AstraZeneca

Statistical Analysis Plan

Study Code	PT010008
NCT#	NCT03313570
Date	17 JULY 2017

A Randomized, Double-Blind, Parallel-Group, 52-Week, Chronic-Dosing, Multi-Center Study to Assess the Safety and Tolerability of PT010, PT009, and PT003 in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

STATISTICAL ANALYSIS PLAN FOR STUDY PT010008

Protocol Number:	PT010008
Investigational Drug and Drug Number:	BGF MDI; PT010 GFF MDI; PT003 BFF MDI; PT009
Indication:	COPD
Dosage Form/Dose:	• BGF MDI 320/14.4/9.6 µg ex-actuator BID • GFF MDI 14.4/9.6 µg ex-actuator BID • BFF MDI 320/9.6 µg ex-actuator BID

PT010008 Protocol Title: A Randomized, Double-Blind, Parallel-Group, 52-Week, Chronic-Dosing, Multi-Center Study to Assess the Safety and Tolerability of PT010, PT009, and PT003 in Subjects with Moderate to Very Severe Chronic Obstructive Pulmonary Disease

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Signed Agreement on Statistical Analysis Plan

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

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
ATC	anatomic therapeutic class
BFF MDI	Budesonide and Formoterol Fumarate Metered Dose Inhaler
BGF MDI	Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler
BID	bis in die, twice daily
bpm	beats per minute
BMD	bone mineral density
BMI	body mass index
C	cortical cataract
CAT	Chronic Obstructive Pulmonary Disease Assessment Test
CCV	cardio- and cerebrovascular
CEC	Clinical Endpoint Committee
CI	confidence interval
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
cm	centimeter
COPD	chronic obstructive pulmonary disease
CTCAE	Common Terminology Criteria for Adverse Events
DBP	diastolic blood pressure
DEXA	dual energy x-ray absorptiometry
DMC	data monitoring committee
DMP	data management plan

E-RS	EXACT Respiratory Symptoms
ECG	electrocardiogram
eCRF	electronic case report form
eDiary	electronic Diary
e.g.	exempli gratia; for example
EoT	end of treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
ex-actuator	dose delivered from the actuator (i.e., mouthpiece) of the MDI
EXACT	Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes
EXACT-RS	Exacerbations of Chronic Pulmonary Disease Tool – Patient Reported Outcomes- Respiratory Symptoms
GFF MDI	Glycopyrronium and Formoterol Fumarate Metered Dose Inhaler
GGT	gamma glutamyl transferase
hCG	human chorionic gonadotropin
HFA	hydrofluoroalkane
HLGT	High Level Group Term
HLT	High Level Term
HR	heart rate
ICF	informed consent form
ICS	inhaled corticosteroid
i.e.	id est; that is
IOP	intraocular pressure
IWRS	interactive web response system
L	liter
LOCS III	Lens Opacities Classification System III
LogMAR	logarithm of the minimum angle of resolution
MACE	major adverse cardiovascular event

MCID	minimal clinically important difference
MDI	metered dose inhaler
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MNAR	missing not at random
µg	microgram
mITT	modified intent-to-treat
mL	milliliter
mm	millimeter
mmHg	millimeter of mercury
msec (ms)	millisecond
NC	nuclear color
NO	nuclear opalescence
OTC	over-the-counter
P	Posterior subcapsular
PCS	potentially clinically significant
PT	preferred term
PT003	Glycopyrronium and Formoterol Fumarate Inhalation Aerosol
PT009	Budesonide and Formoterol Fumarate Inhalation Aerosol
PT010	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol
QA	quality assurance
QC	quality control
QTcF	QT corrected using Fridericia's formula
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure

SD	standard deviation
SMQ	Standard MedDRA Query
SOC	system organ class
SOP	standard operating procedure
TC	telephone call
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO-DD	World Health Organization Drug Dictionary

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SAS

Ventolin

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 PT010008. 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 PT010008-01 Amended Protocol (Version 2.0 dated 18 March 2016) and the PT010008 CRFs (Revision 0.0 dated 06 August 2015).

2. STUDY OBJECTIVES AND ENDPOINTS

2.1 Study Objectives

2.1.1 Primary Objectives

- To evaluate the effect of BGF MDI, GFF MDI, and BFF MDI on bone mineral density (BMD) over 52 weeks.
- To evaluate the effect of BGF MDI, GFF MDI, and BFF MDI on ocular assessments over 52 weeks.

2.1.2 Secondary Objectives

- To assess the safety and tolerability of BGF MDI, GFF MDI, and BFF MDI over 52 weeks.

2.2 Study Endpoints

All assessments are relative to baseline assessments performed during the Study PT010006 Screening Period (between Visit 1 and Visit 4).

2.2.1 Bone Mineral Density Endpoints

2.2.1.1 Primary Bone Mineral Density Endpoint:

- Percent change from baseline in BMD of the lumbar spine measured using Dual Energy X-ray Absorptiometry (DEXA) scans of L2-L4 at Week 52.

2.2.1.2 Other BMD Endpoints:

- Percent change from baseline in total hip BMD measured using DEXA scans at Week 52 and at End of Treatment (EoT).
- Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4 at EoT.

2.2.2 Ocular Endpoints

2.2.2.1 Primary Ocular Endpoint

- Change from baseline in the Lens Opacities Classification System III (LOCS III) (P) Score (Severity of Posterior Subcapsular Cataract) at Week 52.

2.2.2.2 Other Ocular Endpoints

- Change from baseline in each scale of the LOCS III scores at Week 28, Week 52 (Nuclear Opalescence [NO], Nuclear Color [NC], and Cortical Cataract [C] only), and EoT (the last available time point).
- Proportion of subjects with LOCS III grade increases of ≥ 0.5 (Class 1), ≥ 1.0 (Class 2), or ≥ 1.5 (Class 3) units in each of the 4 scales at Week 28, Week 52, and EoT.
- Change from baseline in intraocular pressure (IOP) at Week 28, Week 52, and EoT.
- Proportion of subjects with IOP ≥ 22 mmHg at Week 28, at Week 52, and EoT.
- Proportion of subjects with change from baseline in IOP of ≥ 7 mmHg at Week 28, at Week 52, and EoT.
- Change from baseline in the Logarithm of the Minimum Angle of Resolution (LogMAR) visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) charts at Week 28, Week 52, and EoT.
- Change from baseline in horizontal cup-to-disc ratio at Week 28, Week 52, and EoT.
- Incidence of ocular treatment emergent adverse events (TEAEs) including cataract and glaucoma.

2.2.3 Safety Endpoints

The safety endpoints include:

- Adverse events (AEs).
- 12-lead electrocardiograms (ECGs).
- Clinical laboratory testing.
- Vital signs measurements.

2.2.4 Efficacy Endpoints

- Change from baseline in average daily rescue Ventolin (albuterol sulfate) hydrofluoroalkane (HFA) use.
- Percentage of days with no rescue Ventolin HFA use.
- Rate of moderate or severe chronic obstructive pulmonary disease (COPD) exacerbations.

- Rate of COPD exacerbations of any severity.
- Rate of Severe COPD exacerbations
- Change from baseline in: the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale symptom scores (RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms) over 52 weeks and over each 4-week interval of the 52-week Treatment Period.

3. STUDY DESIGN AND ANALYTICAL CONSIDERATIONS

3.1.1 Overall Study Design and Plan

This is a multi-center, randomized, double-blind, parallel-group, chronic-dosing (52 weeks), supplemental study to assess the effects of PT010, PT009, and PT003 on BMD, ocular assessments, and safety and tolerability in subjects with moderate to very severe COPD.

This 52 week study will be conducted in a sub-set of US subjects who completed the 24-week PT010006 study. The study is to be conducted at approximately 70 sites, contributing approximately 8 subjects per site. Across these sites, approximately 500 subjects randomized to double blind treatment will be included in Study PT010008 to provide approximately 425 subjects to complete the study at Visit 14 (Week 52). Subjects will receive the same treatment (BGF MDI, GFF MDI, or BFF MDI) they were randomized to in Study PT010006.

This safety study will evaluate the effects of BGF MDI, BFF MDI, and GFF MDI on BMD measurement, lenticular opacity, and ocular pressure assessments.

Baseline and demographic characteristics collected in Study PT010006 will be used for subjects participating in this study. Baseline assessments (BMD, lenticular opacity, fundoscopic examination, intraocular pressure, pupil dilatation, and visual acuity assessments) will be performed prior to randomization in Study PT010006. If the first two BMD scans differ by more than 5% (as determined by the local facility) for either site (i.e. first two hip or first two lumbar sites) a third scan should be obtained. The screening period may be extended up to a maximum of 21 additional days if additional time is needed to complete the assessments.

Subjects who complete visit 10a of Study PT010006 will transition to the remaining 28 weeks of treatment by completing Visit 10b (Week 24). Post-baseline lenticular opacity, fundoscopic examination, intraocular pressure, and visual acuity assessments will be performed prior to Visit 11 (Week 28) and Visit 14 (Week 52) or Treatment Discontinuation/Withdrawal Visit. A post-baseline BMD assessment will be performed prior to Visit 14 (Week 52) or Treatment Discontinuation/Withdrawal Visit. Subjects will return to the clinic at Visit 12 (Week 36), and Visit 13 (Week 44) to complete the required study procedures, return used medication and obtain new study drug. Subjects will return to the clinic at Visit 14 (Week 52) to complete the final study visit procedures.

All subjects will continue to receive sponsor-provided Ventolin HFA for rescue use throughout the study.

