AstraZeneca

Statistical Analysis Plan

Study Code	PT010011 / D5980C000013
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Date	16 January 2018

A Randomized, Double-Blind, Two Treatment, Two Period, Chronic Dosing (2 Weeks), Cross-Over, Single-Center Study to Evaluate the Effects of PT003 and Placebo MDI on Specific Image Based Airway Volumes and Resistance in Subjects With Moderate to Severe COPD.

STATISTICAL ANALYSIS PLAN FOR STUDY PT010011

Protocol Number: PT010011

Investigational Drug and Drug Number: BGF MDI; PT010

Indication: COPD

Dosage Form/Dose:
- BGF MDI 320/28.8/9.6 µg ex-actuator

PT010011 Protocol Title: A Randomized Open-label, Single-dose, Single-center, Crossover Study in Healthy Subjects to Assess the Relative Bioavailability of PT010 Administered With and Without a Spacer, and With and Without Oral Charcoal

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Signed Agreement on Statistical Analysis Plan

FINAL SIGN-OFF SIGNATURES

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Change Log			
Version No.	**Effective Date**	**Reason for the Change / Revision**	**Supersedes**

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
ATC	Anatomic Therapeutic Class
$AUC_{0\text{-tlast}}$	Area under the plasma concentration-time curve from 0 to the Time of the Last Measurable Plasma Concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from 0 Extrapolated to Infinity
BDRM	Blinded Data Review Meeting
BGF MDI	Budesonide, Glycopyrronium, and Formoterol Metered Dose Inhaler
BLOQ	Below Limit of Quantification
BP	Blood Pressure
CI	Confidence Interval
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Observed Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
CRF	Case Report Form
DMP	Data Management Plan
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eg	Exempli gratia; for example
GFR	Glomerular Filtration Rate
HR	Heart Rate
IB	Investigators Brochure
ICF	Informed Consent Form
i.e.	Id Est; That Is
λ_z	Apparent Terminal Elimination Rate Constant
LLOQ	Lower Limit of Quantification
MDI	Metered dose inhaler

MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
msec	Millisecond
NCA	Non-Compartmental Analysis
OTC	Over-the Counter
PCS	Potentially Clinically Significant
PK	Pharmacokinetics
PT	Preferred Term
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
QTcF	QT Corrected Using Fridericia's Formula
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
$t_{1/2}$	Apparent Terminal Elimination Half-life
TEAE	Treatment-emergent adverse event
t_{last}	Time to last measurable plasma concentration
t_{max}	Time To Maximum Observed Plasma Concentration
Vd/F	Apparent Volume of Distribution
VS	Vital signs
WHO	World Health Organization
WHO-DD	World Health Organization-Drug Dictionary
WHO-DDE	World Health Organization-Drug Dictionary Enhanced
WHO-HD	World Health Organization-Herbal Dictionary

1. INTRODUCTION

This Statistical Analysis Plan (SAP) outlines the statistical methods for the display, summary and analysis of data to be performed at the end of Pearl Therapeutics, Inc. (Pearl) Study PT010011. The SAP should be read in conjunction with the study protocol. This version of the SAP has been developed using the PT010011 Protocol (Version 1.0 dated 11 September 2017) and the CRF Revision 01 dated 07 November, 2017. This is the main SAP, describing the statistical analyses that will be carried out at the end of the study.

This is a phase I, randomized, open label, single-dose, single center, crossover study to assess the pharmacokinetics (PK) and safety of budesonide, glycopyrronium, and formoterol metered dose inhaler (BGF MDI) in healthy subjects.

The definitions of data sets will be described in separate documents called SDTM specifications and ADaM specifications.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

The primary objectives of this study are the following:

- To assess the total systemic exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without a spacer device
- To assess the lung exposure of budesonide, glycopyrronium, and formoterol administered as BGF MDI with and without oral activated charcoal

2.1.2 Secondary Objective

The secondary objectives of this study are the following:

- To characterize the PK profiles of budesonide, glycopyrronium, and formoterol administered as BGF MDI, with and without a spacer device, and with and without oral charcoal
- To assess the safety of single doses of BGF MDI in healthy subjects

2.2 Study Endpoints

2.2.1 Pharmacokinetic Endpoints

Pharmacokinetics after single-dose administration of BGF MDI will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol for each regimen.

2.2.1.1 Primary PK Endpoints

- Maximum observed plasma concentration (C_{max})
- Area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration ($AUC_{0\text{-}tlast}$)

2.2.1.2 Secondary PK Endpoints

- Time to maximum observed plasma concentration (t_{max})
- Area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0\text{-}\infty}$)

2.2.1.3 Other PK Endpoints

- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Apparent terminal elimination rate constant (λ_z)
- Time to last measurable plasma concentration (t_{last})

2.2.2 Safety Endpoints

- Adverse events (AEs)
- 12-lead electrocardiograms (ECGs)
- Clinical laboratory testing
- Vital sign (VS) measurements

3. STUDY DESIGN AND ANALYTICAL CONSIDERATIONS

3.1 Study Design

This is a Phase I, randomized, open-label, single-dose, single-center, crossover study to assess the PK and safety of BGF MDI in healthy subjects (male or female). The PK profiles of each active ingredient (budesonide, glycopyrronium, and formoterol), will be determined after administration of BGF MDI with a spacer device (test) and without a spacer device (reference), and with and without concomitant administration of activated oral charcoal to estimate lung exposure and total systemic exposure, respectively.

