CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208294Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	April 12, 2016
From	Anthony G. Durmowicz, M.D.
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 208294 NA
Applicant	Pearl Therapeutics
Date of Submission	June 25, 2015
PDUFA Goal Date	April 25, 2016
Proprietary Name / Established (USAN) names	Bevespi Aerosphere/glycopyrrolate and formoterol inhalation aerosol
Dosage forms / Strength	Inhalation Aerosol/9 mcg glycopyrrolate, 4.8 mcg formoterol/actuation. The dose is 2 actuations twice daily
Proposed Indication(s)	…for the long-term, (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Recommended:	Approval

1. Introduction

On June 25, 2015, Pearl submitted a new drug application (NDA) for glycopyrrolate (GP) and formoterol fumarate (FF) inhalation aerosol, 9 and 4.8 mcg/actuation, respectively (proposed tradename Bevespi Aerpsphere), at a dose of 18 mcg GP/9.6 mcg FF (2 actuations) twice daily with a proposed indication for the long-term, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). Bevespi is a combination inhalation product comprised of the antimuscarinic agent, GP, and a long-acting beta-agonist (LABA), FF. Both products are approved either individually or in combination as other inhaled products used to treat bronchospasm in patients with COPD. This NDA submission contains clinical efficacy and safety data to support the proposed indication (b) (4) in COPD patients. Review of this clinical data will be the focus of this review.

2. Background

Several drug classes are available for the treatment of COPD. These include beta-adrenergic agonists, combination products containing long-acting beta-adrenergic agonists and corticosteroids, anticholinergic agents, combination products containing anticholinergic and beta-adrenergic agonists, nonspecific phosphodiesterase inhibitors, and phosphodiesterase-4 inhibitors.

Glycopyrrolate is an antimuscarinic drug that binds to muscarinic receptors. GP has been in clinical use for many years as tablets (Robinul 6 mg), or intra-operatively as an injectable (Robinul 100 mcg/injection every 2-3 minutes). In the United States, an oral formulation (Cuvposa) is indicated for severe drooling in patients 3-16 years of age with neurologic conditions. There are also multiple generic GP products. (b) (4) GP has been recently approved as an inhalation powder (Seebri Neohaler) and in combination with the LABA, indacaterol (Utibron Neohaler) (b) (4) in patients with COPD. Other inhaled anticholinergics are widely used in the U.S. for the treatment of COPD. These include short-acting ipratropium bromide (Atrovent), tiotropium bromide (Spiriva HandiHaler, Spiriva Respimat), aclidinium bromide (Tudorza Pressair), and umeclidinium (in combination with vilanterol as Anoro Ellipta, and as single ingredient Incruse Ellipta). Common antimuscarinic adverse effects include dry mouth, constipation, and urinary retention. The issue of cardiovascular safety and stroke risk in COPD patients who receive inhaled antimuscarinics has also been a topic of interest. However, more recent results from two large tiotropium safety studies in approximately 23,000 COPD patients ("Understanding Potential Long-term Impacts on Function with Tiotropium" or UPLIFT and "Tiotropium Safety and Performance in Respimat" or TIOSPIR) have alleviated much of the concern over cardiovascular safety.

Formoterol is a LABA, and is currently marketed alone as a bronchodilator as a dry powder for inhalation (Foradil Aerolizer) and inhalation solution [Perforomist and Brovana (arformoterol)] and as a combination with mometasone as a metered dose inhaler (Symbicort). Other LABAs currently marketed in the United States for the treatment of COPD alone or as part of a combination product include salmeterol, indacaterol, and vilanterol. Of note,

salmeterol, formoterol, and arformoterol are dosed twice daily and indacaterol (when used in the single drug, Arcapta Neohaler) and vilanterol are dosed once daily.

As a drug class, LABAs have known pharmacologic effects on the cardiovascular system, including increases in heart rate and blood pressure. Labeling for both short-acting and long-acting beta agonists includes a Warnings and Precautions statement regarding these effects, and caution is recommended when used in patients with cardiovascular disorders. LABAs indicated for treatment of asthma have a Boxed Warning indicating that their use increases the risk of asthma-related death and hospitalizations. While this issue has not been observed when used for COPD, an abbreviated Boxed Warning is included in the labels of LABAS indicated for COPD.

The Division had several meetings and discussions with the Applicant over the course of product development. (b) (4) a PIND meeting for the glycopyrrolate/formoterol fumarate combination inhalation aerosol (GFF) was held on April 12, 2010 (IND 107739). Key regulatory interactions included:

GFF PIND Meeting, April 12, 2010:

- Each single ingredient product being evaluated in the combination should be completely characterized and show evidence of efficacy
- Pearl should adequately characterize the dose and dosing regimen of GP and FF to test in the combination product. Consider including active-control arms to further anchor the dose regimen.

GFF Type C Meeting, April 19, 2012:

- Agreement that a BID dosing interval for GP was appropriate.
- Agreement that a 9.6 mcg dose of FF administered BID was appropriate to study in Phase III clinical studies.

GFF EOP-2 Meeting, January 17, 2013:

- Agreement that an 18 mcg dose of GP administered BID was reasonable to take forward into Phase III clinical studies.
- (b) (4) .
- FDA noted that the preferred primary analysis for trough FEV1 is a landmark analysis at 24 weeks.
- FDA agreed that 12-hour serial spirometry in a subset of patients at Day 1 and Week 12 in Phase III trials was reasonable for inclusion in the GFF MDI prescribing information.

Pre-NDA Meeting, July 1, 2014:

- FDA noted that trough FEV1 at Week 24 should be the primary endpoint.

- FDA indicated that, except for event-based endpoints such as exacerbations and use of rescue medications, efficacy should be measured at a landmark timepoint (b) (4)
- FDA indicated that statistical testing procedures should include provisions to control for Type I error for all efficacy endpoints being considered for inclusion in the product label, including onset of action.

