Revised Clinical Study Protocol

Study Code	PT010008
NCT #	NCT03313570
Date	18 March 2016

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

The following Amendment(s) are included in this revised protocol:

Amendment No.	Date of Amendment
Version 1	13 July 2015
Version 2, Amendment 1	18 March 2016

Clinical Trial Protocol: PT010008-01

Study 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
Study Number:	PT010008-01
Study Phase:	III
Product Name:	Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol, PT010 Glycopyrronium and Formoterol Fumarate Inhalation Aerosol, PT003 Budesonide and Formoterol Fumarate Inhalation Aerosol, PT009
EudraCT Number:	2014-005672-29
Indication:	COPD
Investigators:	Multicenter
Sponsor:	Pearl Therapeutics, Inc. 200 Cardinal Way, 2nd Floor Redwood City, CA 94063 1-650-305-2600
Sponsor Contact:	Paul M. Dorinsky MD

	Version Number	**Date:**
Original Protocol	Version 1.0	13 July 2015
Amended Protocol	Version 2.0	18 March 2016

SUMMARY OF CHANGES TO ORIGINAL PROTOCOL VERSION 1.0, DATED [redacted]

The amended study protocol, PT010008-01(Version 2.0), includes the following edits:
Newly added text is shown in **bold font** and deleted text is shown as ~~strikethrough font~~.

No.	Description of Change	Rationale
1	Section 3: Study Endpoints: All assessments are relative to baseline assessments performed during the Study PT010006 Screening Period (between Visit 1 and Visit ~~3~~**4**)	To clarify Screening Period is considered between Visit 1 and Visit 4 and not between Visit 1 and Visit 3 in this section and throughout the document for consistency
2	Section 4.1 Overall Study Design and Plan 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 dilation,** 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 days if additional time is needed to complete the assessments** ~~during Study PT010006 Screening Period (between Visit 1 and Visit 4)~~. A separate informed consent will be obtained **for subjects participating in Study PT010008 prior to any study PT010008 procedures**.~~start of Study PT010006~~. Subjects participating in Study PT010008 who complete visit 10a of Study PT010006 will transition to the remaining 28 weeks of	To clarify how the scan information will be analyzed, to allow adequate time to complete assessments during the screening period, and to ensure consistency across study section and sites Removed a sentence about reference to revisions to SAP or DMC as this is not relevant to this section

	treatment by completing Visit 10b (Week 24). Post-baseline lenticular opacity, fundoscopic examination, intraocular pressure, and visual acuity assessments will be performed **prior to** ~~**at**~~ Visit 11 (Week 28), ~~and at~~ Visit 14 (Week 52) **and Treatment Discontinuation/Withdrawal Visit.** A post-baseline BMD assessment will be performed **prior to** Visit 14 (Week 52) **and Treatment Discontinuation/Withdrawal Visit**. Subjects will return to the clinic at Visit 12 (Week 36), and Visit 13 (Week 44) to return used **medication** and obtain new study drug. Subjects will return to the clinic at Visit 14 (Week 52) to complete final study visit procedures Removed the following sentence: ~~Further details will be provided in the DMC charter and in the Statistical Analysis Plan (SAP~~	
3	Section 5.2. Exclusion Criteria Subjects who meet any of the following criteria will be excluded from the study **(please see the exception noted below the ophthalmologic criteria Section 5.2.2).** Section 5.2.1 Bone Mineral Density Criteria **applied to either hip or lumbar region** 1. Severe ~~osteoarthritis~~ **osteoporosis** 2. T-score <-2.5 at baseline 3. Added**: Subjects unable to achieve an acceptable scan (e.g. due to the patient's inability to be stable during the procedure, due to limitation of scanning equipment to accommodate a subject (~300lbs or ~136kgs) or other characteristics)**.	Added reference to exclusion criteria exception note (at end of Section 5.2.2) for allowance of subjects who meet none of the BMD exclusion criteria but one or more of ophthalmologic exclusion criteria to continue in the study based on the specified conditions Bone Mineral Density exclusion criteria clarified to indicate that it applied to either the lumbar or the hip region and the following criteria were revised: 1. severe osteoarthritis term is corrected to reflect appropriate term "osteoporosis" 2. T-Score revised from a value of "2.5" to minus 2.5 "-2.5" to reflect the excluded value and clarified eligibility when >1 scan was

		required 3. Added exclusion criteria to account for limitations of the scanning equipment
4	Section 5.2.2 Exclusion Criteria Ophthalmologic Criteria **applied to either eye** 1. IOP ≥21mmHg **(lowest of the 3 readings)** 2. Note: Subjects with IOP ≥21mmHg may be treated and re-tested during the screening period. **If the re-test measurements for IOP < 21mmHg this subject may be eligible** **NOTE: Subjects who meet none of the bone mineral density exclusion criteria but who meet one or more ophthalmologic exclusion criteria may be permitted to continue in the study. Such subjects would undergo all study planned assessments except they would undergo no further ophthalmologic exams (all tests included in Section 7.2) during the randomized treatment period. Additionally such subjects would be permitted to continue in the study provided that the following 2 conditions are satisfied:** • **IOP is ≤ 22mmHg either with or without treatment** • **In the opinion of the optometrist/ophthalmologist, the subject does not have a condition (e.g., advanced glaucoma) that the eye health of the subject could be jeopardized by continued participation in the study**	Ophthalmologic exclusion criteria: clarified to indicate that this criteria applies to either eye and the following are revised: 1. The lowest of the 3 IOP readings should be considered to evaluate the exclusion of IOP >21mmHg 2. Note is revised to indicate what re-test value of the IOP could qualify subject's eligibility Added exclusion criteria exception note (at end of Section 5.2.2) for allowance of subjects who meet none of the BMD exclusion criteria but one or more of ophthalmologic exclusion criteria to continue in the study based on the specified conditions
5	Section 5.4.2 Prohibited COPD	To continue alignment with Study PT010006 at the start of this

	Medications 1. Table (Table 5-1). ~~**ICS**~~ was deleted 2. Theophylline details were revised to indicate Theophylline (≤400 mg/day) **is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to randomization in Study PT010006** 3. **Note below this table** Subjects who are steroid dependent and maintained on an equivalent of up to 5 mg oral prednisone per day or ≤10 mg oral prednisone every other day are permitted to enroll in the study provided they have been on a dose of oral steroids **that remains consistent and does not exceed this threshold for the last two weeks prior to randomization (Visit 4) in Study PT010006**	supplemental study
6	Section 5.4.3 Other Prohibited Medications **Inserted Table 5.3 Non-COPD Medications Allowed Under Certain Conditions**	Table 5.3 added to align with Study PT010006 at the start of this supplemental study
7	Section 5.4.3 Other Prohibited Medications Table 5.4 1. Wording before Table 5.4 revised Subjects requiring medications presented in **Table 5.4** are prohibited from participating in this study. **Subjects who recently discontinued use of these medications may be considered for study enrollment provided they have met the minimum Washout Period prior to Visit 1 in Study PT010006.** These medications are prohibited throughout the course of the study, and, should a subject require use of any of the listed medications**, ~~they should be~~**	To continue alignment with Study PT010006 at the start of this supplemental study 1. Wording prior to Table 5.4 revised to allow Investigator judgement 2. Table 5.4 added exception of carvedilol To align with exclusion criteria for CHF Class I and II treatment as these subjects are permitted to participate in the study 3. Table 5.4 footnote revised and description added to align with Study PT010006 4. Table 5.4 footnote revised and description added to align with Study PT010006 and allow

	~~**discontinued**~~ **the investigator should evaluate the appropriateness of continuing the subject in the study** 2. Table 5.4 revised to add **exception of carvedilol for non-specific beta blocking agent** 3. Table 5.4 Footnote added: **Anticonvulsants for seizure or other indications allowed provided the patient was treated with this class of medications during Study PT010006** 4. Table 5.4 Footnote revised: Antipsychotic agents **and tricyclic antidepressants used for previously diagnosed underlying medical conditions are allowed** ~~after consultation with the Peral Medical Monitor~~ **if, in the opinion of the Investigator, there are no concerns regarding patient safety, and if the patient has been on a stable dose for at least 6 weeks**.	Investigator opinion in the treatment of the study subject
8	Section 7.1 Bone Mineral Density Assessments Bone mineral density will be evaluated by taking two sets of DEXA scans **(lumbar spine and hip regions) prior to randomization (Study PT010006 Visit 4**) ~~within 14 days prior to baseline (Screening Visits 1 to 4 in Study PT010006) and within 14 days prior to~~ and Visit 14 (Week 52) **in this study**. After the first scan, **of the lumbar spine and hip region,** the subject will get up from the table, **and** be repositioned, ~~**and another scan taken**~~ **to take another set of scans at these skeletal sites**. If these **first** two 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**	To clarify how the scan information will be analyzed, allow adequate time to complete assessments during the screening period and to ensure consistency across study sites

	maximum of 21 days if additional time is needed to complete the assessments. The results of these scans will be provided by the central testing facility to the investigative site to allow appropriate management of the subject ~~If a subject's T-score is < 2.5~~ **For any clinically relevant reduction in T-score**, the investigator should consider appropriate treatment options **based on local guidelines** for the subject and/or refer them to their local medical doctor or a specialist for treatment. ~~If subsequently treated with bisphosphonates, the subject should be excluded from further BMD measures in this study~~ **If a subject's T-score (hip or lumbar spine) is <-2.5 at screening they are excluded**. Both the lumbar spine L2-L4 and total hip bone density will be measured. The ~~2~~ scans of each skeletal site will be centrally analyzed ~~and averaged~~ to obtain the final result to be used **for data analysis**. ~~The results of these scans will be relayed by the local facility to the investigator to allow appropriate management of the subject~~ Full details can be found in the BMD manual	
9	Section 7.2 Ophthalmologic Assessments 1. The baseline ophthalmologic assessment must be performed **prior to randomization** between Visits 1 and 4 (Screening) of Study PT010006. Two post-baseline ophthalmologic assessments will be performed at Visit 11 (Week 28), and ~~within 14 days prior to~~ Visit 14 (Week 52) **only per exclusion criteria exception noted in Section 5.2.2**. These post-baseline ophthalmologic assessments should be scheduled to occur within two weeks	For #1, Added consistency with respect to baseline assessment being conducted prior to randomization and within 14 days and concept for Visit 14 removed to correct an error for this study. For the two post-baseline ophthalmic assessments added clarification to refer to the exclusion criteria exception noted **in Section 5.2.2** For #2 and # 3, Included pupil dilation and clarified that a certified LOCSIII trained ophthalmologist /optometrist could conduct assessments

	prior to the scheduled clinic visit. Due to diurnal variability of IOP, all ophthalmic examinations following the first ophthalmic examination (~~**screening**~~ baseline) should be scheduled to occur within two hours of the time of day when the baseline ophthalmic examination was performed. The same ophthalmologist should perform the ophthalmic examinations for a given subject at all visits if possible, to ensure consistency. 2. At participating centers, all subjects will be referred to a ~~**pre-**~~certified **LOCSIII trained ophthalmologist/optometrist** for evaluation of **pupil dilation**, lenticular opacities, fundoscopic examination, intraocular pressure (IOP), manifest refraction and visual acuity. This data will also be categorized as normal/abnormal. 3. The Lens Opacities Classification System (LOCS) III grading system will be used to assess lenticular opacities in this study. The following assessments will be performed using a decimalized scale ranging from 0.1 (indicating a completely clear or colorless lens) to either 5.9 (indicating complete opacification on the cortex or posterior capsule for C or P scales) or 6.9 (indicating advanced opacification and brunescence of the nucleus for NO or NC scales). Each assessment will be recorded to the nearest 0.1 as determined by the **certified** ophthalmologist/**optometrist**. 4. Moved the "NOTE: The ophthalmologist/optometrist must not refer to prior LOCS III grades and LOGMAR visual acuities from	For #4 The Note moved with the LOCS III assessment to add relevance For #5 Eligibility criteria clarified with respect to the reading to be considered.

	previous ophthalmic examination at the time of a new examination" with the LOCS III assessment 5. **The lowest reading will be considered to determine eligibility**	
10	Added: **Section 7.3.5: EXACT** **The exacerbations of chronic pulmonary disease tool (EXACT) questionnaire will be captured via the subject eDiary (see Appendix 4)**	To align and include as a eDiary assessment
11	Section 7.6.1: Medical/Surgical History and Physical Examination. Weight, assessed in ordinary indoor clothing with shoes removed will be recorded at Visit 1 **~~(Screening)~~ (PT010006 Screening)** and Visit 10a only. Height will be recorded at Visit 1 **~~(Screening)~~ (PT010006 Screening)** only.	To reference back and align screening procedures with Study PT010006
12	Synopsis and Section 7.7.13 Clinical Endpoint Committee **Updated to change the adjudication committee name to Clinical Endpoint Committee and define their responsibilities**	To clarify that there is one committee for adjudication which is also known as Clinical Endpoint Committee and there are three Clinical Endpoint Adjudication Charters.
13	Synopsis and Section 7.7.14 Data Monitoring Committee **The responsibility was updated to include assessment of all safety data**	To provide clarity that the DMC provides assessment of all safety data not just SAEs.
14	Table 8.1 Revised to move a footnote under footnote "a" from footnote "g" and revise section referenced to the correct section in this Note: a. Scheduling visits: All visits will be scheduled relative to Visit 10a (Week 24) of the lead-in study (PT010006). **Note:** Refer to Section 8.~~6~~8 for procedures that may be required at a premature discontinuation visit. Treatment Discontinuation/Withdrawal Visits will be captured as unscheduled	Table 8.1: Revised the placement of the note to provide relevance and corrected section to reference to Section 8.8 appropriately

	visits **Added Section 8.1 Baseline Assessments.** 1. **The Baseline PT010008 Assessments will be conducted concurrently with PT010006 Screening. All study assessments are to be completed prior to Randomization (Visit 4) in PT010006.** • **Obtain informed consent prior to conducting any Study PT010008 baseline assessments.** • **Register subject in IWRS for Study PT010008 at the same time registering in Study PT010006.** • **Conduct BMD assessments (Refer to Section 7.1)** • **Conduct ocular assessments (Refer to Section 7.2)** 2. **Randomization** • **Review Study PT010008 inclusion/exclusion criteria and confirm subject's eligibility to continue.** • **Obtain subject randomization number and treatment assignment information from IWRS.** **Note : Randomization in PT01008 occurs simultaneously with randomization in Study PT010006 for those patients who qualify for Study PT010008.** • **A reminder phone contact should be made prior to Visit 10b.**	Section 8.1:To add the details of the: 1. Baseline procedures for this supplemental study to connect to the Study PT010006 where these subjects were screened 2. Randomization procedures in alignment with the schedule of events Table 8.1
15	Section 8.3 Visit 10b 1. ~~There are 10 scheduled visits in Study PT010006; the tenth visit is~~ The last visit of the Study PT010006 and the	1. and bullet 3: To clarify BMD/ocular study as PT010008 and align with schedule of events

	first post-baseline visit of the supplemental Study (PT010008). ~~In order to differentiate, assessments conducted at the completion of the supplemental study PT010008, all baseline bone mineral density (Section 7.1) and ocular (Section 7.2) assessments will be captured during Screening (Visits 1 to 4) of Study PT010006~~. Visit 10b will be ~~completed~~ following completion of all Visit 10a study procedures. ~~A reminder phone contact should be made prior to Visit 10b~~ 2. Review BMD/Ocular ~~sub-study~~ inclusion/exclusion criteria 3. Register subject in IWRS to confirm participation in the ~~BMD/Ocular sub-study~~**PT010008 and receive assigned treatment** 4. Subject will administer dose of study drug at home in the evening **Note:** During the ~~sub-~~study subjects will continue on the same treatment that they were assigned in Study PT010006 5. Schedule ophthalmologic assessment to occur ~~within two weeks~~ prior to Visit 11 (Week 28)	2. and bullet 4: Clarified "Note" to remove "sub" study 5. Removed ”within two weeks” for consistency throughout as not required
16	Section 8.4 Visits 11 (Week 28) • Confirm scheduled ocular assessments have been conducted (Visit 11 should be rescheduled if ocular assessments not conducted prior to this visit) **Please refer to the exclusion criteria exception noted in Section 5.2.2 to see if the ocular assessment applies to this visit**.	Added reference to the exclusion criteria exception noted **in Section 5.2.2** to conduct ocular assessment for this visit only if applicable
17	Section 8.7 Visit 14 (Week 52; Final Visit) • Confirm ocular assessments were conducted prior to this visit (Visit 14	Added reference to the exclusion criteria exception noted **in Section 5.2.2** to conduct ocular assessment for this visit

	should be rescheduled if ocular assessments not conducted prior to this visit) **Please refer to the exclusion criteria exception noted in Section 5.2.2 to see if the ocular assessment applies to this visit**	only if applicable
18	Section 9.1: Introduction revised sentence as follows: This ~~is a supplemental study~~ to Study ~~PT010006~~ PT010008 ~~and~~ will be conducted in a subset of US sites participating in Study PT010006, **and will evaluate the following treatments**	Revised to clarify language and reference to appropriate studies (PT010006 and PT010008)
19	Section 9.4.1.1 Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4 **T- and Z- scores will be presented as shifts from baseline to each time point; details will be provided in the SAP.** Section 9.4.1.2 Percent change from baseline in total hip BMD of the hip measured using DEXA scans **The change from baseline in BMD of the lumbar spine hip at Week 52 (and similarly at EoT) will be analyzed ~~using~~ ~~an Analysis of Covariance (ANCOVA) model with treatment group and gender as categorical covariates and~~ similarly to the change from baseline in BMD ~~score, age, and age by gender interaction as continuous covariates~~ of the lumbar spine.** ~~T- and Z- scores will be presented as shifts from baseline to each time point; details will be provided in the SAP. Shift tables reported row percentages calculated using non-missing row totals~~.	Revised to place details in appropriate sections

SYNOPSIS

Sponsor:

Pearl Therapeutics, Inc. ("Pearl")

[redacted]

Names of Finished Products:

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

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

Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, BFF MDI)

Name of Active Ingredients:

Budesonide, Glycopyrronium, and Formoterol Fumarate

Glycopyrronium and Formoterol Fumarate

Budesonide and Formoterol Fumarate

Study 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

Study Number: PT010008-00

Study Phase: Phase III

Primary Objectives:

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

Safety Objectives:

- To assess the safety and tolerability of BGF MDI, GFF MDI, and BFF MDI

Study Design:

This is a randomized, double-blind, parallel-group, 52-week, chronic-dosing, multi-center supplemental study to assess the effects of PT010, PT009, and PT003 on bone mineral density (BMD) measurements, ocular assessments, and safety and tolerability in subjects with moderate to very severe COPD. This 52-week supplemental study will be conducted in a sub-set of subjects participating in Study PT010006. Approximately 70 sites are planned to participate in the study, contributing approximately 8 subjects per site. Across these sites, it is planned that approximately 500 subjects randomized to double-blind treatment only will be included in Study PT010008 to provide approximately (425) subjects who will 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. Subjects randomized to open-label Symbicort TBH in

Study PT010006 will not be enrolled in this supplemental study. The entire study period is scheduled to take approximately 58 weeks for most subjects.

