg/kg [2].

In conclusion, based on the significant safety margins achieved (> 2000 to > 3000-fold) demonstrated, the data from the toxicology studies completed to date are considered appropriate to support the proposed clinical trial [2].

CCI CCI was negative in a battery of genotoxicity tests while in single and repeat dose toxicity studies, transient clinical observations were recorded during the dosing/exposure period which generally recovered upon cessation of dosing; exceptions to this were occasional deaths due to self-injury (primarily recorded in rats) and tube deaths (mice) at very high gas concentrations (at which levels, low oxygen levels were recorded). No other toxicologically important findings were observed in these studies. The NOAELs achieved in the 14-day repeat dose studies provide significant margins to a proposed single human dose of

1.52 mg/kg (2 shots of 45.6 mg CCI/shot) in the proposed clinical study (between > 2000 to > 16000 times) [3].

In conclusion, based on the significant safety margins achieved (> 2000 to > 16000 fold), the data from the toxicology studies completed to date are considered appropriate to support the proposed clinical trial [3].

3.5.2. Risk Assessment for COVID-19 Pandemic

AstraZeneca is committed to supporting the safety and well-being of our study participants, investigators, and site staff. All local regulations and site requirements are being applied in the countries that are affected by the COVID-19 pandemic, including COVID-19 testing of participants if applicable. A benefit/risk assessment has been determined to be positive for the participants that are planned to be enrolled in the proposed clinical trial. As the COVID-19 situation evolves, investigators must use their best judgment to minimize risk to participants during the conduct of the study.

Measures to mitigate the additional risks caused by COVID-19 are:

! This study is going to start enrolling only when the Sponsor and CRO in collaboration deem it is safe to start the study. In addition, the study will not start until the local confinement measures or other safety restrictions linked to the COVID-19 pandemic are lifted by the local authorities.

! Current national laws and local recommendations for prevention of pandemic will be strictly adhered to.

! Subjects will be closely monitored for any signs and symptoms of COVID-19, including fever, dry cough, dyspnea, sore throat and fatigue throughout the study. Once clinical signs of infection are reported by subjects, the PI needs to determine whether samples can

be collected, and safety data can be recorded on site. If not, AEs and concomitant medications will be obtained via phone calls. Daily body temperature measurements during in-house stay and outpatient visits will be implemented.

! The PI will not dose subjects upon identification of any signs of COVID-19 infection.

! Confirmation of COVID-19 infection by optional laboratory assessment will be conducted based on availability (test capacity and turnaround time) of approved tests and on PIs discretion. This would include serology testing at screening and virus testing prior to any admission.

! The probability of virus transmission will be controlled as much as possible by:

∀ Advising the subject to adhere to local requirements for reduction of the public exposure while ambulatory.

∀ All subjects are contacted by phone one day prior to every visit for assessing COVID-19 symptoms and signs and are asked not to attend the site in case of suspected reports. In addition, subjects are asked for any contact with a person who has tested positive for SARS-CoV-2. If applicable, subjects will be referred to the local health care system for further follow-up and treatment.

∀ Physical distancing and person-to-person contact restrictions will be applied during site visits and in-house confinement.

∀ Where physical distancing is not possible, personal protective equipment will be used by subjects (surgical face mask, gloves) and staff (for example, but not limited to masks, gloves, protectors, medical suits) if deemed appropriate by the PI and site staff and guided by local requirements.

∀ Logistical improvements of the site and structural measures of the study site building will be implemented to further improve physical distancing.

3.5.3. Benefits

No benefit for individuals in this study is expected.

4. STUDY OBJECTIVES

4.1. Primary Objective

Table 4–1 Primary Objective and Outcome Measures

Primary Objective	Outcome Measures

To evaluate the relative bioavailability between the test formulations and the reference formulation for FDCs of budesonide, glycopyrronium, and formoterol when delivered as BGF MDI with 3 different propellants.	Cmax, AUCinf, and AUClast for test and reference treatment.

4.2. Secondary Objectives

Table 4–2 Secondary Objectives and Outcome Measures

Secondary Objectives	Outcome Measures
To determine the pharmacokinetic parameters of budesonide, glycopyrronium, and formoterol when administered as 3 different propellant formulations.	tmax, t½λz, MRT, λz, CL/F, Vz/F, TRCmax, TRAUCinf, and TRAUClast.
To assess the safety and tolerability of a combination of budesonide, glycopyrronium, and formoterol when administered as single doses in 3 different propellant formulations in healthy subjects.	AEs/SAEs, vital signs (systolic and diastolic BP, pulse rate, body temperature, SpO_2 and respiratory rate), 12 lead safety and digital ECGs as well as cardiac telemetry, physical examination, laboratory assessments (hematology, clinical chemistry and urinalysis), spirometry, and taste assessments.

Refer to Section 10.9.1 for PK parameters and Section 8.4 for safety variables.

5. SELECTION OF STUDY POPULATION AND RESTRICTIONS

5.1. Selection of Study Population

The PI should keep a subject screening log of all potential subjects who consented and were subjected to screening procedures.

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule. One repeat assessment may be requested per the discretion from the PI (including any laboratory tests, ECG measurements or vital sign measurements) at the screening visit and on admission to the Clinical Unit.

This study will be conducted in healthy male subjects.

5.1.1. Inclusion Criteria

For inclusion in the study, subjects should fulfill the following criteria:

1 Provision of signed and dated, written informed consent prior to any study specific procedures.

2 Healthy, non-smoking male subjects aged 18 – 60 years with suitable veins for cannulation or repeated venipuncture.

3 Subjects must agree to follow the reproductive restrictions as set out in Section 5.2.1.

4 Have a BMI between 18 and 30 kg/m^2 inclusive and weigh at least 50 kg and no more than 100 kg, inclusive.

5 Subjects must have a FEV1 ≥ 80% of the predicted value regarding age, height, and ethnicity at the screening visit.

5.1.2. Exclusion Criteria

Subjects will not enter the study if any of the following exclusion criteria are fulfilled:

1 History or current evidence of a CS disease or disorder (including but not limited to cardiovascular, hepatic, renal, hematological, neurological, endocrine, gastrointestinal, or pulmonary). Significant is defined as any disease that, in the opinion of the PI, would put the safety of the subject at risk through participation, or that could affect the efficacy or safety analysis if the disease/condition exacerbated during the study.

2 History or presence of gastrointestinal, hepatic or renal disease, or any other condition known to interfere with absorption, distribution, metabolism, or excretion of drugs.

3 Any CS illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.

4 Narrow angle glaucoma not adequately treated. All medications approved for control of intraocular pressures are allowed, including topical ophthalmic non-selective β-blockers.

5 Symptomatic prostatic hypertrophy or bladder neck obstruction/urinary retention that, in the opinion of the PI, is CS.

Note: Subjects with trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Visit 1 are excluded from the study.

6 Any cancer except the below:

- Squamous cell and basal cell carcinomas of the skin are allowed in the study.

7 Any CS abnormalities in clinical chemistry, hematology, or urinalysis results, at screening and/or admission to the Clinical Unit as judged by the PI.

8 Any CS abnormal findings in vital signs, after 5 minutes supine rest, at screening and/or Day -1 of each Treatment Period, as judged by the PI.

Note: Out of range tests may be repeated once for each visit at the discretion of the PI. The following are exclusions:

(1) Systolic BP < 90 mmHg or > 140 mmHg.

(2) Diastolic BP < 50 mmHg or > 90 mmHg.

(3) Heart rate < 45 or > 85 bpm.

9 Any clinically important abnormalities in rhythm, conduction or morphology of the resting ECG and any clinically important abnormalities in the 12 lead ECG as considered by the PI.

Note: Out of range test may be repeated once at the discretion of the PI. The following are exclusions:

(1) Prolonged QT interval corrected for HR using Fridericia's formula (QTcF) > 450 ms.

(2) Family history of long QT syndrome.

(3) ECG interval measured from the onset of the P wave to the onset of the QRS complex (PR [PQ]) interval shortening < 120 ms (PR > 110 ms but < 120 ms is acceptable if there is no evidence of ventricular pre excitation).

(4) PR (PQ) interval prolongation (> 240 ms) intermittent second (Wenckebach block while asleep is not exclusive) or third-degree AV block, or AV dissociation.

(5) Persistent or intermittent complete bundle branch block, incomplete bundle branch block, or intraventricular conduction delay with ECG interval measured from the onset of the QRS complex to the J point (QRS) > 119 ms.

10 Any positive result on screening for serum hepatitis B surface antigen, hepatitis C antibody, and HIV antibody.

11 Known or suspected history of drug abuse, as judged by the PI.

12 Participant has a positive RT-PCR test for SARS-CoV-2 prior to randomization.

13 Participant has clinical signs and symptoms consistent with SARS-CoV-2 infection; eg, fever, dry cough, dyspnea, sore throat, fatigue, or laboratory confirmed acute infection with SARS-CoV-2.

14 Participant who had severe course of COVID-19 (extracorporeal membrane oxygenation, mechanically ventilated, Intensive Care Unit stay).

15 Recent (within 14 days prior to admission to the Clinical Unit) exposure to someone who has COVID-19 symptoms or tested positive for SARS-CoV-2.

16 Recent (within 14 days prior to admission to the Clinical Unit) visit to a healthcare facility where COVID-19 patients are being treated.

17 Has a current occupation that involves routine exposure to potential COVID-19 patients or sources of SARS-CoV-2 infection (eg healthcare worker).

18 Receipt of any investigational drug within 30 days or 5 half-lives (whichever is longer) prior to randomization.
Note: subjects consented and screened, but not randomized in this study or a previous Phase I study, are not excluded.

19 Plasma donation within 1 month of screening or any blood donation/loss more than 500 mL during the 3 months prior to screening.

20 History of severe allergy/hypersensitivity or ongoing allergy/hypersensitivity, as judged by the PI, or history of hypersensitivity to drugs with a similar chemical structure or class to BGF.

21 Current smokers or those who have smoked or used nicotine products (including e-cigarettes) within the 3 months prior to screening.