Written Correspondence, April 14, 2015:

- FDA generally agreed with Pearl's proposed approach for handling the analysis of data from the 15 identified fraudulent subjects.

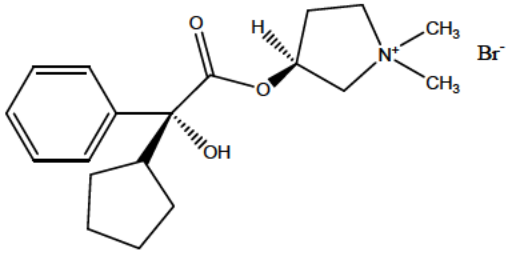
3. Chemistry, Manufacture, and Controls

The recommendation from the CMC team (ONDQA) at the time of this review is pending based on the results from manufacturing facility inspections. A brief overview of the product attributes is summarized below.

The Bevespi Aerosphere drug device combination product is a pressurized metered-dose inhaler for delivery of a combination of micronized glycopyrrolate and micronized formoterol fumarate to patients by oral inhalation.

Glycopyrrolate is a quaternary ammonium salt that is freely soluble in water. The molecular formula is C19H28NO3 ·Br, and the molecular weight is 398.33 g/mol. Glycopyrrolate contains two chiral centers and is a racemate of a 1:1 mixture of the R,S and S,R diastereomers. The active moiety, glycopyrronium, is the positively charged ion free base form of glycopyrrolate.

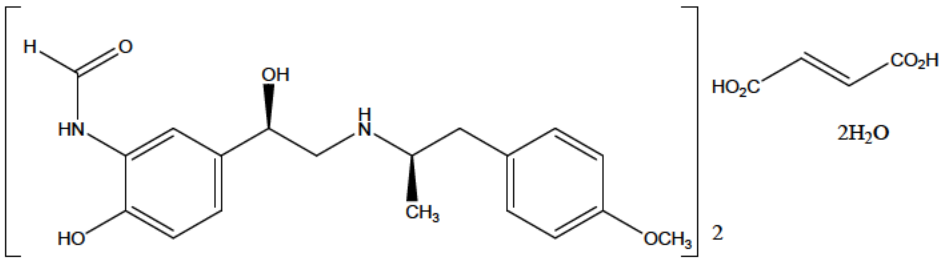
Glycopyrrolate Chemical Structure



Glycopyrrolate (Glycopyrronium Bromide) [(*S*)-3-((*R*)-2-cyclopentyl-2-hydroxy-2-phenylacetoxy)-1,1-dimethylpyrrolidin-1-ium bromide and enantiomer]

Formoterol fumarate is a powder that is slightly soluble in water. The molecular formula is (C19H24N2O4)2.C4H4O4.2H2O and the molecular weight is 840.91 g/mol. Formoterol fumarate also contains two chiral centers and consists of a single enantiomeric pair (a racemate of R,R and S,S).

Formoterol Fumarate Chemical Structure



N-(2-hydroxy-5-((*R*)-1-hydroxy-2-(((*R*)-1-(4-methoxyphenyl)propan-2-yl)amino)ethyl)phenyl)formamide fumarate

and enantiomer

Bevespi Aerosphere also contains porous particles that form a co-suspension with the drug crystals. The porous particles are comprised of the phospholipid, 1, 2- Distearoyl-sn-Glycero-3-Phosphocholine, and calcium chloride.

The drug device combination is formulated as a hydrofluoroalkane (HFA 134a) propelled pressurized metered dose inhaler consisting of a (b) (4) aluminum canister fitted with a crimped-on metering valve, white plastic actuator, an orange dust cap, and a top of canister mounted dose indicator which indicates the number of remaining inhalations in decrements of 20, and advances every 10 inhalations. Human factors studies and clinical trials have demonstrated adequate indicator and overall product performance. The (b) (4) manufacturing process is adequate and has appropriate microbial limit specifications. Each inhaler contains 120 inhalations of drug product.

The drug product is packaged in a foil laminate pouch with enclosed desiccant. Data support a 24 month expiry for the drug product and a 3 month in-use period (after removal of protective packaging).

Priming is necessary to ensure appropriate drug content in each actuation. The initial priming is accomplished by releasing 4 sprays into the air, shaking well before each spray. If the product is not used for more than 7 days it should be re-primed by releasing 2 sprays into the air, again, shaking before each spray. After priming each actuation of the inhaler meters 10.4 mcg of glycopyrrolate (equivalent to 8.3 mcg of glycopyrronium) and 5.5 mcg of formoterol fumarate from the valve which delivers 9 mcg of glycopyrrolate (equivalent to 7.2 mcg of glycopyrronium) and 4.8 mcg of formoterol fumarate from the actuator.

Manufacture and quality control of filled canisters are performed at Aventis Pharma Ltd, Cheshire UK and at AstraZeneca, Dunkerque, France. Stability testing of final product is performed at (b) (4)

4. Nonclinical Pharmacology/Toxicology

The recommendation from the nonclinical review is Approval. A brief overview of nonclinical findings is summarized below. For further details see the pharmacology/toxicology review by Dr. Luqi Pei, dated March 10, 2016).

