STATISTICAL ANALYSIS PLAN FOR STUDY PT010018

Protocol Number:	PT010018
Investigational Drug and Drug Number:	BGF MDI; PT010
Indication:	COPD
Dosage Form/Dose:	• BGF MDI 320/14.4/9.6 µg ex-actuator

PT010018 Protocol Title: A Study to Assess the Pharmacokinetics and Safety of PT010 in Subjects With Moderate to Severe COPD Following Single and Repeat Dose Administration

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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**
1.1	12-Dec-2017	Page 29: changed "AUC_{0-t}, AUC_{0-12}, and $AUC_{0-\infty}$, will be calculated using linear log trapezoidal method." to "AUC_{0-t}, AUC_{0-12}, and $AUC_{0-\infty}$, will be calculated using the linear up/log down method." Page 31: 1st paragraph deleted 'in the Safety Population' at the end. Page 35: added "Figure 2.1.1.1" Page 36: added "Figure 2.2.1.1" and "Figure 2.3.1.1" Page 39: deleted "(PCS)" in "Table 3.5.2" title Page 41: changed to "Safety Population" in "Listing 8.1" subtitle Page 29: Adjusted r^2 value reported in [redacted] must be ≥ 0.8. "For all subjects in the PK Population" added to the below statement: "In addition, all calculated PK parameters for each subject for each analyte will be listed (*Listing 8.2*) for all subjects in the PK Population."	V1.0
1.2	15-Dec-2017	SAP text updated to address comments following delivery of Dry Run 1.	V1.1
1.3	18-Dec-2017	Removal of reference to randomized treatment to indicate study treatment. Abbreviations for C_{min} and C_{av} added to list of abbreviations. T90 added	V1.2

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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
$AUC_{0-tlast}$	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
C_{av}	Average concentration during a dosing interval
CL/F	Apparent Total Body Clearance
C_{max}	Maximum Observed Plasma Concentration
C_{min}	Lowest concentration in the dosing interval
COPD	Chronic Obstructive Pulmonary Disease
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
IEC	Independent Ethics Committee
IRB	Institutional Review Board

λ_z	Apparent Terminal Elimination Rate Constant
LLOQ	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	Millisecond
NCA	Non-Compartmental Analysis
PCS	Potentially Clinically Significant
PK	Pharmacokinetics
PT	Preferred Term
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}
Rlin	Linearity ratio
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
tlast	time of last measurable (positive) concentration
t_{max}	Time To Maximum Observed Plasma Concentration

Vd/F	Apparent Volume of Distribution
WHO	World Health Organization

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 PT010018. 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 PT010018-00 Protocol (Version 1.0 dated 14 June 2017) and the CRF Revision 02 dated 11 September, 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, open label, single center study to assess the pharmacokinetics (PK) and safety of BGF MDI 320/14.4/9.6 µg in subjects with moderate to severe chronic obstructive pulmonary disease (COPD) following a single administration and after repeat dose administration for 7 days.

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

- To assess the PK profile of BGF MDI in subjects with moderate to severe COPD after single dose administration on the first treatment day and after 7 days of repeat dosing.

2.1.2 Safety Objective

- To assess the safety and tolerability of BGF MDI in subjects with moderate to severe COPD after single dose administration on the first treatment day and after 7 days of repeat dosing.

2.2 Study Endpoints

2.2.1 Pharmacokinetic Endpoints

Pharmacokinetics of BGF MDI will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol pre-dose and at various times post-dose on Day 1 and Day 8.