22 Positive screen for drugs of abuse or cotinine at screening or on admission to the Clinical Unit or positive screen for alcohol at screening or on admission to the Clinical Unit.

23 Use of drugs with enzyme-inducing properties such as St John's Wort within 3 weeks prior to the first administration of IMP.

24 Use of any prescribed or non-prescribed medication including antacids, analgesics (other than paracetamol/acetaminophen), herbal remedies, megadose vitamins (intake of 20 to 600 times the recommended daily dose) and minerals during the 2 weeks prior to the first administration of IMP or longer if the medication has a long half-life.

25 Known or suspected history of alcohol abuse or excessive intake of alcohol as judged by the PI.

26 Involvement of any AstraZeneca, Parexel or study site employee or their close relatives

27 Subjects who have previously received BGF.

28 Judgment by the PI that the subject should not participate in the study if they have any ongoing or recent (ie, during the screening period) minor medical complaints that may interfere with the interpretation of study data or are considered unlikely to comply with study procedures, restrictions, and requirements.

29 Vulnerable subjects, eg, kept in detention, protected adults under guardianship, trusteeship, or committed to an institution by governmental or juridical order.

30 History of any respiratory disorders such as asthma, COPD or idiopathic pulmonary fibrosis.

31 Subjects who cannot use an inhaler appropriately and do not demonstrate proper inhalation technique.

32 Subjects who cannot communicate reliably with the PI.

33 Receipt of COVID-19 vaccine (regardless of vaccine delivery platform, eg vector, lipid nanoparticle) less than 7 days prior to the date of randomization (from last vaccination or booster dose).

5.2. Restrictions During the Study

The following restrictions apply for the specified times during the study period:

1 On Day 1 of each treatment period, subjects will be fasted for 8 hours prior to dosing until 4 hours after dosing. No fluids will be allowed apart from water which can be given until 1 hour prior to dosing and then from 2 hours after dosing.

2 Subjects should remain semi-supine (unless specified for certain assessments) for 4 hours after dosing.

3 Subjects should not engage in any strenuous activity from 72 hours prior to check-in until after their final follow-up.

4 Subjects should abstain from alcohol for 72 hours prior to check-in until discharge from the Clinical Unit.

5 Subjects should abstain from caffeine-containing foods and beverages for 24 hours prior to check-in until discharge from the Clinical Unit.

6 Subjects should abstain from grapefruit or grapefruit juice, Seville oranges, quinine (eg, tonic water) from 7 days prior to check-in on Day -1 until discharge from the Clinical Unit.

7 While resident in the Clinical Unit, subjects will receive a standard diet, which excludes all alcohol and grapefruit-containing products. No additional food or beverages must be consumed while in the Clinical Unit.

8 During the subjects' outpatient periods, subjects should abstain from consuming high energy drinks (eg, Red Bull®), and food containing poppy seeds and any OTC medication or herbal preparations until after their final follow-up visit has been completed. Subjects should also limit their caffeine intake to equivalent of 3 servings of coffee per day (1 serving = 12 oz soda, 6 oz coffee, or 8 oz tea). Subjects should consume no more than 2 units of alcohol per day and completely abstain from alcohol from 72 hours prior to check-in.

9 Subjects will be required to abstain from blood or plasma donation until 3 months after the final medical examination at the study follow-up.

10 For the duration of the study, participants must agree to adhere to local requirements for reduction of the public SARS-CoV-2 exposure.

11 While admitted to the Clinical Unit, physical distancing and person-to-person contact restrictions will be applied and explained to participants. Where physical distancing is not possible participants will be asked to use surgical face masks and/or gloves if deemed appropriate by the PI and site staff and guided by local requirements.

For medication restrictions, please refer to Section 7.7.

5.2.1. Reproductive Restrictions

Restrictions

There is no information about the effects that the NGPs used in BGF MDI could have on the development of the fetus in humans. Therefore, it is important that women of childbearing potential who are the partners of male subjects, do not become pregnant during the study and for a total period of 3 months after the male subject has attended the study follow-up.

Male subjects who have been sterilized are required to use one barrier method of contraception (condom) from the time of IMP administration until after the follow-up is completed. The subject must have received medical assessment of the surgical success.

As a precaution, all non-sterilized male subjects should avoid fathering a child by either true abstinence[1] or use a condom and their female partner/spouse has to be either of non-childbearing potential or has to use a highly effective contraception form of birth control, starting from the time of IMP administration until 3 months after the study follow-up visit. The female partner/spouse should be stable on their chosen method of birth control for at least 3 months before first dosing.

Highly effective contraception form of birth control, ie, a form of birth control with a failure rate of less than 1% per year when used consistently and correctly, are:

! Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - Oral
  - Intravaginal
  - Transdermal

! Progestogen-only hormonal contraception associated with inhibition of ovulation
  - Oral
  - Injectable
  - Implantable

! Intrauterine device

! Intrauterine hormone-releasing system

! Bilateral tubal occlusion

[1] Sexual abstinence is defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. It is only acceptable if preferred and usual lifestyle of the subject.

Sperm Donation

Male subjects should not donate sperm for the duration of the study and for at least 3 months after the study follow-up visit.

Pregnancy

Subjects will be instructed that if their partner becomes pregnant during the study this should be reported to the PI. The PI should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject's partner is subsequently found to be pregnant after the subject is included in the study, then consent will be sought from the partner and if granted any pregnancy will be followed and the status of mother and/or child will be reported to the Sponsor after delivery.

A pregnancy notification form and follow-up will be completed.

5.3. Replacement of Subjects

Subjects who are withdrawn from the study due to AEs or changes in safety parameters will not be replaced unless a specific sample size is to be met for statistical purposes and if the Sponsor's responsible physician and the PI agree it is safe to do so. Subjects who withdraw or are withdrawn from the study for other reasons may be replaced following discussion with the Sponsor. Subjects who do not have evaluable PK profiles may be replaced at the discretion of the Sponsor in order to achieve the minimum of 20 evaluable subjects.

6. STUDY STOPPING RULES

Healthy subjects may be discontinued from IMP product in the following situations:

! Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.

! Adverse event.

! Severe noncompliance to study protocol.

! Any significant and clinically relevant changes in the safety parameters (eg, ECG, BP, pulse rate, SpO_2, body temperature, respiratory rate, spirometry, laboratory assessments and AEs) making the continuation of IMP administration unjustified.

6.1. Premature Termination of the Study and Stopping Criteria

The study may be terminated prematurely if:

! The PI and the Sponsor assess that the number and/or severity of AEs justify discontinuation of the study. For instance, when there is at least 1 case of fatal SAE or 2

cases of other SAEs, in both situations considered related to the IMP by the PI and the Sponsor.

! The Sponsor considers the applied doses of the study drug to be no longer relevant.

! The Sponsor decides to discontinue the study.

! Data not known before becomes available and raise concern about the safety of IMP so that continuation would pose potential risks to the subjects.

Premature termination of the study must be mutually agreed upon by the PI and the Sponsor and must be documented. However, study results will be reported according to the requirements outlined in this CSP as far as applicable.

! Study specific withdrawal criteria:

∀ If a subject reports symptoms, which are considered unacceptable by the subject or the PI, he will be withdrawn from the study. In particular:

∀ Two or more healthy subjects, who receive IMP in a cohort, or 3 or more healthy subjects, in total, who received IMP, have a fall in FEV1 ≥ 30%, compared with the pre-dose value within 1 hour after administration of the IMP.

∀ Two or more subjects who receive IMP have QTc prolongation defined as QTcF > 500 ms, or a prolongation from baseline of > 60 ms, confirmed (persistent for at least 5 minutes) and determined post-dose either during continuous 12-lead ECG monitoring or on a repeat 12-lead ECG.

∀ Two or more subjects who receive IMP have tachycardia defined as resting supine HR > 125 bpm persisting for at least 10 minutes.

∀ Two or more subjects who receive IMP have symptomatic bradycardia defined as resting supine HR < 40 bpm or asymptomatic bradycardia defined as resting supine HR < 30 bpm while awake, persisting for at least 10 minutes.

∀ Two or more subjects who receive IMP develop hypertension defined as an increase in resting supine systolic BP > 40 mm Hg to above 180 mm Hg and persisting for at least 10 minutes.

∀ Two or more subjects, who receive IMP, develop hypotension defined as an asymptomatic fall in systolic BP > 20 mmHg to below 70 mmHg persisting for at least 10 minutes, or a symptomatic fall in resting supine systolic BP > 20 mmHg (excluding vasovagal reaction).

∀ Any other severe or serious adverse event that is judged as possibly related to the IMP by the PI.

- One or more subjects who receive IMP fulfill HL according to Appendix C.
- Two or more subjects who receive IMP have confirmed > 3 x ULN of either ALT or AST, or > 2 x ULN for bilirubin or ALP.
- Two or more subjects who receive IMP have confirmed leukocyte count < 2.0 x 10^9/L.
- Two or more subjects who receive IMP have confirmed neutrophil count < 1.0 x 10^9/L.
- Two or more subjects who receive IMP have confirmed platelet count < 75 x 10^9/L.
- Two or more subjects who receive IMP have confirmed serum creatinine increase to > 1.5 x ULN.
- Any case of PHL according to Appendix C.

The appropriate AE form in the CRF is to be completed.

7. TREATMENTS

7.1. Identity of the Investigational Medicinal Product

Details on the identity of the IMP are presented in Table 7–1.