Pearl conducted an abbreviated nonclinical program for Bevespi by relying, in part, on the FDAs previous findings of safety for GP and FF, the individual drug components of Bevespi. Robinul is the oral formulation GP product referenced for GP nonclinical systemic safety information and Symbicort, an approved inhalation product containing FF, was relied on for FF nonclinical safety information. As such, the inhalational toxicology program consisted of GP inhalation studies up to 6 months in rats and dogs, as well as a 3-month inhalation study of the GP and FF combination in dogs to assess for potential toxicological interactions. In 6-month GP studies, drug-related findings were observed in rats, but not dogs. In the rat study, increased hyaline degeneration of the respiratory and olfactory epithelium and laryngeal squamous metaplasia in the larynx were observed in both sexes at 27.5 (mid-dose) and 54.8 (high-dose) mcg/kg/day (pulmonary deposited dose or PDD). An increased incidence of prostate inflammation was also observed in high-dose males. The rat study NOAEL was identified as the mid-dose due to prostate inflammation at the high dose as nasal cavity findings are not considered relevant to humans who will receive Bevespi by the oral inhalation route and the findings in the larynx are considered a rat-specific finding. No drug-related findings were observed in the dog study at doses up to 18.7 mcg/kg/day (PDD). In the 3-month GP and FF in combination study in dogs, drug-related changes were observed in the respiratory tract, liver, and prostate but there were no indications of significant toxicological interactions between GP and FF. The low combination dose (4.3 and 1.1 mcg/kg/day of GP and FF, respectively) was noted as the NOAEL.

Both GP and FF were negative in genotoxicology studies. An evaluation for the carcinogenic potential for GP was not required, as no pre-neoplastic or neoplastic lesions were observed in chronic inhalation GP studies. With regard to FF, the approved label for the reference product, Symbicort, (b) (4) . Regarding reproductive and developmental toxicology, as noted in the Robinul approved oral GP formulation label, GP was not teratogenic in rats (b) (4) but it did cause reduced pup survival and conception rates in rats. Per the Symbicort label, FF was teratogenic in both rats and rabbits. FF also decreased fertility in male rats.

5. Clinical Pharmacology/Biopharmaceutics

The recommended regulatory action from the Clinical Pharmacology/Biopharmaceutics team is for Approval. There are no outstanding clinical pharmacology issues at this time. To support this NDA submission, the Applicant provided information from 11 clinical pharmacology studies, some of which were submitted to support NDA 207923. Highlights of the clinical pharmacology review are summarized here.

- Following oral inhalation of Bevespi, both GP and FF were rapidly absorbed and reached peak plasma levels (Cmax) at 5 minutes and 20-60 minutes, respectively. Mean half-life ranges from 5-10 hours for GP and about 12 hours for FF.

- The thorough QT study was reviewed by the QT-IRT team and no significant QTc prolongation was observed at GP and FF doses in combination up to 115.2 mcg and 38.4 mcg, respectively.
- There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled GP and inhaled FF based on steady-state exposure. Therefore, the relevant findings and/or conclusions for the mono-therapies may be extrapolated to the combination.
- The dose ranging performed in the combination program included full characterization of the individual components (b) (4) and was adequate for the Phase 3 dose selection. Dose selection is further discussed in Section 7.

6. Clinical Microbiology

This drug product is manufactured and packaged (b) (4). Adequate microbial limit specifications are in place.

7. Clinical/Statistical- Efficacy

The key clinical studies relevant to regulatory decision making are shown Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the section 8.

Table 1: Clinical Studies Relevant to Regulatory Decision Making

Trial *(dates)*	Design	Treatment (mcg)	N	Duration	Primary Endpoint(s)	Sites (countries)
Dose Selection for FF						
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_1 AUC_{0-12}	5 sites (AU, NZ)
Dose selection for GP						
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_1 AUC_{0-12}	10 sites (US)
Dose selection for GFF						
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 GFF18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL)	159	7 days, 4-periods	Change from baseline in FEV_1 AUC_{0-12}	20 sites (US)
Phase 3 Confirmatory Trials						
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_1 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	512 440 439	24 weeks	Change from baseline trough FEV_1 at 24 weeks	140 sites (US)

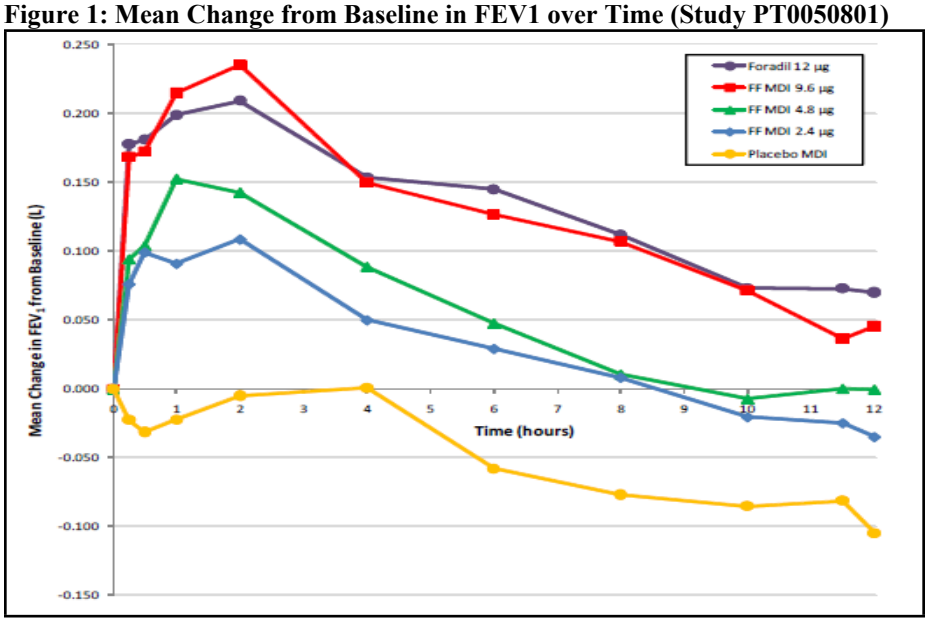
Trial *(dates)*	Design	Treatment (mcg)	N	Duration	Primary Endpoint(s)	Sites (countries)
		PBO bid	224			
Supportive Trials (long-term safety)						
PT003008 *(11/13-12/14)*	R, DB, AC, PG	GFF 18/9.6 bid GP 18 bid FF 9.6 bid SHH 18 qd (OL)	290 219 213 171	28 weeks	Long term safety	205 sites (US, AU, NZ)

