AstraZeneca

Statistical Analysis Plan

Study Code	PT010010
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A Phase I, Randomized, Double-Blind, Parallel-Group Study to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days

STATISTICAL ANALYSIS PLAN FOR STUDY PT010010

Protocol Number:	PT010010
Investigational Drug and Drug Number:	BGF MDI; PT010 GFF MDI; PT003
Indication:	COPD
Dosage Form/Dose:	• BGF MDI 320/14.4/9.6 µg ex-actuator • BGF MDI 160/14.4/9.6 µg ex-actuator • GFF MDI 14.4/9.6 µg ex-actuator

PT010010 Protocol Title: A Phase I, Randomized, Double-Blind, Parallel-Group, Study to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days

Date of Issue: 24 Aug 2017

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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_{0-12}	Area under the plasma concentration-time curve from 0 to 12 hours
AUC_{0-t}	Area under the plasma concentration-time curve from 0 to the Time of the Last Measurable Plasma Concentration
$AUC_{0-\infty}$	Area under the plasma concentration-time curve from 0 Extrapolated to Infinity
BGF MDI	Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler
BID	Bis in die, twice daily
BLOQ	Below Limit of Quantification
BP	Blood Pressure
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Plasma Concentration
COPD	Chronic Obstructive Pulmonary Disease
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic Acid
eCRF	Electronic Case Report Form
eg	Exempli gratia; for example
FSH	Follicle Stimulating Hormone
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GFR	Glomerular Filtration Rate
HbsAg	Hepatitis B Surface Antigen
hCG	Human chorionic gonadotropin
HIV	Human Immunodeficiency Virus
HR	Heart Rate
IB	Investigators Brochure

ICF	Informed Consent Form
i.e.	Id Est; That Is
IEC	Independent Ethics Committee
IRB	Institutional Review Board
λ_z	Apparent Terminal Elimination Rate Constant
LLQ	Lower Limit of Quantification
MDI	Metered dose inhaler
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
µg	Microgram
mL	Milliliter
mm	Millimeter
mmHg	Millimeter of mercury
msec (ms)	Millisecond
NCA	Non-Compartmental Analysis
PCS	Potentially Clinically Significant
PFT	Pulmonary Function Test
PK	Pharmacokinetics
PR	Pulse Rate
PT	Preferred Term
PT003	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
QTcF	QT Corrected Using Fridericia's Formula
RAC(C_{max})	Accumulation ratio for C_{max}
RAC(AUC_{0-12})	Accumulation ratio for AUC_{0-12}
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
TFL	Table, Figure, Listing
t_{max}	Time To Maximum Plasma Concentration
Vd/F	Apparent Volume of Distribution
WHO	World Health Organization

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Respules

Spiriva

Symbicort

Turbuhaler

Vacutainer

Ziploc

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 PT010010. The SAP should be read in conjunction with the study protocol and the electronic Case Report Forms (eCRFs) for the study. This version of the SAP has been developed using the PT010010-03 Amended Protocol (Version 4.0 dated 12 May 2017) and the CRF Revision 2 dated 2 March, 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, double-blind, parallel-group, study to assess the pharmacokinetics (PK) and safety of two dosage strengths of PT010 (BGF MDI 320/14.4/9.6 µg ex-actuator and (BGF MDI 160/14.4/9.6 µg ex-actuator) and a single dosage strength of PT003 (GFF MDI 14.4/9.6 µg ex-actuator) in healthy Chinese adult subjects following a single administration and after chronic administration for 7 days.

The definitions of data sets will be described in separate documents called SDTM specifications and ADaM specifications. A prototype SAS code appendix will not be necessary for this study because the statistics are descriptive in nature, without modeling or hypothesis testing.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objective

- To assess the pharmacokinetic profile of two dosage strengths of BGF MDI (BGF MDI 320/14.4/9.6 µg ex-actuator and (BGF MDI 160/14.4/9.6 µg ex-actuator) and a single dosage strength of GFF MDI (GFF MDI 14.4/9.6 µg ex-actuator) in healthy Chinese adult subjects after a single administration and after chronic administration for 7 days.

2.1.2 Secondary Objective

- To assess the safety and tolerability of two dosage strengths of BGF MDI and a single dosage strength of GFF MDI in healthy Chinese adult subjects after single administration and after chronic administration for 7 days.

2.2 Study Endpoints

2.2.1 Pharmacokinetic Endpoint

Pharmacokinetics of BGF MDI and GFF MDI will be assessed and compared using plasma concentrations of budesonide, glycopyrronium, and formoterol. For the single dose administration, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12, and 24 hours. Following 7 days

of chronic dosing BID, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes and at 1, 2, 4, 8, 10, 12 and 24 hours.

Pharmacokinetic parameters calculated at the first day (Day 1) and last dose (Day 8) during the Treatment Period will include the following:

• Maximum plasma concentration (C_{max})

• Area under the plasma concentration-time curve from 0 to 12 hours (AUC_{0-12})

• Time to maximum plasma concentration (t_{max})

The following PK parameters will be calculated at Day 1 only:

• Area under the plasma concentration-time curve from 0 to the time of the last measureable plasma concentration (AUC_{0-t})

• Area under the plasma concentration-time curve from 0 extrapolated to infinity ($AUC_{0-\infty}$)

• Elimination half-life ($t_{½}$)

• Apparent total body clearance (CL/F)

• Apparent volume of distribution (Vd/F)

• Apparent terminal elimination rate constant (λ_z)

The following will be derived by taking subject level ratios of Day 8 values to Day 1 values:

• Accumulation ratio for C_{max} (RAC [C_{max}])

• Accumulation ratio for AUC_{0-12} (RAC [AUC_{0-12}])

2.2.2 Secondary Endpoint

The safety and tolerability of BGF MDI and GFF MDI will be assessed from physical examination findings, AE (adverse event) reporting including serious adverse event (SAE) reporting, vital signs (blood pressure [BP], pulse rate [PR], respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead safety electrocardiograms (ECG) incorporated in the adverse events tabulation.