Table 7–1 Identity of the Investigational Medicinal Product

Treatment:	A (test)	B (test)	C (reference)
Supplier:	AstraZeneca	AstraZeneca	AstraZeneca
Formulation full name:	Budesonide, glycopyrronium and formoterol fumarate, pressurized inhalation suspension, CCI propellant	Budesonide, glycopyrronium and formoterol fumarate, pressurized inhalation suspension, CCI propellant	Budesonide, glycopyrronium and formoterol fumarate, pressurized inhalation suspension, HFA propellant
Formulation:	BGF MDI CCI	BGF MDI CCI	BGF MDI HFA
Strength/concentration:	CCI	CCI	CCI
Dose:	2 inhalations	2 inhalations	2 inhalations
Route of administration:	Orally inhaled	Orally inhaled	Orally inhaled
Regimen:	Single-dose	Single-dose	Single-dose
Special handling requirements:	Proper priming and subject training	Proper priming and subject training	Proper priming and subject training

Details of the batch numbers will be included in the trial master file and the final CSR. Subject inhalation training will be performed using the Vitalograph AIM inhalation training device supplied by Parexel. As part of this training, subjects will use a placebo Vitalograph HFA MDI. These devices are commercially available in many countries, including the USA, and used specifically for training with the AIM device. In addition to the above, subjects will perform inhalation training with BGF MDI containing placebo (HFA propellant based), supplied by AstraZeneca.

7.2. Supply of Investigational Medicinal Product

The IMP will be supplied by AstraZeneca.

Dispensing and retention of reserve bioequivalence samples of IMP will be performed in accordance with the FDA Code of Federal Regulations 21, Part 320 Bioavailability and Bioequivalence requirements.

7.3. Storage and Handling Procedures

All investigational medicinal products will be stored in a secure facility, details of storage conditions will be provided on the label of the IMP.

AstraZeneca will be permitted, upon request, to audit the supplies, storage, dispensing procedures and records, provided that the blind of the study is not compromised.

7.4. Labeling

Labels will be prepared in accordance with GMP and local regulatory guidelines.

The labels will fulfill GMP Annex 13 requirements and medical device directive for labeling.

7.5. Drug Accountability, Dispensing and Destruction

The IMP provided for this clinical study will be used only as directed in the CSP.

In accordance with GCP, the Investigational Site will account for all supplies of BGF MDI (CCI, CCI, and HFA). Details of receipt, storage, assembly/dispensing and return will be recorded.

All unused supplies of BGF MDI will either be destroyed by Parexel or returned at the end of the study in accordance with instruction by the Sponsor.

7.6. Dose and Treatment Regimens

Subjects will receive single doses of BGF MDI under fasting conditions. Treatments are described in Section 3.2.1.

In each treatment period, the IMP will be administered after an overnight fast of at least 8 hours.

Subjects will be allowed to drink water to prevent dehydration until 1 hour before dosing.

Water will be allowed ad libitum from 2 hours after dosing and a standard meal will be given 4 hours after dosing.

After dosing, subjects will remain semi-supine on their bed or sitting (except when necessary for study procedures) until completion of the 4 hour assessments.

Other restrictions are described in Section 5.2. Data of subjects may be excluded from the PK Analysis Set as described in Section 10.3.2.

Specific precautions will be taken to prevent any contamination of collected PK samples by the particles of IMP inhalations. Administration of IMP will take place in a room separate from the room where blood samples will be drawn. During administration, subjects and clinic personnel will wear protective clothing and gloves according to the routines at the Clinical Unit. The protective clothing and gloves will be discarded immediately after administration in the room used for inhalation if the personnel are going directly to the blood draw area, to avoid subsequent contamination of blood samples. Subjects will also wash their hands and face with soap and water or a disposable wipe after administration of IMP. Subjects must wear a surgical mask for approximately 30 minutes before and after dosing.

All devices must be primed in a separate room (ie, a different room than will be used to administer IMP to subjects) by study personnel before the first use. Study personnel must wear laboratory coats and gloves during IMP inhaler priming and must remove their laboratory coats and gloves immediately after priming is completed in the room where priming was conducted.

At the screening visit, on admission/Day -1, and pre-dose on Day 1 of each treatment period, subjects will be instructed by site staff on the inhalation technique for MDI using the Vitalograph AIM device. In addition, at the same visits, the subjects will be trained to use the placebo BGF MDI inhalers to ensure adequate demonstration of MDI techniques.

Each dose will consist of 2 actuations from the MDI. The second actuation must take place within approximately 30 seconds from the first. At the time of dosing, a healthcare provider will be present to ensure that the required number of actuations of the MDI device is properly administered by the subject and that the subject inhales the full dose by observing that none of the IMP plume escapes the subject’s mouth. The Sponsor will provide the Clinical Unit with instructions for use. The dosing time (recorded as the time of the second inhalation) must be documented on the eCRF.

7.7. Concomitant and Post-study Treatments

If a subject is being considered for enrolment into the study and also being considered for COVID-19 vaccination, the subject must not be randomized until at least 7 days after the last dose of vaccine or booster.

Apart from paracetamol/acetaminophen, no concomitant medication or therapy will be allowed.

The subjects should be instructed that no other medication is allowed, including herbal remedies, vitamin supplements, and OTC products, without the consent of the PI.

Medication, which is considered necessary for the subject's safety and well-being, may be given at the discretion of the PI during the residential period.

When any medication is required, it should be prescribed by the PI. Following consultation with the AstraZeneca Lead Physician, the PI should determine whether the subject should continue in the study. Administration of concomitant medications that may influence the measurement of the PK endpoints may be documented as a protocol deviation after consultation of the PI with AstraZeneca Lead Physician.

7.8. Treatment Compliance

Dosing will take place at the Parexel Early Phase Clinical Unit.

The administration of all IMPs will be recorded in ClinBase™.

Compliance will be assured by direct supervision and witnessing of study drug administration.

7.9. Randomization

7.9.1. Subject Enrolment and Randomization

The PI will ensure:

! Signed informed consent is obtained from each potential subject before any study specific procedures are performed.

! Each potential subject is assigned a unique enrolment number at screening upon signing the Informed Consent.

! The eligibility of each subject is in accordance with the inclusion and exclusion criteria.

! Each eligible subject is assigned a unique randomization code.

Randomization can be done on the evening prior to the day of first dosing (Day 1 of Treatment Period 1).

Randomization codes will be assigned strictly sequentially as subjects become eligible for randomization [codes to be used without leading zero(s)].

When using unique enrolment number, the specific format must be followed (ie, reduced enrolment number "1001" in ClinBase™ and on labels, full enrolment number "E0001001" for outputs).

If a subject withdraws his participation in the study, then his enrolment/randomization code cannot be reused. If a replacement is mandated replacement subjects will receive a new randomization number and will be allocated to the same treatment sequence as the replaced subject.

7.9.2. Procedures for Randomization

Upon completion of the randomization requirements specifications form, the randomization will be produced by Parexel according to the AstraZeneca randomization system (AZRand).

Subjects will be randomized to treatments A, B and C (see Section 3.2.1) in one of 6 sequences as described below.

The number of subject identifiers generated for the study will account for the number of randomized subjects per the sample size calculation (N = 24, see Section 10.4) as well as providing sufficient randomization numbers for replacements, on a like-for-like treatment sequence basis. For this study, a total of 24 subject identifiers will be randomly assigned to the treatment sequence(s): ABC, BCA, CAB, ACB, BAC, CBA. For replacements, an additional 24 subjects will be randomly assigned to the same treatment sequences. For this, an additional set of random numbers will be generated on a like-for-like treatment sequence basis.

7.9.3. Procedures for Handling Incorrectly Randomized Subjects

Subjects who fail to meet the inclusion criteria or meet any exclusion criterion should not, under any circumstances, be randomized into the study. There can be no exceptions to this rule.

Where a subject, who does not meet the selection criteria, is randomized in error and this is identified before dosing, the subject should be withdrawn from the study. If a subject is withdrawn prior to dosing they will be replaced.

If a subject, who does not meet the selection criteria and has been dosed before the error is identified, the subject should be withdrawn and advised to continue safety assessments to ensure their safety. The PI will inform the AstraZeneca Lead Physician of the error and a joint decision made as to whether the subject should be replaced.

7.10. Blinding

7.10.1. Methods for Ensuring Blinding

This is a single blind study with regard to BGF MDI treatment, administered with 3 different propellants (Treatment A, B or C), in which the subjects will remain blinded.

8. MEASUREMENTS AND METHODS OF ASSESSMENTS

8.1. Appropriateness of Measurements

Standard measures to assess PK, safety and tolerability apply during the study. For the single doses of BGF MDI planned to be given during this study, no safety issues are expected.

For timing of assessments refer to Table 3–2.

8.2. Enrolment and Screening Procedures

Viral serology and urine drugs of abuse, alcohol and cotinine will be assessed for eligibility. Use of concomitant medication will also be assessed and reported.

8.3. Pharmacokinetics

8.3.1. Collection of Pharmacokinetic Samples

Blood samples for the determination of plasma concentrations of budesonide, glycopyrronium, and formoterol will be collected for each treatment period as specified in the Schedule of Assessments (Table 3–2).

Samples will be collected, handled, labeled, stored, and shipped as detailed in the Laboratory Manual.

8.3.2. Pharmacokinetic Drug Assays

Blood samples for determination of budesonide, glycopyrronium, and formoterol concentrations in plasma will be analyzed by Covance, on behalf of AstraZeneca, using validated assays. Additional analyses may be conducted on the biological samples to further investigate the presence and/or identity of drug metabolites, if appropriate.

Full details of the analytical method and analyses performed will be described in a separate bioanalytical report.

8.4. Safety and Eligibility Measurements

Safety and tolerability variables will include:

! Adverse events

! Taste assessment

! Vital signs (systolic and diastolic BP, pulse rate, body temperature, SpO_2 and respiratory rate)

! 12-Lead safety and digital ECGs as well as cardiac telemetry

! Physical examination

! Spirometry

! Laboratory assessments (hematology, clinical chemistry, and urinalysis).

Viral serology and drugs of abuse, alcohol and cotinine will be assessed for eligibility. Body weight and use of concomitant medication will also be assessed and reported.

8.4.1. Adverse Events

Refer to Section 11.

8.4.2. Taste Assessment

The taste of BGF MDI will be assessed by administration of a questionnaire after the administration of each dose of the IMP as indicated in Table 3–2.

The questionnaire will be administered to subjects immediately post-dose and 30 minutes following intake of BGF MDI. Subjects will be asked to complete the questionnaire without assistance or influence from site personnel. The questionnaire will be identical for each assessment and will require the subject's opinion on the following questions:

(1) Did you detect a taste in the medicine administered? Yes/No

(2) If yes, on a scale from 1 to 5 (where 1 indicates not unpleasant and 5 indicates extremely unpleasant), rate the detected taste of the medicine.