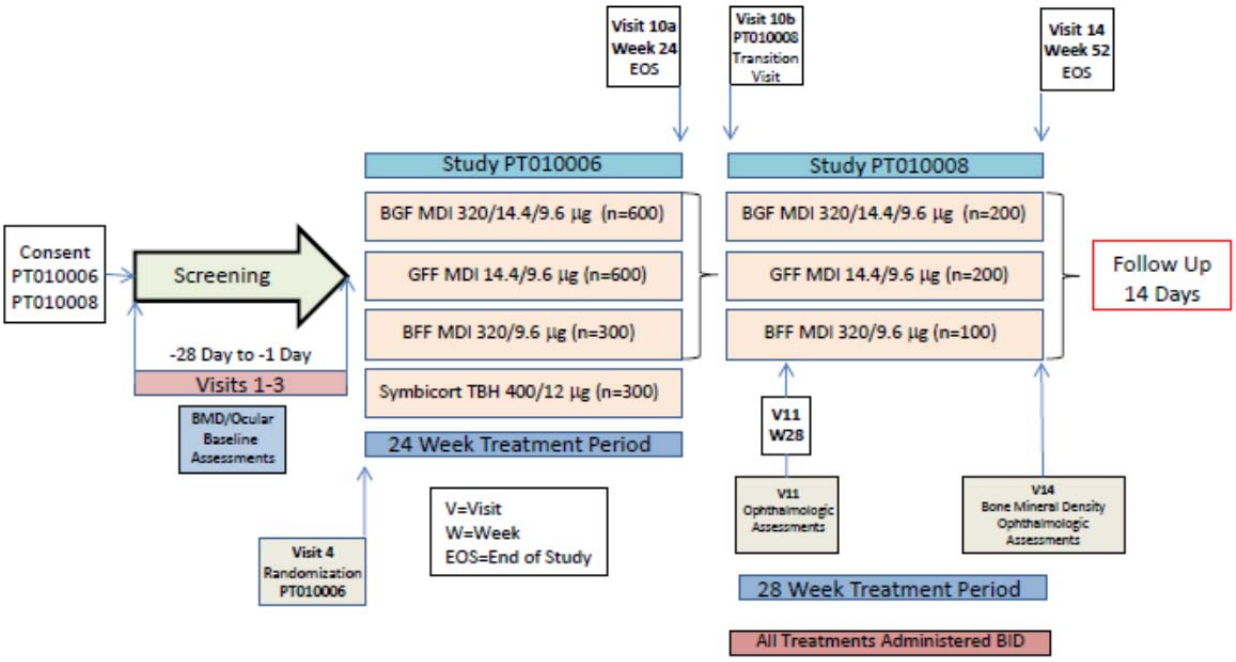
After Visit 14 (Week 52), a follow-up telephone call (TC) will be performed at least 14 days after the last study drug dose. For subjects who withdraw consent, a follow-up telephone call will be scheduled at least 14 days after the last dose of study drug unless the final visit was performed >14 days post the last study dose.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to Protocol Table 8-1). For subjects discontinuing treatment at any time during the study, including the time during which they are participating in Study PT010006, lenticular opacity, fundoscopic examination, intraocular pressure, pupil dilation and visual acuity assessments should be performed as soon as possible. For subjects discontinuing treatment after Visit 10b (Week 24), BMD assessments should also be obtained as soon as possible (Note: Subjects who discontinue prior to Visit 10b will not complete BMD assessments). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. These subjects will be followed for vital status at 52 weeks post-randomization in accordance with the informed consent.

The Schedules of Events and Timed Assessments are in the study protocol.

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

Figure 1 Study Design



Abbreviations: BFF = Budesonide and Formoterol Fumarate; BGF = Budesonide, Glycopyrronium, and Formoterol Fumarate; BID = *bis in die*, twice daily; BMD = Bone Mineral Density; EOS = End of Study; GFF = Glycopyrronium and Formoterol Fumarate; MDI = metered dose inhaler; TBH = Turbuhaler; V = visit; W = week.

3.1.2 Prior, Concomitant, Post-Treatment, Prohibited Medications, and Other Restrictions (if applicable)

All prescription and over-the-counter (OTC) medications taken by the subject within 30 days before Visit 1 (Screening) will be recorded on the prior/concomitant medications eCRF. All concomitant medications taken during the study will be recorded on the Concomitant Medications eCRF page with indication, total daily dose, dose regimen, and dates of drug administration. Refer to the Protocol for information about prohibited medications.

3.2 Hypothesis Testing

Hypothesis testing for change from baseline in LOCS III (P) scores at Week 52 is as follows.

The primary null (H_0) and alternative (H_1) hypotheses with μ representing the mean are:

- H_0: $\mu_{BGF} \geq \mu_{GFF} + 0.5$
  H_1: $\mu_{BGF} < \mu_{GFF} + 0.5$

- H_0: $\mu_{BFF} \geq \mu_{GFF} + 0.5$
  H_1: $\mu_{BFF} < \mu_{GFF} + 0.5$

Hypothesis testing for percent change from baseline in lumbar spine BMD scores is as follows.

The primary null (H_0) and alternative (H_1) hypotheses with γ representing the percent treatment difference are:

- H_0: γ_{BGF}-$\gamma_{GFF} \leq -2$
  H_1: γ_{BGF}-$\gamma_{GFF} > -2$

- H_0: γ_{BFF}-$\gamma_{GFF} \leq -2$
  H_1: γ_{BFF}-$\gamma_{GFF} > -2$

3.3 Interim Analysis

No interim analyses are planned for this study.

The Data Monitoring Committee (DMC) that was initiated in Study PT010006 will also provide systematic and unbiased assessment of safety for Study PT010008 and will review safety data approximately every 6 months. Further detail is given in the DMC Charter.

3.4 Sample Size

[redacted]

4. DATA AND ANALYTICAL QUALITY ASSURANCE

The overall quality assurance 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 (DMP), Data Validation Check Specifications, and Integrated Safety Data Review Plan. Detailed statistical and programming quality control and quality assurance procedures are documented in the Statistical Analysis and Programming QC/QA Plan.

5. ANALYSIS POPULATIONS

5.1 Population Definitions

5.1.1 Safety Population

The Safety Population is defined as all subjects who signed informed consent for PT010008 (i.e. have a non-missing PT010008 informed consent date) and received any amount of study treatment (other than Symbicort). Subjects will be analyzed according to treatment received rather than randomized. If a subject received more than one study treatment, they will be analyzed and included in summaries according to the treatment they received the most. Subjects who received no study treatment will be excluded, as will subjects who have no post-dose safety assessments. A subject who used a study treatment but took less than one full dose of treatment will qualify for this population.

The PT010008 Safety Population is defined as all subjects in the Safety Population who met the PT010008 continuing eligibility criteria at Visit 10b or who attended at least one of Visits 11, 12, 13, or 14. Tabulations for the PT010008 Safety Population will use information only on or after (the date of) Visit 10b.

5.1.2 BMD Analysis Population

The **BMD Analysis Population** is defined as all evaluable subjects in the Safety Population who have a baseline BMD assessment and at least one on-treatment BMD assessment. Subjects will be analyzed according to actual treatment received.

A reason for exclusion from the BMD Analysis Population will include, but is not limited to, the following:

- Subjects received treatment with a post-baseline bisphosphonate medication.

Further criteria may be established at the BDRM (Blinded Data Review Meeting).

5.1.3 Ophthalmologic Analysis Population

The **Ophthalmologic Analysis Population** is defined as all evaluable subjects who have a baseline ophthalmologic assessment and at least one on-treatment ophthalmologic assessment. This may possibly include some subjects who have not met the criteria for inclusion in the Safety Population but who have post-baseline ophthalmologic assessments prior to Visit 10b. Subjects will be analyzed according to actual treatment received.

A reason for exclusion from the Ophthalmologic Analysis Population will include, but is not limited to, the following:

- Subjects underwent a cataract extraction surgery (artificial ocular lens implantation).

Further criteria may be established at the BDRM.

5.1.4 mITT Population

The **mITT Population** is defined as the subgroup of mITT subjects from Study PT010006, who enrolled in PT010008 (i.e. have a non-missing PT010008 informed consent date) and who received any amount of study treatment (other than Symbicort). Subjects will be analyzed according to the active treatment they were assigned to at randomization in Study PT010006. Data collected from both Study PT010006 and PT010008 will be included (other than Symbicort treatment).

6. STATISTICAL ANALYSIS

PT010008 analyses will be performed when the PT010008 final database is available.

All data collected contributing to the analysis will be provided in listings. 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 safety, (including but not limited to BMD and ocular) and efficacy parameters will be summarized by treatment unless specified otherwise.

Demographics will be summarized for the Safety Population. Demographics will also be summarized for the BMD and Ophthalmologic Analysis Populations if these are different from the Safety Population. Analyses of ocular endpoints will be performed on the Ophthalmologic Analysis Population, and those of BMD endpoints will be performed on the BMD Analysis Population. All other safety analyses will be presented for the Safety Population. Some selected adverse event tables (overall summary of AEs, incidence of AEs by SOC, and incidence of SAEs by SOC) will also be repeated for the PT010008 Safety Population. Efficacy will be presented for the mITT Population. Continuous variables will be summarized with descriptive statistics (the number of non-missing values, mean, standard deviation, median, minimum, and maximum). Additionally, the 25^{th} and 75^{th} percentiles will be presented when appropriate based on historical knowledge of the normality or non-normality distribution of underlying data.