3. STUDY DESIGN AND ANALYTICAL CONSIDERATIONS

3.1 Study Design

This is a Phase I, single-center, randomized, double-blind, parallel-group, study to assess the PK and safety and tolerability of two doses of BGF MDI and a single dose of GFF MDI in healthy

Chinese adult subjects. Pharmacokinetics will be assessed following a single administration and after chronic administration for 7 days. Safety will be assessed during the 8-day treatment period and throughout the entire study until subjects are released from participation. All study drugs will be administered by oral inhalation. It is planned that the study will enroll and randomize an estimated 96 eligible subjects to one of three treatment groups in a 1:1:1 ratio to have approximately 90 completed subjects. Subjects will receive one of the following three treatments:

BGF MDI 320/14.4/9.6 µg

BGF MDI 160/14.4/9.6 µg

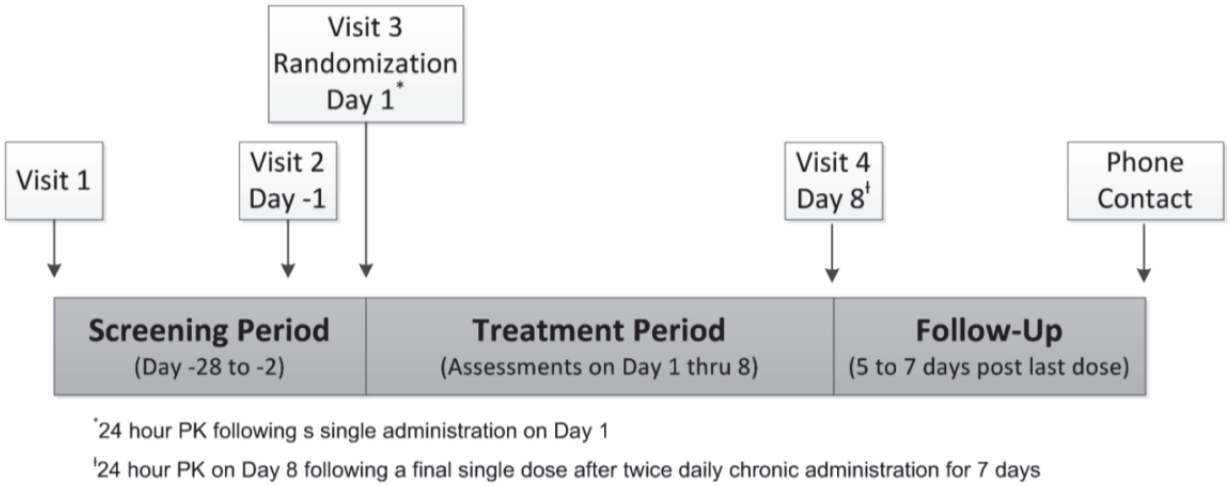
GFF MDI 14.4/9.6 µg

This study includes a Screening Period of up to 28 days and a single Treatment Period of 8 days. A follow-up phone call will be conducted at least 5 days, but no longer than 7 days after completion of the last dose. The maximum participation in the study for each subject is not expected to exceed approximately 43 days.

3.1.1 Overall Study Design and Plan

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

Figure 1 Study Design



Note: All study drugs are administered by oral inhalation. A single dose of study drug will be administered on Day 1 and BID doses will be administered Day 2 through Day 7 of the Treatment Period, with a final single administration of study drug occurring on the morning of Day 8. Administration of study drug should occur at approximately the same time of day.

Subjects who provide informed consent, undergo Screening procedures, and qualify for the study will be randomized in a 1:1:1 ratio to one of three treatments: BGF MDI (320/14.4/9.6 µg), BGF MDI (160/14.4/9.6 µg), or GFF MDI (14.4/9.6 µg). Approximately 32 subjects will be randomized to each treatment arm.

Subjects will be admitted as inpatients to the Clinical Research Unit (hereinafter referred to as "clinic") during the Treatment Period. For the Treatment Period, subjects will be admitted to the clinic on Visit 2 (the day prior to dosing), at which time, continuing eligibility will be assessed. At in-clinic Visit 3 (Day 1 of Treatment), if the subject continues to meet eligibility criteria, the subject will be randomized into the study, admitted into the inpatient study unit and administered their first single dose of study drug.

During the inpatient treatment period, study specified procedures will be performed and will include safety assessments, baseline and pre-, post-dose serial blood draws as defined in Protocol Section 7.3 and in Table 8—1, 8—2, and Table 8—3 of the study protocol. After all protocol specified assessments are completed and safety data has been reviewed by the Principal Investigator (Investigator) or designated staff, the subjects will be discharged from the clinic on Day 9. A follow-up phone call will be conducted 5 days, but no later than 7 days, after the last dose on Day 8.

3.1.2 Prior, Concomitant, Post-Treatment, Prohibited Medications, and Other Restrictions

Investigational therapies are not permitted within 30 days or five half-lives (whichever is longer) prior to beginning the Screening Period.

The use of prescription or over-the counter medications are not permitted within 30 days or five half-lives (whichever is longer) prior to Visit 3 (Day 1).

Acetaminophen will be permitted at doses of ≤2 grams/day as determined to be necessary by the Investigator or medically qualified designee.

With the exception of, contraceptives in female subjects, or need for medication during an emergency ongoing treatment for chronic conditions will not be allowed. Any medications that were being taken prior to signing the informed consent form (ICF) will be documented as prior study drugs and must be stopped prior to entry.

3.1.2.1 Surgical Procedure/Intervention Restrictions

Major surgical interventions are not permitted within 4 weeks of study drug administration (Visit 3) and minor surgical interventions are not allowed within 2 weeks of study drug administration (Visit 3).

3.1.2.2 Dietary Restrictions

Fasting (at least 8 hours) is required for scheduled complete clinical laboratory testing – chemistry and hematology (including glucose and potassium), at Screening Visit 1, Visit 2 (Day -1) and for the 24 hours post-dose sample collection on Day 9.

Fasting is not required for glucose and potassium only blood sample collections on Visit 3 (Day 1) at 30 min and at 2 hours post-dose and on Visit 4 (Day 8) at 30 min, 2 hours and 12 hours post-dose.

Standardized meals will be administered at specified times after observation of fasting time for blood draws. There are no restrictions regarding clear fluid intake.

