Clinical Study Protocol

A Phase I, Randomized, Double-blind, Single-dose, Partial-replicate, 3-way Cross-over Study to Assess the Lung Exposure Bioequivalence of Budesonide, Glycopyrronium, and Formoterol Delivered by BGF MDI HFO Compared with BGF MDI HFA

Parexel Study No.:	PXL266498
Sponsor Study Code:	D5985C00005
IND No./Eudra CT No:	118313
Study Type:	Pharmacokinetics (PK)/Bioequivalence
Study Intervention (Test Product):	Budesonide/glycopyrronium/formoterol (BGF) metered dose inhaler (MDI) formulated with hydrofluoroolefin (HFO) propellant
Study Intervention (Reference Product):	BGF MDI formulated with hydrofluoroalkane (HFA) propellant
Therapeutic Indication:	Chronic Obstructive Pulmonary Disease
Pharmacological Class:	Corticosteroid/Long-acting muscarinic antagonist/Long-acting beta agonist
Development Phase:	Phase I
Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Manufacturer:	AstraZeneca AB 151 85 Södertälje Sweden
Study Center:	Parexel Early Phase Clinical Unit Baltimore Harbor Hospital 3001 S. Hanover St. Baltimore, MD 21225 USA
Date and Version of Original Protocol:	Final 1.0, 31 May 2022
Protocol Amendment No. 1	Final 2.0, 28 June 2022

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.

Confidentiality Statement

PROTOCOL AMENDMENTS

Protocol Amendment No. 1, dated 28 June 2022

The protocol was amended to allow subjects to stay in-house for the duration of the study, change the Follow-up Visit to a phone call, and update assessments.

- The synopsis was updated with regards to the study.
- Study Design (Section 3) and Schedule of Assessments (SoA) (Table 3-1):
  - Updated with subject's in-house stay.
  - Text updated from Follow-up Visit to Follow-up Phone Call.
  - Figure 3-1 updated with visits and Follow-up Phone Call.
  - The SoA Follow-up Visit assessments moved to Day 2 of Treatment Period 3 and separate Follow-up Phone Call column with assessments added.
  - Day -1 pregnancy test updated to either serum or urine test.
  - The SoA footnotes updated to clarify assessments.
- End of study (Section 3.1.2) definition updated to align with study design change.
- Risk assessment for COVID-19 pandemic (Section 3.3.1) sentence deleted.
- Exclusion criteria (Section 4.1.2) and study restrictions (Section 4.2) were updated to reflect in-house stay.
- Pregnancy testing (Section 4.2.1.2) was updated to include either serum or pregnancy testing as per SoA for Day -1.
- Concomitant and post-study treatment(s) (Section 5.5) updated to exclude restricted medications and the required cessation period.
- Reference to the Declaration of Helsinki (Section 8.1) was updated to the latest version.
- Text was updated from Follow-up Visit to Follow-up Phone Call (Section 4.2, Section 5.9, Section 6.3.1.4, and Section 10.1.1).
- Calculation or derivation of pharmacokinetic parameters (Section 10.2.2) was updated to include detailed information.
- General principles for statistical analysis (Section 11.2.1) text was updated to reflect last assessment visit.
- Pharmacokinetics (Section 11.2.6) parameters updated to align in the document.
- Reference list (Section 14) information updated.

PROTOCOL SYNOPSIS

Title of the Study
A Phase I, randomized, double-blind, single-dose, partial-replicate, 3-way cross-over study to assess the lung exposure bioequivalence of budesonide, glycopyrronium, and formoterol delivered by BGF MDI HFO compared with BGF MDI HFA

Principal Investigator (PI)
PPD

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

Parexel Early Phase Clinical Unit Baltimore
Harbor Hospital
3001 S. Hanover St.
Baltimore, MD 21225
USA

Study Rationale
This study will be conducted to demonstrate that budesonide/glycopyrronium/formoterol metered dose inhaler with hydrofluoroolefin (BGF MDI HFO) provides equivalent total lung exposure for budesonide, glycopyrronium, and formoterol compared with the currently approved BGF MDI with hydrofluoroalkane (BGF MDI HFA).
A randomized, double-blind, single-dose, cross-over, partial-replicate study design has been chosen to prevent bias in allocation of treatments in each Treatment Period, to minimize any bias from the subjects, investigator, or sponsor that may affect the study results, and to allow determination of within-subject variability and possible expansion of the bioequivalence criteria limits.

Number of Subjects Planned
A total of 108 subjects will be randomized to ensure at least 96 evaluable subjects.

Study Period
Estimated date of first subject enrolled: July 2022 (signing of informed consent)
Estimated date of last subject completed: March 2023

Study Objectives
The objectives of the study are:
Primary Objective:

- To assess the bioequivalence of the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI HFO compared with BGF MDI HFA.

Secondary Objectives:

- To characterize the pharmacokinetic (PK) profiles of budesonide, glycopyrronium, and formoterol administered as BGF MDI HFO and BGF MDI HFA with oral activated charcoal.
- To assess the safety and tolerability of single doses of BGF MDI HFO and BGF MDI HFA with oral activated charcoal in healthy subjects.

Exploratory Objective:

- Not applicable

Study Design

This is a Phase I, randomized, double-blind, single-dose, single-center, partial-replicate, 3-way cross-over study to assess the PK and safety of BGF MDI in healthy subjects (male or female). Pharmacokinetic profiles of each active ingredient (budesonide, glycopyrronium, and formoterol), will be determined after administration of BGF MDI HFO (test) and BGF MDI HFA (reference) following an overnight fast of at least 8 hours.
Each subject will receive 3 single-dose treatments of BGF MDI:

- Treatment A: BGF MDI HFO 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - test formulation; administered during 1 Treatment Period.
- Treatment B: BGF MDI HFA 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - reference formulation; administered during 2 Treatment Periods.

Subjects will receive treatments in 1 of 3 possible treatment sequences: ABB, BAB, or BBA. The reference formulation will be administered during 2 of the 3 Treatment Periods in order to estimate intra-subject variability.
The study will comprise:

- Screening period: up to 28 days prior to first dosing;
- Three Treatment Periods: subjects will be resident in the Clinical Unit from the morning on the day before dosing with BGF MDI (Day -1 of Treatment Period 1), until 24 hours following the final dose (Day 2 of Treatment Period 3 a washout period of 3 to 7 days between each dose; and
- Follow-up: final outpatient safety Follow-up Phone Call within 3 to 7 days after the last administration of BGF MDI in Treatment Period 3.

Expected Duration of the Study

Each subject will be involved in the study for up to 55 days.

Targeted Study Population

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

Study Intervention

Arm name	BGF MDI HFO	BGF MDI HFA
Intervention name	Budesonide / Glycopyronium / Formoterol fumarate pressurized inhalation suspension, HFO	Budesonide / Glycopyronium / Formoterol fumarate pressurized inhalation suspension, HFA
Type	Combination product	Combination product
Dose formulation	MDI	MDI
Unit dose strength(s) (Delivered dose)	160/7.2/4.8 µg per actuation	160/7.2/4.8 µg per actuation
Dosage level(s)	4 inhalations	4 inhalations
Route of administration	Oral inhalation	Oral inhalation
Use	Experimental	Comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and labeling	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirements	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirements

BGF = budesonide, glycopyrronium, formoterol; HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; IMP = Investigational Medicinal Product; MDI = metered dose inhaler; NIMP = Non-investigational Medicinal Product.

Dosing instructions and dispensing details will be provided by AstraZeneca.
Budesonide, glycopyrronium, and formoterol metered dose inhaler is a combination product (drug + device).

Outcome Endpoints

Safety and Tolerability Endpoints:

Safety and tolerability variables will include

- Adverse events (AEs) / Serious adverse events (SAEs)
- Vital signs (systolic and diastolic blood pressure [BP], pulse rate, body temperature, and respiratory rate)
- 12-lead electrocardiograms (ECGs)
- Physical examination
- Laboratory assessments (hematology, clinical chemistry, and urinalysis).

Viral serology and drugs of abuse, alcohol, and cotinine will be assessed for eligibility. Follicle-stimulating hormone (females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

Pharmacokinetic Endpoints:
Where possible, PK parameters will be assessed for budesonide, glycopyrronium and formoterol.

- Primary PK parameters: AUCinf, AUClast, Cmax
- Secondary PK parameters: tmax, λz, t½λz, MRTinf, CL/F and Vz/F

Additional PK parameters may be determined where appropriate.

Exploratory Endpoints:

- Not applicable

Statistical Methods
Presentation and Analysis of Pharmacokinetic Data:
Plasma concentrations for each analyte (budesonide, glycopyrronium and formoterol) will be listed by treatment occasion, subject, and time point. Plasma concentrations will also be summarized by treatment occasion and for each analyte using protocol scheduled times and appropriate descriptive statistics.
For each analyte, individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale with all treatment occasions overlaid on the same plot and separate plots for each subject. Combined individual plasma concentration versus actual times will be plotted in linear and semi-logarithmic scale for each treatment occasion and analyte.
Geometric mean plasma concentration (± geometric standard deviation) versus nominal sampling time will be plotted in linear and semi-logarithmic (no standard deviation [SD] presented) scale with all treatment occasions overlaid on the same figure.
Plasma PK parameters will be listed and summarized using descriptive statistics for each treatment occasion and analyte. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric co-efficient of variation, arithmetic mean, arithmetic SD, median, minimum, and maximum. For tmax, only n, median, minimum, and maximum will be presented.
The statistical analysis will be performed for the PK analysis set. Pharmacokinetic parameters will be calculated using non-compartmental analysis.
Bioequivalence will be assessed between test treatment BGF MDI HFO and reference treatment BGF MDI HFA, based on the PK analysis set.

Presentation and Analysis of Safety and Eligibility Data:
All 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 group. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment /dose group. 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 the discontinuation of investigational medicinal product (IMP; DAE) will be made and the number of subjects who had any AEs, SAEs, DAEs, 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, ECGs, will be presented. 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 (and/or percentage change) 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 will be flagged in individual listings as well as summarized descriptively using agreed reference ranges (eg, laboratory ranges).

Determination of Sample Size

The sample size for this study was based on the precision in estimating the primary PK parameters AUCinf, AUClast, and Cmax of BGF MDI HFA.
Among the analytes, glycopyrronium has the highest Cmax intra-subject co-efficient of variation at [redacted]%, estimated from a previous single-dose BGF spacer study in healthy volunteers. In studies with higher intra-subject variability larger absolute differences between the logarithmic means can be observed and so a true geometric mean ratio (GMR) of [redacted] is assumed. Given the above assumptions, a sample size of 96 subjects would provide 90% probability of obtaining a 90% confidence interval within the expanded limits of 69.84% to 143.19% for Cmax or the fixed limits of 80% to 125% for AUClast and AUCinf, and a GMR estimate within the bounds of 80% to 125%. To account for a 10% dropout rate 108 subjects will be randomized to achieve at least 96 evaluable subjects.
The number of subject identifiers generated for the study will account for the number of randomized subjects per the sample size calculation (N = 108). For this study, a total of 108 subject identifiers will be randomly assigned to 1 of 3 possible treatment sequences: ABB, BAB, BBA.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Please note: definitions of abbreviations for pharmacokinetic variables are presented in Section 10.2.1 of this protocol.

