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*APPLICATION NUMBER:*

**208294Orig1s000**

**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

Application Type	NDA
Application Number(s)	208294
Priority or Standard	Standard
Submit Date(s)	June 25, 2015
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Division / Office	DPARP / ODE II
Reviewer Name(s)	Stacy Chin, MD
Review Completion Date	March 21, 2016
Established Name	Glycopyrrolate/Formoterol Fumarate
(Proposed) Trade Name	Bevespi Aerosphere
Therapeutic Class	Anticholinergic/long-acting $\beta$ 2 agonist (LABA)
Applicant	Pearl Therapeutics
Formulation(s)	Metered Dose Inhaler
Dosing Regimen	18/9.6 mcg BID
Indication(s)	Long-term maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
Intended Population(s)	Adults with COPD

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The recommended regulatory action from a clinical perspective for glycopyrrolate/formoterol fumarate (GFF) 18 mcg/9.6 mcg twice daily for the long-term, maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD) is Approval.

### 1.2 Risk Benefit Assessment

The proposed indication for glycopyrrolate/formoterol fumarate (GFF) is for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed dose is a fixed combination of 18 mcg glycopyrrolate (GP) and 9.6 mcg formoterol fumarate (FF) administered via metered dose inhaler (MDI) twice daily (BID).

To support the proposed indication, the Applicant provided evidence of efficacy from two 24-week pivotal trials. The trials (3006 and 3007) were randomized, double-blind, placebo-controlled and parallel group in design. The trials were replicate in design, each comparing GFF 18/9.6 mcg BID to placebo and to the GP 18 mcg and FF 9.6 mcg monotherapies BID. In addition, trial 3006 included Spiriva Handihaler 18 mcg once daily as an open-label, active comparator treatment arm. Both trials included patients with moderate to very severe COPD for a blinded treatment period of 24 weeks. Although some patients continued blinded treatment in a 26-week extension study (3008), this study did not include a placebo control and thus was not used to evaluate efficacy for the purposes of this review. The primary efficacy endpoint was trough FEV<sub>1</sub> at Week 24 for both trials.

Results for the comparison of the primary endpoint between GFF and placebo were statistically significant in both trials. Furthermore, GFF demonstrated statistically significant improvements in trough FEV<sub>1</sub> over each of the constituent monotherapy products, GP and FF, demonstrating that both components contributed to the treatment effect. Efficacy was further supported by secondary endpoints peak FEV<sub>1</sub> within 2 hours at week 24 and trough FEV<sub>1</sub> over 24 weeks, both of which demonstrated a statistically significant improvement with GFF as compared to placebo and the monocomponents in each trial. Other endpoints such as SGRQ total score and response rate, rescue medication use, and rate of COPD exacerbations generally favored the efficacy of GFF over placebo and overall were supportive of the primary endpoint analysis. Subgroup analyses based on demographic factors (age, sex, race, and geography) demonstrated findings that were consistent with results in the overall population.

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The primary safety database used to evaluate the safety of GFF included phase 3 trials 3006, 3007, and 3008. Pivotal trials 3006 and 3007 were 24 weeks in duration and placebo-controlled while extension study 3008 was 26 weeks in duration and provided long-term safety data over a total of 52 weeks in a subset of subjects, but lacked a placebo control. In total, 3699 unique subjects were treated (3710 in the safety population including multiple enrollers) and 1036 subjects received GFF, of whom 253 were exposed for 1 year. The extent of exposure was adequate for review given that both components of GFF are older drugs with well-characterized safety profiles and that large safety trials with Spiriva Handihaler and Spiriva Respimat have alleviated many of the previous concerns regarding the cardiovascular safety of anticholinergic drugs.

Safety assessments conducted in the clinical development program included adverse event monitoring, clinical laboratory testing, vital signs, 12-lead ECGs, 24-hour Holter monitoring for a subset of patients, and a thorough QT study and were sufficient to support the safety evaluation of GFF.

A total of 14 deaths (12 during the pivotal trials, 2 during the extension study) occurred in the clinical development program. The percentage of patients with fatal events was <1% overall and for all blinded treatment groups. The number of deaths, cardiovascular deaths in particular, was relatively low given the background mortality rate in COPD patients and distributed fairly proportionately across treatment groups with no discernable pattern by system organ class or preferred term.

With regard to nonfatal SAEs and adverse dropouts, the overall incidences were similar across treatments with no meaningful differences in type or frequency of events reported. An evaluation of adverse events of special interest such as cardiovascular/MACE events and potential beta-adrenergic or anticholinergic-related side effects did not reveal any major differences between treatment groups or identify any new safety signals. Clinical laboratory data, vital sign measurements, serial ECGs and Holter-monitoring were unremarkable and supported the overall safety assessment that there were no new safety concerns raised by data reviewed from the GFF clinical program.

In conclusion, the clinical development program for GFF in COPD provides substantial replicate evidence of a bronchodilator effect that is both statistically significant and likely to be clinically meaningful and also establishes the contribution of the monotherapies to the combination. The safety data from the clinical program are consistent with those observed with similar anticholinergic/LABA products approved for COPD and do not reveal any new safety concerns. With efficacy established and an acceptable safety profile, the benefit/risk profile for GFF is favorable.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

There are no recommendations for a post marketing risk evaluation and mitigation strategy.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

No postmarked requirements or commitments are recommended at the time of this review.

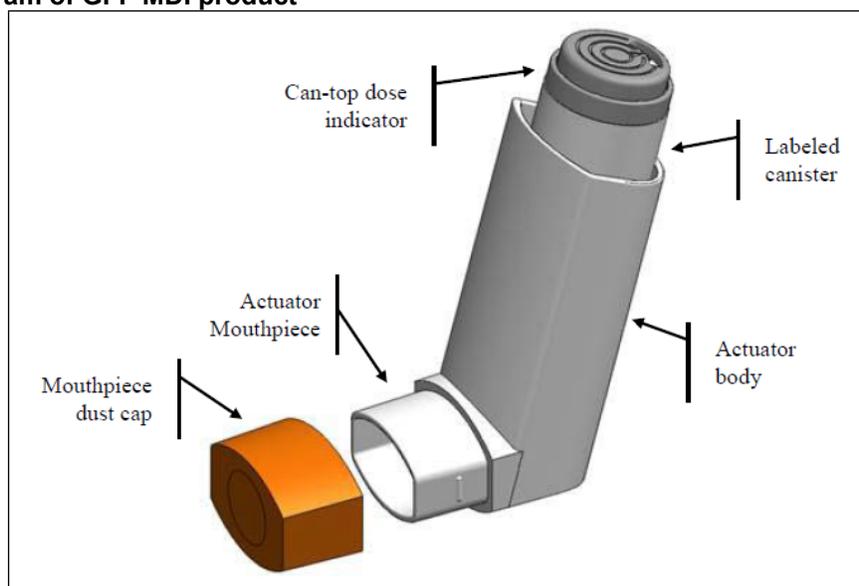
## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

GFF MDI is a fixed-dose combination product comprised of an anticholinergic (glycopyrrolate) and a LABA (formoterol fumarate) intended for the long-term maintenance treatment of airflow obstruction in patients with COPD. While neither formoterol fumarate nor glycopyrrolate are new molecular entities, and are approved and marketed as either individual drug products or components of combination products for COPD, the Applicant, Pearl, to date has not sought marketing approval for either of the individual components.

GFF MDI is formulated as a suspension with micronized glycopyrronium bromide and micronized formoterol fumarate co-suspended with a porous particle excipient comprised of the phospholipid 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC) and calcium chloride (CaCl<sub>2</sub>) in a hydrofluoroalkane (HFA) propellant. The formulation is contained within a (b) (4) aluminum can fitted with a metering valve, a white plastic actuator, an orange plastic dust cap, and a can-top dose indicator. The product is foil overwrapped with desiccant. A diagram of the GFF MDI product is shown in Figure 1. GFF MDI is formulated to contain (b) (4) (b) (4) actuations per canister. Four priming actuations are performed prior to first use, and 120 inhalations (4 inhalations/day for a total of 30 days) are intended for patient use. A total of six re-priming actuations are to be performed after weekly cleaning (2 re-priming actuations after weeks 1, 2, and 3 of continuous use).

**Figure 1. Diagram of GFF MDI product**



Source: Module 2.3, Quality Overall Summary Introduction, Figure 1, p4

## 2.2 Tables of Currently Available Treatments for Proposed Indications

Several drug classes are available to treat patients with COPD, including three approved anticholinergic/LABA inhalation products (Table 1).

**Table 1. Treatments available for COPD**

Class		Generic Name	Brand Name
Beta <sub>2</sub> -adrenergic agonists	Short-acting (SABA)*	Albuterol sulfate	Accuneb ProAir HFA Proventil HFA Ventolin HFA
		Levalbuterol tartrate	Xopenex HFA
		Terbutaline sulfate	Multiple
	Long-acting (LABA)	Salmeterol xinafoate	Serevent Diskus
		Formoterol fumarate	Foradil Aerolizer
		Arformoterol tartrate	Brovana
		Formoterol Solution	Perforomist
		Indacaterol maleate	Arcapta Neohaler
	Olodaterol hydrochloride	Striverdi Respimat	
Anticholinergics		Ipratropium bromide	Atrovent HFA
		Tiotropium bromide	Spiriva Handihaler Spiriva Respimat
		Aclidinium bromide	Tudorza Pressair
		Umeclidinium bromide	Incruse Ellipta
		Glycopyrrolate	Seebri Neohaler
Combination	SABA/anticholinergic	Albuterol/Ipratropium	DuoNeb Combivent Combivent Respimat
	Corticosteroid/LABA	Fluticasone/Salmeterol	Advair Diskus

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		Budesonide/Formoterol	Symbicort
		Fluticasone/Vilanterol	Breo Ellipta
	Anticholinergic/LABA	Umeclidinium/Vilanterol	Anoro Ellipta
		Tiotropium/Olodaterol	Stiolto Respimat
		Glycopyrrolate/Indacaterol	Utibron Neohaler
Xanthines		Theophylline	Multiple
Phosphodiesterase inhibitors	PDE4 Inhibitors	Roflumilast	Daliresp
*General bronchodilator claim, not specifically indicated for COPD			

### 2.3 Availability of Proposed Active Ingredient in the United States

Glycopyrrolate is available in the following forms:

- 1 mg tablet (Robinul)
- 2 mg tablet (Robinul Forte)
- 0.2 mg/mL injection solution (Robinul)
- 1 mg/5 mL oral solution (Cuvposa)
- 15.6 mcg capsule containing dry powder for oral inhalation (Seebri Neohaler)
- 27.5 mcg indacaterol /15.6 mcg glycopyrrolate capsule containing dry powder for oral inhalation (Utibron Neohaler)

Formoterol fumarate is available in the following forms:

- 12 mcg capsule containing dry powder for inhalation (Foradil Aerolizer)
- 20 mcg (unit dose vial) inhalation solution for nebulization (Performorist)
- 15 mcg (unit dose vial) inhalation solution for nebulization (Brovana)
- 80 or 160 mcg budesonide / 4.5 mcg formoterol inhalation aerosol (Symbicort)
- 100 or 200 mcg mometasone / 5 mcg formoterol pressurized MDI (Dulera) – only approved for asthma

### 2.4 Important Safety Issues With Consideration to Related Drugs

Class effects of anticholinergic drugs include worsening of narrow angle glaucoma, urinary retention, and decreased secretions leading to effects such as dry mouth. In addition, the Agency has historically had concerns with the cardiovascular safety of anticholinergics due to an imbalance in mortality observed in the clinical development of tiotropium and in meta-analyses published in the medical literature<sup>1</sup>. As a result, the Agency released Early Communications on March 18, 2008, and October 7, 2008, about the ongoing safety review of Spiriva Handihaler (SHH). To address this concern, two large, randomized, double-blind clinical trials in COPD patients were conducted to evaluate the long-term safety and risk of mortality: the UPLIFT trial comparing SHH to placebo and the TIOSPIR trial comparing SHH to Spiriva Respimat (SR). UPLIFT

<sup>1</sup> Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. JAMA 2008; 300: 1439-50

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evaluated ~6,000 patients over 4 years and demonstrated no increased mortality risk with SHH compared to placebo. TIOSPIR included over 17,000 COPD patients followed for a mean period of 2.3 years. Results from TIOSPIR demonstrated that SR 5 µg was non-inferior (hazard ratio 0.957 [95% CI 0.837, 1.094]) to SHH 18 µg in terms of all-cause mortality, the primary endpoint. Although sub-analyses revealed an increased number of deaths due to myocardial infarction in the SR 5 µg group, this finding was not supported by results for MI-related serious adverse events, major adverse cardiovascular events (MACE), or stroke-related deaths. For further details, refer to the Medical Officer reviews<sup>2</sup>, FDA perspective<sup>3</sup>, and transcripts from the public meetings held by the Pulmonary Allergy Drug Advisory Committee<sup>4,5</sup>.

LABA monotherapy is associated with serious asthma-related adverse events such as death and increased risk of hospitalization; however, the risk is believed to be limited to the asthma population and has not been observed in patients with COPD. Other beta-agonist class effects include tachycardia, palpitations, tremor, nervousness, paradoxical bronchospasm, hypertension, and hypokalemia.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of key interactions that took place between the Agency and the Applicant during the development of GFF is provided below. Prior to submission of this NDA, development of GFF (b) (4) occurred under INDs 107,739 (GFF), (b) (4)

May 4, 2011: Type C Meeting

- The Division expressed concern over a possible DDI because of data showing reduced bioavailability of the single ingredients when administered in a fixed combination.

April 19, 2012: Type C Meeting

- The Division agreed that doses lower than 18 mcg should be explored and that the data supported a BID dosing regimen.
- The Division agreed that 9.6 mcg FF was reasonable to carry forward to Phase 3.
- A thorough QT study of the individual components would not be necessary.

December 21, 2012: Type B EOP2 Meeting

- The Division agreed with selection of GP 18 mcg to carry forward to Phase 3 for GFF and GP based on results from studies 1003 and 3005.

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<sup>2</sup> For NDA 21-395 (S029) dated August 7, 2009 and for NDA 21-936 dated August 28, 2014

<sup>3</sup> Michele TM, Pinheiro S, Iyasu S. NEJM 2010; 363(12):1097-9

<sup>4</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM198006.pdf>

<sup>5</sup> <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM416247.pdf>

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- The Division agreed with pivotal trial designs (b) (4) in extension study 3008 .
- The Division recommended using a single primary endpoint such as trough FEV<sub>1</sub> to compare GFF to its monocomponents since they are both bronchodilators.
- The treatment effect should be measured at a single time point (b) (4) due to the potential for tachyphylaxis.
- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

June 2, 2014: Type B Pre-NDA Meeting

- Primary endpoint should remain morning pre-dose trough FEV<sub>1</sub> at 24 weeks (b) (4) with the expectation that the GFF combination wins on lung function at 24 weeks, the contribution of each component is demonstrated, and COPD exacerbations trend in the right direction. (b) (4)
- (b) (4) the 24 week time point is more appropriate. In addition, the expectation for an anticholinergic/LABA combination is to decrease COPD exacerbations, for which a longer study is needed.
- The 24 week endpoints in studies 3006 and 3007 will provide adequate information for maintenance of efficacy, but the 52 week endpoint in study 3008 will provide little or no useful information since it includes open-label data.
- Regardless of whether week 52 results provide additional information, a single study may not suffice for additional labeling claims.
- The appropriateness of pooling data and patients from 3006 and 3007 into 3008 will be contingent on similar results from 3006 and 3007 and lack of impact on randomization of patient withdrawal
- The determination of efficacy will be based on individual replicate studies not pooled ISE results.
- (b) (4)
- Glycopyrrolate should be used as the established name for the drug product with strength based on the salt.

### 3 Ethics and Good Clinical Practices

#### 3.1 Submission Quality and Integrity

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The NDA was submitted electronically and included complete study reports, appropriate case report forms, and proposed labeling. The submission was appropriately indexed and organized to permit clinical review. Review of the application did not raise any data integrity concerns. With the assistance of the statistical review team, Site 6021 was selected for inspection due to high enrollment and relatively large treatment effect. The Applicant, Pearl Therapeutics, and two other investigators were selected for inspection due to complaints cited in concerned citizen letters received by the Agency.

Table 2 lists the sites, principal investigators, and corresponding trials that were inspected.

### 3.2 Compliance with Good Clinical Practices

The Applicant stated that all clinical studies and trials were conducted in compliance with Good Clinical Practices and submitted a statement certifying that no debarred individuals participated in the conduct of trials included in this NDA. Prior to initiation, each clinical trial protocol and written informed consent form were reviewed and approved by local Institutional Review Boards (IRB) or Independent Ethics Committees (IEC).

### 3.3 Financial Disclosures

The applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. Ten principal investigators and six sub-investigators reported receipt of significant payments from the Applicant or parent company AstraZeneca. All of the investigators with disclosable financial interests received payments for speaking and/or consulting fees for AstraZeneca in addition to three investigators who also served as advisory board members for Pearl Therapeutics and/or Astra Zeneca. The Applicant states that they did not become aware of the financial interests of any of the above investigators until studies PT003006, PT003007, and PT003008 were completed, and therefore, were not able to take any steps to minimize bias during the conduct of the study. However, these payments do not appear to raise questions about the integrity of the data. Enrollment at any particular site was relatively small compared to the overall number of patients, and no single site or investigator appears to be driving the results.

**Table 2. Financial Disclosure Checklist**

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of principal investigators identified: 310		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 16		

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If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):  Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0  Significant payments of other sorts: 16  Proprietary interest in the product tested held by investigator: 0  Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 4 investigators, 15 sub-investigators		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/>

## 4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

### 4.1 Chemistry Manufacturing and Controls

The recommendation from the CMC review team is Approval pending inspections. (see NDA 208-294 CMC review by Drs. Art Shaw and Craig Bertha)

The drug product is a pressurized metered-dose inhaler contained within a (b) (4) aluminum can fitted with a metering valve, a white plastic actuator, an orange plastic dust cap, and a can-top dose indicator. Each actuation of the inhaler delivers 9 mcg of glycopyrrolate and 4.8 mcg of fomoterol fumarate from the actuator.

### 4.2 Clinical Microbiology

The recommendation from the product quality microbiology team is Approval. (see NDA 208-294 clinical microbiology review by Dr. Nutan Mytle)

### 4.3 Preclinical Pharmacology/Toxicology

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The recommendation from the nonclinical review is Approval. A brief overview of nonclinical findings is summarized below. (see NDA 208-294 pharmacology/toxicology review by Dr. Luqi Pei, dated March 10, 2016)

#### General Toxicity

The general toxicity of inhaled glycopyrrolate was evaluated in rats and dogs for 6 months. No observed adverse effect levels (NOAELs) were identified in both studies. Relevant target organs in the rat study were nose, larynx, and prostate; no treatment-related effects were observed in the dog study. In addition, a 3-month study in dogs found no significant drug interactions between inhaled GP and inhaled FF. Safety margins were approximately 5 and 10 times the maximum recommended human dose for GP and FF, respectively.

#### Genetic Toxicity

GP genetic toxicity assays were negative. FF has not been found to be mutagenic or clastogenic in previous tests conducted for inhaled budesonide/formoterol (Symbicort).

#### Carcinogenicity

No carcinogenicity studies of GFF were conducted. No animal studies were conducted to evaluate the carcinogenicity potential of GP because no pre-neoplastic/neoplastic lesions were observed in the 6 month rat inhalation study. Rats and mice treated with FF showed dose-dependent increases in the incidence of leiomyomas in the female reproductive system based on 24-month studies conducted previously for the budesonide/formoterol (Symbicort) development program.

#### Reproductive and Developmental Toxicity

No reproductive and developmental toxicity studies of GP, FF, or GFF were submitted or required. Information for product labeling will be obtained from reference products Robinul Injection and Symbicort for GP and FF, respectively.

### **4.4 Clinical Pharmacology**

#### **4.4.1 Mechanism of Action**

Glycopyrrolate is a long-acting muscarinic antagonist (anticholinergic). In the airways, it exhibits pharmacological effects through inhibition of M3-receptors at the smooth muscle leading to bronchodilation.

Formoterol fumarate is a long-acting beta agonist that acts by binding and activating beta<sub>2</sub>-adrenergic receptors in the lungs, predominantly in bronchial smooth muscle to promote bronchodilation.

#### 4.4.2 Pharmacodynamics

Traditionally, approval for a combination inhalation product for COPD follows the approval of the constituent monocomponents. In this case, neither of the Applicant's individual components are approved as monotherapy products. However, each of the active moieties is commercially available from other manufacturers as both monotherapy and fixed dose combination products for COPD (see Table 1).

Given that the Applicant does not have approved glycopyrrolate or formoterol fumarate monotherapy products, this NDA review includes a brief analysis of the dose-ranging and dose-interval selection data for each of the monocomponents.

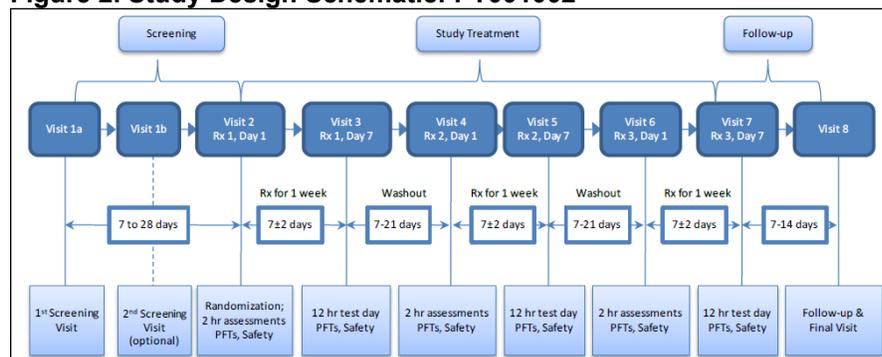
##### Glycopyrrolate Dose and Dosing Regimen Selection

GP dose selection studies primarily included three phase 2 trials evaluating doses ranging from 0.6 mcg to 144 mcg twice daily (Studies PT0010801, PT001002, and PT001003). Active comparator treatment arms of tiotropium bromide (Spiriva Handihaler) and ipratropium bromide (Atrovent HFA) were included to establish the twice daily dosing interval. Data from the multi-dose studies PT001002 and PT001003 are described below.

Study Number	PT001002
Title	A Randomized, Double-Blind, Chronic Dosing (7 days), Three-Period, Six-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of PT001 in Patients with Moderate to Severe COPD, Compared with Atrovent HFA Inhalation Aerosol (Open-Label) as an Active Control
Study dates	May 12, 2011 – October 4, 2011
Study report	November 22, 2013
Sites	9 sites in the U.S.

This was a randomized, double-blind, multiple dose, 3-period crossover study evaluating four doses of GP MDI (4, 6, 18, and 36 mcg BID) in patients with moderate to severe COPD compared to Atrovent HFA 34 mcg QID administered as an open-label active control. The study schematic is shown in Figure 2.

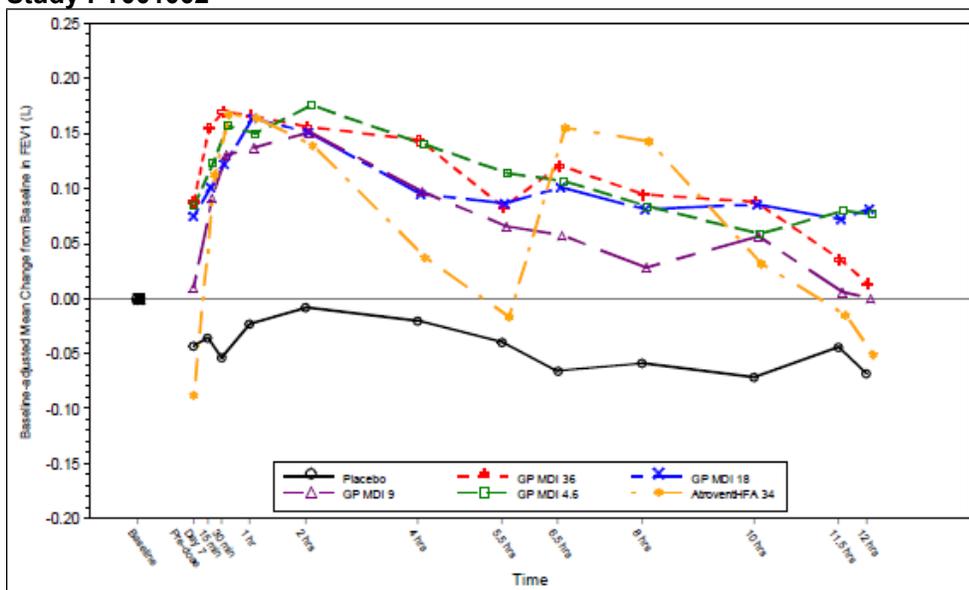
**Figure 2. Study Design Schematic: PT001002**



Source: CSR PT001002, Figure 1, p24

One hundred three patients were randomized and treated, 89 (86%) of whom completed the study. Efficacy analyses were based on the modified ITT (mITT) population which consisted of 91 patients who completed at least two treatment periods with at least one pre-dose assessment on Day 7 for each of those two treatment periods and no significant protocol deviations that might impact efficacy results for those two treatment periods. In analysis of the primary efficacy endpoint, all active treatments (GP MDI and Atrovent) were superior to placebo as measured by FEV<sub>1</sub> AUC<sub>0-12</sub> on Day 7 relative to baseline in the mITT population (Figure 3). However, there was no clear dose-response observed among GP treatments in mean FEV<sub>1</sub> AUC<sub>0-12</sub> difference from placebo on treatment day 7 because GP 4.6 mcg demonstrated the greatest treatment effect (Figure 4). In addition, compared to Atrovent HFA, all GP MDI treatment doses were shown to be non-inferior with respect to FEV<sub>1</sub> AUC<sub>0-12</sub> and to have a similar FEV<sub>1</sub> time profile with regard to onset of action to peak treatment effect within 2 hours. The gradual decrease in GP treatment effect over 12 hours along with similar of results between the first 5.5 hours and the second 6.5 hours (FEV<sub>1</sub> AUC<sub>0-5.5</sub> and FEV<sub>1</sub> AUC<sub>5.5-12</sub>, respectively) with GP MDI doses relative to Atrovent HFA supported the appropriateness of the BID dosing regimen for GP.

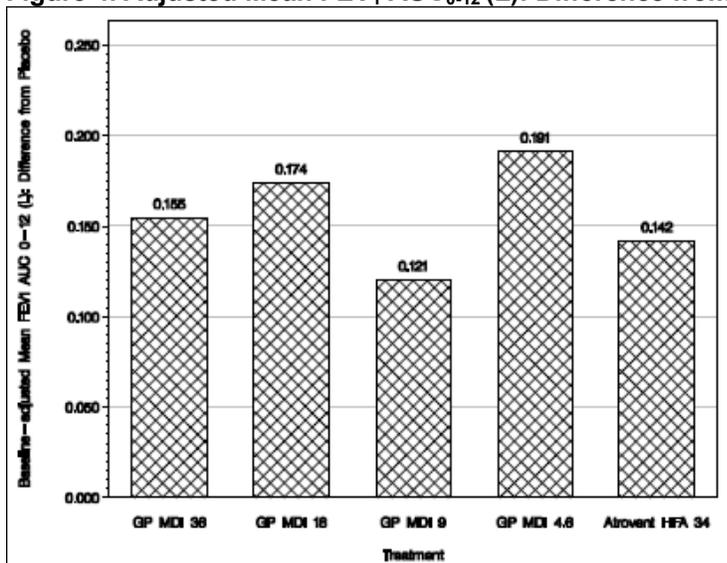
**Figure 3. Adjusted Mean Change from Baseline in FEV<sub>1</sub> (L) Over Time on Treatment Day 7 (mITT): Study PT001002**



Source: CSR PT001002, Figure 2, p85

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Figure 4. Adjusted Mean FEV<sub>1</sub> AUC<sub>0-12</sub> (L): Difference from Placebo on Treatment Day 7 (miTT)

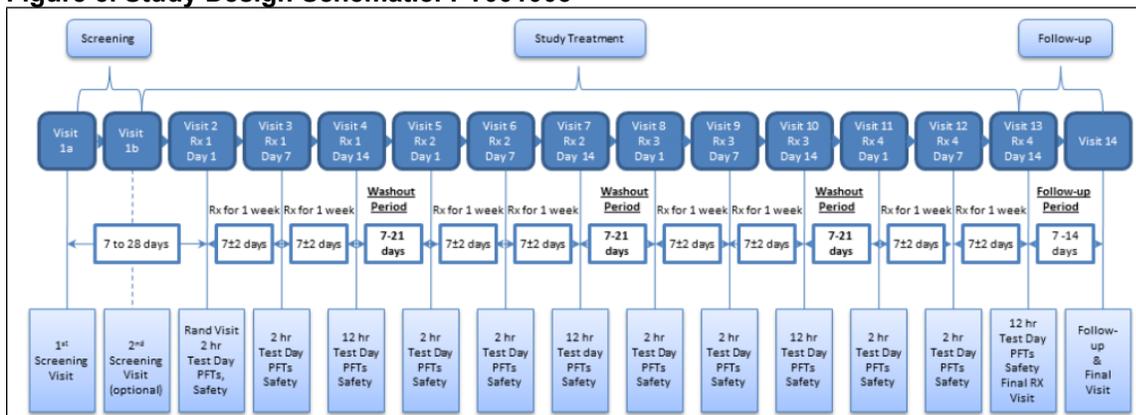


Source: CSR PT001002, Figure 3, p86

Study Number	PT001003
Title	A Randomized, Double-Blind, Chronic Dosing (14 days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Six Doses of PT001 in Patients with Moderate to Severe COPD, Compared with Spiriva Handihaler (Tiotropium Bromide, Open-Label) as an Active Control
Study dates	April 11, 2012 – August 10, 2012
Study report	December 17, 2013
Sites	10 sites in the U.S.

This was a randomized, double-blind, placebo-controlled, multiple dose, 4-period crossover study evaluating eight doses of GP MDI (0.6, 1.2, 2.4, 4.6, 9, and 18 mcg BID) in patients with moderate to severe COPD compared to Spiriva Handihaler (SHH) 18 mcg QD administered as an open-label active control. The study schematic is shown in Figure 5.

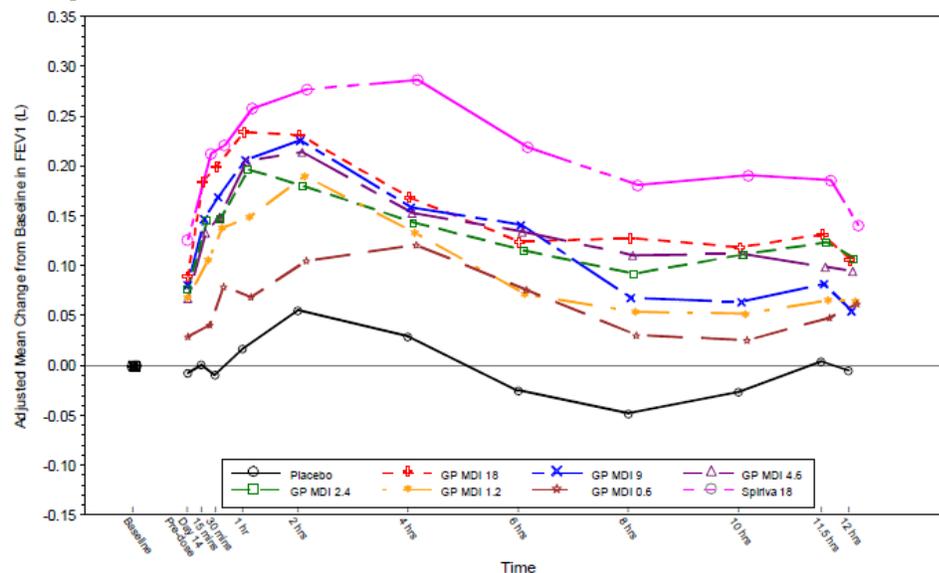
Figure 5. Study Design Schematic: PT001003



Source: CSR PT001003, Figure 1, p29

One hundred forty patients were randomized and treated, 110 (79%) of whom completed the study. Efficacy analyses were based on the mITT population, which consisted of 120 (86%) patients who completed at least two treatment periods with at least one pre-dose assessment on Day 14 for each of those two treatment periods and no significant protocol deviations that might impact efficacy results for those two treatment periods. Note, an exception was made to include subject 4010 who only had 2-hour post-dosing data for one treatment period in the mITT population. For analysis of the primary efficacy endpoint, all active treatments (GP MDI and SHH) were superior to placebo as measured by FEV<sub>1</sub> AUC<sub>0-12</sub> on Day 14 relative to baseline in the mITT population (Figure 6). Although none of the GP MDI doses were statistically non-inferior relative to SHH (based on a lower bound of > -100 mL for FEV<sub>1</sub> AUC<sub>0-12</sub> on Day 14), the greatest treatment effect was observed with SHH, and in general, normal dose-ordering was observed (Figure 7). The onset of action and peak treatment effect within 1 to 2 hours post-dose followed by a gradual decrease in effect over 12 hours were generally similar among GP treatments and consistent with BID dosing. The peak effect with 0.6 mcg was less and occurred later (at 4 hours) compared with higher GP doses.

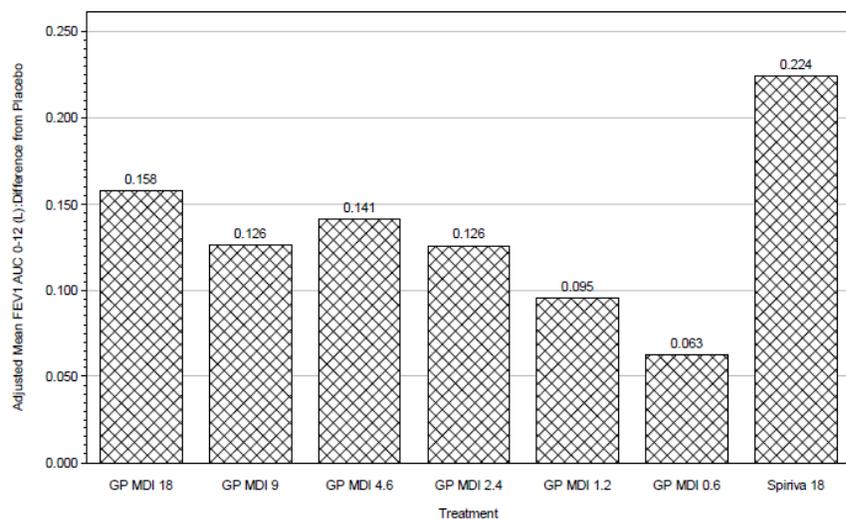
**Figure 6. Adjusted Mean Change from Baseline in FEV<sub>1</sub> (L) Over Time on Treatment Day 14 (mITT): Study PT001003**



Source: CSR PT001003, Figure 2, p104

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Figure 7. Adjusted Mean FEV<sub>1</sub> AUC<sub>0-12</sub> (L): Difference from Placebo on Treatment Day 14 (mITT)



Source: CSR PT001003, Figure 3, p105

Formoterol Fumarate Dose Selection

FF dose selection studies primarily included two phase 2 trials evaluating single doses ranging from 2.4 mcg to 19.2 mcg twice daily (Studies PT005081 and PT005003). Dose selection was based upon a non-inferiority comparison to open-label Foradil Aerolizer 12 mcg.

Study Number	PT005081
Title	A Randomized, Double-Blind, Five-Period, Placebo and Active-Controlled, Cross-Over, Multi-Center Study Evaluating Single Administration of Three Doses of Formoterol Fumarate MDI in Patients with Moderate-to-Severe COPD, Compared to Open-Label Marketed Formoterol (Foradil Aerolizer) as an Active Control
Study dates	November 6, 2008 – May 26, 2009
Study report	October 22, 2009
Sites	5 sites in Australia and New Zealand

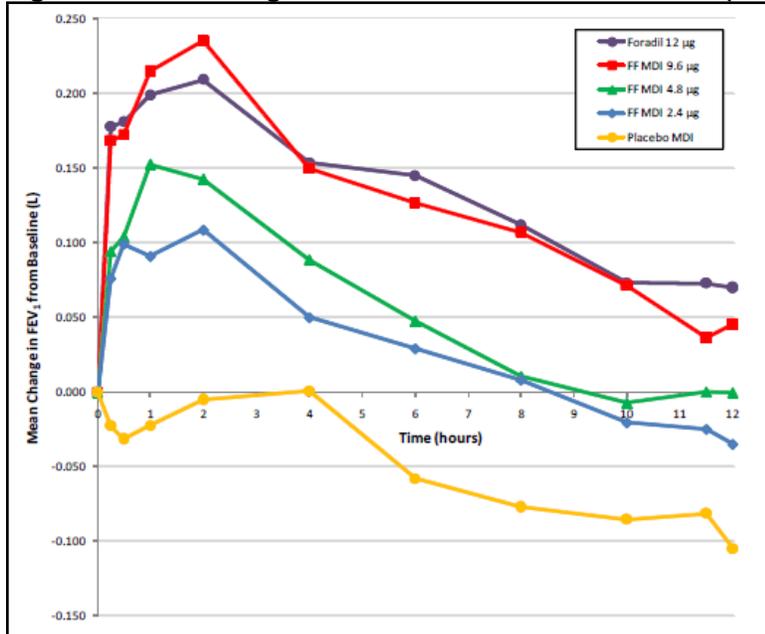
This was a randomized, double-blind, five-period, single-dose, placebo and active-controlled, crossover, multicenter study evaluating three doses of fomoterol fumarate (FF) compared to open-label marketed formoterol (Foradil Aerolizer) as an active control in patients with moderate to severe COPD. Each patient received FF at doses of 2.4, 4.8, and 9.6 mcg, Foradil Aerolizer 12 mcg, and placebo MDI. The position of Foradil Aerolizer and placebo in the sequence was randomized; however, the doses of FF were administered in ascending order to all patients. There was a 3 to 10 day washout between doses.

A total of 34 patients were randomized and treated, while 29 of the patients completed the study. The mITT population consisted of 32 patients because one patient was excluded for protocol violations (smoking and/or personal rescue salbutamol use on study treatment days) and another patient was excluded because spirometry data did not meet criteria for COPD prior to dosing after enrollment. For the primary efficacy

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analysis, the mean change in FEV<sub>1</sub> AUC<sub>0-12</sub> from baseline in the mITT population was statistically superior to placebo for each dose of FF and showed a clear dose-response relationship (Figure 8). Compared to Foradil Aerolizer 12 mcg, the FF 9.6 mcg dose demonstrated a similar FEV<sub>1</sub> time profile curve and was shown to be statistically non-inferior at all time points in terms of change in FEV<sub>1</sub> from baseline using a NI margin of 100 mL (Figure 9).

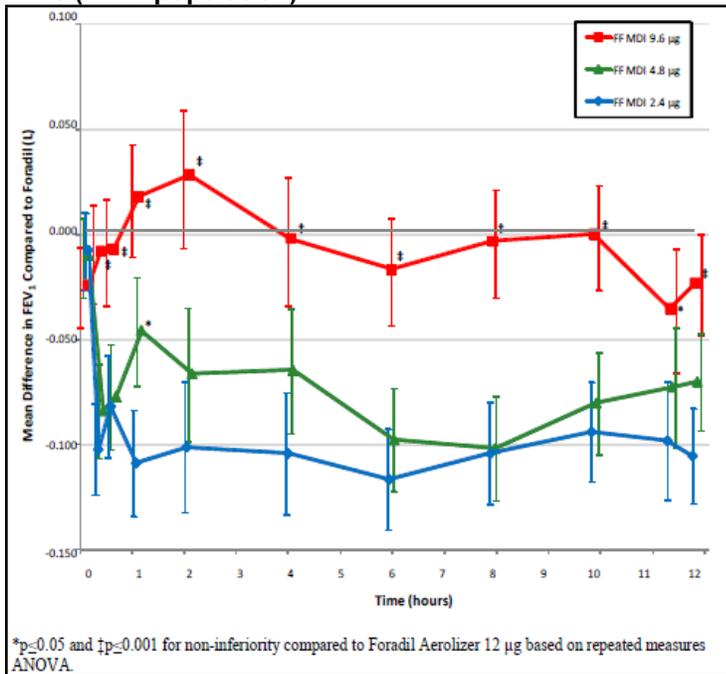
Figure 8. Mean Change from Baseline in FEV<sub>1</sub> Over Time (mITT population)



Source: CSR PT0050801, Figure 7-1, p45

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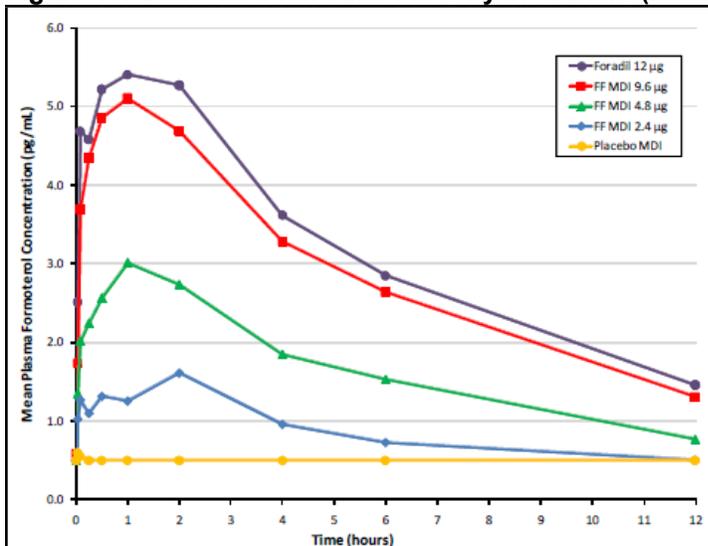
Figure 9. Non-inferiority to Foradil Aerolizer in Mean Change from Baseline in FEV<sub>1</sub> for FF Over Time (mITT population)



Source: CSR PT0050801, Figure 7-3, p50

In addition, PK results from the mITT PK population, which included all 34 randomized patients, demonstrated a linear relationship between dose and systemic exposure with FF 9.6 mcg showing a similar concentration-time profile to that of Foradil Aerolizer 12 mcg (Figure 10).