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

6.1 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 Adverse Events Summaries by Severity and Relationship to Study Drug

For the AE summaries by severity (mild, moderate, or severe), an AE with missing severity will be deemed as severe. For the AE summaries by relationship to study drug, an AE with a missing relationship to study drug will be deemed as definitely related. Imputed values will not be listed in data listings.

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

Data from unscheduled visits will not be used for this analysis, unless a prior or subsequent visit is missing where a value was scheduled to be collected. That is, data obtained during unscheduled visits will be allocated to the scheduled visit prior to the unscheduled visit (not more than 4 weeks prior) if it was missed or to the next missing scheduled visit (not more than 4 weeks subsequent) if the previous scheduled visit was not missing.

Protocol Deviations and Criteria for Exclusion from Study Populations

Reasons subjects were not enrolled in PT010008, including inclusion and exclusion criteria, will be tabulated (*Table 1.1.3*) and listed (*Listing 1.4*).

The definitive criteria for study-population exclusions (including the BMD Analysis Population and the Ophthalmologic Analysis Population) will be established and documented at the BDRM (Blinded Data Review Meeting).

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.

6.2 Subject Disposition and Analysis Populations

A disposition table for PT010008 for all subjects randomized in PT010006 will be provided *(Table 1.1.1).* This tabulation will include the number of subjects in each randomized treatment who were not treated in PT010006 or PT010008, who received the study treatment in PT010006 and PT010008, who discontinued treatment prematurely in PT010008, and who completed the PT010008 study. The number and percentage of randomized subjects included in the Safety,

BMD, Ophthalmologic, mITT, and PT010008 Safety Populations will also be tabulated *(Table 1.1.1)*. Informed consent is listed in *Listing 9.7*.

The numbers of subjects randomized and in the analysis populations will be provided by country, center, and treatment in *Table 1.1.2*.

A summary of reasons subjects were not enrolled in PT010008 will be provided for all subjects screened for PT010008 but not enrolled in PT010008 (*Table 1.1.3*). A listing of reasons subjects were not enrolled in PT010008 will be provided *(Listing 1.4)*. Subjects excluded from the BMD, Ophthalmologic and mITT analysis populations will be summarized (*Table 1.1.4)* for the Safety Population. The reason for exclusion from the BMD, Ophthalmologic, and mITT Populations of a subject or of partial data (at some but not all time points) for a subject will be listed for the Safety Population *(Table 1.1.4)*. Reasons for premature discontinuation from study treatment will be summarized for the Safety Population *(Table 1.1.5).*

The eligibility information (inclusion/exclusion criteria with any waivers granted) of all subjects who are randomized will be listed *(Listing 2.1).*

The number and percentage of subjects with changes in smoking status after the start of study treatment will be tabulated by study treatment, by visit and overall during the study for the Safety Population (*Table 1.8.1) (Listing 1.5)*.

6.3 Demographic and Baseline Characteristics and Extent of Exposure

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

6.3.1 Demography, Physical Characteristics, Baseline

Subject demographics, total CAT score, use of inhaled corticosteroids at screening, and smoking status/history will be summarized for the Safety, BMD and Ophthalmologic Analysis Populations and for subjects screened for PT010008 but not enrolled in PT010008 (*Tables 1.2.1* through *1.2.4,* respectively, and *Listing 1.2*). Inhaled corticosteroid use (yes/no) will be summarized for all populations except for the subjects screened for PT010008 but not enrolled in PT010008.

Demographic and baseline characteristic variables summarized will include the following:

- Age
- Age Group
- Gender
- Race
- Ethnicity

- COPD Assessment Test (CAT) total score and total score category (<10, ≥10, <15, ≥15, <20, ≥20, Missing)
- Used inhaled corticosteroids at Screening (all populations except for subjects screened for PT010008 but not enrolled in PT010008)
- Smoking status (current vs. former smoker)
- Number of years smoked
- Average number of cigarettes smoked per day
- Number of pack years smoked, calculated as (number of cigarettes per day/20) x number of years smoked
- Weight
- Height
- BMI (body mass index)
- Baseline BMD (DEXA Scan) t-score (≤-2.5, >-2.5 and ≤-1, >-1)
- Visual Acuity
- Fundoscopic Examination (Horizontal Cup-to-Disc Ratio)
- Intraocular Pressure
- Whether the subject was taking ophthalmic medications at baseline as eye drops

Screening and pre-treatment CAT data will be listed *(Listing 4.2)*.

Baseline BMD Endpoints (for all BMD endpoints) will be summarized with descriptive statistics for the following two populations: (1) The BMD Analysis Population and (2) Subjects in the Safety Population but Not in the BMD Analysis Population (*Tables 1.2.5* and *1.2.6*). Baseline Ophthalmologic Endpoints (for all ophthalmologic endpoints) will be summarized with descriptive statistics for the following two populations: (1) The Ophthalmologic Analysis Population and (2) Subjects in the Safety Population but Not in the Ophthalmologic Analysis Population (*Tables 1.2.7* and *1.2.8*).

6.3.2 COPD History, Screening/Baseline

Duration of COPD and the number of years prior to the start of study medication that COPD was first diagnosed calculated as (Date of First Dose of Study treatment in the study – Date COPD First Diagnosed) /365.25 will be summarized for the Safety, BMD, Ophthalmologic and mITT Populations by treatment and listed *(Tables 1.5.1* and *1.5.2*, and *Listing 4.1)*. History of moderate or severe COPD exacerbations in the prior year will be summarized and listed *(Table 1.4.4, Table 1.4.5* and *Listing 4.3)*.

Severity and duration of COPD will be summarized by treatment and for all subjects for the Safety and mITT Populations *(Tables 1.3.1* and *Table 1.3.2)*.

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

Medical and Surgical History at Screening will be summarized for the Safety Population and listed for the Safety Population *(Table 1.4.1, and Listing 4.4)*. Cardiovascular medical history of interest at Screening will be summarized for the Safety Population and listed for the Safety Population *(Table 1.4.2 and Listing 4.5)*. Ophthalmic history of interest at Screening will be summarized for the Safety Population and listed for the Safety Population *(Table 1.4.3 and Listing 4.6)*.

Screening Reproductive Status and Pregnancy Testing Results will be listed *(Listing 4.7)*.

Subjects' history of moderate and severe COPD exacerbations within the past 12 months will be summarized for the Safety Population and mITT Population *(Table 1.4.4* and *Table 1.4.5* respectively).

6.3.4 Prior, Concomitant, and Post-Treatment Medications/Treatments

All prescription and OTC medications taken by the subject during 30 days before Screening will be recorded on the Concomitant Medications case report form (CRF) page.

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: 3Q2016 or later).

Multiple ATC assignments: If there are multiple ATC codes assigned to the same concomitant medication, the "primary" one based on a Pearl medical evaluation 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 to the date prior to the last dose of study treatment for the subject. A medication with an onset date on or after the last dose 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.

Concomitant COPD and Non-COPD related medications/treatments will be summarized by preferred term and actual treatment received for the Safety Population *(Tables 1.6.1* and *1.6.2)*. Prior, concomitant/post-treatment COPD and Non-COPD medications will be displayed in separate listings (*Listings 4.7* and *4.8*, respectively).

Reported Prior Medication for COPD and non-COPD-Related Medications will be tabulated for the Safety Population (*Tables 1.5.1* and *1.5.2*) and listed separately (*Listings 4.8* and *4.9,* respectively).

Prior COPD Medications will be tabulated (for the Safety population) for subjects having received any one, two, all three, or none of the following treatments for at least 30 days prior to screening: (1) a muscarinic antagonist, (2) a β2 agonist, and (3) an inhaled corticosteroid *(Table 1.5.3)*. Tabulations for long-acting muscarinic antagonists and long-acting β2 agonists will also be included.

6.3.5 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 of study treatment and last day on study treatment) x 100. 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 (*Table 1.7.1*). The total person-years of exposure for a treatment group, defined as the total exposure in the study across all subjects on the treatment, will also be provided by treatment. The number and percent of subjects with exposure >= 24 weeks and >=48 weeks will also be tabulated.

In addition, a summary of treatment compliance will be provided. 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% (*Table 1.7.1* for the Safety Population). Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) for percent compliance by treatment will also be provided. Treatment compliance will be reported in *Listing 5.3*. 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 9.6*).

6.4 Safety Analyses

All safety analyses for PT010008 are based on the Safety Population. Some selected adverse event tables (overall summary of AEs, incidence of AEs by SOC, and incidence of SAEs by SOC) will also be repeated for the PT010008 Safety Population.

Safety data will be summarized cumulatively over 52 weeks using data observed during PT010006 and PT010008. Analyses involving change from baseline will use baseline values from Study PT010006.

Any AEs, clinically significant laboratory values, vital signs, and ECG values during the Treatment Period will be tabulated according to their onset date into the following study periods and listed.

- Events occurring during the Treatment Period (include events with an onset date on or after the first date of dose and up to and including the day of discontinuation from or completion of study treatment). Events known to have occurred before the time of the first dose of study treatment are not included.
- Events occurring during the Post-treatment-discontinuation Follow-up (include events with an onset date on (or after) the day after discontinuation from or completion of study treatment).

Any AEs, clinically significant laboratory values, vital signs, and ECG values during the Treatment Period will be tabulated and listed. Beginning on the day after the date of discontinuation from or completion of study medication, any new clinically significant ECGs, laboratory values, and vital signs will not be included in the tabulation or the computation of incidence rates, but will still be listed. Any new AEs, SAEs, and deaths during the Post-treatment-discontinuation Follow-up will be tabulated and listed. Tabulations of the incidence of deaths, AEs by SOC, and SAEs by SOC will be provided using information collected after treatment discontinuation or treatment completion (as alternative tables).