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

Dose Selection

Formoterol Fumarate: Dose selection for formoterol fumarate was supported by Study PT0050801, a single-dose, randomized, double-blind, placebo-controlled, crossover trial evaluating 3 doses of formoterol fumarate (FF 9.6, 4.8 and 2.4 mcg), open-label Foradil Aerolizer 12 mcg as an active control, and placebo in 34 subjects with COPD. For the primary analysis, the mean change in $FEV1^{(0\text{-}12\ hr)}$ AUC was statistically superior to placebo for each dose of FF and showed a clear dose-response relationship (Figure 1). Compared to Foradil, the FF 9.6 mcg dose demonstrated a similar FEV1 time profile curve. Notably, the PK of FF 9.6 was lower than that for Foradil. Based on the results of this study, the 9.6 mcg dose of FF was selected to study in phase 3 trials.

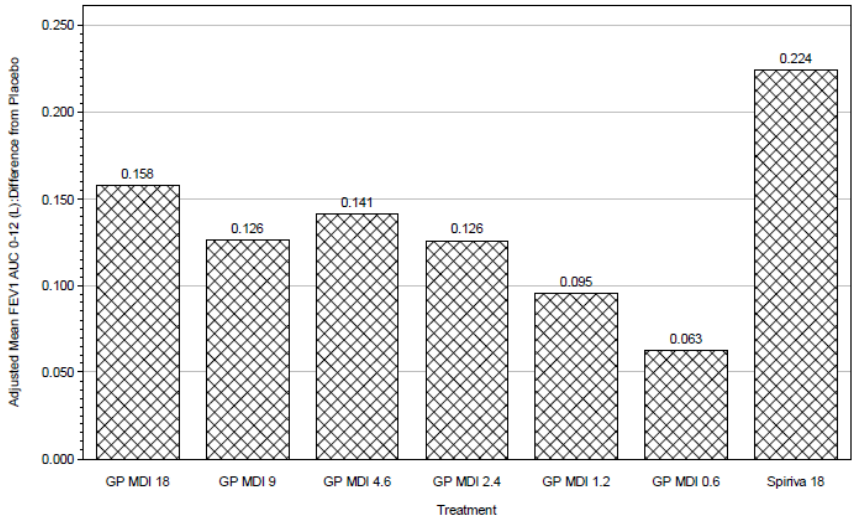
Figure 1: Mean Change from Baseline in FEV1 over Time (Study PT0050801)



Source: Study PT005080 CSR, p. 45

Glycopyrrolate: Dose selection for glycopyrrolate was primarily supported by Study PT001003, a 14-day, randomized, double-blind, placebo-controlled, incomplete-block crossover trial evaluating 6 doses of glycopyrrolate (GP MDI 18, 9, 4.6, 2.4, 1.2, and 0.6 mcg) administered twice daily and open-label Spiriva Handihaler as an active control in 140 subjects with COPD. The primary endpoint was $FEV1^{(0\text{-}12\ hr)}$ AUC. Dose ordering for effect was observed, with the glycopyrrolate 18 mcg demonstrating larger improvements in FEV1 over 12 hours compared with glycopyrrolate 9, 4.6, 2.4, 1.2, and 0.6 mcg (Figure 2).

Figure 2: Mean FEV1$^{(0\text{-}12\ hr)}$ AUC (L): Difference from Placebo on Treatment Day 14 (Study PT001003)