Figure 10. Concentration Time Plots by Treatment (mITT PK population)



Source: CSR PT0050801, Figure 7-4, p52

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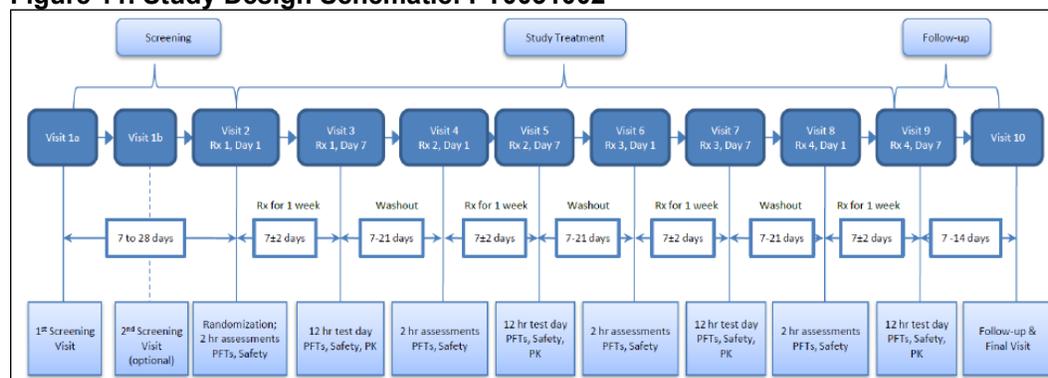
Although not shown, results from Study PT005003, which evaluated single doses of FF 7.2, 9.6, and 19.2 mcg and Foradil 12 and 24 mcg, were consistent with these findings. Systemic exposure following a single administration of FF increased in a dose proportional manner, and exposure between FF 9.6 mcg and Foradil 12 mcg was equivalent as was exposure between FF 19.2 mcg and Foradil 24 mcg.

**Glycopyrrolate/Formoterol Dose Selection**

Study Number	PT0031002
Title	A Randomized, Double-Blind, Chronic Dosing (7days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two doses of PT005, and One Dose of PT001 in Patients with Moderate to Very Severe COPD, Compared with Foradil Aerolizer (12 mcg, Open-Label) and Spiriva Handihaler (18 mcg, Open-Label) as Active Controls
Study dates	March 24, 2010 – October 28, 2010
Study report	July 19, 2012
Sites	15 sites in Australia, New Zealand, and the U.S.

This was a randomized, double-blind, 7-day, 4-period crossover study evaluating two doses of GFF MDI, two doses of FF MDI, and one dose of GP MDI in patients with moderate to very severe COPD compared to Foradil Aerolizer and SHH administered as open-label active controls. Part A was a 4-period, incomplete crossover designed to evaluate eight treatments: GFF 72/9.6 mcg BID, GFF 36/9.6 mcg BID, GP 36 mcg BID, FF 9.6 mcg BID, FF 7.2 mcg BID, placebo BID, Foradil 12 mcg BID, and SHH 18 mcg QD. Part B of the study was a 4-period, full crossover designed to evaluate four treatments: FF 9.6 mcg BID, FF 7.2 mcg BID, placebo BID, and Foradil 12 mcg BID. The study schematic is shown in Figure 11.

**Figure 11. Study Design Schematic: PT0031002**



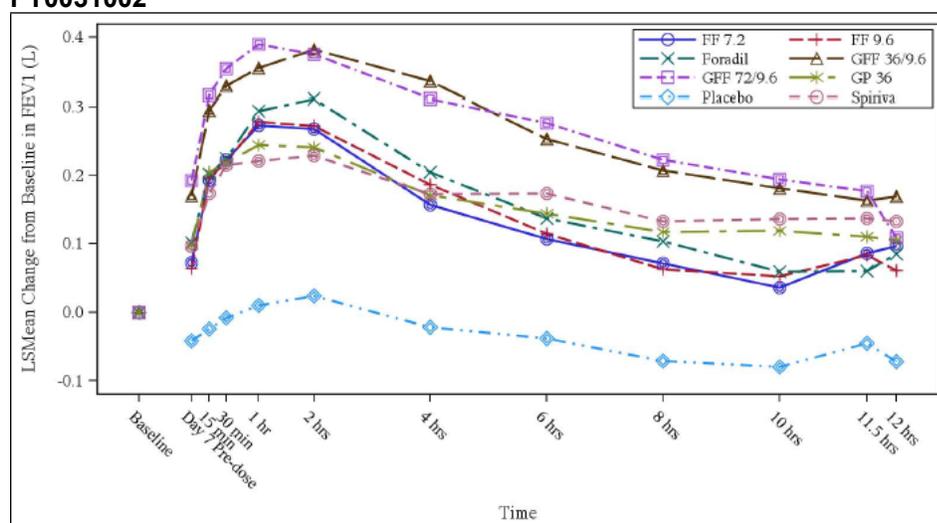
Source: CSR PT0031002, Figure 1, p33

A total of 118 patients were randomized and treated, 68 patients into Part A and 50 patients into Part B of the study. The number of patients who completed all four treatment periods, including spirometry measurements at least 2 hours post-dose in each treatment period was 50 (74%) in Part A and 39 (78%) in Part B. The mITT

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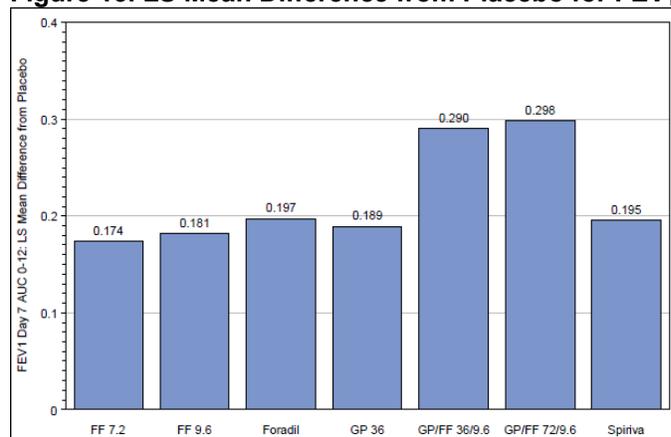
population consisted of patients who completed at least 2 treatment periods for a minimum 2 hours post-dose on Day 7 and had no more than one missing data-point from the 15-minute to 2-hour post-dose time point and was comprised of 104 (88%) patients. For the primary efficacy analysis, all active treatments were superior to placebo for FEV<sub>1</sub> AUC<sub>0-12</sub> on Day 7 relative to baseline in the mITT population (Figure 12 and Figure 13). There was no significant difference between GFF doses, and both demonstrated higher FEV<sub>1</sub> AUC<sub>0-12</sub> responses compared to the GP and FF monocomponents as well as SHH and Foradil active controls. In addition, the FEV<sub>1</sub> AUC<sub>0-12</sub> treatment response on Day 7 was similar between GP 36 mcg and SHH as well as between both doses of FF and Foradil.

**Figure 12. LS Mean Change from Baseline in FEV<sub>1</sub> Over Time on Treatment Day 7 (mITT): Study PT0031002**



Source: CSR PT0031002, Figure 2, p99

**Figure 13. LS Mean Difference from Placebo for FEV<sub>1</sub> AUC<sub>0-12</sub> (L) on Treatment Day 7 (mITT)**



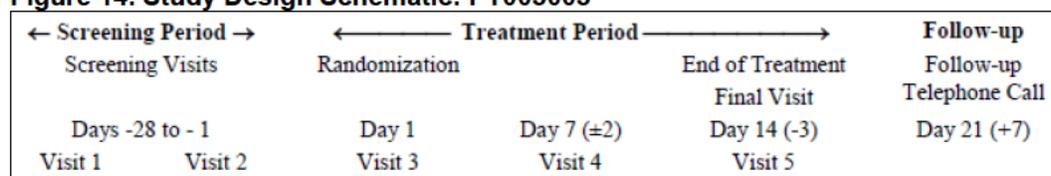
Source: CSR PT0031002, Figure 7, p104

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<b>Study Number</b>	<b>PT003003</b>
Title	A Randomized, Double-Blind, Parallel Group 14-Day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil Aerolizer (12 mcg, Open-Label) as Evaluated by Holter Monitoring in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease
Study dates	May 31, 2011 – November 21, 2011
Study report	November 22, 2013
Sites	15 sites in Australia, New Zealand, and the U.S.

This was a randomized, double-blind, parallel group, 14-day study to evaluate the safety of twice daily dosing of GFF 36/9.6 mcg, GP 36 mcg, and FF 9.6 mcg compared to Foradil 12 mcg in patients with moderate to severe COPD. The study design is depicted in the figure below.

**Figure 14. Study Design Schematic: PT003003**



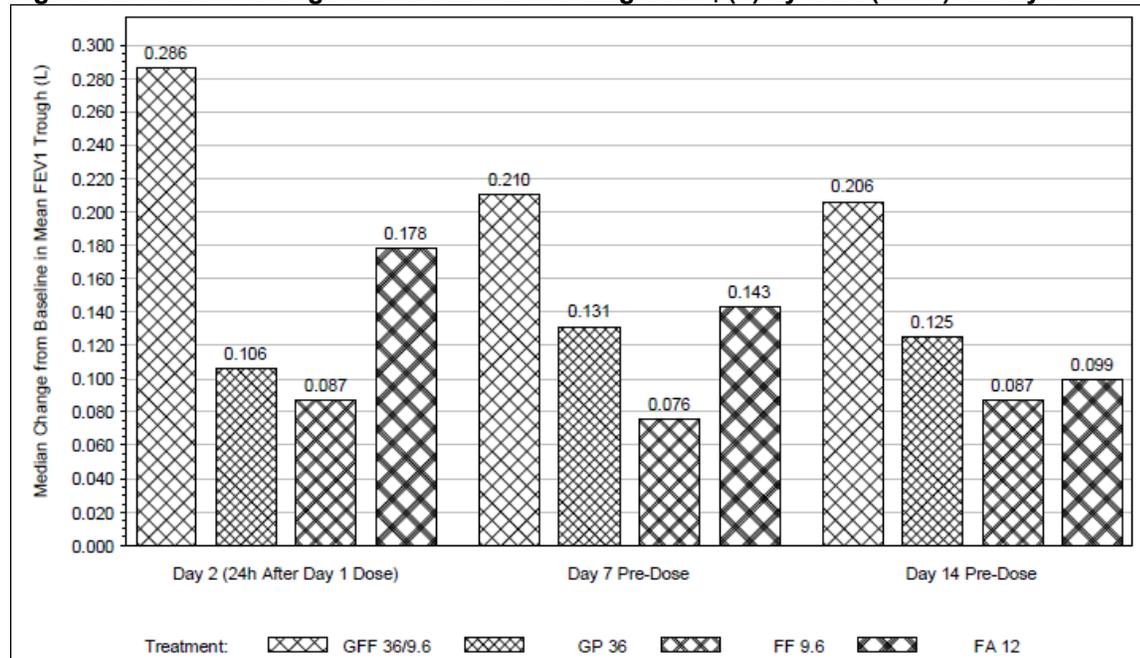
Source: Study protocol PT003003, version 3.0, Section 4.1, p22

A total of 237 patients were randomized to one of four treatments in the study, and of those 230 (97%) completed the 14-day study. The safety population included all patients who received at least one dose of study treatment and had any safety data after starting treatment. The mITT population included all patients who received at least one dose of study medication and had at least one evaluable pre-dose FEV<sub>1</sub> spirometry assessment at baseline and on Day 7 or 14. The primary and secondary safety endpoints in the study were based on 24-hour Holter monitor assessments obtained after the first dose of study treatment on Day 1 and on Day 14 in the safety population. Although statistically significant differences between treatments were observed for some heart rate parameters, the estimated mean changes from baseline in the mean, maximum, minimum, day-time, and night-time heart rate ranged from a 2 beat per minute (bpm) decrease to a 1 bpm increase in any one treatment group, minimal changes which are not clinically meaningful. Regarding ECG parameters, including QTcF changes relative to baseline, there were no apparent differences between treatment groups. Treatment groups were similar with regard to the occurrence of ectopic ventricular and supraventricular events. Tachycardia occurred more frequently than bradycardia; however, the number of bradycardia episodes was numerically higher in the GP-containing treatment groups (GFF and GP). The incidence of cardiac adverse events was more frequent among patients receiving GFF compared to other treatments; the most common reports being tachycardia and asymptomatic ventricular asystole. Three patients met Holter monitoring withdrawal criteria for ventricular asystole of ≥ 2.5 sec duration (GFF) and type II 2<sup>nd</sup> degree AV block (GP); all events were asymptomatic.

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All treatment groups demonstrated improvements in pre-dose trough FEV<sub>1</sub> from baseline by Day 7 of the 14-day treatment period with the greatest treatment effects observed for GFF. For the GFF, FF, and Foradil groups, maximal effect was attained by Day 2, while the maximal effect for the GP group was achieved on Day 7 (Figure 15).

**Figure 15. Median Change from Baseline in Trough FEV<sub>1</sub> (L) by Visit (mITT): Study PT003003**

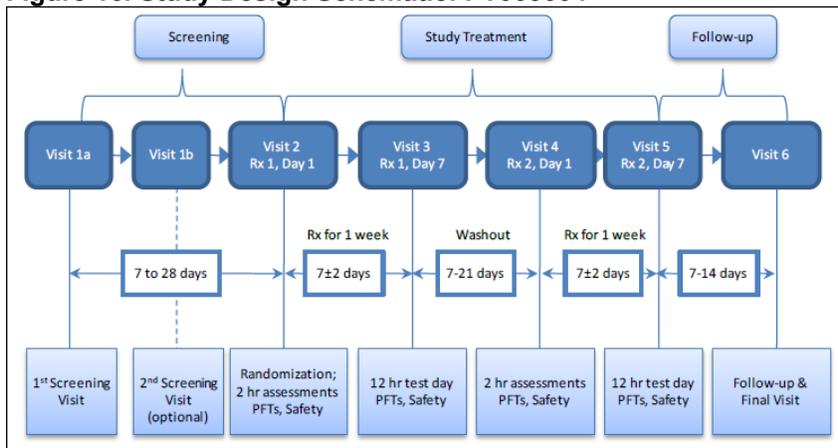


Source: CSR PT003003, Figure 4, p122

Study Number	PT003004
Title	A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared with Its Individual Components (FF MDI and GP MDI) as Active Control
Study dates	July 6, 2011 – November 19, 2011
Study report	December 17, 2013
Sites	14 sites in the U.S.

This was a randomized, double-blind, 7-day incomplete crossover study evaluating four doses of GFF (36/7.2, 36/9.6, 18/9.6, 18/7.2 mcg BID) compared to monocomponents GP 36 mcg BID and FF 9.6 mcg BID in patients with moderate to severe COPD. A schematic of the study design is shown in Figure 16.

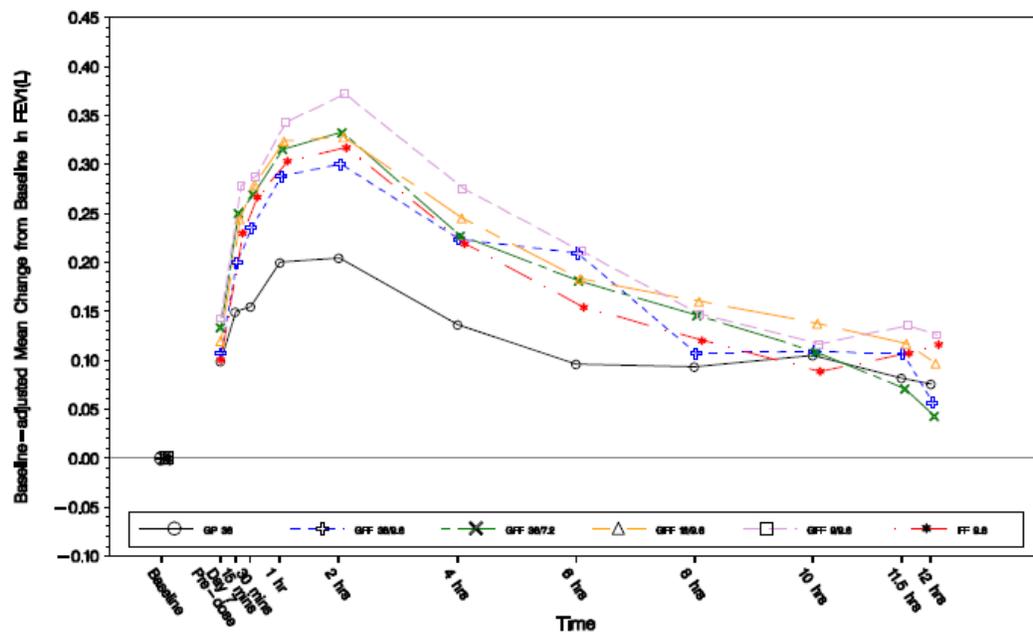
**Figure 16. Study Design Schematic: PT003004**



Source: CSR PT003004, Figure 1, p27

A total of 185 patients were randomized and treated in the study, 155 (84%) of whom completed the study. Efficacy analyses were based on the mITT population, consisting of 146 (79%) patients, defined as those who completed at least two treatment periods with pre-dose data on Day 1 for both treatment periods, at least one pre-dose measurement on Day 7 for both treatment periods, and no significant protocol deviations. Analysis of the primary efficacy endpoint, FEV<sub>1</sub> AUC<sub>0-12</sub> after 7 days of treatment, demonstrated that all doses of GFF had statistically significant improvements compared to GP. However, there was no clear dose response with regard to GFF dose groups or clear difference between GFF and FF dose groups (Figure 17 and Figure 18).

**Figure 17. Adjusted Mean Change from Baseline in FEV<sub>1</sub> (L) Over Time (mITT): Study PT003004**



Source: CSR, Figure 3, p92

**Figure 18. Adjusted Mean FEV<sub>1</sub> AUC<sub>0-12</sub> (L) on Treatment Day 7 (mITT): PT003004**

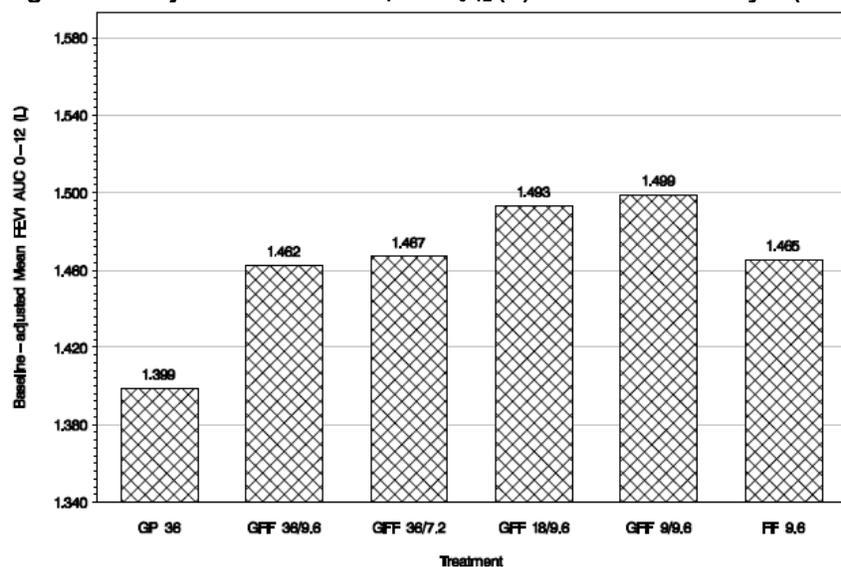


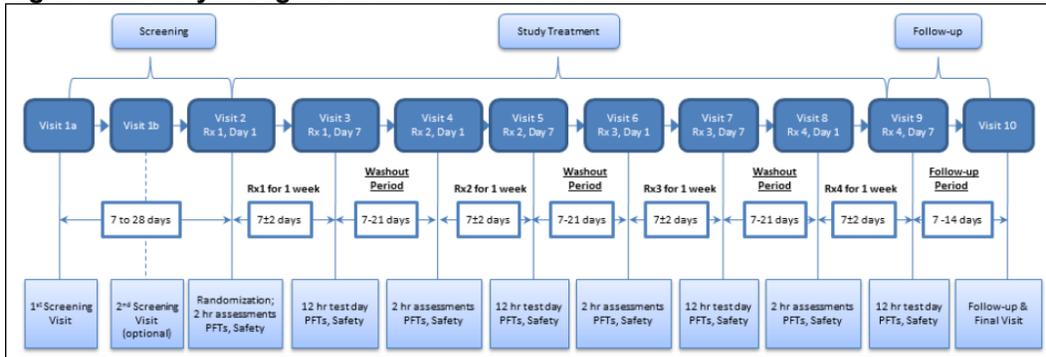
Figure depicts geometric means, the exponentiated values of the LSMeans for FEV<sub>1</sub> AUC<sub>0-12</sub> on the log scale.

Source: CSR PT003004, Figure 2, p91.

Study Number	PT003005
Title	A Randomized, Double-Blind, Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared with Spiriva Handihaler (Tiotropium Bromide 18 mcg) as Active Control
Study dates	May 11, 2012 – September 21, 2012
Study report	December 17, 2013
Sites	20 sites in the U.S.

This was a randomized, double-blind, 7-day, 4-period incomplete crossover study evaluated five doses of GFF (18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6, and 1.2/9.6 mcg), FF 9.6 mcg, and GP 18 mcg in patients with moderate to severe COPD compared with open-label SHH 18 mcg QD as an active control. The study was designed to evaluate varying doses of GP on a background of a fixed FF dose compared to FF to assess the incremental benefit of each successive GP dose. In addition, the study assessed the incremental benefit of each GFF dose compared to GP and SHH monotherapy. A study schematic is shown in Figure 19 below.

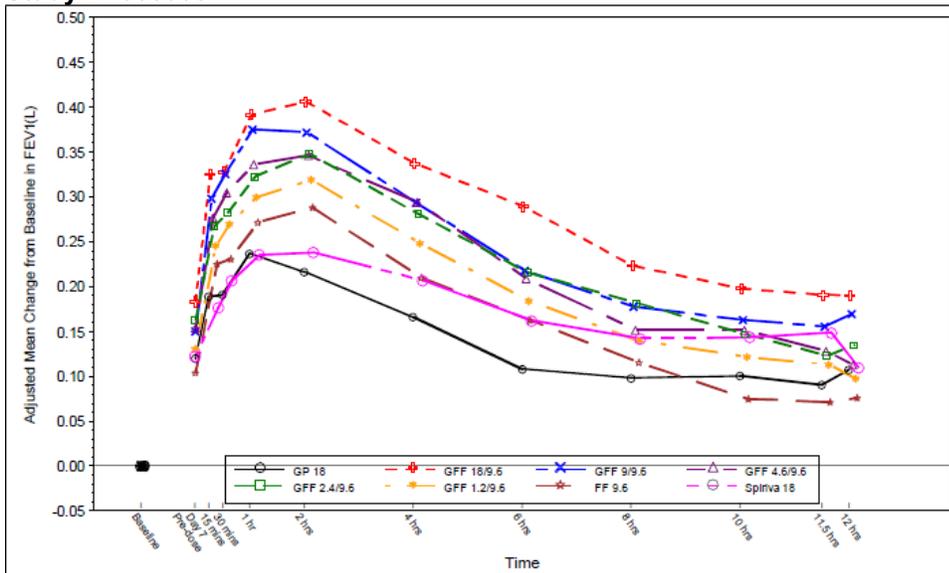
**Figure 19. Study Design Schematic: PT003005**



Source: CSR PT003005, Figure 1, p31

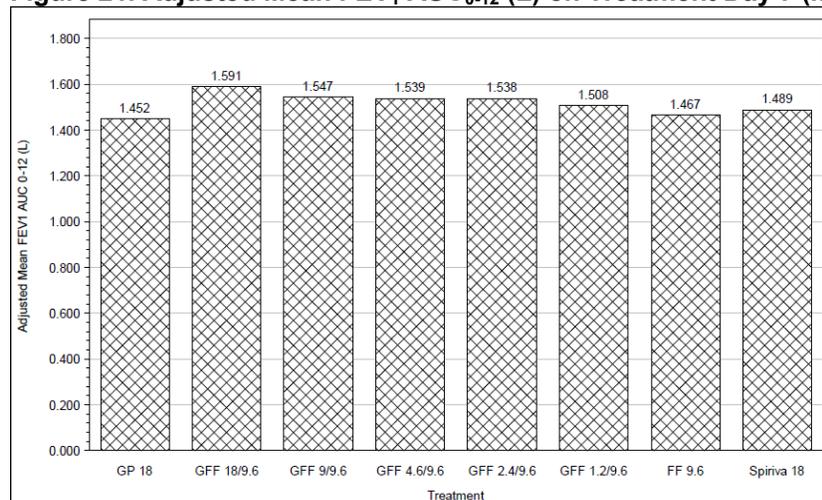
A total of 159 patients were randomized and treated in the study, 120 (76%) of whom completed the study. Efficacy analyses were based on the 132 (83%) patients in the mITT population, defined as subjects who completed at least two treatment periods with at least one pre-dose assessment on Days 1 and 7 of both treatment periods and 2 hours post-dosing on Day 7 for each treatment period. For analysis of the primary efficacy endpoint, FEV<sub>1</sub> AUC<sub>0-12</sub> on Day 7, in the mITT population, GFF 18/9.6 mcg demonstrated statistically significant differences over the monocomponents GP 18 mcg and FF 9.6 mcg (Figure 20 and Figure 21). Although the dose response relationship was relatively flat, there were numerical increases in the FEV<sub>1</sub> response with increasing GFF doses.

**Figure 20. Adjusted Mean Change from Baseline in FEV<sub>1</sub> (L) Over Time on Treatment Day 7 (mITT): Study PT003005**



Source: CSR PT003005, Figure 2, p100

Figure 21. Adjusted Mean FEV<sub>1</sub> AUC<sub>0-12</sub> (L) on Treatment Day 7 (mITT): Study PT003005



Source: CSR PT003005, Figure 3, p101

#### 4.4.3 Pharmacokinetics

The recommendation from the clinical pharmacology review team is Approval. (see NDA 208-294 clinical pharmacology review by Drs. Sheetal Agarwal and Yunzhao Ren)

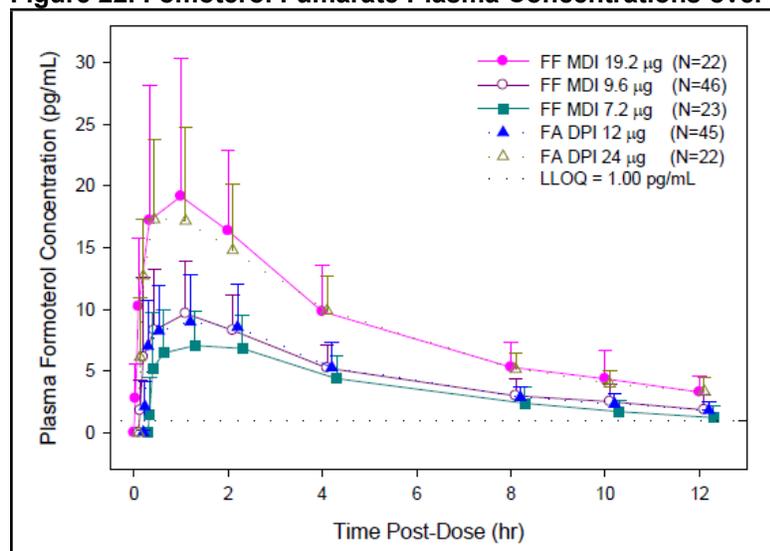
The submission includes a clinical pharmacology program evaluating GFF, GP, FF predominantly in COPD patients but also healthy volunteers.

##### Absorption

GP: Following inhalation in patients with COPD, peak concentrations ( $C_{max}$ ) occurred achieved at 5 minutes. Linear increases in systemic exposure was observed at GP doses 18-144 mcg, and mean half-life ranged from 5-10 hours. Based on the terminal elimination half-life of glycopyrrolate derived with the population PK model, steady state levels are expected to be achieved within 2-3 days of repeated twice daily dosing (i.e., 5 half-lives) with extent of exposure ~2.3 times higher than after the first dose.

FF: Following inhalation in patients with COPD, peak concentrations ( $C_{max}$ ) occurred within 20 to 60 minutes. Linear increases in systemic exposure was observed at FF doses 2.4-12 mcg, and mean half-life was approximately 12 hours. Based on the population PK model, steady state levels of FF are expected to be achieved within 2-3 days of repeated twice daily dosing (i.e., 5 half-lives) with extent of exposure ~1.5 times higher than after the first dose. FF 9.6 mcg demonstrated a comparable PK profile to Foradil Aerolizer 12 mcg (Figure 22). Comparable systemic exposure was observed between FF 19.2 mcg and Foradil 24 mcg. Patients with severe and very severe COPD may have 38% slower absorption than patients with moderate COPD according to the population PK model.

Figure 22. Fomoterol Fumarate Plasma Concentrations over Time, Study PT005003



Source: CSR PT005003, Figure 15, p117

### Distribution

GP: Based on population PK analyses, the estimated  $V_c/F$  (volume of the central compartment), and  $V_2/F$  (volume of the peripheral compartment) are 951 L and 2019 L, respectively.

FF: Based on population PK analyses, the estimated  $V_c/F$  and  $V_2/F$  are 948 L and 434 L, respectively. Over the concentration range of 10-500 nmol/L, plasma protein binding of formoterol ranged from 46% to 58%. The concentrations of formoterol used to assess the plasma protein binding were higher than those achieved in plasma following inhalation of a single 54 mcg dose.

### Metabolism

GP: Based on published literature, metabolism plays a minor role in the overall elimination of glycopyrrolate.

FF: Metabolism primarily occurs by direct glucuronidation and by O-demethylation (mainly via CYP2D6 and CYP2C9) followed by conjugation to inactive metabolites. Secondary metabolic pathways include deformylation and sulfate conjugation.

### Elimination

GP: Following IV administration of 0.2 mg radiolabeled glycopyrrolate, 85% of the dose was recovered in urine at 48 hours with some radioactivity recovered in the bile. The terminal elimination half-life derived from population PK analysis was 11.8 hours.

FF: The excretion of formoterol was studied in four healthy subjects following simultaneous administration of radiolabeled formoterol via the oral and IV routes. In that study, 62% of the radiolabeled formoterol was excreted in the urine while 24% was eliminated in the feces. The terminal elimination half-life derived from population PK analysis was 11.8 hours.

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#### Drug Interactions

No formal drug-drug interaction studies were performed for GP or FF.

#### Special Populations

Population PK analyses demonstrated no significant effect of sex, race/ethnicity, or body weight on the PK of either GP or FF. An analysis performed by the Agency's pharmacometrics reviewer Dr. Ren demonstrated that glycopyrrolate CL/F in elderly COPD adults ( $\geq 65$  years) was approximately 30% lower than that of younger COPD adults. Age did not have significant effect on formoterol clearance.

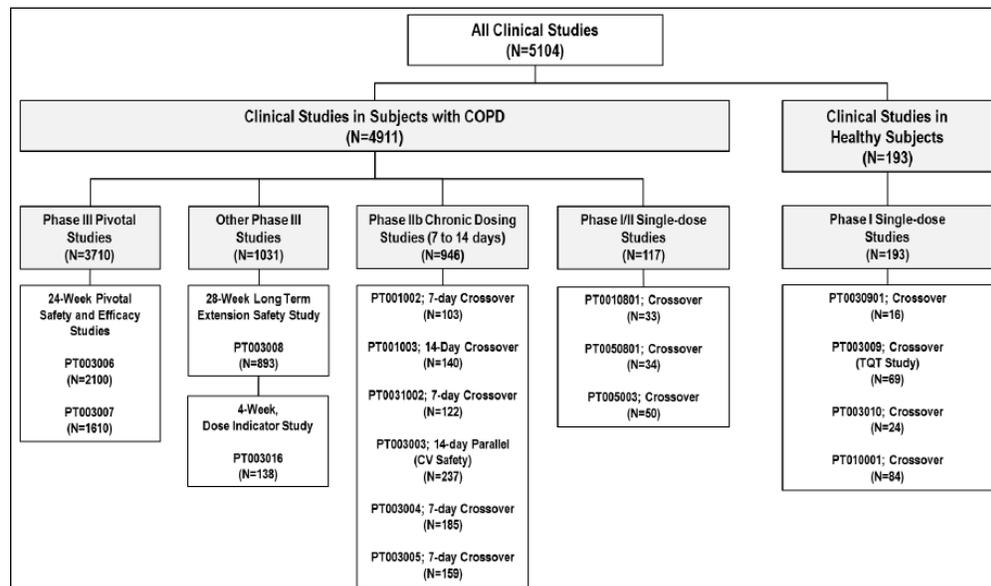
Population PK analyses performed by Dr. Ren also showed that subjects with moderate (45 mL/min) and severe (22.5 mL/min) renal impairment had 31% and 51% lower glycopyrrolate CL/F, respectively, than subjects with normal renal function (94.2 mL/min). The Applicant's population PK analysis of formoterol demonstrated that COPD subjects with moderate renal impairment (45 mL/min) had about 31% lower CL/F than COPD subjects with normal renal function (94.2 mL/min). No dose adjustment will be required for patients with mild to moderate renal impairment; however, the clinical pharmacology team recommends product labeling state that GFF only be used in patients with severe renal impairment or end-stage renal disease if the benefits outweigh the risks since the systemic exposure of GP in this population may be increased.

#### Thorough QT/QTc Study (PT003009)

This study evaluated suprathreshold doses of GFF (144/38.4 mcg) and GP 144 mcg in healthy volunteers to account for potential accumulation at steady state. It is discussed in Section 7.4.5. (also see NDA 208-294 review by the Interdisciplinary Review Team dated September 22, 2015)

## 5 Sources of Clinical Data

Figure 23. Overview of Clinical Development Program for GFF



Abbreviations: COPD=chronic obstructive pulmonary disease; CV=cardiovascular; FF=Formoterol Fumarate; GFF=Glycopyrronium and Formoterol Fumarate; GP=Glycopyrronium; MDI=metered dose inhaler; TQT=Thorough QT/QTc.

Note: The N values include subjects administered any treatment, including GFF MDI, GP MDI, FF MDI, Placebo MDI, Spiriva, and Foradil.

Note: The number of subjects in Study PT003008 (893 subjects) was not included in the total number of subjects for Clinical Studies in Subjects with COPD and All Clinical Studies because these subjects were captured in the counts for Studies PT003006 and PT003007.

Source: ISS, Figure 1-1, p19

### 5.1 Tables of Studies/Clinical Trials

All of the studies and trials listed in the table below evaluated COPD patients, primarily with moderate to severe/very severe disease with the exception of study PT010801 which also included patients with mild COPD.

Trial (dates)	Design	Treatment (mcg)	N	Duration	Primary Endpoint(s)	Sites (countries)
<b>Phase 2 dose selection studies for FF</b>						
PT0050801 (11/08-5/09)	R, DB, PC, AC, XO	FF 2.4 bid FF 4.8 bid FF 9.6 bid FA 12 bid (OL) PBO bid	34	Single dose, 5-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	5 sites (AU, NZ)
PT005003 (5/11-7/11)	R, DB, PC, AC, XO	FF 7.2 bid FF 9.6 bid FF 19.2 bid FA 12 bid (OL) FA 24 bid (OL) PBO bid	50	Single dose, 6-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	3 sites (US)
<b>Phase 2 dose selection for GP</b>						
PT0010801 (4/09-8/09)	R, DB, PC, AC, XO	GP 18 bid GP 36 bid GP 72 bid GP 144 bid SHH 18 qi (OL) PBO bid	33	Single dose, 4-periods	Peak FEV <sub>1</sub> relative to baseline	6 sites (US)

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Trial (dates)	Design	Treatment (mcg)	N	Duration	Primary Endpoint(s)	Sites (countries)
PT001002 (5/11-10/11)	R, DB, PC, AC, XO	GP 0.6 bid GP 1.2 bid GP 2.4 bid GP 4.6 bid GP 9 bid GP 18 bid AV 34 quid (OL) PBO bid	103	7 days, 3-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	9 sites (US)
PT001003 (4/12-8/12)	R, DB, PC, AC, XO	GP 0.6 bid GP 1.2 bid GP 2.4 bid GP 4.6 bid GP 9 bid GP 18 bid SHH 18 qd (OL) PBO bid	140	14 days, 4-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	10 sites (US)
<b>Phase 2 dose selection for GFF</b>						
PT0031002 (3/10-10/10)	R, DB, PC, AC, XO	GFF 36/9.6 bid GP 36 bid FF 9.6 bid FA 12 bid (OL)	118	7 days, 4-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	15 sites (AU, NZ, US)
PT003003 (5/11-11/11)	R, DB, PG, AC	GFF 36/9.6 bid GP 36 bid FF 9.6 bid FA 12 bid (OL)	237	14 days	Change from baseline in 24-hour mean heart rate	15 sites (AU, NZ, US)
PT003004 (7/11-11/11)	R, DB, XO	GFF 9/9.6 bid GFF 18/9.6 bid GFF 36/7.2 bid GFF 36/9.6 bid GP 36 bid FF 9.6 bid	185	7 days, 2-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	14 sites (US)
PT003005 (5/12-9/12)	R, DB, AC, XO	GFF 1.2/9.6 bid GFF 2.4/9.6 bid GFF 4.6/9.6 bid GFF 9/9.6 bid GFF 18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL)	159	7 days, 4-periods	Change from baseline in FEV <sub>1</sub> AUC <sub>0-12</sub>	20 sites (US)
<b>Phase 3 pivotal efficacy and safety trials</b>						
PT003006 (6/13-2/15)	R, DB, PC, AC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL) PBO bid	527 451 452 453 220	24 weeks	Change from baseline trough FEV <sub>1</sub> at 24 weeks	160 sites (US, AU, NZ)
PT003007 (7/13-2/15)	R, DB, PC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid PBO bid	512 440 439 224	24 weeks	Change from baseline trough FEV <sub>1</sub> at 24 weeks	140 sites (US)
<b>Phase 3 long term extension study</b>						
PT003008 (11/13-12/14)	R, DB, AC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL)	290 219 213 171	28 weeks	Long term safety	205 sites (US, AU, NZ)
Abbreviations: AC=active control, AU=Australia, AV=Atrovent, bid=twice daily, COPD=chronic obstructive pulmonary disease, DB=double blind, FA=Foradil Aerolizer, FF=formoterol fumarate, GFF=glycopyrrolate and formoterol fumarate, GP=glycopyrrolate, NZ=New Zealand, OL=open label, PBO=placebo, PC=placebo controlled, PG=parallel group, qd=once daily, qid=four times daily, R=randomized, SHH=Spiriva HandiHaler, US=United States, N=ITT						

## 5.2 Review Strategy

The focus of this review is on the clinical development program conducted in support of GFF 18/9.6 mcg twice daily that is proposed for use as a bronchodilator in patients with COPD. Data to support the selection of dose and dosing interval carried into the phase 3 program have already been reviewed in Section 4.4.2. Therefore, the remainder of this clinical review addresses the data presented in support of efficacy in Section 6 and then safety in Section 7. The phase 3 program primarily consists of two pivotal efficacy and safety trials, PT003006 and PT003007, along with the extension study PT003008 which, because it lacked a placebo control, will only be considered for purposes of the review of safety.