6.4.1 Bone Mineral Density Analyses

All BMD analyses are based on the BMD Population.

End-of-Treatment (EoT) is defined as the latest post-baseline assessment available, either scheduled or unscheduled. For bone mineral density (BMD) parameters, baseline BMD score is defined as the median BMD value of available scans (or values) prior to randomization in PT010006.

6.4.1.1 Percent Change from Baseline in BMD of the Lumbar Spine Measured Using DEXA Scans of L2-L4

The percent change from baseline in BMD of the lumbar spine at Week 52 and at EoT will be analyzed using an Analysis of Covariance (ANCOVA) model. The dependent variable for the ANCOVA analysis will be the natural-logarithmically transformed lumbar spine BMD at 52 weeks (or similarly at EoT) minus the natural-logarithmically transformed lumbar spine BMD at baseline – i.e. the change from baseline after performing a logarithmic transformation to both the week-52 (or similarly EoT) value and the baseline value. The model includes treatment group and gender as categorical covariates, and natural-log-transformed baseline lumbar spine BMD score, age, and age by gender interaction as continuous covariates. Point estimates with 95% confidence interval (CI) for the adjusted mean treatment difference (BGF MDI versus BFF MDI, BGF MDI versus GFF MDI, and BFF MDI versus GFF MDI) will be estimated. Estimates from the ANCOVA model – for within-treatment means and between-treatment mean differences – will be transformed back using the exponential function. After the back-transformation, 1 is subtracted from the within-treatment-mean estimate and the result is multiplied by 100 to provide an estimate of percent change from baseline. After the back-transformation, 1 is subtracted from the between-treatment mean-difference estimate and the result is multiplied by 100 to provide an estimate of percent treatment difference (Llombart et al. 2012). Estimates for the adjusted mean treatment difference will be given as percentages (*Table 2.1.1*). Non-inferiority for lumbar spine BMD scores will be declared if the lower confidence bound for the percent treatment difference is greater than -2. The empirical cumulative distribution function of the logarithm of the ratio to baseline will be plotted by treatment (with all treatments on the same page) for the statistical methods appendix of the CSR.

T-scores will be presented as shifts from baseline to each respective time point. A BMD t-score shift table will be produced using the categories of "≤ -2.5", "> -2.5 and ≤ -1", and "> -1" (*Table 2.1.3*). In the shift table, for each treatment, the subject's BMD baseline t-score category will be cross-tabulated by the subject's post-baseline BMD t-score category during the treatment. Percentages of subjects in each post-baseline BMD t-score category for a treatment will be calculated for each baseline BMD t-score category.

6.4.1.2 Percent Change from Baseline in Total Hip BMD of the Hip Measured Using DEXA Scans

The percent change from baseline in BMD of the total hip at Week 52 and at EoT will be analyzed using an ANCOVA in a similar fashion to the percent change from baseline in BMD of the lumbar spine. The dependent variable for the ANCOVA analysis will be the natural-logarithmically transformed total hip BMD at 52 weeks (or similarly at EoT) minus the natural-logarithmically transformed total hip BMD at baseline – i.e. the change from baseline after performing a logarithmic transformation to both the week-52 (or similarly EoT) value and the baseline value. The natural-log-transformed baseline BMD of the total hip will be used instead of baseline lumbar spine BMD in the model. The estimates with 95% confidence interval for the percent change from baseline within a treatment group and for the adjusted mean percent

treatment difference will be given (*Table 2.1.2*). A BMD t-score shift table will be produced using the categories of "≤ -2.5", "> -2.5 and ≤ -1", and "> -1" (*Table 2.1.4*).

6.4.2 Ocular Analyses

All ocular analyses are based on the Ophthalmologic Population.

The IOP will be measured 3 times per eye and the analysis value will be calculated as the median of the IOP measurements for a given eye.

End-of-Treatment (EoT) is defined as the latest non-missing post-baseline assessment, either scheduled or unscheduled. For ocular assessments, the baseline value is the last value obtained prior to randomization in PT010006.

6.4.2.1 Change from Baseline in Each of the LOCS III (P, NO, NC, and C) Scores

Changes from baseline (assessed at screening) in each scale of the LOCS III scores (P, NO, NC, and C) at each post-randomization visit (Week 28 and Week 52) will be analyzed using a repeated measures linear mixed model. The mixed model will include treatment, visit, and treatment by visit interaction as categorical covariates, and corresponding baseline LOCS III scale score (P, NO, NC, or C), smoking pack years, and age as continuous covariates. For this model, eye (within subject) will be included as a random effect. An unstructured correlation matrix will be used to account for within-subject-within-eye correlation across visits. Point estimates and two-sided 95% confidence intervals (CI) will be computed for pair-wise differences of BGF minus GFF and BFF minus GFF. Non-inferiority for LOCS III (P) scores will be declared if the upper confidence bound is less than 0.5. These LOCS III analysis results are tabulated in *Tables 2.1.5* through *2.1.8*.

Changes from baseline in each scale of the LOCS III scores (P, NO, NC, and C) at EoT will be analyzed using a linear mixed model. The model will include treatment as a categorical covariate and corresponding baseline LOCS III scale score (P, NO, NC, or C), smoking pack years, and age as continuous covariates. Eye (within subject) will be treated as a random effect. Point estimates and two-sided 95% confidence intervals (CI) will be computed for pair-wise differences of BGF minus GFF and BFF minus GFF. Non-inferiority for LOCS III (P) scores will be declared if the upper confidence bound is less than 0.5. These LOCS III analysis results are tabulated in *Tables 2.1.5* through *2.1.8*.

The empirical cumulative distribution function of the change from baseline in the LOCS III (P) score will be plotted by treatment (with all treatments on the same page) for the statistical methods appendix of the CSR.

The analysis of the change from baseline in LOCS III (P) scores at Week 52 will be the primary ocular analysis, with analyses at Week 28 and EoT for P and other subscale scores presented as supportive analyses.

6.4.2.2 Proportion of Subjects with LOCS III Grade Increases of ≥ 0.5 (Class 1), ≥ 1.0 (Class 2), or ≥ 1.5 (Class 3) Units in Each of the 4 Scales

The proportion of subjects with LOCS III grade increases in either eye of ≥ 0.5 (Class 1), ≥ 1.0 (Class 2), and ≥ 1.5 (Class 3) units in each of the 4 scales (P, NO, NC, C) at Week 28, at Week 52, and at EoT will be summarized by treatment group (*Tables 2.1.9* through *2.1.12)*.

6.4.2.3 Change from Baseline in Intraocular Pressure

The change from baseline in IOP at Week 28, Week 52, and EoT will be analyzed using a similar model as described above in section 6.4.2.1 for the LOCS III (P, NO, NC, and C) scores, but with the baseline IOP as a continuous covariate to replace baseline LOCS III scale score in the model (*Tables 2.1.13*) .

6.4.2.4 Proportion of Subjects with IOP ≥ 22 mmHg and the Proportion of Subjects with Change from baseline in IOP of ≥ 7 mmHg

The proportion of subjects with IOP ≥ 22 mmHg and with IOP increases from baseline of ≥ 7 mmHg in either eye at Week 28, Week 52, and EoT will be summarized by treatment group *(Tables 2.1.14* and *2.1.15*, respectively).

6.4.2.5 Change from Baseline in LogMAR Visual Acuity Using ETDRS Charts

The change from baseline in LogMAR visual acuity scores using ETDRS will be analyzed across eyes (irrespective of subject) at each visit by treatment group using descriptive statistics (*Table 2.1.16*). Each subject is to contribute a measure for each eye at each time point.

6.4.2.6 Change from Baseline in Horizontal Cup-to-disc Ratio

The change from baseline in horizontal cup to disc ratio will be summarized across eyes (irrespective of subject) at each visit by treatment group using descriptive statistics (*Table 2.1.17*). Each subject is to contribute a measure for each eye at each time point.

6.4.2.7 Incidence of Ocular TEAEs including Cataract and Glaucoma

The proportion of subjects with ocular TEAEs in each treatment group will be summarized overall and by individual AE including cataract and glaucoma (*Table 2.1.18*).

6.4.3 Adverse Events

The version of the Medical Dictionary for Regulatory Activities (MedDRA) that is current at the time of database lock will be used to code verbatim terms for AEs for final analysis of the data. A glossary of MedDRA preferred terms used for adverse events reported in the study along with the associated Investigator's verbatim term will be provided in *Listing 7.2*.

An adverse event (AE) is considered treatment-emergent if an event occurs after the first dose of study medication in the study, or if the AE worsened during the study after the first dose of study medication in the study (intensity and/or severity changed to a worsened grade. An adverse event that begins on the same date as the first dose of study medication is treatment-emergent if the AE begins after the time of first dose or if the time of AE onset is unknown. Adverse events that occur between the time the subject signs the informed consent form for the PT010006 study and the time when that subject is randomized are to be recorded as medical history unless the event met the definition of a serious AE (SAE).

The number and incidence of AEs, SAEs, adverse events of special interest (AESI) by category, and study drug discontinuations due to adverse events will be summarized by treatment group.

The incidence of an AE will be defined as the number and percentage of subjects experiencing an event. Adverse events will be tabulated at the level of the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and the MedDRA system organ class. Tabulations will be broken down by severity, by relationship to study drug, and AEs leading to treatment discontinuation. No hypothesis tests will be performed.