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

3.1.2.3 Illicit Drugs and/or Drugs of Abuse Restriction

Illicit drugs and/or drugs of abuse will not be allowed from within 1 year of Screening to whenever the subject discontinues the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented.

3.1.2.4 Smoking Restrictions

Smoking is prohibited throughout the duration of the study and 3 months prior to screening. Electronic cigarettes and nicotine supplements will be treated the same way as smoking is considered in the protocol.

3.2 Randomization and Blinding

Following determination of study eligibility, subjects will be randomized in a 1:1:1 ratio to one of the three treatment groups: BGF 320/14.4/9.6 µg, BGF 160/14.4/9.6 µg, or GFF MDI 14.4/9.6 µg.

All treatment arms will be double-blinded.

Randomization numbers will be generated off-site, to ensure allocation concealment, using a permutated block randomization design. The randomization numbers will be printed on sealed envelopes and corresponding component ID codes will be provided within the envelopes. The sealed envelopes are given out sequentially (i.e. there are serially numbered opaque sealed envelopes). Sealed emergency unblinding envelopes will also be provided separately.

Subjects, investigators and the sponsor will be blinded to the treatment administered as described above until the study database is locked. The pharmacist will have access to the unblinded randomized treatment sequence.

3.3 Hypothesis Testing

No formal hypothesis tests will be performed for this study.

3.4 Interim Analysis

There is no interim analysis planned for this study.

3.5 Sample Size

Previous studies with BGF MDI suggest that the inter-subject variability of glycopyrronium after single-dose administration may be as high as [redacted]

3.6 Study Procedures

Study procedures are contained in Table 8—1, 8—2, and Table 8—3 of the study protocol.

3.7 Schedule of Assessments

A schedule of events is provided in Table 8—1 of the study protocol. Detailed schedules of inpatient assessments on Visit 3 (Day 1) and Visit 4 (Day 8) are provided in Table 8—2 and Table 8—3, respectively, 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 [redacted]. Detailed data management procedures are documented in the study Data Management Plan, and 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 violations 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 subjects who receive at least one dose of any blinded study drug.

Safety 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 who have sufficient data to reliably calculate at least one PK parameter and do not have major protocol deviations (to be determined at the BDRM prior to unblinding). A major protocol deviation is a protocol deviation which can affect membership in an analysis population.

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 the PK and Safety Populations. Extent of exposure will also be summarized for the Safety and PK Populations. For the PK Population, descriptive statistics without model adjustment will be used to describe the budesonide, glycopyrrolate and formoterol PK parameters after treatment with two dosage strengths of BGF MDI and single dosage strength of GFF MDI. The Safety Population will be used to summarize safety. Safety and tolerability analyses will be based on descriptive statistics for vital signs, physical examination 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.

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 19.1). Serology testing for HIV, HBsAg, Syphilis Ab, and Hepatitis C antibody will be conducted at the Screening visit.

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

6.2 Pharmacokinetics

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, and throat
- Respiratory
- Cardiovascular
- Musculoskeletal
- Abdominal
- Neurologic
- Extremities
- Dermatologic
- Lymph nodes

6.3.2 Vital Signs

Vital sign determinations, including BP, PR, respiratory rate, and body temperature will be performed after the subject has been supine for a 5-minute period at the Screening Visit, on the day of clinic admission Visit 2 (Day -1), Days 2 through Day 7, and on Visit 3 (Day 1) and Visit 4 (Day 8) within 120 minutes (on Day 1; within 60 minutes on Day 3) prior to administration of study drug and 30 minutes, 2 hours, 4 hours, 12 hours, and 24 hours post administration of study drug.

Potentially clinically significant (PCS) changes in systolic and diastolic blood pressure will be defined based on the following criteria provided by Pearl, Inc.:

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 (PCS) changes in heart rate 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

Any clinically significant abnormality noted post-randomization based on twelve-lead safety ECGs will be recorded as adverse events.

Machine-read ECG parameter data will be provided to the Investigator by local ECG lab(s).

6.3.4 Clinical Laboratory Tests

Laboratory testing (hematology with differential, chemistry and urinalysis) will be performed using standard methods.

Standardized meals will be administered at specified times after observing fasting times for blood draws.

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 4.

Table 3 List of Laboratory Tests

Hematology	Blood Chemistry	
Hematocrit[a] Hemoglobin Serum Iron Ferritin Platelet count Red blood cell (RBC) count White blood cell (WBC) count WBC differential Mean corpuscular volume (MCV) Mean cell haemoglobin (MCH) MCH concentration (MCHC)	Creatinine[b] Potassium (K+)[c] Sodium (Na+) Chloride (Cl-) Magnesium (Mg++) Calcium Inorganic phosphate Glucose[c] Uric Acid Bilirubin (Total) Blood Urea Nitrogen (BUN)	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 and analyzed (positive or negative) for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol (THC)].		
Breathalyzer Test: A breathalyzer test will be performed 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 the screening visit and urine hCG test at admission.		
For females of non-childbearing potential: A serum hCG test at the screening visit and urine hCG test at admission. In addition, a serum, follicle-stimulating hormone (FSH) test for confirmation of non-childbearing status will be performed at screening only.		
Abbreviations: eGFR=estimated glomerular filtration rate; HbsAg=hepatitis B surface antigen; hCG=human chorionic gonadotropin; HIV=human immunodeficiency virus; FSH=follicle-stimulating hormone. [a] Packed cell volume (PCV). [b] eGFR will be calculated by the Modification of Diet in Renal Disease (MDRD) equation following : http://www.columbiamedicine.org/divisions/gharavi/calc_egfr.php **C-MDRD (modified for Chinese) equation:** eGFR = 175 × (Serum Creatinine)-1.234 × (Age)-0.179 × (0.79 if Female) [c] Additionally, within 60 minutes prior to dosing and at 30 min, 2 hours, and 12 hours (Visit 4 only) post-dose of Treatment.		

Table 4 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
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 adverse event 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 is randomized will be summarized as medical history and not as a treatment-emergent adverse event (TEAE).