Abbreviation or special term	Explanation
ABE	average bioequivalence
ADE	Adverse device effect
AE	Adverse event (see definition in Section 6.3.1.1)
AIM	Aerosol inhalation monitor
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BGF	Budesonide, glycopyrronium, formoterol
BLQ	Below the limit of quantification
BMI	Body mass index
BP	Blood pressure
bpm	Beats per minute
CI	Confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
ClinBase™	Parexel's electronic source data capturing and information management system
COPD	Chronic obstructive pulmonary disease
CRF	Case report form
CRO	Contract research organization
CRP	C-reactive protein
CSP	Clinical study protocol
CSR	Clinical study report
CV	Co-efficient of variation
DAE	Adverse event leading to the discontinuation of IMP
DCF	Data clarification form
DMC	Data monitoring committee
DMP	Data management plan
DNA	Deoxyribonucleic acid
DSPC	1,2-distearoyl sn glycero 3-phosphocholine and calcium chloride
DVS	Data validation specification
ECG	Electrocardiogram
EDC	Electronic data capture

Abbreviation or special term	Explanation
EU	European Union
FDA	Food and Drug Administration
FEV1	Forced expiratory volume in the first second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma glutamyl transpeptidase (transferase)
GMP	Good Manufacturing Practice
GWP	Global warming potential
Hb	Hemoglobin
HBsAg	Hepatitis B surface antigen
HCT	Hematocrit
HFA	hydrofluoroalkane
HFO	hydrofluoroolefin
HIV	Human immunodeficiency virus
HL	Hy's Law
IATA	International Airline Transportation Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICS	Inhaled corticosteroid
IDMC	Independent data monitoring committee
IEC	Independent Ethics Committee
Ig	Immunoglobulin
INR	International normalized ratio
IMP	Investigational medicinal product
IRB	Institutional Review Board
LABA	Long-acting β2 agonist
LAMA	Long-acting muscarine agonist
LLN	Lower limit of normal
LLOQ	Lower limit of quantification
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MDI	Metered dose inhaler
MDR	Medical Device Regulation

Abbreviation or special term	Explanation
MDT	Mean dissolution time
MedDRA	Medical Dictionary for Regulatory Activities
n	Number of subjects
NC	Not calculated
NGP	Next generation propellant
NIMP	Non-investigational medicinal products
NOAEL	No-observed-adverse-effect level
NQ	Not quantified
NR	No result
OAE	Other significant adverse events
OTC	Over-the-counter
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
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected for heart rate using Fridericia's formula
RBC	Red blood cell
RR	The time between corresponding points on 2 consecutive R waves on ECG
RSABE	Reference-scaled average bioequivalence
SADE	Serious adverse device effect
SAE	Serious adverse event (see definition in Section 6.3.1.2).
SAP	Statistical Analysis Plan
SD	Standard deviation
SoA	Schedule of assessments
SOC	System Organ Class
SOP	Standard operating procedure
SRC	Safety Review Committee
SUSAR	Suspected unexpected serious adverse reaction
swr	within-subject standard deviation
TBL	Total bilirubin

Abbreviation or special term	Explanation
TCA	Tricyclic anti-depressant
TOST	Two one-sided test
TSH	Thyroid stimulating hormone
UADE	Unanticipated adverse device effect
UK	United Kingdom
ULN	Upper limit of normal
USA	United States of America
USADE	Unanticipated serious adverse device effect
WAD	Windows Allowance Document
WBC	White blood cell

INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Sponsor:	AstraZeneca AB 151 85 Södertälje Sweden
Sponsor's Lead Physician:	PPD
Sponsor's Biostatistician:	PPD
Principal Investigator:	PPD Parexel Early Phase Clinical Unit Baltimore Harbor Hospital 3001 S. Hanover St. Baltimore, MD 21225 USA PPD PPD
Contract Research Organization:	Parexel Early Phase Clinical Unit Baltimore Harbor Hospital 3001 South Hanover St. Baltimore, MD 21225 USA Tel: +1 410-350-7979 Fax: +1 410-354-4281
Clinical Laboratory:	All laboratories used to analyze samples taken for this study will be detailed in the Laboratory Manual
Analytical Laboratory: (pharmacokinetic sample analysis)	All laboratories used to analyze samples taken for this study will be detailed in the Laboratory Manual
Adverse Event Reporting:	AstraZeneca Patient Safety Data Entry Site Tata Consultancy Services Fax: +1 301 5765375 or +1 301 3988009 E-mail: AEMailboxClinicalTrialTCS@astrazeneca.com

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

1. INTRODUCTION

1.1. Background Information

AstraZeneca has developed BGF MDI HFA as a maintenance treatment in adult patients with COPD with moderate to severe airflow obstruction who are not adequately treated by a combination of an ICS and a LABA or a combination of a LABA and a LAMA.

The drug substances in BGF MDI HFA are budesonide, glycopyrronium bromide (glycopyrrolate), and formoterol fumarate dihydrate. Budesonide is a synthetic glucocorticoid receptor agonist with well-established anti-inflammatory properties that exhibits potent glucocorticoid and weak mineralocorticoid activity. Glycopyrronium bromide is a synthetic LAMA, and glycopyrronium is the active moiety of this bromide salt form (9 µg of glycopyrronium bromide is equivalent to 7.2 µg of glycopyrronium). Glycopyrronium exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Formoterol fumarate dihydrate is a synthetic LABA used as its fumarate salt in dihydrate form (5 µg of formoterol fumarate dihydrate is equivalent to 4.8 µg of formoterol fumarate). Formoterol fumarate is a potent and selective LABA that acts locally in the lung as a bronchodilator when inhaled. Formoterol fumarate stimulates β2 adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction. More information on budesonide, glycopyrronium, and formoterol fumarate can be found in the Investigator's Brochure.

The BGF MDI HFA product is formulated with HFA-134a propellant, a liquified compressed gas, in which the budesonide, glycopyrronium bromide, and formoterol fumarate dihydrate are suspended. HFA-134a is a common propellant in pharmaceutical MDI products that provides the force to generate an aerosol to deliver a product inhalation or dose. This drug product is an 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 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. More information on the BGF MDI HFA product is described in the Investigator's Brochure.

The current HFA propellant 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 an NGP that has much lower GWP will allow patients to continue to use MDI type treatments while contributing to AstraZeneca's sustainability efforts.

Development of BGF MDI HFO Product

In an effort to reduce the carbon footprint of the BGF MDI HFA product, AstraZeneca has investigated replacements for HFA-134a propellant with a focus on lower GWP materials with similar properties to HFA-134a to mitigate any impact on the MDI drug product performance, stability, and robustness. AstraZeneca has identified HFO-1234ze propellant as a suitable for replacement of HFA-134a in the BGF MDI HFA product. HFO-1234ze has a near zero GWP and very low photochemical reactivity. In addition, it has very similar physical properties to HFA-134a which will ensure comparable performance of the BGF MDI product. HFO-1234ze, which is available for industrial uses such as refrigeration, has been further purified by the manufacturer by fractional distillation to provide a suitable grade propellant for clinical studies.

A comprehensive nonclinical toxicology program that includes a range of studies to support HFO-1234ze regulatory applications is well advanced. Further information on HFO-1234ze can be found in Appendix A of the Investigator's Brochure.

Additionally, 1 clinical study (D5985C00001) assessing the relative bioavailability between 3 BGF MDIs formulated with 3 different propellants, ie, HFO (test), HFC (test) and HFA (reference), in healthy male adults (age 18 to 60 years) has been completed. Systemic exposure to budesonide, glycopyrronium, and formoterol was similar for BGF MDI HFO, BGF MDI HFC and the reference product BGF MDI HFA. Safety and tolerability data from the study did not raise any safety concerns. There were no deaths, SAEs, or AEs that led to discontinuation of BGF MDI reported during the study. There were no notable differences between the treatments given regarding number of volunteers reporting AEs, number of events, assessed relationship, or severity. No clinically relevant trends were observed for vital signs, physical examination, laboratory results, spirometry, and taste assessment, and no abnormal clinically significant 12-lead safety and digital ECG, as well as cardiac telemetry findings were reported. The combination of BGF when administered as single doses in 3 different propellant formulations demonstrated an acceptable safety profile and was well tolerated in the studied population.

The aim of the current study is to assess the bioequivalence of the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI HFO compared with BGF MDI HFA.

1.2. Rationale for Conducting this Study

The current propellant in BGF MDI HFA (HFA-134a) is known to have a relatively high GWP compared to CO_2 and contributes substantially to AstraZeneca's carbon footprint. In order to address this issue, AstraZeneca is evaluating a potential alternative propellant, HFO, with a much lower GWP which will allow patients to continue to use MDI type treatments

while contributing to AstraZeneca's sustainability efforts. As part of the clinical development program for gaining regulatory approval of BGF MDI HFO, this study is being conducted to demonstrate that it provides equivalent lung exposure for budesonide, glycopyrronium, and formoterol compared with the currently approved BGF MDI HFA.

2. STUDY OBJECTIVES

2.1. Primary Objective

Table 2-1 Primary Objective and Outcome Measures

Primary Objectives	Outcome Measures
To assess the bioequivalence of the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI HFO compared with BGF MDI HFA	Cmax, AUCinf, and AUClast for test and reference treatment

2.2. Secondary Objectives

Table 2-2 Secondary Objectives and Outcome Measures

Secondary Objectives	Outcome Measures
To characterize the PK profiles of budesonide, glycopyrronium, and formoterol administered as BGF MDI HFO and BGF MDI HFA with oral activated charcoal	tmax, λz, t½λz, MRTinf, CL/F and Vz/F
To assess the safety and tolerability of single doses of BGF MDI HFO and BGF MDI HFA with oral activated charcoal in healthy subjects	• AEs and SAEs • Laboratory assessments (hematology, clinical chemistry, and urinalysis) • Physical examination • 12-lead ECGs • Vital signs (systolic and diastolic BP, pulse rate, body temperature, and respiratory rate)

Refer to Section 10.2 for PK variables, and Section 6.3 for safety variables.

2.3. Exploratory Objectives

Not applicable.

3. STUDY DESIGN

3.1. Overall Study Design and Flow Chart

This is a Phase I, randomized, double-blind, single-dose, single-center, partial-replicate, 3-way cross-over study to assess the PK and safety of BGF MDI in healthy subjects (male or female). Pharmacokinetic profiles of each active ingredient (budesonide, glycopyrronium, and formoterol) will be determined after administration of BGF MDI HFO (test) and BGF MDI HFA (reference). The study will comprise:

- A screening period up to 28 days prior to first dosing;
- Three Treatment Periods: subjects will be resident at the Clinical Unit from the morning on the day before dosing with BGF MDI (Day -1 of Treatment Period 1), until 24 hours following the final dose (Day 2 of Treatment Period 3) with a washout period of 3 to 7 days between each dose; and
- Follow-up: final outpatient safety Follow-up Phone Call within 3 to 7 days after the last administration of BGF MDI in Treatment Period 3.

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

- Treatment A: BGF MDI HFO 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - test formulation; administered during 1 Treatment Period.
- Treatment B: BGF MDI HFA 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - reference formulation; administered during 2 Treatment Periods.