Events with Irregular Onset Dates: All treatment-emergent adverse events will be included in the data listings regardless of the completeness of the onset dates. Partial dates will be imputed in order to determine if an AE is treatment-emergent using the imputation rules in Appendix 1; however, imputed dates will not be provided in the data listings.

All adverse events, whether treatment-emergent or not, will be included in the listings. Reported adverse events by system organ class (SOC), preferred term (PT), treatment, country, center, subject and onset day will be provided (*Listing 7.1*). Reported adverse events by treatment, country, center, subject, and onset date will be presented in *Listing 7.3*.

The listing of adverse events will provide the severity, relationship to study drug, action taken and outcome for each adverse event. Any SAEs reported will be listed for all subjects screened (*Tables 4.1.13*). Adverse events leading to permanent discontinuation of study treatment will be listed for the Safety Population *(Table 4.1.10)*.

A listing of any reported deaths during the study (prior to randomization, during Treatment Period, or during the Post-treatment-discontinuation Follow-up) will be provided (*Table 4.1.30c*); study treatment taken prior to the death and the number of days since the last dose of this study treatment at the time of the death will be included in the listing. An overview table will be prepared with the incidences of subjects, for all subjects and for each treatment, with the following: at least one treatment-emergent adverse event, at least one treatment-emergent related adverse event, at least one treatment-emergent serious adverse event, at least one treatment-emergent serious related adverse event, at least one treatment-emergent adverse event leading to premature discontinuation, at least one treatment-emergent serious adverse event leading to

withdrawal, and a report of death for the Safety Population (*Table 4.1.1.1*). This table will also be repeated for the PT010008 Safety Population (*Table 4.1.1.2*).

Summary tabulations of the following will be prepared for all subjects, for each treatment, for each primary SOC, and for each PT within a SOC, the majority which pertain to the Treatment Period:

1. The incidence of all treatment-emergent adverse events by SOC and Preferred Term (*Table 4.1.2.1*). This table will also be repeated for the PT010008 Safety Population (*Table 4.1.2.2*).
2. The incidence of subjects with adverse events by SOC during the Post-treatment-discontinuation Follow-up (*Table 4.1.3)*
3. The incidence of treatment-emergent adverse events occurring in SMQs (Standard MedDRA Queries)/groupings of interest (*Table 4.1.5*).
4. The incidence of non-serious treatment-emergent adverse events occurring in ≥5% of subjects in a treatment (*Table 4.1.6*).
5. The incidence of all treatment-related treatment-emergent adverse events (*Table 4.1.8*).
6. The incidence of discontinuation from study treatment due to a treatment-emergent adverse event (*Table 4.1.9*).
7. The incidence of treatment-emergent serious adverse events by SOC and Preferred Term (*Table 4.1.11.1*). This table will also be repeated for the PT010008 Safety Population (*Table 4.1.11.2*).
8. The incidence of subjects with serious adverse events by SOC during the Post-treatment-discontinuation Follow-up (*Table 4.1.12)*
9. The incidence of all treatment-related treatment-emergent serious adverse events (*Tables 4.1.16*).
10. The incidence of subjects with neoplasm (all cancer) and the incidence of subjects with neoplasm (excluding non-melanoma skin cancer) (*Tables 4.1.17, 4.1.18*).
11. The incidence of all treatment-emergent adverse events by highest severity to treatment *(Tables 4.1.21* through *4.1.23* for the three treatments).
12. The incidence of treatment-emergent adverse events occurring in at least 2% of subjects in any treatment (*Table 4.1.*4 sorted by descending frequency of events in a preferred term).
13. In addition, to control for possible differences in exposure between the treatments, the following AE and SAE summaries will be presented with the frequency and rate of occurrence (total number of events per 1000 person-years of exposure) by treatment, primary SOC, and PT:
    a) Frequency and rate of AEs (*Tables 4.1.7*).
    b) Frequency and rate of SAEs (*Tables 4.1.15*).

c) Frequency and rate of neoplasms (*Tables 4.1.19, 4.1.20*).

6.4.3.1 Adverse Events of Special Interest

Adverse events of special interest (AESIs) have been defined based on known effects of LAMAs, LABAs, and ICS. These include but are not limited to cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs; cardiovascular, tremor effects, hyperglycemia, and hypokalemia for LABAs; and local (e.g., candidiasis and voice effects) and systemic (e.g., bone and skin effects, diabetes control, ocular and taste effects, adrenal suppression) steroid class effects and lung infection for ICS.

Standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) will be utilized when possible, and a selection of high-level group terms (HLGTs), high-level terms (HLTs), and preferred terms (PTs) will be utilized to represent other situations. The terms proposed to be used in the assessment of AESIs associated with ICS, LAMAs, and LABAs are listed in Table 1. Standardized MedDRA queries will be utilized when possible and a selection of preferred terms in other situations (*Appendix 5*).

Table 1 Terms for the Assessment of Adverse Events of Special Interest

Medical Concept	Selection of MedDRA Terms
Adrenal suppression	Adrenal cortical hypofunctions HLT
Agitation or anxiety	Collection of PTs
Anticholinergic effects[a]	Anticholinergic syndrome SMQ Dry mouth PT
Bone fracture	Collection of HLGTs, HLTs, and PTs.
Candidiasis	Collection of PTs
Cardiovascular	Cardiac arrhythmias SMQ Cardiac failure SMQ Ischemic heart disease SMQ Torsades de Pointe/QT prolongation SMQ
Cardiovascular death	Collection of PTs
Cerebrovascular condition	CNS haemorrhages and cerebrovascular conditions SMQ
Diabetes mellitus	Hyperglycaemia/new onset diabetes mellitus SMQ
Dysgeusia or ageusia	Collection of PTs
Dysphonia or aphonia	Collection of PTs
Gastrointestinal	Gastrointestinal perforation, ulceration, haemorrhage or obstruction SMQ Gastrointestinal obstruction SMQ
Headache	Headache (PT)
Hypercortisolism	Collection of PTs

Medical Concept	Selection of MedDRA Terms
Hypertension	Blood pressure ambulatory increased (PT) Blood pressure increased (PT) Blood systolic increased (PT)
Hypokalemia	Collection of PTs
Lower respiratory tract infections other than pneumonia	Bronchitis (PT) Bronchitis viral (PT) Bronchitis bacterial (PT) Lower respiratory tract infection (PT) Lower respiratory tract infection viral (PT) Lower respiratory tract infection bacterial (PT) Infective exacerbation of chronic obstructive airway disease (PT)
Ocular effects	Visual disorders HLT Glaucoma SMQ increased intraocular pressure collection of PTs Cataract collection of PTs
Osteoporosis and osteopenia	Osteoporosis/osteopenia (SMQ)
Palpitation	Palpitations PT
Paradoxical bronchospasm	Collection of PTs
Pneumonia	Collection of PTs
Psychiatric effect	Collection of PTs
Skin effects	Skin atrophy (PT) Skin striae (PT) Acne (PT) Contusion (PT) Ecchymosis (PT) Increased tendency to bruise (PT) Petechiae (PT) Purpura (PT) Malassezia folliculitis (collection of PTs) Hypertrichosisa (collection of PTs) Alopecia (collection of PTs)
Sleep effects	Initial insomnia (PT) Insomnia (PT) Sleep disorder (PT)
Sudden death	Collection of PTs
Throat irritation	Collection of PTs
Tremor	Tremor HLT
Urinary retention	Collection of PTs
Weight gain	Collection of PTs

Abbreviations: CNS=central nervous system.

[a] This medical concept is uniquely associated with LAMAs.

Appendix 5 (which will be based on the latest version of MedDRA available at the time of database lock) provides detail on selection of terms (narrow/wide designations for preferred terms are provided).

Adverse Events in MedDRA SMQs/Groupings of Interest by Term will be tabulated *(Table 4.1.24)*.

6.4.3.2 MACE Events Determined by Clinical Endpoint Committee

The clinical endpoint committee (CEC) will review and adjudicate serious cardiovascular and cerebrovascular (CCV) events as major adverse cardiovascular event (MACE). MACE events are defined as the following:

- Cardiovascular death
- Non-fatal myocardial infarction (MI)
- Non-fatal stroke

The CEC will review and assess these non-fatal serious CCV events and all deaths as to whether or not they fulfill criteria (based on CEC working practices) for MACE.

MACE events will be summarized by adjudicated CRF category and treatment group (*Table 4.1.25*). The assessment of MACE events will include the rate of confirmed MACE events (*Table 4.1.26*). Adjudicated MACE events will be listed in *Listing 7.4*.

The incidence of subjects with adjudicated MACE AEs by category will be summarized in *Table 4.1.27*.

6.4.3.3 Pneumonia Events Determined by Clinical Endpoint Committee

All AEs/SAEs with preferred terms that could relate to pneumonia will be adjudicated to provide a more complete assessment of all physician-reported pneumonias. The incidence of confirmed pneumonia events will be tabulated (*Tables 4.1.28*). The assessment of pneumonia events will include the rate of confirmed pneumonia events (*Table 4.1.29*). Adjudicated pneumonia events will be listed in *Listing 7.4*.

The incidence of subjects with adjudicated pneumonia AEs by category will be summarized in *Table 4.1.27*.