An AE is considered treatment-emergent (TEAE) if the date of onset is on or after the date of first dose of study drug in the study until the final Telephone Follow-up. 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.
- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, blood transfusion) are not considered AEs and the condition that results in the procedure is considered an AE (e.g., bleeding esophageal varices, dental caries).

An AE does **not** include:

- Overdose of either study drug or concurrent medication without any clinical signs or symptoms.
- Non-clinically significant abnormal laboratory values. (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 unexpected AE means any AE in which the specificity or severity is not consistent with the current Investigator’s Brochure (IB).

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 discontinuation)

- 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 (Table 4) 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 the Screening Visits 1 and 2.

6.3.7 Pregnancy Test

A serum hCG test and a urine hCG test at the Screening visit will be conducted for all females.

6.3.8 Concomitant Medications/Treatments

Concomitant medications will be collected 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. Data for all subjects who are randomized will be included in the subject data listings. Data for non-randomized subjects will be listed where available.

All PK and safety parameters will be summarized by treatment 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 Pharmacokinetic Summaries

Data imputation for pharmacokinetic 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 the end-of-treatment summary, 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 screened will be provided (*Table 1.1*). A flow chart of subject distribution will also be provided (*Figure 1.1*). This tabulation will include the number and percentage of subjects in each randomized treatment who were treated with the study treatment, who discontinued treatment prematurely, who withdrew from the study prematurely, and who completed the study. The number and percentage of randomized subjects included in the Safety and PK Populations will also be tabulated (*Table 1.3*). Informed consent is listed in *Listing 1.1*.

A summary of reasons for withdrawal from study treatment 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 by treatment group 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 in each treatment group. For categorical demographic and baseline variables, the frequency and percentage of subjects in each treatment group will be tabulated. Demographic data will be listed (Listing 1.1). Baseline information (including Serology Testing (Listing 4.1) and Medical and Surgical History (Listing 4.2)) will be listed.

Demographic variables summarized will include the following:

- Age
- Gender
- Race
- Ethnicity
- Smoking Status (including number of years smoked, time in years since last smoked)
- Weight
- Height
- 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 randomized 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 2016 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 discontinuation from study treatment for the subject. A medication with an onset date on or after the date of discontinuation 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.

Prior, concomitant, and post-treatment medications will be listed *(Listing 10.1)*.

7.3.3 Extent of Exposure to Study Medication and Compliance

Subject's exposure to a study treatment will be determined by the duration of time (days) for which the doses were administered, defined as "((End date of treatment – Date of first dose of treatment) + 1)". Percent compliance is defined as (total number of puffs of study treatment taken on a study day/total expected puffs taken on a study day) averaged across all days of a subject's dosing between start day of study treatment and last day on study treatment) x 100. For BGF MDI and GFF MDI, the expected number of puffs for a test day which is the last date of treatment will be 2, and the expected number of puffs for the last date of treatment which is not a test day will be 4 when a PM dose is taken but will be 2 otherwise; the expected number of puffs on dates prior to the last date of treatment will be 4.

The number of days of exposure to study treatment will be summarized for each treatment for the Safety Population. The tabulation will include the number and percentage of subjects with 1, 2, 3, 4, 5, 6, 7, and 8 days of exposure. The total person-years of exposure for a treatment group, defined as the total exposure in the study across all subjects in the treatment, will also be provided by treatment *(Table 1.6* for the Safety Population*)*.

In addition, treatment compliance will be provided in this summary. The treatment compliance will be categorized into 7 different groups depending on the degree of compliance: 0 – <20%, ≥20 – <40%, ≥40 – <60%, ≥60 – <80%, ≥80 – ≤100%, >100 – ≤120%, and >120%. Also provided in this summary will be descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for percent compliance by treatment. Treatment compliance will be reported in *Listing 6*. A listing of treatment dosing and dispensing information will be provided

in *Listing 5.* Any comments related to study medication or any other additional study comments will be listed *(Listing 10.5)*.

7.4 Pharmacokinetic Assessments

For the single dose administration, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes, and at 1, 2, 4, 8, 10, 12 and 24 hours.

Following 7 days of chronic dosing BID, time points for PK blood sample collection will be pre-dose within 60 minutes and post-dose at 2, 6, 20, and 40 minutes, and at 1, 2, 4, 8, 10, 12 and 24 hours starting on the morning of the 8th day.

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 the treatment period:

AUC_{0-t}	Area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration
AUC_{0-12}	Area under the plasma concentration-time curve from time 0 to 12 hours post dose
$AUC_{0-\infty}$	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 minutes
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

From the plasma budesonide, glycopyrronium and formoterol concentration-time data, the following PK parameters will be estimated for each subject where possible on Day 8 during the treatment period:

AUC_{0-12}	Area under the plasma concentration-time curve from time 0 to 12 hours post dose
C_{max}	Maximum observed plasma concentration, expressed in concentration units
t_{max}	Time to reach maximum observed plasma concentration (C_{max}), expressed in hours

AUC_{0-t}, AUC_{0-12}, and $AUC_{0-\infty}$, will be calculated using the linear-log 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 treatment 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 (LLQ) should be used in the estimation.
- C_{max} must not be used in the estimation.

In order for the selection to take place the adjusted r^2 value reported in [redacted] must be above 0.7.

$t_{1/2}$ will be calculated as $\ln 2/\lambda_z$.

For the purposes of parameter estimation, plasma concentration values below the LLQ 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 BLOQ 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 LLQ will be assigned a value of ½ LLQ 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).

In addition to the above PK parameters to be calculated on Day 1 and Day 8, accumulation ratios for AUC_{0-12} (RAC [AUC_{0-12}]) and C_{max} (RAC [C_{max}]) will be calculated by taking subject level ratios of Day 8 values to Day 1 values.

All concentration-time data reported by the bioanalytical laboratory, for each analyte, for each treatment, will be listed for subjects in the PK 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 treatment for each analyte will be listed (*Listing 8.2*).

Descriptive statistics for plasma concentrations of budesonide, formoterol, and glycopyrronium, by treatment, visit and time point will be summarized. 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 (of a statistic y) is calculated as GEOCV(y) (%) = 100*sqrt[(exp[var(ln[y])])-1], where sqrt is the square root function and "var" is variance.