An additional separate informed consent will be obtained for subjects participating in Study PT010006 who volunteer to participate in Study PT010008. This study will evaluate the effects of BGF MDI, BFF MDI, and GFF MDI on BMD measurements and ocular assessments. Baseline and demographic characteristics collected in Study PT010006 will be used for subjects participating in this study. Baseline BMD (Dual Energy X-ray Absorptiometry [DEXA] Scans) measurements and ocular assessments (Lens Opacities Classification System [LOCS] III, fundoscopic examination, intraocular pressure, and visual acuity) will be performed during Study PT010006 Screening Period (between Visit 1 and Visit 4).

Subjects participating in PT010008 who complete visit 10a of Study PT010006 will transition to the remaining 28 weeks of treatment by completing Visit 10b (Week 24) of Study PT010008. Post-baseline lenticular opacity, fundoscopic examination, intraocular pressure, and visual acuity assessments will be performed at Visit 11 (Week 28), at Visit 14 (Week 52), and/or at a Premature Discontinuation/Early Withdrawal Visit. A post-baseline BMD measurement will be performed at Visit 14 (Week 52) or at a Premature Discontinuation/Early Withdrawal Visit occurring after Visit 10b. Subjects will return to the clinic at Visit 12 (Week 36) and Visit 13 (Week 44) to return used and obtain new supplies of study drug. Subjects will return to the clinic at Visit 14 (Week 52) to complete final study visit procedures.

A follow up telephone call will be performed at least 14 days after last study drug.

Study Population:

This study will include a subset of approximately 500 randomized subjects participating in Study PT010006 who were randomized to blinded study treatment (BGF MDI, GFF MDI, and BFF MDI). Subjects will continue to receive the same treatment they were randomized to receive in PT010006.

Product, Dose, and Mode of Administration:

Investigational materials will be provided by Pearl Therapeutics (Pearl), as shown below:

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Medications			
BGF MDI (PT010) 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BFF MDI (PT009) 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol Sulfate inhalation aerosol 90 µg[a] ex-actuator	US source: Ventolin® HFA HFA inhalation aerosol will be the US-supplied product." Albuterol sulfate inhalation aerosol. Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	MDI/ 60 or 200 actuations	Taken as directed Supplies are open-label

BID=twice daily; BGF MDI=Budesonide, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; BFF MDI=Budesonide and Formoterol Fumarate Inhalation Aerosol; HFA=Hydrofluroalkane; MDI=Metered Dose Inhaler.

[a] Rescue medication during the study.

All study drugs will be administered by oral inhalation.

Duration of Treatment:

It is planned that each subject will receive study treatment for 52 weeks with the initial 24 weeks of exposure coincident with Study PT010006. It is anticipated that the entire study will take approximately 58 weeks for each individual subject from the time of Screening in Study PT010006.

Bone Mineral Density Endpoints:

The primary BMD endpoint is:

- Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4 at Week 52

Other BMD endpoints include:

- 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

Ocular Endpoints:

The primary ocular endpoint is:

- Change from baseline in the LOCS III Posterior subcapsular (P) Score at Week 52

Other ocular endpoints include:

- 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
- 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 ≥22mmHg at Week 28, at Week 52, and EoT
- Proportion of subjects change from baseline in IOP of ≥7mmHg at Week 28, at Week 52, and EoT
- Change from baseline in 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 TEAEs including cataract and glaucoma

Safety Endpoints:

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

Efficacy Endpoints:

- Change from baseline in average daily rescue Ventolin HFA (albuterol sulfate) use
- Percentage of days with no rescue Ventolin HFA use
- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Change from baseline in: the EXACT total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale scores symptom (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

Statistical Methods:

Primary Analysis for BMD Endpoint:

Analyses of BMD endpoints will be conducted on those randomized subjects who have both baseline and post-baseline BMD results.

The change from baseline in BMD of the lumbar spine at Week 52 will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and gender as categorical covariates and baseline BMD, age, and the interaction between gender and age as continuous covariates.

Primary Analysis for LOCS III Endpoint:

Change from baseline in LOCS III (P) scores at Week 52 will be analyzed using an ANCOVA. The model will include treatment group as a fixed effect, and baseline LOCS III (P) score, smoking pack years, and age as continuous covariates. The model will account for inter-eye correlation by including subject and eye (within subject) as random effects.

Two-sided 95% confidence intervals will be computed for pairwise differences of BGF minus GFF and BFF minus GFF, and non-inferiority will be declared if the upper confidence bound is less than 0.5.

Sample Size:
Assuming a 15% rate of discontinuation through Week 52, a subset of 500 randomized subjects from the PT010006 study will provide 425 subjects with baseline and on-treatment BMD and LOCS III. This sample size will provide approximately 97% power to demonstrate non-inferiority of BGF MDI to GFF MDI in percent change from baseline in BMD for Lumbar Spine L2-L4 at Week 52 based on the lower limit of -2%, true difference of -0.3%, and SD of 4% and approximately 91% power for the non-inferiority comparison of BFF MDI to GFF MDI under identical assumptions. It will provide over 99% power to demonstrate non-inferiority of BGF MDI to GFF MDI (or BFF MDI to GFF MDI) in change from baseline in LOCS III Score (P) at Week 52 based on a margin of 0.5 or more (1-sided, alpha=0.025) assuming no true difference in the means.

Data Monitoring and Clinical Endpoint Committees:

Data Monitoring Committee*:*

An external Data Monitoring Committee (DMC) that was initiated in Study PT010006 will continue to provide systematic and unbiased assessment of safety for Study PT010008. Members of the DMC will review data at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

Clinical Endpoint Committee*:*

An external clinical endpoint committee (CEC) that was initiated in Study PT010006 will continue to provide systematic and unbiased assessment of pre-defined, Investigator reported adverse events for Study PT010008. The committee will consist of experts who will provide a centralized review functioning independently of Pearl. Three Clinical Endpoint Adjudication Charters will outline the clinical endpoints for adjudication.

- Cardiovascular- and Cerebro-vascular (CCV) Clinical Endpoint Adjudication Charter
- Cause-Specific Mortality Clinical Endpoint Adjudication Charter
- Pneumonia Clinical Endpoint Adjudication Charter

Date of Original Approved Protocol: [redacted]

Date of Amendment 1.0 (Version 2.0): [redacted]

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse event
AESI	Adverse event of special interest
ANOVA	Analysis of Covariance
BD	Budesonide
BFF	Budesonide and formoterol fumarate
BGF	Budesonide, glycopyrronium, and formoterol fumarate
BID	*bis in die*, twice daily
BMD	Bone Mineral Density
CCV	Cardio- and cerebro-vascular
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards Of Reporting Trials
COPD	Chronic obstructive pulmonary disease
DEXA	Dual Energy X-ray Absorptiometry
DMC	Data Monitoring Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EoT	End of Treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
FF	Formoterol fumarate
GCP	Good Clinical Practice
GFF	Glycopyrronium and formoterol fumarate
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HFA	Hydrofluoroalkane
IEC	Independent Ethics Committee
IOP	Intraocular Pressure
IRB	Institutional Review Board
LOCS III	Lens Opacities Classification System III

LogMAR	Logarithm of the Minimum Angle of Resolution
MACE	Major adverse cardiovascular events
MDI	Metered dose inhaler
PRO	Patient-reported outcome
PSC	Posterior Subcapsular Cataract
SAE	Serious adverse event
SD	Standard deviation
TBH	Turbuhaler
TC	Telephone call

TRADEMARK INFORMATION

Trademarks Not Owned By Pearl Therapeutics, Inc.

Oxis
Spiriva
Symbicort
Ventolin
Turbuhaler

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common preventable and treatable disease characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and co-morbidities contribute to the overall severity in individual patients. Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality worldwide and results in significant economic and social burden that is both substantial and increasing. Pharmacologic therapy in COPD is used to reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance [Global Initiative for Chronic Obstructive Lung Disease (GOLD, 2014); Japanese Respiratory Society (JRS, 2013).

Bronchodilator medications are central to the symptomatic management of COPD. The principal bronchodilator treatments are β_2-agonists, anticholinergics, and methylxanthines used as monotherapy or in combination. Treatment with long-acting bronchodilators is more convenient and more effective at producing maintained symptom relief than treatment with short-acting bronchodilators.

Regular treatment with inhaled corticosteroids (ICS) improves symptoms, lung function, and quality of life and reduces the frequency of exacerbations in subjects with COPD with a forced expiratory volume in 1 second (FEV_1) value of <60% of predicted. Withdrawal from treatment of ICS may lead to exacerbations in some patients. When combined with a long-acting β_2-agonist (LABA), an ICS is more effective than the individual components in improving lung function, quality of life, and reducing exacerbations in subjects with moderate to very severe COPD [GOLD, 2014].

Pearl Therapeutics, Inc. (hereinafter referred to as Pearl) is developing the fixed-dose ICS/ long-acting anti-muscarinic agent (LAMA)/LABA triple combination product, Budesonide, Glycopyrronium, and Formoterol Fumarate Inhalation Aerosol (PT010), hereafter referred to as budesonide, glycopyrronium, and formoterol fumarate metered dose inhaler (BGF MDI), for the treatment of patients with COPD. Budesonide and Formoterol Fumarate Inhalation Aerosol (PT009, hereinafter referred to as budesonide and formoterol fumarate (BFF) MDI is also being developed as a twice daily (BID) fixed dose ICS/LABA treatment for patients with COPD. Glycopyrronium and Formoterol Fumarate Inhalation Aerosol (PT003) hereinafter referred to as glycopyrronium and formoterol fumarate (GFF) MDI is being developed as a BID maintenance bronchodilator treatment in patients with COPD.

Budesonide is a well-established corticosteroid approved worldwide in monotherapy and combination therapies for treatment of asthma and allergic rhinitis. It is available in both intranasal and orally inhaled formulations. Inhaled budesonide in combination with formoterol fumarate dihydrate, i.e., Symbicort is approved for use in patients with COPD.

Glycopyrronium is a LAMA which exerts its bronchodilatory effect via muscarinic receptors located on smooth muscle cells within the trachea and bronchi. Glycopyrronium is approved in many countries in multiple formulations for different indications, including for the treatment of COPD.

Formoterol fumarate is a selective LABA approved worldwide for use in asthma and COPD. In addition, formoterol fumarate is also approved worldwide in combination with budesonide (e.g., Symbicort® MDI, Symbicort® Turbuhaler® (TBH [AstraZeneca, LP]) for use in patients with asthma and COPD. When inhaled, formoterol fumarate acts locally in the lung as a bronchodilator. Formoterol fumarate stimulates β_2-adrenoreceptors in the airways, inducing airway smooth muscle relaxation and reducing or preventing bronchoconstriction.

1.1 Study Rationale

Patients with COPD are frequently treated with ICS; the impact of ICS use on potential fracture risk is not consistent across published literature [Lehouck, 2011; Weldon, 2009; Christensson, 2008]. Studies in adults with COPD have produced a wide range of results in support of the direct effect of ICS on bone mineral density (BMD) and fracture risk.

It has also been reported that corticosteroid treatment can lead to multiple ocular effects, including cataracts, increased intraocular pressure (IOP) and glaucoma. Furthermore, as the majority of the COPD population is elderly, these observed ocular changes are more likely to be predominant in an elderly population. For example, in the TORCH safety sub-study, the background prevalence of cataracts was high in COPD patients (68.5-75.3% at Screening) [Calverley, 2007].

As a result of the increased occurrence of cataracts, IOP, and glaucoma and the increased risk of bone disorders in patients with COPD, definitive ocular and bone mineral density assessments are included in this 1-year safety study.

2 STUDY OBJECTIVES

2.1 Primary Objective

- 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

2.2 Secondary Objectives

- To assess the safety and tolerability of BGF MDI, GFF MDI, and BFF MDI

3 STUDY ENDPOINTS

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

3.1 Bone Mineral Density Endpoints

3.1.1 Primary Bone Mineral Density Endpoint

- Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4 at Week 52

3.1.2 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

3.2 Ocular Endpoints

3.2.1 Primary Ocular Endpoint

- Change from baseline in the LOCS III (P) Score at Week 52

3.2.2 Other Ocular Endpoints

- Change from baseline in each scale of the LOCS III scores at Week 28, Week 52 (NO, NC, and C only), and EoT
- 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 ≥22mmHg at Week 28, at Week 52, and EoT
- Proportion of subjects change from baseline in IOP of ≥7mmHg at Week 28, at Week 52, and EoT
- Change from baseline in LogMAR visual acuity using 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 TEAEs including cataract and glaucoma

3.3 Safety Endpoints

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

3.4 Efficacy Endpoints

- Change from baseline in average daily rescue Ventolin HFA (albuterol sulfate) use
- Percentage of days with no rescue Ventolin HFA use
- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Change from baseline in: the EXACT total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale scores symptom (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

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a randomized, double-blind, parallel-group, 52-week, chronic-dosing, multi-center supplemental study to assess the effects of PT010, PT009, and PT003 on bone mineral density (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 subjects participating in Study PT010006. Approximately 70 sites are planned to participate in the study, contributing approximately 8 subjects per site. Across these sites, it is planned that approximately 500 subjects randomized to double-blind treatment only will be included in Study PT010008 to provide approximately (425) subjects who will 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. Subjects randomized to open-label Symbicort TBH will not be enrolled in this study, however, since baseline BMD and ocular assessments will be performed prior to randomization all subjects who will eventually be randomized to Symbicort TBH will have a baseline assessment. The entire study period is scheduled to take approximately 58 weeks for most subjects.

This safety study will evaluate the effects of BGF MDI, BFF MDI, and GFF MDI on bone mineral density (BMD) measurement (Johnell, 2002) and lenticular opacity (Chylack, 1993) 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 days if additional time is needed to complete the assessments. A separate informed consent will be obtained for subjects participating in Study PT010008 prior to any study PT010008 procedures.

Subjects participating in Study PT010008 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), Visit 14 (Week 52) and Treatment Discontinuation/Withdrawal Visit. A post-baseline BMD assessment will be performed prior to Visit 14 (Week 52) and Treatment Discontinuation/Withdrawal Visit. Subjects will return to the clinic at Visit 12 (Week 36), and Visit 13 (Week 44) to return used medication and obtain new study drug. Subjects will return to the clinic at Visit 14 (Week 52) to complete final study visit procedures.

All subjects will continue to receive sponsor-provided Ventolin® HFA (albuterol sulfate inhalation aerosol) for rescue use throughout the study.

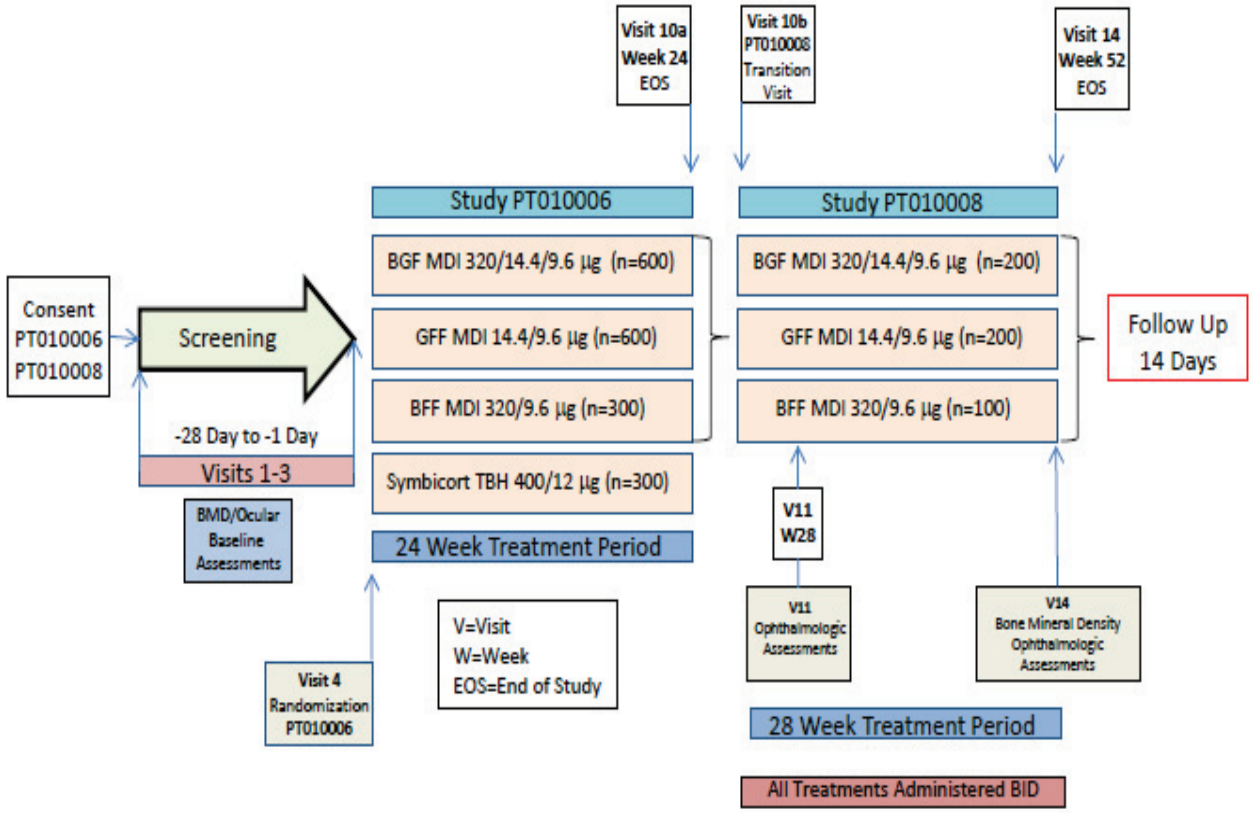
After Visit 14 (Week 52), a follow-up telephone call will be performed at least 14 days after the last study drug dose. For subjects who withdraw consent, schedule a follow-up telephone call at

least 14 days after the last study drug dosing, if the final visit is performed >14 days post last study drug dosing, a follow-up TC will not be required.

If a subject chooses not to continue with study assessments, at a minimum the subject will complete the Treatment Discontinuation/Withdrawal Visit (refer to 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: Subject who discontinues prior to Visit 10b will not complete BMD assessments). These subjects will return to appropriate maintenance COPD medications, per the investigators discretion. A follow-up telephone call will be performed at least 14 days after the last study drug dose. In the event the Treatment Discontinuation/Withdrawal Visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. These subjects will be followed for vital status at 52 weeks post-randomization in accordance with the informed consent.

An overall study design is summarized and displayed in Figure 1.

Figure 1. Study Design



5 STUDY POPULATION SELECTION AND WITHDRAWAL CRITERIA

5.1 Inclusion Criteria

Subjects eligible for enrollment in the study must meet all of the following criteria:

1. Give their signed written informed consent to participate.
2. Subjects must have agreed to participate in Study PT010006.

5.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from the study (please see the exception noted below the ophthalmologic criteria Section 5.2.2).

5.2.1 Bone Mineral Density Criteria applied to either hip or lumbar region

1. Severe osteoporosis
2. T-score < -2.5 at baseline
3. Subjects unable to achieve an acceptable scan (e.g. due to the patient's inability to be stable during the procedure, due to limitation of scanning equipment (~300 lbs or ~136 kgs) or other characteristics)

5.2.2 Ophthalmologic Criteria applied to either eye

4. Inability to dilate pupil ≥6 mm
5. IOP ≥21mmHg (lowest of the 3 readings)

Note: Subjects with IOP ≥21mmHg may be treated and re-tested during the screening period. If the re-test measurements for IOP <21mmHg this subject may be eligible

6. Subjects who have an implanted artificial intraocular lens, i.e., subjects who have undergone, or are scheduled to undergo, cataract removal surgery.