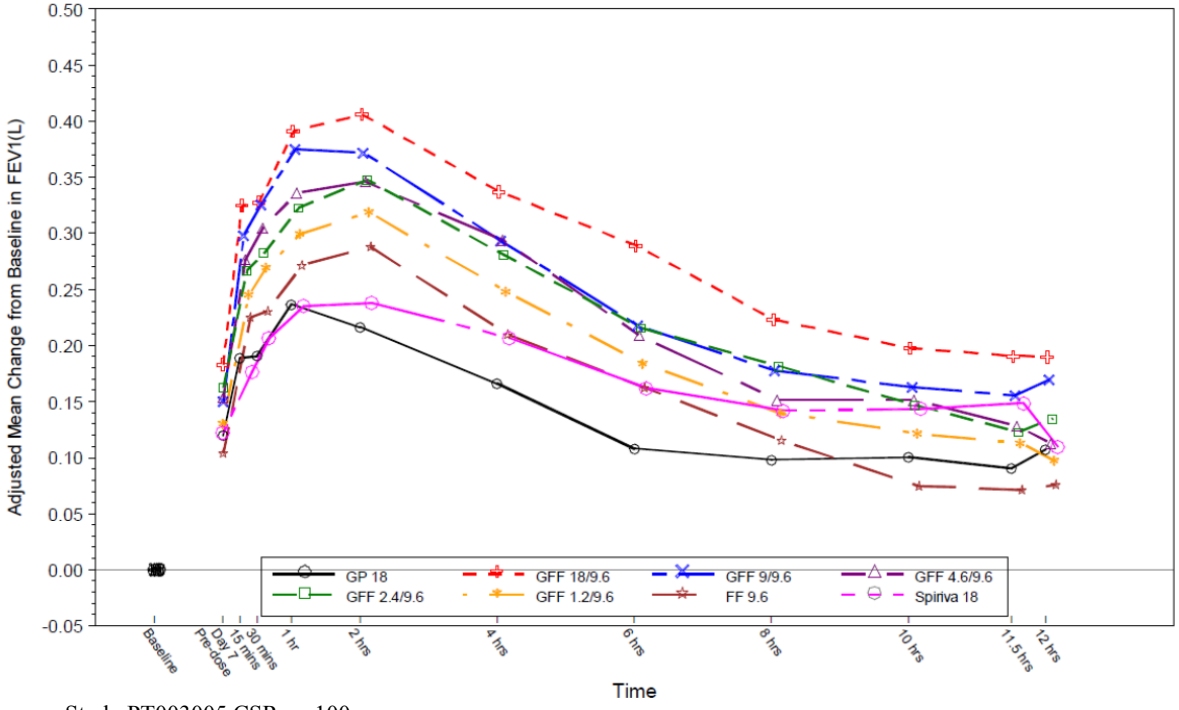


Source: Study PT001003 CSR, p. 105

The difference from placebo in change from baseline in trough FEV1 after 14 days for the 18, 9, 4.6, 2.4, 1.2, and 0.6 mcg doses were 97 mL (95% CI: 45, 149), 88 mL (95% CI: 37, 139), 75 mL (95% CI: 24, 125), 84 mL (95% CI: 33, 135), 76 mL (95% CI: 22, 129), and 37 mL (95% CI: -17, 91), respectively. Previous dose ranging trials in subjects with COPD had demonstrated minimal additional benefit at doses above 18 mcg.

Study PT003005, a 7-day, randomized, double-blind, active-controlled, incomplete-block crossover trial provided additional support for GP dose selection. The study evaluated 5 doses of GP on a background of FF 9.6 mcg (GFF MDI 18/9.6, 9/9.6, 4.6/9.6, 2.4/9.6, and 1.2/9.6 mcg), and the individual components, FF MDI 9.6 mcg and GP MDI 18 mcg, administered as two inhalations twice daily in 159 subjects with COPD. Open-label Spiriva HandiHaler (18 mcg once daily) was included as an active control. The primary endpoint was FEV1$^{(0\text{-}12\ hr)}$ AUC. The results demonstrated that COPD patients who received the GFF 18/9.6 mcg dose had larger improvements in FEV1 over 12 hours compared with the lower doses of 9/9.6, 4.6/9.6, 2.4/9.6, and 1.2/9.6 mcg GFF as well as the GP and FF monocomponents. The difference in FEV1$^{(0\text{-}12\ hr)}$ AUC for the GFF 18/9.6 mcg dose was 139 and 124 mL compared to the GP 18 µg and FF 9.6 monocomponent doses, respectively. GFF 9/9.6, 4.6/9.6, and 2.4/9.6 mcg twice daily demonstrated increases of 95, 87, and 87 mL, respectively compared with GP 18 mcg and 79, 71, and 71 mL, respectively, compared to FF MDI 9.6 mcg. Figure 3 shows mean change from baseline in FEV1 for the GP and FF monocomponents and GFF combinations in Study PT003005.

Figure 3: Adjusted Mean Change from Baseline in FEV1 (L) (Study PT003005)



Source: Study PT003005 CSR, p. 100

Efficacy Study Design

Trials PT003006 and PT003007

Other than the inclusion of a Spiriva HandiHaler (SHH) as an active-control in trial PT003006 (3006), trials 3006 and PT003007 (3007) were identical randomized, double-blind, placebo controlled, parallel group, 24-week trials in patients with moderate-to-severe COPD. The trials enrolled patients with a diagnosis of moderate to severe COPD, with the following pertinent entry criteria: a) 40-80 years of age; b) FEV1 < 80% predicted; and c) current or ex-smokers with a smoking history of > 10 years. Patients on background ICS, LABA, and/or antimuscarinic therapy were switched to Applicant-provided albuterol and/or ipratropium bromide PRN, and ICS bid (if receiving ICS for 4 weeks prior to enrollment). PDE-4 inhibitor use was also allowed if on a stable dose for at least 2 months. Pertinent exclusion criteria included a recent history of unstable ischemic heart disease or myocardial infarction within one year, NYHA Class III/IV CHF, percutaneous coronary intervention or bypass within 3 months unstable, significant cardiac arrhythmia, oxygen use > 12 hr/day, and use of oral steroids > 5 mg qd or 10 mg qod.

Patients were randomized to receive GFF 18/9.6 mcg of GP and FF, respectively, GP 18 mcg, FF 9.6 mcg, SHH 18 mcg (trial 3006 only), or placebo. The primary endpoint for the trials was change from baseline in trough FEV1 response at week 24. Secondary endpoints included peak FEV1, change in FEV1, change in daily rescue medication use, and time to onset. COPD exacerbations, generally defined as a change in the patient's baseline dyspnea, cough, and/or sputum 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 medications, was an exploratory endpoint. Specifically, moderate exacerbations were those that required treatment with systemic steroids and/or antibiotics and severe exacerbations were those that resulted in hospitalization or death.

Efficacy Results

Trough FEV1

The primary efficacy endpoint for both trials 3006 and 3007 was change from baseline in trough FEV1. In each trial, the combination, GFF and both of the monocomponents, GP and FF, demonstrated significant increases in FEV1 (Table 2). Additionally, in each trial GFF was statistically superior to both GP and FF alone.