6.4.3.4 Cause of Death Determined by Clinical Endpoint Committee

Causes of death will be listed (*Table 4.1.30c*) by subject and summarized by treatment for (1) all-cause mortality, (2) mortality of probable cardiovascular cause, (3) mortality of probable respiratory cause and (4) mortality of probable other causes using the Safety Population based on (A) cases reported during the active Treatment Period and (B) cases reported during the active Treatment Period plus the following 14 days. The incidence of subjects with a death event will

be tabulated by adjudicated CRF category and treatment during the Treatment Period (*Table 4.1.30a*) and during the Post-treatment-discontinuation Follow-up (*Table 4.1.30b*). To control for possible differences in exposure between treatments, the death will be summarized with frequency and rate of occurrence (total number of events per 1000 person-years of exposure) by treatment, primary system organ class, and preferred term (*Table 4.1.31*). Adjudicated death events will be listed in *Listing 7.4*.

6.4.4 Clinical Laboratory Measurements

Lab parameters collected include the following:

Table 2 Lab Parameters

Hematology	
Hemoglobin	Mean corpuscular hemoglobin
Hematocrit	Mean corpuscular hemoglobin concentration
White blood cell count with differential	Mean corpuscular volume
Red blood cell count	Eosinophils
Platelet count	
Clinical Blood Chemistry	
Liver Enzyme and Other Liver Function Tests	**Other Clinical Blood Chemistry**
Alanine aminotransferase	Albumin
Aspartate aminotransferase	Blood Urea Nitrogen (BUN)
Alkaline phosphatase	Calcium[a]
Bilirubin, total	Chloride[a]
Gamma-glutamyl transferase	Cholesterol
	Bicarbonate
	Creatinine[a]
	Glucose[a]
	Magnesium
	Potassium[a]
	Phosphate
	Protein, total
	Sodium[a]
Urinalysis	
Macroscopic examination including specific gravity, pH, protein, glucose, ketones, blood, and urobilinogen.	
Other Tests:	
Pregnancy test (women of childbearing potential only): serum hCG at Visit 10a of Study PT010006 and at Visit 14 (Week 52) the Treatment Discontinuation/Withdrawal Visit of this study.	
Creatinine clearance will be estimated by the CKD-EPI formula [Levey, 2009].	
Abbreviations: CKD-EPI=Chronic Kidney Disease Epidemiology Collaboration; hCG=human chorionic gonadotropin. [a] Parameters included in the Basic Metabolic Panel.	

A Clinically Significant Laboratory Abnormality as identified by the investigator after the start of study treatment will be recorded as an Adverse Event and tabulated as an AE in the AE

analysis. Abnormalities occurring prior to the start of treatment will be noted in medical history and presented in a data listing. Per protocol, the criteria for a "clinically significant" laboratory abnormality are:

a. A laboratory abnormality that leads to a dose-limiting toxicity (e.g., an abnormality that results in study drug dose reduction, suspension or discontinuation)
b. A laboratory abnormality that results in any therapeutic intervention (i.e., concomitant medication or therapy)
c. Other laboratory abnormality judged by the Investigator to be of any particular clinical concern (e.g., significant fall in hemoglobin not requiring transfusion)

All laboratory data will be stored in the database with the units in which they were originally reported. Laboratory data not reported in International System of Units (SI units; Système International d'Unités) will be converted to SI units before data analysis.

Individual clinical laboratory variables for hematology and clinical chemistry and kidney function, including creatinine clearance, will be provided in listings (*Listing 8.1* for hematology, *Listing 8.2* for blood chemistry and kidney function, *Listing 8.3* for urinalysis, and *Listing 4.7* for pregnancy test results at screening and after the start of treatment). Data will be listed in SI units where available. Comments for laboratory testing will be listed (*Listing 8.4*). For listings, laboratory values will be flagged as Low or High based on the reference ranges provided by the central laboratory, LabCorp Laboratories (*Appendix 4*).

The baseline measurement for a laboratory parameter will be the last available measurement prior to the start of dosing.

Table 3 Analysis Study Time Windows for Clinical Lab Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose	≥0 min. prior to dose

Note that minutes are rounded to the nearest whole number before applying time windows.

If there are multiple laboratory values for the same parameter at pre-dose of a visit, the last value will be chosen for analysis.

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment and for the pre-dose value and change from baseline at each post-baseline visit and EoT for scheduled lab assessments of continuous laboratory variables including serum potassium and glucose will be tabulated. "End of Treatment" is defined as the last non-missing assessment during the treatment period.

Data from unscheduled visits will not be used for the by-visit summaries but both scheduled-visit values and unscheduled-visit values are candidates for clinically significant values, for the end-of-treatment summary, and for shift tables.

Data from both scheduled and unscheduled visits will be listed. The summaries will be provided by treatment (*Tables 4.1.33* through *4.1.36*, for hematology, chemistry, kidney function, and urinalysis, respectively).

Shift tables will be produced using the categories defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 grades for the Safety Population (*Tables 4.1.37, 4.1.38, Table 4.1.39* and *Table 4.1.40*) for hematology, chemistry, kidney function and urinalysis, respectively). For these shift tables, for each treatment, the subject's pre-dose grade will be cross-tabulated by the subject's maximum post-baseline grade during the treatment; also, the subject's maximum post-baseline grade during treatment will be tabulated for all baseline grades combined. Percentages of subjects in each maximum post-baseline grade for a treatment will be calculated for each pre-dose grade for the treatment and also for all baseline grades combined. Laboratory abnormal values on-treatment will be flagged as High or Low values based on laboratory reference ranges provided by LabCorp Laboratories (found in Appendix 4) as per Pearl, Inc. These flags along with the reference ranges will be provided in the laboratory data listings.

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 following thresholds:

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	<2,000/ 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 or equal to 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.

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 (*Table 4.1.41* and *Table 4.1.42*). For all laboratory parameters other than glucose and potassium noted in Table 2, all laboratory data for the parameter identified as potentially clinically significant for a subject will be listed (*Table 4.1.43*).

6.4.5 Vital Signs

Changes from Baseline in on-treatment supine or seated systolic blood pressure, supine or seated diastolic blood pressure, heart rate, and body temperature will be evaluated, where baseline is defined as the mean of all available pre-dose measurements taken prior to the start of dosing at the Randomization Visit (Visit 4). If there are no Visit 4 pre-dose values, the baseline will be defined as the mean of pre-bronchodilator values at Visit 2 and Visit 3. No hypothesis testing will be performed.

A **Clinically Significant Abnormality** in vital signs identified by the investigator will be recorded as an Adverse Event if it occurs after the start of treatment. These adverse events will be included in the AE summaries; abnormalities prior to the start of treatment will be noted in medical history and listed.

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

Table 5 Potentially Clinically Significant Criteria for Systolic and Diastolic Blood Pressure Parameters

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

Potentially clinically significant (PCS) changes in heart rate will be assessed as follows:

Table 6 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

Vital sign measurements (heart rate, systolic blood pressure, diastolic blood pressure and body temperature) and height and weight during the study will be displayed in a vital signs listing *(Listing 9.1)*.

A summary of baseline weight, height, and BMI will be presented by treatment (*Tables 1.2.1, 1.2.2, 1.2.3* for the Safety, BMD and Ophthalmologic Populations, and in *Table 1.2.4* for All Subjects Screened for PT010008 but Not Enrolled in PT010008 respectively).

Summary statistics (n, mean, median, standard deviation and range) of the absolute value and change from baseline for systolic blood pressure, diastolic blood pressure, heart rate, and body temperature will be tabulated by treatment, visit, and time point. Baseline will be defined as the mean of the values prior to dosing at Visit 4 (Day 1). These summaries (*Table 4.1.44*) will be prepared for baseline and the scheduled post-baseline pre-dose nominal time point at each scheduled post-baseline visit and end of treatment. End of Treatment will be summarized for the scheduled post-baseline pre-dose time point (pre-dose) “End of Treatment” for the pre-dose assessment points is defined as the last non-missing on-treatment assessment available for the pre-dose time point. Post-dose time points are collected in PT010006 but not in PT010008 and

thus will not need to be summarized for PT010008 because they will have been fully summarized in the PT010006 clinical study report (CSR). 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 the end-of-treatment summary. Data from both scheduled and unscheduled visits will be listed. Time windows will be derived for each post-baseline visit using the time intervals for the study time windows detailed in Table 7. No hypothesis tests will be performed.

Table 7 Analysis Study Time Windows for Vital Signs Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose	≥0 min. prior to dose

Note that minutes are rounded to the nearest whole number before applying time windows.

If there are multiple vital sign values for the same parameter at pre-dose assessments after Visit 4 the last value will be chosen for analysis.

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 and for the end-of-treatment summary.

The percentage of subjects with PCS values for vital signs at any time post-dose at a visit will be summarized by treatment based on the criteria in Table 5 and Table 6 (*Table 4.1.45*). All vital sign assessments for subjects with potentially clinically significant values will be listed (*Tables 4.1.46* and *Table 4.1.47*).

6.4.6 12-Lead Electrocardiogram Measurements

Changes from baseline in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated where baseline is defined as the mean of the pre-dose measurements taken prior to the start of treatment at the randomization visit (Visit 4). If there are no Visit 4 pre-dose values, the baseline will be defined as the mean of the pre-bronchodilator values at Visit 2 and Visit 3. The QTcF (Fridericia Corrected QT) 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 treatment and 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 9.2*). Summary statistics (mean, median, standard deviation and range) for raw values and change from baseline

values in Heart Rate, PR Interval, QRS Axis, QRS Interval, QT Interval and QTcF interval will be calculated, where baseline is defined as the mean of the pre-dose measurements taken prior to the start of treatment at Visit 4 (Day 1). These assessments will be tabulated for each treatment for the pre-dose nominal time point (derived using the time intervals for the study time windows detailed below in **Error! Reference source not found.**Table 8) at each visit and at end of treatment (*Table 4.1.48*). "End of Treatment" will be summarized for the scheduled post-baseline pre-dose time-point. Post-dose time points are collected in PT010006 but not in PT010008 and thus will not need to be summarized for PT010008 because they will have been fully summarized in the PT010006 clinical study report (CSR). End of Treatment for each of these assessment points is defined as the last non-missing on-treatment assessment available for the pre-dose time-point. Data from both scheduled and unscheduled visits will be listed. Mean pre-dose change from baseline for heart rate and QTcF will be plotted across post-baseline visits by treatment (*Figures 4.1.48a* and *4.1.48b*). ECG data from subjects with pacemakers will not be included in analyses, but will be listed.