NOTE: Subjects who **meet none** of the bone mineral density exclusion criteria but who **meet one or more** ophthalmologic exclusion criteria may be permitted to continue in the study. Such subjects would undergo all study planned assessments except they would undergo no further ophthalmologic exams (all tests included in Section 7.2) during the randomized treatment period. Additionally such subjects would be permitted to continue in the study provided that the following 2 conditions are satisfied:

- IOP is ≤ 22mmHg either with or without treatment
- In the opinion of the optometrist/ophthalmologist, the subject does not have a condition (e.g., advanced glaucoma) that the eye health of the subject could be jeopardized by continued participation in the study

5.3 Subject Identification

All subjects who participate in this study will maintain the unique screening identification number and unique subject randomization number assigned to them for participation in Study PT0100006.

5.4 Prior, Concomitant, and Prohibited Medications

Any additions, deletions, or changes in the dose of these medications while in the study should be entered on the CRF. Any current ongoing medications, including OTC drugs and herbal supplements, will be allowed provided they are not prohibited by the protocol (refer to Section 5.4) and are approved by the investigator. Subjects should also be instructed to contact the investigator if they develop any illnesses.

All concomitant medications taken during the study will be recorded on the Concomitant Medications CRF page with indication, total daily dose, and dates of drug administration.

5.4.1 Allowed Concomitant Medications to Treat a COPD Exacerbation

Medications to treat an exacerbation should not be used for more than 14 days. Recent data have suggested that treatment with systemic steroids for shorter periods of time results in similar outcomes with less systemic steroid exposure. Therefore, it is recommended that subjects are treated with a 5 day course of steroids and no longer than 14 days.

5.4.2 Prohibited COPD Medications

The following medications used for the treatment of COPD are not permitted during this study. These medications must have been discontinued during the Screening Period of Study PT010006 and are prohibited during this supplemental study (Table 5-1).

Table 5-1. Prohibited COPD Medications

Class of medication
LAMAs
Short-acting muscarinic antagonists (SAMA)
LABAs (inhaled)
Fixed-combinations of LABA/LAMA
Fixed-combinations of LABA/ICS
Fixed-combinations of SABAs and SAMAs
SABAs[a]
Oral β-agonists
Theophylline (total daily dose >400 mg/day)[b]

Abbreviations: ICS=inhaled corticosteroid; LABA=long-acting β_2-agonist; LAMA=long-acting muscarinic antagonist; SABA=short-acting β_2-agonist; SAMA=short-acting muscarinic antagonist

[a] Other than sponsor-provided open-label Ventolin HFA.

[b] Theophylline (≤400 mg/day) is permitted provided the subject has been on a stable dose of therapy for at least 4 weeks prior to Randomization in Study PT010006.

Note:

- During the Treatment Period (Visit 10b to Visit 14), subjects may be treated with systemic corticosteroids if required
- Subjects who are steroid dependent and maintained on an equivalent of up to 5 mg oral prednisone per day or ≤10 mg oral prednisone every other day are permitted to enroll in the study provided they have been on a dose of oral steroids that remains consistent and does not exceed this threshold for the last two weeks prior to randomization (Visit 4) in Study PT010006

The following respiratory medications are not permitted during this study (Table 5-2).

Table 5-2. Other Respiratory/Nasal Medications

Class of Medication
Leukotriene antagonists (e.g., zafirlukast, montelukast and zilueton)
Cromoglycate Nedocromil Ketotifen[a]
[a] Ketotifen eye drops are allowed

5.4.3 Other Prohibited Medications

Table 5.3 lists certain non-COPD medications that can be used under the stated conditions during this study. Each concomitant drug must be individually assessed against all exclusion criteria. If in doubt, the Investigator should contact Pearl's Medical Monitor before randomizing a subject or allowing a new medication to be started:

Table 5.3. Non-COPD Medications Allowed Under Certain Conditions

Medications Allowed Under Certain Conditions	Condition
SSRIs or SNRIs	Treatment regimen has been stable for at least 4 weeks prior to Visit 1 and not altered during the Screening Period, and does not exceed the maximum recommended dose
Intranasal corticosteroids, intranasal antihistamines, or combination thereof	Administered at constant dose and dosing regimen for at least 7 days prior to Screening (Visit 1) and during the Screening Period

Abbreviations: COPD=chronic obstructive pulmonary disease; SNRI=serotonin–norepinephrine reuptake inhibitors; SSRI=selective serotonin reuptake inhibitors

Subjects requiring medications presented in Table 5-4 are prohibited from participating in this study. Subjects who recently discontinued use of these medications may be considered for study enrollment providing they have met the minimum Washout Period prior to Visit 1.

These medications are prohibited throughout the course of the study, and, should a subject

require use of any of the listed medications, the investigator should evaluate the appropriateness of continuing the subject in the study.

Table 5.4. Prohibited Medications

Prohibited Medications
Any drug with potential to significantly prolong the QT interval Other investigational drugs Non-selective beta-blocking agents (exception Carvedilol) Cardiac antiarrhythmics Class Ia, III) Anticonvulsants for seizure disorder [a] Anticonvulsants for other indications [a] Tricyclic antidepressants[b] Monoamine oxidase inhibitors Anti-tumor necrosis factor α (TNF α) antibodies (e.g., infliximab and any other members of this class of drugs) Monoclonal antibodies Antipsychotic drugs [b] Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors and cimetidine Systemic anticholinergics[c] Illicit drugs or drugs of abuse Chinese complementary and alternative bronchodilatory medicines (CAM), i.e., herbal therapies (e.g., *Astragalus membranaceus [*huáng qí]*, Panax ginseng [ginseng products]* and *Cordyceps sinensis. A. membranaceus [ghost moth caterpillar fungus])*[d]
Note: Benzodiazepines are not exclusionary. [a] Anticonvulsants for seizure or other indications allowed provided the patient was treated with this class of medications during Study PT010006 [b] Antipsychotic agents and tricyclic antidepressants used for previously diagnosed underlying medical conditions are allowed if, in the opinion of the Investigator, there are no concerns regarding patient safety, and if the patient has been on a stable dose for at least 6 weeks. [c] Systemic anticholinergics are allowed provided the patient was treated with this class of medications during Study PT010006 [d] Requires case-by-case review by the Investigator to determine appropriate wash-out period, if needed.

5.5 Other Restrictions, Illicit Drugs, or Drugs of Abuse

5.5.1 Illicit Drugs

Illicit drugs or drugs of abuse will not be allowed from Visit 10b to Visit 14 or to whenever the subject withdraws from the study. If any illicit drugs or drugs of abuse are used by the subject during the study, the dates of use and the amount will be documented and the subject will be discontinued at the discretion of the investigator. Medical marijuana is not an exclusionary drug if used for medical purposes, and there is no change in the dose or frequency of consumption.

5.5.2 Dietary Restrictions

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

5.6 Smoking Status

Changes in a subject's smoking status (e.g., stopping or re-starting smoking) may have an impact on the efficacy outcome measures. At all visits the subject will be asked about any recent change in their smoking status (i.e., whether a subject's status has changed from smoker to non-smoker or vice versa). Smoking status changes during the 28-week Treatment Period will be captured in the eCRF, but the subject will be permitted to continue in the study. Subjects will be required to refrain from smoking (including medical marijuana and electronic cigarettes) for at least 4 hours prior to each study visit and throughout the duration of each study visit. Study participants may utilize various nicotine replacement treatments such as chewing gum and patches (PRN), in accordance with recommendations from the Investigator during the entire study visit.

Note: Use of electronic cigarettes will be viewed and managed in the same manner as traditional smoking.

5.7 Reasons and Procedures for Early Discontinuation from the Study

5.7.1 Reasons for Discontinuation

Subjects may be withdrawn from the study at any time at their own request, upon request of the Investigator, or by Pearl at any time or for any reason. A subject who withdraws consent will always be asked about the reason(s) and the presence of any adverse events (AE). All subjects who discontinue for any reason, or their family or healthcare providers, will be contacted 52 weeks post-Randomization to determine vital status, and if appropriate, cause of death (Section 8.8). The subject may voluntarily discontinue treatment at any time without prejudice to further treatment. If a subject experiences any of the changes of concern listed below, a repeat assessment should be obtained, and if confirmed, the Investigator or designee needs to make a determination as to the suitability of continuing the subject in the study. The changes of concern include:

- Calculated QTcF intervals >500 msec, and have increased by 60 msec or more over test day baseline value
- Following dosing, a heart rate increase of >40 bpm from the pre-dose value obtained on that specific test day and the measured value is also >120 bpm
- Following dosing, a systolic blood pressure increase of >40 mmHg from the pre-dose value obtained on that specific test day and the measured value is also >160 mmHg
- Decrease in creatinine clearance to a value ≤30 mL/minute using CKD-EPI formula or a clinically relevant change from baseline as determined by the Investigator
- Hepatic impairment defined as abnormal liver function test of AST, ALT or total bilirubin ≥3 times upper limit of normal on repeat testing

If a subject requires the following prohibited medications, they should be withdrawn from the study:

- Initiation of maintenance therapy with any prohibited medications as listed in Section 5.4.2
- Initiation of maintenance therapy with a LABA (e.g., salmeterol, formoterol, indacaterol, vilanterol, olodaterol) administered alone or in combination with an ICS or a LAMA (e.g., tiotropium, aclidinium, glycopyrronium, umeclidinium)
- Change inhaled maintenance therapy during the course of the study

NOTE: Subjects who suffer an exacerbation (regardless of severity) will remain in the study and continue to take their assigned study drug unless the Investigator decides that it is in the best interest of the subject to discontinue early from the study. The definition and severity of exacerbations are discussed in Section 7.2.2.1. If a female subject becomes pregnant during the course of the study, the subject will be discontinued and the pregnancy will be followed full-term through delivery or final outcome (see Section 7.2.3.4).

6 LABELING, PACKAGING, STORAGE, DISPENSING, AND RETURN OF CLINICAL SUPPLIES

6.1 Subject Information

Clinical supplies will be packaged to support enrollment of the study. Study personnel will have access to an Interactive Web Response System (IWRS) to allocate subjects, to assign drug to subjects and to manage the distribution of clinical supplies. Clinical supplies will be packaged according to a component schedule generated by the Sponsor. Each person accessing the IWRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system and they must not share their assigned PIN with anyone.

6.2 Product Descriptions

Investigational materials will be provided by Pearl as summarized in Table 6-1.

Ventolin HFA will be supplied as open-label MDIs.

Table 6-1. Product Descriptions

Product Name & Dose	Product Strength	Dosage Form/ Fill Count	Administration
Study Drug			
BGF MDI (PT010) 320/14.4/9.6 µg ex-actuator	160/7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
GFF MDI (PT003) 14.4/9.6 µg ex-actuator	7.2/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
BFF MDI (PT009) 320/9.6 µg ex-actuator	160/4.8 µg per actuation	MDI/ 120 inhalations	Taken as 2 inhalations BID
Open-Label Products			
Albuterol Sulfate inhalation aerosol 90 µg[a] ex-actuator	US source: Ventolin® HFA HFA inhalation aerosol will be the US-supplied product." Albuterol sulfate inhalation aerosol. Each inhalation contains 108 µg corresponding to 90 µg albuterol base from the mouthpiece	MDI/ 60 or 200 actuations	Taken as directed Supplies are open-label

BID=twice daily; BGF MDI=Budesonide, Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; GFF MDI=Glycopyrronium and Formoterol Fumarate Inhalation Aerosol; BFF MDI=Budesonide and Formoterol Fumarate Inhalation Aerosol; HFA=Hydrofluroalkane; MDI=Metered Dose Inhaler.

[a] Rescue medication during the study.

Notes: All study drugs will be administered by oral inhalation.

Open-label Ventolin HFA with dose counters will be provided from commercial supplies. Manufacturer's instructions for study drug administration are provided in Appendix 3.

6.3 Primary Packaging and Labeling Information

Investigational materials will be packaged by the Sponsor. Ventolin HFA will be supplied as open-label MDIs.

Blinded Supplies: Each MDI will be labeled with a single label. The MDI actuator will be labeled with a single label. The foil pouch will be labeled with a single label.

Open-label Supplies: Open-label Ventolin HFA will be provided as individually-labeled MDIs. Each MDI will contain a single label. The MDI actuator will be labeled with a single label. Labels will be printed with black ink and may include the following text: Labels will be printed with black ink and may include the following text:

Lot # (Packaging Lot Trace ID) Space for entry of screening # Component ID # Space for entry of randomization # Fill Count & Dosage Form Visit # (Space for Entry of Interval ID)	Storage Conditions Protocol # Country regulatory requirements Sponsor address Translation Key

ID = identification; # = number

6.4 Secondary Packaging and Labeling Information (Box)

Blinded investigational drug and open-label supplies (Ventolin HFA) will be packaged in individual boxes as outlined in Table 6-2. Box configuration is subject to change as a result of packaging constraints.

Table 6-2. Description of Boxes

Drug Supplies	Individual Box Contents
Blinded	1 MDI
Ventolin (albuterol sulfate) HFA	1 MDI

HFA=Hydrofluoroalkane; MDI=metered dose inhaler

Each box will be labeled with a 2-part label printed with black ink and may include the following text:

Packaging Lot ID #	Dosing Instructions (if applicable)
Space for entry of screening #	Storage Conditions
Component ID #	Compound ID - Protocol #
Space for entry of randomization #	Country regulatory requirements
Kit Contents (1 MDI)	Sponsor address (if applicable)
Space for entry of Interval ID	Translation Key (if applicable)
Re-evaluation/Expiration date (if applicable)	

ID = identification; # = number

6.5 Emergency Unblinding of Treatment Assignment

The IWRS should be used in order to unblind subjects and to unmask drug identity. When the Investigator contacts the system to unblind a subject, he/she must provide the requested subject identifying information and confirm the necessity to unblind the subject. Pearl will not provide a disclosure envelope with the clinical supplies.

The Investigator or treating physician may unblind a subject's treatment assignment **only in the case of an emergency**, when knowledge of the study treatment is essential for the appropriate clinical management or welfare of the subject.

Whenever possible, the Investigator must first discuss options with the Medical Monitor or appropriate study personnel **before** unblinding the subject's treatment assignment. If this is impractical, the Investigator must notify Pearl as soon as possible, but without revealing the treatment assignment of the unblinded subject, unless that information is important for the safety of subjects currently in the study. The date and reason for the unblinding must be recorded in the appropriate data collection tool.

6.6 Storage Requirements

Blinded Supplies should be kept in a secured location. BGF MDI, GFF MDI, and BFF MDI should be stored below 25° C (77° F) in a dry place. Excursions permitted up to 30° C (86° F).

Ventolin® HFA supplies: Store between 15°C and 25°C (59°F and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. Do not use or store near heat or open flame. Exposure to temperatures above 120°F (49°C) may cause bursting. Never throw into a fire or incinerator.

The clinical supplies storage area at the site must be monitored by the site staff for temperature consistency with the acceptable storage temperature range specified in accordance with the product label. Documentation of temperature monitoring should be maintained.

6.7 Instructions for Preparation of Treatments for Administration and Dispensing

6.7.1 BGF MDI, GFF MDI, BFF MDI

Individual BGF MDI, GFF MDI, and BFF MDI will be packaged in a foil pouch and contained in an individual visit treatment box. Both the visit treatment box and the foil overwrap will have a label with a component ID number. Confirm that the identifier given by IWRS and the component ID number written on the label are the same. The visit treatment box is labeled with a 2-part label. Write the subject number and treatment visit number on each of the 2-part labels. The 'tear-off' part of the label is to be placed onto the IWRS confirmation report.

All MDIs must be primed before the first use. Priming involves releasing a certain number of sprays (4) into the air before the first use of the inhaler. Shaking and priming the inhaler fills a chamber inside the canister with the correct dose and mix of medication so that the inhaler is ready to use.

The MDI must be primed in a separate room, away from the subject treatment area.
Each dose will consist of 2 puffs from the MDI. Subjects will be dispensed the MDI and instructed to continue taking study medication twice daily, 2 puffs in the morning and 2 puffs in the evening approximately 12 hours apart, until subject returns to the clinic. The MDI should be stored at room temperature by the subject, to avoid temperature extremes, and the products should not be stored in direct sunlight. Refer to Appendix 2 for instructions on administration and cleaning of BGF MDI, GFF MDI, and BFF MDI.

6.7.2 Ventolin HFA®

Refer to Appendix 3 for the manufacturer's instructions on the administration and cleaning of Ventolin HFA.

6.8 Drug Accountability/Return of Clinical Supplies

Under no circumstances will the Investigator(s) allow the study drug to be used other than as directed by this protocol.

Investigational clinical supplies must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secure location to which only the Investigator and designated assistants have access. Storage conditions for the clinical supplies should be observed, monitored and documented. Clinical supplies are to be dispensed only in accordance with the protocol. The Investigator or designee is responsible for keeping accurate records of the clinical supplies received from Pearl, the amount dispensed to and returned by the subject, and the amount remaining at the conclusion of the study. Study medication should be handled in accordance with Good Pharmacy Practices (i.e., gloves should always be worn by study personnel if directly handling tablets or capsules that are returned). The Clinical Monitor should be contacted with any questions concerning investigational products where special or protective handling is indicated. At the end of the study, all clinical supplies including partial and empty containers must be returned as directed by Pearl.

Sites should check with the Pearl representative for appropriate documentation that needs to be completed for drug accountability.

The Investigator or designated assistant should not open individual clinical supply containers until all pre-dose assessments have been completed and the subject is eligible to be randomized/continue with the study. Any deviation from this must be discussed with the Clinical Monitor.

For each subject, all used study drug materials will be collected. Used subject supplies will be kept at room temperature in a secure and locked cabinet until returned to Pearl or designee.

Note: Used study drug will be stored separately from unused study drug.

All product complaints (including device malfunctions) must be reported to Pearl using the Product Complaints Form provided in each site's regulatory binder. Pearl will contact the site to evaluate the nature of the complaint and determine what further action is needed.

7 STUDY PROCEDURES

A schedule of events is provided in Table 8-1.

7.1 Bone Mineral Density Assessments

Bone mineral density will be evaluated by taking two sets of DEXA scans (lumbar spine and hip regions) prior to randomization (Study PT010006 Visit 4) and Visit 14 (Week 52) in this study. After the first scan, of the lumbar spine and hip region, the subject will get up from the table, and be repositioned, to take another set of scans at these skeletal sites. If these first two 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 days if additional time is needed to complete the assessments. The results of these scans will be provided by the central testing facility to the investigative site to allow appropriate management of the subject.

For any clinically relevant reduction in T-score, the investigator should consider appropriate treatment options based on local guidelines for the subject and/or refer them to their local medical doctor or a specialist for treatment. If a subject's T-score (hip or lumbar spine) is <-2.5 at screening they are excluded.

Both the lumbar spine L2-L4 and total hip bone density will be measured. The scans of each skeletal site will be centrally analyzed to obtain the final result to be used for data analysis. For >1 scan the median will be considered for eligibility.

Full details can be found in the BMD manual

7.2 Ophthalmologic Assessments

The baseline ophthalmologic assessment must be performed prior to Randomization between Visits 1 and 4 (Screening) of Study PT010006. Two post-baseline ophthalmologic assessments will be performed at Visit 11 (Week 28), and Visit 14 (Week 52) only per exclusion criteria exception noted in Section 5.2.2. These post-baseline ophthalmologic assessments should be scheduled to occur within two weeks prior to the scheduled clinic visit. Due to diurnal variability of IOP, all ophthalmic examinations following the first ophthalmic examination (baseline) should be scheduled to occur within two hours of the time of day when the baseline ophthalmic examination was performed. The same ophthalmologist should perform the ophthalmic examinations for a given subject at all visits if possible, to ensure consistency.