## 5.3 Discussion of Individual Studies/Clinical Trials

Given the similarity of the two pivotal efficacy and safety trials, the studies are discussed jointly with differences in the protocols noted where relevant. For the remainder of the review, trials will be referred to by the last 4 digits of the study number (e.g., 3006).

### PT003006 and PT003007

Study Number	PT003006
Title	A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo and Spiriva Handihaler (Tiotropium Bromide 18 mcg, Open-Label) as an Active Control
Study dates	June 6, 2013 – February 19, 2015
Study report	May 18, 2015
Sites	160 sites in Australia, New Zealand, and the U.S.
Study Number	PT003007
Title	A Randomized, Double-Blind, Chronic Dosing (24 Weeks), Placebo-Controlled, Parallel Group, Multi-Center Study to Assess the Efficacy and Safety of PT003, PT005, and PT001 in Subjects with Moderate to Very Severe COPD, Compared with Placebo
Study dates	July 9, 2013 – February 25, 2015
Study report	May 27, 2015
Sites	140 sites in the U.S.

### Amendments

The Applicant amended each protocol on two occasions. A summary of the major changes contained within each protocol amendment are provided below.

Amendment #1 (dated November 6 and 11, 2013, for trials 3006 and 3007, respectively)

- Increased the sample size from 1400 to 1751 subjects in trial 3006 and from 1200 to 1376 subjects in trial 3007 to provide additional power for comparing treatment group response at individual visits
- Revised the list of study objectives and endpoints to provide consistency with the statistical analysis plan and “other” efficacy endpoints added (analyses over

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weeks 12-24 and time to treatment failure). No edits were made to change the specification of primary or secondary endpoints

- Modified eligibility criteria for clarity and consistency
- Changed analyses of TDI and SGRQ to the ITT not the symptomatic population
- Revised covariates for analyses of COPD exacerbations
- Removed time to death analysis
- Stated that no AEs will be reported prior to randomization and AEs will not be summarized by exposure time
- Added non-inferiority margin for GP compared to Spiriva Handihaler in trial 3006

Amendment #2 (dated September 11, 2014, for both trials)

- Changed primary efficacy endpoint from change from baseline in morning pre-dose trough FEV<sub>1</sub> over week 12 to 24 to change at week 24
- Increased sample size to 2054 subjects in trial 3006 and 1614 subjects in trial 3007 in order to provide 90% power to demonstrate differences on the new primary endpoint
- Secondary endpoints, peak FEV<sub>1</sub> and SGRQ changed from “over 24 weeks” to “at week 24”
- Changes made for consistency with the SAP
- Modified text to differentiate exacerbation events and calculation of treatment exposure as per FDA recommendations

### Objectives

The primary objective of the study was to compare the efficacy of treatment with GFF MDI, FF MDI, and GP MDI to placebo MDI and to compare the efficacy of GFF MDI to its components on lung function using trough FEV<sub>1</sub> in subjects with moderate to very severe COPD. Secondary objectives were to compare the treatment effects on dyspnea using the Transition Dyspnea Index (TDI) focal score; quality of life using the change in St. George Respiratory Questionnaire (SGRQ) score; symptoms using the change in rescue Ventolin HFA use; time to onset of action on Day 1; and in trial 3006 only, the efficacy of GFF and GP versus Spiriva in terms of change in trough FEV<sub>1</sub>. Exploratory objectives included an evaluation of the treatment effects on PFTs, COPD exacerbations, and subject diary reports of nighttime awakenings, morning and evening rescue Ventolin HFA use, breathlessness, cough, and sputum production.

### Study Design

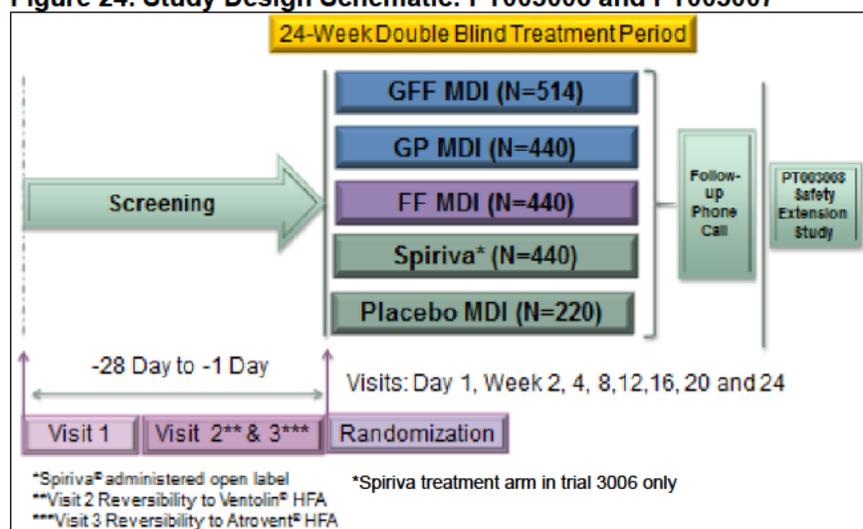
These were 24-week multicenter, randomized, double-blind, parallel group studies with placebo controls designed to assess the efficacy and safety of GFF, GP, and FF MDIs. Trial 3006 had an additional active control arm consisting of open-label Spiriva Handihaler (SHH). Both trials incorporated two sub-studies: 12-hour PFT and PK sub-studies in trial 3006 and 12-hour PFT and 24-hour Holter monitor sub-studies in trial 3007.

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After providing informed consent and undergoing an initial screening visit to determine eligibility, patients entered a 4-week screening period. During the screening period, subjects used sponsor-provided Atrovent QID and Ventolin PRN to control symptoms while undergoing a washout of previous maintenance medications; however, subjects were allowed to continue ICS and/or PDE inhibitors at the same dose. After an adequate washout period, subjects returned to clinic for Visit 2 to determine reversibility of FEV<sub>1</sub> to Ventolin HFA; the spirometry data obtained at this visit were used for the purposes of the inclusion criteria. At Visit 3, reversibility to Atrovent HFA was evaluated; spirometry data from this visit was used to characterize the population but not to determine eligibility. At Visit 4, subjects who continued to meet entry criteria including eDiary compliance >70% and FEV<sub>1</sub> reproducibility criteria were randomized in a 7:6:6:(6):3 ratio to the following treatment arms: GFF, GP, FF, (open-label SHH, trial 3006 only), or placebo. Blinded study medication was administered as two puffs twice daily, while open-label SHH was administered as two inhalations once daily in the morning. Patients continued allowed COPD maintenance medications (ICS, theophylline, or phosphodiesterase-4 inhibitors) throughout the study. A short-acting  $\beta$ 2-adrenergic agonist, Ventolin HFA, was provided as rescue medication for use as needed during the trial. Clinic visits occurred every 2 to 4 weeks during the trial (Figure 24). Subjects who completed Visit 11a at week 24 may have been invited to participate in the safety extension study (PT003008). Subjects who did not participate in the safety extension study received a post-study follow-up phone call at least 14 days after Visit 11a.

Figure 24. Study Design Schematic: PT003006 and PT003007



Source: Clinical Trial Protocol PT003006, Version 3.0, Figure 1, p42

### Patient Population

A total of 2054 and 1614 patients with moderate to very severe COPD were to be randomized into trials 3006 and 3007, respectively, to provide approximately 1650 and 1300 completers for each respective study. Individual study sites were expected to

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contribute 10 to 20 patients each. Note that the protocol for each study was amended to increase the final sample size.

Key Inclusion Criteria

1. Age 40 to 80 years at Visit 1
2. Established clinical history of COPD as defined by ATS/ERS<sup>6</sup> and characterized by airflow limitation that is not fully reversible and progressive airflow limitation associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking
3. Spirometric criteria as follows:
  - a. FEV<sub>1</sub>/FVC < 0.7 at Visits 1, 2, 3, and 4 (pre- and post-bronchodilator measurements at Visits 2 and 3)
  - b. FEV<sub>1</sub> < 80% predicted (as per NHANES III reference equations) and ≥ 750 mL if FEV<sub>1</sub> < 30% predicted at Visits 1 and 2 (post-bronchodilator measurement at Visit 2)
  - c. Average of -60 minute and -30 minutes pre-dose FEV<sub>1</sub> assessments < 80% predicted (as per NHANES III reference equations)
4. Current or former smokers with a history of at least 10 pack-years of cigarette smoking (pack-years = number of cigarettes per day/20 x number of years smoked)
5. Acceptable screening clinical laboratory tests, ECG, and chest X-ray or CT within 6 months prior to Visit 1 (as determined by the Investigator)
6. Women of child-bearing potential with a negative pregnancy test at Visit 1 and agreement to use acceptable contraceptive methods for the duration of the study

Key Exclusion Criteria

1. Significant disease other than COPD which in the opinion of the Investigator may put the patient at risk because of participation in the study or may influence the study results
2. Pregnancy or lactation
3. Asthma, alpha-1 antitrypsin deficiency, or other active pulmonary disease (e.g. active pulmonary tuberculosis, lung cancer, bronchiectasis, sarcoidosis, IPF, primary pulmonary hypertension, uncontrolled sleep apnea)
4. Lung volume reduction surgery, lobectomy or bronchoscopic lung volume reduction within 1 year of Visit 1
5. Poorly controlled COPD
  - a. Hospitalization within 3 months prior to Visit 1 or during the screening period
  - b. Acute worsening requiring treatment with oral corticosteroids or antibiotics within 6 weeks prior to Visit 1 or during the screening period

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<sup>6</sup> Celli BR, MacNee W, Agusti A, et.al., Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004; 23 (6):932-46.

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- c. Stable doses of 5 mg/day or 10 mg every other day of prednisone or equivalent allowed (stable dose for at least 3 months prior to Visit 1 and during the screening period)
6. Lower respiratory tract infection requiring antibiotics within 6 weeks prior to Visit 1 or during the screening period
7. Long-term oxygen therapy or nocturnal oxygen therapy for greater than 12 hours/day
8. Use of non-invasive positive pressure ventilation device (CPAP and BiPAP for sleep apnea syndrome allowed)
9. Change in smoking status or initiation of smoking cessation program within 6 weeks of Visit 1 and throughout screening
10. Inability to perform acceptable, repeatable, or reproducible spirometry, according to ATS criteria
11. Participation in the acute phase of a pulmonary rehabilitation program within 4 weeks prior to Visit 1 or will enter the acute phase of a program during the study.
12. Initiation or alteration of intranasal corticosteroid or antihistamine dose regimens within 7 days of Visit 1 or during screening
13. Unstable ischemic heart disease, left ventricular failure, or documented myocardial infarction within 12 months of enrollment
14. Acute coronary syndrome, percutaneous coronary intervention, or coronary artery bypass graft within past 3 months
15. Congestive heart failure (NYHA Class III/IV)
16. Clinically significant abnormal ECG
  - a. Conduction abnormalities (e.g., left bundle branch block, Wolff-Parkinson-White syndrome, second or third degree AV block)
  - b. Arrhythmias (e.g., atrial fibrillation with irregular ventricular response, atrial flutter, ventricular tachycardia; clinically stable atrial fibrillation treated with anticoagulation and rate control for at least 6 months allowed)
  - c. QTcF > 450 ms for males and > 470 ms for females at Visit 1 and on repeat testing at Visit 2
  - d. Ventricular rate < 45 bpm
  - e. Pathological Q waves  $\leq$  1 year duration compared to screening
  - f. ST-T wave abnormalities deemed clinically significant by the Investigator
  - g. Any other abnormalities deemed clinically by the Investigator
17. Uncontrolled hypertension
18. Seizures requiring anticonvulsants within 12 months prior to Visit 1 (Treatment with anticonvulsant medication for 12 months or more with no seizure events allowed)
19. SSRI or SNRI dose that has not been stable for at least 4 weeks prior to Visit 1 or during screening period
20. Clinically significant symptomatic prostatic hypertrophy or trans-urethral resection of the prostate or full resection of the prostate within 6 months prior to Visit 1
21. Clinically significant bladder neck obstruction or urinary retention
22. Creatinine clearance  $\leq$  50 mL/minute at Visit 1 and on repeat testing prior to Visit 2 (calculated using Chronic Kidney Disease Epidemiology Collaboration formula)

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23. Uncontrolled hypo- or hyperthyroidism, hypokalemia, or hyperadrenergic state
24. Uncontrolled Type I or Type II diabetes
25. Abnormal liver function tests defined as AST, ALT, or total bilirubin  $\geq 1.5$  times upper limit of normal at Visit 1 and on repeat testing prior to Visit 2
26. Cancer that has not been in remission for at least 5 years (squamous cell carcinoma of the skin, basal cell carcinoma of the skin, or localized prostate cancer could be allowed)
27. Inadequately treated glaucoma
28. History of hypersensitivity to  $\beta$ -2 agonists, glycopyrronium or other muscarinic anticholinergics, lactose/milk protein, or any component of the MDI
29. Significant alcohol or drug abuse in the opinion of the Investigator
30. Inability to withhold short-acting bronchodilators for the required 6-hour period prior to spirometry testing at each study visit
31. Inability to abstain from protocol-defined prohibited medications during screening and treatment phases of the study
32. Vaccination with live attenuated vaccine within 30 days prior to Visit 1 or during screening period (inactivated vaccination  $>48$  hours prior to Visit 1 or 4 allowed)
33. Noncompliance with diary completion ( $< 70\%$  completion in the last 7 days preceding Visit 4)
34. History of psychiatric disease, intellectual deficiency, poor motivation, substance abuse, or other conditions that limit validity of informed consent
35. Affiliation with Investigator site or previous enrollment in any trial conducted or sponsored by Pearl Therapeutics, Inc.
36. Poor hand-to-breath coordination requiring use of a spacer device with an MDI
37. Treatment with investigational study drug or device in another clinical trial within the last 30 days or five half-lives prior to Visit 1

Additional exclusion criteria for 24-hour Holter monitor sub-study in trial 3007

1. Pacemaker or implantable cardioverter-defibrillator (ICD)/cardiac resynchronization therapy (CRT)/cardiac resynchronization therapy-defibrillator (CRT\_D) devices
2. Clinically significant abnormalities on baseline Holter monitor recording
  - a. Average HR  $\leq 40$  bpm for any 1 hour
  - b. Second-degree AV block (Type 2) or third-degree AV block
  - c. Sinus pause  $> 2.5$  sec during day or  $> 3$  sec during night
  - d. Any episode of ventricular flutter and/or ventricular fibrillation
  - e. Any episode of non-sustained ventricular tachycardia (VT) with symptoms of hypotension or syncope or asymptomatic non-sustained VT  $> 15$  ventricular premature beats in a row
  - f. Sustained VT  $> 30$  seconds in duration
  - g. Five or more episodes of non-sustained VT / 24 hours
  - h.  $> 500$  ventricular premature beats/hr

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### Concomitant and Prohibited Medications

The following table lists prohibited and permitted concomitant medications along with the required washout periods.

**Table 3. Prohibited and Permitted Medications**

Drug Class	Minimum washout period
<b>Cessation prior to Visit 1</b>	
Depot corticosteroids (including intra-articular, intraocular)	3 months
Systemic corticosteroids (oral, IV, IM) <sup>1,2</sup>	6 weeks
QT prolongating drugs	14 days or 5 half-lives
Investigational drugs	30 days or 5 half-lives
Non-selective beta-blocking agents	7 days
Cardiac antiarrhythmics Class Ia, III	7 days (amiodarone 3 months)
Tricyclic antidepressants	14 days
Monoamine oxidase inhibitors	14 days
TNF- $\alpha$ inhibitors	30 days or 5 half-lives
Monoclonal antibodies	30 days or 5 half-lives
Antipsychotic drugs <sup>3</sup>	30 days
Systemic calcineurin inhibitors, systemic antifungal agents, protease inhibitors, and cimetidine	30 days
Systemic anticholinergics <sup>4</sup>	7 days
<b>Cessation prior to Visit 2</b>	
Long-acting anticholinergics <sup>5</sup>	14 days
Short-acting anticholinergics <sup>5</sup>	6 hours
SABA <sup>6</sup>	6 hours
Fixed combination SABA and short-acting anticholinergics <sup>5,6</sup>	6 hours
LABA <sup>6</sup>	48 hours (indacaterol 7 days)
Fixed combination LABA/ICS <sup>6,7</sup>	7 days
Theophylline <sup>8</sup>	7 days
Leukotriene modifiers	7 days
Cromoglycate	7 days
Nedocromil	7 days
Ketotifen <sup>9</sup>	7 days
<b>Conditionally permitted medications</b>	
Anticonvulsants for seizures	Allowed if stable dose and seizure free for 12 months
Anticonvulsants for other indications	Allowed if stable dose for 3 months and seizure free for 12 months
SSRIs or SNRIs	Allowed if stable dose (not to exceed recommended dose) for 4 weeks prior to Visit 1 and during screening period
Intranasal corticosteroids and/or antihistamines	Allowed if stable dose for 7 days prior to Visit 1 and during screening
Medical marijuana	Allowed if used for medicinal purposes at a stable dose and frequency of consumption
PDE4 inhibitors	Allowed if stable dose for 2 months prior to randomization
Abbreviations: SABA=short-acting beta agonist, LABA=long-acting beta agonist, ICS=inhaled corticosteroid, SSRI=	

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selective serotonin reuptake inhibitors, SNRI= serotonin-norepinephrine reuptake inhibitors, PDE4= phosphodiesterase 4

<sup>1</sup>Maintenance treatment with prednisone (or equivalent)  $\leq 5$  mg/day or  $\leq 10$  mg every other day allowed as long as dose is stable for at least 3 months prior to Visit 1 and remains stable during screening

<sup>2</sup>Systemic corticosteroid treatment allowed during study treatment period (Visits 4 – 11a)

<sup>3</sup>Use for other indications may have been allowed

<sup>4</sup>Stable use (> 1 month) for treatment of overactive bladder allowed

<sup>5</sup>Subjects switched to sponsor-provided Atrovent HFA MDI administered QID prn at Visit 1

<sup>6</sup>Subjects switched to sponsor-provided Ventolin HFA Q4 hours prn at Visit 1

<sup>7</sup>Subjects switched to corresponding ICS monotherapy BID at Visit 1 if maintenance dose had been stable for 4 weeks prior

<sup>8</sup>Total daily doses  $\leq 400$  mg allowed

<sup>9</sup>Eye drops allowed

Source: Clinical trial protocol PT003006, version 3.0, Section 5.4

### Treatments

Subjects were randomized to one of four blinded treatment arms or to an open label active control treatment arm (trial 3006 only).

- Glycopyrrolate (glycopyrronium bromide): 36 mcg daily delivered as 2 puffs (9 mcg per actuation) BID via MDI
- Formoterol fumarate: 19.2 mcg daily delivered as 2 puffs (4.8 mcg per actuation) BID via MDI
- Glycopyrrolate/formoterol fumarate: 36/19.2 mcg daily delivered as 2 puffs (9/4.8 mcg per actuation) BID via MDI
- Placebo: 2 puffs BID via MDI
- Tiotropium bromide: 18 mcg daily delivered as 1 capsule via the Handihaler DPI (open-label; trial 3006 only)

Subjects were instructed to inhale blinded study medication twice daily, 2 puffs in the morning between 6 a.m. and 10 a.m. and 2 puffs in the evening between 6 p.m. and 10 p.m. approximately 12 hours apart. Subjects randomized to open-label tiotropium (SHH) were instructed to inhale the contents of 1 capsule once daily in the morning approximately 24 hours apart according to manufacturer's instructions for use.

Open-label albuterol (Ventolin HFA MDI) inhalation aerosol (90 mcg per actuation) was supplied at Visit 1 for rescue use during the screening and treatment periods. Patients were instructed to record the number of inhalations of rescue medication used during the daytime and nighttime in the eDiary. Open-label ipratropium bromide (Atrovent HFA MDI) inhalation aerosol (17 mcg per actuation) was supplied at Visit 1 for maintenance treatment (2 puffs QID) during the screening period.

Treatment compliance was assessed at each clinic visit through review of electronic diaries.

### Efficacy Assessments

#### Pulmonary Function Testing Procedures

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Spirometry was conducted at Visit 1. Reversibility was evaluated at Visit 2 to Ventolin HFA and at Visit 3 to Atrovent HFA; spirometry was conducted 60 and 30 minutes prior to bronchodilator administration (4 puffs) and at 30 minutes post-bronchodilator. Reversibility was based on a comparison of the average best FEV<sub>1</sub> effort obtained at -60 minutes and -30 minutes pre-bronchodilator to the best FEV<sub>1</sub> effort obtained 30 minutes post-bronchodilator. Reversibility was defined as a post-bronchodilator FEV<sub>1</sub> treatment response of ≥ 12% and ≥ 200 mL. During the study treatment period, spirometry was conducted 60 minutes and 30 minutes prior to study drug administration at each visit (Visits 4 – 11a) as well as 15 and 30 minutes, and 1 and 2 hours post-dose at Visits 4, 5, 7, 8, 10, and 11a (Day 1 and Weeks 2, 8, 12, 20, and 24). An additional spirometry measurement was obtained at 5 minutes post-dose during Visit 4 (Day 1). The mean of the -60 and -30 minute pre-dose spirometry assessments at Visit 4 (Day 1) was used as the baseline spirometry measurements for FEV<sub>1</sub>, FVC, FEF<sub>25-75</sub>, and PEFR. To ensure that the baseline measurement was stable and accurately reflective of patient population COPD severity, the baseline FEV<sub>1</sub> measurements at Visit 4 was required to be within ± 20% or 200 mL of the mean of the pre-dose FEV<sub>1</sub> obtained at the two preceding visits. For the subset of subjects participating in the 12-hour PFT sub-study, additional spirometry assessments were obtained at 4, 6, 8, 10, 11.5, and 12 hours post-dosing at Visits 4 and 8 (Day 1 and Week 12).

**Table 4. Timing of Assessments for 12-hour PFT and PK Sub-Studies: 3006 and 3007**

Clinical Variable <sup>a</sup>	Pre-dosing		Post-dosing												
	-60 min	-30 min	2 min	5 min	15 min	20 min	30 min	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	11.5 hr	12 hr
BDI/TDI <sup>b</sup>	X <sup>†</sup>														
SGRQ <sup>b</sup>	X <sup>†</sup>														
Review of Electronic Diary Data	X <sup>†</sup>														
Vital Signs <sup>c</sup>	X						X		X						X
12-Lead ECG <sup>d</sup>	X						X		X						X
Clinical Laboratory Testing <sup>e</sup>	X <sup>†</sup>														
Spirometry (FEV <sub>1</sub> , FVC, PEFR) <sup>f</sup>	X <sup>g</sup>	X <sup>g</sup>		X <sup>h</sup>	X		X	X	X	X	X	X	X	X	X
PK Sample Collection		X	X	X		X		X	X	X		X	X		X
Study Drug Collection <sup>i</sup>	X <sup>†</sup>														
Record Dose Indicator Reading <sup>g</sup>		X													
Study Drug Dispensing <sup>k</sup>															X

- a. In clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs, and ECG) should be started approximately 5 - 10 minutes ahead of the specified timepoint to ensure that spirometry for FEV<sub>1</sub>, FVC and PEFR assessments will be conducted as close to the specified timepoints as possible (ie, FEV<sub>1</sub>, FVC, and PEFR assessments need to be conducted within ± 15 minutes of specified time prior to study drug administration; ± 5 minutes of specified time for the first 60 minutes post study drug administration; ± 15 minutes of specified timepoint for assessments obtained thereafter).
- b. When BDI/TDI and SGRQ are obtained at the same visit BDI/TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures. BDI/TDI will be obtained at all visits except Visit 5 (Week 2). SGRQ will be obtained at Visit 4 (Day 1), Visit 8 (Week 12) Visit 9 (Week 16), Visit 10 (Week 20), Visit 11a (Week 24) or Premature Discontinuation Visit.
- c. At Visit 4 only, pre-dose vital signs will be collected twice at least five minutes apart. Temperature will be obtained pre-dose; no further temperature assessments required unless clinically indicated.
- d. At Visit 4 only, pre-dose ECG will be collected twice at least five minutes apart.
- e. Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 4 (Day 1) and Visit 8 (Week 12).
- f. Post-dose spirometry assessment will be obtained at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).
- g. To be randomized, all subjects must meet reproducibility criteria. Refer to Section 7.1.1.2 for additional details.
- h. The 5-minute post-dose spirometry assessment will be obtained at Visit 4 (Treatment Day 1) only.
- i. At the start of each treatment visit, subject must withhold all COPD medications, including study medication, rescue Ventolin HFA and ICS for at least 6 hours prior to start of test day procedures.
- j. Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Section 7.1.5 for more details.
- k. Dispense study drug to subject following completion of all post-dose assessments. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing.
- † This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

Note: When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, PK and spirometry.

Source: Clinical trial protocol PT003006, version 3.0, Table 11, p87

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**Table 5. Schedule of Events for 24-hour Holter Monitoring Sub-study: 30007**

Procedures	Screening Period			Treatment Period		
	Visit 3	Visit 3b	Visit 3c	Visit 6	Visit 6b	Visit 6c
24-Hour Holter Monitoring (1 <sup>st</sup> Attempt)	X <sup>a</sup>			X <sup>b</sup>		
Removal of 24-Hour Holter Monitor (1 <sup>st</sup> Attempt) <sup>c</sup>		X			X	
24-Hour Holter Monitoring (2 <sup>nd</sup> Attempt) <sup>d</sup>		X <sup>d</sup>			X <sup>d</sup>	
Removal of 24-Hour Holter Monitor (2 <sup>nd</sup> Attempt) <sup>e</sup>			X <sup>e</sup>			X <sup>e</sup>

- Attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the post-dose spirometry assessments.
- Attach Holter monitoring device and initiate 24-hour Holter Monitor recording following the pre-dose spirometry assessments but 15-30 minutes prior to the administration of the morning dose of study medication.
- Site personnel will determine the acceptability of Holter monitor recording.
- If the Holter monitor recordings fail to meet adequate quality criteria (acceptable tracings for a minimum of 18 hours) on the first attempt, a second attempt will be made for another 24 hours using a new Holter monitor hook-up kit.
- No further attempts will be allowed if the second attempt is unacceptable.

**Note:** Subjects can proceed to Visit 4 (Randomization) or Visit 7 (Week 8) provided no clinically significant findings (as defined in Section 5.2.1 and Section 5.7.1) are reported by iCardiac following review of the Holter monitor recordings.

Source: Clinical trial protocol PT003007, version 3.0, Table 12, p94

### Subject Electronic Diary

Subjects received an eDiary to record study medication administration, morning and evening symptoms (cough, shortness of breath, sputum volume, nighttime awakenings), and use of rescue medication (Ventolin HFA) twice daily during the screening period and for the duration of the treatment period. The eDiary data were reviewed by study personnel at each visit. Subjects were encouraged to complete > 70% of eDiary assessments. Rescue medication use was captured in eDiary entries as number of puffs. Medication compliance was assessed by subject eDiary recordings for the time of dosing with study medication for each day of at-home treatment. To evaluate the accuracy, reliability, and functionality of the dose indicator, subjects also recorded the dose indicator reading from their first MDI over the first 4 weeks of use (for blinded study drug treatment arms only). At each visit, the site staff compared the dose indicator reading from the prior evening entered in the eDiary with the dose indicator reading recorded by the site staff; major discrepancies were reviewed with the subject.

### Subject Questionnaires

#### *Baseline and Transition Dyspnea Indices (BDI and TDI)*

The BDI and TDI instruments assess breathlessness in components related to functional impairment, magnitude of task and magnitude of effort. In this study, the self-administered computerized version was used which includes an initial practice question related to tiredness that is not included in the overall score; screenshots are shown in Appendix 9.4. The BDI score ranges from 0 (very severe impairment) to 4 (no impairment) for each domain that are then added to determine the BDI focal score (0-12 with lower scores indicating worse severity). TDI components are change in functional impairment, change in magnitude of task, and change in magnitude of effort. The TDI score ranges from -3 (major deterioration) to +3 (major improvement) for each domain. The sum of all components yields the TDI focal score (-9 to +9, with lower scores indicating greater deterioration in dyspnea severity). The BDI was completed at Visit 4 (Day 1) prior to study drug administration. The TDI was completed at weeks 4, 8, 12, 16, 20, and 24 or the Premature Discontinuation Visit. Per protocol, subjects were to

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complete the BDI/TDI prior to administration of study drug and prior to completion of the St. George's Respiratory Questionnaire (SGRQ).

#### *St. George's Respiratory Questionnaire (SGRQ)*

The electronic version of the SGRQ contains 50 items divided into three domains: symptoms, activity, and impacts. Scores were calculated for each component and to obtain a total score ranging from 0 to 100 with lower scores indicating less impairment in quality of life. The SGRQ was completed by subjects at Visit 4 (Day 1) and at weeks 12, 16, 20, and 24 or the premature discontinuation visit. Two different versions of the SGRQ were used across regions: in the US, responses were based on a 1-month recall while in Australia and New Zealand responses were based on a 3-month recall. The minimal clinically important difference (MCID) for SGRQ is generally considered to be -4. A copy of the SGRQ is provided in Appendix 9.4.

#### *COPD Assessment Test and Modified Medical Research Council Dyspnea Scale*

In addition to the TDI and SGRQ, two questionnaires, the COPD Assessment Test (CAT) and the Modified Medical Research Council (MMRC) Dyspnea Scale, were administered at Visit 2 and used to describe the burden and symptomatic impact of COPD in enrolled subjects; the results were not used to determine subject eligibility or to assess efficacy of treatment. The COPD Assessment Test (CAT) is a self-administered questionnaire designed to assess the condition of subjects and overall impact of COPD. The CAT has moderate correlations with other instruments such as the MMRC dyspnea scale, SGRQ, and the 6-minute walk test. The Modified Medical Research Council (MMRC) Dyspnea Scale uses a 5-point grading system to assess a subject's level of dyspnea, shortness of breath. Copies of the questionnaires are provided in Appendix 9.4.

#### COPD Exacerbations

Exacerbations were an exploratory endpoint. An exacerbation was defined as a change in the patient's baseline dyspnea, cough, and/or sputum (increase in volume or change in color towards purulence) that lasted 3 or more days, was beyond normal day-to-day variations, was acute in onset and may have warranted a change in regular medication. COPD exacerbations were captured in the COPD Exacerbation eCRF, but were not reported as AEs unless considered an SAE. The severity of COPD exacerbations were classified as follows:

- Mild: exacerbations that did not require systemic steroids or antibiotics and did not result in hospitalization or death
- Moderate: exacerbations that required treatment with systemic steroids and/or antibiotics and did not result in hospitalization or death
- Severe: exacerbations that resulted in hospitalization or death

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**Table 6. Timing of Assessments during Treatment Period (Visits 4-11): Studies 3006 and 3007**

Clinical Variable <sup>a</sup>	Pre-dosing		Post-dosing				
	-60 minutes	-30 minutes	5 minutes	15 minutes	30 minutes	1 hour	2 hours
BDI/TDI <sup>b</sup>	X <sup>c</sup>						
SGRQ <sup>b</sup>	X <sup>c</sup>						
Review of Electronic Diary Data	X <sup>c</sup>						
Vital Signs <sup>e</sup>	X				X		X
12- Lead ECG <sup>d</sup>	X <sup>d</sup>				X		X
Clinical Laboratory Testing <sup>g</sup>	X <sup>c</sup>						
Spirometry (FEV <sub>1</sub> , FVC, PEFR) <sup>f</sup>	X <sup>g</sup>	X <sup>g</sup>	X <sup>h</sup>	X	X	X	X
Study Drug Collection <sup>i</sup>	X <sup>c</sup>						
Record Dose Indicator Reading <sup>j</sup>		X <sup>i</sup>					
Study Drug Dispensing <sup>k</sup>							X

- <sup>a</sup> In clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs, and ECG) should be started approximately 5 - 10 minutes ahead of the specified timepoint to ensure that spirometry for FEV<sub>1</sub>, FVC and PEFR assessments will be conducted as close to the specified timepoints as possible (ie, FEV<sub>1</sub>, FVC, and PEFR assessments need to be conducted within ± 15 minutes of specified time prior to study drug administration; ± 5 minutes of specified time for the first 60 minutes post study drug administration; ± 15 minutes of specified timepoint for assessments obtained thereafter)
- <sup>b</sup> When BDI/TDI and SGRQ are obtained at the same visit BDI/TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures. BDI/TDI will be obtained at all visits except Visit 5 (Week 2). SGRQ will be obtained at Visit 4 (Day 1), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11a (Week 24) or Premature Discontinuation Visit
- <sup>c</sup> At Visit 4 only, pre-dose vital signs will be collected twice at least five minutes apart. Vital signs will be obtained within one hour pre-dosing and at 30 minutes post study drug administration at all treatment visits. At all visits post randomization except Visit 6 (Week 4) and Visit 9 (Week 16) only, vital signs will be obtained at 2 hours post study drug dosing. Temperature will be obtained pre-dose, no further temperature assessments are required unless clinically indicated.
- <sup>d</sup> At Visit 4 only, pre-dose ECG will be collected twice at least five minutes apart. An ECG will be obtained pre-dose and at 30 minutes and 2 hours post-dose at Visit 4 (Day 1), Visit 5 (Week 2), Visit 8 (Week 12), and Visit 11a (Week 24). At Visit 6 (Week 4), only a pre-dose ECG will be obtained.
- <sup>e</sup> Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 4 (Day 1), Visit 6 (Week 4), Visit 8 (Week 12) and Visit 11a (Week 24) only.
- <sup>f</sup> Post-dose spirometry assessment will be obtained at all visits except Visit 6 (Week 4) and Visit 9 (Week 16).
- <sup>g</sup> To be randomized, all subjects must meet reproducibility criteria. Refer to Section 7.1.1.2 for additional details.
- <sup>h</sup> The 5-minute post-dose spirometry assessment will be obtained at Visit 4 (Treatment Day 1) only.
- <sup>i</sup> At the start of each treatment visit, subject must withhold all COPD medications, including study medication, rescue Ventolin HFA and ICS for at least 6 hours prior to start of test day procedures.
- <sup>j</sup> Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Section 7.1.5 for more details
- <sup>k</sup> Dispense study drug for at home use to subject following completion of all post-dose assessments. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing
- <sup>l</sup> This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.

**Note:** When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Source: Clinical trial protocol PT003006, version 3.0, Table 10, p86

## Safety Variables

Safety assessments included physical examinations, vital signs, 12-lead ECG, pregnancy testing, clinical laboratory testing, AEs and SAEs. In addition, 24-hour Holter monitoring was obtained at Visits 3 and 6 during trial 3007. A representative schedule for obtaining efficacy and safety assessments from trial 3006 is shown in

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**Table 7. Schedule of Assessments in 3006 and 3007**

Procedures	Screening Period			Treatment Period									Follow-Up 14 days Post-Dose
	Visit 1	Visit 2	Visit 3	Visit 4 Day 1	Visit 5 Week 2	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12	Visit 9 Week 16	Visit 10 Week 20	Visit 11a Week 24	Discon Visit	
Study Day/Week <sup>a</sup>	Day -28 to -9	Day -21 to -2	Day -19 to -1	Day 1	Wk 2 ±2Days <sup>a</sup>	Wk 4 ±2Days <sup>a</sup>	Wk 8 ±2Days <sup>a</sup>	Wk 12 ±2Days <sup>a</sup>	Wk 16 ±2Days <sup>a</sup>	Wk 20 ±2Days <sup>a</sup>	Wk 24 ±2Days <sup>a</sup>		
Obtain Informed Consent	X												
Review Incl/Excl Criteria	X	X	X	X									
Verify Continued Eligibility					X	X	X	X	X	X	X		
Reversibility <sup>b</sup>		X	X										
Demographics & Medical/Surgical History	X	X	X	X									
Smoking Status	X	X	X	X	X	X	X	X	X	X	X		
COPD Assessment Test (CAT) <sup>c</sup>		X											
MMRC <sup>c</sup>		X											
Prior/Concomitant Medications <sup>d</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Spirometry <sup>e</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Examination <sup>f</sup>	X										X	X	
Vital Signs <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG <sup>h</sup>	X	X	X	X	X	X		X			X	X	
Pregnancy Test <sup>i</sup>	X							X			X	X	
Clinical Laboratory Testing <sup>j</sup>	X			X		X		X			X	X	
Chest X-ray <sup>k</sup>	X												
Adjust COPD Medications <sup>l</sup>	X										X	X	
COPD Exacerbations and Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X
Inhalation Device Training <sup>m</sup>	X												
Study Drug Dispensing/Collection	X <sup>n</sup>			X		X	X	X	X	X	X	X	X
Study Drug Administration <sup>o</sup>				X	X	X	X	X	X	X	X	X	X
BDI/TDI <sup>p</sup>				X		X	X	X	X	X	X	X	X
SGRQ <sup>q</sup>				X				X	X	X	X	X	X
eDiary Training <sup>r</sup>	X												

Procedures	Screening Period			Treatment Period									Follow-Up 14 days Post-Dose
	Visit 1	Visit 2	Visit 3	Visit 4 Day 1	Visit 5 Week 2	Visit 6 Week 4	Visit 7 Week 8	Visit 8 Week 12	Visit 9 Week 16	Visit 10 Week 20	Visit 11a Week 24	Discon Visit	
Review of Electronic Diary <sup>s</sup>		X	X	X								X	
PK Assessments (PK Sub-study) <sup>t</sup>				X				X					
Review/Record Dose Indicator Reading <sup>u</sup>				X	X	X	X	X	X	X	X	X	
HCRU <sup>v</sup>					X	X	X	X	X	X	X	X	
Telephone Contact <sup>w</sup>		X	X	X	X	X	X	X	X	X	X	X	X

- <sup>a</sup> **Scheduling visits:** The maximum Screening Period is 28 days; the earliest a subject can be randomized from Visit 1 Date is 9 Days (7 days for LABA washout plus 1 day between Visit 2 and Visit 3) or 16 days if subject is washing off of tiotropium; Site should make every effort to maintain subjects within the scheduled visit window. Subjects who fall outside the visit window will be placed in the appropriate visit window at the next scheduled visit.
- <sup>b</sup> Subjects will be tested for reversibility to albuterol (Ventolin HFA) at Visit 2 and reversibility to Atrovent HFA at Visit 3; Refer to Section 7.1.1.1 for additional details
- <sup>c</sup> CAT and MMRC will be used to characterize the subject population only and not to be used to determine eligibility to participate in the study
- <sup>d</sup> At all visits beyond Visit 1 (Screening), note time of last dose of short-acting bronchodilator and other COPD medications (if <6 hours, visit should be rescheduled).
- <sup>e</sup> Refer to Section 7.1.1 for spirometry assessments and specific timepoints to be performed at each treatment visit.
- <sup>f</sup> Includes evaluation of weight at Visit 1 (Screening) and Visit 11a (Final Visit) and height at Visit 1 (Screening) only.
- <sup>g</sup> Refer to Section 7.2.2 for vital signs assessments and specific timepoints to be performed at each treatment visit. Weight will be obtained at Visit 1 (screening) and Visit 11a (Final Visit) only.
- <sup>h</sup> Refer to Section 7.2.3 for ECG assessments and specific timepoints to be performed at each treatment visit
- <sup>i</sup> Refer to Section 7.2.4 for clinical laboratory assessments (hematology, chemistry and urinalysis) and specific timepoints to be performed at each treatment visit. Serum pregnancy test will be performed at Visit 1 (Screening) and Visit 11a (Week 24) and a urine pregnancy test will be done at Visit 8 (Week 12).
- <sup>j</sup> Obtain a new Chest X-ray if Chest X-ray or CT performed within the 6 months prior to Visit 1 (Screening) is not available.
- <sup>k</sup> At Visit 1 (Screening), stop prohibited COPD medications and change COPD medications as specified in Section 5.4 (ie, Sponsor-provided Atrovent HFA with or without ICS). At the end of Visit 11a, return subject to pre-study or other appropriate inhaled maintenance COPD medications if the subject will not be participating in the safety extension study (Study PT003008).
- <sup>l</sup> Sites may use sponsor-provided Atrovent HFA or Ventolin HFA to train subjects on the use of MDIs
- <sup>m</sup> Sponsor-provided Atrovent HFA or Ventolin HFA is dispensed only after a subject is determined to be eligible to proceed to Visit 2 (ie, only if a subject meets COPD definition following spirometry assessments at screening).
- <sup>n</sup> In clinic dosing time is recorded as time of the second puff/inhalation. The in clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time if assigned to blinded treatment or 24±2 hours of the prior morning dosing time if assigned to Spiriva.
- <sup>o</sup> When BDI/TDI and SGRQ are obtained at the same visit BDI/TDI will be collected first followed immediately by SGRQ. These PROs must be completed by the subject prior to any other visit procedures.
- <sup>p</sup> Issue and train subjects on eDiary use only after a subject is determined to qualify to proceed to Visit 2
- <sup>q</sup> Refer to Section 7.1.2 for details of electronic diary review.
- <sup>r</sup> Refer to Section 7.2.5 for PK sample collection and specific timepoints to be performed at Visit 4 (Day 1) and Visit 8 (Week 12).
- <sup>s</sup> Refer to Section 7.1.5 for details and instructions on recording dose indicator readings.
- <sup>t</sup> Refer to Section 7.3 for details on HCRU collection.
- <sup>u</sup> 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 (eg, 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).
- <sup>v</sup> Note: When data collection time-points are concurrent, it is recommended that variables be collected in the following order: BDI/TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.