Table 8 Analysis Study Time Window for ECG Assessments

Calculated Study Time Window	Time Interval for the Study Time Window
Pre-dose	≥0 min. prior to dose

Note: The minutes are rounded to the nearest whole number before applying time windows.

If there are multiple ECG values for the same parameter at pre-dose of a visit date (other than for Visit 4), the last value will be chosen for analysis.

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 and for the end-of-treatment summary.

Table 9 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) Change of ≥60 msec from study baseline regardless of initial value
	(4) ≥ 500 msec and ≥ 15 msec change from study baseline

Potentially clinically significant ECG parameter values will be identified based on criteria listed in **Error! Reference source not found.**. The number and percentage of subjects who had such

values observed any time post-dose will be tabulated for each treatment (*Table 4.1.49*) and listed (*Table 4.1.50* for QTcF prolongation). No hypothesis tests will be performed.

6.4.7 Physical Examination

Any physical examination abnormality reported after the start of treatment for a subject is to be reported as an adverse event. Thus, these will be included in listings of adverse events and summarized in adverse event summaries. Abnormalities seen at the Screening physical examinations will be recorded as Medical History and listed.

6.4.8 Control of Type I Error

Since the primary objectives are related to safety, all hypotheses will be tested at nominal alphas. There will be no controls for multiplicity.

6.5 Efficacy Analyses

All efficacy analyses for PT010008 are based on the mITT Population.

Summary statistics will be provided by randomized treatment group.

6.5.1 Rescue Ventolin HFA Use

The number of puffs of rescue Ventolin HFA taken in the previous 12 hours will be recorded in the subject diary in the morning and evening. The mean daily number of puffs of rescue Ventolin HFA used by subjects during the study will be calculated overall and for each of the 4-week intervals during the treatment period and provided in a diary data listing (*Listings 6.1.3* for the Safety Population). Diary data recorded during the last 7 days of the 28-day Screening Period (of PT010006) will be used to calculate the baseline. For every interval of time over which the mean number of puffs of rescue will be calculated for both overall as well as 4-week intervals, records with missing values will be ignored in both the numerator and denominator. As such, the denominator will be adjusted based on the number of days (including half days) with non-missing values. That is, the mean daily number of puffs of daytime rescue use (M_DT) will be set to the total number of daytime puffs divided by the number of half-days when daytime rescue use was recorded. The mean daily number of puffs of nighttime rescue use (M_DN) will be set to the total number of nighttime puffs divided by the number of half-days when the nighttime rescue use was recorded. The mean daily rescue use (puffs) is then two multiplied by the mean of M_DT and M_DN.

The mean change from baseline in rescue use will be summarized by treatment group over 52 weeks and over each post-randomization 4-week interval (Interval 1 to Interval 13) (*Table 3.1.1*).

6.5.2 Percentage of Days with No Rescue Ventolin HFA Use over the Treatment Period

As a supportive analysis, percentage of days with ‘no rescue Ventolin HFA use’ over 52 weeks will be summarized by treatment using descriptive statistics (*Table 3.1.4*). A ‘day with no rescue

use' is defined as any day where the subject reported having taken zero puffs of rescue Ventolin HFA. The rescue Ventolin HFA usage diary data from days where rescue Ventolin HFA usage data is non-missing will be used to ascertain the days with "no rescue Ventolin HFA use". The percentage of days with no rescue use will be calculated as 100 x (number of days with no rescue Ventolin use over the entire treatment period / number of days with non-missing rescue Ventolin use data over the entire treatment period). For the mITT analysis, days after discontinuation of study medication will not be used.

6.5.3 Chronic Obstructive Pulmonary Disease Exacerbations

Rate of COPD Exacerbations

A **COPD exacerbation** will be defined as a change in the subject's usual COPD symptoms that lasts 2 or more days, is beyond normal day-to-day variation, is acute in onset, and may warrant a change in regular medication. The change in symptoms must include at least one major COPD symptom and at least one other major (dyspnea, sputum volume, and sputum color) or minor symptom (cough, wheeze, sore throat, cold symptoms [rhinorrhea or nasal congestion], and fever without other cause).

Exacerbations will be considered **moderate** if they result in:

- Use of systemic corticosteroids and/or antibiotics for at least 3 days; a single depot injectable dose of corticosteroids will be considered equivalent to a 3-day course of systemic corticosteroids.

Exacerbations will be considered **severe** if they result in:

- An inpatient COPD-related hospitalization (documentation stating that the subject was hospitalized for the COPD exacerbation or a record of the subject being admitted for ≥24 hours to an observation area, the emergency department, or other equivalent healthcare facility depending on the country and healthcare system).

- COPD-related death.

Moderate-to-severe COPD exacerbations will be entered in the eCRF.

Additionally, the investigator may identify certain events (recorded on the same CRF page) which don't entirely meet the criteria above as exacerbations; the justifications supporting the investigator's judgment will be recorded on a separate page on the eCRF.

COPD exacerbations not meeting the criteria for moderate or severe COPD exacerbations will be considered to be mild COPD exacerbations. For more detail about moderate-or-severe, severe, and any-severity COPD exacerbation events (and their start and end dates) and how they are operationally defined, see the subsections about "Duration of COPD Exacerbation", "Moderate-

to-Severe Exacerbation and Severe Exacerbation: Operational Definitions", and "Exacerbation of any Severity: Operational Definition".

COPD exacerbations will be considered separate events provided that more than 7 days are between the recorded stop date of the earlier event and start date of the later event.

For the mITT population, the time at risk is defined as time of exposure – not during or within 7 days after an exacerbation (of equal or greater severity) – until the last dosing date. More precisely, this is the amount of time between the date of first dose of study medication and the date of discontinuation from or completion of study medication minus the number of days while the subject was experiencing any exacerbation and minus the seven days subsequent to any exacerbation. Any days subsequent to the date of discontinuation from or completion of study medication are not subtracted.

The rate of exacerbations, the number of exacerbations, and the percentage of subjects who experience exacerbations will be summarized for moderate-or-severe COPD exacerbations (*Tables 3.1.5.1* for the mITT Population). The rate of severe COPD exacerbations and the rate of COPD exacerbations of any severity will be presented in a similar manner (*Tables 3.1.6* and *3.1.7*).

Duration of COPD Exacerbation

For moderate or severe exacerbations, the duration is defined by the length of prescribed treatment (using the eCRF exacerbation page), whereas for mild exacerbations, the duration is defined by the length of symptoms.

For moderate or severe COPD exacerbations, the start date will be defined as the start date of prescribed treatment with a systemic corticosteroid or systemic antibiotic and the stop date will be defined as the last day of prescribed treatment with a systemic corticosteroid or systemic antibiotic. In order to ensure that the same event is not counted twice, concurrent moderate or severe COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event and assigned the maximum severity between the two.

For mild COPD exacerbations, start date will be defined as the onset of worsened symptoms as recorded by the subject in the electronic diary (eDiary), and the stop date will be defined as the last day of worsened symptoms. In order to ensure that the same event is not counted twice, mild COPD exacerbations with start and stop dates equal to or less than 7 days apart will be considered the same event.

In addition, in order to not double count exacerbations that are moderate or severe, eDiary data from dates within 7 days of a moderate or severe exacerbation will not be included as additional mild COPD exacerbations. This implies that continuing worsened symptoms that meet the definition of a mild exacerbation would need to be present at least 2 days prior to the 7-day

period immediately preceding the start date of a moderate or severe COPD exacerbation in order to be considered a separate event. Similarly, worsened symptoms would need to be present for at least 2 days after the 7-day period immediately following a moderate or severe COPD exacerbation to be considered a separate event.

Analyses of each severity of exacerbation will account for the time that subjects are at risk of having an exacerbation of that severity or greater. Time during or immediately following – i.e. within 7 days of – an exacerbation will not be considered as part of the time that the subject was at risk. However, time during or immediately following an exacerbation of lower severity will be included since, for example, a subject experiencing a mild exacerbation is still at risk of the event increasing in severity and becoming a moderate exacerbation. Moderate and severe COPD exacerbations occurring within 7 days of one another will be coalesced into a single COPD exacerbation event with the severity of "severe" (see details below).

Moderate-to-Severe Exacerbation and Severe Exacerbation: Operational Definitions:

- Moderate exacerbations and severe exacerbations will be defined solely based on information from the COPD Exacerbation eCRF page. A time interval from a single COPD exacerbation eCRF page will be designated as being during an event of a moderate-to-severe COPD exacerbation if for that interval: either antibiotics or oral corticosteroids were administered for the exacerbation

Call this time interval a "P-Interval". The start date of the P-Interval is the earliest start date of the above, and the stop date will be defined as the last stop day of the above. If the subject was hospitalized due to the exacerbation or if the exacerbation led to a COPD-related death, then the severity of "severe" will be assigned to this P-interval; otherwise the severity of "moderate" will be assigned. The latter of the stop date of the treatment with a systemic corticosteroid and the stop date of the treatment with an antibiotic will be the end date of the COPD exacerbation (i.e. the end of the P-Interval).