At participating centers, all subjects will be referred to a certified as LOCSIII trained ophthalmologist/optometrist for evaluation of pupil dilation, lenticular opacities, fundoscopic examination, intraocular pressure (IOP), manifest refraction and visual acuity. This data will also be categorized as normal/abnormal.

The Lens Opacities Classification System (LOCS) III grading system will be used to assess lenticular opacities in this study. The following assessments will be performed using a

decimalized scale ranging from 0.1 (indicating a completely clear or colorless lens) to either 5.9 (indicating complete opacification on the cortex or posterior capsule for C or P scales) or 6.9 (indicating advanced opacification and brunescence of the nucleus for NO or NC scales). Each assessment will be recorded to the nearest 0.1 as determined by the certified ophthalmologist/optometrist.
Since the posterior subcapsular region is thought to be the area most characteristically affected by corticosteroid use, the LOCS III (P) score is the primary analysis.

- Nuclear Opalescence (NO scale 0.1 to 6.9) is the average of the opalescence of the two regions of the nucleus
- Nuclear Color (NC scale 0.1 to 6.9) is the grade of color of the posterior subcapsular reflex (a proxy for nuclear color)
- Cortical Cataract (C scale 0.1 to 5.9) is the aggregate area of visible opacification (in the lightly and darkly shadowed) portions of the cortical opacities
- The severity of Posterior Subcapsular Cataract (PSC) will be expressed as a P grade derived from the LOCS III P scale (0.1 to 5.9). With a maximally dilated pupil the LOCS III P grade will be defined as the total area of aggregated component PSCs related to the LOCS III P standards, regardless of where they are located on the posterior capsule. The method for making this assessment will be dealt with in the LOCS III training recordings.

NOTE: The ophthalmologist/optometrist must not refer to prior LOCS III grades and LOGMAR visual acuities from previous ophthalmic examination at the time of a new examination

Fundoscopic examination will include the evaluation of horizontal cup-to-disc ratio for each eye.

Intraocular Pressure: Intraocular pressure (IOP) will be measured using Goldman Applanation Tonometry. Three measures of IOP will be completed for each eye during each ophthalmic examination and all three measures will be recorded. The lowest reading will be considered to evaluate eligibility criteria

Visual acuity and manifest refraction:
Visual acuity (best-corrected distance vision) and manifest refraction (sphere, cylinder and axis) will be assessed during each ophthalmic examination. LogMAR (Logarithm of the Minimum Angle of Resolution) visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) charts will be utilized. Both the visual acuity and manifest refraction values will be captured in the source document.

7.3 Subject Electronic Diary (eDiary) Data Collection

Subjects will continue to use their electronic subject diary (eDiary) provided during participation in Study PT010006 to continue to record time of study medication administration, use of rescue albuterol (Ventolin HFA), and dose indicator reading (if assigned to BGF MDI, GFF MDI or BFF MDI only).

Electronic Diary Compliance Requirement: Subject participation may be terminated at any time during the study for the following reasons:

- Chronic failure, in the judgment of the Investigator, to comply with diary compliance, despite documentation at the site of repeated efforts to reinforce compliance. As defined for this study, compliance requires >70% subject completion of diary assessments. Pearl may also instruct a site to discontinue a subject based on consistent noncompliance

In-clinic dosing times and dose indicator readings will be documented by the site staff and will not be entered by the subject into their eDiary.

The eDiary data report will be available to site personnel through the vendor's server. The eDiary data report should be reviewed by the study personnel at each visit. The review should verify that morning and evening diary entries have been recorded by the subject for compliance requirements. The subject should be reinstructed, as appropriate, on the importance of recording twice daily entries if missing entries are observed.

7.3.1 Rescue Medication Usage

The subject will record the total number of "puffs" of rescue medication (i.e., albuterol sulfate or locally available equivalent product) used on a daily basis in the eDiary. The number of "puffs" of rescue product will be recorded as the number of actuations on the canister. For example, when rescue product is required and 2 actuations are inhaled, this should be recorded as 2 "puffs." In the event the subject requires 4 actuations, this should be recorded as 4 "puffs". Subjects requiring more than 8 puffs per day on 3 consecutive days with worsening symptoms should contact the site.

7.3.2 Medication Compliance

Time of dosing with study medication will be recorded in the subject's eDiary for each day of treatment (except the in-clinic dosing time). Study medication compliance will be checked at all visits, and any issues identified will be documented in the appropriate study files.

7.3.3 Recording of Dose Indicator Reading

The BGF MDI, GFF MDI and BFF MDI will be fitted with a dose indicator to track in life use of the MDI.

Subjects will be instructed to record the dose indicator reading from the MDI in their eDiary.

Prior to dosing at Visit 11 to Visit 14, site personnel will observe the dose indicator reading on the study drug returned by the subject and record the dose indicator reading in the source.

Note: The dose indicator reading recorded by the site staff will be dose indicator reading **observed prior to subject dosing. For new MDIs the recorded count will be the count** following the priming of the MDI but before the subject dose.

At each visit, the site staff will compare the dose indicator reading from the prior evening entered in the subject eDiary with the dose indicator reading recorded by the site staff. For major discrepancies (i.e., >20 puff difference) the site staff will review the major discrepancy with the subject and document reason for the major discrepancy. If appropriate, site staff will retrain the subject on the proper recording of dose indicator reading and/or proper use of the MDI.

7.3.4 Major/minor Symptom Worsening Assessment and Alert System

All major and minor symptoms of a worsening event will be captured at once each morning for the purposes of a symptom worsening alert. The purpose of this alert is to notify both the subject and the site of a potential symptom worsening event that warrants contact between the subject and site for further evaluation.

All questions will have a 24-hour recall period. Questions pertaining to the severity of symptoms versus their usual state will have 3 response options (e.g., How breathless have you been in the last 24 hours? Less breathlessness than usual, Usual level of breathlessness, More breathless than usual) whereas questions related to the presence or absence of a symptom will have a dichotomous response (e.g., Have you had a sore throat in the last 24 hours? No, Yes, I had a sore throat).

An alert will be triggered if 2 or more major symptoms (dyspnea, sputum volume, and sputum color) worsen for 2 consecutive days or if 1 major symptom and 1 minor symptom (sore throat, cold, fever without other cause, cough, and wheeze) worsen for at least 2 consecutive days. When either of these criteria is met, the subject will be alerted via the eDiary to contact the site as soon as possible for further evaluation. Likewise, the study site will be alerted to contact the subject within approximately 24 to 72 hours if he/she has not yet contacted the study site for further evaluation.

7.3.5: EXACT

The exacerbations of chronic pulmonary disease tool (EXACT) questionnaire will be captured via the subject eDiary (see Appendix 4)

7.4 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 or minor symptom from the list below:

- Major COPD symptoms: dyspnea, sputum volume, and sputum color

- Minor COPD symptoms: cough, wheeze, sore throat, cold symptoms (rhinorrhea or nasal congestion), and fever without other cause

If symptoms are acute or have progressed rapidly and require treatment less than two days from onset of symptoms, the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

If a subject's symptoms and the overall clinical findings support the diagnosis of a COPD exacerbation, but the subject has not experienced a worsening of at least one major COPD symptom and at least one other major or minor symptom, the investigator will have to justify the decision for defining the event as an exacerbation and record it in the eCRF.

7.4.1 Severity of COPD Exacerbation

COPD exacerbations will be classified as mild, moderate or severe based on the following criteria:

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

Exacerbations will be considered mild if they do not meet the requirements to be classified as moderate or severe but otherwise fulfill the definition of COPD exacerbation.

7.4.2 Duration of COPD exacerbation

For moderate or severe exacerbations, the duration is defined by the length of prescribed treatment, 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 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.

7.4.3 Approach for Capturing COPD Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be captured based on symptoms as recorded by the subject in the eDiary. COPD exacerbations of any severity will be considered expected study endpoints and will not be reported as adverse events (AEs) unless considered a serious AE (SAE).

7.4.4 Other Information

Pearl Therapeutics will be using an electronic diary (eDiary) to capture daily symptom reporting. If symptoms meet a specific threshold (i.e., one major COPD symptom and at least one other major or minor symptom for 2 consecutive days), the eDiary generates alerts to the subject and the clinical site. This alert is intended to generate a contact between the subject and the clinical investigator. The clinical investigator makes the decision to escalate or initiate treatment (steroids and/or antibiotics and/or hospitalizations).

Circumstances will occur where symptoms are not captured in the eDiary (e.g., technical difficulties, rapid deterioration, or sudden death). In these cases, the investigator or designee will enter the information into the eCRF to capture the symptoms related to a COPD exacerbation.

7.4.5 Investigator-Judged COPD Exacerbations

For events which do not meet the outlined symptom criteria and/or when symptoms have a shorter duration, the investigator can justify the decision for considering the event an exacerbation. Exacerbations could be defined by an investigator when symptoms of COPD warranted urgent treatment due to rapid onset or rapidly progressive symptoms. Such a situation does not allow enough time to strictly fulfill the criteria for symptom duration (≥2 consecutive days). In these cases, the investigator may define such an event as a COPD exacerbation. As clinical presentations may vary among patients with COPD, exacerbations defined by an investigator can be supported by respiratory symptoms that may not strictly fulfill all symptom requirements defined above. Since the investigator will need to document the symptoms that justify his or her decision to begin treatment defining a COPD exacerbation event, all exacerbations in the study will have documented symptoms justifying their clinical relevance.

7.5 Subject Questionnaire

The exacerbations of chronic pulmonary disease tool (EXACT) questionnaire will be captured via the subject eDiary (see Appendix 4).

7.6 Safety Assessments

The safety assessments include physical examination findings, vital signs, ECGs, and clinical laboratory tests in addition to recording of AEs and SAEs.

7.6.1 Medical/Surgical History and Physical Examination

Medical history, including specific cardiovascular history details, will be collected at Visit 1 (Screening) in Study PT010006. A complete physical examination will be performed at the conclusion of Study PT010006 (Visit 10a) and will not be obtained during Visit 10b. A complete physical examination will also be conducted at the Final Visit (Visit 14) or at the Treatment Discontinuation/Withdrawal Visit, if applicable. A complete physical examination will include evaluation of the following: general appearance, skin, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest, heart, abdomen, extremities, and nervous system. Weight, assessed in ordinary indoor clothing with shoes removed will be recorded in Study PT010006 at Visit 1 and Visit 10a only. Height will be recorded at Visit 1 (PT010006 Screening) only.

7.6.2 Vital Sign Measurements

Vital signs, including heart rate (HR) and systolic and diastolic blood pressure (DBP), and temperature will be assessed as outlined below; assessments may be obtained while the subject is resting for 5 minutes in either the supine or seated position.

Vital signs will be obtained at the conclusion of the lead-in study PT010006 (Visit 10a) and will not be obtained during Visit 10b.

At Visits 11 through 13:

- Pre-dose vital signs will be obtained once within 60 minutes prior to study drug dosing
- Post-dose vital signs will be obtained at 30 minutes post study drug dosing

A single set of vital signs will also be obtained at a Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

Temperature will be obtained pre-dose at all visits and will not be repeated at subsequent time points unless clinically indicated. A single set of vital signs will be obtained at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.6.3 12-Lead Electrocardiogram

ECGs will be obtained at the conclusion of Study PT010006 (Visit 10a) and will not be obtained during Visit 10b.

At Visit 12 (Week 36) only, an ECG will be obtained within 60 minutes prior to study drug dosing.

An ECG will also be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

To standardize ECG collection, all sites will be provided with identical ECG equipment [redacted] with customized study-specific software. All study staff responsible for performing ECG collection will receive identical, detailed training at the Investigator meetings as well as site phone training sessions. Each site is required to demonstrate proficiency in the use of the equipment and the ability to perform technically acceptable ECGs prior to performing testing on study subjects. After each test is performed, the ECG data will be transmitted electronically for centralized quality assurance review [redacted] Feedback on the quality of the ECGs will be provided to the investigational site via a site qualification form.

The ECG parameters that will be assessed include heart rate, PR interval, QRS axis, QRS interval, and QT/QTcF interval.

QT intervals and calculated QTcF intervals will be reviewed and checked for gross inaccuracies by the Investigator or designated ECG reviewer. If the calculated QTcF intervals are >500 msec, and have increased by 60 msec or more over test day baseline value, the Investigator will make a determination on the suitability of continuing the subject in the study. If QTcF interval prolongation exceeding these limits is verified during treatment, the subject's medical history should be examined closely for risk factors that may have contributed to the event, including evidence of prior genotyping for hereditary long QT syndromes, if appropriate.

Any sign of arrhythmia should be noted. During treatment, any indication of Torsade de Pointes, a polymorphic ventricular tachyarrhythmia that appears on the ECG as continuous twisting of the vector of the QRS complex around the isoelectric baseline, must be recorded as an AE and reported to the Pearl Medical Monitor.

All such subjects, including subjects with cardiac arrhythmias, should be monitored closely. If appropriate, ECG monitoring should be performed until the QT and QTcF interval and waveform morphology have returned to normal. If the prolongation or abnormal rhythm persists, the Pearl Medical Monitor must be contacted immediately.

7.6.4 Clinical Laboratory Tests

Clinical safety laboratory tests will be analyzed by a central laboratory according to standardized, validated assays. The laboratory will supply detailed instructions and all containers for blood and urine investigations. Blood sample volumes will meet the laboratory's specification. Clinical laboratory tests will be obtained prior to dosing at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b.

Clinical laboratory tests will be obtained prior to dosing at Visit 12 (Week 36). Clinical laboratory tests will be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.6.4.1 Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured prior to dosing at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b.

Hematology assessments will be obtained prior to dosing at Visit 12 (Week 36). Hematology assessments will also be obtained and Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.6.4.2 Clinical Chemistry

Albumin, alkaline phosphatase, blood urea nitrogen (BUN), total bilirubin, calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, γ-GT, blood glucose, total protein, bicarbonate, triglycerides, AST and ALT will be measured prior to dosing at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b.

Clinical chemistry assessments will be obtained at Visit 12 (Week 36). Hematology assessments will also be obtained and Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

Refer to Table 7-1 for a list of study-associated laboratory tests. The central laboratory will supply procedures for the preparation and collection of these samples.

Table 7-1. Clinical Laboratory Tests

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.	

7.6.4.3 Urinalysis

Urinalysis will be measured at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b.

Urinalysis will be obtained prior to dosing at Visit 12 (Week 36). Urinalysis will be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

7.6.4.4 Pregnancy Test

A serum pregnancy test will be performed at the Central Laboratory in pre-menopausal women who are not surgically sterile at the final visit of Study PT010006 (Visit 10a), and will not be obtained during Visit 10b.

A serum pregnancy test will also be obtained at Visit 14 (Week 52) or at the Treatment Discontinuation/Withdrawal Visit, if applicable.

A urine pregnancy test will be performed at Visit 12 (Week 36).

If any of these tests are positive, the subject must be discontinued from the study. The pregnancy test should be performed prior to ECG or blood collection for laboratory assessments.

7.7 Adverse Events

7.7.1 Performing Adverse Events Assessments

The Investigator is responsible for promptly documenting and reporting all AEs observed during the study in the subject's case report form and on the AE Reporting Form. If the AE is "alarming," the Investigator must report the AE immediately to Pearl. In addition, certain AEs (as described in Section 7.4.9) are classified as "serious" and must be reported no later than 24 hours after the Investigator recognizes/classifies the event as an SAE to Pearl or its designee.

In the case of SAEs, after discussing the details of the AE, the Investigator and the Medical Monitor may discontinue the subject prematurely.

7.7.2 Adverse Event Definitions

The following definitions of terms are guided by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), the US Code of Federal Regulations (21 CFR 312.32) and EU Directive 2001/83/EC and are included herein.

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. An AE (also referred to as an adverse experience) can be any unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporally associated with the use of a drug, without any judgment about causality. An AE can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose.

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:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, blood transfusion); the condition that leads to the procedure are an AE (e.g., bleeding esophageal varices, dental caries)
- Overdose of either study drug or concurrent medication without any clinical signs or symptoms
- Non-clinically significant abnormal laboratory values. (If accompanied by signs/symptoms, the signs or symptoms are considered an AE.)

7.7.3 Severity

The Investigator must categorize the severity of each AE according to the following guidelines:

Mild: Associated with no limitation of usual activities or only slight discomfort; generally not requiring alteration or cessation of study drug administration; and/or not needing therapeutic intervention.

Moderate: Associated with limitation of usual activities or significant discomfort; generally requiring alteration or cessation of study drug administration; and/or requiring therapeutic intervention.

Severe: Associated with inability of subject to carry out usual activities or very marked discomfort; considered to be life-threatening; resulting in significant disability or incapacity; and requiring therapeutic intervention.

7.7.4 Relationship

The relationship of each AE to the study drug administration will be assessed by the Investigator after careful consideration, and according to the following guidelines:

Definitely: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; it disappears or decreases on cessation or reduction in study drug dose; and/or it reappears or worsens when the study drug is administered.

Probably: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug; and/or that could not be reasonably explained by other factors such as underlying disease, complications, concomitant drugs, or concurrent treatments.

Possibly: A reaction that follows a reasonable temporal sequence from administration of study drug; that follows a known or expected response pattern to the study drug, but that could reasonably have been produced by a number of other factors including underlying disease, complications, concomitant drugs, or concurrent treatments.

Not Related: A reaction for which sufficient data exist to indicate that the etiology is unrelated to the study drug.

7.7.5 Chronic Obstructive Pulmonary Disease Exacerbations

All moderate or severe COPD exacerbations must be captured using the COPD Exacerbation eCRF. Mild COPD exacerbations will be captured based on symptoms as recorded by the subject in the eDiary. COPD exacerbations of any severity will be considered expected study endpoints and will not be reported as adverse events (AEs) unless considered a serious AE (SAE).

Exacerbation(s) of COPD is expected to occur as a progression of disease despite standardized drug treatment, or treatment(s) with combination therapies. As a result, the Sponsor has classified this event as a protocol specified criteria expected event. Any individual case safety reports received related to exacerbation of COPD will not be submitted on an expedited basis as a Suspected Unexpected Serious Adverse Reaction (SUSAR) unless otherwise required as per the Sponsor's medical assessment.

7.7.6 Adverse Events of Special Interest

Certain AEs have been identified as adverse events of special interest (AESIs) due to the class of drugs being studied. Additional adverse events of special interest, including increased IOP, glaucoma, other ocular AE's and fractures will be defined in the SAP. Some events are described below but this is not a comprehensive list of all AESIs.

7.7.6.1 LABA and LAMA Effects

Known effects of LAMAs and LABAs include cardiovascular effects, ocular disorders, urinary retention, gastrointestinal disorders, and anticholinergic effects for LAMAs and cardiovascular and tremor effects for LABAs.

7.7.6.2 Local Steroid Effects

Local steroid effects include oral candidiasis, hoarseness candidiasis, oropharyngeal candidiasis, dysphonia, and throat irritation.

7.7.6.3 Pneumonia

In order to adequately assess and characterize the risk of pneumonia in patients in a non-biased manner, an external, independent pneumonia adjudication committee (PAC) will review all adverse events reported as pneumonia to ensure appropriate pre-defined and clinically consistent pneumonia criteria are met.