(3) If yes, please provide a short text description of the taste.

8.4.3. Vital Signs

The following variables will be collected after the subject has rested in the supine position for at least 5 minutes:

! Systolic BP (mmHg)

! Diastolic BP (mmHg)

! Pulse rate (bpm)

! Respiratory rate (breaths per minute)

! Body temperature (°C)

! SpO_2 (%)

The measurement of vital signs will be carried out according to the relevant Parexel SOPs.

8.4.4. Electrocardiograms

8.4.4.1. Resting 12-lead Electrocardiogram

A 10-second twelve-lead safety ECG will be obtained after the subject has been resting in the supine position for at least 10 minutes at all timepoints listed in Schedule of Assessments (Table 3–2) and whenever it is required by the PI. All ECGs will be evaluated with respect to rhythm, HR, and PR, RR, QRS, QT, and QTcF intervals from the 12-lead safety ECG, and the PI will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is CS or not, and the abnormality will be recorded. The PI or delegate will evaluate the printout of the safety ECG in real-time.

The date/time and the physician interpretation (normal, abnormal CS, abnormal NCS) for the safety ECGs will be recorded in the eCRF and stored as source documents.

8.4.4.2. Electronic Capture of 12-Lead Continuous Digital ECG

The AstraZeneca ECG Center will perform the dECG analysis in this study, using the EClysis© system, version 4.0, or higher. V2 will be used as the primary analysis lead, with lead V5 as the primary back-up lead and lead II as the secondary back-up lead, for all time points when lead V2 is found to be unsuitable for analysis.

At the time points specified in the Schedule of Assessments (Table 3–2), 12-lead continuous dECG files will be recorded using the site's Mortara Telemetry Surveyor equipment, according to the agreed Parexel and AstraZeneca ECG Center standard procedures for settings/configuration, recording and transfer of dECGs.

The same recording device will be used for each subject, at all timepoints, when possible. Date and time settings must be checked on the Mortara Telemetry Surveyor at the start of each study day and aligned with an official timekeeper.

The metadata of each file will be checked by the responsible personnel at the study site to ensure that the files transferred to the AstraZeneca central dECG files repository have correct metadata.

Skin preparation must be thorough and electrode positions must be according to standard 12-lead ECG placement. Permanent electrodes will be applied at least 30 minutes before first study recording and left in place for the duration of each relevant study day.

Subjects will rest in a supine position for at least 10 minutes before the start of each recording. The subject should be in the same supine body position (maximum 30 degrees flexion of the hip and feet not in contact with the footboard) at each recording time point during the study.

From the continuous dECG files received at the AstraZeneca ECG Center, the EClysis© system will extract continuous files of at least 5 minutes length at CSP-indicated time points in the Time Schedule for Digital Electrocardiogram Assessments (Table 3–3). The extraction window can be adjusted by the responsible ECG Scientific Advisor during the metadata approval procedure, based on the 'clinical logs' received from the site. As standard, from each dECG extracted window, 10-second ECGs will then be extracted by the EClysis© system twice per minute and automatically analyzed by the software. The ECG Scientific Advisor will perform all necessary manual corrections of the ECG annotations provided automatically by EClysis©. All dECGs from one subject will be analyzed by a single reader in a blinded manner.

The AstraZeneca ECG Center Cardiologist will finally review all data and perform all necessary adjustments before locking the data into a read--only state. From the locked data, the numerical values for the ECG intervals and amplitudes will then be made accessible on a secure file share of the AstraZeneca dECG central repository to accredited Data Management specialists for conversion into SAS® files.

The following dECG variables will be reported by the AstraZeneca ECG Center: RR, PR, QRS and QT intervals from the lead defined as the primary analysis lead, as well as potential T-wave morphology changes.

Derived parameters (QTcF, HR and others, as applicable) are calculated by the study statistician or delegate.

8.4.4.3. Real-Time ECG (Cardiac Telemetry)

A 12-lead real-time cardiac telemetry ECG will be performed for 4 to 6 hours on the day before dosing, and from at least 30 minutes pre-dose until 24 hours post-dose on dosing days, using the Mortara Surveyor Telemetry 12-leads system.

The telemetry monitoring system will be reviewed by the PI or research nurse and paper printouts of any clinically important events will be stored as source data.

8.4.5. Physical Examination

Full

The complete physical examinations will include an assessment of the general appearance, respiratory, cardiovascular, abdomen, skin, head, and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal and neurological systems.

Brief (Abbreviated)

The brief physical examinations will include an assessment of the general appearance, skin, abdomen, cardiovascular system and respiratory.

8.4.6. Spirometry

Spirometry will be performed by a technologist or a qualified designee to ensure subjects achieve optimal lung function and using standardized equipment that meets or exceeds the ATS/ERS joint recommendations.

The subject will be in a seated position during spirometry. The following variables will be recorded:

! Forced expiratory volume in one second

! Forced expiratory volume in one second percentage of predicted value

! Forced vital capacity

! Forced vital capacity percentage of predicted value

! FEV1/FVC ratio

! Forced expiratory flow from 25 % to 75 % of the forced vital capacity

! Forced expiratory flow from 25-75 % of the forced vital capacity – percentage of predicted value

The predicted normal values will be based on the equations derived from the NHANES III dataset for adult men.

The highest value for FEV1 and FVC will be recorded, even if these are not from the same maneuver. The FEF25-75 % is taken from the blow with the largest sum of FEV1 and FVC. An assessment of “normal” or “abnormal” will be included, however no statistical assessment of mean change from baseline will be done, since this is a healthy population.

The ATS/ERS guidelines for repeatability and acceptability will be followed. The same device will be used for each subject during the 3 Treatment Periods. It is recommended that a subject’s spirometry assessments should be performed on the same spirometry device during study participation, however if that is not possible due to operational/logistic aspects, screening and follow-up assessment spirometry could be performed on different devices

assuming that the same type of spirometry device/using the same measurement technology will be used for that purpose.

8.4.7. Laboratory Assessments

8.4.7.1. Hematology

Hematology	
White blood cell (WBC) count	Neutrophils absolute count[a]
Red blood cell (RBC) count	Lymphocytes absolute count[a]
Hemoglobin (Hb)	Monocytes absolute count[a]
Hematocrit (HCT)[a]	Eosinophils absolute count[a]
Mean corpuscular volume (MCV)[a]	Basophils absolute count[a]
Mean corpuscular hemoglobin (MCH)[a]	Platelets
Mean corpuscular hemoglobin concentration (MCHC)[a]	Reticulocytes absolute count[a]

[a] Screening, Day -1 of Treatment Period 1 and Follow-up only

8.4.7.2. Serum Clinical Chemistry

Serum Clinical Chemistry	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea[a]	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin[a]	Total Bilirubin
Calcium[a]	Unconjugated bilirubin
Phosphate[a]	Free T_4[b]
Glucose (fasting)	TSH[b]
C-reactive protein (CRP)[a]	Cardiac troponin I

[a] Screening, Day -1 of Treatment Period 1 and Follow-up only [b] Screening only

8.4.7.3. Urinalysis

Urinalysis	
Glucose	
Protein	

Blood	
Microscopy (if positive for protein or blood): RBC, WBC, Casts (Cellular, Granular, Hyaline)	

8.4.7.4. COVID-19 Testing

COVID-19 Testing (Nasopharyngeal Swab)	
SARS-CoV-2 RT-PCR	

8.4.7.5. Viral Serology

Vi al Serology	
HIV I and II	Hepatitis C Virus antibody
Hepatitis B surface antigen (HBsAg)	

8.4.7.6. Drugs of Abuse, Alcohol and Cotinine

Drugs of Abuse and Alcohol	
Amphetamine/Ecstasy	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates
Cocaine	Phencyclidine
Opiates	Urine Creatinine
Cotinine	Buprenorphine
Tricyclic anti-depressants (TCA)	Oxycodone
Methamphetamine	3,4-Methylenedioxymethamphetamine (MDMA)

Drugs of abuse and cotinine screen will be done via a urine sample; alcohol screen will be done via a serum sample.

8.4.8. Concomitant Medication

Refer to Section 7.7.

8.5. Procedures for Handling of Biological Samples

8.5.1. Storage and Destruction of Biological Samples

Samples will be disposed of, on instruction from AstraZeneca, after the CSR has been finalized, unless samples are retained for additional or future analyses.

8.5.1.1. Pharmacokinetic Samples

Pharmacokinetic samples will be disposed of after the bioanalytical report finalization or 6 months after issuance of the draft bioanalytical report (whichever is earlier), unless requested for future analyses.

Pharmacokinetic samples may be disposed of or anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic samples to further evaluate and validate the analytical method. Any results from such analyses may be reported separately from the CSR.

Incurred sample reproducibility analysis or additional assay development, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the CSR but separately in a bioanalytical report.

8.5.2. Labeling and Shipment of Biohazard Samples

Samples will be labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B of this CSP 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials will not be shipped and no further samples will be taken from the subject unless agreed with AstraZeneca and appropriate labeling, shipment and containment provisions are approved.

8.5.3. Chain of Custody of Biological Samples

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

The PI will ensure full traceability of collected biological samples from the subjects while in storage at the center until shipment and will keep documentation of receipt of arrival.

The sample receiver will keep full traceability of samples while in storage and during use, until used, disposed of, or until further shipment or disposal (where appropriate) and will keep documentation of receipt of arrival.

Samples retained for further use will be registered in the AstraZeneca biobank system during the entire life cycle.

8.5.4. 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 if not already analyzed and the action documented.

As collection of donated biological samples is an integral part of the study then the subject is withdrawn from further study participation. If the subject withdraws consent for the genetic component of the study, then they may continue in the study.

AstraZeneca ensures the central laboratory(ies) 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 Clinical Unit.

9. DATA QUALITY ASSURANCE AND DATA MANAGEMENT

9.1. Quality Control and Source Data Verification

Source data verification will be conducted with due regard to subject confidentiality.