Descriptive statistics for PK parameters of budesonide, glycopyrronium, and formoterol, will be summarized by treatment and visit. 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 parameter t_{max}, 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, formoterol, and glycopyrronium, will be presented for each treatment and each visit on the linear/linear scale and on the linear/log-linear scale.

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*).

7.5 Safety Assessments

Safety data will be summarized by treatment and listed. The safety of BGF MDI and GFF MDI will be assessed from physical examination findings, AE reporting including SAE reporting, vital signs (BP, PR, respiratory rate, and body temperature), clinical laboratory values (hematology, chemistry, and urinalysis), and findings from 12-lead ECGs. The incidence of AEs and SAEs will be tabulated by treatment. Summary statistics of assessed laboratory values will be tabulated by treatment.

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

Vital sign measurements (PR, BP, body temperature, and respiratory rate) as collected on eCRFs (see Section 6.3.2) during the study will be displayed in a vital sign listing, as well as weight and height (collected at the Screening visit) (*Listing 10.2*).

Summary statistics (n, mean, median, standard deviation, minimum and maximum) of pre-dose (in the respective period) and post-dose values (in the respective period) as well as changes from baseline values for systolic blood pressure, diastolic blood pressure and pulse rate will be tabulated by treatment group (*Table 3.4.1*). Baseline is defined (computationally) as the mean of all available pre-dose measurements taken on Day 1 prior to the start of dosing with study drug.

The percentage of subjects with potentially clinically significant values for vital signs at any time post-dose at a visit will be summarized by treatment based on the criteria in Table 1 and Table 2 *(Table 3.4.2)*. They will also be listed (*Tables 3.4.3 and 3.4.4*).

7.5.3 12-Lead Electrocardiogram

All clinically significant abnormalities after the first dosing through the treatment period until follow-up telephone will be reported as TEAEs and followed closely by the Investigator in order to assure the safety of the study subject.

7.5.4 Clinical Laboratory Tests

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) of assessment values for laboratory testing (hematology with differential (*Table 3.3.1*), serum chemistry including estimated eGFR (*Table 3.3.2 and 3.3.3*) will be tabulated by treatment group at each time point and at each visit. Urinalysis results will be listed (*Listing 9.3*) and tabulated (*Table 3.3.5*). Changes from baseline will also be summarized by treatment group at 24 hours post-dose at Day 8 (Visit 4). Baseline is the last assessment during the screening period (e.g. Visit 2).

Individual clinical laboratory variables for hematology, serum chemistry including estimated eGFR and urinalysis will be provided in listings (*Listings 9.1 - 9.3*).

Glucose and potassium will also be collected within 30 minutes and 2 hours post-dose at Visit 3, and 60 minutes pre-dose, and 30 minutes, 2 hours, 12 hours, and 24 hours post-dose at Visit 4. The values as well as the changes from baseline for each visit and time point will be summarized by treatment (Table 3.3.4). Baseline is the last assessment prior to the first dose of study treatment. Glucose and potassium are also included into the complete laboratory assessment at Visit 2.

For glucose and potassium, the frequency and percentage of potentially clinically significant values will be summarized by treatment group, at each post-dose timepoint (*Table 3.3.4*). Potentially clinically significant values for serum potassium and blood glucose may be found in Table 4 (CTCAE Version 4.03). Potentially clinically significant laboratory values for potassium, glucose, and other laboratory parameters will be listed (*Tables 3.3.6, 3.3.7, and 3.3.8*).

Shifts from baseline to 24 hours post-dose at Visit 4 (Day 9), based on reference ranges (Low, Normal, High), will be presented by treatment group for hematology and serum chemistry (*Table 3.3.9*) and for urinalysis (*Table 3.3.10*). Baseline is the last assessment during the screening period (e.g. Visit 2) for all laboratory assessments.

Many laboratory abnormalities observed during the course of a study will be included under a reported AE describing a clinical syndrome (e.g., 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.

7.5.5 Adverse Events

Treatment-emergent AEs (TEAEs) 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 treatment-emergent or not, will be included in the Listings.

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 a TEAE will be defined as the number of subjects experiencing an event.

An overall table of subjects with at least one TEAE will be summarized by treatment group, for subjects with AEs related to study treatment, with SAEs, with SAEs related to study treatment, with AEs leading to early discontinuation from study treatment, with SAEs leading to early withdrawal from study treatment, and with deaths (*Table 3.1.1*).

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

TEAEs will be summarized by (maximum) severity, with respect to SOC and preferred terms by treatment group (*Tables 3.2.1 – 3.2.3*).

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

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 listings (*Listing 10.1*). 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, as well as presented by treatment group (*Table 1.5.1*). 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.

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 PT010010, Version 2.1 dated 15 Nov 2016.

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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Analysis Set: PK Population

Figure 2.1.2 Mean Plasma Budesonide Concentration-Time Profile after Single Dose Administration on Day 1 and Chronic Dose Administration on Day 8 (Log-Linear Scale)

Analysis Set: PK Population

Table 2.1.2 Descriptive Statistics for Pharmacokinetic Parameters of Budesonide by Treatment and Visit

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Figure 2.2.1 Mean (+/- SE) Plasma Glycopyrronium Concentration-Time Profile after Single Dose Administration on Day 1 and Chronic Dose Administration on Day 8 (Linear-Linear Scale)

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Figure 2.2.2 Mean Plasma Glycopyrronium Concentration-Time Profile after Single Dose Administration on Day 1 and Chronic Dose Administration on Day 8 (Log-Linear Scale)

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Table 2.2.2 Descriptive Statistics for Pharmacokinetic Parameters of Glycopyrronium by Treatment and Visit

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Figure 2.3.2 Mean Plasma Formoterol Concentration-Time Profile after Single Dose Administration on Day 1 and Chronic Dose Administration on Day 8 (/Log-Linear Scale)

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(Analysis Set: PK Population)

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Figure 2.6.2 Individual Plasma Concentration-Time Profile of Formoterol after Single Dose Administration on Day 1 and Chronic Dose Administration on Day 8 (Log-Linear Scale)

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(Analysis Set: Safety Population)

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Table 3.3.3 Summary of Laboratory Results by Time of Assessment – Glucose and Potassium

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Table 3.3.9 Shifts from Baseline[a] to Day 8 Pre-Dose Laboratory Data – Hematology and Chemistry

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Listing 10.5 Listing of Comments

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APPENDIX 3: 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.