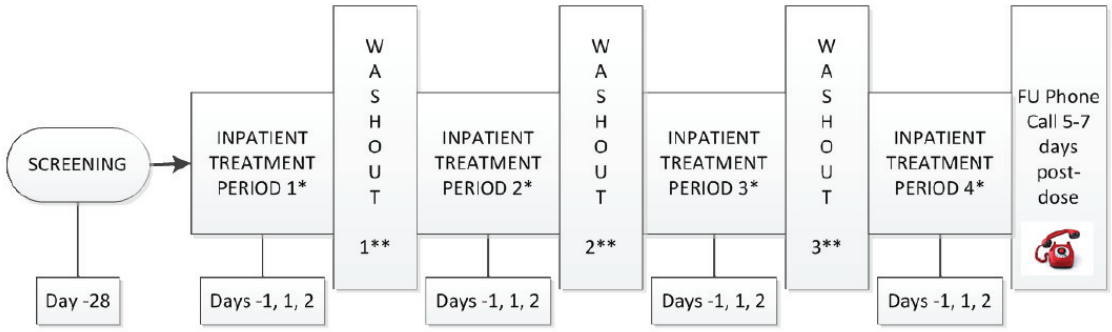
Approximately 56 healthy male or female subjects will be randomized in this study in order to ensure approximately 48 subjects complete all 4 Treatment Periods. Subjects who withdraw from the study after receiving at least 1 dose of study drug will not be replaced. Subjects who are re-screened will maintain 1 screening number throughout the study. The study will be conducted at a single center in the US.

This study includes a Screening Period of up to 28 days and four single-dose Treatment Periods during which subjects will be resident from the afternoon before dosing with BGF MDI until at least 24 hours after dosing and discharged on the morning of Day 2 of each Treatment Period. There will be a washout period of 5 to 14 days after Treatment Periods 1, 2, and 3. A follow-up phone call will take place within 5 to 7 days following the last administration of BGF MDI.

3.1.1 Overall Study Design and Plan

The overall study design is summarized and illustrated in Figure 1.

Figure 1 Study Design



*BGF 320/28.8/9.6 µg will be administered at each Treatment Period:
With and without spacer, with and without charcoal (4 regimens; 8 possible regimen sequences)

** Washout is a minimum of 5 to a maximum of 14 days between each Treatment Period

After providing informed consent, subjects will undergo screening procedures. Subjects meeting eligibility criteria will be enrolled into the study and admitted to the study site as an inpatient on Day -1 of Treatment Period 1, at which time continuing eligibility will be assessed. Device training will be conducted during screening, on admission to each Treatment Period, and prior to dosing on Day 1 of each Treatment Period. In addition to training with a placebo MDI device, additional inhalation training tools may be used to help ensure the subjects are able to use the MDI device correctly.

Study drug will be administered, under fasted conditions, on the morning of Day 1 of each Treatment Period, at approximately the same time of day throughout the study (± 30 minutes). Eligible subjects will receive a single dose of BGF MDI 320/28.8/9.6 µg administered as follows:

- Without a spacer device and without charcoal (regimen A)
- With a spacer device and without charcoal (regimen B)
- Without a spacer device and with charcoal (regimen C)
- With a spacer device and with charcoal (regimen D)

Subjects will receive all 4 regimens (1 regimen per Treatment Period) in 1 of 8 possible regimen sequences: AB CD, AB DC, BA CD, BA DC, CD AB, CD BA, DC AB, or DC BA.

The regimen sequences allow for subjects who might drop out after completing only 2 Treatment Periods to be included in the PK statistical analysis.

Randomization will be performed on the morning of first dosing (Day 1, Treatment Period 1). Randomization codes will be assigned strictly sequentially in ascending order as subjects become eligible.

During their inpatient stay, subjects will undergo safety assessments and have an indwelling intravenous cannula for serial PK blood draws. Subjects will be discharged on the morning of Day 2 of each Treatment Period after all protocol-specified assessments are completed. There will be a washout period of 5 to 14 days after Treatment Periods 1, 2 and 3.

A follow-up phone call will be conducted 5 to 7 days after Treatment Period 4 dosing or after the last dose of study drug, whichever comes first.

3.1.2 Prior, Concomitant, Prohibited Medications

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 over the counter (OTC) products, without the consent of the Investigator.

When any medication is required, it should be prescribed by the Investigator. Following consultation with the Medical Monitor, the Investigator must determine whether or not the subject should continue in the study.

The Investigator or designated qualified personnel will assess and record concomitant medication usage on the eCRF. Concomitant medication usage will be assessed at screening and throughout the study.

3.2 Randomization and Blinding

This study will be conducted as a 4-period, 8-sequence, 4-regimen, crossover design. The experimental design was chosen to be balanced with respect to period, sequence and first-order

carryover effects. Thus eligible subjects will be equally randomized to 1 of the following 8 regimen sequences: AB CD, AB DC, BA CD, BA DC, CD AB, CD BA, DC AB, or DC BA.