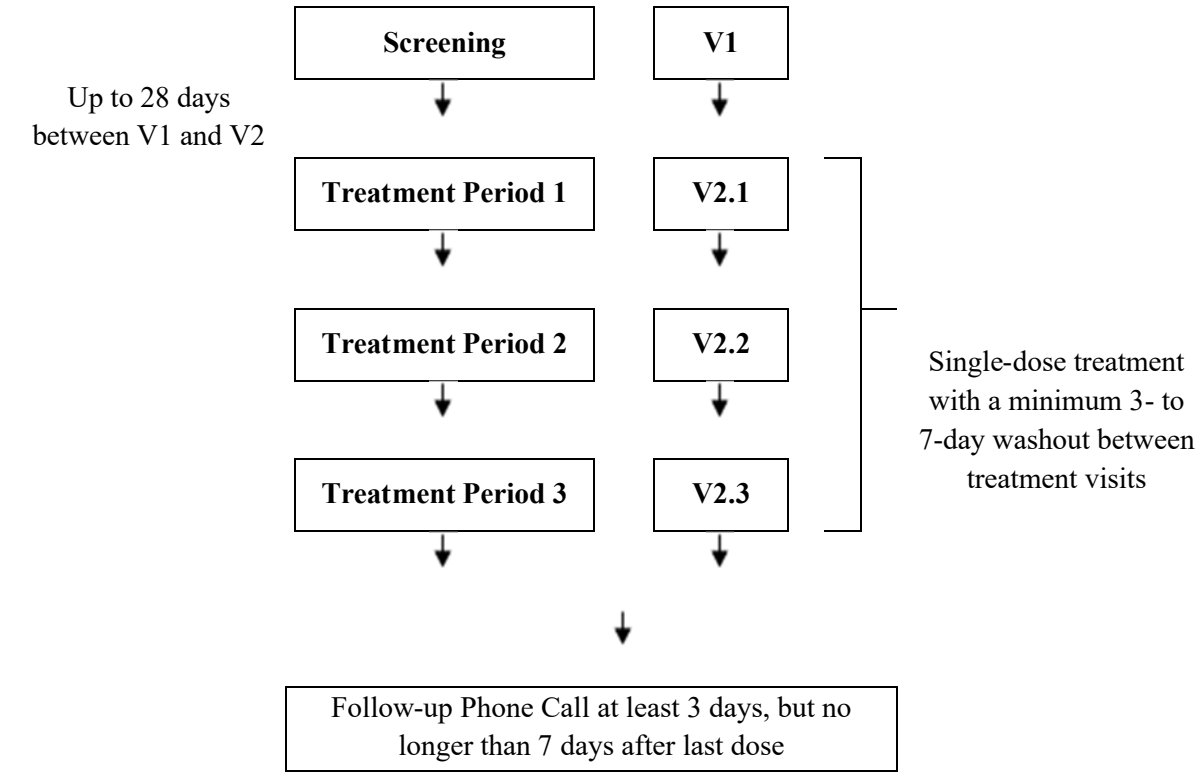
Subjects will receive treatments in 1 of 3 possible treatment sequences: ABB, BAB, or BBA. The reference formulation will be administered during 2 of the 3 Treatment Periods in order to estimate intra-subject variability.

A total of 108 healthy male and female subjects will be randomized to ensure at least 96 evaluable subjects.

Details of IMP administration are provided in Section 5.4.4.

The study flow-chart with the flow of events for all treatments, depending on the subject's assigned randomization (see Section 5.1) is presented in Figure 3-1. The SoA displaying assessments/tasks and time points is presented in Table 3-1.

Figure 3-1 Study Flow Chart



V = visit

Table 3-1 Schedule of Assessments

		Treatment Periods 1, 2, and 3 [a]			
	Screening	**Day -1**	**Day 1 to 2**	**Early Termination Visit (within 3 to 7 days post final dose)**	**Follow-up Phone Call (within 3 to 7 days post final dose)**
Informed Consent	X				
Assignment of enrollment number	X				
Inclusion/exclusion criteria	X	X [b]			
Demographic data	X				
Medical history	X				
Urinary drug/cotinine and serum alcohol screen	X	X [b]			
Concomitant medication		X	X	X	X
Serology	X				
COVID-19 testing	X	X [b]			
FSH (post-menopausal women only)	X				
Pregnancy testing (females only)	X (serum)	X (serum/urine)	X (urine) [c]	X (urine)	
Randomization			X (Day 1 of Treatment Period 1) [d]		
Study residency:					
Check-in		X (morning)			

		Treatment Periods 1, 2, and 3 [a]			
	Screening	**Day -1**	**Day 1 to 2**	**Early Termination Visit (within 3 to 7 days post final dose)**	**Follow-up Phone Call (within 3 to 7 days post final dose)**
Check-out			X Day 2 (24 hours post-dose in Treatment Period 3)		
Inhalation Practice Device and inhalation training with placebo and with AIM trainer	X	X	X (prior to dosing)		
IMP administration			Day 1 (0 hours of each Treatment Period)		
Oral activated charcoal administration			[redacted] g immediately before inhalation of IMP; [redacted] g immediately after mouth-rinsing (done within 5 minutes after the inhalation of IMP); [redacted] g 1 hour after inhalation of IMP; [redacted] g 2 hours after inhalation of IMP		
Safety and tolerability:					
Adverse events	X [e]	X	X	X	X
Vital Signs (BP, pulse rate, body temperature, and respiratory rate)	X	X	X	X	

		Treatment Periods 1, 2, and 3 [a]			
	Screening	**Day -1**	**Day 1 to 2**	**Early Termination Visit (within 3 to 7 days post final dose)**	**Follow-up Phone Call (within 3 to 7 days post final dose)**
12-lead ECG	X		X [c]	X	
Spirometry	X				
Clinical laboratory evaluations	X		X [c]	X	
Urinalysis	X		X [c]	X	
Physical examination	X	X [f]	X [c]	X	
Body weight	X		X [c]	X	
Pharmacokinetics					
Plasma for budesonide, glycopyrronium, and formoterol			pre-dose and 2, 5, 10, 20, 30, and 45 minutes post-dose, and 1, 2, 4, 8, 12 and 24 hours post-dose		

AIM = aerosol inhalation monitor; BP = blood pressure; COVID = corona virus disease; ECG = electrocardiogram; FSH = follicle-stimulating hormone; IMP = Investigational Medicinal Product; SAE = serious adverse event.

[a] There will be a 3 to 7-day washout period between each dose administration.
[b] Day -1 of Treatment Period 1.
[c] Assessments will only be performed on Day 2 Treatment Period 3 before subject is discharged from the Clinical Unit.
[d] Randomization can be done on the evening prior to the day of first dosing (Day -1 in Treatment Period 1).
[e] Serious adverse events will also be collected during screening.
[f] A brief physical examination will be performed.

3.1.1. 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. Another aspect for the proposed timing is that physiological assessments such as heart rate or BP as well as inquiring for AEs should not be accidentally influenced by physical interventions such as a venous puncture. The sequence at a particular time point is:

1 12-lead electrocardiograms
2 Vital signs (BP and pulse rate, body temperature, and respiratory rate)
3 PK blood sampling

Pre-dose assessments (except for pre-dose PK assessments) may be performed up to 60 minutes prior to dosing. In the event of a delay due to technical or logistical issues with the vital signs assessment, PK blood sampling should be prioritized.

Details of acceptable tolerance windows for safety and PK assessments will be included in a WAD which will be agreed upon and signed off before the start of the study.

3.1.2. End of Study

The end of study is defined as the last subject's Follow-up Phone Call from the Clinical Unit.

3.1.3. Expected Duration of the Study

Each subject will be involved in the study for up to 55 days.

Table 3-2 Expected Duration of Each Study Part

Screening	**Up to 28 days prior to first dosing.**
Treatment Periods 1, 2, and 3	Three Treatment Periods: Subjects will be resident at the Clinical Unit from the morning on the day before dosing with BGF MDI (Day -1 of Treatment Period 1) until (Day 2 of Treatment Period 3) 24 hours following the final dose, with 3- to 7-day washout periods.
Follow-up	Phone call within 3 to 7 days after the last administration of BGF MDI.
Total Duration	Up to 55 days.

BGF MDI = budesonide, glycopyrronium, formoterol metered dose inhaler.

3.2. Rationales for Study Design and Dose Selection

3.2.1. Rationale for Study Design

The primary objective of this study is to establish the lung-exposure bioequivalence for budesonide, glycopyrronium, and formoterol between BGF MDI HFO and BGF MDI HFA. For this reason, subjects will be randomized to prevent bias in allocation of treatments in each Treatment Period. The study is double-blind to minimize any bias from the subjects,

investigator, or sponsor that may affect the study results. A partial-replicate design, ie, reference product administered on 2 occasions will allow determination of within-subject variability and possible expansion of the bioequivalence criteria limits. The design of the study is consistent with regulatory guidance regarding the conduct of bioequivalence studies.

3.2.2. Dose Rationale

The dose to be administered (ie, 4 inhalations) is higher than the approved therapeutic dose (2 inhalations) in order to increase drug exposure and calculate reliable PK parameters.

This study will employ a partial-replicate design in which the reference treatment is administered on 2 occasions in order to assess within-subject variability and potentially widen the 90% CI limits (see Section 11).

BGF MDI HFA and BGF MDI HFO will both be administered with oral activated charcoal in order to block gastrointestinal absorption of budesonide, glycopyrronium, and formoterol, and provide an estimate of lung absorption.

3.3. Risk-benefit Assessment

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. Overall, BGF MDI is well tolerated, especially considering that this study includes only single-dose administrations.

Since the test product is a reformulation 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.
- Inhaler device of reformulated drug is same as previous inhaler.
- NGPs are not expected to be environmentally damaging.
- One clinical trial with the NGP-based products has been completed with acceptable safety results.

Hydrofluoroolefin (HFO)

Hydrofluoroolefin 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) toxicology studies. Refer to the Investigator's Brochure for more details on nonclinical studies with HFO.

Additionally, safety and tolerability data from the clinical study assessing the relative bioavailability between 3 BGF MDIs formulated with 3 different propellants (see Section 1.1), did not raise any safety concerns. The combination of BGF when administered as single doses

in 3 different propellant formulations demonstrated an acceptable safety profile and was well tolerated in the studied population.

The significant safety margins achieved in the toxicology studies, and the safety data from the clinical relative bioavailability study completed to date support the proposed clinical trial.

3.3.1. Risk Assessment for COVID-19 Pandemic

AstraZeneca is committed to supporting the safety and well-being of the study subjects, 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 subjects if applicable. As the COVID-19 situation evolves, investigators must use their best judgment to minimize risk to subjects 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 investigator 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 investigator 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 investigator's 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.
  - If applicable, all subjects will be 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.

3.3.2. Benefits

No benefit for individuals in this study is expected.

4. STUDY POPULATION

4.1. Selection of Study Population

The investigator 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.

This study will be conducted in healthy male and female subjects. The study may not necessarily be balanced regarding gender. The study was not formally powered to detect differences between genders for the primary endpoint. It is not planned to perform sub-analyses on gender.

4.1.1. 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 and/or female subjects aged 18 – 60 years with suitable veins for cannulation or repeated venipuncture.
3 Females must have a negative pregnancy test at screening and on admission to the unit, must not be lactating, confirmed at screening and fulfill the criteria detailed in Section 4.2.1.
4 Have a BMI between 18 and 35 kg/m^2 inclusive and weigh at least 50 kg and no more than 120 kg inclusive.
5 Subjects must have a FEV1 ≥ 80% of the predicted normal value and an FEV1/FVC > 70% regarding age, height, and ethnicity at the screening visit.
6 Subjects must demonstrate proper inhalation technique and have the ability to properly use an MDI device after training.

4.1.2. Exclusion Criteria

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

1 History of any clinically significant disease or disorder which, in the opinion of the investigator, may either put the volunteer at risk because of participation in the study, or influence the results or the volunteer's ability to participate in 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 clinically significant illness, medical/surgical procedure, or trauma within 4 weeks of the first administration of IMP.