Table 2: Pre-dose Trough FEV1 at Week 24 in Trials 3006 and 3007 (ITT Population)

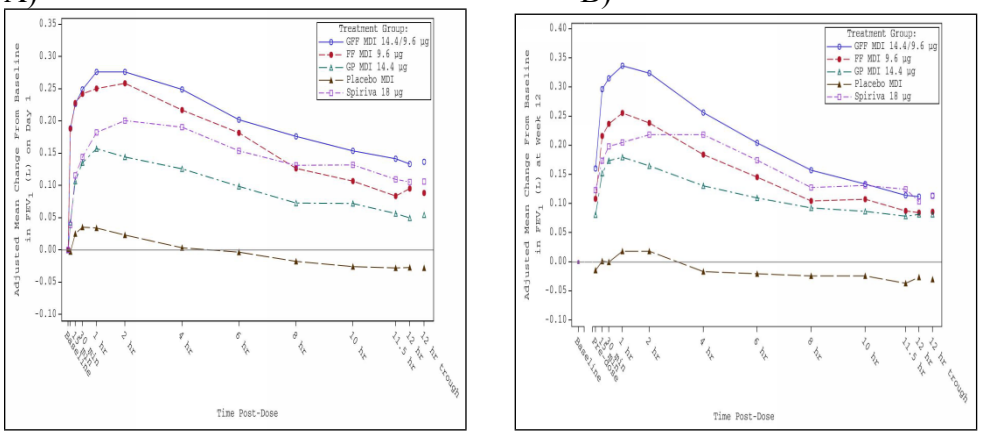
Treatment	N	Change (mL)	Difference from Placebo (95% CI)	Difference from GP (95% CI)	Difference from FF (95% CI)
Trial 3006					
GFF	429	126	150 (114,186)	59 (31, 88)	64 (36, 92)
FF	367	62	86 (49, 123)	-5 (-34, 25)	
GP	344	66	91 (53, 128)		
SHH	390	105	129 (92, 166)	38 (9, 67)	
Placebo	161	-24			
Trial 3007					
GFF	433	116	103 (67, 140)	54 (25, 83)	56 (27, 85)
FF	350	61	47 (10, 85)	-2 (-32, 28)	
GP	367	63	49 (12, 87)		
Placebo	170	13			

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
Source: CSR Tables PT003006, Table 2.1.1, p370 and CSR Tables PT003007, Table 2.1.1, p304

In both trials 3006 and 3007, serial spirometric evaluations were performed throughout the 12-hour dosing interval in a subset of subjects (n=718 and n=585, respectively) at Day 1 and Week 12. Differences between treatments in Δ trough FEV1 appeared on Day 1 and were maintained through week 24 in both trials (Figures 4 and 5).

Figure 4: Change in Trough FEV1 from Baseline on Day 1 (A) and Week 12 (B), Trial 3006

A) B)



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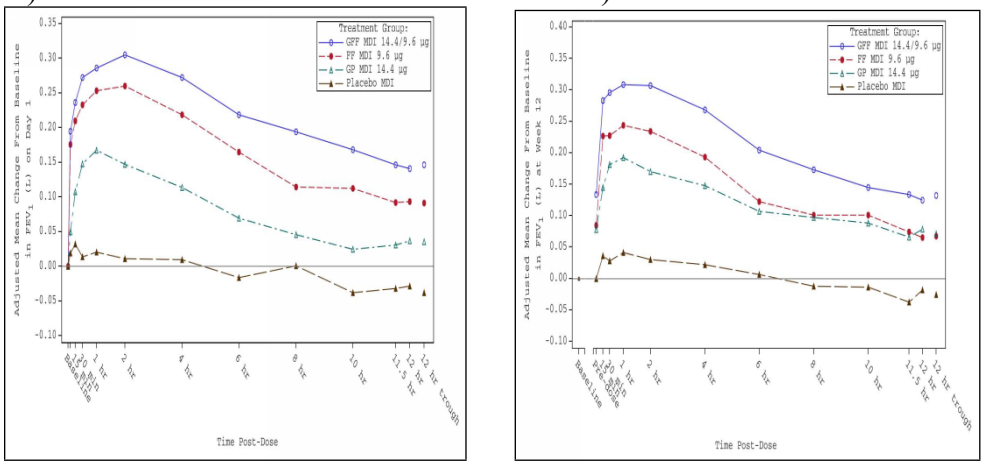
Source: Study PY003006 CSR, Figures 2.18.1B and 2.19.1B, p. 139 and 143, respectively

Figure 5: Change in Trough FEV1 from Baseline on Day 1 (A) and Week 12 (B), Trial 3007

A) B)



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Source: Study PY003007 CSR, Figures 2.18.1B and 2.19.1B, p. 140 and 142, respectively

Peak FEV1 and Time to Onset:

Peak FEV1 was defined as the maximum FEV1 recorded within 2 hours after the morning dose of trial medication. For each trial, the combination product, GFF, as well as each monocomponent, was superior to placebo in peak change in trough FEV1 (Table 3). GFF was also superior to each monocomponent.

Table 3: Peak Change from Baseline in FEV1 within 2 Hours Post-dose at Week 24, Trials 3006 and 3007

Treatment Arm	N	Baseline (L)	Δ from Baseline (mL)	Difference from Placebo	Difference from GP	Difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
Trial 3006						
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)		
SHH	388	1.287 (0.5)	259 (11)	194 (154, 234)	36 (4, 68)	
Placebo	160	1.330 (0.5)	65 (17)			
Trial 3007						
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
Source: Study PT003006 and PT003007 CSRs ,Table 2.3.1, p. 751 and Table 2.3.1, p. 568, respectively

With regard to time of 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 FEV1 was statistically significant. Compared to placebo, time to statistically significant effects was less than five minutes for the combination product GFF as well as each of its component monotherapies (Table 4). It is notable that when measured at later time points (week 2 and week 12), the contribution of GP to the GFF combination is greater than on Day 1 which supports the hypothesis that the peak effect of antimuscarinic agents takes several weeks to be seen (see the statistical review by Dr. Abugov for additional data regarding these findings).