3.3 Hypothesis Testing

No formal hypothesis tests will be performed for this study.

3.4 Sample Size

This study is being conducted for estimation purposes. [redacted] a sample size of 48 subjects completing the study will provide [redacted] probability to observe a 1-sided [redacted] lower confidence bound for the geometric mean ratio (D/C) that is greater than [redacted]

3.5 Study Procedures

Study procedures are contained in Table 8-1, Table 8-2, and Table 8-3 and detailed in Section 7 and Section 8 of the study protocol.

3.6 Schedule of Assessments

A schedule of events for screening, treatment, and follow-up is provided in Table 8-1 of the study protocol. Detailed schedules of inpatient assessments on Day 1 during inpatient treatment periods 1, 2, and 3 are provided in Table 8-2 and inpatient assessments on Day 1 during inpatient treatment period 4 are provided in Table 8-3, of the study protocol.

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance (QA) procedures for the study data, statistical programming and analyses are described in Standard Operating Procedures (SOPs) of Everest Clinical Research. Detailed data management procedures are documented in the study Data Management Plan (DMP), Data Validation Check Specifications, and Integrated Safety Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

The study endpoints and analytic approaches are both prospectively defined and documented in the protocol and in this SAP. The SAP will be finalized, and protocol deviations will be identified and decisions for inclusion and exclusion of subjects from the PK Population will be made at the Blinded Data Review Meeting (BDRM) prior to the database lock and data analysis.

5. ANALYSIS POPULATIONS

5.1 Population Definitions

5.1.1 Safety Population

The **Safety Population** is defined as all randomized subjects who receive at least one dose of BGF MDI.

Safety and tolerability analyses will be performed on data from all subjects in the Safety Population. Analyses will be according to treatment received.

5.1.2 Pharmacokinetic (PK) Population

The **PK Population** is defined as all subjects in the Safety Population set for whom at least one of the primary PK parameters for a given analyte can be calculated and who have no important protocol deviations thought to impact the analysis of the PK data. Major protocol deviations can result in exclusion of all data from a particular subject from the PK Population or require exclusion of data from a specific analyte, timepoint and/or subsequent timepoints for an endpoint. Protocol deviations for exclusion of subjects or data from the PK Population will be agreed by the study team and documented prior to database lock.

Reasons for exclusion from the PK Population will documented in the BDRM minutes prior to database lock; these minutes will be included in an appendix to the Clinical Study Report.

Pharmacokinetic analyses will be performed on data from all subjects in the PK Population. Analyses will be according to treatment received.

5.2 Populations for Analyses

Demographics and baseline characteristics will be summarized descriptively for both the PK and Safety Populations. Extent of exposure will also be summarized for the Safety Population. For the PK Population, descriptive statistics without model adjustment will be used to describe the budesonide, glycopyrronium, and formoterol PK parameters by regimen. The Safety Population will be used to summarize safety. Safety and tolerability analyses will be based on descriptive statistics for vital signs, and laboratory measurements as appropriate, and also on frequencies of AEs (including any AEs based on ECG findings) as well as the number and proportion of subjects with AEs.

6. SPECIFICATION OF ENDPOINTS AND VARIABLES

6.1 Demographics and Baseline Characteristics

General demographic information such as age, race, ethnicity, gender, weight, and height will be collected at the Screening visit. Age will be calculated as the integer part of (Informed Consent date – Birth date)/365.25. For additional details please refer to the Data Handing rules outlined in Appendix 1.

Medical/surgical history will be collected on the eCRF during the Screening period. Medical history will be coded using the latest version of the Medical Dictionary for Regulatory Activities (currently MedDRA 20.1).

The definitions for the derived demographic or baseline characteristic variables can be found in Appendix 1.

6.2 Pharmacokinetics

Pharmacokinetics of BGF MDI with and without spacer and with or without oral charcoal will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol pre-dose and at various times post-dose on Day 1 of each treatment period. See Section 7.4.

6.3 Safety Assessments

6.3.1 Physical Examination

Any clinically significant physical examination abnormality reported after the start of study medication will be reported as an adverse event. These adverse events will be included in the AE summaries.

The physical examination will include:

- Documentation of height (Screening only)
- Documentation of weight (Screening only)
- General appearance
- Head, eyes, ears, nose, throat, and neck (including thyroid),
- Respiratory
- Cardiovascular
- Musculoskeletal
- Abdominal
- Neurologic
- Extremities
- Dermatologic
- Lymph nodes

6.3.2 Vital Signs

Vital sign determinations, including blood pressure (BP) and heart rate (HR) will be performed after the subject has been supine for a 5-minute period at the Screening Visit, on the day of each clinic admission (Day -1), on Day 1 prior to study drug administration, and on Day 2 of Treatment Period 4.

Potentially clinically significant (PCS) changes in systolic and diastolic blood pressure will be defined based on the criteria listed in Table 1.