2.2.1.1 Primary PK Endpoints

- Maximum plasma concentration (C_{max})
- Area under the plasma concentration-time curve from 0 to 12 hours (AUC_{0-12})
- Area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration ($AUC_{0-tlast}$) (Day 1 only)

2.2.1.2 Secondary PK Endpoints

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

2.2.1.3 Other PK Endpoints

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

- Apparent terminal elimination half-life ($t_{1/2}$)
- Apparent total body clearance (CL/F)
- Apparent volume of distribution (Vd/F)
- Terminal elimination rate constant (λ_z)

The following will be derived based on 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}])
- Linearity ratio (Rlin [$AUC_{0-12}/AUC_{0-\infty}$])

2.2.2 Safety Endpoints

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

3. STUDY DESIGN AND ANALYTICAL CONSIDERATIONS

3.1 Study Design

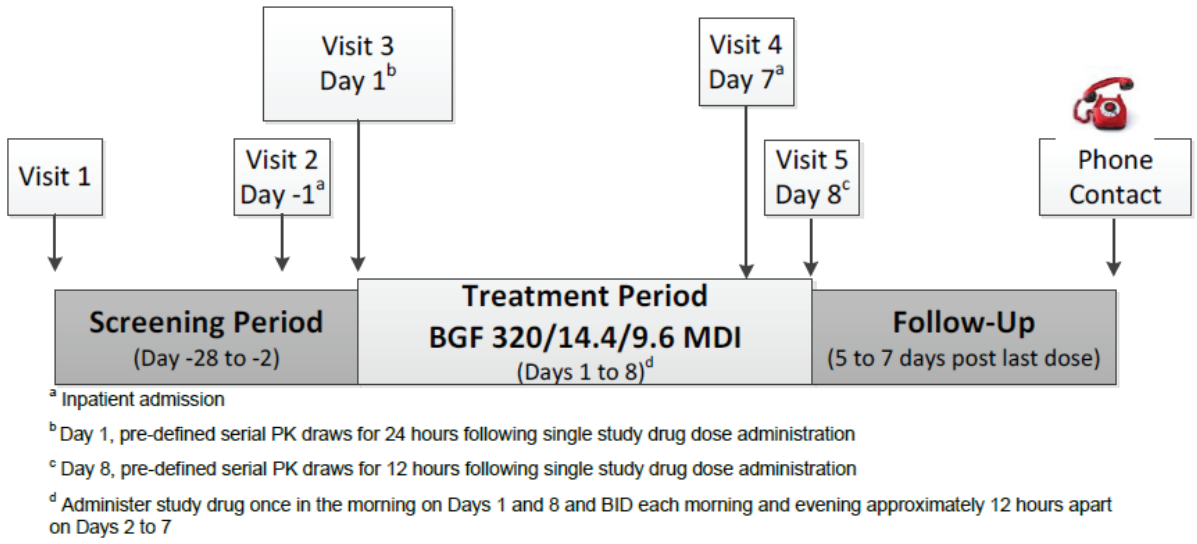
This is a Phase I, single-center, open-label, study to assess the PK and safety and tolerability of BGF MDI in subjects with moderate to severe COPD. Pharmacokinetics will be assessed following a single administration and after repeat dose administration for 7 days. Safety will be assessed during the 8-day treatment period and throughout the entire study until subjects are released from participation. The study drug will be administered by oral inhalation. It is planned that the study will enroll an estimated 30 eligible subjects to have approximately 24 completers for the assessment of single and multiple dose PK of BGF MDI 320/14.4/9.6 µg in subjects with COPD.

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 up to 7 weeks, with an expected range of participation between 2.5 to 7 weeks.

3.1.1 Overall Study Design and Plan

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

Figure 1 Study Design



[a] Inpatient admission

[b] Day 1, pre-defined serial PK draws for 24 hours following single study drug dose administration

[c] Day 8, pre-defined serial PK draws for 12 hours following single study drug dose administration

[d] Administer study drug once in the morning on Days 1 and 8 and BID each morning and evening approximately 12 hours apart on Days 2 to 7

Note: All study drugs are administered by oral inhalation. A single dose of study drug will be administered on Day 1 (Visit 3) 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 (Visit 5). Administration of study drug should occur at approximately the same time of day for all morning dosing and at the same time of day for all evening dosing.