To standardize the diagnosis of pneumonia a clinically consistent definition of pneumonia will be implemented, which will require the following:

1. Clinical diagnosis of pneumonia by the investigator

2. Documentation of chest imaging obtained within 14 days of the diagnosis of pneumonia that is compatible with the diagnosis of pneumonia
3. Treatment with antibiotics (and/or if appropriate antiviral and/or antifungal agents)
4. At least 2 of the following clinical signs, symptoms, or laboratory findings:
   - Increased cough
   - Increased sputum purulence or production
   - Adventitious breath sounds on auscultation
   - Dyspnea or tachypnea
   - Fever
   - Elevated white blood cell counts
   - Hypoxemia

The PAC will be empowered to request any additional information, including copies of chest X-rays or CT scans if needed, to confirm the pneumonia diagnosis.

Radiographs will be evaluated locally and the results (infiltrate compatible with pneumonia (yes/no) will be entered in the eCRF. If the investigator becomes aware that a diagnosis of pneumonia was made without a chest image having been performed, he or she should obtain a chest image (frontal and lateral) up to 10 to 14 days after the date of pneumonia diagnosis.

7.7.6.4 Paradoxical Bronchospasm

Monitoring for paradoxical bronchospasm will occur through spontaneous reporting.

7.7.7 Major Adverse Cardiovascular Events (MACE)

Due to the prevalence of cardiovascular diseases in patients with COPD, MACE will be evaluated according to pre-defined criteria as described in the Charters. CCV and Mortality Adjudication Committees will review and adjudicate serious CCV events as MACE and are defined as the following:

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

Charters will be established to govern these processes prior to the First Patient First Visit.

7.7.8 Clinical Laboratory Adverse Events

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). 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 (i.e., 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 clinically significant or not clinically significant for the subject.

7.7.9 Serious Adverse Events

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 or 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 or suspected adverse reaction is considered “life-threatening’ if, in the view of the Investigator or Sponsor, its occurrence places the subject or 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.

7.7.9.1 Reporting of Serious Adverse Events

In agreeing to the provisions of this protocol, the Investigator accepts all legal responsibilities for AE identification, documentation, grading, assignment of causality, and prompt notification of SAEs to Pearl Pharmacovigilance or designee. All SAEs must be reported to Pearl Therapeutics no later than 24 hours after the Investigator recognizes/classifies the event as an SAE. At a minimum, a description of the event and the Investigator's judgment of causality must be provided at the time of the initial report using the appropriate form (e.g., SAE Report Form). After the initial report, as necessary, the Investigator must provide any additional information on a SAE to Pearl Pharmacovigilance within 2 working days after he/she receives that information. This follow-up information will be a detailed written report that may include copies of hospital records, case reports, and autopsy reports, and other pertinent documents.

Post-study SAEs following the last dose of study drug must be reported to Pearl as described in Section 7.4.9.4.

The Investigator is responsible for continuing to report any new or relevant follow-up information that he/she learns about the SAE.

7.7.9.2 Supplemental Investigations of SAEs

The Investigator and supporting personnel responsible for subject care should discuss with the Medical Monitor any need for supplemental investigations of SAEs. The results of these additional assessments conducted must be reported to Pearl. If a subject dies during participation in the study and a post-mortem examination is performed, a copy of the autopsy report must be submitted to Pearl.

7.7.9.3 Post-Study Follow-Up of Adverse Events

Any AEs that are unresolved at the subject's last AE assessment in the study are followed up by the Investigator for as long as medically indicated, but without further recording in the eCRF. Pearl retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

7.7.9.4 Notification of Post-Study Serious Adverse Events

Investigators are not obligated to actively follow subjects after the completion of the study. However, if the Investigator becomes aware of a post-study SAEs occurring up to 14 days following the last dose of study drug must be reported to Pearl, whether or not the event is attributable to study drug. All SAEs must be reported to Pearl no later than 24 hours after the Investigator recognizes/classifies the event as an SAE.

7.7.9.5 Investigational Research Board/Independent Ethics Committee Notification of Serious Adverse Events

The Investigator is responsible for promptly notifying her/his Investigational Research Board/Independent Ethics Committee (IRB/IEC) of all SAEs, including any follow-up

information, occurring at her/his site and any SAE regulatory report, including any follow-up reports that he/she receives from Pearl. Documentation of the submission to the IRB/IEC must be retained for each safety report. The Investigator is also responsible for notifying Pearl if their IRB/IEC requires revisions to the ICF or other measures based on its review of an SAE report.

7.7.9.6 Health Authority Safety Reports

Pearl or its representatives will submit a safety report to the Food and Drug Administration (FDA) and/or any other appropriate regulatory agencies, for any suspected adverse reaction that is both serious and unexpected within the appropriate time frame.

Pearl or its representatives will send copies of each safety report submitted to the FDA and/or other regulatory agencies to the Investigators who are actively participating in Pearl-sponsored clinical studies. Safety reports must be submitted to the appropriate IRB/IEC as soon as possible. Documentation of the submission to the IRB/IEC must be retained for each safety report.

7.7.10 Overdose

An overdose is defined as a dose greater than the high dose level evaluated in this study as described in Section 6.2 (Product Descriptions) that results in clinical signs and symptoms. In the event of an overdose of study medication, the Investigator should use clinical judgment in treating the overdose and contact the study Medical Monitor. The Investigator should refer to the relevant document(s) for detailed information regarding warnings, precautions, contraindications, AEs, and other significant data pertaining to the study drug(s) being used in this study. Such document may include, but not be limited to, the Investigator's Brochure for BGF MDI, BFF MDI, GFF MDI, and approved product labeling for open-label products.

7.7.11 Pregnancy

To ensure subject safety, each pregnancy in a female subject from Visit 1 (Screening) until study completion must be reported to Pearl within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. Pregnancy should be recorded on a Paper Pregnancy Report Form and reported by the Investigator to Pearl Pharmacovigilance or designee. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the Pearl study drug of any pregnancy outcome. Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.7.12 Use of Steroids during the Study

At each visit, subjects will be asked whether they have been administered oral, intramuscular, or intravenous corticosteroids since last visit. Use of oral, intramuscular, or intravenous corticosteroids for the management of COPD exacerbations or other condition is not a reason

for early termination. Use of corticosteroids should be documented. Subjects who are being treated for a COPD exacerbation with oral corticosteroids or have been treated for a COPD exacerbation with oral corticosteroids within 14 days of the scheduled visit will be allowed to perform PFTs under close medical supervision. The Investigator can decide to stop PFTs if subject safety is at risk or symptoms make it difficult for the subject to continue.

Subjects treated with oral, intramuscular, or intravenous corticosteroids for other indications will follow their visit schedule. If a subject requires intraocular corticosteroids, this should be fully documented and the Investigator should make a determination as to the suitability of the subject continuing in the study.

7.7.13 Clinical Endpoint Committee

An external clinical endpoint committee (CEC) that was initiated in Study PT010006 will continue to provide systematic and unbiased assessment of pre-defined, Investigator reported adverse events for Study PT010008. The committee will consist of experts who will provide a centralized review functioning independently of Pearl. Three Clinical Endpoint Adjudication Charters will outline the clinical endpoints for adjudication.

- Cardiovascular and Cerebrovascular (CCV) Clinical Endpoint Adjudication Charter
- Cause-Specific Mortality Clinical Endpoint Adjudication Charter
- Pneumonia Clinical Endpoint Adjudication Charter

7.7.13.1 Cardiovascular and Cerebrovascular (CCV) Clinical Endpoint Adjudication Charter

A Cardiovascular and Cerebrovascular (CCV) Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of non-fatal serious CCV events and classification of Major Adverse Cardiovascular Event (MACE). The CEC will review potential clinical endpoints to determine if the event meets MACE criteria.

7.7.13.2 Cause-Specific Mortality Clinical Endpoint Adjudication Charter

A Cause-Specific Mortality Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of the cause of deaths. The CEC will review fatal reports to determine if the event meets MACE criteria. Cardiovascular deaths will be classified as MACE.

7.7.13.3 Pneumonia Clinical Endpoint Adjudication Charter

A Pneumonia Clinical Endpoint Adjudication Charter will be referenced for the review and assessment of all pneumonia-related events to ensure appropriate pre-defined and clinically consistent pneumonia criteria are met.

7.7.14 Data Monitoring Committee

An external Data Monitoring Committee (DMC) that was initiated in Study PT010006 will continue to provide systematic and unbiased assessment of safety for Study PT010008.

Members of the DMC will review data at predetermined intervals. If significant safety issues arise in between scheduled meetings, ad hoc meetings will be scheduled to review the data. Based on the safety implications of the data, the DMC may recommend modification or termination of the study.

7.8 Termination of the Study

An Investigator may choose to discontinue study participation at any time with sufficient notice by the Investigator for any reason as per the terms of the contract with Pearl.

Pearl reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the Investigator, if instructed to do so by Pearl, in a time frame that is compatible with the subjects' wellbeing.

8 STUDY ACTIVITIES

A schedule of events is provided in Table 8-1.

Table 8-1. Schedule of Events

Procedures	Treatment Period						Follow-Up
	*Baseline Visits 1-4 (PT010006) -28 to -1	Transition Visit (from PT010006) Visit 10b Week 24	Visit 11 Week 28	Visit 12 Week 36	Visit 13 Week 44	Visit 14 Week 52	14 Days Post-Dose
Study Day/Week[a]			**Week 28 ±7 Days[a]**	**Week 36 ±14 Days[a]**	**Week 44 ±14 Days[a]**	**Week 52 ±7 Days[a]**	**Week 54 +7 Days[a]**
Obtain Informed Consent	X	X					
Review Incl/Excl Criteria	X	X					
Verify Continued Eligibility			X	X	X	X	
Smoking Status			X	X	X	X	
Physical Examination						X	
Prior/Concomitant Medications[b]			X	X	X	X	X
COPD Exacerbations and Adverse Events			X	X	X	X	X
Adjust COPD Medications[c]						X	
Vital Signs[d]			X	X	X	X	
Urine Pregnancy Test[d]				X			
Serum Pregnancy Test[d]						X	
12-Lead ECG[d]				X		X	
Clinical Laboratory Testing[d]				X		X	
Bone Mineral Density Assessments[d]	X					X	
Ocular Assessments[d]	X		X			X	
Study Drug Dispensing/Collection	X	X	X	X	X	X	
Review of Electronic Diary Data[d]			X	X	X	X	
Study Drug Administration[e]	X	X					
Record Dose Indicator Reading[e]	X		X	X	X	X	
Telephone Contact[f]	X[f]		X[f]	X[f]	X[f]	X[f]	X[g]

a. Scheduling visits: All visits will be scheduled relative to Visit 10a (Week 24) of the lead-in study (PT010006).
Note: Refer to Section 8.8 for procedures that may be required at a premature discontinuation visit. Treatment Discontinuation/Withdrawal Visits will be captured as unscheduled visits.

b. At all visits, note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).

c. At the end of Visit 14, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

d. Refer to Section 7 for specific assessments and specific time points to be performed at each treatment visit.

e. In-clinic dosing time recorded as time of the second puff/inhalation. In-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time if assigned to blinded treatment.

f. It is recommended that sites call the subject on the day before a scheduled visit and remind the subject of the expectations for the upcoming visit (e.g. Dosing appropriately the day before the visit, withholding COPD medications the morning of the scheduled visit, bring all study drug and eDiary to the visit, etc.).

g. Refer to Section 8.7 for details of the follow-up telephone call.

*Note The screening period may be extended up to a maximum of 21 days if additional time is needed to complete the assessments

8.1 Baseline Assessments

The Baseline PT010008 Assessments will be conducted concurrently with PT010006 Screening. 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 days if additional time is needed to complete the assessments All study assessments are to be completed prior to Randomization (Visit 4) in PT010006.

- Obtain informed consent prior to conducting any Study PT010008 baseline assessments.
- Register subject in IWRS for Study PT010008 at the same time registering in Study PT010006.
- Conduct BMD assessments (Refer to Section 7.1)
- Conduct ocular assessments (Refer to Section 7.2)

8.2 Randomization

- Review Study PT010008 inclusion/exclusion criteria and confirm subject's eligibility to continue.
- Obtain subject randomization number and treatment assignment information from IWRS.

Note : Randomization in PT01008 occurs simultaneously with randomization in Study PT010006 for those patients who qualify for Study PT010008.

- A reminder phone contact should be made prior to Visit 10b.

8.3 Visit 10b

The last visit of the Study PT010006 and the first post-baseline visit of Study (PT010008). -Visit 10b will be following completion of all Visit 10a study procedures.

- Review BMD/Ocular inclusion/exclusion criteria
- Confirm all visit 10a procedures have been completed before proceeding to register subjects in IWRS
- Register subject in IWRS to confirm participation in the PT010008 and receive assigned treatment
- Confirm subject's ability to use MDI correctly (provide training as needed)
- Return electronic diary to subjects and provide retraining if appropriate
- When assigned blinded study drug site personnel will complete priming in the clinic before dispensing to the subject for at home use
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits

- Record/document the dose indicator reading. The dose indicator count recorded by the site staff will be dose indicator count observed after priming but prior to subject dosing. Refer to Section 7.2.1.3 for more details
- Subject will administer dose of study drug at home in the evening

  Note: During the study subjects will continue on the same treatment that they were assigned in Study PT010006.
- Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule ophthalmologic assessment to occur prior to Visit 11 (Week 28)
- Schedule visit 11 to occur after ocular assessments are conducted and ensure subject has adequate supply of study drug including a replacement MDI kit and sponsor-provided rescue Ventolin HFA

8.4 Visits 11 (Week 28)

- Confirm scheduled ocular assessments have been conducted (Visit 11 should be rescheduled if ocular assessments not conducted prior to this visit) Please refer to the exclusion criteria exception noted in Section 5.2.2 to see if the ocular assessment applies to this visit.
- Review and verify subject's eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled)
- Confirm the subject took their last dose of randomized study medication as scheduled. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance. Review EXACT for completion as part of the eDiary review
- Review smoking status and prior/concomitant medications
- Review all prior medications and ensure adherence to COPD regimen
- Record COPD exacerbations and AEs (if any)
- Obtain vital signs within 60 minutes prior to dosing
- Return electronic diary to subjects and provide retraining if appropriate
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit
- For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.2.1.3 for more details

- **Administer in-clinic study drug dosing from the new kit assigned at the visit**
- Obtain vital signs 30 minutes post study drug dosing
- Subjects will be instructed to track study drug dosing in their electronic diary between study clinic visits
- Subject will be instructed to dose while at home from the site-primed MDI **only**, unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 1 for dose indicator reading instructions)
  - If the dose indicator registers ≤10 puffs remaining, and their next scheduled study clinic visit is not the following day
  - If these replacement conditions are met, subjects will be instructed to open one of their replacement kits, prime the MDI and start using for at home dosing until the next scheduled study clinic visit
  - Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule next visit and ensure subject has adequate supply of study drug including **two** replacement MDI and sponsor-provided rescue Ventolin HFA
- Follow up telephone call one day prior to scheduled visit

8.5 Visit 12 (Week 36)

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled)
- Confirm the subject took their last dose of randomized study medication as scheduled. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance. Review EXACT for completion as part of the eDiary review
- Review smoking status and prior/concomitant medications
- Review all concomitant medications and ensure adherence to COPD regimen
- Record COPD exacerbations and adverse events (if any)
- Obtain vital signs within 60 minutes prior to dosing
- Obtain 12-lead ECG within 60 minutes prior to study drug dosing
- Perform urine pregnancy test

- Obtain clinical laboratory samples prior to study drug dosing
- Return electronic diary to subjects and provide retraining if appropriate
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- If assigned to blinded study drug, record/document the dose indicator readings of the used device and the replacement device
- For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.2.1.3 for more details
- **Administer in-clinic study drug dosing from the new kit assigned at the visit**
- Obtain vital signs 30 minutes post study drug dosing
- Subjects will be instructed to track study drug dosing in their electronic diary between study clinic visits
- Subject will be instructed to dose while at home from the site-primed MDI **only**, unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 1 for dose indicator reading instructions)
  - If the dose indicator registers ≤10 puffs remaining, and their next scheduled study clinic visit is not the following day
  - If these replacement conditions are met, subjects will be instructed to open one of their replacement kits, prime the MDI and start using for at home dosing until the next scheduled study clinic visit
  - Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule next visit and ensure subject has adequate supply of study drug including **two** replacement MDI kits and sponsor-provided rescue Ventolin HFA
- Follow up telephone call one day prior to scheduled visit

8.6 Visit 13 (Week 44)

- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled)

- Confirm the subject took their last dose of randomized study medication as scheduled. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance. Review EXACT for completion as part of the eDiary review
- Review smoking status and prior/concomitant medications
- Review all concomitant medications and ensure adherence to COPD regimen
- Record COPD exacerbations and adverse events (if any)
- Obtain vital signs within 60 minutes prior to dosing
- Return electronic diary to subjects and provide retraining if appropriate
- Prior to dosing, site personnel will use IWRS to assign subjects a new kit of study drug for in-clinic dosing and to continue dosing at home until the next scheduled visit
- Refer to Section 6.7 for detailed instructions for preparation of treatments for administration. These instructions are to be adhered to and are relevant to all study treatment visits
- If assigned to blinded study drug, record/document the dose indicator readings of the used device and the replacement device
- For new MDIs, the recorded count will be the count following the priming of the device but before the subject doses. Refer to Section 7.2.1.3 for more details
- **Administer in-clinic study drug dosing from the new kit assigned at the visit**
- Obtain vital signs 30 minutes post study drug dosing
- Subjects will be instructed to track study drug dosing in their electronic diary between study clinic visits
- Subject will be instructed to dose while at home from the site-primed MDI **only**, unless all of the following **replacement conditions** are met:
  - Dose indicator is in the red zone (See Appendix 1 for dose indicator reading instructions)
  - If the dose indicator registers ≤10 puffs remaining, and their next scheduled study clinic visit is not the following day
  - If these replacement conditions are met, subjects will be instructed to open one of their replacement kits, prime the MDI and start using for at home dosing until the next scheduled study clinic visit
  - Subjects will be instructed to bring their eDiary and all study medication (including used study drug, replacement MDI kit and sponsor-provided rescue Ventolin HFA) to the next scheduled clinic visit
- Schedule ophthalmologic assessments and BMD assessments to occur within two weeks prior to Visit 14 (Week 52)

- Schedule visit 14 to occur after ocular assessments and BMD assessments are conducted and ensure subject has adequate supply of study drug including **two** replacement MDI kits and sponsor-provided rescue Ventolin HFA
- Follow up telephone call one day prior to scheduled visit

8.7 Visit 14 (Week 52; Final Visit)

- Confirm ocular assessments were conducted prior to this visit (Visit 14 should be rescheduled if ocular assessments not conducted prior to this visit) Please refer to the exclusion criteria exception noted in Section 5.2.2 to see if the ocular assessment applies to this visit
- Confirm BMD assessments were conducted prior to this visit (Visit 14 should be rescheduled if BMD assessment not conducted prior to this visit)
- Confirm subject eligibility to continue
- Collect study drug including sponsor-provided Ventolin HFA
- Determine time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, the visit must be rescheduled)
- Confirm the subject took their last dose of randomized study medication as scheduled. If the time of dosing was not in accordance with the protocol, then the visit must be rescheduled
- Review subject diary for data collection compliance. Review EXACT for completion as part of the eDiary review
- Review smoking status and prior/concomitant medications
- Perform physical examination, including weight
- Review all concomitant medications and ensure adherence to COPD regimen
- Record COPD exacerbations and adverse events (if any)
- Obtain vital signs
- Perform serum pregnancy test
- Obtain 12-lead ECG
- Obtain clinical laboratory samples
- Collect subject eDiary
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug
- Return subject to pre-study or appropriate maintenance COPD medications
- Schedule the follow-up telephone call at least 14 days from Visit 14

8.8 Unscheduled Visit and Treatment Discontinuation/Withdrawal Visit

Repeat assessments, if needed, will be captured in unscheduled visits.