Source: Clinical trial protocol PT003006, version 3.0, Table 9, p85

## Efficacy Endpoints

### Primary endpoint

- Change from baseline (average of -60 and -30 minute measurements on Day 1/Visit 4) in morning pre-dose trough FEV<sub>1</sub> at Week 24

Secondary endpoints

- Change from baseline in morning pre-dose trough FEV<sub>1</sub> over 24 weeks
- Peak change from baseline in FEV<sub>1</sub> within 2 hours post-dosing at Week 24
- Change from baseline in SGRQ total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

Other efficacy endpoints

On Day 1

- Change from baseline at each post-dose time point in FEV<sub>1</sub> as well as FEV<sub>1</sub> AUC<sub>0-2</sub> and peak change from baseline in FEV<sub>1</sub>
- Proportion of subjects achieving an improvement from baseline in FEV<sub>1</sub> using different thresholds (e.g.,  $\geq 10\%$ ,  $\geq 12\%$ ,  $\geq 200$  mL, and  $\geq 12\%$  and  $\geq 200$  mL)

Over 24 weeks

- Rate of all COPD exacerbations
- Time to first COPD exacerbation of any severity
- Rate of moderate or severe COPD exacerbations
- Time to first moderate or severe COPD exacerbation
- Time to treatment failure
- Additional spirometry assessments over 24 weeks, over weeks 12 to 24, and at each post-randomization visit
  - Change from baseline in morning pre-dose trough for FEV<sub>1</sub>, FVC, PEF<sub>R</sub>, and FEF<sub>25-75</sub>
  - Peak change from baseline through 2 hours post-dose in FEV<sub>1</sub>, FVC, PEF<sub>R</sub>, and FEF<sub>25-75</sub>
  - FEV<sub>1</sub> AUC<sub>0-2</sub>, FVC AUC<sub>0-2</sub>, PEF<sub>R</sub>, AUC<sub>0-2</sub>, and FEF<sub>25-75</sub>, AUC<sub>0-2</sub>
- Percentage of days with “no rescue Ventolin HFA use”
- Percentage of nights with “no nighttime awakenings”
- Percentage of nights with “fewer than three nighttime awakenings”
- Percentage of days with “no daytime symptoms”
- Change from baseline in mean daily total symptom score as well as each individual symptom (cough, shortness of breath, sputum volume, nighttime awakenings, and Ventolin HFA use), the mean morning total and individual symptom scores, and the mean evening total and individual symptom scores over 24 weeks, over weeks 12 to 24, and over each 4-week interval of the 24 week treatment period
- Change from baseline at each post-randomization visit for SGRQ total score
- TDI focal score at each post-randomization visit
- Individual components of the TDI at each post-randomization visit
- Percentage of subjects achieving a MCID threshold of  $\geq 1$  unit in TDI
- Change in individual domain scores of SGRQ over 24 weeks and at each post-randomization visit
- Percentage of subjects achieving an MCID threshold of  $\geq 4$  units on average in SGRQ total score

### PFT Sub-Study Endpoints

#### Primary

- FEV<sub>1</sub> AUC<sub>0-12</sub> at Week 12

#### Additional

- Serial spirometry parameters including FEV<sub>1</sub> AUC<sub>0-6</sub>, FEV<sub>1</sub> AUC<sub>6-12</sub>, and peak change in FEV<sub>1</sub>
- FEV<sub>1</sub> AUC<sub>0-12</sub> on Day 1
- FVC, PEFR, and FEF<sub>25-75</sub> evaluated using AUC<sub>0-12</sub>, AUC<sub>0-2</sub>, and peak change from baseline
- Change from baseline in FEV<sub>1</sub>, FVC, FEF<sub>25-75</sub>, and PEFR at each post-dose time point through 12 hours post-dose including the change from baseline in 12-hour post-dose trough

### Health Care Resource Utilization Endpoints

- Number of days missed from work
- COPD-related and non-COPD related telephone calls and visits to healthcare providers
- ER visits
- Hospitalizations, including days in hospital, days in ICU, days in CCU
- Intubations

### Analysis Populations

- Intent to treat (ITT) population: all randomized subjects who received at least one dose of study treatment; analyzed according to assigned treatment
- Per protocol (PP) population: subset of ITT population with post-randomization data obtained prior to any major protocol deviations
- Symptomatic population: subset of ITT population with CAT scores of  $\geq 10$  at Visit 4
- Safety population: all randomized subjects who received at least one dose of study treatment; analyzed according to treatment received
- PK population: all randomized and treated subjects with sufficient data to reliably calculate at least one PK parameter, regardless of completion of both PK visits on Day 1 and week 12; analyzed according to treatment received

### Statistical Analyses

#### Primary efficacy endpoint

The primary analysis was conducted using the ITT population. The change from baseline in pre-dose trough FEV<sub>1</sub> was analyzed using a repeated measures (RM) linear model. Baseline was defined as the average of the non-missing -60 minute and -30 minute values obtained prior to dosing at Visit 4 (Day 1). The analysis of covariance (ANCOVA) model included baseline FEV<sub>1</sub> and reversibility to Ventolin HFA as continuous covariates; and visit, treatment, treatment by visit interaction, smoking status at baseline, and ICS use at baseline as categorical covariates. Two-sided p-values and

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point estimates with two-sided 95% confidence intervals (CI) were produced for each treatment difference. The comparison of GP MDI to SHH was for non-inferiority with a NI margin of 85 mL.

Secondary and other endpoints

*Spirometry endpoints*

Additional supportive analyses of morning pre-dose trough FEV<sub>1</sub> included change from baseline at week 24 and over the entire 24 week treatment period in the PP population, treatment differences over weeks 12 to 24 and at individual time points estimated by the RM model, comparisons to SHH estimated from the RM model, and the analysis of weighted average (WAVE). WAVE was calculated as the weighted average change from baseline over 24 weeks (or over 12 to 24 weeks) using the exposure time represented by each clinic visit as the weights. It was analyzed using an ANCOVA with baseline and reversibility to Ventolin as continuous covariates and smoking status at baseline and ICS use at baseline as categorical covariates. Other spirometry endpoints such as change from baseline in FEV<sub>1</sub> AUC<sub>0-2</sub>, morning pre-dose trough FVC, PEFR, and FEF<sub>25-75</sub> were analyzed in a similar manner to the primary endpoint. The proportion of subjects achieving an improvement from baseline in FEV<sub>1</sub> on Day 1 during the first 2 hours post-dosing using different thresholds (e.g., ≥ 10%, 12%, 200 mL and 12% and 200 mL) was analyzed using logistic regression with baseline and reversibility to Ventolin as continuous covariates, and treatment, smoking status at baseline and ICS use at baseline as categorical covariates. P-values and odds ratios with 95% CI were produced for each treatment comparison.

*Peak FEV<sub>1</sub>*

The peak change from baseline in FEV<sub>1</sub> within 2 hours post-dosing at week 24 and over 24 weeks was analyzed similarly to the primary endpoint analysis.

*SGRQ*

The difference between treatment groups in the change from baseline in SGRQ at week 24 and over 24 weeks was evaluated using a similar RM approach as for the primary endpoint. The comparison of GP to SHH was for non-inferiority with a NI margin of 4.0. As additional supportive analyses, the difference between treatments at each of the individual visits, for each of the individual domains, and for responder rates (defined as an improvement of 4.0 points or more on average over the treatment period) were evaluated. Logistic regression was used to compare the treatment groups with baseline SGRQ and reversibility to Ventolin as continuous covariates; and treatment, smoking status at baseline, and ICS use at baseline as categorical covariates. P-values and odds ratios with 95% CI were produced for each treatment comparison. In addition to the ITT population, supportive analyses were conducted using the symptomatic and PP populations.

*Rescue medication use*

The mean daily number of puffs of rescue Ventolin was calculated overall and for each of the 4-week intervals during the treatment period. Diary data recorded during the last

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7 days of the screening period was used to calculate baseline. The differences between treatment groups in the change from baseline in rescue Ventolin use over 24 weeks, over each 4-week interval, over weeks 12 to 24, daytime rescue use, and nighttime rescue use were evaluated using a similar RM approach as for the primary endpoint. Instead of visit, the number of the relevant 4-week interval was used as a categorical covariate in the model. The comparison of GP to SHH was for non-inferiority with an NI margin of 1.0 puff.

Percentage of days with no rescue Ventolin use over 24 weeks was summarized by treatment and analyzed using ANCOVA as for the pre-dose FEV<sub>1</sub> WAVE described above, but with baseline average daily rescue Ventolin use as a covariate instead of baseline FEV<sub>1</sub>.

*Onset of action*

The onset of action was determined for each treatment using the 5 and 15 minute post-dosing FEV<sub>1</sub> assessments from Day 1. The onset of action for each product was defined as the first time point where the difference from placebo was statistically significant. Comparisons were performed using ANCOVA models similar to pre-dose FEV<sub>1</sub> WAVE.

*COPD exacerbations*

The rate of all COPD exacerbations of any severity was analyzed using negative binomial regression. COPD exacerbations were considered separate events if they were separated by 7 or more days. Exposure to the randomized medication was used as an offset variable. Treatment were compared adjusting for baseline percent predicted FEV<sub>1</sub>, baseline CAT score, baseline COPD exacerbations history, smoking status at baseline, season at baseline, and ICS use at baseline. The time to first COPD exacerbation of any severity was analyzed using Cox regression model for the ITT population. The model included treatment, baseline percent predicted FEV<sub>1</sub>, baseline COPD exacerbation history, baseline CAT score, smoking status at baseline, season at baseline, and ICS use at baseline. Subjects who did not experience an exacerbation were censored at the week 24 visit. Subjects who withdrew from the study without experiencing an exacerbation were censored at the date of the withdrawal. The rate of moderate and severe COPD exacerbations and the time to first moderate or severe exacerbation were analyzed similarly to the COPD exacerbations of any severity. Additional analyses of the rate of COPD exacerbations was performed with imputation of a moderate exacerbation at the time of dropout for subjects withdrawing prematurely from the study unless an exacerbation had already been recorded at that time.

*Time to treatment failure*

Treatment failure was defined as a moderate or severe COPD exacerbation or discontinuation from the study for any reason. The time to treatment failure was analyzed using a Cox regression model for the ITT population. The model included treatment, baseline percent predicted FEV<sub>1</sub>, baseline COPD exacerbation history, baseline CAT score, smoking status at baseline, season at baseline, and ICS use at

baseline. Subjects who did not experience a treatment failure were censored at week 24. Estimated hazard ratios along with 95% CI and p-values were calculated.

#### *Symptom scores*

The mean daily total symptom score, the mean morning symptom score, and the mean evening symptom score were calculated for each subject over each 4-week interval of the 24-week treatment period. The last 7 days of the screening period were used to calculate the baseline. The mean change from baseline in the daily, morning, and evening symptom scores were analyzed using a similar model as for the morning pre-dose trough FEV<sub>1</sub> to estimate treatment effects over 24 weeks and over weeks 12-24. The percentage of nights with no nighttime awakenings, fewer than 3 nighttime awakenings, and percentage of days with no daytime symptoms were analyzed over 24 weeks in the same manner as for pre-dose FEV<sub>1</sub> WAVE except with baseline average daily nighttime awakenings/daily daytime total symptom score as a covariate instead of baseline FEV<sub>1</sub>.

#### *Health Care Resource Utilization*

COPD- and non-COPD-related HCRU were summarized by treatment group.

#### Handling of missing data

If subjects were missing either of the pre-dose trough FEV<sub>1</sub> assessments, the value for that visit was calculated from the single measurement. If subjects were missing both pre-dose values, morning pre-dose trough FEV<sub>1</sub> at that visit was not calculated. For peak FEV<sub>1</sub>, subjects were included in the ITT analyses as long as they had at least one non-missing post-dose value during the first 2 hours post-dose. Missing data of the SGRQ total score was not imputed. For rescue Ventolin use, the denominator was adjusted based on the number of days (including half days) with non-missing values.

#### Control of Type I error

For GP and FF treatment comparisons to placebo, the Applicant controlled for Type I error in the US and other countries/regions where co-primary endpoints are not required by using a sequential approach for the primary endpoint and then within each comparison for the secondary measures used a combination of sequential and simultaneous approaches as depicted below.

- Primary endpoint: change from baseline in morning pre-dose trough FEV<sub>1</sub> at week 24
- Secondary endpoint #1: morning pre-dose trough FEV<sub>1</sub> over 24 weeks
- Secondary endpoint #2: peak FEV<sub>1</sub> at week 24
- Secondary endpoints #3-6: SGRQ at week 24, rescue Ventolin HFA use over 24 weeks, FEV<sub>1</sub> at 5 minutes post-dosing on Day 1, and FEV<sub>1</sub> at 15 minutes post-dosing on Day 1

For GFF, Type I error was controlled for all comparisons to placebo and components for FEV<sub>1</sub> as well as comparison to placebo for TDI using the following hierarchical sequence:

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→ If the comparisons of FF and GP to placebo were significant for the primary endpoint of morning pre-dose trough FEV<sub>1</sub>, then GFF was sequentially compared to placebo, FF, and GP using morning pre-dose trough FEV<sub>1</sub> using a two-sided alpha level of 0.05.

→ If significant, GFF was compared sequentially to placebo, and then GP for TDI using a two-sided alpha of 0.05.

→ If significant, GFF was compared sequentially to placebo, FF, and then GP for peak FEV<sub>1</sub> over 24 weeks using a two-sided alpha of 0.05

→ if significant, SGRQ over 24 weeks, rescue Ventolin HFA use over 24 weeks and FEV<sub>1</sub> at 5 and 15 minutes post-dose on Day 1 (vs placebo) were interpreted inferentially with a simultaneous control of Type I error within each comparison using the Hochberg procedure with a two-sided alpha level of 0.05.

→ If the comparisons of GFF to its components were significant for trough FEV<sub>1</sub>, GFF was compared to open-label SHH using two-sided alpha level of 0.05 for morning pre-dose trough FEV<sub>1</sub> and then TDI. After passing TDI in the hierarchical testing scheme, no further adjustment was made for multiplicity.

Safety endpoints

Summary statistics were performed for analyses of the safety endpoints in the safety population. Causes of death were determined by an adjudication committee.

**PT003008**

Study Number	PT003008
Title	A 28-Week, Multi-Center, Randomized, Double-Blind, Parallel-Group, Active-Controlled Safety Extension Study to Evaluate the Safety and Efficacy of PT003, PT001, and PT005 in Subjects with Moderate to Very Severe COPD, With Spiriva Handihaler as an Active Control
Study dates	November 19, 2013 – December 26, 2014
Study report	June 3, 2015
Sites	205 sites in Australia, New Zealand, and the U.S.

**Amendments**

There was one protocol amendment dated September 12, 2014. Major changes to the protocol included the following:

- Other efficacy endpoints added – time to treatment failure and percentage of days with no daytime symptoms
- Classification of COPD exacerbation severity was revised for consistency with the definitions in trials 3006 and 3007
- Removed inactivated and live attenuated vaccines as prohibited medications for eligibility
- Primary analyses of TDI and SGRQ to be conducted in the ITT rather than the symptomatic population
- Non-inferiority margin of GP to SHH for rescue medication use added
- Analysis of time to treatment failure added

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- Analyses of COPD exacerbations revised to reflect underlying data distribution and covariates revised to include CAT scores and remove reversibility to Ventolin
- Revisions to provide consistency with the SAP

**Objectives**

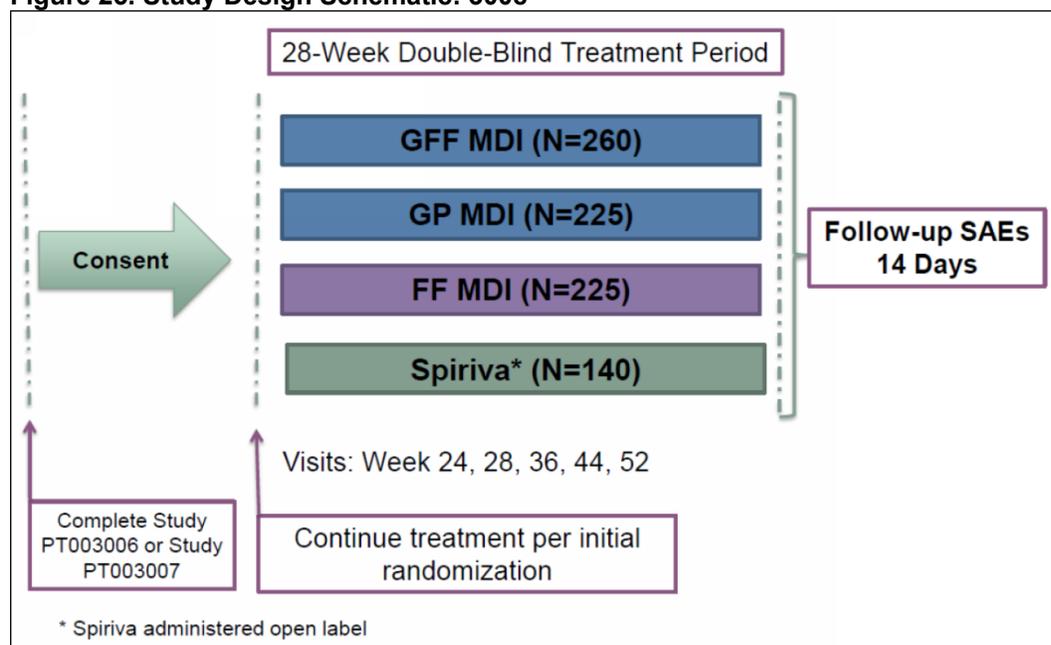
The primary objective was to evaluate the long-term safety and tolerability of GFF MDI 18/9.6 mcg BID, GP MDI 18 mcg BID, FF MDI 9.6 mcg BID, and SHH dry powder inhaler 18 mcg QD in subjects with moderate to very severe COPD over 52 weeks. The secondary objectives were to compare the efficacy of treatment with GFF to its components on lung function, dyspnea, quality of life, and symptoms over 52 weeks

**Study Design**

This was a 28-week multi-center, randomized, double-blind, parallel group extension study of trials 3006 and 3007. Spiriva Handihaler was included as an open-label active control arm. Subjects were randomly invited through the centralized IWRS to participate in the extension study, but subjects must have completed study 3006 or 3007 to be eligible. In this study, subjects remained on their treatment assigned from study 3006 or 3007. Because the extension study did not have a placebo control arm, subjects assigned to placebo in studies 3006 and 3007 were not invited to participate. Therefore, to maintain the blind, a proportion (10%) of subjects assigned to blinded active treatment in studies 3006 and 3007 were not invited to participate in the extension study until the targets for enrollment were met. All subjects in the SHH arm meeting the inclusion criteria were invited into the trial until target enrollment was achieved.

The last visit at week 24 of the lead-in studies was also the first visit of the extension study. To differentiate, the assessments conducted at the completion of studies 3006 and 3007 were captured as Visit 11a, and at the initial assessment of study 3008 as Visit 11b. Visit 11b began immediately after completion of Visit 11a procedures. All subjects who were eligible and willing to participate in study 3008 signed an informed consent form prior to conduct of any study assessments specific to the extension study. Following enrollment at Visit 11b (week 24), subjects attended four additional study visits at weeks 28, 36, 44, and 52. A study schematic is shown in the figure below.

**Figure 25. Study Design Schematic: 3008**



Source: Clinical trial protocol PT003008, version 2.0, Figure 1, p29

### Study Population

Approximately 850 subjects from trials 3006 and 3007 were to be enrolled in study 3008 to provide 700 subjects to complete the study.

### Inclusion Criteria

1. Provided written informed consent
2. Completed treatment phase of the lead-in study either PT003006 or PT003007
3. Compliance with Study PT003006 or Study PT003007 study procedures and study drug dosing
4. No medical contraindication as judged by the PI

### Exclusion Criteria

1. Requiring and currently being administered contraindicated medications

### Concomitant Medications

The permitted and prohibited medications for study 3008 were the same as for the lead-in studies.

### Treatments

With the exception of the placebo control arm, subjects continued the same treatments from trials 3006 and 3008, and dosing instructions remained unchanged.

## **Efficacy Assessments**

### Pulmonary Function Testing procedures

Spirometry measurements were obtained at 60 and 30 minutes prior to study drug administration at Visits 12 – 15 (weeks 28, 36, 44, and 52). Additional measurements were obtained at 15 minutes, 30 minutes, 1 and 2 hours post-dosing at Visits 13 and 15 (week 36 and 52). Because spirometry was conducted at the conclusion of the lead-in studies at Visit 11a, there were no spirometry measurements for the initial extension study visit (Visit 11b).

### Subject Electronic Diary

Subjects continued to use the eDiary provided during participation in the lead-in studies to record the time of study drug administration, morning and evening symptoms, use of rescue Ventolin, and dose indicator reading (for blinded treatment arms). Rescue Ventolin HFA use was recorded as total number of puffs used on a daily basis. Medication compliance was assessed at each clinic visit by checking the eDiary recordings. At each clinic visit, the dose indicator reading from the prior evening in the eDiary entered by the subject was compared to the dose indicator reading on the MDI recorded by the staff.

### Subject Questionnaires

Extension study 3008 utilized the same two questionnaires employed in the lead-in studies. The TDI was completed at all visits and the premature discontinuation visit. The SGQR was completed at Visits 13 and 15 (week 36 and 52) or the premature discontinuation visit.

### COPD Exacerbations

Exacerbations were defined and captured in the same manner as in studies 3006 and 3007.

## **Safety Variables**

Safety assessments included physical exam findings, pre- and post-dose vital signs, 12-lead ECGs, clinical laboratory tests, and recording of AEs and SAEs. Clinical labs included hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count), chemistry (albumin, alkaline phosphatase, total bilirubin, calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, GGT, glucose, total protein, AST, ALT, bicarbonate, and triglycerides), urinalysis, and pregnancy tests.

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**Table 8. Schedule of Assessments: PT003008**

Procedures	Treatment Period						Follow-Up 14 Days Post-Dose
	Visit 11b Week 24	Visit 12 Week 28	Visit 13 Week 36	Visit 14 Week 44	Visit 15 Week 52	Discon <sup>§</sup> Visit	
Study Day/Week <sup>a</sup>	Wk 24 ±7 Days	Wk 28 ±7 Days <sup>a</sup>	Wk 36 ±7 Days <sup>a</sup>	Wk 44 ±7 Days <sup>a</sup>	Wk 52 ±7 Days <sup>a</sup>		Wk 54 +7 Days <sup>a</sup>
Obtain Informed Consent	X						
Review Incl/Excl Criteria	X						
Verify Continued Eligibility		X	X	X	X		
Smoking Status		X	X	X	X		
Prior/Concomitant Medications <sup>b</sup>		X	X	X	X	X	X
Spirometry <sup>c</sup>		X	X	X	X		
Physical Examination					X	X	
Vital Signs <sup>d</sup>		X	X	X	X	X	
12-Lead ECG <sup>e</sup>			X		X	X	
Pregnancy Test <sup>f</sup>			X		X	X	
Clinical Laboratory Testing <sup>f</sup>			X		X	X	
Adjust COPD Medications <sup>g</sup>					X	X	
COPD Exacerbations and Adverse Events		X	X	X	X	X	X
Study Drug Dispensing/Collection	X	X	X	X	X	X	
Study Drug Administration <sup>h</sup>		X	X	X	X		
TDI <sup>i</sup>		X	X	X	X	X	
SGRQ <sup>i</sup>			X		X	X	
Review of Electronic Diary Data <sup>j</sup>		X	X	X	X	X	
Record Dose Indicator Reading <sup>k</sup>	X	X	X	X	X	X	
HCRU <sup>l</sup>		X	X	X	X	X	
Telephone Contact <sup>m</sup>		X	X	X	X		X

<sup>a</sup> **Scheduling visits:** All visits will be scheduled relative to Visit 4 (Treatment Day 1, Randomization) of the lead-in studies (Study PT003006 or Study PT003007). Thus Visits 12, 13, 14, and 15, will be scheduled 28, 36, 44, and 52 weeks ± 7 days of Visit 4 of the lead-in studies respectively.

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

<sup>c</sup> Refer to Section 7.1.1 for spirometry assessments and specific time points to be performed at each treatment visit.

<sup>d</sup> Refer to Section 7.2.2 for vital signs assessments and specific time points to be performed at each treatment visit. Weight will be obtained at Visit 15 only.

<sup>e</sup> Refer to Section 7.2.3 for ECG assessments and specific time points to be performed at each treatment visit.

<sup>f</sup> Refer to Section 7.2.4 for clinical laboratory assessments (hematology, chemistry and urinalysis) and specific time points to be performed at each treatment visit. Serum pregnancy test will be performed at Visit 15 (Week 52) and a urine pregnancy test will be done at Visit 13 (Week 36).

<sup>g</sup> At the end of Visit 15, return subject to pre-study or other appropriate inhaled maintenance COPD medications.

<sup>h</sup> In-clinic dosing time is recorded as time of the second puff inhalation. The in-clinic dosing time should be timed to be within 12±2 hours of the prior evening dosing time if assigned to blinded treatment or 24±2 hours of the prior morning dosing time if assigned to Spiriva.

<sup>i</sup> When TDI and SGRQ are obtained at the same visit TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures.

<sup>j</sup> Refer to Section 7.1.2 for details of electronic diary review.

<sup>k</sup> Refer to Section 7.1.5 for details and instructions on recording dose indicator readings.

<sup>l</sup> Refer to Section 7.3 for details on HCRU collection.

<sup>m</sup> 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).

§ - Illustrates the procedures that may be required at a premature discontinuation visit. Note: Premature discontinuation visits will be captured as unscheduled visits (See Section 8.4).

Note: Where data collection time-points are concurrent, variables should be collected in the following order: TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry

Source: Clinical trial protocol PT003008, version 2.0, Table 8, p59

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**Table 9. Timed Assessments: PT003008**

Clinical Variable <sup>a</sup>	Pre-dosing		Post-dosing			
	-1 hour	-30 minutes	15 minutes	30 minutes	1 hour	2 hours
TDI <sup>b</sup>	X <sup>†</sup>					
SGRQ <sup>b</sup>	X <sup>†</sup>					
Review of Electronic Diary Data	X <sup>†</sup>					
Vital Signs <sup>c</sup>	X <sup>†</sup>			X		X <sup>c</sup>
12- Lead ECG <sup>d</sup>	X <sup>†</sup>			X <sup>d</sup>		X <sup>d</sup>
Clinical Laboratory Testing <sup>e</sup>	X <sup>†</sup>					
Spirometry (FEV <sub>1</sub> , FVC, PEFR) <sup>f</sup>	X	X	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>	X <sup>f</sup>
Study Drug Collection <sup>g</sup>	X <sup>†</sup>					
Record Dose Indicator Reading <sup>h</sup>		X <sup>†</sup>				
Study Drug Dispensing <sup>i</sup>						X <sup>†</sup>

- <sup>a</sup> In-clinic dosing time is recorded as time of the second puff. Safety assessments (vital signs, and ECG) should be started approximately 5 - 10 minutes ahead of the specified time point to ensure that spirometry for FEV<sub>1</sub>, FVC and PEFR assessments will be conducted as close to the specified time points as possible (i.e., FEV<sub>1</sub>, FVC, and PEFR assessments need to be conducted within ± 15 minutes of specified time prior to study drug administration.
- <sup>b</sup> When TDI and SGRQ are obtained at the same visit TDI will be collected first followed immediately by SGRQ. These questionnaires must be completed by the subject prior to any other visit procedures. TDI and SGRQ will be obtained at Visit 13 (Week 32) and Visit 15 (Week 52) only.
- <sup>c</sup> Post-dose Vital signs will be obtained at two hours post study drug dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only. Temperature will be obtained pre-dose; no further temperature assessments required unless clinically indicated.
- <sup>d</sup> Pre-dose ECG will be obtained once within one hour prior to dosing and a post-dose ECG will be obtained at 30 minutes and two hours post study drug dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only.
- <sup>e</sup> Clinical laboratory tests (hematology, chemistry and urinalysis) will be obtained prior to dosing at Visit 13 (Week 36) and Visit 15 (Week 52) only.
- <sup>f</sup> Spirometry assessments will be obtained at 15 and 30 minutes, and 1 and 2 hours post-dosing of study drug Visit 13 (Week 36) and Visit 15 (Week 52) only.
- <sup>g</sup> At the start of each treatment visit, subject must withhold all COPD medications, including study medication, rescue Ventolin HFA and ICS for at least 6 hours prior to start of test day procedures.
- <sup>h</sup> Site staff will record the dose indicator reading at each visit. The dose indicator reading recorded by the site staff will be dose indicator count observed prior to subject dosing. For new MDIs the recorded count will be the count following the priming of the device but before the subject dose. Refer to Section 7.1.5 for more details.
- <sup>i</sup> Dispense study drug for home use to subject following completion of all post-dose assessments. See Section 6.7 for Instructions for Preparation of Treatments for Administration and Dispensing.
- <sup>†</sup> This is not a timed assessment. Sites should plan to perform these activities so as not to interfere with collection of timed assessments such as spirometry.
- Note: Where data collection time-points are concurrent, variables must be collected in the following order: TDI, SGRQ, vital signs, ECG, clinical laboratory assessments, and spirometry.*

Source: Clinical trial protocol PT003008, version 2.0, Table 9, p61

## Endpoints

### Safety Endpoints

AEs, vital signs, 12-lead ECG parameters, and clinical laboratory parameters over 52 weeks

### Efficacy Endpoints

In general, the primary, secondary, other efficacy, and health care resource utilization endpoints were the same as in trials 3006 and 3007. Differences are noted below:

- Endpoints analyzed over 52 weeks
- TDI focal score over 52 weeks added as a secondary endpoint (included as a co-primary endpoint in trials 3006 and 3007 for EU)
- No “Day 1” endpoints (time to onset of action, change from baseline in FEV<sub>1</sub> within 2 hours post-dose, etc.)
- No sub-study endpoints

### Statistical Plan

Analyses included all non-placebo data from trials 3006 and 3007 in order to minimize the impact of dropouts and to allow inferences to be made over 52 weeks. Baseline for all subjects was considered the original baseline values obtained in trial 3006 or 3007.

#### *Adverse Events*

All AEs starting on or after the time of first inhalation of study drug were classified as treatment emergent. AEs were summarized for two data sets: one contained all non-placebo data from studies 3006, 3007, and 3008, and the other contained only subjects and AEs from study 3008. Additional analyses of AEs by patient years of exposure were also conducted to adjust for variable amounts of exposure between groups. Major adverse cardiovascular events (MACE) and causes of death were summarized by treatment group. Comparisons between groups for time to first MACE or time to death were performed using a Cox proportional hazards model with adjustments for age and disease severity (MACE) or baseline percent predicted FEV<sub>1</sub> (cause of death).

#### *Clinical labs, vital signs, ECGs*

Analyses of these endpoints were provided as summary statistics, shift tables, and potentially clinically significant values.

#### Efficacy analyses

##### *Spirometry endpoints*

The primary endpoint of change from baseline in morning pre-dose trough FEV<sub>1</sub> over 52 weeks was analyzed in the same manner as in studies 3006 and 3007 with the addition of lead-in study as a categorical covariate. Other spirometry endpoints including peak change from baseline in FEV<sub>1</sub> within 2 hours post-dosing, and change from baseline in FEV<sub>1</sub> AUC<sub>0-2</sub>, FVC, PEFR, and FEF<sub>25-75</sub> over 52 weeks were analyzed similarly.

##### *SGRQ and TDI endpoints*

SGRQ was analyzed in the same manner as in trials 3006 and 3007 with the addition of lead-in study as a categorical covariate.

The TDI focal score was analyzed in the same manner as SGRQ except BDI from Visit 4 in the lead-in studies replaced baseline FEV<sub>1</sub> as a continuous covariate in the model. The comparison of GP to SHH used a NI margin of 1.0. For responder analyses, responders were defined as a response of 1.0 point or more on average over the treatment period.

##### *Rescue medication use*

Rescue Ventolin use and percentage of days with no rescue Ventolin use was analyzed similar to the method described for trials 3006 and 3007.

##### *COPD Exacerbations and Time to treatment failure*

These endpoints were defined and analyzed in the same manner as in trials 3006 and 3007 with the addition of lead-in study as a covariate.

### Symptom scores

The symptom score endpoints were analyzed in the same manner as in trials 3006 and 3007.

### Type I error control

Type I error was controlled by the specification of a primary efficacy measure (change from baseline in morning pre-dose trough FEV<sub>1</sub> over 52 weeks) and a limited set of secondary efficacy measures (change from baseline in TDI focal score over 52 weeks, peak change from baseline in FEV<sub>1</sub> within 2 hours post-dosing over 52 weeks, change from baseline in SGRQ over 52 weeks, mean daily number of puffs of rescue Ventolin HFA). No additional controls were in place since this was primarily a safety study.

## **6 Review of Efficacy**

### **Efficacy Summary**

The proposed indication for glycopyrrolate/formoterol fumarate (GFF) is for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. The proposed dose is a fixed combination of 18 mcg glycopyrrolate (GP) and 9.6 mcg formoterol fumarate (FF) administered via metered dose inhaler (MDI) twice daily (BID).

To support the proposed indication, the Applicant provided evidence of efficacy from two 24-week pivotal trials. The trials (3006 and 3007) were randomized, double-blind, placebo-controlled and parallel group in design. The trials were replicate in design, each comparing GFF 18/9.6 mcg BID to placebo and to the GP 18 mcg and FF 9.6 mcg monotherapies BID. In addition, trial 3006 included Spiriva Handihaler 18 mcg once daily as an open-label, active comparator treatment arm. Both trials included patients with moderate to very severe COPD for a blinded treatment period of 24 weeks. Although some patients continued blinded treatment in a 26-week extension study (3008), this study did not include a placebo control and thus was not used to evaluate efficacy for the purposes of this review. The primary efficacy endpoint was trough FEV<sub>1</sub> at Week 24 for both trials.

Results for the comparison of the primary endpoint between GFF and placebo were statistically significant in both trials. Furthermore, GFF demonstrated statistically significant improvements in trough FEV<sub>1</sub> over each of the constituent monotherapy products, GP and FF, demonstrating that both components contributed to the treatment effect. Efficacy was further supported by secondary endpoints peak FEV<sub>1</sub> throughout the treatment period and trough FEV<sub>1</sub> over 24 weeks, both of which demonstrated a statistically significant improvement with GFF as compared to placebo and the monocomponents in each trial. Other endpoints such as SGRQ total score and response rate, rescue medication use, and rate of COPD exacerbations generally favored the efficacy of GFF over placebo and overall were supportive of the primary endpoint analysis. Subgroup analyses based on demographic factors (age, sex, race,

and geography) demonstrated findings that were consistent with results in the overall population.

Based on the available data, GFF has a significant effect on bronchodilation compared to placebo and to the GP and FF monocomponent products. The results provide substantial replicate evidence of efficacy for the proposed GFF product and indication in COPD.

## 6.1 Indication

The proposed indication for GFF is for the long-term maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease, including chronic bronchitis and/or emphysema.

### 6.1.1 Methods

Fifteen subjects participated in more than one pivotal trial or more than once in the same pivotal trial at different clinical research sites. Four of these subjects (Subjects 1, 2, 9, and 10 in the table below) received study drug concurrently in more than one trial (either at two sites within the same trial, during trials 3006 and 3007, or during trials 3006/3007 and 3008), and thus were excluded from ITT and PP populations for those participation periods. For the remaining 11 subjects who did not have overlapping study drug treatment, the Applicant decided which analysis populations these subjects should be assigned to in each trial prior to database lock. These subjects were eligible for the ITT and PP populations for the first trial exposure, but excluded from the PP population for the second trial exposure. There were five subjects with multiple subject IDs who participated at more than one site within the same trial, but did not overlap in treatment exposure; these subjects were eligible for the ITT and PP populations for the first exposure, but excluded from the ITT and PP populations for the second exposure. A summary of the ITT, PP, and safety population assignments for each subject is provided in the table below. Of note, some subjects are represented more than once under different unique subject ID's in the ITT population. Because the multiple enrollers represented a very small percentage of the overall study population, their inclusion in the ITT population did not affect the primary efficacy analyses, and therefore, the ITT population defined by the Applicant was used for all efficacy assessments. Refer to the biostatistics review dated March 15, 2016, by Dr. Robert Abugov for more details.

**Table 10. Subjects with Multiple Identification Numbers: ITT, PP, and Safety Populations**

Subject	Subject ID	Trial	Treatment group	ITT population	PP population	Safety population	Early d/c
1	145039	3006	SHH	N	N	N	Y
	152030	3006	GFF	N	N	N	Y
	426004	3007	GFF	N	N	N	Y
2	049029	3006	SHH	N	N	N	Y
	355030	3007	PBO	N	N	N	Y
3	006030	3006	GFF	Y	Y	Y	Y

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Subject	Subject ID	Trial	Treatment group	ITT population	PP population	Safety population	Early d/c
	344015	3007	FF	Y	N	Y	Y
4	023004	3006	FF	Y	Y	Y	Y
	329011	3007	GFF	Y	N	Y	N
5	004027	3006	FF	Y	Y	Y	N
	426028	3007	FF	Y	N	Y	Y
6	070010	3006	GP	Y	Y	Y	N
	316008	3007	PBO	Y	N	Y	Y
7	066001	3006	GP	Y	Y	Y	N
	407051	3007	GP	Y	Y	Y	Y
8	025018	3006	SHH	Y	N	Y	Y
	360002	3007	PBO	Y	Y	Y	Y
9	079005	3006	GP	Y	Y	Y	N
	369012	3007	GFF	N	N	N	Y
	079005	3008	GP	N	N	N	Y
10	032005	3006	GP	Y	Y	Y	N
	434003	3007	GP	N	N	N	Y
	435011	3007	FF	N	N	N	Y
11	023021	3006	GP	Y	Y	Y	N
	028031	3006	FF	N	N	Y	Y
12	023019	3006	FF	Y	Y	Y	Y
	028030	3006	FF	N	N	Y	Y
13	056004	3006	FF	Y	Y	Y	N
	112050	3006	PBO	N	N	Y	Y
14	127002	3006	FF	Y	Y	Y	Y
	132014	3006	FF	N	N	Y	Y
15	328024	3007	FF	Y	Y	Y	N
	305070	3007	FF	N	N	Y	Y

Source: CSR PT003006 and PT003007, Tables 6-4

### 6.1.2 Demographics

Demographics and baseline characteristics for the pooled ITT population from trials 3006 and 3007 are provided in Table 11 and Table 12. Note, the number of patients reflects the number of unique subjects. Subjects who may have been included in the ITT population under multiple subject ID numbers are represented in these tables only once.