The Clinical Unit will allow the study monitor and Sponsor representative direct access to all study documents, medical files and source documents to enable verification of the study data, while maintaining the anonymity of the subject and confidentiality of the data.

Internal quality control will be performed at all stages of the study by the Clinical Unit.

9.2. Audit/Inspections

The Clinical Unit facilities and all study data/documentation may be audited/inspected by independent auditor/inspector/any representatives of regulatory authorities. The PI must allow the applicable persons access to all relevant facilities and data/documents. The PI must be available to discuss any findings/issues.

If an audit was performed, the audit certificate will be included in the CSR.

9.3. Study Monitoring

The conduct of the study will be monitored by an independent Parexel monitor or a subcontracted monitor to ensure compliance with applicable regulatory requirements and GCP. The summary of the documentation of the monitoring visits will form part of the study documentation and will be archived as such.

9.4. Data Collection

The ClinBase™ system is an electronic source data capturing and information management system. The system combines all aspects of source data capturing with process control and clinical study management. All clinical and laboratory data, except those which are paper-based or provided by external vendor, will be collected in ClinBase™. Only paper-based data will be subject to data entry. For electronic source data, no data entry will be performed.

The responsible study monitor will check data at the monitoring visits to the Clinical Unit. The PI will ensure that the data collected are accurate, complete and legible. Data will be monitored within ClinBase™ by the study monitor before being exported. Any changes made during monitoring will be documented with a full audit trail within ClinBase™.

9.4.1. Case Report Forms and Source Documents

All data obtained using paper collection methods during the clinical study will be recorded in ClinBase™. All source documents from which ClinBase™ entries are derived should be placed in the subject's personal records.

The original ClinBase™ entries for each subject will be checked against source documents by the study monitor. Instances of missing or uninterpretable data will be discussed with the PI for resolution.

9.4.2. Access to Source Documents

During the course of the clinical study, a study monitor will make Clinical Unit visits to review protocol compliance, compare ClinBase™ entries and individual subject's personal records, assess IMP accountability and ensure that the clinical study is being conducted according to pertinent regulatory requirements. ClinBase™ entries will be verified against source documents. The review of medical records will be handled confidentially to ensure subject anonymity.

Checking of the ClinBase™ entries for completeness and clarity and verifying with source documents, will be required to monitor the clinical study for compliance with GCP and other regulations. Moreover, regulatory authorities of certain countries, IRBs may wish to carry out source data inspections on-site, and the Sponsor's clinical quality assurance group may wish to carry out audits. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and subject confidentiality. The PI assures the Sponsor of the necessary support at all times.

9.5. Data Management

Parexel will utilize standardized and validated procedures and systems to collect, process and file the clinical data of this study. Any system used will be compliant with FDA 21 CFR Part 11 requirements.

A DMP will be prepared to describe the processes and data-flow within the clinical study. Timelines, versions for the computer systems and the coding will be defined in the DMP, and if applicable, Sponsor specific requests will also be documented within. The DMP will be finalized before first dose, where possible, but before database lock.

A DVS will be created to outline the validation checks to be performed during the study. The DVS must be finalized before data validation.

After the data has been monitored by the responsible study monitor all data received will be reviewed, logged and filed.

The raw data intended for further processing will be checked by standard routines or according to the DVS and queries will be generated and sent to the PI for review and resolution. Corrections resulting from these queries will be confirmed on the Data Clarification Forms. This process will be repeated until no further discrepancies are found. The data will then be declared as clean. Applicable documentation will be stored in the study files.

Only trained study staff will have access to the clinical database and every change in data will have a full audit trail.

10. STATISTICAL METHODS

10.1. Overview

The statistical methodology below describes the statistical analysis as it is foreseen when the study is being planned.

If circumstances should arise during the study rendering the analysis inappropriate, or if in the meantime improved methods of analysis should come to light, different analyses may be performed. A separate SAP will not be written for the study. Any deviations from the statistical methodology defined in this protocol, reasons for such deviations and all alternative/additional statistical analyses that may be performed will be described in the CSR. Such changes to analyses may be written into an abbreviated SAP, if appropriate. The verification and review of all statistical modeling assumptions will be documented appropriately.

10.2. General Statistical Methodology

All original and derived parameters as well as demographic and disposition data will be listed and described using summary statistics. All safety data (scheduled and unscheduled) will be presented in the data listings.

Demographic and baseline data will be summarized for the Randomized Set. Pharmacokinetic data will be summarized by treatment based on the PK Analysis Set. Safety and tolerability data will be summarized by treatment for the Safety Analysis Set.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, standard deviation [SD], median, minimum and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n > 3$. If no subjects have data at a given timepoint, then only $n = 0$ will be presented. If $n < 3$, only the n, minimum and maximum will be presented. If $n = 3$, only the n, median, minimum and maximum will be presented. The other descriptive statistics will be left blank.

The following rules will apply to any repeated safety assessments occurring within each treatment period:

! If the repeated measurement of a specific parameter occurs prior to IMP administration (Day 1), then the last obtained value prior to dosing will be used in the descriptive statistics and in the calculation of changes from baseline;

! If the repeated measurement of a specific parameter occurs after IMP administration (Day 1), then the first (non-missing) value after dosing will be used in descriptive statistics and in the calculation of changes from baseline.

The planned sequence for measurement of multiple assessments at the same time point is described in Section 3.3.5.

For safety assessments performed at screening and the follow-up, the following rules will apply for any repeated assessments:

! If the repeated assessment occurs at screening the last available value will be used in the summary statistics;

! If the repeated assessment occurs at the follow-up visit the first non-missing assessment will be used in the summary statistics.

All statistical analyses and production of tables, figures and listings will be performed using SAS® version 9.4 or later.

10.2.1. Rounding Conventions for Safety Data

The following rules will be followed with regard to the number of decimal places and presentation of data in the tables and listings:

! All data will be listed according to the number of decimal places or significant figures presented in the original data.

! Arithmetic mean and median are presented using 1 decimal place more than the original data using the number of digits of the individual data + 1.

! Arithmetic SD is presented using the number of digits of the individual data+ 2.

! Percentages will be presented to 2 decimal places.

! A maximum of 3 decimal places will apply to all summary statistics.

10.2.2. Missing Data

Missing dates and times in the AE data will be handled as described in Section 10.10.1.
Concentrations that are NQ in the PK data will be handled as described in Section 10.9.2.

There will be no imputations of other missing data. All subjects who received at least 1 inhalation of the IMP will be included into the safety analyses as far as the data permit.

10.3. Study Populations

10.3.1. Safety Analysis Set

The Safety Analysis Set will include all subjects who received at least 1 inhalation of any BGF MDI formulated treatment. This includes all original and replacement subjects where the 1 inhalation criterion is met.

Unless otherwise stated, the Safety Analysis Set will be used for the presentation of all safety analyses. Exposure to IMP will also be presented using the Safety Analysis Set.

10.3.2. Pharmacokinetic Analysis Set

The PK Analysis Set will consist of all subjects in the Safety Analysis Set for whom at least 1 of the primary PK parameters can be calculated, and who have no important protocol deviations thought to impact on the analysis of the PK data.

Clinical PK of BGF MDI are described in Section 3.2.

Data from subjects may be excluded from the PK Analysis Set as a result of the following:

! Subjects for whom the pre-dose concentration is > 5% of Cmax for budesonide, glycopyrronium, or formoterol in a specific treatment period will be excluded from the statistical analysis of the affected analyte.

A subject may be excluded from the analysis due to certain AE affecting PK profiles, but the exclusion will be only for the specific treatment period in which the AE occurred.

The exclusion of any subjects or time points from the calculation of the PK parameters will be documented by the PK Scientist including the reason(s) for exclusion.

The available concentration data and PK parameter data for any subjects excluded from the PK Analysis Set will be listed only. Concentration data for subjects excluded from the PK Analysis Set will be presented in the individual figures of concentration versus time plots, using the Safety Analysis Set.

10.3.3. Randomized Set

The Randomized Set will consist of all subjects randomized into the study.

10.4. Determination of Sample Size

This is a pilot PK study to determine the relative bioavailability between 2 formulations of BGF MDI with NGPs compared with the current formulation with HFA propellant. Therefore, no sample size calculation has been performed.

It is expected that 48 healthy subjects will be randomized to a 6-sequence Williams design for 3 periods and 3 treatments: ABC, BCA, CAB, ACB, BAC, CBA, in order to ensure at least 20 evaluable subjects at the end of the last treatment period.

Subjects are considered evaluable if they have an evaluable PK profile, ie, (1) receive active treatment, (2) do not significantly violate protocol inclusion or exclusion criteria, or deviate

significantly from the protocol, and (3) do not have unavailable or incomplete data which may influence the PK analysis.

10.5. Protocol Deviations

Protocol deviations are considered any deviation from the CSP relating to a subject, and include the following:

! Inclusion/exclusion criteria deviations

! Dosing deviations (eg, incorrect treatment received, subject was not fasted as per the protocol requirements prior to and after dosing)

! Time window deviations for safety and/or PK assessments

! Subjects receiving prohibited concomitant medications

! Other procedural and study conduct deviations recorded by the Clinical Unit on a protocol deviation log

The criteria for the assessment and reporting of protocol deviations will be stipulated in a separate study specific PDS document. This will include a WAD which stipulates tolerance windows for safety and PK assessments. Measurements performed within these tolerance windows will not be considered as protocol deviations and will not be reported.

All protocol deviations will be discussed at the data review meeting prior to database hard lock in order to define the analysis sets for the study.

Important protocol deviations will be listed by subject.

Protocol deviations will be handled in accordance with Parexel SOPs.

For handling of protocol amendments, see Section 1.6.

10.6. Subject Disposition

A randomization listing will be presented and include the following: each subject's randomization number, the subject's full enrolment number, the planned treatment sequence and the actual treatment sequence to which the subject has been randomized and the country where the study center is located.