4 History of narrow angle glaucoma not adequately treated and/or change in vision that may be relevant. All medications approved for control of intraocular pressures are allowed, including topical ophthalmic non-selective β-blockers and prostaglandin analogues.

5 History of 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 Unresectable cancer that has not been in complete remission for at least 5 years.
Note: Patients with squamous cell and basal cell carcinoma of the skin are allowed in the study.

7 Any clinically significant abnormalities in clinical chemistry, hematology, or urinalysis results, at screening as judged by the investigator.

8 Any clinically significant abnormal findings in physical examination, or vital signs at screening, as judged by the investigator.

9 Any clinically significant abnormalities on 12-lead ECG at screening, as judged by the investigator.
Note: Subjects with ECG QTcF interval (corrected for heart rate using Fridericia's formula [QTcF]) > 480 msec will be excluded. Subjects with high degree atrioventricular block II or III, or with sinus node dysfunction with clinically significant pauses who are not treated with a pacemaker will also be excluded.

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

11 Subject has a positive RT-PCR test for SARS-CoV-2 prior to randomization.

12 Subject 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.

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

14 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.

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

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

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

18 While admitted to the Clinical Unit, physical distancing and person-to-person contact restrictions will be applied and explained to subjects. Where physical distancing is not possible subjects 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.

19 Known or suspected history of drug abuse, as judged by the investigator.

20 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.

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

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

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

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

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

26 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.

27 Known or suspected history of alcohol or drug abuse or excessive intake of alcohol as judged by the investigator.

28 Excessive intake of caffeine-containing drinks or food (eg, coffee, tea, chocolate) as judged by the investigator. Excessive intake of caffeine defined as the regular consumption of more than 600 mg of caffeine per day (eg, > 5 cups of coffee) or would likely be unable to refrain from the use of caffeine-containing beverages during confinement at the investigational site.

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

30 Subjects who have previously received BGF MDI HFO.

31 Judgment by the investigator 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.

32 Subjects who cannot communicate reliably with the investigator.

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

4.2. 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 not lie fully 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 Phone Call.

4 Prior to each Treatment Period, subjects should abstain from alcohol for 72 hours prior to check-in until after their last PK sampling. Subjects should also abstain from alcohol for 72 hours before their final Follow-up Phone Call.

5 Prior to each Treatment Period, 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 after their Follow-up Phone Call.

7 During admission periods, 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 Phone Call 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 admission to the Clinical Unit.

Additional related restrictions may be implemented based on local guidance and/or Clinical Unit requirements.

For medication restrictions, please refer to Section 5.5.

4.2.1. Reproductive Restrictions

4.2.1.1. Women of Non-Childbearing Potential

Women of non-childbearing potential are defined as female subjects who are permanently surgically sterilized or post-menopausal.

Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy at least six weeks before screening but excludes bilateral tubal ligation. Bilateral oophorectomy alone is acceptable only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

Females are considered post-menopausal if they have had amenorrhea for at least 12 months or more following cessation of all exogenous hormonal treatments and without an alternative medical cause and the FSH level is in the post-menopausal range.

4.2.1.2. Women of Childbearing Potential

A woman is considered of childbearing potential, ie, fertile, following menarche and until becoming post-menopausal unless permanently sterile. Female subjects of childbearing potential must use one highly effective form of birth control. A highly effective method of contraception is defined as one that can achieve a failure rate of less than 1% per year when used consistently and correctly. At enrollment, WOCBP who are sexually active with a non-sterilized male partner should be stable on their chosen method of highly effective birth control, and willing to remain on the birth control until at least 14 days after last dose of study intervention. Cessation of contraception after this point should be discussed with a responsible physician. Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and lactational amenorrhea method are not acceptable methods of contraception. Female condom and male condom should not be used together. All WOCBP must have a negative serum pregnancy test result at Screening Visit.

Highly effective birth control methods are listed below:

- 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
- Vasectomized partner (only acceptable provided that partner is the sole sexual partner of the subject and that the vasectomized partner has received medical assessment of the surgical success)
- Sexual abstinence defined as complete abstinence from intercourse when it is the preferred and usual lifestyle of the subject (however, periodic abstinence eg, calendar, ovulation, symptothermal, post-ovulation methods, and withdrawal are not acceptable methods of contraception).

Pregnancy Testing

Women of childbearing potential can be included only after a negative highly sensitive serum pregnancy test. Additionally, serum or urine pregnancy testing will be done as per the SoA (Table 3-1).

Pregnancy

If the subject becomes pregnant during the study this should be reported to the investigator. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. The 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.

4.2.1.3. Male Subjects

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

4.3. Replacement of Subjects

Subjects who are withdrawn from the study due to any reason will not be replaced.

5. STUDY CONDUCT

5.1. Subject Enrollment and Randomization

The investigator 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 enrollment 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 in the evening prior to the day of or in the morning before first dosing (Day -1 or Day 1 of Treatment Period 1).

Randomization codes will be assigned sequentially as subjects become eligible for randomization (codes to be used without leading zero[s]). Randomization numbers will be generated within the AstraZeneca randomization system (Calyx).

The following specific format must be followed for unique enrollment number; reduced enrollment number "1001" in ClinBase™ and on labels, full enrollment number "E0001001" for outputs.

If a subject withdraws his/her participation in the study, then his/her enrollment/randomization code cannot be reused. For each treatment sequence, an additional set of random numbers will be generated with Calyx.

5.1.1. Procedures for Randomization

Upon completion of the randomization request form, the randomization will be produced by Calyx.

The number of subject identifiers generated for the study will account for the number of randomized subjects per the sample size calculation (N = 108, see Section 11.4). For this study, a total of n × 3 subject identifiers will be randomly assigned to 1 of 3 possible treatment sequences: ABB, BAB, BBA where:

- Treatment A: BGF MDI HFO 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - test formulation; administered during 1 Treatment Period.
- Treatment B: BGF MDI HFA 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal – reference formulation; administered during 2 Treatment Periods.

5.2. 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, who does not meet the selection criteria, has been dosed before the error is identified, the subject should be advised to continue safety assessments to ensure their safety.

5.3. Blinding and Procedures for Unblinding the Study

5.3.1. Methods for Ensuring Blinding

This study is double blinded with regard to treatment (BGF MDI administered with 2 different propellants [Treatment A or B]), ie, the sponsor, the investigator, all clinical staff involved in the clinical study, the subjects, and the study monitor will remain blinded, unless safety concerns or a regulatory requirement necessitate unblinding.

The PK analyst will remain blinded during the study conduct.

The PK analyst will be unblinded to perform the final PK analyses after all subjects have completed the study, final bioanalytical results are available and all required study data are considered clean. This may occur prior to database lock.

The following personnel will have access to the randomization lists from study start:

- The AstraZeneca staff carrying out the labeling and packaging of subject specific treatments
- Pharmacy staff preparing the study medication
- Bioanalytical staff analyzing plasma samples.

The randomization lists should be kept in a secure location until database lock.

5.3.2. Methods for Unblinding the Study

The treatment code should not be broken, except in medical emergencies when the appropriate management of the subject requires knowledge of the treatment randomization or regulatory requirements exist (eg, for - SAEs). If an emergency unblinding becomes necessary, the investigator should notify the sponsor prior to unblinding, if possible, unless identification of the IMP is required for emergency therapeutic measures. If an investigator or subject is prematurely unblinded, the subject must be withdrawn from the clinical study and procedures

accompanying withdrawal are to be performed. The decision to break the blind will be made on a case-by-case basis and, if possible, such emergencies are to be discussed with AstraZeneca prior to disclosure of the treatment allocation. If the blind is broken, the date, time, and reason, together with the identity of the person responsible must be recorded in ClinBase™ and any associated AE report.

The investigator will document and report the action to AstraZeneca staff.

Details of the code breaking procedure will be provided in the Safety Review and Management Plan.

5.4. Study Intervention

Study intervention is defined as any investigational intervention(s), marketed product(s), or placebo intended to be administered to or medical device(s) utilized by a study subject according to the study protocol.

5.4.1. Investigational Products

Details on the identity of the investigational product are presented in Table 5-1.

Table 5-1 Investigational Products

Arm name	BGF MDI HFO	BGF MDI HFA
Intervention name	Budesonide / Glycopyronium / Formoterol fumarate pressurized inhalation suspension, HFO	Budesonide / Glycopyronium / Formoterol fumarate pressurized inhalation suspension, HFA
Type	Combination product	Combination product
Dose formulation	MDI	MDI
Unit dose strength(s) (Delivered dose)	160/7.2/4.8 µg per actuation	160/7.2/4.8 µg per actuation
Dosage level	4 inhalations	4 inhalations
Route of administration	Oral inhalation	Oral inhalation
Use	Experimental	Comparator
IMP and NIMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor

Arm name	BGF MDI HFO	BGF MDI HFA
Packaging and labeling	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirements	Study intervention will be provided in an MDI. Each MDI will be labeled as required per country requirements

BGF = budesonide, glycopyrronium, formoterol; HFA = hydrofluoroalkane; HFO = hydrofluoroolefin; IMP = Investigational Medicinal Product; MDI = metered dose inhaler; NIMP = Non-investigational Medicinal Product.

Dosing instructions and dispensing details will be provided by AstraZeneca.

Budesonide, glycopyrronium, and formoterol metered dose inhaler is a combination product (drug + device).

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. Per inclusion criterion, subjects must demonstrate the proper inhalation technique and have the ability to properly use an MDI device after training.

Non-IMP supplies will include placebo inhalers for inhalation training. Inhalation training will also be conducted using the AIM training device.

Oral activated charcoal will also be a Non-IMP and will be administered during each Treatment Period.

5.4.2. Medical Devices

The AstraZeneca manufactured device constituents part of the combination product provided for use in this study is,

- Metered Dose Inhaler (Approved)

Instructions for medical device use are provided in the Investigator's Brochure and Combination Products Product of Summary characteristics.

All device constituent part device deficiencies (including malfunction, use error and inadequate labeling) shall be documented and reported by the investigator throughout the clinical investigation (see Section 6.3.1.8) and appropriately managed by the sponsor.

5.4.3. Supply of Investigational Product

The investigational product will be supplied by AstraZeneca as individual subject kits.

A technical agreement or Item Requirement Schedule between the investigator and AstraZeneca will be in place to cover all pharmacy-related activities, detailing roles and responsibilities prior to receipt of the investigational product(s) at the clinical unit.

A release document signed by a legally authorized qualified person in EU/UK or Pharmacist in USA at the clinical unit will be placed in the appropriate section of the Trial Master File to document labeling and dispensing of the investigational product(s) to the subject.

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

5.4.4. Dose and Treatment Regimens

Each subject will receive single doses (4 inhalations) of BGF MDI HFO or BGF MDI HFA on Day 1 of each Treatment Period.

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

Each subject will receive 3 single-dose treatments of BGF MDI:

- Treatment A: BGF MDI HFO 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - test formulation; administered during 1 Treatment Period.
- Treatment B: BGF MDI HFA 160/7.2/4.8 µg ex-actuator; 4 inhalations as a single dose with oral activated charcoal - reference formulation; administered during 2 Treatment Periods.

Oral activated charcoal will be administered during each treatment. Immediately before dosing with the IMP, subjects will receive [CCI] g of oral activated charcoal (approximately [CCI] mL) which they are to mouth-rinse and swallow. Immediately after IMP administration, subjects will receive another [CCI] g of oral activated charcoal to mouth-rinse and swallow. This will be repeated at 1 and 2 hours post-dose. Post administration of each dose of oral activated charcoal, subjects will rinse their mouths twice with 30 to 60 mL of water which is to be mouth-rinsed and swallowed.