Subjects who provide informed consent, will be provided a unique subject number at Screening and undergo Screening procedures. Only subjects continuing to meet entry inclusion/exclusion criteria on Day 1 will be assigned a unique subject enrollment number and will be dosed in the study.

Subjects will be admitted to the clinic on Day -1 and discharged on Day 2 and return for clinic admission on the evening of Day 7, with discharge on Day 8 after all assessments are complete.

During the inpatient treatment period, study specified procedures will be performed and will include safety assessments and pre-, post-dose serial blood draws as defined in Protocol Section 7.5 and in Table 8-1, Table 8-2, and Table 8-3 of the study protocol. Upon completion of the study, a follow-up phone call will be conducted at least 5 days but no longer than 7 days from the date of last administration on Visit 5 (Day 8).

3.1.2 Prior, Concomitant, Prohibited Medications

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

All formulations of budesonide, glycopyrronium, or formoterol fumarate used as monotherapy or in combination to treat COPD or any other condition are prohibited for a minimum of 4 weeks before Visit 1 and during the study.

All subjects entering the study on allowed inhaled COPD maintenance therapies for the management of their COPD should have been maintained on a stable dose of this treatment for at least 4 weeks prior to Visit 1. These COPD maintenance will be withheld after their last dose for the day on Day -1 (Visit 2) and throughout the study.

Short acting bronchodilators will be withheld 6 hours prior to spirometry assessment at the Screening Visit and throughout the study except study-provided Ventolin HFA for use as needed for symptom relief. Additional prohibited COPD medications and associated cessation periods prior to Visit 1 are summarized in Table 5-2 of the study protocol. Other prohibited medications are summarized in Section 5.4.2 of the study protocol.

3.2 Randomization and Blinding

This study is open-label, single arm study so no blinding or randomization occurred in the study.

3.3 Hypothesis Testing

No formal hypothesis tests will be performed for this study.

3.4 Sample Size

This study is descriptive in nature. [redacted]

3.5 Study Procedures

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

3.6 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 5 (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 treated subjects who receive at least one dose of 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 treated subjects who have sufficient data to reliably calculate at least one PK parameter for at least one analyte and who do not have major protocol deviations which affect the PK analysis. Major protocol deviations can result in exclusion of all data collected for 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 upon by the study team and documented prior to database lock.

Steady state is expected to be achieved within 3 days for all analytes (budesonide, glycopyrronium, and formoterol). If a subject has missed any of the scheduled doses in the 3 days prior to Day 8, the Day 8 concentration data for that subject will be excluded from the PK Population and will not contribute to the non-compartmental analysis.

Reasons for exclusion from the PK Population will documented in the Blinded Data Review meeting 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 after treatment with BGF MDI. The Safety Population will be used to summarize safety. Safety and tolerability analyses will be based on descriptive statistics for vital signs, ECG, 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 will be assessed using plasma concentrations of budesonide, glycopyrronium, and formoterol pre-dose and at various times post-dose on Day 1 and Day 8 (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 BP and heart rate will be performed after the subject has been supine for a 5-minute period at the Screening Visit, on the day of clinic admission (Day -1; Visit 2), and on the day of clinic admission (Day 7, Visit 4), and Visit 5 (Day 8) within 60 minutes prior to administration of study drug and 12 hours post administration of study drug (Day 8 only).

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

A **Clinically Significant Abnormality** for a 12-Lead ECG measurement identified by the investigator as a clinically significant abnormality will be recorded as an Adverse Event 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.

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

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

6.3.4 Clinical Laboratory Tests

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

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 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+) 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) at Screening and at inpatient admission days for drugs of abuse including amphetamine, opiate, cocaine, barbiturates, benzodiazepines, and marijuana [tetrahydrocannabinol (THC)].		
Alcohol Breathalyzer Test: A breathalyzer test will be performed at Screening and at inpatient admission days for the presence of alcohol (positive or negative).		
For all females: A serum hCG test at Screening and urine hCG test on inpatient admission days.		
[a] Packed cell volume (PCV). [b] eGFR will be calculated by the Chronic Kidney Disease Epidemiology Collaboration Equation		

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
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 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 an SAE.