Table 11. Demographics for Pooled ITT Population, Pivotal Trials 3006 and 3007

	GFF N=1035	FF N=884	GP N=889	Placebo N=441	SHH N=450	Total N=3699
<b>Age (years)</b>						
Mean (SD)	63 (8)	63 (8)	63 (8)	63 (9)	63 (9)	63 (8)
Median	63	63	63	64	63	63
Range	40 – 80	40 – 80	40 – 80	40 – 80	40 – 80	40 – 80
<b>Age Group, n (%)</b>						
≥ 65 years	461 (45)	397 (45)	405 (46)	206 (47)	203 (45)	1672 (45)

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	GFF N=1035	FF N=884	GP N=889	Placebo N=441	SHH N=450	Total N=3699
<b>Sex, n (%)</b>						
Female	473 (46)	392 (44)	392 (44)	194 (44)	182 (40)	1633 (44)
<b>Race, n (%)</b>						
White	941 (91)	809 (92)	812 (91)	400 (91)	402 (89)	3364 (91)
Black or African American	81 (8)	67 (8)	65 (7)	38 (9)	37 (8)	288 (8)
Native Hawaiian or Pacific Islander	0	0	2 (<1)	3 (1)	1 (<1)	6 (<1)
American Indian or Alaskan Native	2 (<1)	3 (<1)	3 (<1)	0	5 (1)	13 (<1)
Asian	7 (1)	2 (<1)	2 (<1)	0	0	11 (<1)
Australia or New Zealand	2 (<1)	0	1 (<1)	0	3 (1)	6 (<1)
Other	2 (<1)	3 (<1)	4 (<1)	0	2 (<1)	11 (<1)
<b>Ethnicity, n (%)</b>						
Hispanic/Latino	35 (3)	30 (3)	22 (3)	14 (3)	16 (4)	117 (3)
<b>BMI kg/m<sup>2</sup></b>						
Mean (SD)	28 (6)	28 (6)	29 (6)	28 (7)	28 (7)	28 (6)
Median	27	27	28	27	28	27
Range	15 – 53	15 – 61	14 – 50	14 – 61	16 – 59	14 – 61

Source: Module 5.3.5.3, ISE, Table 3-6, p86

Table 12. COPD Baseline Characteristics

	GFF N=1035	FF N=884	GP N=889	Placebo N=441	SHH N=450	Total N=3699
<b>Smoking status<sup>1</sup>, n (%)</b>						
Current	549 (53)	494 (56)	471 (53)	236 (54)	238 (53)	1988 (54)
Ex-smoker	486 (47)	390 (44)	418 (47)	205 (47)	212 (47)	1711 (46)
<b>Number of pack-years smoked<sup>2</sup></b>						
Mean (SD)	51 (27)	52 (26)	50 (26)	52 (27)	53 (27)	52 (26)
<b>ICS use at baseline, n (%)</b>						
Yes	368 (36)	322 (36)	334 (38)	166 (38)	164 (36)	1354 (37)
<b>Total CAT Score<sup>3</sup>, n (%)</b>						
≥ 20	445 (43)	391 (44)	406 (46)	184 (42)	191 (42)	1617 (44)
<b>COPD severity, n (%)</b>						
Mild (GOLD 1)	1 (<1)	0	1 (<1)	0	0	2 (<1)
Moderate (GOLD 2)	553 (53)	466 (53)	474 (53)	233 (53)	237 (53)	1963 (53)
Severe (GOLD 3)	441 (43)	376 (43)	358 (40)	185 (42)	181 (40)	1541 (42)
Very Severe (GOLD 4)	40 (4)	42 (5)	56 (6)	23 (5)	32 (7)	193 (5)
<b>Duration of COPD (years)</b>						
n	1035	882	888	440	450	3695
Mean (SD)	8 (6)	8 (7)	8 (6)	8 (6)	8 (6)	8 (6)

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	GFF N=1035	FF N=884	GP N=889	Placebo N=441	SHH N=450	Total N=3699
Median	6	6	6	6	7	6
Min, Max	0.1, 37	0.1, 56	0, 51	0, 34	0.1, 41	0, 56
<b>Moderate/Severe<sup>4</sup> COPD exacerbations within past 12 months</b>						
Number of subjects, n (%)	265 (26)	184 (21)	198 (22)	118 (27)	116 (26)	881 (24)
Number of events	380	250	275	157	163	1225
Mean number exacerbations per subject	0.4	0.3	0.3	0.4	0.4	0.3
<b>Lung function at screening</b>						
Pre-Ventolin FEV <sub>1</sub> (L), n	1035	884	889	441	450	3699
Mean (SD)	1.308 (0.5)	1.321 (0.5)	1.281 (0.5)	1.291 (0.5)	1.307 (0.5)	1.302 (0.5)
Post-Ventolin FEV <sub>1</sub> (L), n	1007	871	871	434	429	3612
Mean (SD)	1.524 (0.5)	1.536 (0.6)	1.506 (0.5)	1.507 (0.5)	1.531 (0.5)	1.521 (0.5)
Reversible <sup>5</sup> to Ventolin, n (%)	510 (49)	445 (50)	446 (50)	218 (49)	227 (50)	1846 (50)
Post-Atrovent FEV <sub>1</sub> , n	1015	869	870	432	438	3624
Mean (SD)	1.515 (0.5)	1.522 (0.6)	1.486 (0.5)	1.491 (0.5)	1.499 (0.5)	1.505 (0.5)
Reversible <sup>5</sup> to Atrovent, n (%)	508 (49)	409 (46)	429 (48)	204 (45)	204 (45)	1754 (48)
<sup>1</sup> Former smokers defined as smoking cessation for at least 6 weeks prior to first screening visit <sup>2</sup> Number of pack-years calculated by (number of cigarettes per day/20) x number of years smoked <sup>3</sup> Total CAT score ranges from 0 to 40 with higher scores representing poorer health status. Experts suggest that scores ≥ 20 have high/very high impact requiring more interventions ( <a href="http://www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/copd.php">http://www.thoracic.org/members/assemblies/assemblies/srn/questionnaires/copd.php</a> ) <sup>4</sup> Moderate or severe exacerbations defined as those requiring treatment with systemic steroids and/or antibiotics <sup>5</sup> Reversible define as pre to post bronchodilator improvement in FEV <sub>1</sub> of ≥ 12% and ≥ 200 mL Source: Module 5.3.5.3, ISE, Tables 3-8, 3-10, and 3-12						

Demographic and baseline characteristics were generally well-balanced across treatment arms. In the overall study population, 8% of subjects were Black or African American and 3% were Hispanic; given that the majority of study sites were in the U.S., these percentages also reflect the percentage of subjects from the U.S. The study population includes a sufficient percentage of subjects from these racial and ethnic backgrounds to accurately represent the age-adjusted percentages of non-Hispanic black (5.7%) and Hispanic (1.7%) adults aged 40-79 years with moderate or worse lung obstruction between 2007-2012 in the U.S.<sup>7</sup> The majority of subjects had either

<sup>7</sup> Tillet T, Paulose-Ram R, and Brody D. Lung Obstruction Among Adults Aged 40-79: United States, 2007-2012. NCHS Data Brief. 2015; 180:1-8

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Bevespi Aerosphere Inhalation Aerosol (glycopyrrolate/formoterol fumarate MDI) moderate/GOLD II (53%) or severe/GOLD III (42%) disease with the remainder (5%) having very severe/GOLD IV disease. Pre-bronchodilator FEV<sub>1</sub> was balanced across treatment groups, and approximately half of subjects had baseline reversibility to Ventolin or Atrovent.

### 6.1.3 Subject Disposition

The disposition of patients participating in the two pivotal efficacy trials is provided in Table 13. There was no meaningful difference between trials 3006 and 3007; therefore, pooled data is presented.

**Table 13. Subject Disposition for Pivotal Trials 3006 and 3007**

	GFF	FF	GP	Placebo	SHH	Total
<b>Randomized/Treated*</b>	<b>Number of Patients</b>					
Pooled 3006/3007	1039	891	891	444	453	3718
3006	527	452	451	220	453	2103
3007	512	439	440	224	--	1615
<b>Intent-To-Treat (ITT)</b>	<b>Number of Patients</b>					
Pooled 3006/3007	1036	886	890	442	451	3705
3006	526	449	451	219	451	2096
3007	510	437	439	223	--	1609
<b>Disposition</b>	<b>Number of Patients (% of pooled ITT)</b>					
Completed week 24, pooled	861 (83)	716 (81)	710 (80)	325 (74)	391 (87)	3003 (81)
3006	429 (41)	370 (42)	345 (39)	160 (36)	391 (87)	1695 (46)
3007	432 (42)	346 (39)	365 (41)	165 (37)	--	1308 (35)
Completed week 12, pooled	936 (90)	770 (87)	776 (87)	355 (80)	415 (92)	3252 (88)
Early discontinuation <sup>†</sup> , pooled	175 (17)	170 (19)	180 (20)	117 (27)	60 (13)	702 (19)
<b>Reason for withdrawal, pooled</b>						
Administrative reasons	2 (<1)	5 (1)	1 (<1)	2 (1)	1 (<1)	11 (<1)
Adverse event	56 (5)	40 (5)	45 (5)	30 (7)	20 (4)	191 (5)
Lack of efficacy	11 (1)	11 (1)	20 (2)	16 (4)	3 (1)	61 (2)
Lost to follow-up	18 (2)	16 (2)	16 (2)	4 (1)	5 (1)	59 (2)
Major protocol deviation	2 (<1)	7 (1)	1 (<1)	0	2 (<1)	12 (<1)
Physician decision	3 (<1)	10 (1)	10 (1)	11 (3)	3 (1)	37 (1)
Protocol specified criteria	23 (2)	23 (3)	25 (3)	14 (3)	5 (1)	90 (2)
Withdrawal by subject	60 (6)	58 (7)	62 (7)	39 (9)	21 (5)	240 (7)
*Includes subjects with multiple identification numbers who were not eligible for the ITT population; multiple subject IDs considered separate subjects.						
†Early discontinuation defined as failure to complete both the final visit and the follow-up telephone call						
Source: Reviewer generated table in JReview using DS (DSTERM and DSDECOD variables) and ADSL (ARM variable; RANDFL=Y and TRTFL=Y, then ITTFL=Y; COMPLFL=Y; COMPV8FL=Y) datasets for trials 3006 and 3007						

### ITT Population

The ITT population was defined as all subjects randomized to treatment and administered at least one dose of study drug with the exception of the subjects who

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 enrolled in the trials under multiple subject IDs as described in the Methods section above.

#### Early discontinuations/Withdrawals

The percentage of patients who did not complete the trials was higher for the placebo arm (27%) compared to the blinded active treatment arms (17-20%), and lowest for the open-label SHH active treatment arm (13%). The most commonly reported reason for withdrawal was “withdrawal by subject” and “adverse event”, both of which were higher for the placebo arm compared to active treatment arms. In addition, withdrawal due to “lack of efficacy” was more common in the placebo group. The “major protocol deviations” encompass the 12 subjects in the ITT population who participated in the pivotal trials more than once under multiple subject ID numbers.

#### 6.1.4 Analysis of Primary Endpoint(s)

Both pivotal trials share the same primary endpoint of change from baseline in pre-dose trough FEV<sub>1</sub> at week 24. Baseline was defined as the average of the non-missing -60 minute and -30 minute values obtained prior to dosing at Visit 4 (Day 1). The primary endpoint is an appropriate and commonly used endpoint in COPD trials. The trough FEV<sub>1</sub> treatment response at week 24 showing the comparisons to placebo as well as between active treatment arms is provided in Table 14.

**Table 14. Primary Endpoint Analysis: Pre-dose Trough FEV<sub>1</sub> at Week 24 in Pivotal Trials 3006 and 3007 (ITT Population)**

Treatment Arm	N	BL in Liters	Δ from BL in mL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
<b>Trial 3006</b>						
GFF	429	1.263 (0.5)	126 (10)	150 (114, 186)	59 (31, 88)	64 (36, 92)
FF	367	1.260 (0.5)	62 (11)	86 (49, 123)	-5 (-34, 25)	
GP	344	1.261 (0.5)	66 (11)	91 (53, 128)		
SHH	390	1.285 (0.5)	105 (10)	129 (92, 166)	38 (9, 67)	
Placebo	161	1.327 (0.5)	-24 (16)			
<b>Trial 3007</b>						
GFF	433	1.288 (0.5)	116 (10)	103 (67, 140)	54 (25, 83)	56 (27, 85)
FF	350	1.327 (0.5)	61 (11)	47 (10, 85)	-2 (-32, 28)	
GP	367	1.284 (0.5)	63 (11)	49 (12, 87)		
Placebo	170	1.256 (0.5)	13 (16)			
Abbreviations: BL=Baseline, FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, LS=Least Squares, SHH=Spiriva Handihaler 18 mcg QD Baseline defined as mean of all evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4). LS Mean includes the following covariates: baseline FEV <sub>1</sub> , percent reversibility to Ventolin, baseline smoking status, baseline ICS use, treatment, visit, and treatment by visit interaction						

In both trials, the trough FEV<sub>1</sub> response was statistically significantly higher for GFF compared to placebo and to each of the constituent monocomponents, GP and FF, demonstrating the contribution of each component. Serving as a benchmark for anticholinergic monotherapy, SHH led to greater improvements in trough FEV<sub>1</sub> than GP, but had less of a treatment effect than GFF. However, the SHH treatment arm was not blinded, and therefore interpretation of those results are limited.

### 6.1.5 Analysis of Secondary Endpoints(s)

The secondary endpoints for the individual trials were as follows:

- Change from baseline in morning pre-dose trough FEV<sub>1</sub> over 24 weeks
- Peak change from baseline in FEV<sub>1</sub> within 2 hours post-dosing at Week 24
- Change from baseline in SGRQ total score at Week 24
- Change from baseline in average daily rescue Ventolin HFA use over 24 weeks
- Time to onset of action on Day 1

Control for Type I error was discussed in Section 5.3. Results for each of the secondary endpoints in the individual trials are provided below.

#### Trough FEV<sub>1</sub> over 24 weeks

The results for change from baseline in trough FEV<sub>1</sub> over 24 weeks were consistent with the results from the primary endpoint analysis. Figure 26 and Figure 27 depict trough FEV<sub>1</sub> at each study visit. Similar results were seen in trough FEV<sub>1</sub> response at week 12 and over weeks 12 to 24. However, peak effect appears to occur by week 8 and then gradually decreases and plateaus over time.

**Table 15: Pre-dose Trough FEV<sub>1</sub> over 24 Weeks in Pivotal Trials 3006 and 3007 (ITT Population)**

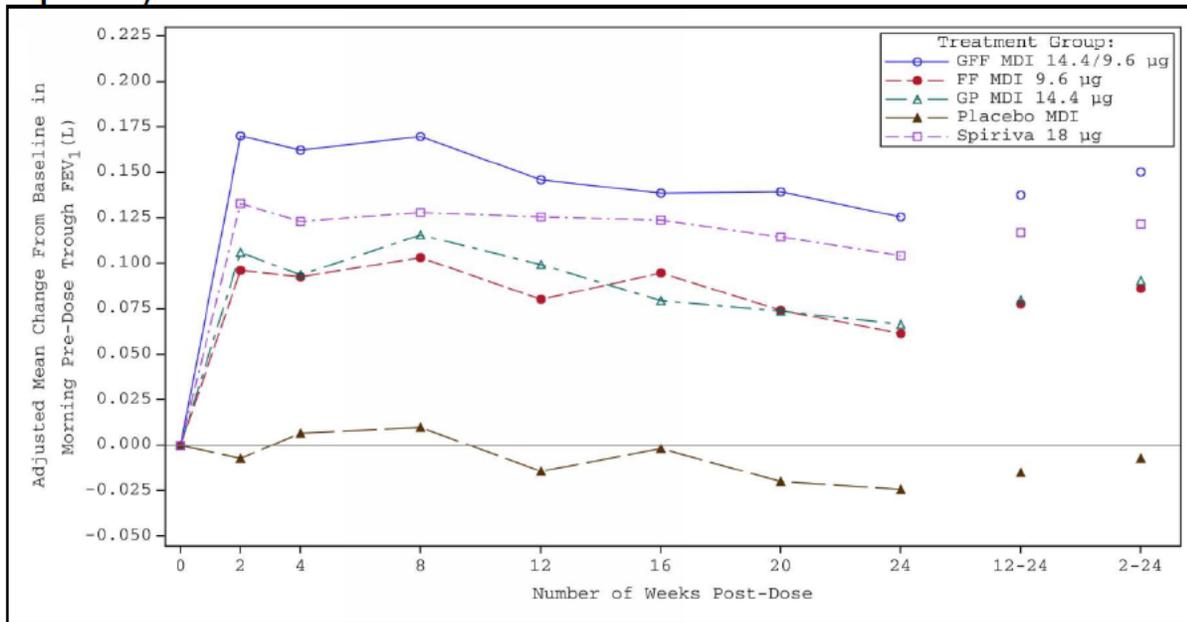
Treatment Arm	N	BL in Liters	Δ from BL in mL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
<b>Trial 3006</b>						
GFF	519	1.270 (0.5)	150 (7)	158 (132, 183)	60 (39, 80)	64 (44, 84)
FF	439	1.279 (0.5)	86 (8)	93 (67, 120)	-4 (-25, 17)	
GP	440	1.249 (0.5)	91 (8)	98 (71, 124)		
SHH	446	1.274 (0.5)	122 (8)	129 (103, 155)	31 (10, 52)	
Placebo	208	1.281 (0.5)	-7 (11)			
<b>Trial 3007</b>						
GFF	503	1.288 (0.5)	137 (7)	129 (103, 155)	55 (34, 76)	57 (36, 78)
FF	434	1.319 (0.5)	80 (8)	72 (45, 98)	-2 (-24, 19)	
GP	434	1.269 (0.5)	82 (8)	74		

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Treatment Arm	N	BL in Liters	$\Delta$ from BL in mL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
Placebo	216	1.249 (0.5)	8 (11)	(47, 100)		

Abbreviations: BL=Baseline, FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, LS=Least Squares, SHH=Spiriva Handihaler 18 mcg QD  
 Baseline defined as mean of all evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4). LS Mean includes the following covariates: baseline FEV<sub>1</sub>, percent reversibility to Ventolin, baseline smoking status, baseline ICS use, treatment, visit, and treatment by visit interaction  
 Source: CSR Tables PT003006, Table 2.1.1, p347 and CSR Tables PT003007, Table 2.1.1, p288

**Figure 26. Adjusted Mean Change from Baseline in Trough FEV<sub>1</sub> Over Time in Trial 3006 (ITT Population)**

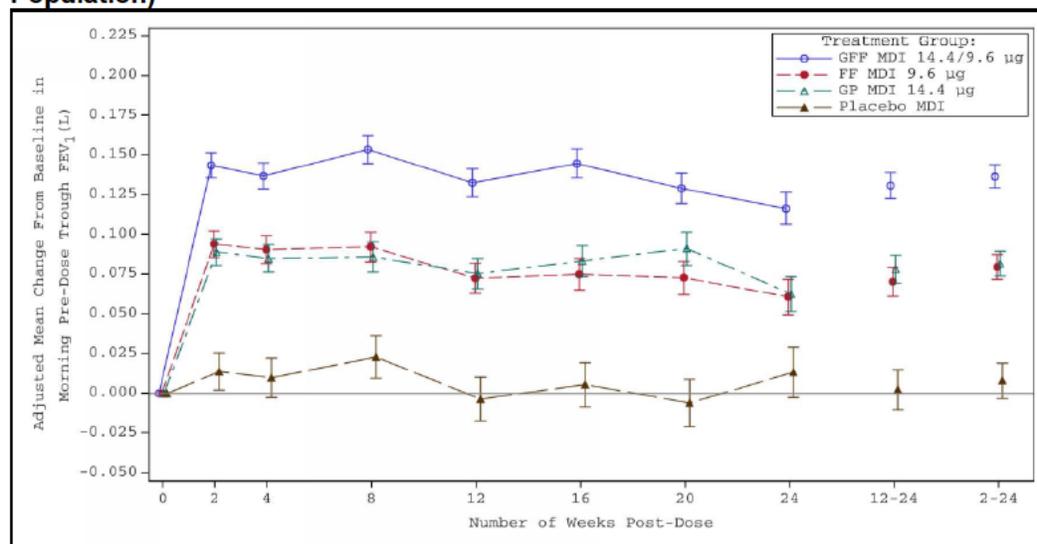


Bars represent standard error. The final time point (2-24) represents data over 24 weeks and begins with the first visit assessed (Day 1) for this endpoint.

Source: CSR Figures PT003006, Figure 2.1.1.1, p13

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**Figure 27. Adjusted Mean Change from Baseline in Trough FEV<sub>1</sub> Over Time in Trial 3007 (ITT Population)**



Bars represent standard error. The final time point (2-24) represents data over 24 weeks and begins with the first visit assessed (Day 1) for this endpoint.

Source: CSR Figures PT003007, Figure 2.1.1.1, p13

**Peak FEV<sub>1</sub>**

The peak FEV<sub>1</sub> was defined as the maximum FEV<sub>1</sub> recorded within 2 hours after the morning dose. Measurements from day 1 and week 24 are shown in Table 16; the week 24 time point was designated as a secondary endpoint. Peak FEV<sub>1</sub> was driven primarily by the FF component of GFF.

**Table 16. Peak Change from Baseline in FEV<sub>1</sub> within 2 Hours Post-dose on Day 1 and Week 24: Trials 3006 and 3007 (ITT Population)**

Treatment Arm	N	BL in Liters	Δ from BL in mL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
<b>Trial 3006</b>						
<b>Day 1</b>						
GFF	526	1.273 (0.5)	331 (7)	236 (213, 260)	118 (100, 137)	28 (10, 47)
FF	448	1.277 (0.5)	303 (7)	208 (184, 232)	90 (71, 110)	
GP	450	1.248 (0.5)	213 (7)	118 (94, 142)		
SHH	449	1.277 (0.5)	245 (7)	150 (126, 174)	32 (12, 51)	
Placebo	219	1.276 (0.5)	95 (10)			
<b>Week 24</b>						
GFF	428	1.262 (0.5)	356 (11)	291 (252, 331)	133 (102, 164)	93 (63, 124)
FF	367	1.260 (0.5)	263 (12)	198 (158, 238)	40 (8, 72)	
GP	343	1.257 (0.5)	223 (12)	158 (117, 199)		

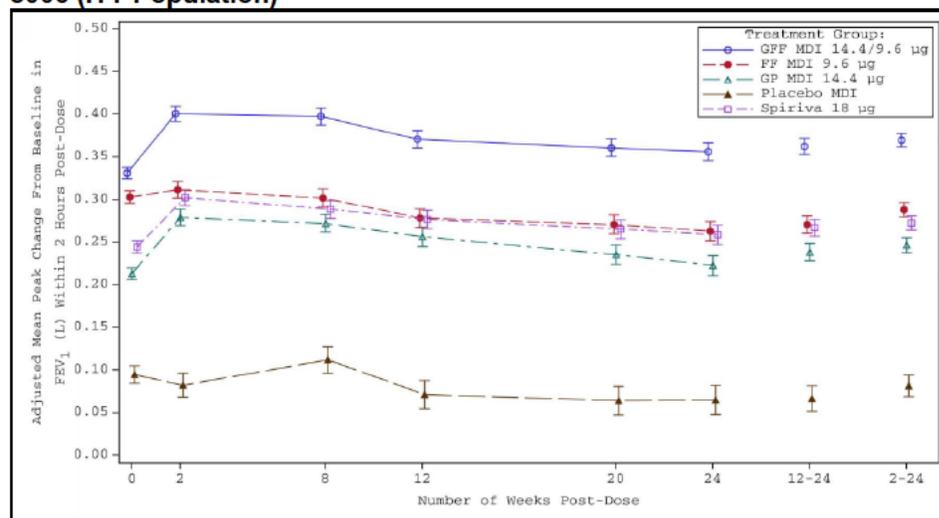
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Treatment Arm	N	BL in Liters	$\Delta$ from BL in mL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
SHH	388	1.287 (0.5)	259 (11)	194 (154, 234)	36 (4, 68)	
Placebo	160	1.330 (0.5)	65 (17)			
<b>Trial 3007</b>						
<b>Day 1</b>						
GFF	510	1.287 (0.5)	342 (7)	237 (212, 261)	127 (107, 147)	34 (14, 54)
FF	436	1.319 (0.5)	308 (8)	203 (178, 228)	93 (73, 114)	
GP	439	1.265 (0.5)	215 (8)	110 (85, 135)		
Placebo	223	1.247 (0.5)	105 (11)			
<b>Week 24</b>						
GFF	431	1.288 (0.5)	350 (11)	267 (226, 308)	126 (94, 159)	81 (49, 114)
FF	346	1.326 (0.5)	268 (12)	185 (143, 227)	45 (11, 79)	
GP	365	1.283 (0.5)	223 (12)	140 (99, 182)		
Placebo	165	1.254 (0.5)	83 (18)			

Abbreviations: BL=Baseline, FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, LS=Least Squares, SHH=Spiriva Handihaler 18 mcg QD  
 Baseline defined as mean of all evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4). LS Mean includes the following covariates: baseline FEV<sub>1</sub>, percent reversibility to Ventolin, baseline smoking status, baseline ICS use, treatment, visit, and treatment by visit interaction  
 Source: CSR Tables PT003006, Table 2.3.1, p751; CSR Tables PT003007, Table 2.3.1, p568

Figures displaying peak FEV<sub>1</sub> measurements over the course of each trial are shown below. There is a gradual decline in the peak FEV<sub>1</sub> attained starting from week 12 that levels off through the end of the study at week 24.

**Figure 28. Adjusted Mean Change from Baseline in Peak FEV<sub>1</sub> within 2 Hours Post-dose in Trial 3006 (ITT Population)**

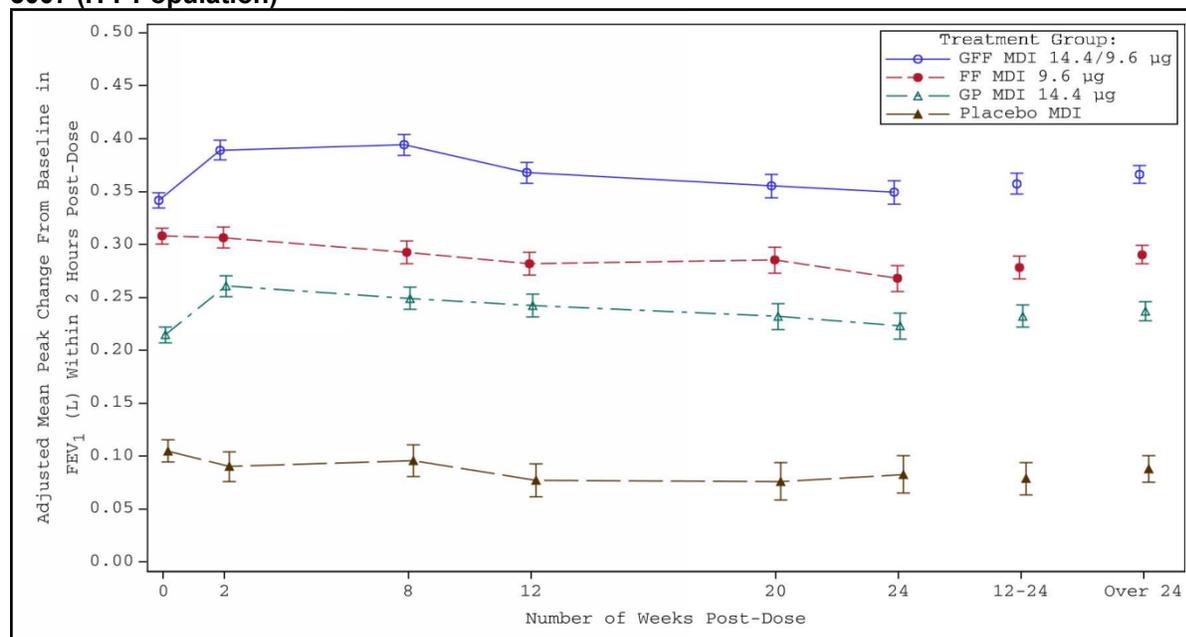


Bars represent standard error.

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Source: CSR Figures PT003006, Figure 2.3.1, p109

**Figure 29. Adjusted Mean Change from Baseline in Peak FEV<sub>1</sub> within 2 Hours Post-dose in Trial 3007 (ITT Population)**



Bars represent standard error.

Source: CSR Figures PT003007, Figure 2.3.1, p108

**St. George's Respiratory Questionnaire (SGRQ)**

The change from baseline in SGRQ total score at week 24 demonstrated a statistically significant difference from placebo in trial 3006 and a numerical trend toward improvement in trial 3007 as shown in Table 17; however, both failed to achieve a mean difference from placebo of at least -4.0, the change in score which has been identified as the minimal clinically important difference (MCID).<sup>8</sup> Although the change in total score was designated as a secondary endpoint, the responder rate likely represents a better way to assess for a possible clinical benefit for an individual patient. For this analysis, responders are defined as patients who achieved the MCID, a reduction in their total SGRQ total score of  $\geq 4$  units. Results for the Week 24 responder rate analysis, the Agency's preferred method of assessing SGRQ, are shown in Table 18.

**Table 17. Change from Baseline in SGRQ Total Score at Week 24: Trials 3006 and 3007 (ITT Population)**

Treatment Arm	N	BL	$\Delta$ from BL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF

<sup>8</sup> Jones PW. Eur Respir J. 1994; 7(1):55-62

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		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
<b>Trial 3006</b>						
GFF	432	47.3 (17)	-3.3 (0.6)	-2.52 (-4.6, -0.4)	-2.33 (-4.0, -0.7)	-0.64 (-2.3, 1.0)
FF	371	46.8 (18)	-2.7 (0.6)	-1.87 (-4.1, 0.3)	-1.69 (-3.4, 0.1)	
GP	350	46.9 (17)	-1.0 (0.6)	-0.19 (-2.4, 2.0)		
SHH	389	46.4 (17)	-2.6 (0.6)	-1.79 (-4.0, 0.4)	-1.6 (-3.3, 0.1)	
Placebo	161	46.9 (18)	-0.8 (0.9)			
<b>Trial 3007</b>						
GFF	430	48.2 (18)	-3.0 (0.6)	-1.72 (-3.8, 0.4)	-0.78 (-2.4, 0.9)	-0.66 (-2.3, 1.0)
FF	352	48.2 (18)	-2.3 (0.6)	-1.03 (-3.2, 1.1)	-0.12 (-1.8, 1.6)	
GP	362	47.8 (18)	-2.2 (0.6)	-0.94 (-3.1, 1.2)		
Placebo	170	47.0 (18)	-1.2 (0.9)			
Abbreviations: BL=Baseline, FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, LS=Least Squares, SHH=Spiriva Handihaler 18 mcg QD LS Mean included the following covariates: baseline SGRQ total score, percent reversibility to Ventolin HFA, baseline smoking status, baseline ICS use, treatment, visit, and treatment by visit interaction Source: CSR Tables PT003006, Table 2.4.1.1, p803 and CSR Tables PT003007, Table 2.4.1.1, p604						

**Table 18. SGRQ Responder Analyses at Week 24 in Trials 3006 and 3007 (ITT Population)**

Treatment Arm	N	Responders (%)	Vs Placebo		Vs GP		Vs FF	
			Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value	Odds Ratio (95% CI)	p-value
<b>Trial 3006</b>								
GFF	526	198 (37)	1.49 (1.1, 2.1)	0.02	1.39 (1.1, 1.8)	0.01	1.11 (0.9, 1.5)	0.43
FF	449	157 (35)	1.34 (0.9, 1.9)	0.11	1.25 (0.9, 1.7)	0.12		
GP	451	138 (30)	1.07 (0.8, 1.5)	0.71				
SHH	451	173 (39)	1.58 (1.1, 2.3)	0.01				
Placebo	219	63 (28)						
<b>Trial 3007</b>								
GFF	510	203 (40)	1.31 (0.9, 1.8)	0.11	1.23 (0.9, 1.6)	0.14	1.29 (1.0, 1.7)	0.06
FF	437	147 (34)	1.02 (0.7, 1.4)	0.93	0.95 (0.7, 1.3)	0.71		
GP	439	153 (35)	1.07 (0.8, 1.5)	0.70				
Placebo	223	75 (34)						
Source: CSR Tables PT003006, Table 2.4.3.1, p971; CSR Tables PT003007, Table 2.4.3.1, p716								

Rescue Ventolin use

There was a statistically significant decrease in rescue medication use with each active treatment compared to placebo (Table 19). Moreover, the decrease in rescue Ventolin HFA use was consistent over time, and while both daytime and nighttime Ventolin use

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decreased, the main decrease was in daytime use. The percentage of days with no rescue Ventolin HFA use was 48%, 48%, 45%, 41%, and 36% for GFF, FF, GP, SHH, and placebo groups, respectively, in trial 3006. Similar results were observed in trial 3007 with percentage of Ventolin free days of 49%, 46%, 40%, and 35% for GFF, FF, GP, and placebo groups, respectively. This is not unexpected since all active treatment groups were receiving long-acting bronchodilators (antimuscarinic, beta agonist or both) chronically.

**Table 19. Mean Change from Baseline in Daily Number of Rescue Ventolin HFA Puffs Over 24 Weeks: Trials 3006 and 3007 (ITT Population)**

Treatment Arm	N	BL	Δ from BL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
<b>Trial 3006</b>						
GFF	525	3.2 (3)	-0.8 (0.1)	-1.08 (-1.4, -0.7)	-0.26 (-0.5, 0.01)	-0.01 (-0.3, 0.3)
FF	446	3.4 (4)	-0.8 (0.1)	-1.08 (-1.4, -0.7)	-0.25 (-0.5, 0.03)	
GP	449	3.4 (4)	-0.5 (0.1)	-0.83 (-1.2, -0.5)		
SHH	449	3.4 (4)	-0.4 (0.1)	-0.74 (-1.1, -0.4)	0.08 (-0.2, 0.4)	
Placebo	218	3.4 (4)	0.3 (0.2)			
<b>Trial 3007</b>						
GFF	510	3.2 (4)	-1.0 (0.1)	-1.04 (-1.4, -0.7)	-0.57 (-0.8, -0.3)	-0.29 (-0.6, -0.03)
FF	437	3.5 (4)	-0.7 (0.1)	-0.75 (-1.1, -0.4)	-0.28 (-0.6, -0.01)	
GP	438	3.6 (4)	-0.4 (0.1)	-0.47 (-0.8, -0.1)		
Placebo	223	3.9 (4)	0 (0.1)			
Abbreviations: BL=Baseline, FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, LS=Least Squares, SHH=Spiriva Handihaler 18 mcg QD Baseline defined as average number of daily puffs of rescue Ventolin during the last 7 days of the 10-14 day screening period. LS Mean included the following covariates: baseline mean daily puffs of Ventolin, percent reversibility to Ventolin HFA, baseline smoking status, baseline ICS use, treatment, visit, and treatment by visit interaction Source: CSR Tables PT003006, Table 2.5.1, p983 and CSR Tables PT003007, Table 2.5.1, p728						

Time to onset

The Applicant defined onset of action as the first time point (5 or 15 minutes post-dose) where the difference from placebo for change in baseline for FEV<sub>1</sub> was statistically significant. Although this definition doesn't necessarily translate to a clinically meaningful bronchodilator effect as statistical significance could be achieved merely by increasing the sample size, the mean treatment difference from placebo at 5 minutes with GFF was relatively large (~185 mL) in both trials, although driven almost entirely by the FF component (Table 20). By week 2, the GP component contributes more to the bronchodilator effect observed at 5 minutes (see biostatistics review by Dr. Robert Abugov). Because spirometry was not obtained any earlier than 5 minutes post-dose, there was no difference in the mean and median time to onset.

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**Table 20. Change from Baseline in FEV<sub>1</sub> at 5 minutes Post-dose on Day 1: Trials 3006 and 3007 (ITT Population)**

Treatment Arm	N	BL	Δ from BL	Δ from BL	Treatment difference from Placebo	Treatment difference from GP	Treatment difference from FF
		Mean (SD)	Median	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
<b>Trial 3006</b>							
GFF	418	1.274 (0.5)	175	185 (5)	187 (168, 205)	143 (128, 158)	3 (-12, 18)
FF	366	1.284 (0.5)	175	182 (5)	184 (165, 203)	140 (125, 155)	
GP	363	1.268 (0.5)	40	42 (6)	44 (25, 63)		
SHH	364	1.289 (0.5)	47	48 (6)	50 (31, 69)		
Placebo	172	1.280 (0.5)	2	-2 (8)			
<b>Trial 3007</b>							
GFF	429	1.293 (0.5)	180	192 (6)	186 (164, 207)	140 (122, 157)	17 (0, 0.03)
FF	375	1.320 (0.5)	166	175 (6)	169 (147, 191)	123 (105, 140)	
GP	371	1.289 (0.5)	52	52 (6)	46 (24, 68)		
Placebo	179	1.260 (0.5)	6	6 (9)			
Abbreviations: BL=Baseline, FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, LS=Least Squares, SHH=Spiriva Handihaler 18 mcg QD Baseline defined as mean of all evaluable 60 and 30 minute pre-dose values on Day 1 (Visit 4). LS Mean includes the following covariates: baseline FEV <sub>1</sub> , percent reversibility to Ventolin, baseline smoking status, baseline ICS use, treatment, visit, and treatment by visit interaction Source: CSR Tables PT003006, Table 2.6.1, p1058; CSR Tables PT003007, Table 2.6.1, p778							

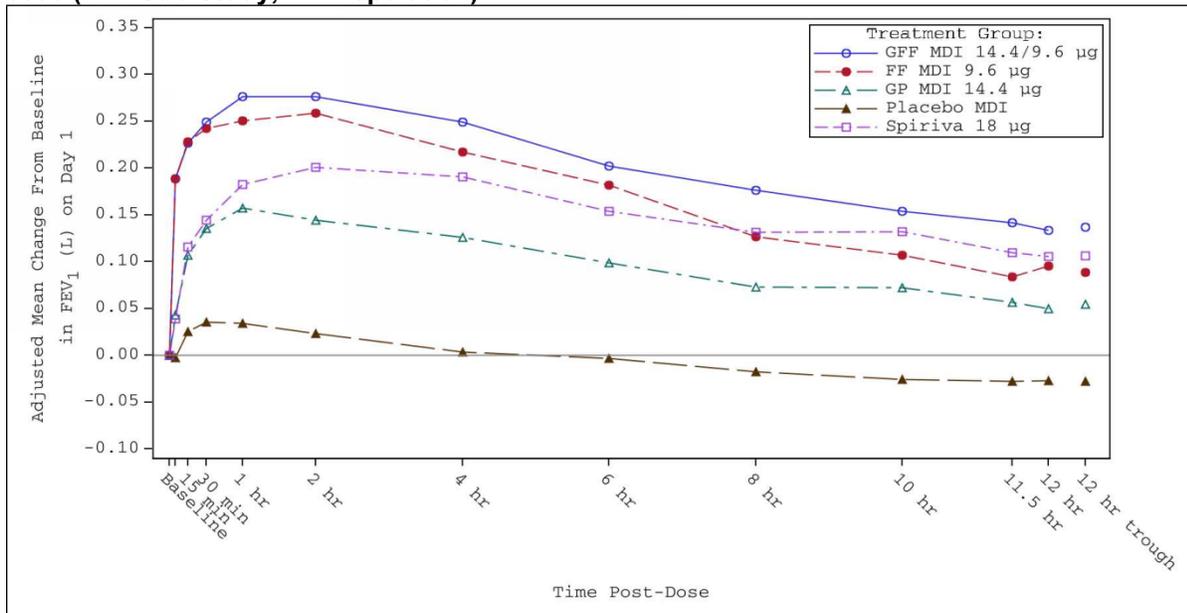
### 6.1.6 Other Endpoints

#### Serial Spirometry

A subset of subjects (718 in trial 3006 and 585 in trial 3007) were included in a 12-hour PFT sub-study to evaluate the treatment response in lung function parameters over 12 hours on day 1 and week 12. The primary efficacy endpoint for the PFT sub-study was the FEV<sub>1</sub> AUC<sub>0-12</sub> at week 12 in the ITT population, the results for which were statistically significant compared to placebo for all active treatment arms in both trials. The FEV<sub>1</sub> time profiles at each time point are shown for trial 3006 (Figure 30 and Figure 31) and trial 3007 (Figure 32 and Figure 33) below.