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

Other restrictions, including posture control are described in Section 4.2. Data of subjects may be excluded from the PK analysis set as described in Section 11.1.3.

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 self-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 4 actuations from the MDI. Each actuation must take place within approximately 30 seconds from the previous. 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 self-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 fourth inhalation) must be documented on the eCRF.

5.4.5. Labeling

Bulk labels for IMP will be prepared in accordance with GMP and local regulatory guidelines. The labels will fulfill GMP Annex 13 requirements.

5.4.6. Storage and Handling Procedures

The IMP will be stored in a secure facility, details of storage conditions will be provided on the label of the investigational product.

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.

5.5. Concomitant and Post-study Treatment(s)

If a subject is being considered for enrollment 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, hormone replacement therapy, and systemic contraceptives, 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 investigator.

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

When any medication is required, it should be prescribed by the investigator. Following consultation with AstraZeneca Lead Physician, the investigator should determine whether or not 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 investigator with AstraZeneca Lead Physician.

5.6. Study Intervention Compliance

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

The administration of all study intervention will be recorded in ClinBase™.

Compliance will be assured by direct supervision and witnessing the self-administration of study intervention.

5.6.1. Drug Accountability, Dispensing and Destruction

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

In accordance with GCP, the Clinical Unit will account for all supplies of BGF MDI HFO and BGF MDI HFA. Details of receipt, storage, assembly/dispensing and return will be recorded.

All used and unused supplies of BGF MDI HFO and BGF MDI HFA will either be destroyed by Parexel or returned at the end of the study in accordance with instruction by the sponsor. The certificate of delivery and destruction must be signed, in accordance with instruction by AstraZeneca. Destruction must not take place unless the responsible person at AstraZeneca has approved it.

5.7. Discontinuation of Study Intervention and Withdrawal from Study

Dosing for any individual subject will be stopped if the subject experiences a possibly drug-related SAE or a possibly drug-related significant non-serious AE, which in the opinion of the investigator warrants discontinuation of the subject from the active protocol for his or her well-being.

Healthy subjects may be discontinued from study intervention in the following situations:

- Healthy subject decision. The healthy subject is at any time free to discontinue treatment, without prejudice to further treatment.
- Severe non-compliance to study protocol.

It may be necessary for a subject to permanently discontinue study intervention. If study intervention is permanently discontinued, the subject should be encouraged to remain in the study and complete the remainder of the study visits and procedures. See the SoA (Table 3-1) for data to be collected at the time of discontinuation of study intervention and follow-up and for any further evaluations that need to be completed.

Note that discontinuation from study intervention is NOT the same thing as a withdrawal from the study.

If a subject experiences any of the changes listed below, the study intervention must be discontinued:

- Development of exclusion criteria or other safety reasons as judged by the investigator during the Treatment Period
- Pregnancy or breastfeeding
- Paradoxical bronchospasm

The appropriate AE form in the CRF must be completed.

5.7.1. Procedures for Withdrawal of a Subject from the Study

If a subject withdraws or is withdrawn from the study, the subject will be encouraged to return to the Clinical Unit for an Early Termination Visit to ensure the subjects safety.

5.8. Premature Termination of the Study

The study will be terminated prematurely if:

- The investigator and the sponsor assess that the number and/or severity of AEs justify discontinuation of the study.
  For instance, when there is 1 case of fatal SAE or 2 cases of other SAEs, in both

situations considered at least possibly related to the IMP by the investigator 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.
- New data become 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 investigator 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.

5.9. Duration of Post-treatment Follow-up Period

The Follow-up Phone Call should occur within 3 to 7 days after the last administration.

6. COLLECTION OF STUDY VARIABLES

6.1. Recording of Data

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 the SoA (Table 3-1).

6.2. Enrollment and Screening Procedures

Viral serology and urine drugs of abuse, alcohol and cotinine will be assessed for eligibility. Follicle-stimulating hormone (females only), pregnancy testing (females only) and use of concomitant medication will also be assessed and reported.

6.3. Safety and Eligibility Measurements

Safety and tolerability variables will include:

- Adverse events
- Laboratory assessments (hematology, clinical chemistry, and urinalysis)
- Physical examination
- 12-lead ECG
- Vital signs (systolic and diastolic BP, pulse rate, body temperature, and respiratory rate)

6.3.1. Adverse Events

6.3.1.1. 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 intervention has been administered.

6.3.1.2. 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 anomaly 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 non-serious 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.

6.3.1.3. 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.

6.3.1.4. Recording of Adverse Events

Time Period for Collection of Adverse Events

Adverse events will be collected from the start of screening throughout the Treatment Period up to and including the Follow-up Phone Call.

Serious adverse events will be recorded from the time of informed consent.

If the investigator becomes aware of an SAE with a suspected causal relationship to the IMP that occurs after the end of the clinical study in a subject treated by him or her, the investigator shall, without undue delay, report the SAE to the sponsor.

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 investigator for as long as medically indicated, but without further recording in 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.

Variables

The following variables will be collected for each AE:

- AE term (diagnosis/verbatim)
- The date and time when the AE started and stopped
- Intensity
- Whether the AE is serious or not
- Investigator causality rating against the investigational product (yes or no)
- Outcome

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

- Date AE met criteria for serious AE
- Date investigator became aware of serious AE
- Adverse event is serious due to
- Date of hospitalization
- Date of discharge from hospital
- Probable cause of death
- Date of death
- Autopsy performed (yes/no)
- Causality assessment in relation to study procedure(s)
- Causality assessment to other medication

The following intensity ratings will be used:

- Mild (awareness of sign or symptom, but easily tolerated)
- Moderate (discomfort sufficient to cause interference with normal activities)
- Severe (incapacitating, with inability to perform normal activities)

It is important to distinguish between serious and severe AEs:

- Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.3.1.2.
- 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.

Causality Collection

The investigator will assess causal relationship between investigational product and/or investigational medicinal devices and each AE and/or incident, 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. For medical devices, a guide to the interpretation of the causality question can be found in Appendix D.

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 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.

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 or are considered to be clinically relevant as judged by the investigator (which may include, but not limited to, consideration as to whether treatment, or non-planned visits were required, or other action was taken with the study intervention, eg, dose adjustment or drug interruption).

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 investigator should use the clinical, rather than the laboratory term (eg, anemia versus low Hb value).

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

Hy's Law

Cases where a subject shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x 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.

Adverse Events Associated with Use of ICS, LAMAs, and LABAs

Certain AEs have been identified as associated to the class of drugs being studied. Known effects of LAMAs and LABAs include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular and tremor effects for LABAs. Local corticosteroid effects include oral candidiasis, hoarseness, oropharyngeal candidiasis, dysphonia, and throat irritation. Systemic corticosteroid effects include fractures, osteoporosis/osteopenia, adrenal suppression, and adrenal cortical hypofunctions. These AEs will be captured as described and presented in summary tabulation in the CSR.

6.3.1.5. 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 ClinBase™.

If any SAE occurs in the course of the study, then the investigator 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 investigator to ensure that all the necessary information is provided to the AstraZeneca Patient Safety data entry site **within 1 calendar day** of initial receipt for fatal and life-threatening events and **within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up will be undertaken immediately.

Investigators 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.

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

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

The reference document for definition of expectedness/listedness is the Investigator's Brochure for the AstraZeneca drug.

6.3.1.6. Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the investigator to the sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects 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 investigators.

For all studies, investigator safety reports must be prepared for SUSARs according to local regulations (for studies utilizing medical devices – according to European MDR 2017/745 for clinical device research) and sponsor policy and forwarded to investigators as necessary.

An investigator 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.

6.3.1.7. Medical Device-related Safety Events

The definitions of medical device-related safety events can be found in Appendix D. Medical device deficiencies are covered in Section 6.3.1.8.

6.3.1.8. Medical Device Deficiencies

Drug/device combination products are being provided for use in this study. In order to fulfill regulatory reporting obligations worldwide, the investigator is responsible for the detection and documentation of events meeting the definitions of medical device deficiency that occur during the study with such medical devices.

The definition of a medical device deficiency for device constituent of a combination product is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

The AstraZeneca medical device complaint report will be used to collect the deficiency.

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

6.3.1.8.1. Time Period for Detecting Medical Device Deficiencies

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

The method of documenting medical device deficiency is provided in Appendix D.

6.3.1.8.2. Follow-up for Medical Device Deficiencies

- Follow-up applies to all subjects, including those who discontinue study intervention.
- The investigator is responsible for ensuring that follow-up includes any supplemental investigations as indicated to elucidate the nature and/or causality of the deficiency.
- New or updated information will be recorded on the originally completed form with all changes signed and dated by the investigator.

6.3.1.8.3. Prompt Reporting of Medical Device Deficiencies to Sponsor

- Medical device deficiencies will be reported to the sponsor within 24 hours after the investigator determines that the event meets the protocol definition of a medical device deficiency.

- The Medical device deficiency Paper Report Form will be sent to the sponsor by e-mail. If e-mail is unavailable, then telephone should be utilized.
- The sponsor will be the contact for the receipt of medical device deficiency reports.

6.3.1.8.4. Regulatory Reporting Requirements for Device Deficiencies

- The investigator will promptly report all medical device deficiencies occurring with any medical device provided for use in the study in order for the sponsor to fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.
- The investigator, or responsible person according to local requirements (eg, the head of the medical institution), will comply with the applicable local regulatory requirements relating to the reporting of medical device deficiencies to the IRB.
- For further guidance on the definition of an SAE, see Appendix D of the CSP.

6.3.2. Laboratory Assessments

6.3.2.1. Hematology

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

6.3.2.2. Serum Clinical Chemistry

Serum Clinical Chemistry	
Sodium	Alkaline phosphatase (ALP)
Potassium	Alanine aminotransferase (ALT)
Urea	Aspartate aminotransferase (AST)
Creatinine	Gamma glutamyl transpeptidase (GGT)
Albumin	Total Bilirubin (TBL)
Calcium	Unconjugated bilirubin
Phosphate	
Glucose(fasting)	
C-reactive protein (CRP)	
Thyroxine (T_4) [a]	Follicle-stimulating hormone (FSH) [b]
Thyroid stimulating hormone (TSH) [a]	

[a] Screening only

[b] Post-menopausal women

6.3.2.3. Urinalysis

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

6.3.2.4. Pregnancy Testing

Pregnancy test (females only)	
Human-beta chorionic gonadotrophin	

6.3.2.5. Viral Serology

Viral Serology	
Human immunodeficiency virus (HIV) I and II	Hepatitis C Virus antibody
Hepatitis B surface antigen (HBsAg)	

6.3.2.6. Drugs of Abuse, Alcohol and Cotinine

Drugs of Abuse and Alcohol Testing	
Amphetamine / Ecstasy	Benzodiazepines
Ethanol	Methadone Metabolites
Cannabinoids	Barbiturates
Cocaine	Phencyclidine
Opiates	Urine Creatinine
Cotinine [a]	
Tricyclic anti-depressants (TCA)	

[a] Screening only

Drugs of abuse screen will be done via a urine sample. Alcohol screen will be done via a serum sample.

6.3.2.7. COVID-19 Testing

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

[a] Screening only

6.3.3. 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

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

6.3.4. Electrocardiograms

Safety 12-lead ECGs will be performed at the time points specified in the SoA (Table 3-1).

Safety 12-lead ECGs will allow the site investigator to review the ECG tracings at bedside and determine any potential abnormalities and risks.