APPENDIX 1: DATA HANDLING RULES

Programming of the tables, listings and figures will be performed using [redacted] or a more recent version. The following table presents the algorithms to be used in [redacted] to calculate the derived variables, including rules for handling other missing data or partial dates, or irregular/unexpected data issues.

Category	Description	Data Handling Rule
1. Age (years)	Age (years)	Age = integer part of ([Informed Consent date – Birth date + 1]/365.25)
2. Smoking History	Former smoker	Former smokers are defined as those who have stopped smoking for at least 6 months prior to Screening (Visit 1).
	Months Since a Former Smoker Quit	(Date of Screening Visit 1 – Date Former Smoker Quit)/30.4375.
3. Medical History	Medical History Begin Date of Condition	Begin date of condition will be imputed for all subjects as the 1st of the month for the purpose of computing the onset day.
4. Surgical History	Surgical History Date of Surgery	Date of surgery will be imputed for all subjects as the 1st of the month for the purpose of computing the onset day.
5. First and Last Treatment Dates	date/time of first and last dose of a study treatment	The date and time (24 hr. clock) of the first dose of study treatment will be taken from the Dosing eCRF. The date of the last dose of study treatment will be the last date of dosing from the Dosing eCRF for the treatment.
6. Last Visit Date	Date of Last Visit	Date of last visit according to the Visit eCRF.
7. Last Study Participation Date (STDM variable, typically named RFPENDTC)	Last Study Participation Date (STDM variable, RFPENDTC), where SDTM denotes Study Data Tabulation Model	Last study participation date is defined as last known date of contact which would be the later of the following dates: last visit date, date of the last dose, date of last contact if lost-to-follow-up, date of telephone follow-up, or death date.
8. Study Day Definitions	**Study Day** for assessment/event which occurs on or after the start of study treatment	Study Day = Date of assessment/event – date of the first dose of study treatment + 1.
	Study Day for assessments/events on	**Study Day** for assessments/events on days prior to the first dose of study treatment in the

Category	Description	Data Handling Rule
	days prior to the first dose of study treatment in the study	study
	Study Day Post-Treatment of Assessment or event which occurs after study treatment	Study Day = 'P' concatenated with the number of days post-treatment that the assessment or event occurred which is defined as Date of assessment/event – date of last dose of study treatment.
	Study Day of Randomization	Study Day of Randomization = date of randomization – date of the first dose of study treatment in the study + 1. Study Day is 1 if baseline day is on the day of randomization.
	First Dose Day	**First Dose Day** in the study is defined as the study day of the first dose of study treatment in the study (Study Day 1).
	Last Dose Day	**Last Dose Day** in the study is defined as the study day of the last dose of study treatment in the study (defined as the last date of dosing from the Dosing CRF pages).
	Last Study Day	**For subjects who did not receive study treatment in the study (e.g., Non-Randomized subjects)**, Last Study Day is defined as (the later of the last visit date and the date of last contact for subjects lost-to-follow-up from the Study Completion/Early Discontinuation CRF) – Date of Screening Visit + 1. **For subjects who received study treatment in the study,** Last Study Day is defined as (the later of the last visit date and the date of last contact for subjects lost-to-follow-up from the Study Completion/Early Discontinuation CRF) – first dose date in the study + 1.
	Days Since Last Dose for event (e.g., Death)	**Days Since Last Dose** is defined as date of event – date of last dose of study treatment.
	The duration of any event	The duration of any event is defined as (stop date – start date + 1).
9. Duration of event	The duration of any event	The duration of any event is defined as (stop date – start date + 1).

Category	Description	Data Handling Rule
10. Multiple assessments for the same visit	Vital Signand Laboratory assessments	• All data will be listed in data listings. • The last of multiple valid assessments within a post-baseline study time window will be used for summaries and statistical testing. • If there are multiple laboratory values for the same parameter at post-baseline pre-dose of a visit, the last value will be chosen for analysis. The mean of all available pre-dose vital sign measurements for a vital sign parameter taken prior to the start of dosing for the Treatment Period will be used for calculation of baseline for a parameter.
11. Special Lab Value Handling (not including PK values)	Lab values with a prefix such as: '>', '<', '+' and 'Less than' Etc.	• '>': use the available original value +0.001 in the analyses. • '<': use the available original value –0.001 in the analyses. • '+': use the available original value without the prefix in the analyses. • '>=': use the available original value in the analyses. • '<=': use the available original value in the analyses.
12. Prior. concomitant, and post-treatment medication / treatment	Prior, concomitant, and post-treatment medication/treatment	**1.** Prior medication/treatment: is any medication/treatment taken prior to the first dose of study medication in the study (or the date of the randomization visit, Visit 3, if the date of the start of study medication is missing), even if this medication/treatment continued into the study medication treatment period. A medication/treatment will be considered prior if the start date of the medication/treatment is missing or the medication/treatment start date is before

Category	Description	Data Handling Rule
		first dose date of study medication in the study (or the date of the randomization visit, Visit 3, if the date of the start of study medication is missing). **2.** A medication/treatment will be identified as a concomitant medication/treatment if any of the following are true: o The start date is on or after the date of the start of study treatment (or the date of randomization, Visit 3, if missing), but prior to the date of completion of study medication (for subjects not having discontinued treatment early) or the date of discontinuation of study medication (for subjects who discontinued treatment early). o The end date is prior to the date of completion of study medication (for subjects not having discontinued treatment early) or the date of the discontinuation of study medication (for subjects who discontinued treatment early), but the end date is on or after the start of study medication in the study (or the date of the randomization visit, Visit 3, if missing). The medication/treatment is checked as 'Ongoing', and the start date of the medication/treatment is prior to the date of completion of study medication (for subjects not having discontinued treatment early) or the date of the discontinuation of study medication (for subjects who discontinued treatment early). **3.** A medication with an onset date on or after the date of completion of study medication (for subjects not having discontinued