Table 1 Potentially Clinically Significant Criteria for Systolic and Diastolic Blood Pressure Parameters

Parameter (mmHg)	Post-Baseline Criteria
Systolic Blood Pressure, increase	≥180 mmHg and increase from baseline ≥20 mmHg
Systolic Blood Pressure, decrease	≤90 mmHg and ≥20 mmHg decrease from baseline
Diastolic Blood Pressure, increase	≥105 mmHg and increase from baseline ≥15 mmHg
Diastolic Blood Pressure, decrease	≤50 mmHg and ≥15 mmHg decrease from baseline

Potentially clinically significant changes in HR will be assessed as follows:

Table 2 Potentially Clinically Significant Criteria for Heart Rate Parameters

Parameter	Post-Baseline Criteria
Tachycardia Event	≥110 bpm and increase ≥15% from baseline
Bradycardia Event	≤50 bpm and decrease ≥15% from baseline

6.3.3 12-Lead Electrocardiogram

A **Clinically Significant Abnormality** for a 12-Lead ECG measurement identified by the investigator as a clinically significant abnormality will be recorded as an AE if it occurred after the start of study treatment. These adverse events will be included in the AE summaries.

All 12-Lead ECG measurements for the Safety Population will be listed.

Potentially clinically significant ECG parameter values will be identified based on criteria listed in Table 3.

Table 3 Criteria for PCS ECG Values

Parameter	Post-Baseline Criteria
QTcF Prolongation	(1) ≥ 500 msec if < 500 msec at study baseline and ≥ 15 msec change from study baseline
	(2) ≥ 530 msec if ≥ 500 msec at study baseline and ≥ 15 msec change from study baseline
	(3) ≥ 500 msec and ≥ 15 msec change from study baseline
	(4) Change of ≥60 msec from study baseline regardless of initial value

msec = millisecond

6.3.4 Clinical Laboratory Tests

Laboratory testing (hematology with differential, chemistry and urinalysis) will be performed using standard methods. The laboratory parameters to be assessed in this study are listed below in Table 4.

Potentially Clinically Significant Laboratory Values Above/Below a Clinically Relevant Threshold on-treatment, based on CTCAE 4.03 and other criteria, will be identified based on the thresholds in Table 5.

Table 4 List of Laboratory Tests

Hematology	Blood Chemistry	
Hematocrit[a] Hemoglobin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential Mean corpuscular volume (MCV) MCH concentration (MCHC)	Creatinine[b] Potassium (K+) Sodium (Na+) Chloride (Cl-) Magnesium (Mg++) Calcium Inorganic phosphate Glucose Urea Bilirubin (Total)	Bilirubin (direct) Alanine aminotransferase (ALT) Aspartate aminotransferase (AST) Gamma-Glutamyltransferase (GGT) Alkaline phosphatase Total Protein Albumin
Urinalysis: Macroscopic examination routinely including specific gravity, pH, protein, glucose, ketones, blood and urobilinogen. A microscopic examination will be performed if warranted based on macroscopic results.		
Urine drug screen: A urine sample will be collected at screening and Day-1 of each treatment period and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, cotinine, and marijuana [tetrahydrocannabinol (THC)].		
Alcohol Breathalyzer Test: A breathalyzer test will be performed at screening and Day -1 of each treatment period for the presence of alcohol (positive or negative).		
Serology: Testing for HbsAg, Hepatitis C antibody, and HIV will be performed at screening only. Results of each serology test will be reported as either positive or negative.		
For females who are not post-menopausal: A serum hCG test at screening and urine hCG test at admission will be performed during each of the 4 Treatment Periods.		
For females of non-childbearing potential: A serum hCG test at screening will be performed. In addition, a serum FSH test for confirmation of non-childbearing status will be performed at screening.		
[a] Packed cell volume (PCV). [b] Serum creatinine value will be used to calculate eGFR using Chronic Kidney Disease Epidemiology Collaboration Equation (according to National Kidney Disease Education Program) - CKD-EPI.		

Table 5 Potentially Clinically Significant (PCS) Laboratory Parameter Criteria

Parameter	Post-Baseline Criteria
Hematology	
Hemoglobin	<8.0 g/dL (<80 g/L)
	Increase of >40 g/L to a value above the ULN
White Blood Cell Count	<2000/µL
	>35,000/µL

Parameter	Post-Baseline Criteria
Platelet Count	<50,000/µL
	>999,000/µL
Chemistry	
eGFR-EPI	<30 mL/min/1.73 m^2
AST	>3 x ULN
ALT	>3 x ULN
Alkaline Phosphatase	>5 x ULN
Total Bilirubin	>2 x ULN
Blood Glucose* (random values)	<2.2 mmol/L (<39.6 mg/dL)
	>13.9 mmol/L (>250 mg/dL) if baseline is below 10.0 mmol/L (180 mg/dL), > 16.7 mmol/L (>300 mg/dL) if baseline is greater than 10.0 mmol/L (180 mg/dL)
Serum Potassium	<3.0 mmol/L
	>6.0 mmol/L

*CTCAE 4.03 criteria are based on fasting glucose values. However, subjects were not required to fast prior to obtaining blood glucose values.

6.3.5 Adverse Events

Adverse events (AEs) will be collected from the time of administration of the first dose of study drug to the time of the Follow-Up Telephone Call Visit, study termination, or study exit. AEs will be characterized by severity and relationship to study drug. The incidence of an AE will be defined by the number of subjects experiencing an event.