Subjects and/or data excluded from the PK Analysis Set will be listed including the planned treatment sequence and reason for exclusion. Subject disposition will be summarized by treatment sequence and will include the following information: number of subjects randomized, number and percentage of subjects participating in 3 treatment periods, 2 treatment periods and 1 treatment period only, number and percentage of subjects completing

the study and the number and percentage of subjects who were withdrawn (including reasons for withdrawal). Disposition data will be presented (listed and summarized) based on the Randomized Set.

Subject discontinuations will be listed including the treatment sequence, date of study exit, study period of exit, last treatment received, duration of treatment and reason for discontinuation for all subjects randomized. A listing of informed consent response will also be presented.

10.7. Demographic and Baseline Data

Demographic variables (age, race, ethnicity, height, weight and BMI) will be listed by subject. Demographic characteristics (age, race and ethnicity) and subject characteristics (height, weight and BMI) will be summarized by treatment sequence and overall for the Randomized Set, and for the PK Analysis Set should there be a difference between the analysis set. The denominator for percentages will be the number of randomized subjects or PK Analysis Set as applicable.

Medical history data will be listed by subject including planned treatment sequence, visit, description of the verbatim term, MedDRA SOC, MedDRA Preferred Term, start date, and stop date (or ongoing if applicable).

10.8. Prior and Concomitant Medication and Drug Administration

10.8.1. Prior and Concomitant Medication

Prior medications are those that started and stopped prior to the first dose of IMP; all medications taken after first dosing are considered as concomitant (including medications that started prior to dosing and continued after). Prior medication started within 3 months prior to the first dose of IMP will be recorded also in the concomitant medication module of ClinBase™.

Prior and concomitant medication will be listed by subject and will include the following information: planned treatment sequence, reported name, Preferred Term, the route of administration, dose, frequency, start date/time, duration and indication. Prior and concomitant medication will be coded according to the Sponsor’s drug dictionary.

The duration will be calculated as:

Duration = end date/time – start date/time

The duration may be presented in hours or days in the listing depending on the applicability to the emerging data. For medications with partial or completely missing start date/times and/or end date/times, the duration will not be calculated.

Medications with missing or partial start date/time and/or end date/time such that it is not possible to classify as prior or concomitant will be considered as concomitant in the listings.

10.8.2. Drug Administration

Drug administration dates and times will be listed for each subject and treatment period.

10.9. Pharmacokinetic Analysis

10.9.1. Pharmacokinetic Parameters and Methods of Derivations

The PK parameters of the plasma concentration data will be derived by Covance, on behalf of the Clinical Pharmacokinetic Alliance, AstraZeneca R&D, using non-compartmental methods in Phoenix® WinNonlin® Version 8.1 or higher (Certara USA, Inc).

Data permitting, the following PK parameters will be derived for budesonide, glycopyrronium, and formoterol from plasma concentrations.

Primary PK Parameters

AUCinf	Area under the concentration-time curve from time zero extrapolated to infinity. AUCinf is estimated by AUClast + Clast/#z where Clast is the last observed quantifiable concentration (Day 1 only)
AUClast	Area under the plasma concentration- curve from time zero to the time of last quantifiable concentration
Cmax	Maximum observed concentration

Secondary PK Parameters

tmax	Time to reach maximum observed concentration
t½λz	Terminal elimination half-life, estimated as (ln2)/λz
MRT	Mean residence time in the systemic circulation extrapolated to infinity
λz	Terminal elimination rate constant, estimated by log-linear least squares regression of the terminal part of the concentration-time curve
CL/F	Apparent total body clearance of drug after extravascular administration
Vz/F	Apparent volume of distribution during the terminal phase after extravascular administration
TRCmax	Treatment ratio for Cmax [Test Treatment (A or B)/ Reference Treatment (C)], derived by dividing the Cmax of the test treatment by the reference treatment
TRAUCinf	Treatment ratio for AUCinf [Test Treatment (A or B)/ Reference Treatment (C)], derived by dividing the AUCinf of the test treatment by the reference treatment

TRAUClast	Treatment ratio for AUClast [Test Treatment (A or B)/ Reference Treatment (C)], derived by dividing the AUClast of the test treatment by the reference treatment

The following diagnostic parameters for plasma PK analysis will be provided:

λz, Interval or λz upper and λz lower	The time interval (h) of the log-linear regression to determine t½λz.
λzN	Number of data points included in the log-linear regression analysis.
Rsq adj	Regression coefficient adjusted for λzN, goodness of fit statistic for calculation of λz. Reporting criteria: where Rsq_adj of < 0.8, parameters derived using λz will be flagged in the data listings and excluded from descriptive and inferential statistics.
λz span ratio	Time period over which λz was determined as a ratio of t½λz. Reporting criteria: where t½λz is estimated over less than 3 half-lives, the value will be flagged in the data listings and excluded from descriptive statistics.
tlast	Time to last quantifiable concentration.
AUCextr (%)	Percentage of AUCinf obtained by extrapolation, calculated as [(Clast/#z)/AUCinf * 100]. Reporting criteria: where AUCextr is greater than 20%, AUCinf and parameters derived from this will be flagged in the data listings and excluded from descriptive and inferential statistics.

Additional PK parameters may be determined where appropriate.

The PK parameters will be calculated/estimated according to AZ standards, Guideline Pharmacokinetic Evaluations in Clinical Studies v3 Feb 2020.

Pharmacokinetic analysis will, where data allow, be carried out using actual elapsed times determined from the PK sampling and dosing times recorded in the database. If actual elapsed times are missing, nominal times may be used.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis. Handling of BLQ concentrations will be according to AZ standards, Guideline Pharmacokinetic Evaluations in Clinical Studies v3 Feb 2020.

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ. Where there are just 3 quantifiable concentrations, at least 1 of these concentrations should follow the peak concentration.

10.9.2. Presentation of Pharmacokinetic Data

All PK concentrations, parameter summaries and statistical analyses will be presented for the PK Analysis Set. The PK concentration and parameter listings will be presented for the Safety Analysis Set and will include all reportable individual PK results. Individual PK concentration and parameter data for any subjects not included in the PK Analysis Set or excluded from the

descriptive summary tables, figures and/or inferential statistical analyses will be included in the listings and flagged with an appropriate footnote.

Tables, listings and figures for PK concentration and PK parameter data will be presented according to the most recent version of the AZ CPE TFL standards, that includes applicable descriptive statistics, handling of individual concentrations below the LLOQ for listings, descriptive statistics and figures, and precision and rounding rules for concentrations and PK parameter data.

10.9.2.1. Plasma Concentration Data

A listing of individual PK blood sample collection times, derived sampling time deviations and concentrations for all analytes at each protocol scheduled time point will be presented for all subjects in the Safety Analysis Set. Listings will be presented by Treatment and Visit.

For each analyte, plasma concentrations for each scheduled time point will be summarized by Treatment and Visit using appropriate descriptive statistics. Individual concentrations with collection time deviations of greater than ± 10% from the protocol scheduled time will be used in the PK analysis but will be flagged for exclusion from the summary tables and corresponding figures.

Protocol scheduled times will be used to present the PK concentration summary tables and corresponding geometric mean concentration-time figures.

10.9.2.2. Pharmacokinetic Parameter Data

All reportable PK parameters, including diagnostic parameters, will be listed for the Safety Analysis Set for each subject by treatment, where treatments are pooled across periods and visit, for each analyte separately.

All PK parameters will be summarized for the PK Analysis Set separately for each analyte by treatment, where treatments are pooled across periods, using appropriate descriptive statistics.

Three values are required as a minimum for PK parameters to be summarized. Two values are presented as a min and max with the other descriptive statistics as NC.

If 1 or more values for a given parameter is zero (or imputed with zero), then no geometric statistics will be calculated for that parameter and the results for geometric statistics will be set to NC.

10.9.2.3. Graphical Presentation of Pharmacokinetic Data

Data permitting, the following figures may be presented as appropriate:

! Figures for the gmean plasma concentration-time data (with ± gSD error bars) presented on both linear and semi-logarithmic scales (without ± gSD error bars) using scheduled post-dose time plotted separately for each analyte and all treatments overlaid on the same plot.

! Individual subject plasma concentration-time data for each analyte graphically presented separately on both linear and semi-logarithmic scales using actual time post-dose:

∀ By subject with all treatments for the same subject overlaid on the same plot

∀ Overlaying individual plots by treatment with all subject's data in the same treatment overlaid on the same plot (separate plots for each analyte/treatment)

! Individual Test/Reference Treatment Ratios for Cmax, AUCinf and AUClast plotted by parameter, to include the gmean ratio and 90% CI for each treatment comparison and each analyte separately.

All geometric mean plots or overlaying individual plots showing all subjects by treatment will be based on the PK Analysis Set. Individual plots by subject will be based on the Safety Analysis Set. Scatter plots for individual PK parameters versus treatment will present both summary and individual subject parameter data for each treatment including only subjects in the PK Analysis Set.

For consistency, the plasma concentration values used in the gmean concentration-time plots will be those given in the descriptive statistics summary table for each time point. Concentrations that are NQ will be handled as described for the descriptive statistics; if the gmean is NQ, the value plotted will be zero for linear plots and missing for semi-logarithmic plots. Any gmean ± gSD error bar values that are negative will be truncated at zero on linear concentration-time plots and omitted from semi-logarithmic plots.

10.9.3. Statistical Analysis of Pharmacokinetic Data

The relative bioavailability will be assessed between the test treatments and the reference treatment separately (CCI propellant [Treatment A] vs HFA propellant [Treatment C] and CCI propellant [Treatment B] vs HFA propellant [Treatment C]) separately for each analyte based on the PK Analysis Set.

For each analyte, the statistical analyses will be performed using a linear mixed-effects analysis of variance model using the natural logarithm of AUCinf, AUClast, and Cmax as the response variables, with sequence, period, treatment as fixed effects and subject nested within sequence as random effect. Pairwise statistical models will be fit to the data such that, the analysis for each comparison will be conducted excluding the data from the treatment that is not relevant for the comparison in question. For each analysis, transformed back from the logarithmic scale, geometric means together with the CIs (2-sided 95%) and the intra-subject CV for AUCinf, AUClast, and Cmax for each treatment will be estimated and presented. In

addition, ratios of geometric means together with CIs (2-sided 90%) will be estimated for each treatment comparison and presented. The 90% CI of the geometric mean ratios of the PK parameters will be evaluated against the standard bioequivalence range of 80.00% to 125.00%.