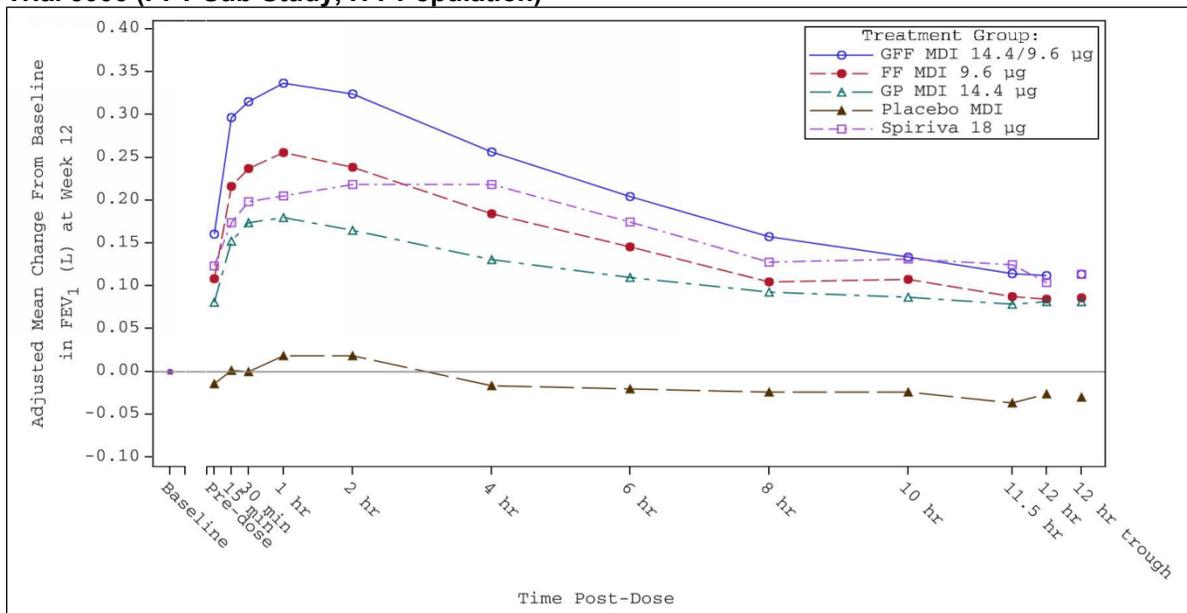
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**Figure 30. Adjusted Mean Change from Baseline in FEV<sub>1</sub> over 12 hours Post-dose on Day 1: Trial 3006 (PFT Sub-Study, ITT Population)**



Source: CSR Figures PT003006, Figure 2.18.1B, p139

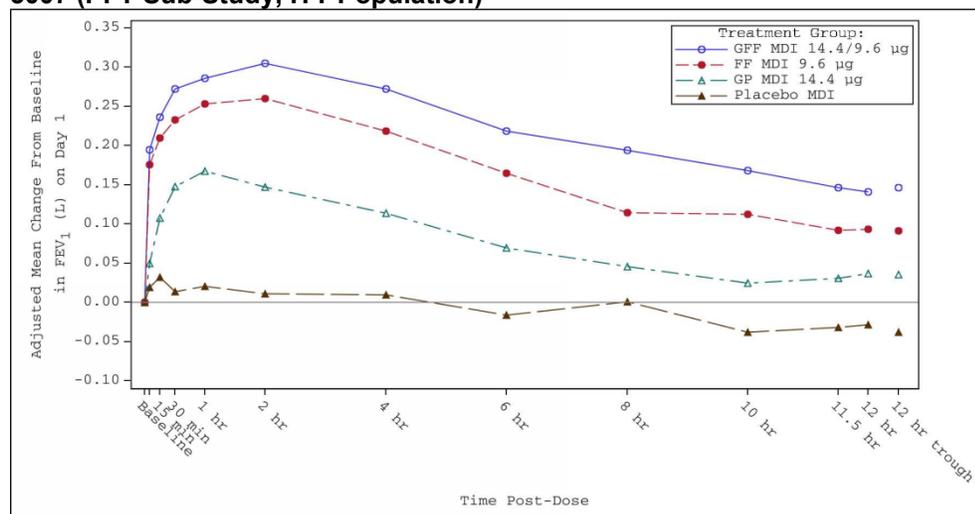
**Figure 31. Adjusted Mean Change from Baseline in FEV<sub>1</sub> over 12 hours Post-dose at Week 12: Trial 3006 (PFT Sub-Study, ITT Population)**



Source: CSR Figures PT003006, Figure 2.19.1B, p143

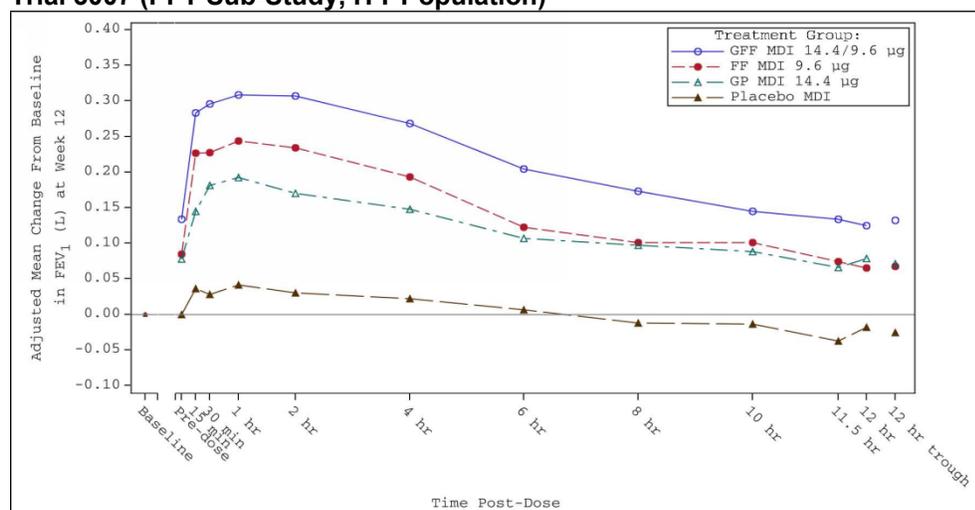
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**Figure 32. Adjusted Mean Change from Baseline in FEV<sub>1</sub> over 12 hours Post-dose on Day 1: Trial 3007 (PFT Sub-Study, ITT Population)**



Source: CSR Figures PT003007, Figure 2.18.1B, p140

**Figure 33. Adjusted Mean Change from Baseline in FEV<sub>1</sub> over 12 hours Post-dose at Week 12: Trial 3007 (PFT Sub-Study, ITT Population)**



Source: CSR Figures PT003007, Figure 2.19.1B, p142

**COPD exacerbations**

The rate of moderate to severe COPD exacerbations over 24 weeks as well as the hazard ratio for time to first moderate to severe exacerbation are shown in Table 21. Although there is trend toward exacerbation reduction in the active treatment groups in each trial, none of the effects demonstrate a statistically significant difference from placebo. It is also notable that the improvement is almost entirely based upon moderate COPD exacerbations since very few severe exacerbations (those requiring hospitalization) occurred.

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 NDA 208294

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**Table 21. Moderate to Severe COPD Exacerbations in Trials 3006 and 3007 (ITT Population)**

	Trial 3006					Trial 3007			
	GFF N=526	FF N=449	GP N=451	SHH N=451	PBO N=219	GFF N=510	FF N=437	GP N=439	PBO N=223
<b>Number and percentage of subjects with exacerbations, n (%)</b>									
Moderate	95 (18)	79 (18)	86 (19)	80 (18)	44 (20)	76 (15)	77 (18)	79 (18)	44 (20)
Severe	16 (3)	7 (2)	17 (4)	8 (2)	4 (2)	10 (2)	9 (2)	9 (2)	3 (1)
Moderate or Severe	106 (20)	85 (19)	103 (23)	87 (19)	47 (22)	85 (17)	83 (19)	88 (20)	47 (21)
<b>Rate of moderate to severe exacerbations</b>									
Adjusted rate per year <sup>1</sup>	0.57	0.51	0.62	0.50	0.69	0.45	0.61	0.55	0.61
Rate ratio vs placebo (95% CI)	0.83 (0.6, 1.2)	0.75 (0.5, 1.1)	0.90 (0.6, 1.3)	0.74 (0.5, 1.1)	--	0.74 (0.5, 1.1)	1.0 (0.7, 1.5)	0.91 (0.6, 1.4)	--
<b>Time to first moderate to severe exacerbation</b>									
Comparison to placebo Hazard ratio (95% CI)	0.79 (0.6, 1.1)	0.82 (0.6, 1.2)	1.0 (0.7, 1.4)	0.76 (0.5, 1.1)	--	0.68 (0.5, 1.0)	0.88 (0.6, 1.3)	0.88 (0.6, 1.3)	--
Abbreviations: FF=formoterol fumarate 9.6 mcg BID, GFF=glycopyrrolate/formoterol fumarate 18mcg/9.6 mcg BID, GP=glycopyrrolate 18 mcg BID, PBO=placebo, SHH=Spiriva Handihaler 18 mcg QD COPD exacerbations considered separate events provided that ≥7 days were between recorded stop and start dates. Rate of exacerbations per year = total number of exacerbations / total years of exposure across all subjects for the treatment. Time during an exacerbation or in the 7 days following an exacerbation was not included in the calculation of exposure. Time to COPD exacerbation (weeks) = (date of 1 <sup>st</sup> COPD exacerbation – first treatment administration date +1) / 7 <sup>1</sup> Adjusted for baseline percent predicted FEV1, baseline COPD exacerbation history (yes/no), baseline CAT score, smoking status at baseline (former/current), season at baseline (winter/spring/summer/fall), ICS use at baseline (yes/no) Source: CSR Tables PT003006, Tables 2.54.1 and 2.55, p1877 and 1887; PT003007, Tables 2.54.1 and 2.55, p1360 and 1370									

### Transitional Dyspnea Index (TDI)

This endpoint was likely included for registration with the EMA and other regulatory bodies since the weaknesses of this instrument preclude its use to support a dyspnea claim in the U.S. as discussed previously during a Pulmonary and Allergy Drug Advisory Committee meeting on September 6, 2002. Nonetheless, based on change of ≥1 unit, determined to be the minimally important difference, there was improvement in total symptom scores over 24 weeks for each active treatment group over placebo in both trials, with the largest improvements in the GFF group.

### 6.1.7 Subpopulations

There was no significant impact of gender, age class (≥ or < 65 years), race, or region (US vs ex-US) on efficacy. The primary endpoint results for each subgroup favored GFF over placebo and over each of the monocomponents. However, subgroup analyses, particularly by race, are limited by the relatively small number of subjects in certain subpopulations. For instance, 8% of subjects in the pivotal studies were Black or African American and 3% were Hispanic while less than 1% were Asian. Although the percentages are lower than the proportion of each racial/ethnic subgroup in the overall U.S. population, they are sufficiently representative of the proportion with COPD.

Subgroup analyses based on disease characteristics such as COPD severity (moderate/severe/very severe), smoking status (former/current), baseline ICS use

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(yes/no), baseline reversibility to Ventolin HFA (yes/no), and baseline reversibility to Atrovent HFA (yes/no) demonstrated primary endpoint results that again favored GFF over placebo and each of the monocomponents. Similar treatment responses were demonstrated within each subgroup with following exception: patients who had bronchodilator reversibility to either Ventolin or Atrovent at baseline had greater improvements in trough FEV<sub>1</sub> at 24 weeks than patients without baseline reversibility to a bronchodilator.

### **6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations**

The phase 3 program evaluated a single fixed dose combination of GFF compared to the single ingredient components, GP and FF, and the application puts forward only the GFF 18mcg/9.6 mcg BID dose for approval. See Section 4.4 for a discussion for the trials supporting dose selection in the phase 3 trials.

### **6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects**

The LSM change from baseline in morning pre-dose trough FEV<sub>1</sub> over 52 weeks at the end of the 28-week extension study 3008 was 133 mL (95% CI 122, 144) in the GFF group compared to 76 mL (95% CI 64, 88), 68 mL (95% CI 56, 80), 107 mL (95% CI 91, 124) in the GP, FF, and SHH groups, respectively. These results include the ITT population from the lead-in trials 3006 and 3007 and extension study 3008. FEV<sub>1</sub> results from only patients who entered study 3008 were slightly higher for all treatment groups except SHH. Although it appears as if the FEV<sub>1</sub> treatment response was relatively stable over time across treatment groups, the interpretation of this data is limited by the absence of a placebo-control in the 28-week extension study and does not take into account factors such as drop-outs and missing data.

### **6.1.10 Additional Efficacy Issues/Analyses**

A dedicated open-label, uncontrolled dose indicator study (PT003016) showed a 96% correlation between dose indicator and doses taken as recorded by patients in eDiaries over a 4-week period. This study was conducted due to the relatively low (~83-84%) consistency between subject-reported count and dose indicator count recorded in the eCRF at week 4 in the pivotal trials. As one might expect, the subject-reported count tended to be lower than the dose indicator count since subjects had to record the dose taken in their eDiary. There was high consistency between dose counts at week 2 in both trials (91-93%). Refer to the CMC review by Drs. Arthur Shaw and Craig Bertha for a more in depth review of study PT003016.

## **7 Review of Safety**

### **Safety Summary**

The primary safety database used to evaluate the safety of GFF included two phase 3 trials (3006 and 3007) and the safety extension study, 3008. Pivotal trials 3006 and 3007 were 24 weeks in duration and placebo-controlled while extension study 3008 was 26 weeks in duration and provided long-term safety data over a total of 52 weeks in a subset of subjects, but lacked a placebo control. In total, 3699 unique subjects were treated (3710 in the safety population including multiple enrollers) and 1036 subjects received GFF, of whom 253 were exposed for 1 year. The extent of exposure was adequate for review given that both components of GFF are older drugs with well-characterized safety profiles and that large safety trials with Spiriva Handihaler and Spiriva Respimat have alleviated many of the previous concerns regarding the cardiovascular safety of anticholinergic drugs.

Safety assessments conducted in the clinical development program included adverse event monitoring, clinical laboratory testing, vital signs, 12-lead ECGs, 24-hour Holter monitoring for a subset of patients, and a thorough QT study and were sufficient to support the safety evaluation of GFF.

A total of 14 deaths (12 during the pivotal trials, 2 during the extension study) occurred in the clinical development program. The percentage of patients with fatal events was <1% overall and for all blinded treatment groups. The number of deaths, cardiovascular deaths in particular, was relatively low given the background mortality rate in COPD patients and distributed fairly proportionately across treatment groups with no discernable pattern by system organ class or preferred term.

With regard to nonfatal SAEs and adverse dropouts, the overall incidences were similar across treatment with no meaningful differences in type or frequency of events reported. An evaluation of adverse events of special interest such as cardiovascular/MACE events and potential beta-adrenergic or anticholinergic-related side effects did not reveal any major differences between treatment groups or identify any new safety signals. Clinical laboratory data, vital sign measurements, serial ECGs and Holter-monitoring were unremarkable and supported the overall safety assessment.

In conclusion, the size of the safety database and extent of exposure were adequate to permit review. The safety data for the GFF development program are consistent with those observed with similar anticholinergic/LABA products approved for COPD and do not reveal any new safety concerns. The safety profile of GFF is acceptable.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The primary safety database used to evaluate safety included two phase 3 pivotal trials (3006 and 3007) along with the safety extension study 3008, all of which have been described previously. All trials were randomized, double-blind, and parallel group in design. The placebo control arm in the pivotal trials was not carried forward into the extension study, so while theoretically blinded, subjects participating in study 3008 recognized that they were receiving active study drug. To a limited extent, crossover phase 2 studies provided an evaluation of a dose-response; however, these studies were much shorter in duration, only 7 to 14 days in length, and therefore, were not included in the primary safety database.

### 7.1.2 Categorization of Adverse Events

Adverse events (AEs) were defined as any untoward medical occurrence associated with the use of a drug in humans whether or not considered drug related. A serious adverse event (SAE) was defined as any AE which resulted in death, was immediately life-threatening, resulted in persistent or significant disability/incapacity, required or prolonged patient hospitalization, was a congenital anomaly/birth defect, or was deemed serious due to any other medically important condition (i.e., if based upon appropriate medical judgment, it was an important medical event that may have jeopardized the patient, and may have required medical or surgical intervention to prevent one of the other above mentioned outcomes). AEs that occurred between signing of the informed consent and randomization were summarized as medical history and were not considered a treatment emergent adverse event (TEAE) unless the event met criteria for an SAE. AEs that were ongoing at the follow-up or final visit were followed until the event stabilized or resolved; however, investigators were not obligated to actively follow subjects after the completion of the study. If investigators became aware of post-study SAEs occurring up to 14 days after the last dose of study drug, they were to report the event to the Applicant regardless of causality or relatedness. Adverse events from all trials were coded according to MedDRA, version 17.1. In general the Applicant's coding of events from verbatim terms provided by investigators and subjects to preferred terms (PTs) appears appropriate and consistent across trials and treatment groups.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The clinical development program to support the safety of GFF, (b) (4) includes 17 completed studies: 13 in subjects with COPD and 4 in healthy subject volunteers. The Applicant's grouping of studies is depicted in Figure 34. Many of the studies are not relevant to the review of safety either because of the patient population or limited number of doses. This safety review focuses on the Applicant's phase 3

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Integrated Summary of Safety (ISS) consisting of safety data from the 24-week pivotal trials 3006 and 3007. To evaluate long-term safety over 52 weeks of treatment, data from the pooled pivotal studies were integrated with the 28-week extension study 3008; however, it should be noted that exposure in the placebo group was only 24 weeks since a placebo treatment arm was not carried into extension study 3008. Therefore, tables representing data from all three trials include the placebo group as a reference, but directly comparing the incidence over placebo should be done with caution.

However, in nearly all cases the incidence over 52 weeks did not vary substantially from the incidence over the 24-week placebo controlled portion of the study. Lastly, the Applicant's phase 2 grouping of the shorter dose-ranging studies were used to evaluate dose-related adverse effects.

Figure 34. Integrated Study Groupings

Integrated Study Groupings in Subjects with COPD				
Phase III Pivotal Studies Grouping	Phase III Pivotal and Long-term Studies Grouping		Phase IIb Chronic Dosing (7- to 14-Day) Studies Grouping	
GFF, GP, FF MDI	GFF, GP, FF MDI		GFF, GP, FF MDI	GP MDI
PT003006	PT003006		PT0031002	PT001002
PT003007	PT003007		PT003003	PT001003
	PT003008		PT003004	
			PT003005	
Studies Not Integrated				
Phase IIIb Dose Indicator Study in Subjects with COPD	Phase I/II Single-Dose Studies in Subjects with COPD		Phase I Single-Dose Studies in Healthy Subjects	
GFF MDI	GP MDI	FF MDI	GFF, GP, FF MDI	GFF, GP MDI
PT003016	PT0010801	PT0050801	PT0030901	PT003009 <sup>a</sup>
		PT005003		PT003010
			GFF MDI	
			PT010001	

Abbreviations: COPD=chronic obstructive pulmonary disease; FF=Formoterol Fumarate; GFF=Glycopyrronium and Formoterol Fumarate; GP=Glycopyrronium; ISS=Integrated Summary of Safety; MDI=metered dose inhaler.

<sup>a</sup> Study PT003009, a thorough QT study, included GFF MDI 14.4/9.6 µg and suprathreshold doses of GFF MDI 115.2/38.4 µg and GP MDI 115.2 µg, but did not include any FF MDI dose.

Source: ISS, Table 1-4, p47

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent and duration of exposure in controlled clinical trials to GFF adequately meets ICH guidelines for the safety evaluation of drugs intended for chronic use of a non-life threatening disease. While the clinical trial safety database is smaller in size and scope than that of some other approved inhaled anticholinergic/LABA drugs for COPD, particularly for 1-year exposure, the safety data provided by the Applicant is sufficient for the proposed GFF product which combines two older drugs with well-characterized safety profiles, neither of which are a new molecular entity. In addition, large safety trials

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with SHH and Spiriva Respimat (UPLIFT and TIOSPIR) have alleviated the previous concerns surrounding cardiovascular safety of anticholinergic drugs. Summaries of the extent of exposure in the phase 3 clinical development program and subject disposition in extension study 3008 are provided in Table 22 and Table 23, respectively.

**Table 22. Summary of Treatment Exposure**

	GFF	FF	GP	Placebo	SHH
<b>Phase 3 ISS</b>					
Treated	1036	890	890	443	451
Exposure in days					
Mean (SD)	155 (39)	151 (45)	150 (43)	141 (54)	158 (34)
Median (Min, Max)	169 (2, 207)	169 (1, 220)	169 (1, 195)	169 (4, 202)	169 (1, 220)
Exposure in patient-years	439	367	366	171	195
<b>Phase 3 ISS + extension study</b>					
Treated	1036	890	890	443	451
Exposure in days					
Mean (SD)	206 (101)	194 (100)	195 (101)	141 (54)	227 (105)
Median (Min, Max)	169 (2, 402)	169 (1, 387)	169 (2, 393)	169 (4, 202)	170 (4, 382)
Exposure in patient-years	585	473	476	171	281

Source: ISS, Table 1-12, p66; CSR PT003008, Table 6-16, p 114

**Table 23. Subject Disposition, Extension Study 3008**

	GFF	FF	GP	SHH	Total
<b>Safety Population</b>	<b>Number of Patients</b>				
	290	213	219	171	893
<b>Disposition</b>	<b>Number of Patients (% of Safety Population)</b>				
Completed	253 (87)	187 (88)	191 (87)	147 (86)	778 (87)
Early discontinuation	37 (13)	26 (12)	28 (13)	24 (14)	115 (13)
<b>Reason for withdrawal</b>					
Administrative reasons	1 (<1)	0	0	4 (2)	5 (1)
Adverse event	12 (4)	4 (2)	7 (3)	3 (2)	26 (3)
Lack of efficacy	2 (1)	2(1)	1 (1)	0	5 (1)
Lost to follow-up	1 (<1)	2 (1)	3 (1)	4 (2)	10 (1)
Major protocol deviation	0	0	1 (1)	0	1 (<1)
Physician decision	0	1 (1)	1 (1)	0	2 (<1)
Protocol specified criteria	10 (3)	3 (1)	4 (2)	6 (4)	23 (3)
Withdrawal by subject	11 (4)	14 (7)	10 (5)	7 (4)	42 (5)

Source: Reviewer generated table in JReview using ADSL (SAF08FL=Y, TRTA and COMPLFL variables) and DS (DSDECOD and DSTERM variables) datasets from PT003008

As discussed in Section 6.1.1, the Applicant noted that several subjects enrolled either in the same study or more than one pivotal study under multiple subject identification numbers. Two subjects, representing five unique subject identification numbers, received overlapping treatments in trials 3006 and 3007, and thus were excluded entirely from the ITT and safety populations. Subjects who participated in both trials or

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in more than one study site within a trial, but did not receive overlapping treatments were included in the safety population. Two subjects, representing six unique subjects IDs, were included in the safety population of trial 3006, but not trial 3007. Refer back to Table 10 for the complete listing of subjects included in the safety population. Of note, the overall number of subjects in the Applicant's safety population represents the number of unique subject ID's rather than number of unique subjects since some subjects are counted more than once. However, none of these subjects experienced death or a serious adverse event, and the relatively small number of subjects had no substantial impact on the evaluation of other AEs. Therefore, the Applicant's inclusion of these subjects in the safety population appears reasonable and the safety analysis presented in this review utilizes the safety population defined by the Applicant.

### **7.2.2 Explorations for Dose Response**

Only single doses of the GP and FF monocomponents and GFF combination product were evaluated in the phase 3 program; however, numerous doses were explored in phase 2 dose-ranging studies as discussed in Section 4.4.2.

### **7.2.3 Special Animal and/or In Vitro Testing**

No special animal and/or *in vitro* testing was conducted or required to provide additional safety information for GFF.

### **7.2.4 Routine Clinical Testing**

Routine clinical testing in the primary efficacy and long-term safety extension trials consisted of serum chemistry (albumin, alkaline phosphatase, total bilirubin, calcium, total cholesterol, magnesium, phosphate, sodium, potassium, chloride, creatinine, GGT, glucose, total protein, AST, ALT, bicarbonate, and triglycerides), hematology (hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count), urinalysis, and 12-lead ECGs. Safety lab tests and ECGs were analyzed/reviewed by a central laboratory/facility. In addition, 24-hour Holter monitoring was conducted in a subset (~36%) of patients in trial 3007. The routine clinical testing was adequate.

### **7.2.5 Metabolic, Clearance, and Interaction Workup**

Population PK analyses were performed to evaluate the effects of demographic factors on metabolism and clearance. Other than an evaluation of the interaction between the two components, the clinical development program did not include any formal drug-drug interaction studies. See Section 4.4.3 for a more detailed discussion.

## 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The clinical development program identified adverse events of special interest (AESI), primarily based on the known pharmacological effects of the two drug classes (LAMA and LABA) contained in the combination. The AESI categories included: cardiovascular adverse events, tremor, urinary effects, ocular effects, gastrointestinal events, anticholinergic effects, and paradoxical bronchospasm. The results of these analyses are provided in Section 7.3.5.

## 7.3 Major Safety Results

### 7.3.1 Deaths

A total of 12 treatment-emergent deaths (on treatment or within 14 days post-treatment) occurred in the pivotal trials. Two additional deaths occurred during the extension study (acute myocardial infarction in the SHH group and one cardiac arrest in the FF group). Note, some subjects had more than one reported AE associated with their death.

**Table 24. Summary of Deaths by SOC and PT, Phase 3 Trials (3006, 3007, 3008), Safety Population**

System Organ Class / Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451	Total N=3710
<b>Number of subjects with any fatal AE, n (%)</b>	5 (0.5)	2 (<1)	1 (<1)	1 (<1)	5 (1.1)	14 (<1)
<b>Cardiac disorders</b>						
Acute myocardial infarction	1 (<1)	0	0	0	1 (<1)	2 (<1)
Cardiac arrest	1 (<1)	2 (<1)	0	0	0	3 (<1)
<b>Gastrointestinal disorders</b>						
Nausea	0	1 (<1)	0	0	0	1 (<1)
Small intestinal obstruction	0	1 (<1)	0	0	0	1 (<1)
<b>General disorders and administration site conditions</b>						
Death	1 (<1)	0	0	1 (<1)	0	2 (<1)
Sudden cardiac death	0	0	0	0	1 (<1)	1 (<1)
<b>Injury, poisoning and procedural complications</b>						
Gunshot wound	1 (<1)	0	0	0	0	1 (<1)
Overdose	0	0	0	0	1 (<1)	1 (<1)
<b>Metabolism and nutrition disorders</b>						
Hyperglycaemia	0	1 (<1)	0	0	0	1 (<1)
Hyperkalaemia	0	1 (<1)	0	0	0	1 (<1)
Hyperphosphataemia	0	1 (<1)	0	0	0	1 (<1)
Hypocalcaemia	0	1 (<1)	0	0	0	1 (<1)
Hypoglycaemia	0	1 (<1)	0	0	0	1 (<1)
Metabolic acidosis	0	1 (<1)	0	0	0	1 (<1)
<b>Neoplasms benign, malignant and unspecified (including cysts and polyps)</b>						
Metastatic neoplasm	1 (<1)	0	0	0	0	1 (<1)
<b>Psychiatric disorders</b>						
Completed suicide	0	0	0	0	1 (<1)	1 (<1)
Intentional self-injury	0	0	0	0	1 (<1)	1 (<1)
Psychotic disorder	0	1 (<1)	0	0	0	1 (<1)

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System Organ Class / Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451	Total N=3710
<b>Renal and urinary disorders</b>						
Bladder cyst	1 (<1)	0	0	0	0	1 (<1)
Renal failure acute	0	1 (<1)	0	0	0	1 (<1)
<b>Respiratory, thoracic and mediastinal disorders</b>						
Acute respiratory failure	0	1 (<1)	0	0	0	1 (<1)
Pneumonia aspiration	0	0	1 (<1)	0	0	1 (<1)
<b>Vascular disorders</b>						
Peripheral artery thrombosis	0	1 (<1)	0	0	0	1 (<1)

Source: Reviewer generated table in JReview using ISS Phase 3 datasets, ADSL (SAFFL=Y; TRT01A variable) and ADAE (TRTEMFL=Y and DTHFL=Y; AEBODSYS and AEDECOD variables) and PT003008 datasets, ADSL (SAFFL=Y, TRT01A variable) and ADAE (TRTEMFL=Y, DTHFL=Y, APHASE=extension; AEBODSYS and AEDECOD variables)

The Applicant also employed an external adjudication committee to determine the primary cause of death for each fatality as either cardiovascular, respiratory, or “other” in nature. Across treatment groups there were no major imbalances in frequencies of death by either SOC and PT or the adjudicated primary cause of death; however, the overall number of deaths was low and as a result the number of deaths within each category are too small to interpret. Although there were several deaths in the SHH treatment group that appear to be suicidal in nature, the fact that a suicidality signal was not observed during larger studies in the SHH clinical development program or during its extensive post marketing history is reassuring.

### 7.3.2 Nonfatal Serious Adverse Events

A listing of nonfatal SAEs by SOC and PT that occurred during the 24-week pivotal trials and 26-week extension study is provided in Table 25. Only PTs that were reported by 2 or more subjects are listed individually. Related PTs have been combined and are denoted with an asterisk.

**Table 25. Nonfatal SAEs by SOC and PT over 52 Weeks in the Safety Population (Trials 3006, 3007, and 3008)**

System Organ Class / Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451
Subjects with SAEs in 3006/ 3007, n (%)	76 (7)	65 (7)	72 (8)	30 (7)	32 (7)
Subjects with SAEs in 3008, n(%) <sup>†</sup>	36 (12)	14 (7)	17 (8)	---	12 (7)
<b>Blood and lymphatic system disorders</b>	1 (0.1)	0	0	1 (0.2)	0
<b>Cardiac disorders</b>	14 (1)	3 (0.3)	12 (1)	6 (1)	2 (0.4)
(Acute) myocardial infarction, myocardia ischemia*	5 (0.5)	1 (0.1)	3 (0.3)	4	0
Atrial fibrillation	4 (0.4)	1 (0.1)	2 (0.2)	0	0
Atrial flutter	0	0	2 (0.2)	0	0
Atrioventricular block, complete, second degree*	0	1 (0.1)	1 (0.1)	1 (0.2)	0
Bradycardia	0	0	2 (0.2)	0	0
Cardiac failure congestive	0	0	2 (0.2)	0	1 (0.2)
Coronary artery disease, occlusion, stenosis*	2	0	2	1 (0.2)	1 (0.2)
<b>Ear and labyrinth disorders</b>	0	1 (0.1)	0	0	0
<b>Endocrine disorders</b>	0	0	0	0	1 (0.2)

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System Organ Class / Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451
<b>Gastrointestinal disorders</b>	<b>11 (1)</b>	<b>9 (1)</b>	<b>8 (1)</b>	<b>0</b>	<b>4 (1)</b>
Abdominal pain, lower, upper*	3 (0.3)	2 (0.2)	0	0	0
(Upper) Gastrointestinal haemorrhage*	0	2 (0.2)	1 (0.1)	0	0
(Small) Intestinal obstruction*	1	1 (0.1)	3 (0.3)	0	2
Pancreatitis acute, chronic*	1 (0.1)	1 (0.1)	0	0	0
<b>General disorders and administration site conditions</b>	<b>8 (1)</b>	<b>7 (1)</b>	<b>3 (0.3)</b>	<b>2 (1)</b>	<b>2 (0.4)</b>
Chest discomfort, chest pain, non-cardiac chest pain*	6 (0.6)	6 (0.7)	3 (0.3)	2 (0.5)	1 (0.2)
<b>Hepatobiliary disorders</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>2 (0.4)</b>
Cholecystitis, acute cholecystitis*	0	1 (0.1)	0	0	1 (0.2)
Cholelithiasis	1 (0.1)	0	0	1 (0.2)	1 (0.2)
<b>Infections and infestations</b>	<b>22 (2)</b>	<b>12 (1)</b>	<b>23 (3)</b>	<b>8 (2)</b>	<b>6 (1)</b>
Bronchitis	0	0	1 (0.1)	1 (0.2)	0
Cellulitis, cellulitis staphylococcal*	1 (0.1)	0	1 (0.1)	1 (0.2)	2 (0.4)
Diverticulitis	0	2 (0.2)	1 (0.1)	0	0
Influenza	1 (0.1)	1 (0.1)	0	0	0
Pneumonia; lobar, bacterial, pneumococcal, necrotising atypical*	18 (2)	6 (0.7)	15 (2)	4 (1)	2 (0.4)
Sepsis, septic shock, urosepsis, post-procedural sepsis*	2 (0.2)	0	4 (0.4)	1 (0.2)	1 (0.2)
Urinary tract infection, pyelonephritis*	2 (0.2)	1 (0.1)	0	2 (0.5)	0
<b>Injury, poisoning and procedural complications</b>	<b>3 (0.3)</b>	<b>6 (1)</b>	<b>8 (1)</b>	<b>2 (1)</b>	<b>4 (1)</b>
Alcohol poisoning	0	0	2 (0.2)	0	0
Fall	0	1 (0.1)	0	0	1 (0.2)
Fibula fracture	0	1 (0.1)	1 (0.1)	0	1 (0.2)
Rib fracture	0	1 (0.1)	1 (0.1)	1 (0.2)	0
<b>Investigations</b>	<b>0</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>	<b>0</b>
<b>Metabolism and nutrition disorders</b>	<b>3 (0.3)</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>	<b>1 (0.2)</b>
<b>Musculoskeletal and connective tissue disorders</b>	<b>4 (0.4)</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>
Osteoarthritis	1 (0.1)	0	0	1 (0.2)	0
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>	<b>15 (1)</b>	<b>9 (1)</b>	<b>8 (1)</b>	<b>2 (1)</b>	<b>8 (2)</b>
Bladder cancer, bladder neoplasm, transitional cell carcinoma*	1 (0.1)	0	3 (0.3)	0	0
Breast cancer	2 (0.2)	0	0	1 (0.2)	0
Laryngeal cancer, laryngeal cancer (stage 0)	0	1 (0.1)	0	0	1 (0.2)
Lung adenocarcinoma	1 (0.1)	2 (0.2)	1 (0.1)	1 (0.2)	0
Lung neoplasm malignant	2 (0.2)	2 (0.2)	0	0	0
Oropharyngeal/oral cavity squamous cell carcinoma*	0	0	1 (0.1)	0	1 (0.2)
Prostate cancer	0	2 (0.2)	1 (0.1)	0	0
Squamous cell carcinoma of lung	2 (0.2)	0	0	0	3 (0.7)
Squamous cell carcinoma of skin	1 (0.2)	0	0	0	1 (0.2)
<b>Nervous system disorders</b>	<b>4 (0.4)</b>	<b>4 (0.4)</b>	<b>6 (1)</b>	<b>0</b>	<b>2 (0.4)</b>
Cerebrovascular accident	1 (0.1)	0	1 (0.1)	0	0
Convulsion, generalised tonic-clonic seizure*	0	0	1 (0.1)	0	1 (0.2)

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System Organ Class / Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451
Dizziness, pre-syncope*	2	0	0	0	0
Syncope	0	1 (0.1)	3 (0.3)	0	0
Transient ischaemic attack	0	2 (0.2)	1 (0.1)	0	1 (0.2)
<b>Psychiatric disorders</b>	<b>0</b>	<b>1 (0.1)</b>	<b>6 (1)</b>	<b>0</b>	<b>1(0.2)</b>
Anxiety	0	0	2 (0.2)	0	0
Suicide attempt	0	0	2 (0.2)	0	0
<b>Renal and urinary disorders</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>2 (0.2)</b>	<b>1 (0.2)</b>	<b>0</b>
Renal failure acute	0	1 (0.1)	0	1 (0.2)	0
<b>Reproductive system disorders</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>37 (4)</b>	<b>25 (3)</b>	<b>35 (4)</b>	<b>13 (3)</b>	<b>12 (3)</b>
Acute respiratory distress syndrome	1 (0.1)	0	2 (0.2)	0	0
Acute respiratory failure	2 (0.2)	4 (0.4)	2 (0.2)	2 (1)	0
Chronic obstructive pulmonary disease	32 (3)	19 (2)	30 (3)	11 (3)	12 (3)
Pulmonary embolism	2 (0.2)	0	1 (0.1)	1 (0.2)	0
Respiratory failure	4 (0.4)	0	2 (0.2)	0	0
<b>Skin and subcutaneous tissue disorders</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>	<b>1 (0.2)</b>	<b>0</b>
<b>Surgical and medical procedures</b>	<b>0</b>	<b>0</b>	<b>1 (0.1)</b>	<b>0</b>	<b>0</b>
<b>Vascular disorders</b>	<b>9 (1)</b>	<b>6 (1)</b>	<b>4 (0.4)</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>
Aortic aneurysm	1 (0.1)	3 (0.3)	0	0	0
Deep vein thrombosis	2 (0.2)	1 (0.1)	0	0	1 (0.2)
Hypertension, essential hypertension, malignant hypertension*	1 (0.1)	1 (0.1)	3 (0.3)	0	0
Hypertensive crisis, emergency*	1 (0.1)	1 (0.1)	0	0	0
Peripheral artery stenosis	2 (0.2)	0	0	0	0
Peripheral vascular disorder	1 (0.1)	1 (0.1)	0	0	0

†Percentage of subjects enrolled in study 3008  
 Source: Reviewer generated table in JReview using ISS phase 3 datasets, ADSL (SAFFL=Y) and ADAE (TRTEMFL=Y, AESER=Y, DTHFL≠Y)

In general, the PTs reported as nonfatal SAEs were balanced across treatment groups. The most commonly reported PT was COPD followed by pneumonia; however, most other PTs were reported for only two patients or fewer in any one treatment group. While more cardiac disorder SAEs occurred in the GFF (1%) and GP (1%) treatment groups compared to either the FF (0.3%) or SHH (0.4%) groups, the frequencies were similar to the placebo group (1%).

In extension study 3008, there was a higher percentage of subjects reporting nonfatal SAEs in the GFF treatment group (12%) compared to other active treatment groups (FF 7%, GP 8%, SHH 7%). However, the overall pattern of nonfatal SAEs mirrored the pivotal trials – the most common PTs were COPD and pneumonia, which were relatively balanced across treatment groups, while the remainder of events occurred in only 1 or 2 subjects. There was no apparent increase in any particular type of event with prolonged use during the 26 week extension study.

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A comparison of nonfatal SAEs by SOC/PT and by Standard MedDRA Queries (SMQs) between the GFF and placebo groups did not reveal any additional safety concerns. Although cardiovascular-related SMQs predominated, the differences in frequency versus placebo were relatively small.

### 7.3.3 Dropouts and/or Discontinuations

A summary of adverse events leading to dropout (discontinuation of study treatment or withdrawal from the trial, including fatal SAEs) is provided in Table 26. Nonfatal adverse events leading to dropout are presented by SOC and PT in Table 27. Only PTs that were reported by 2 or more subjects are listed individually; however, related PTs have been combined and are denoted with an asterisk.