Category	Description	Data Handling Rule
		treatment early) or on or after the date of discontinuation of study medication (for subjects who discontinued treatment early) will not be considered concomitant, but will be considered a **Post-Treatment medication**. **4.** Any medication/treatment which cannot be identified as Prior, Concomitant, or Post-Treatment will be considered as being in each of the possible categories depending on available information
13. Adverse event	Missing severity	For the AE summary by severity, an AE with missing severity will be deemed as Severe. Imputed values will not be listed in data listings.
	Missing relationship to study drug	For AE summary by relationship, an AE with a missing relationship to study drug will be deemed as Definitely related. Imputed values will not be listed in data listings.
	Treatment-emergent adverse event	An adverse event is considered treatment-emergent if an event occurs (or if there was a worsening [intensity and/or severity changed to worsened grades]) after the first dose of randomized study medication and on or before the date of discontinuation from or completion of randomized study medication. An adverse event that begins on the same date as the first dose of randomized study medication is treatment-emergent if the AE begins after the time of first dose or if the time of AE onset is unknown. A non-serious adverse event will not be considered to be treatment-emergent if its date of onset is after the date of completion of study medication (for subjects not having discontinued treatment early) or after the date of discontinuation from study medication (for subjects who discontinued treatment early). An SAE will not be considered to be treatment-emergent if its date of onset is after the date of completion of study medication (for subjects

Category	Description	Data Handling Rule
		not having discontinued treatment early) or after the date of discontinuation from study medication (for subjects who discontinued treatment early).
		If the AE start date is partial/missing, then • If AE start date is completely missing, then the AE is considered as treatment-emergent. • If both AE start month and day are missing and AE start year is the same or after the first dose year, then the AE is considered as treatment-emergent. • If AE start day is missing and AE start year and month are the same or after the first dose year and month, then the AE is considered as treatment-emergent. Missing/incomplete (partial) AE start and end dates will not be imputed for data listings.
14. Treatment Duration	Treatment |Duration	Treatment duration is defined as Date of last dose of a study treatment - Date of first dose of a study treatment +1.
15. Total Years of Exposure	Total years of exposure to study treatment	Total exposure (years) for a treatment as a whole is defined as the sum of all days of exposure for a treatment /365.25.
16. Exposure (days)	Exposure (days)	Exposure is defined as (Date of the last dose of the study treatment – Date of first dose of the study treatment + 1).
17. Total Expected Puffs	Total expected number of puffs taken of a study treatment	The expected number of puffs for a test day which is the first date of treatment or the last date of treatment will be 2, the expected number of puffs for the last date of treatment which is not a test day will be 4 when a PM dose has been taken and then 2 otherwise, and the expected number of puffs on dates after the first date of treatment and prior to the last date of treatment will be 4. Thus, for test treatments, the total expected number of puffs will be 4 x (treatment end date – treatment start

Category	Description	Data Handling Rule
		date-1) + expected number of puffs on last day of treatment + expected number of puffs on first day of treatment.
18. Treatment Compliance (%)	Treatment Compliance (%) for a treatment	Percent compliance is defined as (total number of puffs of study treatment taken on a study day/total expected puffs taken on a study day) averaged across all days of a subject's dosing between start of study treatment and last day on study treatment) x 100. For MDI test treatments, the expected number of puffs for a test day which was the first or the last date of treatment is 2, the expected number of puffs for the last date of treatment which was not a test day is 4 when a PM dose was taken and then 2 otherwise; the expected number of doses on dates after the first date of treatment and prior to the last date of treatment is 4.
19. Hard coding	Hard coding for data analysis	Hard Coding is not allowed during data analysis unless if agreed in writing by the Sponsor.
20. PK analysis	Considerations to be made in the calculation of AUC and λ_z and for descriptive statistics	The following considerations will be made in the calculation of AUC and λ_z and descriptive statistics: • AUC will be calculated by the linear-log trapezoidal method • The final selection of samples for calculation of λ_z will be based on visual inspection of individual log-concentration-time profiles. • The time range of samples used to estimate λ_z should preferably exceed the derived terminal half-life $t_{½}$ (= ln 2/λ_z). This consideration may affect the interpretability of the estimated λ_z and $t_{½}$. • All the samples used to calculate λ_z should ideally fall in the log-linear elimination phase. PK modeling may

Category	Description	Data Handling Rule
		be used as a complementary tool to determine the start of the elimination phase, i.e., where the decline in plasma concentration is mainly due to elimination. • At least three samples above LLQ obtained during the log-linear elimination phase will be included in the calculation of the λ_z . If there are not at least three samples above the LLQ in the log linear elimination phase, λ_z will not be estimated. • All values below LLQ will be ignored (set to missing) in the non-compartmental analysis for computing pharmacokinetic parameters except that Day 1 pre-dose concentrations below the LLQ will be set to 0. For descriptive statistics for concentrations and for the concentration figures, all values below LLQ will be assigned a value of ½ LLQ 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).

APPENDIX 3 CTCAE LABORATORY TEST CRITERIA FOR SHIFT TABLES AND CENTRAL LABORATORY REFERENCES RANGES FOR USE IN FLAGGING ABNORMAL VALUES

Trial Sponsor: Pearl Therapeutics, Inc.