Additionally, the median difference in untransformed tmax between the test treatments and the reference treatment for each analyte and the 90% CIs for the median differences will be calculated using the non-parametric Hodges-Lehmann method.

10.10. Analysis of Safety Data

Safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, minimum, median, maximum) by treatment. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment. The analysis of the safety variables will be based on the Safety Analysis Set. However, the safety data for the replacement subjects may also be presented separately from the original subjects so as not to attenuate any potential safety signals stemming from less than full exposure to the investigational product.

Adverse events will be summarized by Preferred Term and SOC using MedDRA vocabulary. Furthermore, listings of SAEs and adverse events that led to withdrawal will be made and the number of subjects who had any AE, SAEs, AEs that led to withdrawal, and AEs with severe intensity will be summarized. SAEs will be recorded from time of informed consent.

Tabulations and listings of data for vital signs, clinical laboratory tests, digital ECG and 12-lead safety ECGs (listings only), telemetry (listings only) and spirometry will be presented. Results from the taste assessment will be presented separately in listings only. Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE. Data will be summarized for the observed values at each scheduled assessment, together with the corresponding changes from the baseline when baseline is defined. Clinical laboratory data will be reported in Système International units in the CSR.

Out-of-range values for safety laboratory assessments will be flagged in individual listings as well as summarized descriptively using agreed standard reference ranges and/or extended reference ranges (eg, AZ, program, or laboratory ranges).

10.10.1. Adverse Events

All AEs will be coded using the latest version of the MedDRA vocabulary and will be listed for each subject. Adverse events with a start date and time before dosing in Treatment Period 1 will be captured as medical history.

Adverse events will be assigned to a treatment based on the start date/time of the AE in relation to dosing in that period; for tabulation purposes the AE will then be assigned to the treatment received in the respective treatment period as follows:

! Treatment Period 1: AEs with start date/time at the time of or after dosing in Treatment Period 1 until the time of dosing in Treatment Period 2.

! Treatment Period 2: AEs with start date/time at the time of or after dosing in Treatment Period 2 until the time of dosing in Treatment Period 3.

! Treatment Period 3: AEs with start date/time at the time of or after dosing in Treatment Period 3 until the final follow-up visit.

Adverse events with missing start dates/times will be handled as follows:

! If the start date is completely missing but the end date is known and shows that the AE ended on or after the first dose date, then the start date will be imputed as the first day of dosing; if the end date is known and shows that the AE ended before the first dose date, then the screening date will be used for the start date. If the end date is non-informative (ie, is missing or does not contain enough information), the start date will be imputed as the first date of dosing;

! If only the start day is missing the day will be imputed as the first day on which a dose was given in that month unless the end date is known and shows that the AE ended before a dose was given in that month; in which case the date will be imputed as 01. If the end date is non-informative (ie, is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known month. If the month is not a dosing month the date will be imputed as 01;

! If the start day and month are missing the date will be imputed as the first day of dosing in the known year unless the end date is known and shows that the AE ended before a dose was given in that year; in which case the start day and month will be imputed as 01Jan or with the date of screening if this is later. If the end date is non-informative (ie, is missing or does not contain enough information), the start date will be imputed as the first date of dosing in the known year. If the year is not a year of dosing then the date will be imputed as 01Jan or with the date of screening if this is later;

! Missing times will be imputed as 00:00 h or with the time of dosing for events starting on a dosing day.

For purposes of the AE summaries, the following will apply:

! AEs with unknown intensity will be treated as “severe” for the tabulations.

! AEs with unknown relationship will be treated as "related" for the tabulations.

! AEs with unknown seriousness will be treated as "serious" for the tabulations.

There will be no imputation of AE data for the data listings. All data will be listed as recorded in the CRFs.

Adverse events with onset (start date/time) after dosing in Treatment Period 1, up to and including the final follow-up visit, will be summarized by treatment (where treatments will be pooled across treatment periods) and overall for all subjects, including tabulations by causality and severity (mild, moderate and severe). All tabulations will be presented by SOC and Preferred Term using MedDRA vocabulary, with the exception of the causality and severity (mild, moderate and severe) tables, which will be presented by Preferred Term only.

All tabulations will include the number and percentage of subjects. In addition, a separate tabulation will be presented showing the number of events by treatment and Preferred Term.

Finally, an overview summary of all AEs will be presented, separately for the number and percentage of subjects and the number of events. This will include categories for any AE, AEs that led to discontinuation, AEs with outcome of death, and SAEs.

Adverse events will be listed by subject and treatment and the following information will be included in the listings: verbatim term, SOC, Preferred Term and lowest level term, start date/time, end date/time, time from last dose, causality, action taken, whether the AE was classified as serious and the outcome. Furthermore, separate listings of SAEs, DAEs and AEs that led to death will be presented.

10.10.2. Vital Signs

The results of the vital signs measurements (including SpO_2) will be listed by subject and time point including the date/time of the assessment, changes from baseline and repeat/unscheduled measurements. The baseline for vital signs measurements will be the last pre-dose assessment on Day 1 in each treatment period. Descriptive statistics will be presented by treatment (where treatments will be pooled across treatment periods) and time point for both observed values and changes from baseline, for all post baseline time points, excluding the follow-up visit.

10.10.3. Electrocardiograms

10.10.3.1. Resting 12-lead Electrocardiogram

12-Lead ECG results will be listed for each subject with overall interpretation by the PI as "Normal", "Abnormal CS" and "Abnormal NCS".

10.10.3.2. Digital Electrocardiogram (dECG)

From the dECG data, the following parameters will be derived:

! QTcF will be calculated as $QTcF = QT*RR^{-1/3}$, where the QT interval is in milliseconds and the RR interval is in seconds.

! Heart rate will be calculated, based on the RR interval as HR = 60/RR interval, where the RR interval is in seconds.

Calculation of derived parameters will be performed after smoothing of QT and RR data.

The dECG data will be smoothed on an individual basis before performing the derivations above and prior to calculation of any changes from baseline or descriptive statistics. For each subject it will be done as follows: the mean value of all the measurements will be taken provided that at least 4 measurements are present and the time between the first and last is greater than 2.75 minutes or else, the smoothed value at the corresponding target time point will be set to missing.

Digital ECG results will be listed by treatment for each subject and time point and will include all individual and smoothed values of PR, RR, QRS, QT interval, and the derived values of QTcF and HR. All smoothed and derived parameters will have changes from baseline derived and presented.

Descriptive statistics will be presented by treatment and time point for smoothed values and changes from baseline of smoothed values of PR, RR, QRS, QT; derived values and changes from baseline for QTcF and HR will also be included. The baseline for the dECG measurements will be the (smoothed) pre-dose assessment on Day 1 in each treatment period.

Outliers with respect to QTcF will also be tabulated for the following categories:

! Absolute value > 450 ms and ≤ 480 ms

! Absolute value > 480 ms and ≤ 500 ms

! Absolute value > 500 ms

! Increase from baseline > 30 ms and ≤ 60 ms

! Increase from baseline > 60 ms

All calculations of dECG parameters and reporting described in this section will be performed by Parexel.

10.10.3.3. Real-Time ECG (Cardiac Telemetry)

Cardiac telemetry results will be listed including overall assessment, specifics of abnormalities and the start and stop date/time.

10.10.4. Physical Examination and Body Weight

The baseline/screening results of the physical examination will be documented in medical history for each subject.

Any new or aggravated clinically relevant abnormal medical physical examination finding compared to the baseline assessment will be reported as an AE.

Body weight will be listed by subject and time point.

10.10.5. Laboratory Assessments

Hematology and clinical chemistry values will be listed by subject and time point including changes from baseline and repeat/unscheduled measurements. Summary tabulations including absolute value and changes from baseline to 24 hours post-dose will be presented by treatment and time point for the Safety Analysis Set. The baseline for the measurements will be the Day -1 assessment performed prior to dosing in each treatment period.

Any laboratory parameters with results from the laboratory given as "< xx" or "> xx" in the database will be imputed with the absolute value of the number without the sign (eg, < 2.2 will be imputed as 2.2) for the descriptive statistics and changes from baseline.

The listings will include the following information: test name, date of measurement, reference range, result and flags for any measurements that are outside the reference range (eg, AstraZeneca, program, or laboratory ranges). Clinical laboratory data will be reported in System International units in the CSR.

Additional listings will be presented for the following:

! Urinalysis (macroscopic and microscopic, if applicable)

! The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

10.10.6. Additional Safety Variables

10.10.6.1. Spirometry

Spirometry results will be listed by subject and time point, including changes from baseline and repeat/unscheduled measurements. Summary tabulations including absolute value and changes from baseline will be presented by treatment and time point for the Safety Analysis

Set. The baseline for the measurements will be the pre-dose assessment performed on Day 1 in each treatment period.

10.10.6.2. Taste Assessment

The results of the taste assessment will be listed for each subject and treatment, where applicable.

10.11. Analysis of Exploratory Data

Not applicable.

11. ADVERSE EVENTS

11.1. Definitions

11.1.1. Definition of Adverse Events

An AE 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 unfavorable and unintended sign (eg, 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.

11.1.2. Definitions of Serious Adverse Event

A SAE is an AE occurring during any study phase (ie, run-in, treatment, washout, follow-up), that fulfills one or more of the following criteria:

! Results in death

! Is immediately life-threatening

! Requires in-patient hospitalization or prolongation of existing hospitalization

! Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions

! Is a congenital abnormality or birth defect

! Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.

For further guidance on the definition of a SAE, see Appendix A of this CSP.