6.3.4.1. Safety 12-lead ECGs

A 10-second 12-lead safety ECG will be obtained after the subject has been resting in the supine position for at least 10 minutes at all time points listed in SoA (Table 3-1) and whenever it is required by the investigator. All ECGs will be evaluated with respect to rhythm; heart rate; and PR, RR, QRS, QT, and QTcF intervals from the 12-lead safety ECG, and the investigator will judge the overall interpretation as normal or abnormal. If abnormal, it will be decided whether the abnormality is clinically significant or not, and the abnormality will be recorded. The investigator or delegate will evaluate the safety ECG in real time.

The date/time and the physician interpretation (normal, abnormal clinically significant, abnormal not clinically significant) for the safety ECGs will be recorded in the ClinBase™ and stored as source documents.

6.3.5. 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 (beats per minute [bpm])
- Body temperature (°C)
- Respiratory rate (breaths per minute)

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

6.3.6. 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
- FEV1/FVC ratio

Spirometry must meet both acceptability and repeatability criteria according to ATS/ERS 2019 recommendations (Graham et al. 2019). Calculated predicted spirometry results will be obtained using the Global Lung Initiative equations (Quanjer et al. 2012).

6.4. Pharmacokinetics

6.4.1. Collection of Pharmacokinetic Samples

6.4.1.1. Plasma 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 SoA (Table 3-1).

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

6.4.2. Pharmacokinetic Drug Assays

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

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

6.5. Pharmacodynamics

Not applicable

6.6. Pharmacogenetics

Not applicable

6.7. Biomarkers

Not applicable

6.8. Immunogenicity

Not applicable

6.9. Metabolites

Not applicable

6.10. Taste Assessment

Not applicable

7. BIOLOGICAL SAMPLES PROCEDURES

All biological samples will be collections will be performed by trained staff and in accordance with the Clinical Unit's SOPs.

7.1. Total Blood Volume

The maximum volume to be drawn from each subject, including repeat samples, must not exceed 500 mL in total in any 55-day period of a study.

7.2. Handling, 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.

7.2.1. 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 and/or individual PK 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, 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.

7.3. 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.

7.4. Chain of Custody of Biological Samples

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

The investigator 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.

7.5. 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.

8. REGULATORY AND ETHICAL CONSIDERATIONS

8.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki (Fortaleza, Brazil, October 2013) and CIOMS International Ethical Guidelines:
  - Applicable ICH GCP Guidelines (eg, ICH E6[R2])
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator's Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- AstraZeneca will be responsible for obtaining the required authorizations to conduct the study from the concerned Regulatory Authority. This responsibility may be delegated to a CRO, but the accountability remains with AstraZeneca.
- The investigator will be responsible for providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European Regulation 536/2014 for clinical studies (if applicable), European MDR 2017/745 for clinical device research (if applicable), and all other applicable local regulations.

8.2. Data Protection

- Subjects will be assigned a unique identifier. Any subject records or datasets that are transferred to the sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure and use of their data must also be explained to the subject in the informed consent.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

All clinical study findings and documents will be regarded as confidential. The investigator and members of his/her 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 investigator.

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

8.3. Informed Consent Process

- The investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary, and they are free to refuse to participate and may withdraw their consent at any time and for any reason during the study. Subjects or their legally authorized representative defined as ‘an individual, or judicial, or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research’, will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB or Clinical Unit.
- The medical record must include a statement that written informed consent was obtained before the subject was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the subject or the subject’s legally authorized representative.

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

8.4. 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.

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 investigator must allow the applicable persons access to all relevant facilities and data/documents. The investigator 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 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 investigator 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 investigator 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, IECs/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 investigator 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 dataflow 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 investigator for review and resolution. Corrections resulting from these queries will be confirmed on the DCFs. 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. EVALUATION AND CALCULATION OF VARIABLES

10.1. Safety Variables

10.1.1. Adverse Events

All AEs will be coded using MedDRA vocabulary, and will be listed for each subject. A TEAE is defined as an AE with onset (start date/time) after dosing the first dose of IMP in Treatment Period 1.

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:

- Screening: all AEs with start date/time prior to dosing in Treatment Period 1.
- 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 Phone Call.

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.

Adverse events 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. Furthermore, separate listings of SAEs, DAEs, and AEs that led to death will be presented.

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.

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 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 with outcome of death and SAEs.

10.1.2. 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 values and changes from baseline will be presented by time point for the safety analysis set. The baseline for the measurements will be the screening assessment performed prior to dosing in Treatment Period 1. Shift tables will also be presented.

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)
- Pregnancy testing (including FSH)
- The results of viral serology and the drugs of abuse and alcohol screen will not be listed in the CSR.

10.1.3. Physical Examination

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.

10.1.4. Resting 12-lead Electrocardiogram

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

10.1.5. Vital Signs

The results of the vital signs measurements 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 screening assessment. Descriptive statistics will be presented by treatment and time point for both observed values and changes from baseline.

10.2. Pharmacokinetic Variables

Where possible, the PK parameters will be assessed for budesonide, glycopyrronium and formoterol.

10.2.1. Plasma Parameters

Primary PK Parameters

AUCinf	Area under plasma concentration-time curve from zero to infinity
AUClast	Area under the plasma concentration-curve from zero to the last quantifiable concentration
Cmax	Maximum observed plasma (peak) drug concentration

Secondary PK Parameters

tmax	Time to reach peak or maximum observed concentration or response following drug administration
t½λz	Half-life associated with terminal slope (λz) of a semi-logarithmic concentration-time curve
MRTinf	Mean residence time of the unchanged drug in the systemic circulation from zero to infinity
λz	Terminal 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 from plasma after extravascular administration
Vz/F	Volume of distribution (apparent) at steady state following extravascular administration (based on terminal phase)

Additionally, Test (Treatment A) to reference (Treatment B) ratios for AUCinf, AUClast and Cmax will be calculated for each individual subject.

The following diagnostic parameters for plasma PK analysis will be listed, but not summarized:

λz upper and λz lower	The time interval (h) of the log-linear regression to determine t½
λzN	Number of data points used for λz determination
Rsq_adj	Statistical measure of fit for the regression used for λz determination adjusted for the number of used data points (n obs)
AUCextr	Extrapolated area under the curve from tlast to infinity, expressed as percentage of AUCinf

Additional PK parameters may be determined where appropriate.

10.2.2. Calculation or Derivation of Pharmacokinetic Parameters

The PK analyses of the plasma concentration data for budesonide, glycopyrronium and formoterol will be performed by AstraZeneca R&D.

PK parameters will be derived using non-compartmental methods with Phoenix® WinNonlin® Version 8.2, or higher and/or SAS® Version 9.4, or higher. All descriptive and inferential statistical computations will be performed using SAS® Version 9.4, or higher.

PK analysis will, where possible, be carried out using actual times recorded in the raw data. If actual times are missing, nominal times will be used.

Plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero. After the first quantifiable concentration, any NQ plasma concentrations will be set to missing for all concentration profiles. Where 2 or more consecutive concentrations are NQ at the end of a profile, the profile will be deemed to have terminated and therefore any further quantifiable concentrations will be set to missing for the calculation of the PK parameters unless it is considered to be a true characteristic of the profile of the drug.

If an entire concentration-time profile is NQ, the profile will be excluded from the PK analysis.

Terminal elimination half-life, calculated as (ln2)/λz, will be estimated by log-linear least squares regression of the terminal part of the concentration-time curve. For the determination of λz, the start of the terminal elimination phase for each subject will be defined by visual inspection and will be the first point at which there is no systematic deviation from the log-linear decline in plasma concentrations. A minimum of 3 data points will be used in calculating λz, and the duration of time over which λz is recommended to be at least 3 times the subsequently estimated terminal half-life. Where an elimination half-life is estimated over less than 3 times the subsequently estimated terminal half-life, it will be flagged and

commented upon in the study report. AUCinf is estimated by AUClast + Clast/λz where Clast is the observed last quantifiable drug concentration. The AUCinf values where the percentage extrapolation is greater than 20% will be flagged in the data listings.

AUCs (including AUCinf and AUClast) will be calculated using the linear trapezoidal method when concentrations are increasing and the logarithmic trapezoidal method when concentrations are decreasing.

The minimum requirement for the calculation of AUC will be the inclusion of at least 3 consecutive plasma concentrations above the LLOQ, with at least 1 of these concentrations following Cmax.

10.3. Pharmacodynamic Variable(s)

Not applicable

10.4. Pharmacogenetics

Not applicable

10.5. Exposure - Response Analyses

Not applicable

10.6. Taste Assessment

Not applicable

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1. Description of the Analysis Sets

11.1.1. General Principles

11.1.2. Safety Analysis Set

The safety analysis set will include all subjects who received at least 1 inhalation of any BGF MDI.

Unless otherwise stated, the safety analysis set will be used for the presentation of all demographic and disposition data, as well as all safety analyses. Exposure to IMP will also be presented using the safety analysis set.

11.1.3. Pharmacokinetic Analysis Set

The PK analysis set will include all randomized subjects who have at least 1 primary PK parameter that can be calculated and have no important protocol deviations that will impact the analysis of the PK data.

Subjects may be excluded from the PK analysis set as a result of the following:

- Data from subjects for whom the pre-dose concentration is > 5% of Cmax for BGF MDI in a specific Treatment Period

Clinical PK of BGF MDI is described in Section 2.

A subject may be excluded from the analysis 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 reasons 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.

11.1.4. Randomized Set

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

11.2. Methods of Statistical Analyses

11.2.1. General Principles

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. An 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.

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 all randomized subjects. Pharmacokinetic data will be summarized by treatment. Safety and tolerability data will be summarized by treatment, if applicable.

Frequency counts (number of subjects [n] and percentages) will be made for each qualitative variable. Descriptive statistics (n, mean, SD, median, minimum, and maximum) will be calculated for each quantitative variable (unless otherwise stated). Descriptive statistics will only be presented if $n \geq 3$.

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 3.1.1.

For safety assessments performed at screening and the last visit, 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 Day 2 Treatment Period 3 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 9.2 or later.

11.2.2. Missing Data

Missing dates and times in the AE data will be handled as described in Section 10.1.1. Concentrations that are NQ in the PK data will be handled as described in Section 11.2.6.

There will be no imputations of other missing data. All subjects will be included into the safety analyses as far as the data permit.

11.2.3. Subject Characteristics

A randomization listing will be presented and include the following: each subject's randomization number, the subject's full enrollment number, the treatment to which the subject has been randomized and the country where the Clinical Unit is located.

Subjects and/or data excluded from the PK analysis set will be listed including the reason for exclusion. Subject disposition will be summarized and will include the following information: number of subjects randomized and dosed, 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 based on all subjects randomized.

Subject discontinuations will be listed including the date of study exit, duration of treatment and reason for discontinuation. A listing of informed consent response will also be presented.

11.2.3.1. Demographic and Baseline Data

Demographic variables (age, gender, race, ethnicity, height, weight, and BMI) will be listed by subject. Demographic characteristics (age, gender, race, and ethnicity) and subject characteristics (height, weight, and BMI) will be summarized separately for all randomized subjects. The denominator for percentages will be the number of randomized subjects.

Medical history data will be listed by subject including visit, description of the disease/procedure, MedDRA SOC, MedDRA Preferred Term, start date and stop date (or ongoing if applicable).

A summary of the number and percentage of subjects who had relevant medical histories will be presented by treatment sequence and for all subjects for the medical history Preferred Term.

11.2.4. Prior and Concomitant Medication and Drug Administration

11.2.4.1. 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: 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.