All AEs that occur at the time of and following the first administration of study drug through the final telephone follow-up will be considered as being Treatment-Emergent Adverse Events (TEAEs).

An AE is considered as On-Treatment if the onset date of the adverse event is on or after the first day of dose of study treatment, and up to and including the date completion of study treatment or the last day of premature discontinuation from study treatment +1 day. An adverse event that begins on the same date as the first dose of study treatment is On-treatment if the AE begins after the time of first dose or if the time of AE onset is unknown.
An AE is considered as Post-treatment if the onset date of the adverse event is after the date completion of study treatment or on or after the last day of premature discontinuation from study 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 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 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

A serum hCG test at Screening and a urine hCG test on inpatient admission days 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.

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 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 shift tables and for determining incidence of clinically significant values.

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*). This tabulation will include the number and percentage of subjects 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 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 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). Baseline information 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, average number of cigarettes smoked per day)
- 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 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 Enhanced (WHO-DDE) + WHO HD 3Q2017 (September 2017) or later, and C3 format coding will be used.

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 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 10.1.1)*.

7.3.3 Extent of Exposure to Study Medication and Compliance

Subject's exposure to 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. The expected number of puffs will be 2 on Day 1 and Day 8, and the expected number of puffs will be 4 on Day 2 through Day 7.

The number of days of exposure to study treatment will be summarized 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, defined as the total exposure in the study across all subjects, will also be provided *(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 (*Table 1.6*). Treatment compliance will be reported in *Listing 6.1.* 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

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, 18, and 24 hours.

Following 7 days of repeat 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, and 12 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:

$AUC_{0\text{-}tlast}$	Area under the plasma concentration-time curve from 0 to the time of the last measurable plasma concentration
$AUC_{0\text{-}12}$	Area under the plasma concentration-time curve from time 0 to 12 hours post dose
$AUC_{0\text{-}\infty}$	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 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
tlast	time of last measurable (positive) concentration

From the plasma budesonide, glycopyrronium and formoterol concentration-time data, $AUC_{0\text{-}12}$, C_{max} and t_{max} will be estimated for each subject where possible on Day 8 during the treatment

period. In addition, Fluctuation, Swing, C_{av}, and C_{min} will be estimated and reported where feasible on Day 8.

Fluctuation	Degree of fluctuation $[(C_{max}-C_{min})/C_{av}]$
Swing	$[(C_{max}-C_{min})/C_{min}]$
C_{av}	Average concentration during a dosing interval.
C_{min}	The lowest concentration in the dosing interval, expressed in concentration units

AUC_{0-t}, AUC_{0-12}, and $AUC_{0-\infty}$, will be calculated using the linear up/log down 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 limit of quantification (BLOQ) 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 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 that are BLOQ 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).

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.

Steady state is expected to be achieved after 3 consecutive days of dosing for budesonide, glycopyrronium, and formoterol.

The linearity ratio (Rlin [$AUC_{0-12}/AUC_{0-\infty}$]) will also be calculated, for which the AUC_{0-12} on Day 8 is divided by the $AUC_{0-\infty}$ on Day 1.

To estimate the RAC values and Rlin, natural-log transformed AUC_{0-12}, $AUC_{0-\infty}$, and C_{max} of budesonide, glycopyrronium, and formoterol between Day 8 and Day 1, will be analyzed using a mixed model with day as a fixed effect and subject as a random effect. A separate mixed model will be fit for each analyte and ratio type. For each analyte, the estimated ratio of geometric least square mean (LSM) for Day 8 to Day 1 and the corresponding 90% confidence interval (CI) will be determined by exponentiating the mean difference between Day 8 and Day 1 and the associated CI (on the logarithm scale). The estimated ratio of geometric LSM and its corresponding 90% CI will be an estimate of RAC or Rlin with the 90% CI.