Adverse events will be collected and coded using the latest version of MedDRA available at the time of database lock for this study. The study physician will review the adverse event coding.

Adverse events that occur between the time the subject signs the informed consent form for the study and the time when that subject receives the first dose of study drug will be summarized as medical history and not as an AE unless the event meets the definition of a serious adverse event (SAE).

An AE is considered as On-Treatment if the onset date of the adverse event is on or after the day of the first dose of randomized treatment, and up to and including the date completion of randomized treatment or the last day of premature withdrawal from randomized treatment +1 day. An adverse event that begins on the same date as the first dose of randomized treatment is On-treatment if the AE begins after the time of first dose or if the time of AE onset is unknown. All on-treatment AEs are refered to as treatment emergent adverse events (TEAEs).

An AE is considered as Post-treatment if the onset date of the adverse event is after the date completion of randomized treatment or on or after the last day of premature withdrawal from randomized treatment +2 days.

Adverse events will be listed in adverse event data listings (*Listing 7.1*).

Events with Irregular Start Dates: All adverse events will be included in the tabulations regardless of the completeness of the onset dates.

Adverse events include, but are not limited to:

- Any symptom or condition not previously reported by the subject (medical history).
- An exacerbation of a pre-existing symptom or condition.
- A significant increase in frequency or intensity of a pre-existing episodic event or condition.
- A drug interaction.
- A condition first detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.

An AE does not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, blood transfusion); the condition that results in the procedure is considered an AE (e.g., bleeding esophageal varices, dental caries).
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.
- Abnormal laboratory values that are not clinically significant. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE).

An AE is considered “serious” if, in the view of the Investigator or Sponsor, it results in any of the following outcomes:

- Death
- A life-threatening AE
- In patient hospitalization or prolongation of existing hospitalization

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon appropriate judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in subject hospitalization, or the development of drug dependency or drug abuse.

Hospitalization for a pre-existing condition, including elective procedures, which has not worsened, does not constitute an SAE.

An AE is considered “life-threatening’ if, in the view of the Investigator or Sponsor, its occurrence places the subject at immediate risk of death. It does not include an adverse reaction or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

An AE or suspected adverse reaction is considered unexpected if it is not listed in the current investigator brochure or is not listed at the specificity or severity that has been observed.

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., elevated BUN and creatinine in the setting of an AE of renal failure, or decreased hemoglobin in a case of bleeding esophageal varices). In such cases, the laboratory abnormality itself (e.g., elevated creatinine in a setting of renal failure) does not need to be recorded as an AE. However, isolated laboratory abnormalities should be reported as AEs if they are considered to be clinically significant by the Investigator.

Criteria for a "clinically significant" laboratory abnormality are:

- A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension, or study withdrawal)

- A laboratory abnormality that results in any therapeutic intervention (e.g., concomitant medication or therapy)

- Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

For laboratory abnormalities that do not meet the above criteria but are outside of normal range (e.g., < or > normal reference range), the Investigator should indicate whether the value is potentially clinically significant or not clinically significant for the subject.

6.3.6 Urine Drug Screening/Alcohol Breath Testing

A urine sample will be collected and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol (THC)]. A breathalyzer test will be performed for the presence of alcohol (positive or negative). Both tests will be conducted at Screening and at inpatient admission days.

6.3.7 Pregnancy Test

For females who are not post-menopausal, a serum hCG test at screening and urine hCG test at admission will be performed during each of the 4 Treatment Periods. For females of non-childbearing potential, a serum hCG test at screening will be performed. In addition, a serum FSH test for confirmation of non-childbearing status will be performed at screening.

6.3.8 Concomitant Medications/Treatments

Concomitant medications will be collected for for all visits of the study.

Any medications that were being taken prior to signing the ICF will be documented as prior study medications and must be stopped prior to entry.

Concomitant medications will be coded using the latest version of the World Health Organization (WHO) Drug Dictionary Enhanced (WHO DDE) and the WHO Herbal Dictionary (WHO-HD).

7. STATISTICAL ANALYSIS

All data collected on the CRF and contributing to the analysis will be provided in listings, except for data collected only for confirmation of study entry criteria and for study management purposes.

All PK and safety parameters will be summarized unless specified otherwise.

Continuous variables will be summarized with descriptive statistics: the number of non-missing values, mean, standard deviation, median, minimum, and maximum.

Categorical variables will be summarized with frequency counts and percentages (where appropriate).

7.1 Data Handling Rules and Definitions, Including Handling of Missing Data

Missing data will be maintained as missing in the analysis datasets, unless specified otherwise. For variables where missing data are imputed, the analysis dataset will contain a new variable with the imputed value, and the original variable value will be maintained as missing.

Data imputation for PK summaries is detailed in Section 7.4.

Data Imputation for Adverse Events Summaries by Severity and Relationship to Study Drug

For the AE summaries by severity, an AE with missing severity will be deemed as severe. For AEs that could be associated with any study procedure the causal relationship is implied as 'yes'. Imputed values will not be listed in data listings.