Premature discontinuations visits will be captured as unscheduled visits. The following minimum procedures should be completed at the Premature Discontinuation Visit:

- Collect all study drugs
- Record COPD exacerbations and adverse events (if any)
- Review concomitant medications
- Conduct a physical examination, including vital signs
- Perform ECG and collect blood samples for hematology and chemistry
- Collect a blood sample for pregnancy test for women of child bearing potential
- Collect subject eDiary
- Inform subject about reporting all SAEs up to 14 days following the last dose of study drug
- Return subject to pre-study or appropriate maintenance COPD medications
- Capture the subject discontinuation reason
- Schedule a follow-up telephone call (TC) 14 days post last study drug dosing. If the discontinuation visit is performed > 14 days post last study drug dosing a follow-up TC will not be required
- Schedule ocular assessments as early as practical
- If after Visit 10b (Week 24), schedule BMD measurement as early as practical

8.9 Follow-up Telephone Call

Subjects will be followed-up within 14 days after the last study drug dosing. The following information will be requested:

- Review previously on-going COPD exacerbations and AEs (if any)
- Review concomitant medications

Note: For subjects who withdraw consent, schedule a follow-up TC at least 14 days after the last study drug dosing unless the visit is performed >14 days post last study drug dosing, a follow-up TC will not be required. For treatment discontinuation subjects, a telephone follow-up call is not required as long as at least one post treatment study visit is completed.

8.10 Vital Status Confirmation at Week 52

All subjects who discontinue study treatment after Visit 10b will have their vital status confirmed at 52 weeks post-randomization.

To confirm the vital status and cause of death, if appropriate, the following attempts will be made:

- The first and second attempts may be conducted as telephone follow-up call to the subject within 2 weeks after 52 weeks post-randomization
- The third attempt will be by certified mail to the subject's address provided at the time of informed consent within 3 weeks after 52 weeks post-randomization
- The fourth attempt will be made as a telephone follow-up call to the next of kin/emergency contact provided at the time of informed consent within 4 weeks 52 weeks post-randomization
- A fifth attempt will be made through a certified letter to the next of kin/emergency contact provided at the time of informed consent within 5 weeks after 52 weeks post-randomization

After the fifth attempt, the study site will contact the national death registries (if available in that country) to confirm date and cause of death.

8.11 Completion of Study

The investigator will document the completion or the reason for early withdrawal by a subject in the eCRF. The following categories should be used to describe these events in the eCRF:

- Subject discretion (document reason)
- Investigator considers it to be in the best interest of the subject
- Adverse events(s)
- Administrative reasons (e.g., early termination of the study)
- Subject lost-to-follow-up
- Lack of efficacy
- Major protocol violation
- Death
- Completion of the study
- Protocol specified criteria such as heart rate, systolic or diastolic blood pressure, or use of prohibited medications (see Section 5.7)

9 PLANNED STATISTICAL METHODS

9.1 Introduction

This Study PT010008 will be conducted in a subset of US sites participating in Study PT010006, and will evaluate the following treatments:

- BGF MDI (320/14.4/9.6 µg BID)
- GFF MDI (14.4/9.6 µg BID)
- BFF MDI (320/9.6 µg BID)

Across these sites, it is planned that approximately 500 subjects randomized to double-blind treatment only will provide approximately 425 subjects who will complete the study. Subjects will receive the same treatment (BGF MDI, GFF MDI, or BFF MDI) they were randomized to in Study PT010006. Subjects randomized to open-label Symbicort TBH will not be enrolled in this study.

This study will evaluate the safety of BGF MDI, BFF MDI, and GFF MDI on bone mineral density (BMD) measurement and ophthalmologic assessment.

Baseline and demographic characteristics will be collected in Study PT010006 with the exceptions of baseline BMD and lenticular opacity and ocular pressure measurements. Baseline BMD and lenticular opacity and ocular pressure measurements will be performed prior to Visit 4 (Randomization) of Study PT010006. A separate informed consent will be obtained for subjects participating in Study PT010008.

9.2 Protocol Variables

All efficacy assessments are relative to baseline assessments obtained at Screening (Visits 1 to 3) in Study PT010006.

9.2.1 Study Endpoints

9.2.2 Primary Bone Mineral Density Endpoint

- Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4 at Week 52

9.2.3 Other Bone Mineral Density Endpoints

- Percent change from baseline in BMD of the hip measured using DEXA scans at Week 52 and at EoT
- Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4 at EoT

9.2.4 Primary Ocular Endpoint

- Change from baseline in the LOCS III (P) Score at Week 52

9.2.5 Other Ocular Endpoints

- Change from baseline in each scale of the LOCS III scores at Week 28, Week 52 (NO, NC, and C only), and EoT
- 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 ≥22mmHg at Week 28, at Week 52, and EoT
- Proportion of subjects change from baseline in IOP of ≥7mmHg at Week 28, at Week 52, and EoT
- Change from baseline in LogMAR visual acuity using 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 TEAEs including cataract and glaucoma

9.2.6 Safety Endpoints

The safety endpoints for this study include:

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

9.2.7 Efficacy Endpoints

- Change from baseline in average daily rescue Ventolin HFA (albuterol sulfate) use.
- Percentage of days with no rescue Ventolin HFA use
- Rate of moderate or severe COPD exacerbations
- Rate of COPD exacerbations of any severity
- Change from baseline in: the EXACT total score, the 11-item EXACT Respiratory Symptoms (E-RS) Total Score (RS-Total Score), as well as 3 subscale scores symptom (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

9.3 Study Populations

The following analysis populations are defined in this study:

- The **Safety Population** will consist of all subjects enrolled in PT010008 who receive any amount of study medication. Subjects will be analyzed according to treatment received rather than randomized. If a subject received more than 1 randomized treatment, they will be analyzed and included in summaries according to the treatment they received the most. Subjects receiving no study treatment will be excluded, as will subjects who have no post-dose safety assessments. (Note that a subject who used a study treatment, but took less than 1 full dose of treatment will qualify for this population).
  Note: The statement that a subject had no AEs also constitutes a safety assessment
- The **BMD Analysis Population** is defined as all evaluable subjects in the Safety Population who have a baseline BMD assessment and at least 1 on-treatment BMD assessment. Subjects will be analyzed according to actual treatment received
- The **Ophthalmologic Analysis Population** is defined as all evaluable subjects in the Safety Population who have a baseline ophthalmologic assessment and at least 1 on-treatment ophthalmologic assessment. Subjects will be analyzed according to actual treatment received
- The **mITT Population** is defined as the subgroup of mITT subjects from Study PT010006, who enrolled in PT010008. Subjects will be analyzed according to the active treatment they were assigned to at randomization in Study PT010006. (Note that a subject who used a study treatment, but took less than one full dose of treatment will qualify for this population). Data from both Study PT010006 and Study PT010008 will be included

Exclusions from the ophthalmologic and BMD population will be defined in the SAP.

Analyses will be performed as follows:

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 ophthalmologic 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. Efficacy will be presented for mITT population.

9.4 Safety Analyses

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

9.4.1 Analysis of BMD Endpoints

9.4.1.1 Percent change from baseline in BMD of the lumbar spine measured using DEXA scans of L2-L4

The change from baseline in BMD of the lumbar spine at Week 52 (and similarly at EoT) will be analyzed using an Analysis of Covariance (ANCOVA) model with treatment group and gender as categorical covariates, and baseline BMD score, age, and age by gender interaction as continuous covariates.

T- and Z- scores will be presented as shifts from baseline to each time point; details will be provided in the SAP.

9.4.1.2 Percent change from baseline in total hip BMD of the hip measured using DEXA scans

The change from baseline in BMD of the hip at Week 52 (and similarly at EoT) will be analyzed similarly to the change from baseline in BMD of the lumbar spine.

9.4.2 Analysis of Ocular Endpoints

9.4.2.1 Change from baseline in each of the LOCS III (NO, NC, C, and P) scores

Change from baseline in the LOCS III (P) scores at each post-randomization visit will be analyzed using an Analysis of Covariance (ANCOVA). The model will include treatment group as a fixed effect, and baseline LOCS III (P) score, smoking pack years, and age as continuous covariates. The model will account for inter-eye correlation by including subject and eye (within subject) as random effects.

Two-sided 95% confidence intervals will be computed for pairwise differences of BGF minus GFF and BFF minus GFF, and non-inferiority will be declared if the upper confidence bound is less than 0.5. 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 being supportive.

The above analyses will be repeated for the other 3 LOCS III (NO, NC, and C) scores, but with the corresponding baseline LOCS III scale score as a covariate.

9.4.2.2 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 at Week 28, at Week 52, and at EoT will be summarized by treatment group.

9.4.2.3 Change from baseline in intraocular pressure (IOP)

The change from baseline in IOP at Week 28, Week 52, and EoT will be analyzed using a similar model as for the LOCS III (P) score at 52 weeks, but with the baseline IOP as a covariate.

9.4.2.4 Proportion of subjects with IOP ≥22mmHg and the proportion of subjects with change from baseline in IOP of ≥7 mmHg

The proportion of subjects with IOP ≥22 mmHg in either eye at Week 28, Week 52, and EoT will be summarized by treatment group. Similarly, the proportion of subjects with IOP increases from baseline of ≥7 mmHg in either eye at Week 28, Week 52, and EoT will be summarized.

9.4.2.5 Change from baseline in LogMAR visual acuity using ETDRS charts

Change from baseline in LogMAR visual activity scores will be summarized for each eye at each visit by treatment group using descriptive statistics.

9.4.2.6 Change from baseline in horizontal cup-to-disc ratio

Change from baseline in horizontal cup-to-disc ratio will be summarized for each eye at each visit by treatment group using descriptive statistics.

9.4.2.7 Incidence of ocular TEAEs including cataract, glaucoma

The proportion of subjects with ocular TEAEs in each treatment group will be summarized overall, as well as by individual AE. AEs qualifying as ocular AEs include cataract and glaucoma.

9.4.3 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. The number and incidence of adverse events, serious adverse events, adverse events of special interest by category, confirmed AEs of pneumonia, and study drug discontinuations due to adverse events will be summarized by treatment group. They 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.

9.4.4 Cardio- and Cerebrovascular Events Determined by Adjudication Committee

CCV and Mortality Adjudication Committees will review and adjudicate serious CCV events as MACE. MACE events are defined as the following:

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

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

MACE events will be summarized by treatment group.

9.4.5 Pneumonia Events Determined by Adjudication 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 assessment of pneumonia events will include the overall rates of pneumonia.

9.4.6 Clinical Laboratory Measurements

Summary statistics (n, mean, median, standard deviation, minimum, and maximum) for the baseline assessment (Day 1) and for the pre-dose value and change from baseline at pre-dose value of post-baseline visits with scheduled lab assessments of continuous laboratory variables, including serum potassium and glucose will be tabulated.

Shift tables relative to the normal reference ranges will be produced using the categories defined by the CTCAE Version 4.03 grades. 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.

The number and percent of subjects with potentially clinically significant (PCS) lab values will be summarized. Potentially clinically significant values for serum potassium are <3.0 mmol/L or >6.0 mmol/L, and for blood glucose <2.2 mmol/L or >13.9 mmol/L. Potentially clinically significant values for labs will be defined in the SAP. No hypothesis tests will be performed.

9.4.7 Vital Signs

Summary statistics (mean, median, standard deviation and range) for absolute values and change from baseline values will be tabulated for each treatment and assessment time. For vital signs, baseline values will be defined as the average of the values prior to dosing at the randomization visit (Visit 4). Potentially clinically significant values for vital signs will be defined in the SAP and the percentage of subjects with PCS values will be summarized. No hypothesis tests will be performed.

9.4.8 Electrocardiograms

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 average of the pre-dose measurements taken prior to the start of treatment at the randomization visit (Visit 4). The QTcF (Fridericia Corrected QT) is defined as ($QT/[RR^{1/3}]$). Heart rate (bpm) is estimated as 60,000/RR. These assessments will be tabulated for each treatment and assessment time. Potentially clinically significant values for ECG parameters will be defined in the SAP, and the percentage and number of subjects with PCS ECG values will be tabulated. No hypothesis tests will be performed.

9.4.9 Exposure

The duration of exposure to study medication (in days), the person-years of exposure, the mean number of doses, and number and percentage of subjects who are compliant will be summarized by treatment group. All exposure summaries will be generated for the safety population by actual treatment received.

9.5 Analyses of Efficacy Endpoints

Analyses of efficacy will be performed using the mITT Population.

9.5.1 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. For every period of time for which the mean number of puffs of rescue will be calculated, 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.

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).

9.5.2 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 using descriptive statistics. A ‘day with no rescue use’ is defined using rescue Ventolin HFA usage data from days where rescue Ventolin HFA usage data is non-missing as any day where the subject reported no puffs of rescue Ventolin HFA.

9.5.3 Chronic Obstructive Pulmonary Disease Exacerbations

The rate of moderate or severe COPD exacerbations will be summarized by treatment group. Chronic obstructive pulmonary disease exacerbations will be considered separate events provided that 7 or more days are between the recorded stop date of the earlier event and start

date of the latter. For moderate or severe COPD exacerbations, the start date is 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. The rate of COPD exacerbations of any severity will be presented in a similar manner.

Duration of COPD Exacerbation

For moderate or severe exacerbations, the duration is defined by the length of prescribed treatment, 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 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.

9.5.4 Exacerbations of Chronic Pulmonary Disease Tool (EXACT)

The EXACT is a 14-item 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. 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).

9.5.5 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.

9.6 Randomization

Randomization is conducted as part of PT010006.

9.7 Experimental Design

This study will be conducted as parallel-group and double-blind.

9.8 Sample Size

Assuming a 15% rate of discontinuation through Week 52, a subset of 500 randomized subjects from the PT010006 study will provide 425 subjects with baseline and on-treatment BMD and LOCS III assessments. This sample size will provide approximately 97% power to demonstrate non-inferiority of BGF MDI to GFF MDI in percent change from baseline in BMD for Lumbar Spine L2-L4 at Week 52 based on the lower limit of -2%, true difference of -0.3%, and SD of 4% and approximately 91% power for the non-inferiority comparison of BFF MDI to GFF MDI under identical assumptions. It will provide over 99% power to demonstrate non-inferiority of BGF MDI to GFF MDI (or BFF MDI to GFF MDI) in change from baseline in LOCS III Score (P) at Week 52 based on a margin of 0.5 or more (1-sided, alpha=0.025) assuming no true difference in the means.

9.9 Data Validation and Transformation

9.10 Analysis Plan

All analyses will be specified in a detailed SAP that will be accompanied by table and data listing shells with mock graphical representations. The analysis plan will be approved by signature before database lock and unblinding.

9.11 Handling of Missing Data

Missing data will not be imputed. All analyses will be based on observed data.

9.12 Statistical Software

Data processing, statistical screening, descriptive reporting and analysis of the efficacy and safety data will be performed using [redacted] Graphs may also be produced using [redacted]

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Regulatory Authority Approval

Pearl will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country-specific regulatory requirements prior to a site initiating the study in that country.

10.2 Ethical Conduct of the Study and Institutional Review Board or Independent Ethics Committee Approval

The study will be conducted in accordance with Good Clinical Practice (GCP). These standards respect the following guidelines:

- Guideline for Good Clinical Practice E6 (R1): Consolidated Guideline (International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use, May 1996).

- US CFR dealing with clinical studies (21 CFR parts 50, 54, 56, and 312).

- Declaration of Helsinki, concerning medical research in humans (Ethical Principles for Medical Research Involving Human Subjects) [http://www.wma.net/en/10home/index.html].

- Any additional regulatory requirements.

The Investigator (or Pearl, where applicable) is responsible for ensuring that this protocol, the site's ICF, and any other information that will be presented to potential subjects (eg, advertisements or information that supports or supplements the ICF) are reviewed and approved by the appropriate IRB/IEC. The Investigator agrees to allow the IRB/IEC direct access to all relevant documents. The IRB/IEC must be constituted in accordance with all applicable regulatory requirements.

Pearl will provide the Investigator with relevant document(s)/data that are needed for IRB/IEC review and approval of the study. If the protocol, the ICF, or any other information that the IRB/IEC has approved for presentation to potential subjects is amended during the study, the Investigator is responsible for ensuring the IRB/IEC reviews and approves, where applicable, these amended documents. The Investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IRB/IEC approval of the amended form before new subjects consent to take part in the study using this version of the form. The IRB/IEC approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to Pearl promptly.

10.3 Subject Information and Consent

The study will be conducted in accordance with applicable subject privacy requirements. The proposed ICF, which must be in compliance with applicable regulations, must be reviewed and approved by the IRB/IEC and Pearl prior to initiation of the study.

The Investigator will be responsible for obtaining written informed consent from potential subjects prior to any study-specific screening and entry into the study. A copy of the signed ICF will be provided to the subject. The original will be retained by the Investigator.

10.4 Laboratory Accreditation

Any laboratory facility intended to be used for analysis of clinical laboratory samples required by this protocol must provide evidence of adequate licensure or accreditation according to the prevailing regulations in that state and/or country. Reference values and/or normal ranges for the test results must be provided to Pearl. Pearl must be notified promptly in writing of any changes occurring in reference values during the course of the study.

10.5 Confidentiality

10.5.1 Confidentiality of Data

By signing this protocol, the Investigator affirms to Pearl that information furnished to the Investigator by Pearl will be maintained in confidence and such information will be divulged to the IRB/IEC, or similar or expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the Investigator, except to the extent that it is included in a publication.

10.5.2 Confidentiality of Subject/Patient Records

By signing this protocol, the Investigator agrees that Pearl (or representative), IRB/IEC, or Regulatory Agency representatives may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject/patient agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject/patient will be identified by unique code only; full names/initials will be masked prior to transmission to Pearl. In addition, the Investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable laws (i.e., Health Insurance Portability and Accountability Act), rules and regulations.

10.6 Quality Control and Assurance

Pearl is responsible for implementing and maintaining quality control and quality assurance systems with written SOPs to ensure that Studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of GCP, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical study.

10.7 Data Management

Data management procedures and information for this protocol will be provided by Pearl or their designee.

10.8 Study Monitoring

In accordance with applicable regulations, GCP, and Pearl procedures, clinical monitors will contact the site prior to subject enrollment to review the protocol and data collection procedures with site staff. In addition, the monitor will periodically contact the site, including conducting on-site visits. The extent, nature, and frequency of on-site visits will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design complexity, and enrollment rate.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate, and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP, and all applicable regulatory requirements

The Investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

Upon completion of the study, the monitor will conduct the following activities in conjunction with the Investigator or site staff, as appropriate:

- Return of all study data to Pearl
- Data queries
- Accountability, reconciliation, and arrangements for unused investigational product(s)
- Review of site study records for completeness

After the final review of the study files, the files should be secured for the appropriate time period as specified in Section 10.9. The Investigator will also permit inspection of the study files by Pearl's Quality Assurance auditors, and authorized representatives of the FDA or other applicable regulatory agencies.