**Table 26. Summary of Dropouts Related to Adverse Events in Phase 3 Trials**

	<b>GFF</b>	<b>FF</b>	<b>GP</b>	<b>Placebo</b>	<b>SHH</b>
	<b>N</b>	<b>N</b>	<b>N</b>	<b>N</b>	<b>N</b>
	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>	<b>n (%)</b>
3006/3007*	1036	890	890	443	451
	64 (6)	47 (5)	55 (6)	33 (7)	22 (5)
3008†	290	213	219	--	171
	17 (6)	6 (3)	9 (4)	--	6 (4)
<b>Total*</b>	<b>81 (8)</b>	<b>53 (6)</b>	<b>64 (7)</b>	<b>33 (7)</b>	<b>28 (6)</b>

Source: ISS Table 2-11, p105 and CSR PT003008, Table 7-29, p193  
 \*percentages based on entire safety population  
 †percentage based on number of subjects enrolled in PT003008

**Table 27. Nonfatal adverse events leading to discontinuation, Trials 3006, 3007, and 3008 (Safety Population)**

<b>SOC/PT</b>	<b>GFF N=1036</b>	<b>FF N=890</b>	<b>GP N=890</b>	<b>Placebo N=443</b>	<b>SHH N=451</b>
<b>Number of nonfatal adverse dropouts, n (%)</b>	<b>77 (7)</b>	<b>51 (6)</b>	<b>63 (7)</b>	<b>32 (7)</b>	<b>23 (5)</b>
<b>Blood and lymphatic system disorders</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>2 (0.2)</b>	<b>0</b>	<b>0</b>
Leukocytosis	0	0	2 (0.2)	0	0
<b>Cardiac disorders</b>	<b>8 (0.8)</b>	<b>5 (0.6)</b>	<b>11 (1)</b>	<b>3 (0.7)</b>	<b>2 (0.4)</b>
(Acute) myocardial infarction, ischemia*	2 (0.2)	1 (0.1)	3 (0.3)	3 (0.7)	0
Angina pectoris	0	0	1 (0.1)	0	0
Atrial fibrillation	2 (0.2)	1 (0.1)	1 (0.1)	0	0
Atrial flutter	1 (0.1)	0	2 (0.2)	0	0
Atrioventricular block, second degree*	0	1 (0.1)	1 (0.1)	0	0
Bundle branch block left	2 (0.2)	0	1 (0.1)	0	0
Cardiac failure congestive	1 (0.1)	0	1 (0.1)	0	1 (0.2)
Coronary artery disease, occlusion*	0	0	2 (0.2)	0	0
Extrasystoles	0	1 (0.1)	1 (0.1)	0	0
Ischaemic cardiomyopathy	1 (0.1)	0	1 (0.1)	0	0
<b>Eye disorders</b>	<b>1 (0.1)</b>	<b>2 (0.2)</b>	<b>0</b>	<b>1 (0.2)</b>	<b>0</b>
Diplopia, vision blurred*	1 (0.1)	1 (0.1)	0	0	0

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SOC/PT	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451
<b>Gastrointestinal disorders</b>	<b>4 (0.4)</b>	<b>3 (0.3)</b>	<b>3 (0.3)</b>	<b>2 (0.5)</b>	<b>1 (0.2)</b>
Dyspepsia, gastritis*	1 (0.1)	0	0	1 (0.2)	0
(Small) Intestinal obstruction*	0	1 (0.1)	0	0	1 (0.2)
Nausea, retching, vomiting*	1 (0.1)	0	2 (0.2)	2 (0.5)	0
<b>General disorders and administration site conditions</b>	<b>6 (0.6)</b>	<b>4 (0.4)</b>	<b>4 (0.4)</b>	<b>5 (1)</b>	<b>0</b>
Chest discomfort, pain, non-cardiac chest pain*	1 (0.1)	2 (0.2)	3 (0.3)	3 (0.7)	0
Fatigue, malaise*	4 (0.4)	2 (0.2)	1 (0.1)	0	0
<b>Hepatobiliary disorders</b>	<b>1 (0.1)</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>
<b>Immune system disorders</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.2)</b>	<b>0</b>
<b>Infections and infestations</b>	<b>15 (1)</b>	<b>7 (0.8)</b>	<b>15 (2)</b>	<b>4 (0.9)</b>	<b>2 (0.4)</b>
Bronchitis	0	1 (0.1)	1 (0.1)	3 (0.7)	0
Candida infection, fungal infection*	2 (0.2)	0	0	0	0
Pneumonia, atypical, lobar, necrotising*	11 (1)	3 (0.3)	9 (1)	1 (0.2)	2
Sepsis, septic shock*	1 (0.1)	0	1 (0.1)	0	0
Upper respiratory tract infection, nasopharyngitis*	0	1 (0.1)	1 (0.1)	0	0
Urinary tract infection, pyelonephritis*	2 (0.2)	0	1 (0.1)	0	0
<b>Injury, poisoning and procedural complications</b>	<b>1 (0.1)</b>	<b>2 (0.2)</b>	<b>1 (0.1)</b>	<b>0</b>	<b>1 (0.2)</b>
<b>Investigations</b>	<b>6 (0.6)</b>	<b>3 (0.3)</b>	<b>3 (0.3)</b>	<b>0</b>	<b>0</b>
Electrocardiogram QT prolonged, ECG change*	1 (0.1)	1 (0.1)	1 (0.1)	0	0
Hepatic enzyme increased, liver function test abnormal*	4 (0.4)	1 (0.1)	0	0	0
Neutrophil count increased, white blood cell count increased*	0	0	2 (0.2)	0	0
<b>Metabolism and nutrition disorders</b>	<b>1 (0.1)</b>	<b>0</b>	<b>3 (0.3)</b>	<b>1 (0.2)</b>	<b>0</b>
Hypernatraemia	1 (0.1)	0	1 (0.1)	0	0
<b>Musculoskeletal and connective tissue disorders</b>	<b>2 (0.2)</b>	<b>1 (0.1)</b>	<b>0</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>
Arthralgia	0	0	0	1 (0.2)	1 (0.2)
Muscle spasms	1 (0.1)	1 (0.1)	0	0	0
<b>Neoplasms benign, malignant and unspecified</b>	<b>7 (0.7)</b>	<b>3 (0.3)</b>	<b>4 (0.4)</b>	<b>2 (0.5)</b>	<b>4 (0.9)</b>
Bladder cancer, transitional cell carcinoma*	0	0	1 (0.1)	1 (0.2)	0
Breast cancer	1 (0.1)	0	0	0	1 (0.2)
Lung adenocarcinoma	1 (0.1)	2 (0.2)	0	1 (0.2)	0
Lung neoplasm malignant	2 (0.2)	0	0	0	0
Squamous cell carcinoma of lung	2 (0.2)	0	0	0	1 (0.2)
<b>Nervous system disorders</b>	<b>6 (0.6)</b>	<b>3 (0.3)</b>	<b>4 (0.4)</b>	<b>0</b>	<b>1 (0.2)</b>
Cerebrovascular accident, transient ischemic attack*	1 (0.1)	0	1 (0.1)	0	0
Convulsion, generalised tonic-clonic seizure*	0	0	2 (0.2)	0	1 (0.2)
Dizziness, presyncope*	2 (0.2)	0	0	0	0
Headache	1 (0.1)	2 (0.2)	1 (0.1)	0	0
Tremor	2 (0.2)	1 (0.1)	1 (0.1)	0	0
<b>Psychiatric disorders</b>	<b>0</b>	<b>1 (0.1)</b>	<b>5 (0.6)</b>	<b>1 (0.2)</b>	<b>0</b>
Agitation	0	0	2 (0.2)	0	0
Depression, major depression*	0	0	2 (0.2)	0	0
<b>Renal and urinary disorders</b>	<b>2 (0.2)</b>	<b>1 (0.1)</b>	<b>1 (0.1)</b>	<b>1 (0.2)</b>	<b>0</b>
<b>Respiratory, thoracic and mediastinal disorders</b>	<b>37 (4)</b>	<b>19 (2)</b>	<b>32 (4)</b>	<b>15 (3)</b>	<b>9 (2)</b>
Acute respiratory distress syndrome	1 (0.1)	0	1 (0.1)	0	0
Acute respiratory failure, respiratory failure*	4 (0.4)	1 (0.1)	1 (0.1)	1 (0.2)	0

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SOC/PT	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451
Bronchospasm, bronchospasm paradoxical, wheezing*	1 (0.1)	2 (0.2)	0	1 (0.2)	0
Chronic obstructive pulmonary disease	24 (2)	12 (1)	24 (3)	8 (2)	8 (2)
Cough, productive cough*	1 (0.1)	1 (0.1)	1 (0.1)	0	0
Dyspnea	3 (0.3)	3 (0.3)	2 (0.2)	7 (2)	1 (0.2)
Oropharyngeal pain	0	1 (0.1)	2 (0.2)	0	0
Pulmonary arterial hypertension, pulmonary hypertension*	1 (0.1)	0	1 (0.1)	0	0
Pulmonary embolism	2 (0.2)	0	0	0	0
<b>Skin and subcutaneous tissue disorders</b>	<b>1 (0.1)</b>	<b>0</b>	<b>0</b>	<b>1 (0.2)</b>	<b>1 (0.2)</b>
Rash, rash generalized*	1 (0.1)	0	0	0	1 (0.2)
<b>Surgical and medical procedures</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>0</b>	<b>1 (0.2)</b>
<b>Vascular disorders</b>	<b>0</b>	<b>3 (0.3)</b>	<b>5 (0.6)</b>	<b>2 (0.5)</b>	<b>1 (0.2)</b>
Deep vein thrombosis	0	1 (0.1)	0	0	1 (0.2)
Hypertension	0	0	3 (0.3)	1 (0.2)	0

Source: Reviewer generated table in JReview using ISS Phase 3 datasets: ADSL (SAFFL=Y by TRT01A) and ADAE (TRTEMFL=Y, ADFL=Y, DTHFL≠Y, AESDTH≠Y by AEBODSYS and AEDECOD)

The overall percentage of patients with any TEAE leading to discontinuation is generally balanced across treatment groups. In addition, the percentage of adverse dropouts due to cardiac disorders was also similar across treatment groups. The most commonly reported PTs for adverse dropouts were COPD and pneumonia, but no major differences were observed based on treatment. Most PTs were reported for two patients or fewer. Similar to the findings for nonfatal SAEs in study 3008, there was a higher percentage of adverse dropouts in the GFF group as compared to the other active treatment groups, but again the pattern of AEs remained the same. Adverse dropouts were primarily due to COPD and pneumonia while the remainder of events occurred in only one or two subjects with no apparent increase in any particular type of event.

### 7.3.4 Significant Adverse Events

Fatal and nonfatal serious adverse events in addition to adverse events leading to treatment discontinuation are discussed in Sections 7.3.1, 7.3.2, and 7.3.3, respectively. There were no events leading to dose reduction, as dose reduction was not performed in the phase 3 trials. An analysis of common adverse events by severity is provided in Section 7.4.1.

### 7.3.5 Submission Specific Primary Safety Concerns

Based on historical concerns and the known pharmacological effects of the two classes of drugs in the GFF combination (anticholinergic/LABA), the following adverse events of special interest (AESI) were evaluated more closely: cardiovascular effects, beta-adrenergic effects (e.g. tremor, paradoxical bronchospasm), and anticholinergic effects (e.g., urinary retention, dry mouth, ocular effects).

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Cardiovascular Adverse Events

Significant cardiovascular events such as those that were serious or led to dropout were shown in the sections above, and there were no substantial differences in the frequency of overall cardiac events across treatment groups. For some individual PTs such as atrial fibrillation, the incidence was slightly higher in the GFF treatment group, but the numerical differences were quite small and not consistently seen when all TEAEs (i.e., non-serious, not leading to dropout) were included.

The Applicant also conducted an analysis of MACE events (Major Adverse Cardiovascular Events) defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. All nonfatal cardiovascular events as well as all deaths were reviewed by an Adjudication Committee. The results shown in Table 28 from the placebo-controlled pivotal trials 3006 and 3007 and extension study 3008 revealed similar results with no further safety issues being identified. As a reminder, the placebo group represents 24 weeks of exposure while the active treatment groups represent 52 weeks of exposure; nonetheless, both the frequency and the exposure-adjusted rate of MACE events were low and relatively similar across treatment groups.

**Table 28. Major Adverse Cardiovascular Events (MACE) in Trials 3006, 3007, 3008 (Safety Population)**

Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451	Total N=3710
<b>Number of subjects with any MACE event</b>	<b>8 (0.8)</b>	<b>4 (0.4)</b>	<b>5 (0.6)</b>	<b>2 (0.5)</b>	<b>4 (0.9)</b>	<b>23 (0.6)</b>
Acute myocardial infarction	2 (0.2)	1 (0.1)	1 (0.1)	1 (0.2)	0	5 (0.1)
Cardiac arrest	1 (0.1)	1 (0.1)	0	0	0	2 (0.1)
Cardiac failure acute	1 (0.1)	0	0	0	0	1 (<0.1)
Cardiac failure congestive	0	0	1 (0.1)	0	2 (0.4)	3 (0.1)
Cerebral hemorrhage	0	0	1 (0.1)	0	0	1 (<0.1)
Cerebrovascular accident	1 (0.1)	0	1 (0.1)	0	0	2 ( 0.1)
Coronary artery occlusion	0	0	1 (0.1)	0	0	1 (<0.1)
Death	1 (0.1)	0	0	0	0	1 (<0.1)
Myocardial infarction	2 (0.2)	0	0	1 (0.2)	1 (0.2)	4 (0.1)
Peripheral artery thrombosis	0	1 (0.1)	0	0	0	1 (<0.1)
Pulmonary edema	0	1 (0.1)	0	0	0	1 (<0.1)
Sudden cardiac death	0	0	0	0	1 (0.2)	1 (<0.1)

Source: Reviewer generated table in JReview using ISS Phase 3 datasets ADSL (SAFFL=Y by TRT01A) and ADAE (TRTEMFL=Y, MACEFL=Y)

Anticholinergic and Beta-adrenergic Side Effects

The table below lists TEAEs that occurred over 52 weeks that could potentially be related to the pharmacologic action of the GP or FF component of the combination product that were identified by this reviewer. In general, no clinically meaningful imbalances were observed. Consistent with these findings, the anticholinergic SMQ revealed no major difference between the GFF and placebo treatment groups.

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**Table 29. Potential Beta-adrenergic and Anticholinergic Drug Class Effects in Trials 3006, 3007, and 3008 (Safety Population)**

AESI Category / Preferred Term	GFF N=1036	FF N=890	GP N=890	Placebo N=443	SHH N=451
<b>Beta-adrenergic effects</b>					
Tachycardia	4 (0.4)	4 (0.4)	3 (0.3)	0	2 (0.4)
Tremor	10 (1)	6 (0.7)	3 (0.3)	0	1 (0.2)
Resting Tremor	0	1 (0.1)	0	0	0
Bronchospasm Paradoxical	0	0	0	1 (0.2)	0
Bronchospasm	1 (0.1)	2 (0.2)	0	0	0
Hypokalemia	5 (0.5)	3 (0.3)	11 (1)	1 (0.2)	1 (0.2)
Blood potassium decreased	1 (0.1)	0	1 (0.1)	0	0
Hyperglycemia	11 (1)	4 (0.4)	6 (0.7)	3 (0.7)	1 (0.2)
Blood glucose abnormal	1 (0.1)	0	0	0	0
Blood glucose increased	3 (0.3)	4 (0.4)	6 (0.7)	1 (0.2)	0
Diabetes mellitus	6 (0.6)	2 (0.2)	1 (0.1)	0	2 (0.4)
Glucose tolerance impaired	0	1 (0.1)	0	0	0
Hyperglycaemic hyperosmolar nonketotic syndrome	1 (0.1)	0	0	0	0
Impaired fasting glucose	0	0	1 (0.1)	0	0
Type 2 diabetes mellitus	8 (0.8)	1 (0.1)	2 (0.2)	0	2 (0.4)
<b>Anticholinergic effects</b>					
Urinary retention	3 (0.3)	2 (0.2)	1 (0.1)	0	3 (0.7)
Diplopia	1 (0.1)	2 (0.2)	0	1 (0.2)	0
Dry eye	3 (0.3)	1 (0.1)	1 (0.1)	0	1 (0.2)
Glaucoma	0	0	1 (0.1)	0	2 (0.4)
Vision blurred	4 (0.4)	2 (0.2)	1 (0.1)	0	2 (0.4)
Dry mouth	14 (1)	5 (0.6)	6 (0.7)	1 (0.2)	9 (2)
Constipation	10 (1)	14 (2)	14 (2)	3 (0.7)	5 (1)
Ileus	0	1 (0.1)	0	0	0
Intestinal obstruction	1 (0.1)	0	2 (0.2)	0	1 (0.2)
Small intestinal obstruction	0	2 (0.2)	1 (0.1)	0	1 (0.2)
Source: Reviewer generated table using ISS Phase 3 datasets ADSL (SAFFL=Y by TRT01A) and ADAE (TRTEMFL=Y)					

In addition, based on the available data, there appeared to be no substantial difference in the frequency or type of AEs reported based on concomitant medication use. Approximately 17% and 16% of patients, respectively, reported concomitant use of non-potassium sparing diuretics or beta-adrenergic receptor antagonists.

#### 7.4 Supportive Safety Results

An evaluation of Standard MedDRA Queries (SMQs) comparing GFF, GP, or FF to placebo did not reveal any additional safety signals or concerns. An analysis of SMQs by subgroup (sex, race, country, age, and COPD severity) was similarly reassuring.

### 7.4.1 Common Adverse Events

Common TEAEs reported for 2% or more of patients in any treatment group in all phase 3 trials over 52 weeks are presented in Table 30.

**Table 30. Common TEAEs (Frequency ≥ 2% in Any Active Treatment Group and Greater Than Placebo) Over 52 Weeks in Trials 3006, 3007, and 3008 (Safety Population)**

System Organ Class / Preferred Term	GFF N=1036	FF N=890	GP N=890	SHH N=451	Placebo* N=443
<b>Infections and infestations</b>					
Nasopharyngitis	70 (7)	55 (6)	38 (4)	28 (6)	28 (6)
Upper respiratory tract infection	39 (4)	35 (4)	39 (4)	23 (5)	22 (5)
Sinusitis	33 (3)	35 (4)	25 (3)	18 (4)	13 (3)
Urinary tract infection	36 (4)	16 (2)	24 (3)	18 (4)	10 (2)
Bronchitis	25 (2)	16 (2)	30 (3)	16 (4)	12 (3)
Pneumonia	26 (3)	15 (2)	24 (3)	6 (1)	10 (2)
Influenza	15 (1)	12 (1)	10 (1)	9 (2)	2 (1)
Tooth abscess	17 (2)	8 (1)	7 (1)	9 (2)	2 (1)
<b>Respiratory, thoracic and mediastinal disorders</b>					
Cough	44 (4)	30 (3)	30 (3)	21 (5)	12 (3)
Chronic obstructive pulmonary disease	33 (3)	20 (2)	34 (4)	14 (3)	13 (3)
Oropharyngeal pain	18 (2)	20 (2)	16 (2)	11 (2)	5 (1)
<b>Gastrointestinal disorders</b>					
Diarrhea	19 (2)	19 (2)	15 (2)	12 (3)	8 (2)
Gastroesophageal reflux disease	9 (1)	6 (1)	9 (1)	14 (3)	2 (1)
Dry mouth	14 (1)	5 (1)	6 (1)	9 (2)	1 (<1)
<b>Musculoskeletal and connective tissue disorders</b>					
Back pain	30 (3)	22 (3)	27 (3)	17 (4)	10 (2)
Arthralgia	22 (2)	11 (1)	16 (2)	11 (2)	2 (1)
Muscle spasms	19 (2)	17 (2)	6 (1)	9 (2)	4 (1)
Pain in extremity	17 (2)	5 (1)	8 (1)	10 (2)	3 (1)
<b>Nervous system disorders</b>					
Headache	17 (2)	26 (2)	22 (3)	9 (2)	4 (1)
*Placebo control group only treated for 24 weeks in trials 3006 and 3007 Source: Response to IR submitted 11/2/15, Table 7-3, p5 and confirmed by reviewer in JMP Clinical using ADSL dataset (TRT01AN) from ISS Phase 3 and revised ADAE with placebo dataset from PT003008 (submitted on 11/6/15) where TRTEMFL=Y					

No meaningful difference in type of common TEAEs reported when the pivotal lead-in trials and extension study were analyzed separately or when evaluating the exposure-adjusted rate over 52 weeks. The majority of events occurred during the lead-in studies, but incidence relative to other treatment groups remained the same.

For the purposes of product labeling, the prescribing information will report TEAEs from the placebo-controlled 24-week lead-in trials, 3006 and 3007, that occurred at an incidence ≥2% in the GFF group and greater than placebo, which include cough and urinary tract infection.

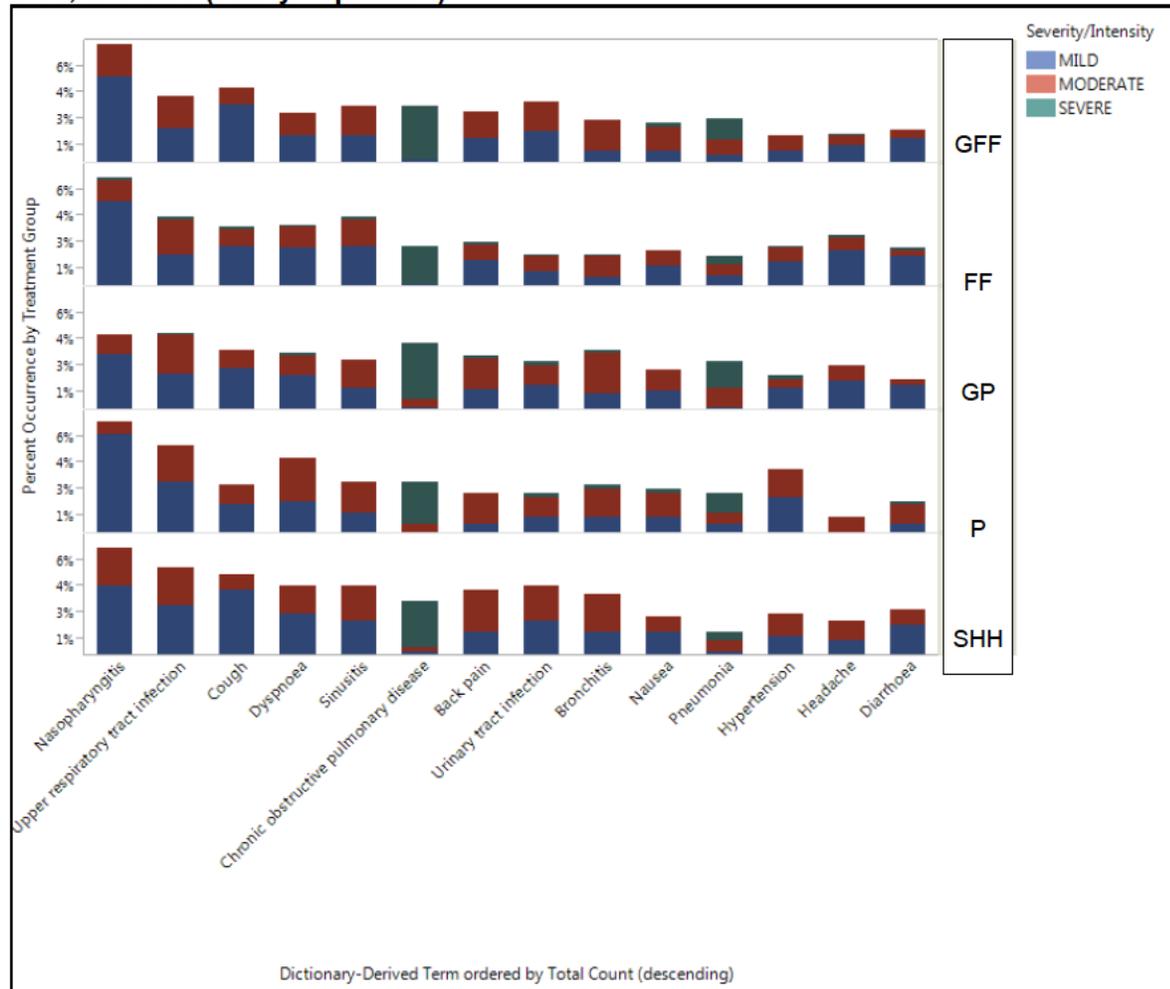
TEAEs that occurred with an incidence between 1 and 2% in the GFF group and greater than placebo included the PTs: arthralgia, chest pain, tooth abscess, muscle

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spasms, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue acute sinusitis, and contusion.

The figure below is a bar graph depicting common TEAEs color-coded by severity. Most of the common AEs were mild to moderate in severity. Severe AEs were primarily due to COPD and pneumonia, but occurred with similar frequency across treatment groups.

**Figure 35. Common TEAEs with  $\geq 2\%$  Frequency by Treatment Group and Severity: Trials 3006, 3007, and 3008 (Safety Population)**



Source: Reviewer generated figure in JMP Clinical using ISS Phase 3 datasets (Events, AE Distribution, Dictionary Derived Term Level, Body System Organ Class Group Level, Treatment variable=TRTA01N, Treatment emergent events, 2 percent occurrence threshold, AE Stacking by Severity/Intensity).

### 7.4.2 Laboratory Findings

No clinically meaningful differences were observed between treatment groups with regard to hematology or chemistry labs, and specifically, there was no signal for hypokalemia or hyperglycemia in the GFF treatment group. No Hy's law cases were identified.

### **7.4.3 Vital Signs**

No clinically meaningful effects on heart rate or blood pressure were noted during the 24-week pivotal trials or 26-week extension study.

### **7.4.4 Electrocardiograms (ECGs)**

Cardiovascular safety was assessed via ECG and Holter monitoring in phase 2 and 3 trials. In pivotal trials 3006 and 3007, 12-lead ECGs were obtained within 1 hour pre-dose and at 30 minutes and 2 hours post-dose on Day 1 and at Weeks 2, 12, and 24. In the subset of patients participating in the PFT sub-study, an additional ECG measurement was obtained at 12 hours post-dose on Day 1 and Week 12. In extension study 3008, ECGs were obtained at the same time points at Weeks 36 and 52. In the pooled phase 3 trials, mean changes in heart rate, QTcF, PR and QRS intervals pre- and post-dose as well as from baseline to Week 24 were small, clinically insignificant, and similar across treatment groups. Likewise, the proportion of patients identified as having a potentially clinically significant ECG abnormality was balanced among treatment groups, and few were associated with SAEs or TEAEs leading to treatment discontinuation. No additional findings were observed in the extension study 3008.

In addition, 24-hour Holter monitoring was conducted in a subset of patients in pivotal trial 3007 on Day 28 and in phase 2 study PT003003 on Day 14. In trial 3007, the Holter monitoring sub-study included a total of 587 subjects; the primary endpoint was change from baseline in mean heart rate averaged over 24 hours at Week 4. There were no substantial changes or differences among treatment groups in heart rate or ectopic events. In study PT003003, subjects with moderate to severe COPD received GFF 36/9.6 mcg, GP 36 mcg, FF 9.6 mcg, or Foradil Aerolizer 12 mcg twice daily for 14 days. The primary safety endpoint was the change from baseline in 24-hour mean heart rate at Day 14 as measured by continuous 24-hour Holter monitoring. In the 233 subjects with at least 18 hours of evaluable data at each time point, there were no clinically meaningful differences in mean heart rate; however, cardiac events (primarily tachycardia and asymptomatic ventricular asystole) occurred at a slightly higher frequency in the GFF group.

The thorough QT study conducted by the Applicant is described in Section 7.4.5 below.

Overall, the ECG findings taken in conjunction with the cardiovascular TEAEs in the GFF safety database do not suggest the presence of a concerning cardiovascular safety signal for inhaled GFF 18/9.6 mcg twice daily.

### **7.4.5 Special Safety Studies/Clinical Trials**

The Applicant conducted a randomized, blinded, five-period crossover cardiac conduction/“Thorough QT” study (PT003009) in 69 healthy subjects who received GFF 18/9.6 mcg, GFF 144/38.4 mcg, GP 144 mcg, placebo, and a single oral dose of

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moxifloxacin 400 mg. Adequate assay sensitivity was established with the moxifloxacin control. No significant QTc prolongation effect of GFF was detected in the study. Study results were reviewed in detail by the Interdisciplinary Review Team for QT Studies (review dated September 22, 2015).

#### **7.4.6 Immunogenicity**

As a combination of two small molecules, GFF is not anticipated to induce an immune response, and thus immunogenicity was not assessed.

### **7.5 Other Safety Explorations**

#### **7.5.1 Dose Dependency for Adverse Events**

Across phase 2 studies, there was no consistent dose dependent increase in overall adverse events or adverse events of special interest such as dry mouth, tremor, or paradoxical bronchospasm. The absence of a dose response relationship for AEs that are typically dose dependent (i.e., dry mouth, tremor) may be due to the relatively short treatment duration of these studies, which ranged from a single dose up to 2 weeks.

#### **7.5.2 Time Dependency for Adverse Events**

The majority of TEAEs occurred in the 24-week pivotal trials during which there was a placebo-control to provide a comparison for incidence rates. Fewer TEAEs occurred in the 26-week extension study during which all subjects were receiving active treatment. There was no pattern of late-onset AEs to cause concern for extended chronic use.

#### **7.5.3 Drug-Demographic Interactions**

Subgroup safety analyses based on baseline demographic information demonstrated no meaningful differences regarding the pattern or frequency of TEAEs and SAEs related to age, sex, or race. Some exceptions were within the subset of subjects  $\geq 75$  years of age who reported higher frequencies of COPD, headache, nasopharyngitis, and upper respiratory tract infection compared to those  $< 75$  years; however, events were relatively balanced across treatment groups. Between subjects  $< 65$  years and  $\geq 65$  years of age AEs were generally similar. There was also a higher incidence of SAEs in black/African American subjects compared with white subjects in the GFF treatment group (13% vs 7%); however, the pattern of events was similar to that seen in the overall population and the proportion of black subjects in the safety population is relatively small (8%).

#### **7.5.4 Drug-Disease Interactions**

Subgroup analyses based on baseline COPD disease severity showed no meaningful differences in frequency or type of TEAEs between subjects with moderate and severe COPD. In the small subset of subjects with very severe COPD (5% of safety

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population), the overall incidence of TEAEs was similar to that in moderate and severe COPD; however, bronchitis, COPD, and pneumonia were reported more frequently by those with severe disease in the GP treatment group. Although this difference was isolated to the GP group, possibly due to the small number of patients, it is not surprising to observe a higher incidence of respiratory AEs in those with more severe disease at baseline.

The Applicant also conducted safety analyses to compare incidence of TEAEs and SAEs in diabetic vs non-diabetic patients, current vs former smokers, and baseline ICS use and found no clinically meaningful differences based on these subgroups.

### **7.5.5 Drug-Drug Interactions**

No formal drug-drug interaction studies were conducted as part of the clinical development program for GFF.

## **7.6 Additional Safety Evaluations**

### **7.6.1 Human Carcinogenicity**

No long-term trials have been conducted to assess for carcinogenicity of GFF or GP in animals or humans. However, two-year carcinogenicity studies have been conducted for oral administration of FF in mice and inhalation administration in rats. The results showed a dose-dependent increase in the incidence of leiomyomas of the genital tract in female rodents (uterine leiomyoma, mesovarian leiomyoma and uterine leiomyosarcoma).

### **7.6.2 Human Reproduction and Pregnancy Data**

No pregnancies occurred in any female subject or in partners of any male subject in the GFF clinical development program.

### **7.6.3 Pediatrics and Assessment of Effects on Growth**

The Applicant requests a waiver for conducting pediatric studies, based on the rationale that COPD is a disease exclusive to the adult population. This reviewer finds the justification for the waiver to be acceptable.

### **7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound**

Given the nature of the drug substances, drug abuse, withdrawal, and rebound are not anticipated for this combination product. Additionally, the mode of administration via inhalation and low systemic bioavailability make abuse less likely.

## 7.7 Additional Submissions / Safety Issues

The Applicant provided a 120-day safety update on October 22, 2015. This submission includes safety data from two completed studies and six ongoing studies which are summarized in Table 31.

**Table 31. Studies Included in the 120-Day Safety Update**

Study	Objective	Design	N	Treatments*	Duration	Status
PT003012	24-hour lung function (FEV <sub>1</sub> AUC <sub>0-24</sub> )	R, DB, PC, XO	43	GFF 18/9.6 PBO	4 weeks	Complete
PT009001	Lung function (FEV <sub>1</sub> AUC <sub>0-12</sub> ), PK, safety	R, DB, XO	180	BFF 320/9.6 BFF 160/9.6 BFF 80/9.6 BD 320 FF 9.6	28 days	Complete
PT001004	Lung function in Japanese patients	R, DB, PC, XO	60	GP 36 GP 18 GP 9 PBO	7 days	Ongoing
PT003001	24-hour lung function	R, DB, PC, AC, XO	80	GFF 18/9.6 PBO SR 5 (OL)	4 weeks	Ongoing
PT003013	Effects of use with and without a spacer	R, OL, XO	60	GFF 18/9.6 GFF 18/9.6 + VHC	1 week	Ongoing
PT003014	Lung function (trough FEV <sub>1</sub> )	R, DB, PG, PC	1614	GFF 18/9.6 GP 18 FF 9.6 PBO	24 weeks	Ongoing
PT001101	Lung function (peak FEV <sub>1</sub> )	R, DB, PC, AC, XO	200	GP 36 GP 18 GP 9 GP 4.6 GP 2.4 SD 50 PBO	14 days	Ongoing
PT010005	Exacerbation rate	R, DB, PG	8000	BGF 320/18/9.6 BGF 160/18/9.6 GFF 18/9.6 GP 18 BFF 320/9.6 PBO	52 weeks	Ongoing

\*All treatments in mcg and administered BID (twice daily)

Abbreviations: BFF=budesonide and formoterol fumarate, BD=budesonide, PBO=placebo, GP=glycopyrrolate, FF=formoterol fumarate, GFF=glycopyrrolate/formoterol, SR=Spiriva Respimat, SD=Serevent Diskus, R=randomized, DB=double-blind, PC=placebo control, AC=active control, XO=crossover, PK=pharmacokinetics, VHC=valved holding chamber, AUC=area under the curve

The 120-Day Safety Update for the ongoing studies covers the reporting period from March 7 through July 31, 2015. Data from ongoing studies remain blinded. No treatment emergent deaths have occurred in any of the studies. The type and frequency of non-fatal SAEs is consistent with what was observed in the larger phase 3 clinical program. Overall, no new or unexpected events were identified in the 120-Day Safety Update that change the safety assessment.

## 8 Postmarket Experience

GFF MDI is not available for marketing in any country.

## 9 Appendices

### 9.1 Literature Review/References

The application included a listing of four literature references, but no systematic literature review. A PubMed search [search terms: glycopyrrolate AND formoterol AND chronic obstructive pulmonary disease; no limits] yielded 7 references. These articles, many of which were publications related to the glycopyrrolate/indacaterol fixed dose combination, were reviewed briefly, and no new information was identified that would change the risk/benefit assessment.

#### References

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2. For NDA 21-395 (S029) dated August 7, 2009 and for NDA 21-936 dated August 28, 2014
3. Michele TM, Pinheiro S, Iyasu S. *NEJM* 2010; 363(12):1097-9
4. <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM198006.pdf>
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6. Celli BR, MacNee W, Agusti A, et.al., Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J.* 2004; 23 (6):932-46.
7. Tilert T, Paulose-Ram R, and Brody D. Lung Obstruction Among Adults Aged 40-79: United States, 2007-2012. *NCHS Data Brief.* 2015; 180:1-8
8. Jones PW. *Eur Respir J.* 1994; 7(1):55-62

### 9.2 Labeling Recommendations

Labeling discussions were ongoing at the time of this review. In general, we recommended revisions throughout the prescribing information to provide consistency among other similar approved product labels. The major clinical revisions to the label are summarized below:

Section 14.2 Dose Ranging Trials: Streamlined to include information from a single dose-ranging study for each monocomponent [REDACTED] (b) (4)



### 9.3 Advisory Committee Meeting

The risk-benefit assessment of anticholinergic and LABA therapies in the treatment of COPD is well-established, and neither glycopyrrolate nor formoterol fumarate are NMEs. Therefore, an advisory committee meeting was not required for this application.

### 9.4 Protocol Questionnaires for Trials PT003006 and PT003007

#### Baseline Dyspnea Index (BDI)

CHOOSE THE SENTENCE THAT BEST DESCRIBES YOUR TIREDNESS

MOVE THE ARROW TO THE BOX NEXT TO YOUR SELECTION AND CLICK  
ON THE MOUSE, OR TAP THE BOX.  
IF YOU CHANGE YOUR MIND JUST CLICK OR TAP IN ANOTHER BOX  
WHEN FINISHED CLICK OR TAP THE NEXT BUTTON.

<input type="checkbox"/>	NONE
	I have not felt tired.
<input type="checkbox"/>	SLIGHT
	I have felt tired occasionally.
<input type="checkbox"/>	MODERATE
	I have felt tired about half the time.
<input type="checkbox"/>	SEVERE
	I have felt tired much of the time.
<input type="checkbox"/>	VERY SEVERE
	I have felt tired all of the time.

---

NOW YOU WILL GIVE RATINGS ABOUT YOUR SHORTNESS OF BREATH.

WHEN FINISHED WITH YOUR RATING ON A DISPLAY, CLICK OR TAP NEXT.

IF YOU HAVE QUESTIONS AT ANY TIME JUST NOTIFY THE STAFF.  
\*\*\* PLEASE CLICK OR TAP THE NEXT BUTTON TO BEGIN \*\*\*

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CHOOSE THE SENTENCE THAT BEST DESCRIBES YOUR BREATHLESSNESS

WHEN FINISHED WITH YOUR RATING ON A DISPLAY, CLICK OR TAP NEXT.

NONE  
I can perform usual activities without shortness of breath.

SLIGHT  
I am short of breath in at least one activity, but have not completely stopped any activity.

MODERATE  
I can't do at least one usual activity due to shortness of breath.

SEVERE  
I can't do most or all activities due to shortness of breath.

VERY SEVERE  
I can't do most or all activities and would be unable to work due to shortness of breath.

NEXT

CHOOSE THE SENTENCE THAT BEST DESCRIBES YOUR BREATHLESSNESS

WHEN FINISHED WITH YOUR RATING ON A DISPLAY, CLICK OR TAP NEXT.

NONE  
I am short of breath only with extraordinary tasks, such as carrying very heavy loads on level ground, carrying lighter loads uphill, or running. No shortness of breath with ordinary tasks.

SLIGHT  
I am short of breath only with major tasks, such as walking up a steep hill, climbing one or more flights of stairs, or carrying a moderate load on level ground.

MODERATE  
I am short of breath with average tasks, such as walking up a gradual hill, climbing less than one flight of stairs, or carrying a light load on the level.

SEVERE  
I am short of breath with light tasks, such as walking on level ground or standing.

VERY SEVERE  
I am short of breath at rest, while sitting, or lying down.

NEXT

CHOOSE THE SENTENCE THAT BEST DESCRIBES YOUR BREATHLESSNESS

WHEN FINISHED WITH YOUR RATING ON A DISPLAY, CLICK OR TAP NEXT.

NONE  
I am short of breath only with the greatest imaginable effort.

SLIGHT  
I am short of breath with extreme effort. I must pause only if the activity requires extreme effort.

MODERATE  
I am short of breath with moderate effort. I need to pause and it takes longer to complete the task than the average person.

SEVERE  
I am short of breath with little effort. I need to pause frequently and it takes at least 50 % longer to complete the task than the average person.

VERY SEVERE  
I am short of breath with no effort.

NEXT

Source: CSR PT003006, Appendix 16.1.12

Transition Dyspnea Index (TDI) Questionnaire

**THIS IS A PRACTICE SESSION.**

THIS PROGRAM ASKS YOU TO RATE WHETHER YOUR SHORTNESS OF BREATH HAS  
GOTTEN BETTER, GOTTEN WORSE, OR STAYED THE SAME SINCE YOUR LAST VISIT.  
RATINGS ARE MADE BY ADJUSTING THE LENGTH OF A BAR.  
THE BAR'S LENGTH IS CHANGED BY CLICKING OR TAPPING THE GRADUATED  
SCALE. CLICK OR TAP THE 'UP' AND 'DOWN' BUTTONS FOR FINE ADJUSTMENT.  
\*\*\* PLEASE CLICK OR TAP THE NEXT BUTTON TO CONTINUE \*\*\*

**NEXT**

PLEASE RATE CHANGES IN HOW TIRED YOU ARE IN GENERAL  
COMPARED TO YOUR PREVIOUS BDI VISIT IN APRIL, 2015  
\*\*\* PLEASE CLICK OR TAP THE NEXT BUTTON TO CONTINUE \*\*\*

**NEXT**

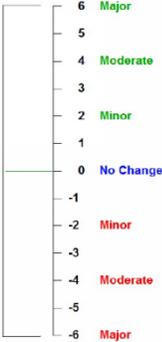
**TIREDNES** 0.0 ▲

IMPROVEMENT  
(Better)

DETERIORATION  
(Worse)

AT YOUR PREVIOUS BDI VISIT YOU CHECKED:  
I have not felt tired.

0.0 ▼



**NEXT**

PLEASE RATE CHANGES IN YOUR SHORTNESS OF BREATH  
RELATED TO ACTIVITIES  
COMPARED TO YOUR PREVIOUS BDI VISIT IN APRIL, 2015  
\*\*\* PLEASE CLICK OR TAP THE NEXT BUTTON TO CONTINUE \*\*\*

**NEXT**

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**ACTIVITIES**

0.0 ▲

6 Major  
5  
4 Moderate  
3  
2 Minor  
1  
0 No Change  
-1  
-2 Minor  
-3  
-4 Moderate  
-5  
-6 Major

IMPROVEMENT  
(Better)

AT YOUR PREVIOUS BDI VISIT YOU CHECKED:  
I can perform usual activities without shortness of breath.

DETERIORATION  
(Worse)

▲

0.0 ▼

NEXT

PLEASE RATE CHANGES IN YOUR SHORTNESS OF BREATH  
 RELATED TO TASKS  
 COMPARED TO YOUR PREVIOUS BDI VISIT IN APRIL, 2015

\*\*\* PLEASE CLICK OR TAP THE NEXT BUTTON TO CONTINUE \*\*\*

NEXT

**TASKS**

0.0 ▲

6 Major  
5  
4 Moderate  
3  
2 Minor  
1  
0 No Change  
-1  
-2 Minor  
-3  
-4 Moderate  
-5  
-6 Major

IMPROVEMENT  
(Better)

AT YOUR PREVIOUS BDI VISIT YOU CHECKED:  
I am short of breath only with extraordinary tasks, such as carrying very heavy loads on level ground, carrying lighter loads uphill, or running. No shortness of breath with ordinary tasks.