Table 4: Time to Onset: Change from Baseline in FEV1 at 5 minutes Post-dose on Day 1: Trials 3006 and 3007

Treatment Arm	N	Baseline (L)	Δ from Baseline (mL)	Difference from Placebo	Difference from GP	Difference from FF
		Mean (SD)	LS Mean (SE)	LS Mean (95% CI)	LS Mean (95% CI)	LS Mean (95% CI)
Trial 3006						
GFF	418	1.274 (0.5)	185 (5)	187 (168, 205)	143 (128, 158)	3 (-12, 18)
FF	366	1.284 (0.5)	182 (5)	184 (165, 203)	140 (125, 155)	
GP	363	1.268 (0.5)	42 (6)	44 (25, 63)		
SHH	364	1.289 (0.5)	48 (6)	50 (31, 69)		
Placebo	172	1.280 (0.5)	-2 (8)			
Trial 3007						
GFF	429	1.293 (0.5)	192 (6)	186 (164, 207)	140 (122, 157)	17 (0, 0.03)
FF	375	1.320 (0.5)	175 (6)	169 (147, 191)	123 (105, 140)	
GP	371	1.289 (0.5)	52 (6)	46 (24, 68)		
Placebo	179	1.260 (0.5)	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
Source: Study PT003006 and PT003007 CSRs, Table 2.6.1, p. 1058 and Table 2.6.1, p. 778, respectively

The St. George's Respiratory Questionnaire (SGRQ):

For change in SGRQ, the GFF combination product was statistically superior to placebo in trial 3006 but not in trial 3007. However, the difference in SGRQ compared to placebo of -2.52 and -1.72, for trials 3006 and 3007, respectively, did not reach the minimal clinically important difference (MCID) of -4. Responder rates for SGRQ were also assessed with responders defined as those patients who achieved the -4 change from baseline MCID for SGRQ. Compared to placebo, the GFF combination provided statistically significant improvements in SGRQ response rates in trial 3006 but not in 3007 (Table 5). Also, in trial 3006, but not in 3007, patients treated with GFF had significantly greater response rates compared to patients treated with GP monocomponent.

Table 5: SGRQ Responder Analyses at Week 24 (Trials 3006 and 3007)

Treatment Arm	N	Responders (%)	Compared to Placebo	Compared to GP	Compared to FF
			Odds Ratio (95% CI)	Odds Ratio (95% CI)	Odds Ratio (95% CI)
Trial 3006					
GFF	526	198 (37)	1.49 (1.1, 2.1)	1.39 (1.1, 1.8)	1.11 (0.9, 1.5)
FF	449	157 (35)	1.34 (0.9, 1.9)	1.25 (0.9, 1.7)	
GP	451	138 (30)	1.07 (0.8, 1.5)		
SHH	451	173 (39)	1.58 (1.1, 2.3)		
Placebo	219	63 (28)			
Trial 3007					
GFF	510	203 (40)	1.31 (0.9, 1.8)	1.23 (0.9, 1.6)	1.29 (1.0, 1.7)
FF	437	147 (34)	1.02 (0.7, 1.4)	0.95 (0.7, 1.3)	
GP	439	153 (35)	1.07 (0.8, 1.5)		
Placebo	223	75 (34)			

Source: Study PT003006 and PT003007 CSRs, Table 2.4.3.1, p. 971 and Table 2.4.3.1, p. 716, respectively

Rescue medication use:

As would be expected in a trial where all active treatment groups were receiving chronic bronchodilator use, there was a statistically significant decrease in rescue medication use (albuterol supplied as Ventolin HFA) with each active treatment (GFF, GP, FF, and SHH) compared to placebo. However, this difference amounted to mean decrease in albuterol use of about one puff (one half of one dose/day). This is not unexpected since all active treatment groups were receiving long-acting bronchodilators (antimuscarinic, beta agonist or both) chronically.

Efficacy Conclusions

Overall, the data support efficacy of GFF 18/9.6 mcg (Bevespi Aerosphere) as a maintenance treatment of airflow obstruction in patients with COPD. Based on the available data, GFF FDC inhalation aerosol (9 and 4.8 mcg/actuation of GP and FF, respectively) at a dose of 2 actuations twice daily demonstrated a significant effect on bronchodilation compared to the individual monocomponents. Data from secondary and exploratory endpoints (SGRQ, rescue medication use, and exacerbations) support its efficacy as a bronchodilator.

8. Safety

To evaluate the safety of GFF 18/9.6 mcg twice daily, Pearl submitted a pooled safety database that included the 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 trial 3008 was 26 weeks in duration and provided long-term safety data over a total of 52 weeks in a subset of subjects. There were a total of 3699 unique subjects in the pooled safety database of which 1036 subjects received GFF and 253 patients exposed to GFF for one year. The extent of exposure was reasonable given that both components of GFF are older drugs with well-characterized safety profiles and that large safety trials with other inhaled

antimuscarinic agents have alleviated much of the previous concern over cardiovascular safety risks of inhaled antimuscarinics in patients with COPD.

As trials 3006 and 3007 were placebo-controlled and the safety findings of the extension trial 3008 were similar, this review of safety will focus on the pooled 24-week database for trials 3006 and 3007. In the trial 3006/3007 pooled population 24-week pooled safety database, demographics of the treatment group populations was very similar. Overall, the majority of the subjects were White (91%) and male (56%), with a mean age of 63 years. Approximately 8% of subjects were African American which is relatively representative of the U.S. population. Fifty-four % of patients were current smokers; the mean number of pack-years smoked for the overall population was 26. Patients had mostly moderate and severe COPD with 53% meeting GOLD 2 and 42% meeting GOLD 3 criteria. Despite this severity, patients had relatively few exacerbations in the year prior to enrollment with a mean of 0.3 exacerbations/subject. Mean post-bronchodilator FEV1 was 1.52L with 50% meeting reversibility criteria of increase in FEV1 of $\geq$ 12% and $\geq$ 200 mL.