Data Imputation for Laboratory, Vital Sign, and ECG Summaries (Continuous Parameters)

By-visit and by-timepoint summaries will be based on scheduled visits and/or timepoints (i.e. no time windows), as applicable. Data from unscheduled visits and/or timepoints will not be used for by-visit or by-timepoint summaries but will be included in the listings. Data from both scheduled and unscheduled visits will be used for shift tables and for determining incidence of clinically significant values. End-of-treatment refers to the last visit during study treatment when an assessment was made.

Data Imputation (All Laboratory Summaries)

Laboratory values of '>=x' or '<=x' will be taken as the value of x in the analyses. If a laboratory value is prefixed with'>': the available original value +0.001 will be used for table summaries; if a laboratory value is prefixed with '<', then the original value –0.001 will be used in table summaries.

Study Dates and Day of Assessment or Event

Study Day and Day of Assessment or Event definitions are provided in Appendix 1, Data Handling Rules.

7.2 Subject Disposition and Analysis Populations

A disposition table for all subjects randomized will be provided (*Table 1.1*). This tabulation will include the number and percentage of subjects who were treated with the study treatment, who completed the study, who withdrew from the study prematurely (early termination) along with the reason for study withdrawal. The number and percentage of subjects included in the Safety and PK Populations will also be tabulated by regimen (*Table 1.3*). Informed consent is listed in *Listing 1.1*.

A summary of reasons for withdrawal from study treatment by regimen sequence will be summarized for the Safety Population *(Table 1.2).* These reasons will be listed in *Listing 1.2*.

7.3 Demographic and Baseline Characteristics

Demographic data will be summarized for both the Safety and PK Populations (Tables 1.4.1 and 1.4.2). Continuous demographic and baseline variables will be summarized by tabulating the number of subjects, mean, standard deviation (SD), median, minimum, and maximum values. For categorical demographic and baseline variables, the frequency and percentage of subjects will be tabulated. Demographic data will be listed (Listing 1.1). Medical and Surgical History (Listing 4.2) will be listed.

Demographic variables summarized will include the following:

- Age
- Gender
- Race
- Ethnicity
- Smoking Classification (Smoking status - including number of years smoked, time in years since last smoked, average number of cigarettes smoked per day)
- Weight (kg)
- Height (cm)
- BMI (body mass index, derived from weight and height, equal to weight in kg divided by the square of height in m)

7.3.1 Medical and Surgical History at Screening, Reproductive Status, and Pregnancy Testing

Relevant medical history, based on the opinion of the Investigator, will be obtained from the subject at Screening, and recorded on the source document. Medical history will capture the subject's family health history, history of hospitalization, and history of surgeries.

Medical and Surgical History at Screening will be listed for all subjects *(Listing 4.2)*.

Screening Reproductive Status and Pregnancy Testing Results will be listed *(Listing 10.4)*.

7.3.2 Prior and Concomitant Medications/Treatments

Coding: Verbatim medication/treatment terms will be coded by [redacted] and will be assigned a preferred term and an ATC (anatomic therapeutic class) term using the latest version of the World Health Organization Drug Dictionary (WHO-DD) available (version: 3Q 2017 or later).

Multiple ATC assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on medical evaluation by study physician will be used. All

prior medication taken by the subject within 30 days of Screening for the study and all concomitant therapy taken by the subject while on study will be recorded in the eCRF.

Prior medication/treatment is any medication/treatment taken prior to study treatment, even if this medication continued to be taken on the day of the start of study treatment in the study or afterward *(Appendix 1)*.

Concomitant medication/treatment is any medication/treatment reported as being taken after the start of the study treatment in the study and being taken on or before the date prior to completion of or withdrawal from study treatment for the subject. A medication with an onset date on or after the date of study withdrawal from or completion of randomized study treatment for the subject will not be considered concomitant, but will be considered a **Post-Treatment medication/treatment**.

Any medication/treatment which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the categories that are possible from the available information.

Reported prior, concomitant, and post-treatment medications will be listed *(Listing 10.1.1 and Listing 10.1.2)*.

7.3.3 Extent of Exposure to Study Medication

A listing of treatment dosing and dispensing information will be provided in *Listing 5.1.* Any comments related to study medication or any other additional study comments will be listed *(Listing 10.5)*.

7.4 Pharmacokinetic Assessments

Time points for PK blood sample collection will be pre-dose within 60 minutes prior to dosing and post-dose at 2, 6, 20, and 40 minutes, and at 1, 2, 4, 8, 12, and 24 hours.

Actual sampling time points relative to dosing will be used for PK assessments and analysis where available. It is expected that the actual sampling time will generally be available. In any (likely rare) cases when the actual sampling time was not recorded, the scheduled time may be used. This is considered preferable to ignoring a valid concentration measurement.

The concentration-time data reported by the bioanalytical laboratory will be evaluated for inclusion in the PK analysis dataset.

The PK analysis will be performed for subjects in the PK Population.