DETERIORATION  
(Worse)

▲

0.0 ▼

NEXT

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PLEASE RATE CHANGES IN YOUR SHORTNESS OF BREATH  
RELATED TO EFFORT  
COMPARED TO YOUR PREVIOUS BDI VISIT IN APRIL, 2015

\*\*\* PLEASE CLICK OR TAP THE NEXT BUTTON TO CONTINUE \*\*\*

**NEXT**

---

**EFFORT**  ▲

IMPROVEMENT  
(Better)

AT YOUR PREVIOUS BDI VISIT YOU CHECKED:  
*I am short of breath with no effort.*

DETERIORATION  
(Worse)

▼

6	Major
5	
4	Moderate
3	
2	Minor
1	
0	No Change
-1	
-2	Minor
-3	
-4	Moderate
-5	
-6	Major

**NEXT**

Source: CSR PT003006, Appendix 16.1.12

**St. George's Respiratory Questionnaire (SGRQ)**

St. George's Respiratory Questionnaire  
PART 1

Please describe how often your respiratory problems have affected you over the past 4 weeks.

Please check (✓) one box for each question:

	almost every day	several days a week	a few days a month	only with respiratory infections	not at all
1. Over the past 4 weeks, I have coughed:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
2. Over the past 4 weeks, I have brought up phlegm (sputum):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
3. Over the past 4 weeks, I have had shortness of breath:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
4. Over the past 4 weeks, I have had wheezing attacks:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
5. How many times during the past 4 weeks have you suffered from severe or very unpleasant respiratory attacks?					
				Please check (✓) one:	
				more than 3 times	<input type="checkbox"/>
				3 times	<input type="checkbox"/>
				2 times	<input type="checkbox"/>
				1 time	<input type="checkbox"/>
				none of the time	<input type="checkbox"/>
6. How long did the worst respiratory attack last? (Go to Question 7 if you did not have a severe attack)					
				Please check (✓) one:	
				a week or more	<input type="checkbox"/>
				3 or more days	<input type="checkbox"/>
				1 or 2 days	<input type="checkbox"/>
				less than a day	<input type="checkbox"/>
7. Over the past 4 weeks, in a typical week, how many good days (with few respiratory problems) have you had?					
				Please check (✓) one:	
				No good days	<input type="checkbox"/>
				1 or 2 good days	<input type="checkbox"/>
				3 or 4 good days	<input type="checkbox"/>
				nearly every day was good	<input type="checkbox"/>
				every day was good	<input type="checkbox"/>
8. If you wheeze, is it worse when you get up in the morning?					
				Please check (✓) one:	
				No	<input type="checkbox"/>
				Yes	<input type="checkbox"/>

PART 2

**Section 1**

How would you describe your respiratory condition? Please check (✓) one:

The most important problem I have   
Causes me quite a lot of problems   
Causes me a few problems   
Causes no problems

If you have ever held a job: Please check (✓) one:

My respiratory problems made me stop working altogether   
My respiratory problems interfere with my job or made me change my job   
My respiratory problems do not affect my job

**Section 2**

*These are questions about what activities usually make you feel short of breath these days.*

For each statement please check (✓) the box that applies to you these days:

	True	False
Sitting or lying still	<input type="checkbox"/>	<input type="checkbox"/>
Washing or dressing yourself	<input type="checkbox"/>	<input type="checkbox"/>
Walking around the house	<input type="checkbox"/>	<input type="checkbox"/>
Walking outside on level ground	<input type="checkbox"/>	<input type="checkbox"/>
Walking up a flight of stairs	<input type="checkbox"/>	<input type="checkbox"/>
Walking up hills	<input type="checkbox"/>	<input type="checkbox"/>
Playing sports or other physical activities	<input type="checkbox"/>	<input type="checkbox"/>

**Section 3**

*These are more questions about your cough and shortness of breath these days.*

For each statement please check (✓) the box that applies to you these days:

	True	False
Coughing hurts	<input type="checkbox"/>	<input type="checkbox"/>
Coughing makes me tired	<input type="checkbox"/>	<input type="checkbox"/>
I am short of breath when I talk	<input type="checkbox"/>	<input type="checkbox"/>
I am short of breath when I bend over	<input type="checkbox"/>	<input type="checkbox"/>
My coughing or breathing disturbs my sleep	<input type="checkbox"/>	<input type="checkbox"/>
I get exhausted easily	<input type="checkbox"/>	<input type="checkbox"/>

**Section 4**

*These are questions about other effects that your respiratory problems may have on you these days.*

For each statement, please check (✓) the box that applies to you these days:

	True	False
My cough or breathing is embarrassing in public	<input type="checkbox"/>	<input type="checkbox"/>
My respiratory problems are a nuisance to my family, friends or neighbors	<input type="checkbox"/>	<input type="checkbox"/>
I get afraid or panic when I cannot catch my breath	<input type="checkbox"/>	<input type="checkbox"/>
I feel that I am not in control of my respiratory problems	<input type="checkbox"/>	<input type="checkbox"/>
I do not expect my respiratory problems to get any better	<input type="checkbox"/>	<input type="checkbox"/>
I have become frail or an invalid because of my respiratory problems	<input type="checkbox"/>	<input type="checkbox"/>
Exercise is not safe for me	<input type="checkbox"/>	<input type="checkbox"/>
Everything seems too much of an effort	<input type="checkbox"/>	<input type="checkbox"/>

**Section 5**

*These are questions about your respiratory treatment. If you are not receiving treatment go to section 6.*

For each statement, please check (✓) the box that applies to you these days:

	True	False
My treatment does not help me very much	<input type="checkbox"/>	<input type="checkbox"/>
I get embarrassed using my medication in public	<input type="checkbox"/>	<input type="checkbox"/>
I have unpleasant side effects from my medication	<input type="checkbox"/>	<input type="checkbox"/>
My treatment interferes with my life a lot	<input type="checkbox"/>	<input type="checkbox"/>

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**Section 6**

*These are questions about how your activities might be affected by your respiratory problems.*

For each statement, please check (✓) the box that applies to you because of your respiratory problems:

	True	False
I take a long time to get washed or dressed	<input type="checkbox"/>	<input type="checkbox"/>
I cannot take a bath or shower, or I take a long time to do it	<input type="checkbox"/>	<input type="checkbox"/>
I walk slower than other people my age, or I stop to rest	<input type="checkbox"/>	<input type="checkbox"/>
Jobs such as household chores take a long time, or I have to stop to rest	<input type="checkbox"/>	<input type="checkbox"/>
If I walk up one flight of stairs, I have to go slowly or stop	<input type="checkbox"/>	<input type="checkbox"/>
If I hurry or walk fast, I have to stop or slow down	<input type="checkbox"/>	<input type="checkbox"/>
My breathing makes it difficult to do things such as walk up hills, carry things up stairs, light gardening such as weeding, dance, bowl or play golf	<input type="checkbox"/>	<input type="checkbox"/>
My breathing makes it difficult to do things such as carry heavy loads, dig in the garden or shovel snow, jog or walk briskly (5 miles per hour), play tennis or swim	<input type="checkbox"/>	<input type="checkbox"/>
My breathing makes it difficult to do things such as very heavy manual work, ride a bike, run, swim fast, or play competitive sports	<input type="checkbox"/>	<input type="checkbox"/>

**Section 7**

*We would like to know how your respiratory problems usually affect your daily life.*

For each statement, please check (✓) the box that applies to you because of your respiratory problems:

	True	False
I cannot play sports or do other physical activities	<input type="checkbox"/>	<input type="checkbox"/>
I cannot go out for entertainment or recreation	<input type="checkbox"/>	<input type="checkbox"/>
I cannot go out of the house to do the shopping	<input type="checkbox"/>	<input type="checkbox"/>
I cannot do household chores	<input type="checkbox"/>	<input type="checkbox"/>
I cannot move far from my bed or chair	<input type="checkbox"/>	<input type="checkbox"/>

*Here is a list of other activities that your respiratory problems may prevent you from doing. (You do not have to check these, they are just to remind you of ways your shortness of breath may affect you):*

- Going for walks or walking the dog
- Doing activities or chores at home or in the garden
- Sexual intercourse
- Going to a place of worship, or a place of entertainment
- Going out in bad weather or into smoky rooms
- Visiting family or friends or playing with children

Please write in any other important activities that your respiratory problems may stop you from doing:

.....

.....

.....

Now please check the box (one only) that you think best describes how your respiratory problems affect you:

- It does not stop me from doing anything I would like to do
- It stops me from doing one or two things I would like to do
- It stops me from doing most of the things I would like to do
- It stops me from doing everything I would like to do

*Thank you for completing this questionnaire. Before you finish would you please make sure that you have answered all the questions.*

Source: Clinical trial protocol PT003007, version 3.0; Appendix 8, p160

**COPD Assessment Test (CAT)**

Your name:

Today's date:



How is your COPD? Take the COPD Assessment Test™ (CAT)

This questionnaire will help you and your healthcare professional measure the impact COPD (Chronic Obstructive Pulmonary Disease) is having on your wellbeing and daily life. Your answers, and test score, can be used by you and your healthcare professional to help improve the management of your COPD and get the greatest benefit from treatment. For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response for each question.

**Example:** I am very happy    0  1  2  3  4  5    I am very sad

	SCORE
<div style="display: flex; justify-content: space-between;"> <span>I never cough</span> <span>0 1 2 3 4 5</span> <span>I cough all the time</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>I have no phlegm (mucus) in my chest at all</span> <span>0 1 2 3 4 5</span> <span>My chest is completely full of phlegm (mucus)</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>My chest does not feel tight at all</span> <span>0 1 2 3 4 5</span> <span>My chest feels very tight</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>When I walk up a hill or one flight of stairs I am not breathless</span> <span>0 1 2 3 4 5</span> <span>When I walk up a hill or one flight of stairs I am very breathless</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>I am not limited doing any activities at home</span> <span>0 1 2 3 4 5</span> <span>I am very limited doing activities at home</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>I am confident leaving my home despite my lung condition</span> <span>0 1 2 3 4 5</span> <span>I am not at all confident leaving my home because of my lung condition</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>I sleep soundly</span> <span>0 1 2 3 4 5</span> <span>I don't sleep soundly because of my lung condition</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<div style="display: flex; justify-content: space-between;"> <span>I have lots of energy</span> <span>0 1 2 3 4 5</span> <span>I have no energy at all</span> </div>	<input style="width: 30px; height: 30px;" type="text"/>
<b>TOTAL SCORE</b>	<input style="width: 30px; height: 30px;" type="text"/>

COPD Assessment Test and CAT logo is a trademark of the GlaxoSmithKline group of companies. © 2009 GlaxoSmithKline. All rights reserved.

Source: Clinical trial protocol, PT003007, version 3.0; Appendix 7, p159

**Modified Medical Research Council Dyspnea Scale**

Grade	Description of Breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of my breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Source: Clinical trial protocol PT003006, version 3.0, Table 7, p68

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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STACY J CHIN  
03/21/2016

ANTHONY G DURMOWICZ  
03/21/2016

<b>MEDICAL OFFICER REVIEW</b>			
<b>Division Of Pulmonary, Allergy and Rheumatology Drug Products (HFD-570)</b>			
<b>APPLICATION:</b> NDA 208-294	<b>NAME:</b> Glycopyrrolate/formoterol fumarate		
<b>APPLICANT/SPONSOR:</b> Pearly Therapeutics	<b>CATEGORY:</b> LAMA/LABA		
<b>MEDICAL OFFICER:</b> Stacy Chin, MD	<b>ROUTE:</b> Oral inhalation		
<b>TEAM LEADER:</b> Anthony Durmowicz, MD	<b>DATE:</b> 8/24/2015		
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
6/25/2015	6/25/2015	SD1	Initial NDA
<b><u>REVIEW SUMMARY:</u></b>			
<p>Pearl Therapeutics submitted a new NDA for glycopyrrolate/formoterol fumarate (GFF) (b) (4) fixed dose combination for the proposed indication of the long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. It will be administered via metered dose inhaler (MDI). The proposed dose for GFF is 18 mcg for the glycopyrrolate component and 9.6 mcg for the formoterol fumarate component. Neither of the monocomponents is approved (b) (4); however, there is extensive clinical experience with both drug substances in other product formulations.</p> <p>The clinical development program for GFF in COPD primarily included nine dose-ranging studies, two pivotal efficacy and safety trials, and one safety extension study. There were two dose-ranging studies (PT005081 and PT 005003) for the formoterol fumarate (FF) monocomponent which evaluated doses ranging from 2.4 to 19.2 mcg twice daily and included Foradil Aerosolizer as the active comparator benchmark. There were three dose-ranging studies (PT 0010801, PT001002, and PT001003) for the glycopyrrolate (GP) monocomponent which evaluated doses ranging from 0.6 to 144 mcg twice daily and included Atrovent and Spiriva Handihaler as active comparators. There were four dose-ranging studies (PT0031002, PT003003, PT003004, and PT003005) for GFF that explored fixed dose combinations ranging from 1.2/9.6 mcg (1.2 mcg GP and 9.6 mcg FF) to 36/9.6 mcg (36 mcg GP and 9.6 mcg FF) twice daily. Phase 3 trials consisted for two 24-week placebo-controlled, parallel group studies (PT003006 and PT003007) in COPD patients. Doses used in the pivotal trials were GFF 18/9.6 mcg twice daily, GP 18 mcg twice daily, and FF 9.6 mcg twice daily. Study PT003007 also included an open label Spiriva Handihaler treatment arm. Selected patients from the two pivotal trials were enrolled in the long-term extension study (PT003008) which continued for an additional 28 weeks.</p> <p>Based on preliminary review of trials PT003006 and PT003007, GFF demonstrated a statistically significant improvement in the primary endpoint, change from baseline in trough FEV1 at week 24, compared to placebo and demonstrated added benefit above each monocomponent. In addition, preliminary review of the two pivotal trials and extension study PT003008 did not reveal any new safety concerns for this LAMA/LABA combination product; however, the rather small size of the safety database relative to other COPD development programs will be a review issue.</p> <p>This submission is adequately indexed, organized, and complete to allow for review. An OSI site inspection will be requested given the number of GCP complaints received. At this time, no major issues have been identified which would limit review of this application. The filing checklist and slides from the filing meeting held on 8/3/2015 are attached.</p>			
<b>RECOMMENDED REGULATORY ACTION</b>			
<b>NDA/SUPPLEMENTS:</b>	<b>X</b>	<b>FILEABLE</b>	<b>NOT FILEABLE</b>
<b>OTHER ACTION:</b>	<b>COMMENTS FOR SPONSOR</b>		

NDA Number: 208-294

Applicant: Pearl Therapeutics Stamp Date: 6/25/2015

Drug Name: glycopyrrolate/formoterol fumarate inhalation aerosol NDA: original

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.			X	eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?			X	505(b)(2) Robinul Injection (NDA 17558)
<b>DOSE</b>					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product i.e., appropriately designed dose-ranging studies)?	X			9 dose-ranging studies

	Content Parameter	Yes	No	NA	Comment
	<p>Dose selection for formoterol fumarate (FF)</p> <ul style="list-style-type: none"> <li>• Study Number: PT0050801</li> <li>• Study Title: A Randomized, Double-blind, Five-period, Placebo and Active-controlled, Cross-over, Multi-centre Study Evaluating Single Administration of Three Doses of Formoterol Fumarate MDI in Patients with Moderate-to-Severe COPD, Compared to Open-Label Marketed Formoterol (FORADIL® AEROLIZER®) as an Active Control</li> <li>• Sample Size: 34</li> <li>• Arms: FF 2.4, 4.8, and 9.6 mcg bid, Foradil 12 mcg bid, placebo</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence 0000 - 5.3.4.2 Patient PD and PK/PD Study Reports [Study ID - Study Title]</a> =</li> </ul> <ul style="list-style-type: none"> <li>• Study Number: PT005003</li> <li>• Study Title: A Randomized, Double-Blind, Single-Dose, Six-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Three Doses of PT005, in Patients with Moderate to Severe COPD, Compared with Foradil® Aerolizer® (12 and 24 µg Open-Label) as Active Controls</li> <li>• Sample size: 50</li> <li>• Arms: FF 7.2, 9.6, 19.2 mcg bid; Foradil 12, 24 mcg bid; placebo</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence 0000 - 5.3.4.2 [Study ID] - [[Study Title]] - pt005003 - A Randomized, Double-Blind, Single-Dose, Six-Treatment, Placebo-Controlled, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Three Doses of PT005, in Patients with Moderate to Severe COPD, Compared with Foradil Aerolizer (12 and 24 g Open-Label) as Active Controls</a></li> </ul> <p>Dose selection for glycopyrrolate (GP)</p> <ul style="list-style-type: none"> <li>• Study Number: PT0010801</li> <li>• Study Name: A Randomized, Double-blind, Single Dose, Four-period, Six-treatment, Placebo-controlled, Balanced, Incomplete Block, Cross-over, Multi-center, Ascending Dose Study of Four Doses of PT001 MDI in Patients with Mild to Moderate COPD, Compared to Open Label Tiotropium 18 µg (Administered via the Handihaler) as an Active Control</li> <li>• Sample size: 33</li> <li>• Arms: GP 18, 36, 72, 144 mcg bid; Spiriva Handihaler 18 mcg qd; placebo</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence 0000 - 5.3.4.2 [[Study ID]] - [[Study Title]] - pt0010801 - A randomized, d ouble-blind, single dose, four-period, six-treatment, placebo-controlled, balanced, incomplete block, cross-over, multicenter, ascending dose study of four doses of PT001 MDI in patients with mild to moderate COPD, compared to open label tiotropium 18 g</a></li> </ul>				

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	<p><a href="#">administered via the Handihaler) as an active control</a></p> <ul style="list-style-type: none"> <li>• Study Number: PT001002</li> <li>• Study Name: A Randomized, Double-Blind, Chronic Dosing (7 Days), Three-Period, Six-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of PT001 in Patients With Moderate to Severe COPD, Compared with Atrovent® HFA Inhalation Aerosol (Open-Label) as An Active Control</li> <li>• Sample Size: 103</li> <li>• Arms: GP 0.6, 1.2, 2.4, 4.6, 9, 18 mcg bid; Atrovent 34 mcg qid, placebo</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence 0000 - 5.3.5.1 [[Study ID]] - [[Study Title]] - pt001002 - A Randomized, Double-Blind, Chronic Dosing (7 Days), Three-Period, Six-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of PT001 in Patients With Moderate to Severe COPD, Compared with Atrovent HFA Inhalation Aerosol (Open-Label) as An Active Control</a></li> </ul> <ul style="list-style-type: none"> <li>• Study Number: PT001003</li> <li>• Study Name: A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (14 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Six Doses of PT001 in Patients With Moderate to Severe COPD, Compared with Spiriva® Handihaler® (Tiotropium Bromide, Open-Label) as An Active Control</li> <li>• Sample Size: 140</li> <li>• Arms: GP 0.6, 1.2, 2.4, 4.6, 9, 18 mcg bid; Spiriva Handihaler 18 mcg qd, placebo</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence 0000 - 5.3.5.1 [[Study ID]] - [[Study Title]] - pt001003 - A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (14 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Six Doses of PT001 in Patients With Moderate to Severe COPD, Compared with Spiriva Handihaler Tiotropium Bromide, Open-Label) as An Active Control</a></li> </ul> <p>Dose selection for glycopyrrolate/formoterol fumarate (GFF)</p> <ul style="list-style-type: none"> <li>• Study Number: PT0031002</li> <li>• Study Name: A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two Doses of PT005 and One Dose of PT001 in Patients With Moderate to Very Severe COPD, Compared With Foradil® Aerolizer® (12</li> </ul>				

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	<p>µg, Open-Label) and Spiriva® Handihaler® (18 µg, Open-Label) as Active Controls</p> <ul style="list-style-type: none"> <li>• Sample Size: 118</li> <li>• Arms: GFF 36/9.6 mcg bid, FF 36 mcg bid, GP 36 mcg bid, Foradil 12 mcg bid</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence - 5.3.5.1 [[Study ID]] - [[Study Title]] - pt0031002 - A Randomized, Double-Blind (Test Products and Placebo), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Placebo-Controlled, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Two Doses of PT003, Two Doses of PT005 and One Dose of PT001 in Patients With Moderate to Very Severe COPD, Compared With Foradil Aerolizer (12 g, Open-Label) and Spiriva Handihaler 18 g, Open-Label) as Active Controls</a></li> <li>• Study Number: PT003003</li> <li>• Study Name: A Randomized, Double-Blind, Parallel Group, 14-DayDay, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil® Aerolizer® (12 µg, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)</li> <li>• Sample Size: 237</li> <li>• Arms: GFF 36/9.6 mcg bid, FF 9.6 mcg bid, GP 36 mcg bid, Foradil 12 mcg bid</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence - 5.3.5.1 [[Study ID]] - [[Study Title]] - pt003003 - A Randomized, Double-Blind, Parallel Group, 14-Day, Multi-Center Study to Evaluate the Safety of PT003, PT005, PT001 and Foradil Aerolizer (12g, Open-Label) as Evaluated by Holter Monitoring, in Patients with Moderate to Severe Chronic Obstructive Pulmonary Disease (COPD)</a></li> <li>• Study Number: PT003004</li> <li>• Study Name: A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Control</li> <li>• Sample Size: 185</li> <li>• Arms: GFF 9/9.6, 18/9.6, 36/7.2, 36/9.6 mcg bid, GP 36 mcg bid, FF 9.6 mcg bid</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence - 5.3.5.1 [[Study ID]] - [[Study Title]] - pt003004 - A Randomized, Double-Blind, Chronic Dosing (7 Days), Two-Period, Six-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Four Doses of GFF MDI in Patients With Moderate to Severe COPD, Compared With Its Individual Components (FF MDI and GP MDI) as Active Controls</a></li> </ul>				

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	<ul style="list-style-type: none"> <li>• Study Number: PT003005</li> <li>• Study Name: A Randomized, Double-Blind (Test Products), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared With Spiriva® Handihaler® (Tiotropium Bromide 18 µg) as Active Control</li> <li>• Sample Size: 159</li> <li>• Arms: GFF 1.2/9.6, 2.4/9.6, 4.6/9.6, 9/9.6, 18/9.6 mcg bid, GP 18 mcg bid, FF 9.6 mcg bid, Spiriva Handihaler 18 mcg qd</li> <li>• Location in submission: <a href="#">Application 208294 - Sequence - 5.3.5.1 [[Study ID]] - [[Study Title]] - pt003005 - A Randomized, Double-Blind (Test Products), Chronic Dosing (7 Days), Four-Period, Eight-Treatment, Incomplete Block, Cross-Over, Multi-Center Study to Assess Efficacy and Safety of Five Doses of PT003, One Dose of PT001 and One Dose of PT005 in Patients With Moderate to Severe COPD, Compared With Spiriva Handihaler (Tiotropium Bromide 18 g) as Active Control</a></li> </ul>				
<b>EFFICACY</b>					
14.	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1: PT003006 Indication: COPD</p> <p>Pivotal Study #2: PT003007 Indication: COPD</p>	X			Two 24-week pivotal trials with 28-week extension study
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
16.	Do the endpoints in the pivotal studies conform to previous	X			

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.				
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?			X	Majority of data from US
<b>SAFETY</b>					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
19.	Has the applicant submitted adequate information to assess the arrhythmogenic potential of the product ( <i>e.g.</i> , QT interval studies, if needed)?	X			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?			X	
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>1</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>2</sup> used for mapping investigator verbatim terms to preferred terms?	X			MedDRA 17.1
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> ,			X	

<sup>1</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>2</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	label comprehension, self selection and/or actual use)?				
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			X	
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			X	Majority of data from US
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE?** Yes

## NDA 208-294 Glycopyrrolate/Formoterol Fumarate Inhalation Aerosol for COPD Pearl Therapeutics

Stacy Chin, MD  
Clinical Filing Review  
August 3, 2015

1

### Overview

- Name: Glycopyrrolate/formoterol fumarate (Bevespi Aerosphere)
- Class: LAMA/LABA
- Indication: Long-term, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema
- Dose: 18 mcg GP/9.6 mcg FF bid
- Route: inhalation via MDI

2

### Regulatory History

Date	Meeting Highlights
	(b) (4)
4/12/10 GFF PIND	<ul style="list-style-type: none"> <li>• Characterize and show efficacy of each monocomponent</li> <li>• Characterize dose and dosing regimen of GP and FF to test in GFF, consider including active control arms</li> </ul>
5/27/11 Type C	<ul style="list-style-type: none"> <li>• Initial concern for DDI alleviated by in vitro data</li> <li>• Evaluate range of GP doses, including ineffective dose, to fully characterize dose response curve</li> </ul>
4/19/12 Type C	<ul style="list-style-type: none"> <li>• Data support BID dosing for GP</li> <li>• Doses lower than 18 mcg GP should be explored</li> <li>• 9.6 mcg FF reasonable for Ph3</li> <li>• Thorough QT study of monocomponents not necessary</li> <li>• 24-hr Holter monitoring in subset of Ph3 patients acceptable</li> </ul>

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## Regulatory History

Date	Meeting Highlights
12/21/12	<ul style="list-style-type: none"> <li>GP 18 mcg dose acceptable for Ph3</li> <li>Agreement with pivotal trial design, (b) (4)</li> </ul>
EOP2	<ul style="list-style-type: none"> <li>Recommend single primary endpoint (e.g. trough FEV1) to compare GFF to monocomponents</li> <li>Analysis of primary endpoint should be at single time point (24 wks)</li> </ul>
6/2/14	<ul style="list-style-type: none"> <li>Primary endpoint should remain morning pre-dose trough FEV1 at 24 weeks (b) (4)</li> </ul>
Pre-NDA	<ul style="list-style-type: none"> <li>Expectation that GFF wins on lung function at 24 weeks, contribution of each component is demonstrated, and COPD exacerbations trend in right direction</li> <li>Extension study may not be sufficient to support labeling claims</li> <li>Agreement with plan for safety data submission</li> <li>Glycopyrrolate should be used as established name</li> </ul>
3/3/15	<ul style="list-style-type: none"> <li>Interpretation of OL Spiriva results will be review issue</li> <li>Proposal to control Type 1 error within each treatment comparison for secondary endpoints not acceptable</li> </ul>
WRO	
4/14/15	<ul style="list-style-type: none"> <li>Agreement with Pearl's plan to handle analysis of data from 15 fraudulent subjects</li> </ul>
WRO	

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## Clinical Trials – Dose Selection

FF	GFF
PT005081 – SD, XO, (N=34) <ul style="list-style-type: none"> <li>FF 2.4, 4.8, 9.6</li> <li>Foradil 12 (OL)</li> <li>Placebo</li> </ul>	PT0031002 – 7d, XO, (N=118) <ul style="list-style-type: none"> <li>GFF 36/9.6</li> <li>GP 36</li> <li>FF 9.6</li> <li>Foradil 12 (OL)</li> <li>**PT003003 – 14d, PG, (N=237)               <ul style="list-style-type: none"> <li>GFF 36/9.6</li> <li>GP 36</li> <li>FF 9.6</li> <li>Foradil 12 OL</li> </ul> </li> </ul>
PT005003 – SD, XO, (N=50) <ul style="list-style-type: none"> <li>FF 7.2, 9.6, 19.2</li> <li>Foradil 12, 24 (OL)</li> <li>Placebo</li> </ul>	PT003004 – 7d, XO, (N=185) <ul style="list-style-type: none"> <li>GFF 9/9.6, 18/9.6, 36/7.2, 36/9.6</li> <li>GP 36</li> <li>FF 9.6</li> </ul>
GP <ul style="list-style-type: none"> <li>*PT0010801 – SD, XO, (N=33)               <ul style="list-style-type: none"> <li>GP 18, 36, 72, 144</li> <li>SHH 18 (OL)</li> <li>Placebo</li> </ul> </li> <li>PT001002 – 7d, XO, (N=103)               <ul style="list-style-type: none"> <li>GP 0.6, 1.2, 2.4, 4.6, 9, 18</li> <li>Atrovent 34 (OL)</li> <li>Placebo</li> </ul> </li> <li>PT001003 – 14d, XO, (N=140)               <ul style="list-style-type: none"> <li>GP 0.6, 1.2, 2.4, 4.6, 9, 18</li> <li>SHH 18 (OL)</li> <li>Placebo</li> </ul> </li> </ul>	PT003005 – 7d, XO, (N=159) <ul style="list-style-type: none"> <li>GFF 1.2/9.6, 2.4/9.6, 4.6/9.6, 9/9.6, 18/9.6</li> <li>GP 18</li> <li>FF 9.6</li> <li>SHH 18 (OL)</li> </ul>

FF=Formoterol fumarate  
 GP=glycopyrrolate  
 GFF=glycopyrrolate formoterol fumarate  
 SHH=Spiriva Handihaler  
 All BID dosing except for SHH (QD) and Atrovent (QID)  
 Majority of studies in US  
 Moderate to severe COPD patients

Primary endpoints: Change from baseline in FEV<sub>1</sub>, AUC<sub>0-12</sub>  
 \*Peak FEV1 relative to baseline  
 \*\*Change in 24-hr mean heart rate from baseline

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## Clinical Trials – Phase 3

Trial (dates)	Design	Treatment (mcg)	N	Duration	Primary Endpoint	Sites (countries)
<b>Phase 3 pivotal efficacy and safety trials</b>						
PT003006 (6/13-2/15)	R, DB, PC, AC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL) PBO bid	527 451 452 453 220	24 weeks	Change from baseline trough FEV <sub>1</sub> at 24 weeks	160 sites (US, AU, NZ)
PT003007 (7/13-2/15)	R, DB, PC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid PBO bid	512 440 439 224	24 weeks	Change from baseline trough FEV <sub>1</sub> at 24 weeks	140 sites (US)
<b>Phase 3 long term extension study</b>						
PT003008 (11/13-12/14)	R, DB, AC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL)	290 219 213 171	28 weeks	Long term safety	205 sites (US, AU, NZ)

Eligibility criteria: 40-80 years old, COPD (ATS/ERS), FEV<sub>1</sub>/FVC <0.70, post-bronchodilator FEV<sub>1</sub><80% predicted, ≥10 pack-year smoking hx; excluded significant cardiac disease, poorly controlled COPD/other diseases, long term oxygen therapy

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## Efficacy – Phase 3

- Primary Endpoint
  - Change from baseline in morning pre-dose trough FEV1 at Week 24
- Secondary Endpoints
  - Change from baseline in morning trough FEV1 over 24 weeks
  - Peak change from baseline in FEV1 within 2hrs post-dose at Week 24
  - Change in SGRQ total score at Week 24
  - Rescue medication use over 24 weeks
  - Time to onset of action on Day
- Other Endpoints
  - Exacerbations (rate, time to first)
  - Time to treatment failure
  - Nighttime awakenings
  - TDI focal score
  - Additional timepoints for FEV1, SGRQ, rescue medication use
- Labeling claims for (b) (4)



## Safety – Exposure in Pivotal Trials

Exposure	GFF MDI 14.4/9.6 µg (N=1036)	FF MDI 9.6 µg (N=890)	GP MDI 14.4 µg (N=890)	Placebo MDI (N=443)	Spiriva 18 µg (N=451)	All Subjects (N=3710)
<b>Number of Days of Exposure<sup>a</sup></b>						
n	1036	890	890	443	451	3710
Mean (SD)	154.8 (39.1)	150.5 (44.5)	150.0 (43.4)	140.8 (54.4)	158.3 (33.7)	151.4 (43.2)
Median	169.0	169.0	169.0	169.0	169.0	169.0
Min, Max	2, 207	1, 220	2, 199	1, 195	4, 202	1, 220
<b>Total Person-Years of Exposure<sup>b</sup></b>	439.0	366.7	365.5	170.7	195.4	1537.3

Abbreviations: FF=formoterol fumarate; GFF=glycopyrronium and formoterol fumarate; GP=glycopyrronium; Max=maximum; MDI=metered dose inhaler; Min=minimum; SD=standard deviation.

<sup>a</sup> Number of days of exposure=(End date of treatment in Study PT003006 or PT003007 – Date of first dose of treatment in Study PT003006 or PT003007)+1.

<sup>b</sup> Total person-years of exposure for a treatment group was the total exposure (years) in the studies across all subjects in the treatment.

\*1 year exposure: 253 GFF, 187 FF, 191 GP, 147 SHH (Total 893 subjects in Study 3008)

Source: Summary of Clinical Safety, Table 1-8. Note GP dose listed is for glycopyrronium (equals 18 mcg glycopyrrrolate)



## Safety – Disposition in Pivotal Trials

	GFF MDI 14.4/9.6 µg (N=1036) n (%)	FF MDI 9.6 µg (N=890) n (%)	GP MDI 14.4 µg (N=890) n (%)	Placebo MDI (N=443) n (%)	Spiriva 18 µg (N=451) n (%)	All Subjects (N=3710) n (%)
Not Treated	0	0	0	0	0	0
Treated	1036 (100.0)	890 (100.0)	890 (100.0)	443 (100.0)	451 (100.0)	3710 (100.0)
Completed Week 12	936 (90.3)	770 (86.5)	776 (87.2)	355 (80.1)	415 (92.0)	3252 (87.7)
Completed Week 24	861 (83.1)	716 (80.4)	710 (79.8)	325 (73.4)	391 (86.7)	3003 (80.9)
Early Discontinuation <sup>a</sup>	175 (16.9)	174 (19.6)	180 (20.2)	118 (26.6)	60 (13.3)	707 (19.1)
<b>Reason for Early Discontinuation</b>						
Adverse Event(s)	56 (5.4)	40 (4.5)	45 (5.1)	30 (6.8)	20 (4.4)	191 (5.1)
Lack of Efficacy	11 (1.1)	12 (1.3)	20 (2.2)	16 (3.6)	3 (0.7)	62 (1.7)
Subject Discretion	60 (5.8)	58 (6.5)	62 (7.0)	39 (8.8)	21 (4.7)	240 (6.5)
Investigator's Decision	3 (0.3)	10 (1.1)	10 (1.1)	11 (2.5)	3 (0.7)	37 (1.0)
Lost to Follow-up	18 (1.7)	16 (1.8)	16 (1.8)	4 (0.9)	5 (1.1)	59 (1.6)
On or Before Week 24	18 (1.7)	16 (1.8)	16 (1.8)	4 (0.9)	5 (1.1)	59 (1.6)
After Week 24	0	0	0	0	0	0
Administrative Reasons	2 (0.2)	5 (0.6)	1 (0.1)	2 (0.5)	1 (0.2)	11 (0.3)
Major Protocol Violation	2 (0.2)	10 (1.1)	1 (0.1)	1 (0.2)	2 (0.4)	16 (0.4)
Protocol-Specified Criteria	23 (2.2)	23 (2.6)	25 (2.8)	14 (3.2)	5 (1.1)	90 (2.4)

Source: Module 2, SCS, Table 1-5

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## Safety – Adverse Events

	GFF MDI 14.4/9.6 µg (N=1036)	FF MDI 9.6 µg (N=890)	GF MDI 14.4 µg (N=890)	Placebo MDI (N=443)	Spiriva 18 µg (N=451)
	n (%) [Events]	n (%) [Events]	n (%) [Events]	n (%) [Events]	n (%) [Events]
At least 1 TEAE	617 (59.6) [1539]	506 (56.9) [1272]	500 (56.2) [1323]	255 (57.6) [611]	283 (62.7) [754]
Drug-related * TEAEs	117 (11.3) [190]	98 (11.0) [154]	99 (11.1) [174]	46 (10.4) [75]	46 (10.2) [82]
Serious TEAEs	80 (7.7) [104]	66 (7.4) [81]	73 (8.2) [113]	31 (7.0) [43]	36 (8.0) [42]
Drug-related * serious TEAEs	7 (0.7) [8]	4 (0.4) [4]	11 (1.2) [16]	1 (0.2) [1]	1 (0.2) [1]
TEAEs leading to early discontinuation	64 (6.2) [88]	47 (5.3) [71]	55 (6.2) [100]	33 (7.4) [46]	22 (4.9) [23]
Deaths – All Causes					
During Treatment Period	4 (0.4) [5]	1 (0.1) [14]	0	1 (0.2) [1]	4 (0.9) [4]
During Treatment Period + 14 Days	5 (0.5) [6]	1 (0.1) [14]	1 (0.1) [1]	1 (0.2) [1]	4 (0.9) [4]

Common TEAEs (>2% and greater than placebo): cough, UTI

Source: Module 2, SCS, Table 2-1

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## Safety – MACE (Ph3 Safety Pop)

BOC	PT	FF MDI 9.6 µg N=890	GFF MDI 14.4/9.6 N=1036	GF MDI 14.4 µg N=890	Placebo MDI N=443	Spiriva 18 µg N=451	Total N=3210
Cardiac disorders	Acute myocardial infarction	1 (0.1%)	2 (0.2%)	1 (0.1%)	1 (0.2%)	0	5 (0.1%)
	Cardiac arrest	0	1 (0.1%)	0	0	0	1 (<0.1%)
	Cardiac failure acute	0	1 (0.1%)	0	0	0	1 (<0.1%)
	Cardiac failure congestive	0	0	1 (0.1%)	0	1 (0.2%)	2 (0.1%)
	Coronary artery occlusion	0	0	1 (0.1%)	0	0	1 (<0.1%)
	Myocardial infarction	0	1 (0.1%)	0	1 (0.2%)	0	2 (0.1%)
	Death	0	1 (0.1%)	0	0	0	1 (<0.1%)
General disorders and administration site conditions	Sudden cardiac death	0	0	0	0	1 (0.2%)	1 (<0.1%)
	Cerebral ischemia	0	0	1 (0.1%)	0	0	1 (<0.1%)
Nervous system disorders	Cerebrovascular accident	0	1 (0.1%)	1 (0.1%)	0	0	2 (0.1%)
	Pulmonary edema	1 (0.1%)	0	0	0	0	1 (<0.1%)
Respiratory, thoracic and mediastinal disorders	Peripheral artery thrombosis	1 (0.1%)	0	0	0	0	1 (<0.1%)
Vascular disorders		1 (0.1%)	0	0	0	0	1 (<0.1%)
<b>Total Subjects</b>		<b>8 (0.9%)</b>	<b>7 (0.7%)</b>	<b>6 (0.6%)</b>	<b>2 (0.4%)</b>	<b>2 (0.4%)</b>	<b>19 (0.6%)</b>

Source: Reviewer generated in JReview (Safety Population Flag=Y, Treatment Emergent Flag=Y, Confirmed MACE Flag=Y)



## Preliminary Conclusions

- Fileable
- DSI/Audit
  - Most sites in US
  - Concerned citizen complaint
  - Complaint re: ongoing studies
- Advisory Committee Meeting not needed
- No 74-day letter comments
- Potential review issues: safety

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## Extra slides

## Safety – 52 Weeks

	<b>GFF MDI</b> <b>14.4/9.6 µg</b> <b>(N=1036)</b> <b>n (%)</b> <b>[Events]</b>	<b>FF MDI</b> <b>9.6 µg</b> <b>(N=890)</b> <b>n (%)</b> <b>[Events]</b>	<b>GP MDI</b> <b>14.4 µg</b> <b>(N=890)</b> <b>n (%)</b> <b>[Events]</b>	<b>Spiriva</b> <b>18 µg</b> <b>(N=451)</b> <b>n (%)</b> <b>[Events]</b>
At least 1 TEAE	669 (64.6) [2044]	538 (60.4) [1524]	533 (59.9) [1625]	312 (69.2) [977]
Drug-related <sup>a</sup> TEAEs	129 (12.5) [215]	106 (11.9) [163]	109 (12.2) [200]	54 (12.0) [104]
Serious TEAEs	114 (11.0) [155]	78 (8.8) [96]	90 (10.1) [135]	49 (10.9) [56]
Drug-related <sup>a</sup> serious TEAEs	8 (0.8) [9]	6 (0.7) [6]	11 (1.2) [16]	1 (0.2) [1]
TEAEs leading to early discontinuation	81 (7.8) [114]	53 (6.0) [81]	64 (7.2) [110]	28 (6.2) [29]
Deaths (all causes) <sup>b</sup>				
During Treatment Period	4 (0.4)	2 (0.2)	0	5 (1.1)
During Treatment Period + 14 days	5 (0.5)	2 (0.2)	1 (0.1)	5 (1.1)

Source: CSR PT003008, Table 7-1, p117

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/s/  
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08/24/2015

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