11.2.4.2. Study Intervention Administration

Study intervention dates and times will be listed for each subject and Treatment Period.

11.2.5. Safety and Tolerability

All safety data (scheduled and unscheduled) will be presented in the data listings. Continuous variables will be summarized using descriptive statistics (n, mean, SD, min, median, max) by treatment group. Categorical variables will be summarized in frequency tables (frequency and proportion) by treatment/dose group. The analysis of the safety variables will be based on the safety analysis set.

Adverse events will be summarized by Preferred Term and SOC using MedDRA vocabulary. Furthermore, listings of SAEs and DAEs will be made and the number of subjects who had any AEs, SAEs, DAEs 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, ECGs, will be presented. 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 (and/or percentage change) from the baseline when baseline is defined. Clinical laboratory data will be reported in the units provided by the clinical laboratory for the SRC meeting, and in Système International units in the CSR.

Out-of-range values for safety laboratory will be flagged in individual listings as well as summarized descriptively using agreed reference ranges (eg, laboratory ranges).

11.2.6. Pharmacokinetics

A listing of PK blood sample collection times, as well as derived sampling time deviations will be provided. Plasma concentrations and PK parameters will be summarized by treatment group and analyte (budesonide, glycopyrronium and formoterol) using appropriate descriptive statistics. Where possible, the following descriptive statistics will be presented: n, geometric mean, geometric CV, arithmetic mean, arithmetic SD, median, minimum, and maximum. For tmax, only n, median, minimum, and maximum will be presented.

The geometric mean is calculated as the exponential of the arithmetic mean calculated using log-transformed data.

The CV% is calculated as $100 \cdot \sqrt{(\exp(s^2) - 1)}$ where s is the SD of the log-transformed data.

Concentration data will be presented to the same number of significant figures as the data received from the bioanalytical laboratory; for PK parameters, the listings will be presented according to the following rules:

- Cmax – will be presented to the same number of significant figures as received from the bioanalytical laboratory
- tmax, λz lower and λz upper time limit – will be presented as received in the data, usually to 2 decimal places
- AUCinf, AUClast, t½λz, λz, CL/F, MRTinf, Vz/F, AUCextr, R sq adj will be presented to 3 significant figures
- λzN – will be presented as an integer (no decimals)

For PK concentration data all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures.

For PK parameters data the descriptive statistics will be presented according to the following rules:

- Cmax, AUCinf, AUClast, t½λz, λz, CL/F, MRTinf, Vz/F – all descriptive statistics will be presented to 4 significant figures with the exception of the minimum and maximum which will be presented to 3 significant figures
- tmax, λz lower and λz upper – all descriptive statistics will be presented as received in the data, usually to 2 decimal places
- λzN, N - present as integer

Plasma concentrations that are NQ or if there are missing values (eg, NR) will be handled as follows:

- Where there is NR, these will be set to missing.
- At a time point where less than or equal to 50% of the values are NQ, all NQ values will be set to the LLOQ, and all descriptive statistics will be calculated.
- At a time point where more than half of the values are NQ, the mean, SD, geometric mean and CV% will be set to NC. The maximum value will be reported from the individual data, and the minimum and median will be set to NQ.
- If all values are NQ at a time point, no descriptive statistics will be calculated for that time point. Not calculated will be written in the field for SD and CV% and NQ will be written in fields for mean, geometric mean, minimum, median, and maximum.
- The number of NQ values (n below LLOQ) will be reported for each time point.

Three observations > LLOQ are required as a minimum for a plasma concentration to be summarized. Two observations > LLOQ are presented as a minimum and maximum with the other summary statistics as NC.

Data from subjects excluded from the PK analysis set will be included in the data listings, but not in the descriptive statistics or in the inferential statistics.

Plasma concentrations for each analyte (budesonide, glycopyrronium and formoterol) will be listed by treatment occasion, subject and time point. Plasma concentrations will also be summarized by treatment occasion and for each analyte using protocol scheduled times and appropriate descriptive statistics.

The statistical analysis will be performed for the PK analysis set. Pharmacokinetic parameters will be calculated using non-compartmental analysis.

For each analyte, individual plasma concentrations versus actual time will be plotted in linear and semi-logarithmic scale with all treatment occasions overlaid on the same plot and separate plots for each subject. Combined individual plasma concentration versus actual times will be plotted in linear and semi-logarithmic scale for each treatment occasion and analyte. Geometric mean plasma concentration (± gSD) versus nominal sampling time will be plotted in linear and semi-logarithmic (no SD presented) scale with all treatment occasions overlaid on the same figure.

For mean plots, BLQ values will be handled as described for the summary tabulations; for individual plots plasma concentrations which are NQ prior to the first quantifiable concentration will be set to a value of zero (linear plots only). After the first quantifiable concentration, any NQ plasma concentrations will be regarded as missing. All plots will be

based on the PK analysis set, with the exception of individual plots by subject which will be based on the safety analysis set.

Bioequivalence:
Bioequivalence will be assessed between test treatment BGF MDI HFO and reference treatment BGF MDI HFA based on the PK analysis set.

US Approach:

To establish the bioequivalence of the test treatment BGF MDI HFO and reference treatment BGF MDI HFA, the GMR and 90% CIs will be analyzed for PK parameters Cmax, AUClast, AUCinf of analytes budesonide, glycopyrronium and formoterol.

The TOST will be performed via a linear mixed effects model, with log-transformed PK parameter as dependent variable; sequence and period as fixed effects; subject and treatment nested within subject as random effects. The estimated GMR with 90% CIs will be provided.

For any of Cmax, AUClast or AUCinf, if the swr of the reference treatment is < 0.294 (ie, within-subject CV is < 30%), then the ABE method will be used. The acceptance criteria for 90% CIs of GMR are the fixed limits 80% to 125%.

For any of Cmax, AUClast or AUCinf, if swr is ≥ 0.294 that shows high intra-subject variability, then the RSABE method will be used. The acceptance limits for 90% CIs of GMR are expanded to [U, L] = e ± k·swr, where k = 0.893.

GMR must lie within 80% and 125%, regardless of the expanded acceptance limits for 90% CIs.

The acceptance criteria for GMR and the acceptance criteria for 90% CIs of GMR must be satisfied for each PK parameter and each analyte to conclude the bioequivalence.

Proposed SAS Code for PK Bioequivalence Analysis with Replicate Designs:

The FDA guidance for Industry document "Statistical approaches to establish bioequivalence" specifies the bioequivalence analysis of replicated design using a linear mixed effects model, with log-transformed PK parameter as dependent variable; sequence and period as fixed effects; subject and treatment (nested within subject) as random effects (FDA Guidance 2001).

The proposed SAS code of PROC MIXED with SEQ, SUBJ, PER, and TRT identifying sequence, subject, period, and treatment variables, respectively, and Y denoting the response measure (eg, log[AUC], log[Cmax]) being analyzed is:

PROC MIXED;

```
CLASSES SEQ SUBJ PER TRT;
MODEL Y = SEQ PER TRT/ DDFM=SATTERTH;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.1;
RUN;
```

EU Approach:

To establish the bioequivalence of the test treatment BGF MDI HFO and reference treatment BGF MDI HFA, the GMR and 90% CIs will be analyzed for PK parameters Cmax, AUClast of analytes budesonide, glycopyrronium, and formoterol.

The TOST will be performed via an analysis of variance model, with log-transformed PK parameter as dependent variable; sequence, period, treatment, and subject within sequence as fixed effects. The estimated GMR with 90% CIs will be provided.

For Cmax, if the swr of the reference treatment is < 0.294 (ie, within-subject CV is $< 30\%$) the ABE method will be used. The acceptance criteria for 90% CIs of GMR are the fixed limits 80% to 125%.

For Cmax, if swr is ≥ 0.294 (ie, within-subject CV is $\geq 30\%$) that shows high variability, then the ABEL method will be used. When swr is ≥ 0.294 and ≤ 0.472 (ie, within-subject CV is $\geq 30\%$ and $\leq 50\%$), the acceptance limits for 90% CIs of GMR are expanded to $[U, L] = e \pm k \cdot swr$, where $k = 0.760$. If within-subject CV exceeds 50%, then the acceptance limits are capped at 69.84% to 143.19%.

The ABE method will be applied for AUClast. The acceptance criteria for 90% CIs of GMR are the fixed limits 80% to 125%.

GMR must lie within 80% and 125%, regardless of the expanded acceptance limits for 90% CIs.

The acceptance criteria for GMR and the acceptance criteria for 90% CIs of GMR must be satisfied for each PK parameter and each analyte to conclude the bioequivalence.

Proposed SAS Code for PK Bioequivalence Analysis with Replicate Designs:

The EU approach compatible with CHMP guideline specifies the bioequivalence analysis of replicated design using an analysis of variance model, with log-transformed PK parameter as dependent variable; sequence, period, treatment and subject within sequence as fixed effects (Annex I EMA, EMA Guideline 2010).

The proposed SAS code of PROC GLM with SEQ, SUBJ, PER, and TRT identifying sequence, subject, period, and treatment variables, respectively, and Y denoting the response measure (eg, log[AUC], log[Cmax]) being analyzed is:

```
PROC GLM;
CLASS TRT SUBJ PER SEQ;
MODEL Y= SEQ SUBJ (SEQ) PER TRT;
ESTIMATE "TEST-REF TRT -1+1;
TEST H=SEQ E=SUBJ(SEQ);
LSMEANS TRT / ADJUST=T PDIFF=CONTROL("R") CL ALPHA=0.10;
RUN;
```

11.3. 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 protocol deviation specification 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 8.1.

11.4. Determination of Sample Size

The sample size for this study was based on the precision in estimating the primary PK parameters AUCinf, AUClast, and Cmax of BGF MDI HFA.

Among the analytes, glycopyrronium has the highest Cmax intra-subject CV at [redacted]%, estimated from a previous single-dose BGF spacer study in healthy volunteers. In studies with higher intra-subject variability larger absolute differences between the logarithmic means can be observed and so a true GMR of [redacted] is assumed (Tothfalusi and Endrenyi 2011). Given the above assumptions, a sample size of 96 subjects would provide 90% probability of obtaining a 90% CI within the expanded limits of 69.84% to 143.19% for Cmax or the fixed limits of 80% to 125% for AUClast and AUCinf, and a GMR estimate within the bounds of 80% to 125%. To account for a 10% dropout rate 108 subjects will be randomized to achieve at least 96 evaluable subjects.

The number of subject identifiers generated for the study will account for the number of randomized subjects per the sample size calculation (N = 108). For this study, a total of 108 subject identifiers will be randomly assigned to 1 of 3 possible treatment sequences: ABB, BAB, BBA.

12. IMPORTANT MEDICAL PROCEDURES TO BE FOLLOWED BY THE INVESTIGATOR

12.1. Medical Emergencies and AstraZeneca Contacts

In case of medical emergency, the primary contact is the PI. The PI may contact the sponsor's Lead Physician. If the PI cannot be reached, the site's staff will contact the PI's deputy or may contact sponsor's Lead Physician.

Name	Role in the Study	Contact Details
PPD	Principal Investigator	Parexel Early Phase Clinical Unit Baltimore Harbor Hospital 3001 S. Hanover St. Baltimore, MD 21225 USA PPD PPD
PPD	Sponsor's Lead Physician	PPD

12.2. Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except if the pregnancy is discovered before the study subject has received any study intervention.

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

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

Please refer to Section 4.2.1.2 for further details.

12.2.1. Maternal Exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital anomalies/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital anomaly) should be followed up and documented even if the subject was discontinued from the study.