PK parameters will be estimated by non-compartmental analysis (NCA) using the software [redacted]

From the plasma budesonide, glycopyrronium and formoterol concentration-time data, the following PK parameters will be estimated for each subject where possible on Day 1 of each treatment period:

$AUC_{0\text{-}tlast}$	Area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration
$AUC_{0\text{-}\infty}$	Area under the plasma concentration-time curve from time 0 extrapolated to infinity
C_{max}	Maximum observed plasma concentration, expressed in concentration units
t_{max}	Time to reach maximum observed plasma concentration (C_{max}), expressed in hours
λ_z	Terminal elimination rate constant, calculated from the slope of the terminal portion of the ln(drug concentration) versus time curve
$t_{1/2}$	Apparent terminal elimination half-life, expressed in hours, calculated as ln2/ λ_z
CL/F	Apparent total body clearance
Vd/F	Apparent volume of distribution
t_{last}	Time to last measurable plasma concentration

$AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$, will be calculated using the linear up/log down trapezoidal method.

The PK parameters C_{max} and time to C_{max} (t_{max}) will be obtained from the observed values.

λ_z will be estimated for each subject where feasible by linear regression analysis, calculated from the slope of the terminal portion of the ln(drug concentration) versus time curve. Selection of data points to include in the estimation of λ_z for each subject for each analyte will be based on the following criteria:

- All samples used should preferably fall in the log-linear elimination phase.
- At least 3 samples above lower limit of quantification (LLOQ) should be used in the estimation.
- C_{max} must not be used in the estimation.
- Adjusted r^2 value reported in [redacted] must be ≥ 0.8.

For the purposes of parameter estimation, plasma concentration values below the LLOQ will be set to missing in the NCA with the exception of those values reported at Day 1 pre-dose. Day 1 pre-dose concentrations that are below the limit of quantification (BLOQ) will be set to zero (per [redacted] SOP) for the NCA. Concentrations measured after the Day 1 dose of study medication that are below the lower limit of quantification will set to missing values (per [redacted] SOP) for the NCA. Missing values (e.g., no blood sample collected, no value obtained at analysis) will be treated as missing and excluded from the NCA. If there are ≥2 consecutive missing concentration values, the estimation of PK parameters will be evaluated on a case-by-case basis.

For descriptive statistics for concentrations and for the concentration figures, all values below LLOQ will be assigned a value of ½ LLOQ except for Day 1 pre-dose which will be assigned a value of 0 (no geometric mean will be calculated for Day 1 pre-dose).

Descriptive statistics for plasma concentrations of budesonide, glycopyrronium, and formoterol, by regimen and nominal time point will be summarized using the PK Population. Descriptive statistics will include the number of observations (n), mean (CV%), SD, standard error (SE), median, minimum (min), maximum (max), geometric mean, and geometric coefficient of variation (*Tables 2.1.1, 2.2.1, and 2.3.1*). The geometric coefficient of variation is calculated as GEOCV(y) (%) = 100*sqrt[(exp[var(ln[y])])-1], where sqrt is the square root function and "var(ln[y])" is natural-log scale variance.

Descriptive statistics for PK parameters of budesonide, glycopyrronium, and formoterol, will be summarized by regimen. Descriptive statistics will include the number of observations (n), mean (CV%), SD, median, min, max, geometric mean, and geometric coefficient of variation. For the PK parameters t_{max} and t_{last}, only the number of observations (n), mean, median, minimum (min), and maximum (max) will be presented (*Tables 2.1.2, 2.2.2, and 2.3.2*).

The plasma concentration-time profiles for individual and mean plasma concentrations of budesonide, glycopyrronium, and formoterol will be plotted for each treatment and each visit on the linear/linear scale and on the linear/log-linear scale for the Safety Population.

Mean and individual plots will be separate for each analyte. Nominal sampling time points relative to dosing will be used for all mean plots. Actual sampling time points will be used for all individual plots (mean plots in *Figures 2.1.1* through *2.3.2* and individual plots in *Figures 2.4.1* through *2.6.2*).

All concentration-time data reported by the bioanalytical laboratory, for each analyte, will be listed for subjects in the Safety Population (*Listing 8.1*). Actual sample collection times will be detailed in the listing along with the scheduled nominal sample collection times. In addition, all calculated PK parameters for each subject for each analyte will be listed (*Listing 8.2*).

The treatment ratio of each of the test formulations (regimen B or regimen D) will be compared to the reference formulations (regimen A or regimen C) for budesonide, glycopyrronium, and formoterol.

The statistical analysis will be conducted separately for the following:

- Total systemic exposure: regimen B versus regimen A (*Table 2.1.3, Table 2.2.3, Table 2.3.3*)

- Lung exposure: regimen D versus regimen C *(Table 2.1.4, Table 2.2.4, Table 2.3.4)*

Treatment comparisons of primary PK parameters will be assessed on the difference of log-transformed C_{max}, $AUC_{0\text{-}tlast}$, and $AUC_{0\text{-}\infty}$ of budesonide, glycopyrronium, and formoterol using a 2-sided 90% CI approach based on an analysis of variance model including period, sequence, regimen, and subject within sequence as fixed effects. Estimated geometric mean ratios with 90% CIs will be provided.

Only the data for the comparison under investigation will be included in the statistical analysis, e.g., when comparing regimen B and regimen A, the data for the other regimens will be removed from the dataset. Subjects must have a primary PK parameter available for both regimens for a given analyte under consideration in order to be included in a specific analysis. A subject may therefore be included in the analysis for one parameter and not for another.