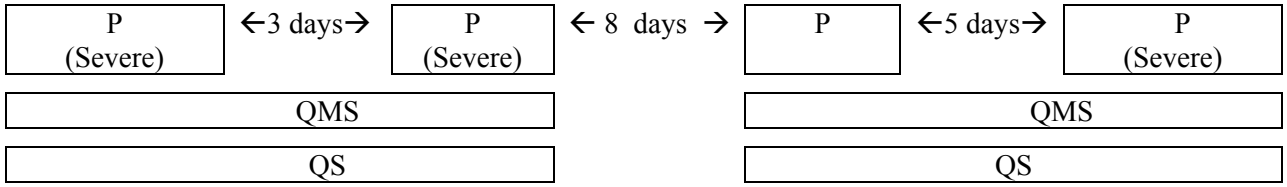
- An overarching interval of (any number of) such P-Intervals – including any P-Intervals with an end date not more than 7 days prior to the start date of some other P-Interval or with a start date not more than 7 days after the end date of some other P-Interval – and including the days in any gaps between them – will be called an "QMS-Interval". This QMS-interval will represent the consolidated duration of several exacerbations recorded on different CRF pages. This QMS-Interval will be considered to be a single event of a moderate-or-severe COPD exacerbation. See

- Figure 2.

- A P-Interval of severe COPD exacerbation is called a "severe" P-Interval. Any QMS interval that contains at least one "severe" P-Interval will also be called a "QS-Interval". This QS-

Interval will be considered to be a single event of a severe COPD exacerbation. See **Error! Reference source not found.**.

Figure 2 Overarching Intervals of Moderate-to-Severe (QMS) and Severe (QS) COPD Exacerbations



A P-interval is a moderate-to-severe COPD exacerbation instance from a single CRF page.
In a "Severe" P-Interval [denoted in the figure as "P (severe)"], the maximum severity of the COPD exacerbation is "severe".
A QMS interval is an overarching moderate-or-severe COPD exacerbation event encompassing multiple CRF pages.
A QS interval is an overarching severe COPD exacerbation event encompassing multiple CRF pages.

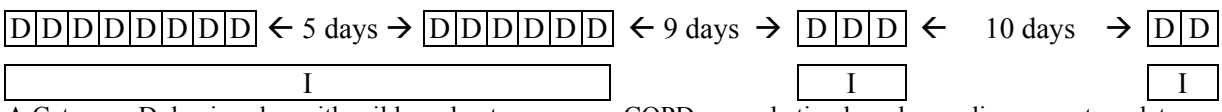
Exacerbation of any Severity: Operational Definition:

- Using eDiary data, a day will be designated as being during an event of a COPD exacerbation of some severity if (1) there was at least one major symptom and there was at least one other major or minor symptom and if (2) on an adjacent day there was at least one major symptom and there was at least one other major or minor symptom. Denote such a day as a "Category-D" day.

- An interval of (any number of) such Category-D days – including any Category-D days not more than 7 days apart from some other Category-D day – and including the days in any gaps between them – will be called an "I-Interval". See Figure 3.

- An overarching interval coalescing (any number of) P-Intervals and I-Intervals – including any such P-or-I-intervals with an end date not more than 7 days prior to the start date of some other P-or-I-Interval or with a start date not more than 7 days after the end date of some other P-or-I-interval – and including the days in any gaps between them – will be called a "QQ-Interval". This QQ-interval will represent the consolidated duration of several exacerbations recorded on different CRF pages or identified from subject diary data. This QQ-Interval will be considered to be a single event of an any-severity COPD exacerbation. See Figure 4.

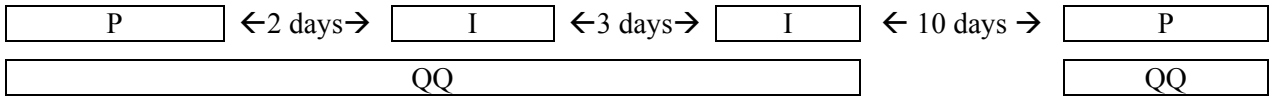
Figure 3 Overarching Intervals (I) of Mild-Moderate-or-Severe COPD Exacerbation Events Based on e-Diary Symptom Data



A Category-D day is a day with mild-moderate-or-severe COPD exacerbation based on e-diary symptom data.

An I-Interval is an overarching mild-moderate-or-severe COPD exacerbation event encompassing multiple clusters of e-diary symptom days.

Figure 4 Overarching Intervals (QQ) of Mild-Moderate-or-Severe COPD Exacerbation Events Incorporating Both CRF Data and e-Diary Symptom Data



A P-Interval is a moderate-to-severe COPD exacerbation instance from a single CRF page.
An I-Interval is an overarching mild-moderate-or-severe COPD exacerbation event based on e-diary symptom data.
A QQ-Interval is an overarching mild-moderate-or-severe COPD exacerbation event – encompassing multiple P-Intervals and I-Intervals – incorporating both CRF data and e-diary symptom data.

In summary, we combine CRF based moderate-or-severe COPD exacerbation events if they are close enough together in time (
Figure 2). We also combine severe COPD exacerbation events with other severe COPD exacerbation events or with moderate-or-severe COPD exacerbation events if they are close enough together in time (**Error! Reference source not found.**) – thus forming a single severe COPD exacerbation event. We also combine mild-moderate-or-severe COPD exacerbations if they are close enough together in time; this coalescing is done first within-data-source (CRF [
Figure 2] or diary [Figure 3]) and then between the two sources (Figure 4).

Time-at-Risk for COPD Exacerbations of Various Severities: Operational Definition

- During a time when a subject is not experiencing a severe COPD exacerbation (i.e. QS interval) – and is not in the seven days following a severe COPD exacerbation – a subject is considered to be at risk of having a severe exacerbation. During a time when a subject is not experiencing a moderate-or-severe COPD exacerbation (i.e. QMS interval) – and is not in the seven days following a moderate-or-severe COPD exacerbation – a subject is considered to be at risk of having a moderate-or-severe exacerbation. During a time when a subject is not experiencing an any-severity COPD exacerbation (i.e. QQ interval) – and is not in the seven days following an any-severity COPD exacerbation – a subject is considered to be at risk of having an any-severity exacerbation.

Overarching coalesced intervals (i.e. events) of COPD exacerbation will be listed for severe exacerbations, moderate -to-severe exacerbations, and any-severity exacerbations (*Listing 6.1.2.3*). A severe COPD exacerbation event must be classified also as a moderate-to-severe event and also as an any-severity event. A moderate-to-severe COPD exacerbation event must be classified also as an any-severity event.

The count of COPD exacerbations of any severity is the number of QQ-Intervals (for a subject) as defined previously. Time during an exacerbation (of any severity) or in the 7 days following an exacerbation (of any severity) will not be included in the calculation of exposure (i.e. time at

risk). Data related to COPD exacerbations of any severity are summarized in *Table 3.1.7* and listed in *Listings 6.1.2.1, 6.1.2.2 and 6.1.2.3*.

6.5.4 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

The EXACT is a 14-item patient reported outcome (PRO) daily diary which will be used to measure the effect of treatment on exacerbations, and on the severity of respiratory symptoms. The E-RS is an 11-item subset which will be used to measure the effect of treatment on the severity of respiratory symptoms.

Mean change from baseline in: the daily EXACT Total Score, the daily total symptom score (RS-Total Score), as well as 3 subscale scores, RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms, will be calculated over each 4-week interval of the 52-week Treatment Period and over the entire 52-week Treatment Period. The last 7 days of the Screening Period from lead-in Study PT010006 will be used to calculate the baseline. The mean change from baseline in RS-Total Score, RS-Breathlessness, RS-Cough and Sputum, and RS-Chest Symptoms will be summarized by treatment group over 52 weeks and over each post-randomization 4-week interval (Interval 1 to Interval 13) (*Tables* and *Figures 3.1.8* and *3.1.9* and *Tables 3.1.10, 3.1.11* and *3.1.12*).

EXACT data will be listed in *Listing 6.1.5*.

6.5.5 Baselines and Baseline Covariates for Analysis:

For the diary symptom score parameters (including EXACT) and rescue medication usage, baseline will be the mean of the non-missing values from the diary data collected in the last seven days of the Screening Period.

Baseline COPD exacerbation history 0, 1, $\geq$ 2 moderate or severe exacerbations) (from the Visit 1 CRF page) is the number of COPD exacerbations in the last 12 months.

ICS (inhaled corticosteroid) use at screening (Yes or No) is to be determined with the input of medical expert(s) based on a list of medications that subjects were taking during the screening period (and which may be but are not necessarily ongoing medications) prior to unblinding of the study database.

Baseline age is the age in years at the time of Informed Consent.

6.5.6 Visits and Time Windows for Visit-Based Efficacy Assessments:

Efficacy data obtained during unscheduled visits will not be used for by-visit analyses. Efficacy from scheduled and unscheduled visits will be listed.

7. CHANGES FROM METHODS PLANNED IN THE PROTOCOL

The rate of severe COPD exacerbations has been added as an efficacy endpoint.

Any further changes to statistical methods planned in the protocol or in this statistical analysis plan will be documented in a revision to this statistical plan prior to database lock, or identified in the clinical study report.

8. STATISTICAL SOFTWARE

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be [redacted]

9. REFERENCES

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