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

The designated AstraZeneca representative works with the investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 or 5 calendar days for SAEs (see CSP process for SAE reporting) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

Please refer to Section 4.2.1.2 for further details.

12.2.2. Paternal Exposure

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

13. LEGAL AND ADMINISTRATIVE ASPECTS

13.1. 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.

13.2. 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 investigator. The investigator 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.

13.3. 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.

14. REFERENCE LIST

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15. 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 adverse event (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 serious adverse event (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 one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an Important Medical Event; medical judgment must be used.

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

A Guide to Interpreting the Causality Question

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

- Time Course. Exposure to suspect drug. Has the subject actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?
- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?
- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?
- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.
- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? AstraZeneca would not normally recommend or support a re-challenge.
- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship?

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

- Is this a recognized feature of overdose of the drug?
- Is there a known mechanism?

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

The causality assessment is performed based on the available data including enough information to make an informed judgment. With no available facts or arguments to suggest a causal relationship, 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 (IATA) classifies biohazardous 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 (DGR) 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:

- 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 human immunodeficiency virus (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 UN 3373 and IATA 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.**
- An IATA 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

Introduction

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

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

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

The investigator will also review adverse event (AE) data (for example, for AEs that may indicate elevations in liver biochemistry) for possible PHL events.

The investigator participates, together with AstraZeneca clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether HL criteria are met. HL criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug-Induced Liver Injury (DILI) caused by the investigational medicinal product (IMP).

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

Definitions

Potential Hy's Law

Aspartate aminotransferase (AST) or ALT ≥ 3 x upper limit of normal (ULN) **together with** TBL ≥ 2 x ULN at any point during the study following the start of study medication irrespective of an increase in alkaline phosphatase (ALP).

Hy's Law (HL)

Aspartate aminotransferase or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x 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.

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:

- Aspartate aminotransferase ≥ 3 x ULN
- Alanine aminotransferase ≥ 3 x ULN
- Total bilirubin ≥ 2 x ULN

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

- Notify the AstraZeneca representative.
- Determine whether the subject meets PHL criteria (see Section 2 within this appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF module(s).

Follow-Up

Potential Hy's Law Criteria not met

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

- Inform the AstraZeneca representative that the subject has not met PHL criteria.
- Perform follow-up on subsequent laboratory results according to the guidance provided in the clinical study protocol (CSP).

Potential Hy's Law Criteria met

If the subject does meet PHL criteria the investigator will:

- Notify the AstraZeneca representative who will then inform the central Study Team.
- Within 1 day of PHL criteria being met, the investigator will report the case as an SAE of PHL; serious criteria "Important Medical Event" and causality assessment "yes/related" according to CSP process for SAE reporting.
- For subjects that met PHL criteria prior to starting IMP, the investigator is not required to submit a PHL SAE unless there is a significant change[1] in the subject's condition.

[1] 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

- The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study subjects' follow-up (including any further laboratory testing) and the continuous review of data.
  - Subsequent to this contact the investigator will:
    - Monitor the subject until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated. Completes follow-up SAE Form as required.
    - Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician. This includes deciding which the tests available in the HL laboratory kit should be used (if applicable).
    - Complete the 3 liver CRF modules as information becomes available.

Review and Assessment of Potential Hy's Law Cases

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

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

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

Where There Is an Agreed Alternative Explanation for the AST or ALT and TBL Elevations, a Determination of Whether the Alternative Explanation Is an AE Will Be Made and Subsequently Whether the AE Meets Any 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 AstraZeneca standard processes

in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

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

- Send updated SAE (report term "Hy's Law") according to AstraZeneca standard processes
  - The "Medically Important" seriousness criterion should be used if no other seriousness 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:

- Provide 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 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.

Laboratory Tests

The list below represents the standard, comprehensive list of follow-up tests which are recommended but not mandatory when using a central laboratory. For studies using a local laboratory, the list may be modified based on clinical judgment. Any test results need to be recorded.

Hy's Law laboratory kit for central laboratories (18 December 2018)		
Additional standard biochemistry and coagulation tests	GGT LDH Prothrombin time INR	
Viral hepatitis	IgM anti-HAV IgM and IgG anti-HBc HBsAg HBV DNA	IgG anti-HCV HCV RNA * IgM anti-HEV HEV RNA
Other viral infections	IgM & IgG anti-CMV IgM & IgG anti-HSV IgM & IgG anti-EBV	
Alcoholic hepatitis	Carbohydrate deficient transferrin (CD-transferrin)	
Autoimmune hepatitis	Antinuclear antibody (ANA) Anti-Liver/Kidney Microsomal Ab (Anti-LKM) Anti-Smooth Muscle Ab (ASMA)	
Metabolic diseases	alpha-1-antitrypsin Ceruloplasmin Iron Ferritin Transferrin Transferrin saturation	

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

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Appendix D Medical Device AEs, ADEs, SAEs, SADEs, USADEs and Medical Device Deficiencies: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting in Medical Device Studies

- The definitions and procedures detailed in this appendix are in accordance with International Organization for Standardization 14155 and European Medical Device Regulation (MDR) 2017/745 for clinical device research (if applicable), in particular Medical Device Coordination Group (MDCG) 2020-10/1 Safety reporting in clinical investigations of medical devices.
- Both the investigator and the sponsor will comply with all local reporting requirements for medical devices.
- The detection and documentation procedures described in this protocol apply to all sponsor medical devices provided for use in the study. See Section 5.4 for details of sponsor medical devices.

Definition of Medical Device AE and ADE

Medical device AE and ADE Definition

- An adverse event (AE) is any untoward medical occurrence in a clinical study subject, users, or other persons, temporally associated with the use of study intervention, whether or not considered related to the investigational medical device. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of an investigational medical device. This definition includes events related to the investigational medical device or comparator and events related to the procedures involved.
- An adverse device effect (ADE) is defined as an AE related to the use of an investigational medical device. This definition includes any AE resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device as well as any event resulting from use error or from intentional misuse of the investigational medical device.

Definition of Medical Device SAE, SADE and USADE

A medical device serious adverse event (SAE) is an any SAE that:

- Led to death.
- Led to serious deterioration in the health of the subject, that either resulted in:
  - A life-threatening illness or injury. The term “life-threatening” in the definition of “serious” refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe.
  - A permanent impairment of a body structure or a body function.

  - Inpatient or prolonged hospitalization. Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered an SAE.
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
  - Chronic disease (MDR 2017/745).
- Led to fetal distress, fetal death, or a congenital anomaly or birth defect.

SADE Definition

- A serious adverse device effect (SADE) is defined as an ADE that has resulted in any of the consequences characteristic of an SAE.
- Any medical device deficiency that might have led to an SAE if appropriate action had not been taken, intervention had not occurred, or circumstances had been less fortunate.

USADE Definition

- An unanticipated SADE (USADE) (also identified as UADE in United States Regulations 21 CFR 813.3), is defined as a SADE that by its nature, incidence, severity, or outcome has not been identified in the current risk analysis (see Section 3.4 for risk-benefit assessment of the device).

Definition of Medical Device Deficiency

Medical Device Deficiency Definition

- A medical device deficiency is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. Medical device deficiencies include malfunctions, use errors, and information supplied by the manufacturer.

Recording and Follow-up of AE and/or SAE and Medical Device Deficiencies

AE, SAE, and Medical Device Deficiency Recording

- When an AE/SAE/medical device deficiency occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator will then record all relevant AE/SAE/medical device deficiency information in the subject's medical records, in accordance with the investigator's normal clinical practice and on the appropriate form.
- It is **not** acceptable for the investigator to send photocopies of the subject's medical records to the Sponsor in lieu of completion of the AE/SAE/medical device deficiency form.

- There may be instances when copies of medical records for certain cases are requested by the Sponsor. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- For medical device deficiencies, it is very important that the investigator describes any corrective or remedial actions taken to prevent recurrence of the deficiency.
  - A remedial action is any action other than routine maintenance or servicing of a medical device where such action is necessary to prevent recurrence of a medical device deficiency. This includes any amendment to the medical device design to prevent recurrence.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE/SAE/medical device deficiency reported during the study and assign it to one of the following categories:

- Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with an SAE. "Severe" is a category used for rating the intensity of an event; both AEs and SAEs can be assessed as severe.
- An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, **not** when it is rated as severe.

Assessment of Causality

The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE/medical device deficiency. A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship, cannot be ruled out. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated. The investigator will also consult the Investigator's Brochure and/or Product Information, for marketed products in his/her assessment.

For each AE/SAE/medical device deficiency, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE/medical device deficiency and has provided an assessment of causality. There may be situations in which an SAE has occurred and the

investigator has minimal information to include in the initial report to the Sponsor. However, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor.

The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment. The causality assessment is one of the criteria used when determining regulatory reporting requirements.

For the purpose of harmonizing reports, each SAE will be classified according to five different levels of causality. The sponsor and the investigators will use the following definitions to assess the relationship of the SAE to the investigational[2] device or procedures.

Not related: Relationship to the device or procedures can be excluded when:

- the event has no temporal relationship with the use of the investigational device or the procedures.
- the serious event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible.
- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the serious event.
- the event involves a body-site or an organ not expected to be affected by the device or procedure.
- the serious event can be attributed to another cause (eg, an underlying or concurrent illness/clinical condition, an effect of another device, drug, treatment, or other risk factors).
- the event does not depend on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

- Unlikely: The relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained.
- Possible: The relationship with the use of the investigational device is weak but cannot be ruled out completely. Alternative causes are also possible (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment). Cases where relatedness cannot be assessed or no information has been obtained should also be classified as possible.

[2] Investigational device: any device object of the clinical investigation, including the comparators

- Probable: The relationship with the use of the investigational device seems relevant and/or the event cannot be reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the serious event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures.
- the event has a temporal relationship with investigational device use/application or procedures.
- the event involves a body-site or organ that
  - the investigational device or procedures are applied to.
  - the investigational device or procedures have an effect on.
- the serious event follows a known response pattern to the medical device (if the response pattern is previously known).
- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the serious event (when clinically feasible).
- other possible causes (eg, an underlying or concurrent illness/ clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out.
- harm to the subject is due to error in use.
- the event depends on a false result given by the investigational device used for diagnosis, when applicable.

In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the serious event.

Follow-up of AE/SAE/Medical Device Deficiency

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE/SAE/medical device deficiency as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the investigator will provide the Sponsor with a copy of any post-mortem findings including histopathology.
- New or updated information will be recorded in the originally completed form.
- The investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting to the Sponsor via Paper Data Collection Tool

- Facsimile transmission of the SAE paper data collection tool is the preferred method to transmit this information to the study physician.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE paper data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the SAE paper data collection tool within the designated reporting time frames.
- Contacts for SAE reporting can be found in the Safety Handling Plan.

Reporting of SADEs

SADE Reporting to the Sponsor

NOTE: There are additional reporting obligations for medical device deficiencies that are potentially related to SAEs that must fulfill the legal responsibility to notify appropriate regulatory authorities and other entities about certain safety information relating to medical devices being used in clinical studies.

- Any medical device deficiency that is associated with an SAE must be reported to the sponsor within 24 hours after the investigator determines that the event meets the definition of a medical device deficiency.
- The sponsor will review all medical device deficiencies and determine and document in writing whether they could have led to an SAE. These medical device deficiencies will be reported to the regulatory authorities and IRBs/IECs as required by national regulations.
- Contacts for SAE reporting can be found in the Safety Handling Plan.

SIGNATURE PAGE

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