The residual variance component from the model estimating Rlin will provide an estimate of intra-subject variability. The model-based geometric coefficient of variation for the model which estimates Rlin is calculated as 100*sqrt[(exp[residual_variance_component])-1], where sqrt is the square root function and residual_variance_component is the residual variance component from the model estimating Rlin. This model-based geometric coefficient of variation will be displayed.

If the effective rate of drug accumulation is estimable, the time to reach steady state will be estimated for each analyte using the methodology of Panebianco and Maes (Panebianco and Maes 2009). T_{90} will be reported.

Descriptive statistics for plasma concentrations of budesonide, glycopyrronium, and formoterol, by day and time point will be summarized using the Safety 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 day. 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, glycopyrronium, and formoterol will be plotted 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*).

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*) for all subjects in the PK Population.

7.5 Safety Assessments

Safety data will be summarized and listed. The safety assessments for BGF MDI included 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

Vital sign measurements (PR, BP) 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 heart rate will be tabulated (*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 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

The QTcF is defined as [QT/($RR^{1/3}$)]. Heart rate (bpm) is estimated as 60,000/RR, where RR is in units of ms. These assessments will be tabulated for each assessment time.

A **Clinically Significant Abnormality** for a 12-Lead ECG measurement identified by the investigator as a clinically significant abnormality will be recorded as an Adverse Event 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 (*Listing 10.6*). Summary statistics (mean, median, standard deviation and range) for raw values in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated. These assessments will be tabulated for each scheduled timepoint at each visit (*Table 3.5.1*). Data from unscheduled visits will not be used for the by-visit summaries. Data from both scheduled and unscheduled visits will be listed. ECG data from subjects with pacemakers will not be included in analyses, but will be listed.

Data from unscheduled visits will not be used for the by-visit summaries but both scheduled-visit data and unscheduled-visit data are candidates for clinically significant values.

Potentially clinically significant ECG parameter values will be identified based on listed criteria. The number and percentage of subjects who had such values observed any time post-dose will be tabulated (*Table 3.5.2*) and listed (*Table 3.5.3*).

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*) will be tabulated at each time point and at each visit. Urinalysis results will be listed (*Listing 9.3*) and tabulated (*Table 3.3.3*). Changes from baseline will also be summarized at Day 8 (Visit 5). Baseline is the last assessment during the screening period.

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

Shifts from baseline to Visit 5 (Day 8), based on reference ranges (Low, Normal, High), will be presented for hematology and serum chemistry (*Table 3.3.4*) and for urinalysis (*Table 3.3.5*). Baseline is the last assessment during the screening period 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.

Potentially clinically significant laboratory values will be identified based on listed criteria. Since a reduction in potassium and an increase in blood glucose are known class effects of beta-agonists, all potassium or glucose assessments for subjects who experienced newly occurring or worsening potentially clinically significant values after start of the study treatment will be provided in separate listings (*Tables 3.3.7* and *3.3.8*). For all laboratory parameters other than glucose and potassium, all laboratory data for the parameter identified as potentially clinically significant for a subject will be listed (*Table 3.3.9*).

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 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 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 discontinuation from study treatment, with SAEs leading to early withdrawal from study treatment, 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) for the Safety Population (*Table 3.1.2*).

On-treatment AEs will be summarized by (maximum) severity, with respect to SOC and preferred terms (*Table 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, Table 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 listing (*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. 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 PT010018, Version 1.0 dated 14 June 2017.

10. STATISTICAL SOFTWARE

[redacted] or later in the UNIX environment will be used for all statistical analyses.

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

11. REFERENCES

[redacted]

APPENDIX 1: DATA HANDLING RULES

This appendix is provided in a separate document.

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APPENDIX 3: SAS 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.