Protocol Number: PT010010-01

Investigational Drug: Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010, BGF metered dose inhaler [MDI])

Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003, GFF MDI)

Indication: COPD

Drug Number: PT010

Dosage Form/Strength:

- BGF MDI 320/14.4/9.6 µg ex-actuator BID
- BGF MDI 160/14.4/9.6 µg ex-actuator BID
- GFF MDI 14.4/9.6 µg ex-actuator BID

Protocol Title: A Phase I, Randomized, Double-Blind, Parallel-Group, Study to Assess the Pharmacokinetics and Safety of Two Doses of PT010 and a Single Dose of PT003 in Healthy Chinese Adult Subjects Following A Single Administration and After Chronic Administration for 7 Days

CTCAE LABORATORY TEST CRITERIA

Investigations				
	Grade			
Adverse Event	1	2	3	4
Alanine aminotransferase increased	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Alkaline phosphatase increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	>ULN – 3.0 x ULN	>3.0 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	>ULN – 1.5 x ULN	>1.5 – 3.0 x ULN	>3.0 – 10.0 x ULN	>10.0 x ULN
Cholesterol high	>ULN – 300 mg/dL; >ULN –7.75 mmol/L	>300 – 400 mg/dL; >7.75 –10.34 mmol/L	>400 – 500 mg/dL; >10.34 –12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Creatinine increased	>1 – 1.5 x baseline; >ULN -1.5 x ULN	>1.5 – 3.0 x baseline; >1.5 -3.0 x ULN	>3.0 baseline; >3.0 – 6.0 xULN	>6.0 x ULN
Chloride				
GGT increased	>ULN – 2.5 x ULN	>2.5 – 5.0 x ULN	>5.0 – 20.0 x ULN	>20.0 x ULN
Hematocrit	n/a	n/a	n/a	n/a

Investigations				
	Grade			
Adverse Event	1	2	3	4
Hemoglobin increased	Increase in >0 – 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 – 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	n/a
Anemia (hemoglobin decreased)	Hemoglobin (Hgb) <LLN– 10g/dL; <LLN – 6.2 mmol/L; <LLN – 100 g/L	Hgb <10.0 – 8.0 g/dL; <6.2 – 4.9 mmol/L; <100 – 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Serum Iron	n/a	n/a	n/a	n/a
Ferritin	n/a	n/a	n/a	n/a
Red blood cells (erythrocytes)	n/a	n/a	n/a	n/a
Leukocytosis (White blood cell increased) (a)	n/a	n/a	>100,000/mm^3	Clinical manifestations of leucostasis; urgent intervention indicated

Investigations				
	Grade			
Adverse Event	1	2	3	4
White blood cell decreased	<LLN – 3000/mm^3; <LLN – 3.0 x 10^9/L	<3000 – 2000/mm^3; <3.0 – 2.0 x 10^9 /L	<2000 – 1000/mm^3; <2.0 – 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
White blood cell differential	n/a	n/a	n/a	n/a
Platelet count decreased	<LLN – 75,000/mm3; <LLN – 75.0 x 10^9/L	<75,000–- 50,000/mm3; <75.0 – 50.0 x 10^9/L	<50,000 – 25,000/mm3; <50.0 – 25.0 x 10^9/L	<25,000/mm3; <25.0 x 10^9/L
Mean corpuscular volume	n/a	n/a	n/a	n/a
Mean cell hemoglobin (MCH)	n/a	n/a	n/a	n/a
MCH concentration	n/a	n/a	n/a	n/a

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Acidosis	pH <normal, but >=7.3	-	pH <7.3	Life-threatening consequences
Alkalosis	pH >normal, but <=7.5	-	pH >7.5	Life-threatening consequences
Urea	n/a	n/a	n/a	n/a
Blood Urea Nitrogen (BUN)	n/a	n/a	n/a	n/a
Proteinuria	1+ proteinuria; urinary protein <1.0g/24 hrs	Adults: 2+ proteinuria; urinary protein 1.0 – 3.4 g/24 hrs. Pediatric: urin P/C (protein/creatinine) ratio 0.5 - 1.9	Adults: urinary protein >=3.5 g/24 hrs; Pediatric: urine P/C >1.9	n/a
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 - 13.5 mg/dL; >3.1 - 3.4 mmol/L; Ionized calcium >1.6 - 1.8 mmol/L; hospitalization indicated	Corrected serum calcium of >13.5 mg/dL; >3.4 mmol/L; Ionized calcium >1.8 mmol/L; life-threatening consequences

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hyperglycemia	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Hyperkalemia (Potassium Increased)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Hypermagnesemia (Magnesium Increased)	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	n/a	>3.0 - 8.0 mg/dL; >1.23 - 3.30 mmol/L	>8.0 mg/dL; >3.30 mmol/L; life-threatening consequences
Hypernatremia (Sodium Increased)	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Hypertriglyceridemia	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
Hypoalbuminemia (Albumin Decreased)	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypocalcemia (Calcium Decreased)	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium<LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0- 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 - 6.0 mg/dL; <1.75 - 1.5 mmol/L; Ionized calcium <0.9- 0.8 mmol/L; hospitalizationindicated	Corrected serum calcium of <6.0 mg/dL; <1.5 mmol/L;Ionized calcium <0.8 mmol/L;life-threatening consequences
Hypoglycemia (Glucose Decreased)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Hypokalemia (Potassium Decreased)	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Hypomagnesemia (Magnesium Decreased)	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 - 0.7 mg/dL; <0.4 - 0.3 mmol/L	<0.7 mg/dL; <0.3 mmol/L; life-threatening consequences
Hyponatremia (Sodium Decreased)	<LLN - 130 mmol/L	n/a	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences

Metabolism and Nutrition Disorders				
	Grade			
Adverse Event	1	2	3	4
Hypophosphatemia (Phosphate Decreased)	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences

Renal and Urinary Disorders				
	Grade			
Adverse Event	1	2	3	4
Chronic kidney disease	eGFR (estimated Glomerular Filtration Rate) or CrCl (creatinine clearance) <LLN -60 ml/min/1.73 m^2 or proteinuria 2+ present; urine protein/creatinine >0.5	eGFR or CrCl 59 - 30 ml/min/1.73 m^2	eGFR or CrCl 29 - 15 ml/min/1.73 m^2	eGFR or CrCl <15 ml/min/1.73 m^2; dialysis or renal transplant indicated

Acute kidney injury	Creatinine level increase of >0.3 mg/dL; creatinine 1.5 - 2.0 x above baseline	Creatinine 2 – 3 x above baseline	Creatinine >3 x baseline or >4.0 mg/dL; hospitalization indicated	Life-threatening consequences; organ failure; urgent operative intervention indicated
(a) Grade 1 and Grade 2 not categorized in CTCAE4; Grade 1 and 2 based on reference laboratory alert criteria of 40,000 /mm^3 (LabCorp)				

Protocol Reference Range Definitions

For reference range definitions, refer to the document pt010010 lab range site 001 20170405.pdf