To investigate the effect of the spacer on the PK parameters ($AUC_{0\text{-}tlast,}$ $AUC_{0\text{-}\infty}$ and C_{max}), summaries of the budesonide, glycopyrronium, and formoterol $AUC_{0\text{-}tlast,}$ $AUC_{0\text{-}\infty}$ and C_{max} pararmeters by exposure quartiles will be presented. The quartiles are established based on values from without spacer only; then the AUC and Cmax values and the ratios for with:without spacer are summarized for each of the quartiles.

Data will be divided into quartiles based on $AUC_{0\text{-}tlast}$ reported during treatment without the spacer.

7.5 Safety Assessments

Safety data will be summarized by regimen and listed for the Safety Population. The safety assessments for BGF MDI will include AEs and SAEs, vital signs (BP, HR), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead ECGs. The incidence of on-treatment AEs and SAEs will be tabulated. Summary statistics of assessed laboratory values will also be tabulated.

7.5.1 Physical Examination

Any clinically significant physical examination abnormality reported after the start of study medication was to be reported as an adverse event. Thus, these will be included in listings of adverse events and summarized in adverse event summaries.

7.5.2 Vital Signs

Subjects with out-of-range values will be listed (*Listing 10.2*). All clinically significant abnormalities after administration of randomized study drug will be reported as AEs.

7.5.3 12-Lead Electrocardiogram

Subjects with out-of-range values will be listed (*Listing 10.6*). All clinically significant abnormalities after administration of randomized study drug will be reported as AEs.

7.5.4 Clinical Laboratory Tests

Subjects with out-of-range hematology, chemistry, and urinalysis results will be listed (*Listings 9.1 - 9.3*). All clinically significant abnormalities after administration of randomized study drug will be reported as AEs.

7.5.5 Adverse Events

On-treatment AEs will be included in tabular format, for subjects who meet the criteria for the Safety Population. Listings for AEs will present all AEs in the database for all subjects (*Listings*

7.1 and 7.2). All AEs, whether on-treatment or not, will be included in the Listings. Pre-treatment SAEs will also be listed (*Listing 7.3)*.

Analysis endpoints for AEs include both the numbers of treatment-emergent AEs as observed by the investigational team or reported by the subject, and the numbers of subjects experiencing treatment-emergent adverse events. The incidence of an on-treatment AE will be defined as the number of subjects experiencing an event.

An overall summary of subjects with at least one on-treatment AE, with AEs related to study treatment, with SAEs, with SAEs related to study treatment, with AEs leading to early withdrawal from the study, with SAEs leading to early withdrawal from the study, and with deaths will be presented (*Table 3.1.1*).

The frequency and percentage of subjects experiencing a specific on-treatment AE will be tabulated by system organ class (SOC) and preferred term (PT) by regimen for the Safety Population (*Table 3.1.2*).

On-treatment AEs will be summarized by (maximum) severity, with respect to SOC and preferred terms by regimen (*Tables 3.2.1*).

If applicable, deaths (PT) will be included as part of AE/SAE analysis, including appropriate information such as date where available.

Post-treatment AEs will be listed separately (*Table 3.1.3 and Tables 3.2.2*).

7.5.6 Urine Drug Screening and Alcohol Breath Testing

Urine Drug Screening/Alcohol Breath Testing conducted during the study will be provided in a listing (*Listing 10.3*).

7.5.7 Pregnancy Test

Pregnancy testing results conducted during the study will be provided in a listing (*Listing 10.4*).

7.5.8 Prior/Concomitant Medications/Treatments

Prior and concomitant medications will be provided in a listing (*Listing 10.1.1 and Listing 10.1.2*). Information from both complete and partial dates will be utilized. Medications with end date of 'Ongoing' are considered concomitant. Should there not be sufficient information to determine whether a medication is prior or concomitant the status will be considered to be both prior and concomitant.

Concomitant medications and treatments will be summarized for the Safety Population. Frequency tables will present the frequency and proportion of subjects having received at least one concomitant medication during the course of the trial. Results will also be summarized with respect to subjects' receiving medications by coded preferred term (Table 1.5.1).

8. ANALYSES PERFORMED BEFORE DATABASE CLOSURE

Not applicable.

9. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

This SAP outlines the statistical methods for the display, summary and analysis of data collected within the scope of Pearl Therapeutics Inc. Protocol PT010011, Version 1.0 dated 11 September 2017.

10. STATISTICAL SOFTWARE

[redacted] environment will be used for all statistical analyses.

[redacted] will be used for all PK parameter calculations.

11. REFERENCES

[redacted]

[redacted] will be used for all PK parameter calculations.

APPENDIX 1: DATA HANDLING RULES

This appendix is provided in a separate document.

APPENDIX 2: TABLE OF CONTENTS FOR END-OF-TEXT TABLES, LISTINGS, AND FIGURES

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APPENDIX 3: [redacted] CODE FOR STATISTICAL ANALYSES

This appendix is provided in a separate document.

APPENDIX 4: CTCAE LABORATORY TEST CRITERIA FOR SHIFT TABLES AND CENTRAL LABORATORY REFERENCE RANGES FOR USE IN FLAGGING ABNORMAL VALUES

This appendix is provided in a separate document.