There were 12 deaths in the pooled phase 3 trials with 6 in the GFF treatment group; all reported once (small bowel obstruction, cardiac arrest, MI, gun-shot wound, neoplasm, and bladder cyst). It is notable that 2 patients in the SHH treatment group died of self-inflicted injuries. There were 2 additional deaths in the 3008 extension study (acute MI in one patient in the SHH group and cardiac arrest in one patient in the FF monocomponent group). Overall, death was a relatively rare occurrence in the 24-week pooled safety database. Causes of death were those that can be seen in an older, COPD population with no particular cause of death predominant.

Serious adverse events (SAEs) were also relatively infrequent and balanced across treatment groups. In the 24-week pooled safety database, 32 subjects reported SAEs (7% GFF, 7% FF, 8% GP, and 7% placebo). The most frequent SAE was “COPD” reported in 2-3% of patients in each treatment group. Another SAE that was relatively frequent was pneumonia reported in 1-2% of patients in each treatment group.

In addition, adverse events (AEs) leading to premature discontinuation were again relatively uncommon and balanced. Slightly more patients who received placebo discontinued due to an AE (7.4%) compared to patients in active treatment groups (4.9-6.2%). As would be expected, AEs reported for the respiratory, thoracic, and mediastinal SOC resulted in the most discontinuations with COPD being the most common AE leading to discontinuation with 1-2% across active treatment and placebo groups. Analysis of SAEs and AEs leading to discontinuation do not raise concern for any new safety concerns.

Given the historical concern with the anticholinergic class of drugs, adverse events of interest included adjudicated major adverse cardiovascular events (MACE).

Overall, adjudicated MACE and/or cardiovascular deaths in the GFF phase 3 pooled data occurred infrequently, were relatively balanced, and do not raise any concerns (GFF: 0.7%, FF: 0.3%, GP: 0.6%, SHH: 0.4, and placebo: 0.5%).

Adverse events typical of the antimuscarinic and LABA drug classes were reported infrequently as well. Tremor was the most common beta-adrenergic effect AE and was reported in 1% and 0.8% of patients treated with GFF or FF, respectively. Dry mouth was the most common antimuscarinic AE occurring in 1%, 0.7%, and 2% of patients treated with GFF, GP, and SHH, respectively.

The most common adverse events in the 24-week pooled safety database that occurred with an incidence of ≥ 1% in the GFF group and higher than placebo were arthralgia, chest pain, tooth abscess, muscle spasm, headache, oropharyngeal pain, vomiting, pain in extremity, dizziness, anxiety, dry mouth, fall, influenza, fatigue, acute sinusitis, and contusion. There were no clinically meaningful changes in laboratory parameters, vital signs, and or ECGs.

Safety Conclusions
In summary, the safety data for the GFF development program in COPD do not reveal any new anticholinergic- or LABA-related safety concerns. Adverse events were few and generally those observed were similar to other approved anticholinergic and LABA products. The safety data submitted support the use of GFF 18/9.6 mcg for the long-term, (b) (4) maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease.

9. Advisory Committee Meeting

A pulmonary allergy drug advisory committee (PADAC) meeting was not required for this submission as the safety and efficacy of an anticholinergics, such as GP, and LABAs, such as FF, in the maintenance treatment of COPD are well understood.

10. Pediatrics

The indication for GFF 18/9.6 mcg (Bevespi Aerosphere) is for treatment of patients with COPD only. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required that relate to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

- Financial Disclosure: The applicant submitted acceptable financial disclosure statements and has stated that no debarred individuals were used in the conduct of the trials included in this NDA. All trials were conducted in accordance with accepted ethical standards. For trials 3006, 3007, and 3008, there were a total of 16 investigators (out of a total of 310) who reported disclosable financial investigators with significant payments of other sorts. Given that the trials were large randomized, double-blinded, controlled trials and each investigator was only responsible for enrolling a relatively small number of patients, it was determined that this financial disclosure information did not significantly affect the conduct of the trials.
- DSI audits conducted for three investigators selected on the basis of high enrollment and/or relatively large treatment effect or due to complaints and allegations regarding study conduct. In addition, the Applicant, Pearl Therapeutics, was inspected as a result of complaints regarding inadequate oversight of the studies. Based on the inspection of

three clinical sites and the Applicant, Pearl, by the Office of Scientific Investigation, the data reported to the Applicant by the clinical sites and subsequently by the Applicant to the NDA appear to be reliable and judged able to be used to support the requested indication. The Applicant's oversight of the studies also appeared to be adequate. The anonymous complaints and allegations regarding lack of oversight by the Applicant and other study site were not substantiated during the inspections.

12. Labeling

- Physician Labeling: The label was reviewed by various disciplines within DPARP, the Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were made to reflect the data accurately and better communicate the findings to healthcare providers. The labeling language in the Warnings and Precautions and Clinical Trials sections were edited to include the information relevant for an antimuscarinic/beta-agonist combination for COPD. Labeling is being finalized at the time of this review.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

The recommended regulatory action for this NDA is for approval of GFF 18/9.6 mcg inhalation aerosol (Bevespi Aerosphere) for the for the long-term, twice-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD).

- Risk Benefit Assessment

The overall risk-benefit assessment supports the use of GFF 18/9.6 mcg inhalation aerosol (Bevespi Aerosphere) in patients with COPD who require more than one bronchodilator.

1. Recommendation for Post-marketing Risk Management Activities

No additional post-marketing risk management activities are recommended beyond standard pharmacovigilance methods.

2. Recommendation for other Post-marketing Study Commitments

None

3. Recommended Comments to Applicant

No additional comments are recommended to be conveyed.

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/s/

ANTHONY G DURMOWICZ
04/12/2016