Adverse Events for malignant tumors reported during a study should generally be assessed as SAEs. If no other seriousness criteria apply, the 'important medical event' criterion should be used. In certain situations, however, medical judgment on an individual event basis should be applied to clarify that the malignant tumor event should be assessed and reported as a NonSerious AE. For example, if the tumor is included as medical history and progression occurs during the study, but the progression does not change treatment and/or prognosis of the malignant tumor, the AE may not fulfill the attributes for being assessed as serious, although reporting of the progression of the malignant tumor as an AE is valid and should occur. Also, some types of malignant tumors, which do not spread remotely after a routine treatment that does not require hospitalization, may be assessed as Non-Serious; examples include Stage 1 basal cell carcinoma and Stage 1A1 cervical cancer removed via cone biopsy.

11.1.3. Other Significant Adverse Events

During the evaluation of the AE data, an AstraZeneca medically qualified expert will review the list of AEs that were not reported as SAEs or where relevant DAEs and withdrawal from the study. Based on the expert's judgment, significant AEs of particular clinical importance may, after consultation with the Global Safety Physician, be considered OAEs and reported as such in the CSR. A similar review of other data from laboratory tests, vital signs, ECGs and other safety assessments will be performed for identification of OAEs.

Examples of these are marked hematological and other laboratory abnormalities, and certain events that lead to intervention (other than those already classified as serious), dose reduction or significant additional treatment.

11.2. Recording of Adverse Events

11.2.1. Time Period for Collection of Adverse Events

Adverse Events will be collected from the first dose of IMP throughout the treatment period up to and including the follow-up visit.

SAEs will be recorded from the time of informed consent.

11.2.2. Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the PI for as long as medically indicated, but without further recording in the ClinBase™.

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.

11.2.3. Variables

The following variables will be collected for each AE:

! AE diagnosis/description

! The date and time when the AE started and stopped

! Intensity

! Whether the AE is serious or not

! Principle Investigator causality rating against the investigational product (yes or no)

! Action taken with regard to IMP

! AE caused subject's withdrawal from study (yes or no)

! Outcome

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

! Date AE met criteria for serious AE

! Date PI became aware of serious AE

! Adverse Event is serious due to

! Date of hospitalization

! 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

The following intensity ratings will be used:

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 Section 11.1.2.

! 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. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE.

11.2.4. Causality Collection

The PI 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, any additional drug and study procedures. 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 A of this CSP.

11.2.5. 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 personnel: *"Have you had any health problems since you were last asked?"*, or revealed by observation will be collected and recorded in the ClinBase™.

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.

11.2.6. Adverse Events Based on Examinations and Tests

The results from protocol-mandated laboratory tests, vital signs, ECGs and other safety assessments will be summarized in the CSR.

Deterioration as compared to baseline in protocol-mandated laboratory values, vital signs, ECGs and other safety assessments should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the investigational product.

If deterioration in a laboratory value or vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result, or vital sign will be considered as additional information.

Wherever possible the reporting PI should use the clinical, rather than the laboratory term (eg, anemia versus low hemoglobin value).

In the absence of clinical signs or symptoms, clinically relevant deteriorations in nonprotocol-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.

11.2.7. Hy's Law

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

11.3. 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 ClinBase™.

If any SAE occurs in the course of the study, then PIs or other site personnel will inform appropriate AstraZeneca representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

The designated AstraZeneca representative will work with the PI 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 AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

PIs or other site personnel will inform AstraZeneca representatives of any follow-up information on a previously reported SAE immediately, or **no later than 24 hours** of when he or she becomes aware of it.

11.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the PI to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities toward 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 the local regulatory 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, IRB, and PIs.

For all studies except those utilizing medical devices investigator safety reports must be prepared for SUSAR according to local regulatory requirements and Sponsor policy and forwarded to PIs as necessary.

A PI who receives an investigator safety report describing a SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB, if appropriate according to local requirements.

12. LEGAL AND ADMINISTRATIVE ASPECTS

12.1. Archiving of Study Documents

All source documents generated in connection with the study will be retained in the limited access file storage area, respecting the privacy and confidentiality of all records that could identify the subjects. Direct access is allowed only for authorized people for monitoring and auditing purposes. Source documents will be handled, stored and archived according to in house procedures.

The Investigator's Site File will be archived by the CRO for 15 years after completion of the study.

12.2. Publication of Study Results

All of the study information and data collected during the study are confidential and the property of AstraZeneca. After completion of the study, AstraZeneca may prepare a joint publication with the PI. The PI must undertake not to submit any data from this CSP for publication without prior consent of AstraZeneca at a mutually agreed time.

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

12.3. Clinical Study Report

An integrated CSR will be prepared in accordance with the standards of the ICH guideline for structure and content of CSRs (ICH E3). Copies of the CSR will be provided to the IRB and the national regulatory authority in accordance with regulatory requirements and Parexel SOPs. In the event of premature termination of the study or other conditions specified in ICH E3, an abbreviated CSR may be prepared.

13. REFERENCE LIST

1 Investigator's Brochure, Budesonide, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (BGF MDI); Budesonide and Formoterol Fumarate Inhalation Aerosol

(BFF MDI); Budesonide Inhalation Aerosol (BD MDI); Glycopyrronium Inhalation Aerosol (GP MDI) (Also known as PT010 [BGF MDI], PT009 [BFF MDI], PT008 (BD MDI); PT001 (GP MDI); Edition Number 7.0, 27 May 2020.

2 Clinical Study Protocol: Addendum 1. Information for novel gaseous pMDI propellant, CCI Edition Number 1.0, 30 June 2020.

3 Clinical Study Protocol: Addendum 2. Information for novel gaseous pMDI propellant, CCI. Edition Number 1.0, 30 June 2020.

4 FDA Guidance for Industry 'Food-Effect Bioavailability and Fed Bioequivalence Studies'. December 2002. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/food-effectbioavailability-and-fed-bioequivalence-studies.

5 FDA Guidance for Industry 'Drug-induced liver injury: Premarketing clinical evaluation'. July 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf.

14. APPENDICES

Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event

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 (eg, hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a SAE, although the reasons for it may be (eg, bronchospasm, laryngeal edema). 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.

Important Medical Event or Medical Intervention

Medical and scientific judgment 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, hospitalization, disability or incapacity but may jeopardize the subject or may require medical intervention to prevent 1 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 judgment must be used.

Examples of such events are:

! Angioedema not severe enough to require intubation but requiring intravenous hydrocortisone treatment.

! Hepatotoxicity caused by paracetamol/acetaminophen overdose requiring treatment with N-acetyl cysteine.

! Intensive treatment in an emergency room or at home for allergic bronchospasm.

! Blood dyscrasias (eg, neutropenia or anemia requiring blood transfusion) or convulsions that do not result in hospitalization.

! Development of drug dependency or drug abuse.

A Guide to Interpreting the Causality Question

The following factors should be considered when deciding if there is a "reasonable possibility" that an AE may have been caused by the IMP.

! 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?

! Dechallenge 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 other etiology such as the underlying disease, other drugs, other host or environmental factors.

! Rechallenge experience:
Did the AE reoccur if the suspected drug was reintroduced after having been stopped?

Note: AstraZeneca would not normally recommend or support a rechallenge.

! 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.

Appendix B International Airline Transportation Association 6.2 Guidance Document

Labeling and Shipment of Biohazard Samples

International Airline Transportation Association classifies bio hazardous agents into 3 categories (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm). For transport purposes the classification of infectious substances according to risk groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). 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 for example, Ebola and Lassa Fever viruses. Category A pathogens:

Are to be packed and shipped in accordance with IATA Instruction 602.

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

! UN 3373 – Biological Substance, Category B

! Are to be packed in accordance with UN3373 and IATA Instruction 650.

Exempt refers to all other materials with minimal risk of containing pathogens.

! Clinical trial samples will fall into Category B or Exempt under IATA regulations.

! Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging. (http://www.iata.org/whatwedo/cargo/dangerous_goods/infectious_substances.htm)

! **Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.**

! International Airline Transportation Association compliant courier and packaging materials should be used for packing and transportation. Packing should be done by an IATA certified person, 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. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Actions Required in Cases of Combined Increase of Aminotransferase and Total Bilirubin - Hy's Law

C 1 Introduction

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

During the course of the study the PI will remain vigilant for increases in liver biochemistry. The PI 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 PI will also review AE data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The PI participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than DILI caused by the IMP.

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

C 2 Definitions

Potential Hy's Law (PHL)

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN at any point during the study following the start of study medication irrespective of an increase in ALP.

Hy's Law (HL)

Aspartate aminotransferase or ALT ≥ 3 × ULN **together with** TBL ≥ 2 × ULN, where no other reason, other than the IMP, can be found to explain the combination of increases, eg, elevated ALP indicating cholestasis, viral hepatitis, another drug.

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

C 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:

! Alanine aminotransferase ≥ 3 × ULN

! Aspartate aminotransferase ≥ 3 × ULN

! Total bilirubin ≥ 2 × ULN

The PI 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 Section C 2 for definitions) by reviewing laboratory reports from all previous visits.

! Promptly enter the laboratory data into the laboratory CRF module(s).

C 4 Follow-up

C 4.1 Potential Hy's Law Criteria not met

If the subject does not meet PHL criteria the PI 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 CSP.

C 4.2 Potential Hy's Law Criteria met

If the subject does meet PHL criteria the PI will:

! Notify the AstraZeneca representative who will then inform the central Study Team.

! Within 1 day of PHL criteria being met, the PI 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 PI is not required to submit a PHL SAE unless there is a significant change[#] in the subject's condition.

! The Study Physician contacts the PI, 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 PI 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 etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which of the tests available in the HL laboratory kit should be used (if applicable).
- Complete the 3 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 TBL) 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 PI, this may be in consultation with the Study Physician if there is any uncertainty.

C 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 PI 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 PI 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 module(s).

! If the alternative explanation is an AE/SAE: update the previously submitted PHL SAE and AE CRF entries 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 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 PHL, (report term now 'Hy's Law case') ensuring causality assessment is 'related to IMP' and the seriousness criterion 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.

REFERENCES

Aithal GP, Watkins PB, Andrade RJ, et al. Case definition and phenotype standardization in drug induced liver injury. Clinical Pharmacology & Therapeutics 2011;89(6):806–15.

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

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