10.9 Retention of Data

Documents that individually and collectively permit evaluation of the conduct of the study and the quality of the data produced must be maintained for review by Pearl's quality assurance auditors and by all applicable regulatory authorities. The period of time these documents must be maintained is governed by applicable regulations. Pearl or its designee will inform the Investigator when these documents may be destroyed. Pearl or its designee must be notified in writing at least 6 months prior to the intended date of disposal of any study record related to this protocol to allow Pearl to make alternate storage arrangements.

10.10 Financial Disclosure

The Principal Investigator or sub-Investigators named on the Form FDA 1572 or the locally accepted alternate Investigator Statement form, will need to complete a financial disclosure form prior to study initiation, at any time during the study execution if new information needs to be disclosed, and for 1 year after study completion. Investigators should make the IRB/IEC aware of any financial interests that the Investigator has in the investigational product.

10.11 Investigator's Final Report

Shortly after completion of the Investigator's participation in the study, the Investigator will submit a written report to Pearl.

10.12 Publication Policy

Pearl intends to publish the results of all of the clinical studies that it sponsors in compliance with the Declaration of Helsinki (http://www.wma.net/en/10home/index.html). Consistent with the recommendations of the editors of several leading medical journals, the International Committee of Medical Journal Editors (ICMJE), authorship of publications resulting from Pearl -sponsored studies should fairly recognize the activities of those that have made a significant contribution to the study. Thus, it is anticipated that authorship will reflect the contribution made by Pearl personnel, the Investigators and others involved, such as statisticians.

In recent years, issues about conflicts of interest and accuracy of the study data have been raised in the medical press. Accordingly, Pearl has developed publication guidelines as described below:

1. **Responsibility:** Each Principal Investigator is responsible for the accuracy and completeness of all data from their site. Pearl (or its representatives) is responsible for the accuracy of the data entered into the study databases and for the accuracy of the analyses conducted.
2. **Sponsor Review of External Manuscripts:** Consistent with the previous bullet point, drafts of any and all publications or presentations that may arise from this study must be submitted at least 30 days prior to submission for publication or presentation to Pearl for

review, approval, and to ensure consistency with the policy in this protocol. Pearl will have the right to request appropriate modification to correct facts and to represent its opinions, or the opinions of the publication committee, if these differ with the proposed publication.

3. **Confidentiality:** Investigators will conduct all interactions with Pearl and with third parties consistent with the executed confidentiality agreements. While publication, by intention, presents the critical scientific data in a public forum, some information (such as future plans, results of nonclinical studies, or chemical formulae) may still need to remain confidential.
4. **Medical Journal Review:** Consistent with the intention of Pearl to publish the study in a fair and accurate manner, Pearl supports diligence in the publication review process of medical journals. Accordingly, upon request, all pertinent study data and information will be made available as supplemental information for journal editors and reviewers to evaluate and audit, e.g., protocol and amendments, data tabulations. The journal and reviewers will need to make arrangements to maintain the confidentiality of such supplemental information, where relevant, and Pearl will make suitable arrangements to ensure that the identity of journal reviewers is kept confidential. Records will be maintained of reviewers and the respective documents and datasets that were reviewed by each of them.
5. **Reporting of Clinical Trial Results:** To provide transparency in the conduct and reporting of randomized clinical trials, Pearl reports clinical findings based on the guidance of The CONSORT (Consolidated Standards of Reporting Trials) Statement (CONSORT, 2010) and a 25-item checklist which is intended to improve the reporting of a randomized controlled Study, and to facilitate reader understanding of the Study design, conduct, analysis and interpretation, and to support their ability to assess the validity of its results.
6. **Internet Clinical Trial Listing:** In addition, also consistent with the recommendations of the ICMJE, Pearl will make available appropriate information regarding the study via the internet. This will include registration and listing of the study on www.clinicaltrials.gov, the US National Institutes of Health listing of clinical trials, and other clinical trial listings as appropriate (e.g., EUdraCT; https://eudract.ema.europa.eu). Per AstraZeneca policy, Pearl posts clinical study protocols for public viewing when a manuscript is published in a medical journal. Prior to being made public, the protocol is reviewed by AstraZeneca Intellectual Property.

11 REFERENCE LIST

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12 APPENDICES

Appendix 1 Dose Indicator Reading

For the purposes of this study, when recording the dose indicator display value, review the indicator display at the top of the MDI and record the number of inhalations remaining that matches the chart below:

130 Count (Actuation) Version Shown				
 If your dose indicator display looks like this record **120+**	 If your dose indicator display looks like this record **120**	 If your dose indicator display looks like this record **110**	 If your dose indicator display looks like this record **100**	 If your dose indicator display looks like this record **90**
 If your dose indicator display looks like this record **80**	 If your dose indicator display looks like this record **70**	 If your dose indicator display looks like this record **60**	 If your dose indicator display looks like this record **50**	 If your dose indicator display looks like this record **40**
 If your dose indicator display looks like this record **30**	 If your dose indicator display looks like this record **20**	 If your dose indicator display looks like this record **10**	 If your dose indicator display looks like this record **0**	

Appendix 2 Subject Instructions for Use of BGF MDI, GFF MDI, and BFF MDI

How do I store the Inhaler?

- The inhaler should be stored below 25°C (77°F) in a dry place. Excursions permitted up to 30°C (86°F).
- The contents of the canister are under pressure. Do not puncture or throw the canister into a fire or incinerator. Do not use or store it near heat or open flame. Storage above 120ºF may cause the canister to burst.
- **Keep the product and all medicines out of the reach of children.**

For Oral Inhalation Only

Parts of the Inhaler:

- The parts of your inhaler are seen in **Figure 1.**

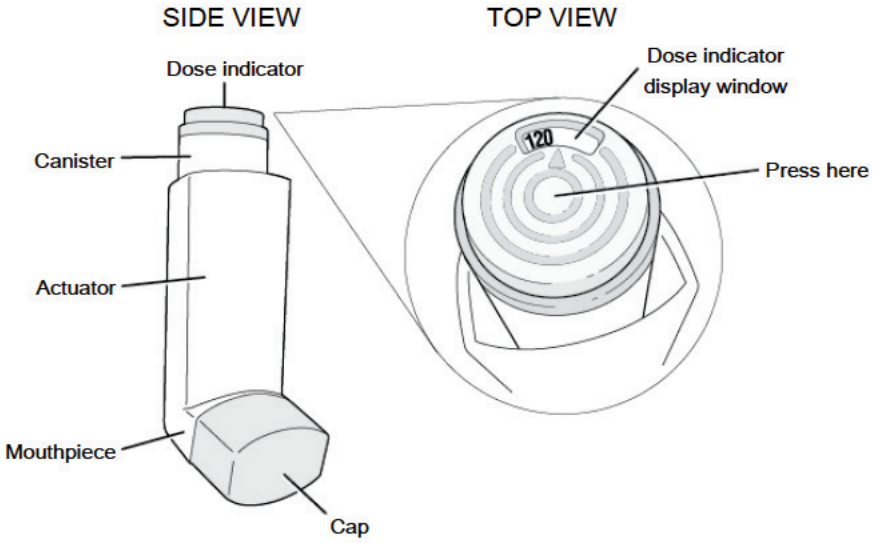


Figure 1

- The **Dose indicator** lets you know about how many puffs are left in your inhaler and is the part of the inhaler that is pressed to dispense a puff of medication. **See Figure 1.**
- The **Dose indicator** should be pointing just to the right of 120 when your inhaler is new. **See Figure 1.**
- The **Dose indicator** has numbers for every 20 puffs. The **Dose indicator** display will move after every tenth puff.
- For example, if the **Dose indicator** is pointing to 120 (**see Figure 2a**) and you take 10 puffs it will move between 120 and 100. This means that there are 110 puffs of medicine left (**see Figure 2b**). After 10 more puffs are used, the **Dose indicator** pointer will move to the number 100. This means that there are 100 puffs of medicine left (**see Figure 2c**).

Figure 2a
120 puffs

Figure 2b
110 puffs

Figure 2c
100 puffs

- The **Dose indicator** number will continue to change after every 20 puffs.
- When the number in the **Dose indicator** window changes to 20 and the color behind the number changes to red, this means that there are only 20 puffs left in your inhaler. **See Figure 2d.**

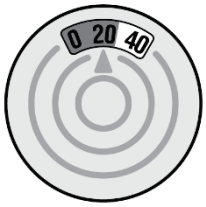
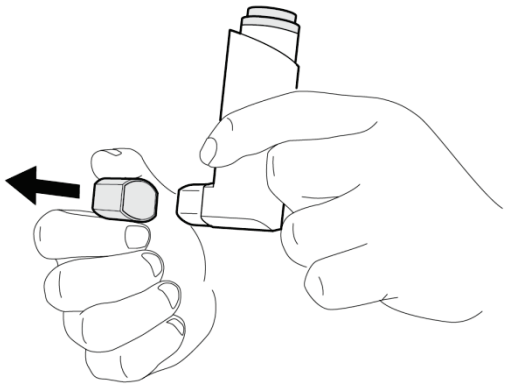


Figure 2d

Preparing the Inhaler for Use:
The inhaler comes in a foil pouch that contains a drying packet (desiccant).

- Take the inhaler out of the foil pouch.
- Throw away the pouch and the drying packet. Do not eat or inhale the contents of the drying packet.
- Remove the **Cap** from the **Mouthpiece** as shown in **Figure 3.**

Figure 3



Prime the inhaler before you use it for the first time.

Priming the Inhaler:

- Check inside the **Mouthpiece** for objects before use.
- Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4a**.
- Shake the inhaler well before each puff.
- Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister** (**see Figure 1)** until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece as shown in Figure 4b**. Note: It is normal to hear a soft click from the dose indicator as it counts down during use.
- Repeat this priming step 3 more times for a total of 4 times, shaking the inhaler each time before you press it.
- After completing the 4 priming puffs, your inhaler is now primed ready to use for the first time.

You must re-prime your inhaler again if you have not used it in more than 7 days. Take the cap off the mouthpiece and shake and spray the inhaler 2 times into the air away from your face.

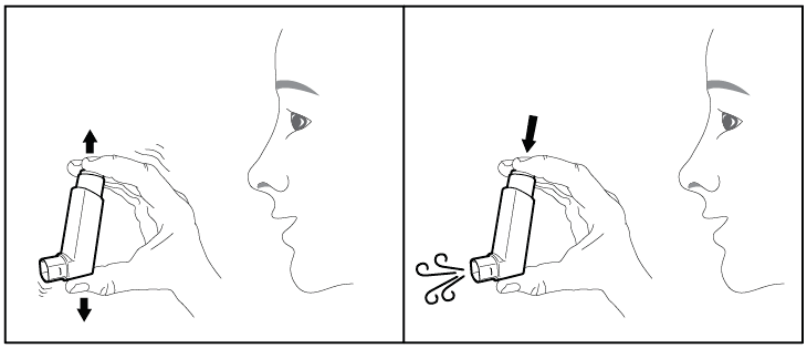


Figure 4a

Figure 4b

Using the Inhaler:
Your dose of medicine comes from **2 puffs** from the inhaler.
Refer to **Figure 5** for Step 1 through Step 8.

- **Step 1**: Remove the **Cap** from the **Mouthpiece**.
- **Step 2**: Shake the inhaler well before each puff.
- **Step 3**: While holding the inhaler with the **Mouthpiece** pointing towards you breathe out through your mouth to empty as much air from your lungs as possible.

- **Step 4**: Close your lips around the **Mouthpiece** and tilt your head back slightly to make sure your tongue is away from the **Mouthpiece**.
- **Step 5**: Take a deep breath in (inhale) slowly through your mouth while pressing down firmly on the center (not 'off center') of the **Dose indicator** until the **Canister** stops moving in the **Actuator** and a puff has been released. Then, stop pressing the **Dose indicator**.
- **Step 6**: When you have finished breathing in, remove the **Mouthpiece** from your mouth and hold your breath for 10 seconds or as long as comfortable.
- **Step 7**: Then, breathe out normally.

Take your second puff of medicine by repeating Step 2 through Step 7.

- **Step 8:** Replace the **Cap** back on the **Mouthpiece.**

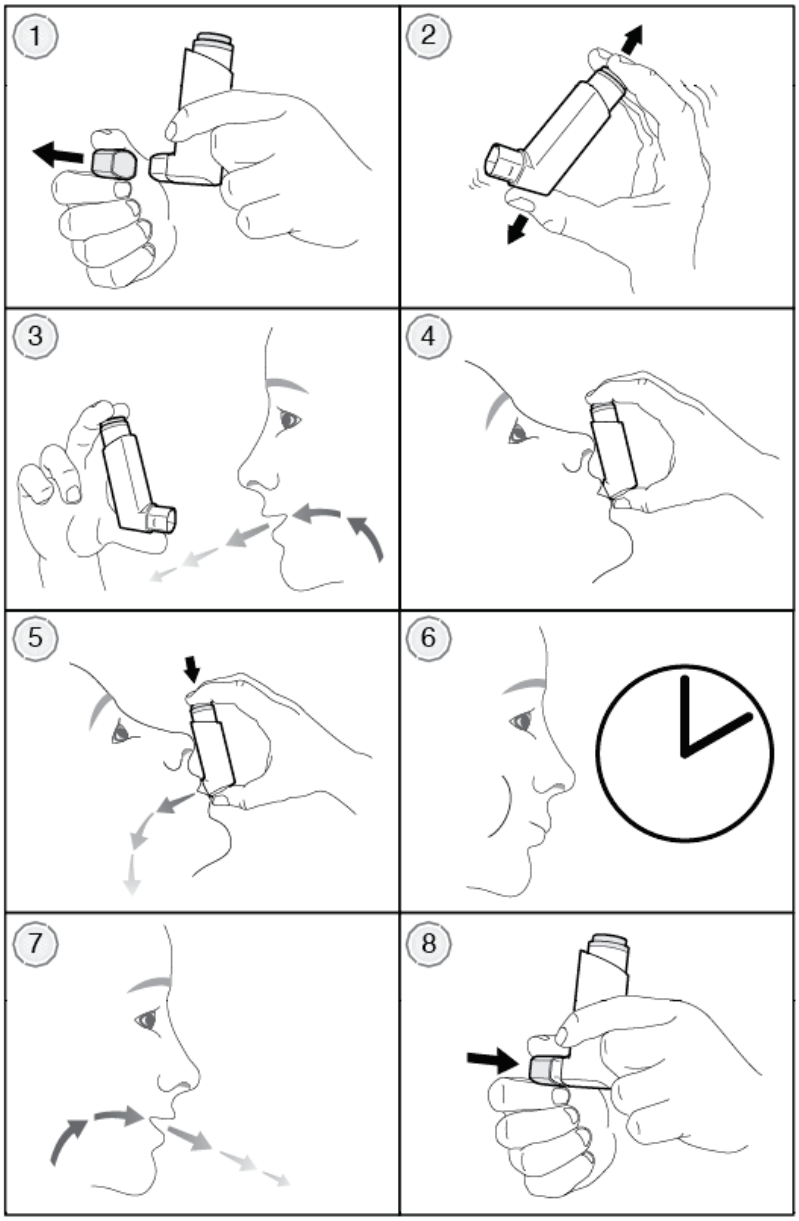


Figure 5

How to clean the Inhaler:

It is very important to keep your inhaler clean so medicine will not build-up and block the spray through the **Mouthpiece. See Figure 6**.

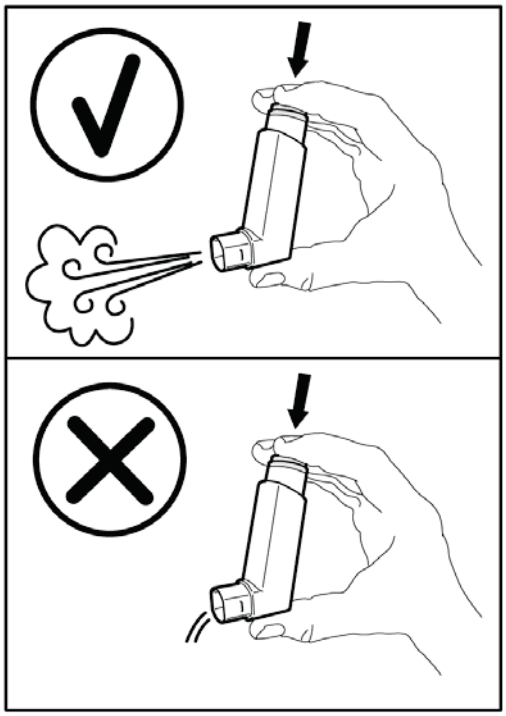
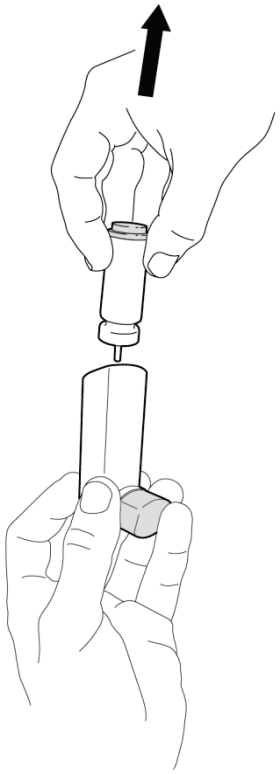


Figure 6

The **Canister** should be gently pulled from the top of the **Actuator** once a week and the **Actuato**r cleaned. **Do not clean the Canister or let it get wet.**

- **Step 1**: Pull the **Canister** out of the **Actuator** as shown in **Figure 7.**

Figure 7



- **Step 2**: Set the **Canister** aside where it will not get wet.
- **Step 3**: Take the **Cap** off the **Mouthpiece.**
- **Step 4:** Rinse the **Actuator** through the top with warm running water for 30 seconds. Then rinse the actuator again through the Mouthpiece (**see Figure 8**).

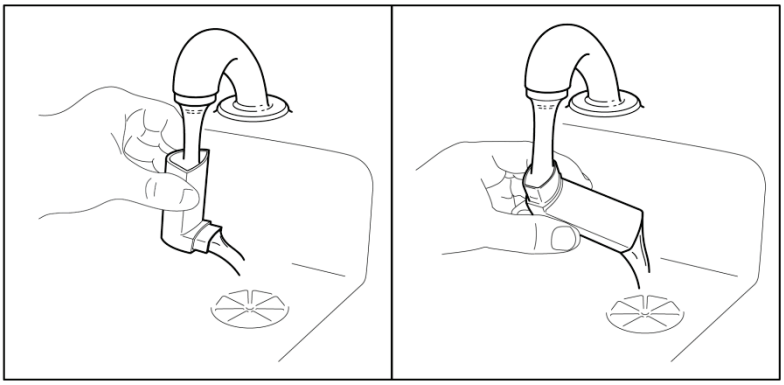


Figure 8

- **Step 5:** Shake all of the water droplets out of the **Actuator**.
- **Step 6:** Look in the **Actuator** and the **Mouthpiece** to make sure it is clean and clear**.**

Repeat **Step 4** through **Step 6**, until the **Actuator** and the **Mouthpiece** are clean and clear.

- **Step 7:** Let the **Actuator** dry completely, such as overnight as shown in **Figure 9**. **Do Not** put the **Canister** back into the **Actuator** if it is still wet.

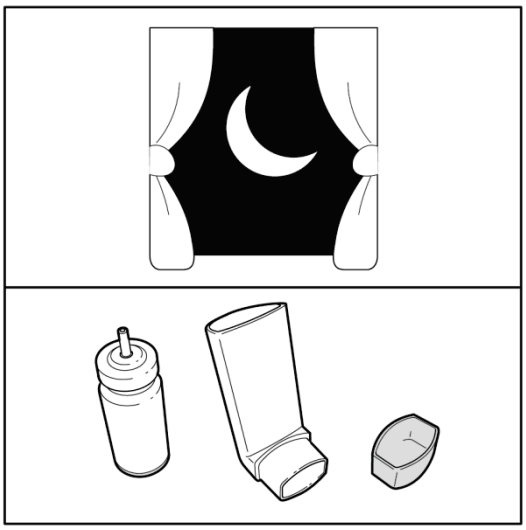


Figure 9

Reassembly of the Inhaler and Instructions for Use after Cleaning:

- After the **Actuator** is completely dry, gently press the **Canister** down in the **Actuator** as shown in **Figure 10.** It is not necessary to press down on the **Canister** hard enough to cause a puff to be released.

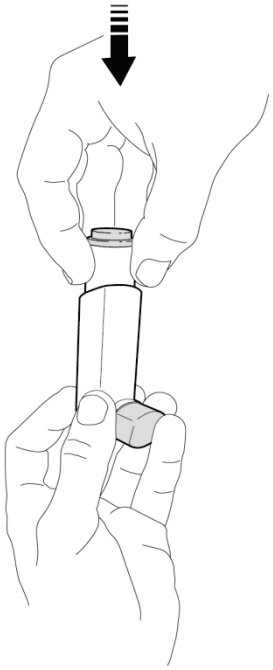


Figure 10

- Re-prime your inhaler 2 times after each cleaning.
- Hold the **Actuator** with the **Mouthpiece** pointing away from you and others as shown in **Figure 4**.
- Shake the inhaler well before each puff.
- Push down fully on the center (not 'off center') of the **Dose indicator** on top of the **Canister** until the **Canister** stops moving in the **Actuator** to release a puff from the **Mouthpiece**.
- Repeat this re-priming step 1 more time for a total of 2 times.
- After re-priming your inhaler 2 times, your inhaler is now ready to use.

Appendix 3 Instructions for Use of Ventolin HFA Inhalation Aerosol Device

Instructions for Use
For Oral Inhalation Only
Your VENTOLIN HFA inhaler

- The metal canister holds the medicine. **See Figure A.**

Figure A

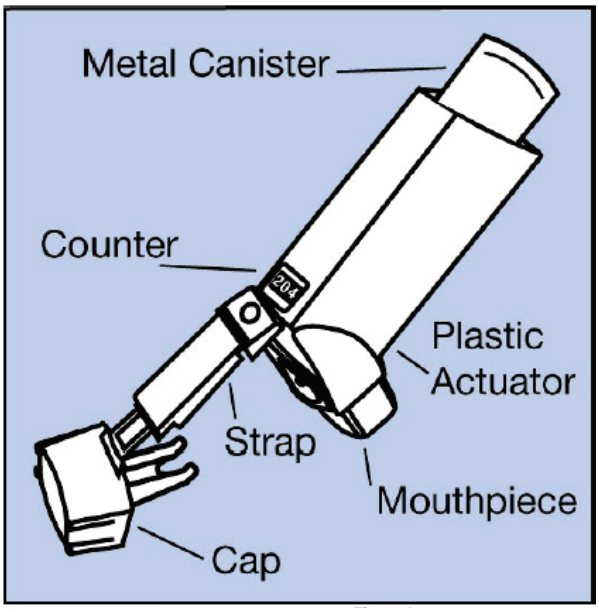


Figure A

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator. **See Figure B.**

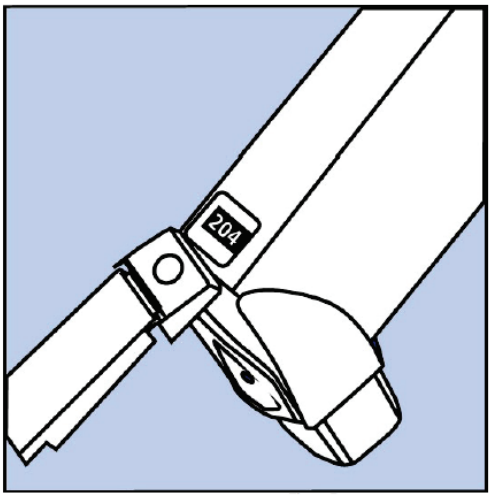


Figure B

- The counter starts at either **204 or 064,** depending on which size inhaler you have. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at **000**.
- Do not try to change the numbers or take the counter off the metal canis ter. The counter cannot be reset, and it is permanently attached to the canister.
- The blue plastic actuator sprays the medicine from the canister. The actuator has a protective cap that covers the mouthpiece. **See Figure A.** Keep the protective cap on the mouthpiece when the canister is not in use. The strap keeps the cap attached to the actuator.
- **Do not** use the actuator with a canister of medicine from any other inhaler.
- **Do not** use a VENTOLIN HFA canister with an actuator from any other inhaler.

Before using your VENTOLIN HFA inhaler

Before you use VENTOLIN HFA for the first time, you must prime the inhaler so that you will get the right amount of medicine when you use it.
To prime the inhaler, take the cap off the mouthpiece and shake the inhaler well. Then spray the inhaler 1 time into the air away from your face. **See Figure C. Avoid spraying in eyes.**

Figure C

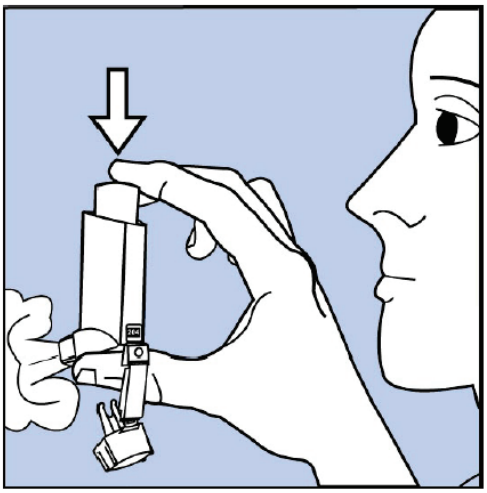


Figure C

- Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read **200** or **060**, depending on which size inhaler you have. **See Figure D.**

Figure D

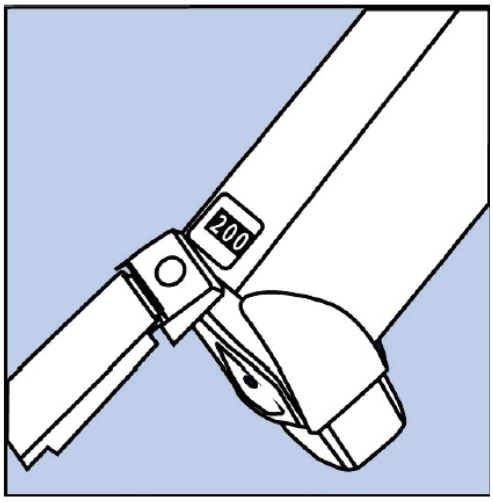


Figure D

You must prime your inhaler again if you have not used it in more than 14 days or if you drop it. Take the cap off the mouthpiece and shake and spray the inhaler 4 times into the air away from your face.

How to use your VENTOLIN HFA inhaler
Follow these steps every time you use VENTOLIN HFA.
Step 1. Make sure the canister fits firmly in the actuator. The counter should show through the window in the actuator.
Shake the inhaler well before each spray.
Take the cap off the mouthpiece of the actuator. Look inside the mouthpiece for foreign objects, and take out any you see.
Step 2. Hold the inhaler with the mouthpiece down. **See Figure E.**

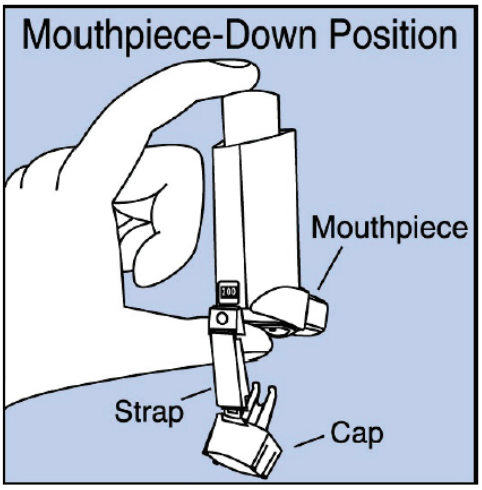


Figure E
Step 3. Breathe out through your mouth and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it. **See Figure F.**

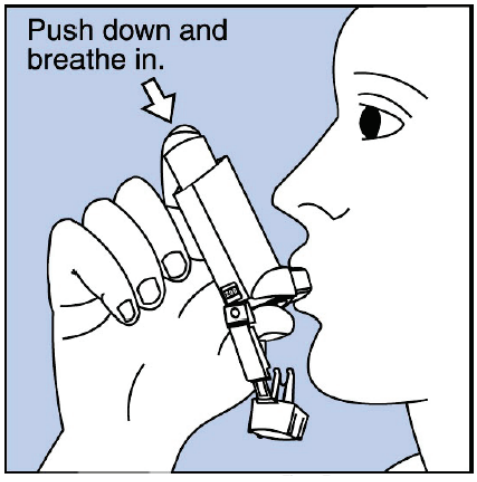


Figure F

Step 4. Push the top of the canister **all the way down** while you breathe in deeply and slowly through your mouth. **See Figure F.**

Step 5. After the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

Step 6. **Hold your breath for about 10 s econds,** or for as long as is comfortable. **Breathe out slowly as long as you can.**

If your healthcare provider has told you to use more sprays, wait 1 minute and shake the inhaler again. Repeat Steps 2 through Step 6.

Step 7. Put the cap back on the mouthpiece after every time you use the inhaler. Make sure it snaps firmly into place.

Cleaning your VENTOLIN HFA inhaler
Clean your inhaler at least 1 time each week. You may not see any medicine build-up on the inhaler, but it is important to keep it clean so medicine build-up will not block the spray. **See Figure G.**

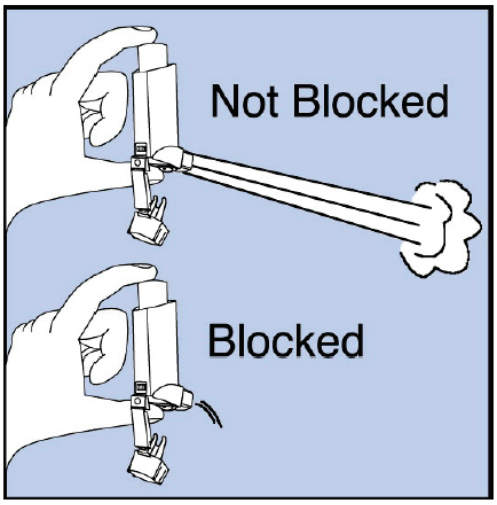


Figure G

Step 8. Take the canister out of the actuator, and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.

Step 9. Hold the actuator under the faucet and run warm water through it for about 30 seconds. **See Figure H.**

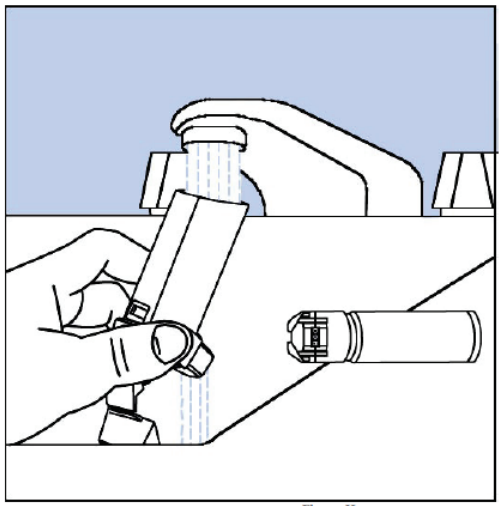


Figure H

Step 10. Turn the actuator upside down and run warm water through the mouthpiece for about 30 seconds. **See Figure I.**

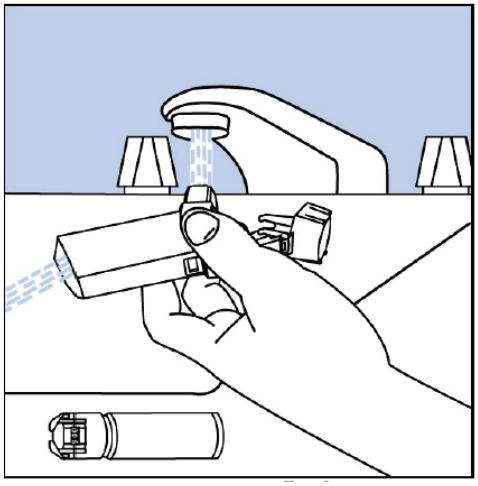


Figure I

Step 11. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat Steps 9 and 10.

Step 12. Let the actuator air-dry overnight. **See Figure J.**

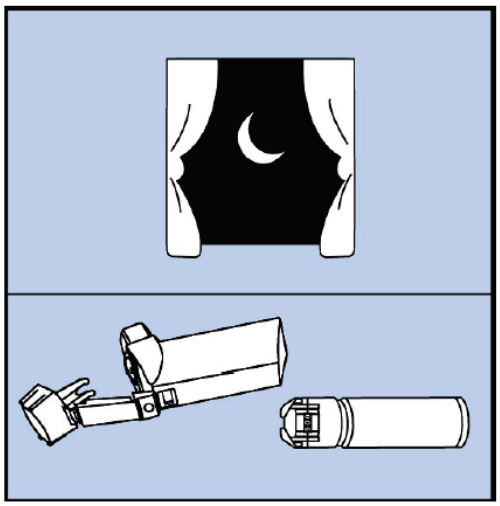


Figure J

Step 13. When the actuator is dry, put the protective cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly. Shake the inhaler well, remove the cap, and spray the inhaler once into the air away from your face. (The counter will count down by 1 number.) Put the cap back on
the mouthpiece.

If you need to use your inhaler before the actuator is completely dry:

- Shake as much water off the actuator as you can.
- Put the cap on the mouthpiece and then put the canister in the actuator and make sure it fits firmly.
- Shake the inhaler well and spray it 1 time into the air away from your face.
- Take your VENTOLIN HFA dose as prescribed.
- Follow cleaning Steps 8 through 13 above.

Appendix 4 Exacerbations of Chronic Obstructive Pulmonary Disease Tool (EXACT) – Patient-Reported Outcomes

(The samples provided here is for illustrative purposes only)

EXACT version 1.1-English (Universal)

Description	Required Text	Translation
Title	EXACT Daily Diary	EXACT Daily Diary
DD	Daily Diary	Daily Diary
Q 1 of 14	Question 1 {1} of 14	Question 1 {1} of 14
Instructions	As you answer the following questions, please select the option that best describes your experience.	As you answer the following questions, please select the option that best describes your experience.
1		
	Did your chest feel congested today?	Did your chest feel congested today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
2		
	How often did you cough today?	How often did you cough today?
	Not at all	Not at all
	Rarely	Rarely
	Occasionally	Occasionally
	Frequently	Frequently
	Almost constantly	Almost constantly
3		
	How much mucus (phlegm) did you bring up when coughing today?	How much mucus (phlegm) did you bring up when coughing today?
	None at all	None at all
	A little	A little
	Some	Some
	A great deal	A great deal
	A very great deal	A very great deal
4		
	How difficult was it to bring up mucus (phlegm) today?	How difficult was it to bring up mucus (phlegm) today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Quite a bit	Quite a bit
	Extremely	Extremely

Description	Required Text	Translation
5		
	Did you have chest discomfort today?	Did you have chest discomfort today?
	Not at all	Not at all
	Slight	Slight
	Moderate	Moderate
	Severe	Severe
	Extreme	Extreme
6		
	Did your chest feel tight today?	Did your chest feel tight today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
7		
	Were you breathless today?	Were you breathless today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
8		
	Describe how breathless you were today:	Describe how breathless you were today:
	Unaware of breathlessness	Unaware of breathlessness
	Breathless during strenuous activity	Breathless during strenuous activity
	Breathless during light activity	Breathless during light activity
	Breathless when washing or dressing	Breathless when washing or dressing
	Present when resting	Present when resting
9		
	Were you short of breath today when performing your usual personal care activities like washing or dressing?	Were you short of breath today when performing your usual personal care activities like washing or dressing?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
10		
	Were you short of breath today when	Were you short of breath today when

Description	Required Text	Translation
	performing your usual indoor activities like cleaning or household work?	performing your usual indoor activities like cleaning or household work?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
11		
	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?	Were you short of breath today when performing your usual activities outside the home such as yard work or errands?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
	Too breathless to do these	Too breathless to do these
12		
	Were you tired or weak today?	Were you tired or weak today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
13		
	Last night, was your sleep disturbed?	Last night, was your sleep disturbed?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely

Description	Required Text	Translation
14		
	How scared or worried were you about your lung problems today?	How scared or worried were you about your lung problems today?
	Not at all	Not at all
	Slightly	Slightly
	Moderately	Moderately
	Severely	Severely
	Extremely	Extremely
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Training Material	Recommended Text	Translation (if available)
Standardized instruction given to patients with PDA training and with take-home instruction manual	Please complete your diary every evening, just before you go to bed.	Please complete your diary every evening, just before you go to bed.

Appendix 5 Sponsor Signature

Study 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

Study Number: PT010008-01

Final Date: [redacted]

This clinical study protocol was subject to critical review and has been approved by the sponsor. The following personnel contributed to writing and/or approving this protocol:

Signed [redacted] Date: [redacted]

Pearl Therapeutics, Inc.

Appendix 6 Investigator's Signature

Study 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

Study Number: PT010008-01

Final Date: [redacted]

I agree:

- To assume responsibility for the proper conduct of the study at this site
- To conduct the study in compliance with the protocol and with any other study conduct procedures provided by Pearl Therapeutics, Inc. (hereafter referred to as Pearl)
- Not to implement any changes to the protocol without agreement from Pearl and prior review and written approval from the Institutional Review Board/Independent Ethics Committee, except where necessary to eliminate an immediate hazard to the subjects, or for administrative aspects of the study (where permitted by all applicable regulatory requirements)
- That I am aware of, and will comply with Good Clinical Practices and all applicable regulatory requirements
- That I am thoroughly familiar with the appropriate use of the investigational product(s), and other information provided by Pearl including, but not limited to, the following: the protocol and the current Investigators Brochure (IB)
- To ensure that all persons assisting me with the study are qualified, adequately informed about the investigational product(s) and of their study-related duties and functions
- To supply Pearl with any necessary information regarding ownership interest and financial ties; to promptly update this information if any relevant changes occur during the course of the study and for 1 year following completion of the study; and agree that Pearl may disclose any information it has about such ownership interests and financial ties to regulatory authorities
- I agree to report all information or data in accordance with the protocol and any other study conduct procedures provided by Pearl
- That since the information in this protocol and IB is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited
- To accurately transfer all required data from each subject's source document to the electronic case report forms (eCRFs). The eCRFs will be provided to Pearl in a timely manner at the completion of the study, or as otherwise specified by Pearl
- To allow authorized representatives of Pearl or regulatory authority representatives to conduct on-site visits to review, audit, and copy study documents. I will personally meet with these representatives to answer any study-related questions

Signature:_____ Date:_____

Name: _____

Affiliation: _____