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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	April 25, 2016
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	208294
Applicant Name:	Pearl Therapeutics, Inc., an AstraZeneca Group Company
Date of Submission:	June 25, 2015
PDUFA Goal Date:	April 25, 2016
Proprietary Name:	Bevespi Aerosphere
Established Name:	Glycopyrrolate and formoterol fumarate
Dosage form:	Inhalation Aerosol
Strength:	Glycopyrrolate 9 mcg and formoterol fumarate 4.8 mcg
Proposed Indications:	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Action:	Approval

1. Introduction

Pearl submitted this 505(b)(2) new drug application for use of Bevespi Aerosphere (glycopyrrolate 9 mcg and formoterol fumarate 4.8 mcg inhalation aerosol) for long-term maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is two inhalations (glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg) twice daily. The application is based on clinical efficacy and safety studies. This summary review will provide an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include short- and long-acting beta-2 adrenergic agonists, short- and long-acting anticholinergics, combination drug products containing short- and long-acting beta-2 adrenergic agonists and short- and long-acting anticholinergics, combination drug products containing long-acting beta-2 adrenergic agonists (LABAs) and corticosteroids, and products containing methylxanthines, and phosphodiesterase-4 (PDE4) inhibitors. There are a smaller number of drug classes available for reducing exacerbations in COPD. These include long-acting anticholinergics, combination drug products containing LABA and inhaled corticosteroids (ICS), and PDE inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

Bevespi Aerosphere is a new inhalation product comprised of the long-acting anticholinergic glycopyrrolate and the LABA formoterol fumarate. The anticholinergic glycopyrrolate has been in clinical use for many years as tablets (Robinul 6 mg), intra-

operatively as an injectable (Robinul 100 mcg/injection), and as an oral solution (Cuvposa) for severe drooling in pediatric patients with neurologic conditions. Novartis developed glycopyrrolate as an inhalation product for use in COPD patients as a single entity product (NDA 207923 for Seebri Neohaler, approved in October 2015) and as a combination drug product with indacaterol (NDA 207930 for Utibron Neohaler, approved in October 2015). The LABA formoterol fumarate is currently approved as inhalation product as a single ingredient dry powder (Foradil Aerolizer), as an inhalation solution (formoterol as Perforomist, and arformoterol as Brovana), and as a combination with inhaled corticosteroids (Symbicort, and Dulera). The applicant, Pearl, has developed glycopyrrolate as an inhalation aerosol as a combination drug product with formoterol fumarate, which is the subject of this NDA.

There are three combination drug products containing long-acting anticholinergics and LABAs approved for marketing in the US for treatment of patients with COPD. Anoro Ellipta, containing the long-acting anticholinergic umeclidinium and the LABA vilanterol, was approved in November 2013. Stiolto Respimat, containing the long-acting anticholinergic tiotropium and the LABA olodaterol, was approved in May 2015. Utibron Neohaler, containing the long-acting anticholinergic glycopyrrolate and the LABA indacaterol was approved in October 2015.

In subsequent sections of this review, safety concerns with anticholinergics and LABAs are discussed, followed by a discussion of key regulatory interaction between the Agency and Pearl related to this application.

Glycopyrrolate:

Glycopyrrolate has been available in oral and injectable formulations for multiple years, and as inhalation product since 2015 (NDA 207923 for Seebri Neohaler, and NDA 207930 for Utibron Neohaler). Inhaled anticholinergics are widely available in the U.S. and worldwide for the treatment of COPD. In the US, one short-acting anticholinergic, ipratropium bromide, and three other long-acting anticholinergics, 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) are currently available.

In the past safety concerns of stroke and cardiovascular death have been raised with the use of these drug products in patients with COPD, and thus have been the subject of previous FDA advisory committee meetings. [1] These concerns have been alleviated based on data from large studies with Spiriva HandiHaler and Spiriva Respimat. [2, 3]

[1] FDA Early Communication about Ongoing Safety Review of Tiotropium. http: //ww fda.gov/cder/drug/early_comm/tiotropium htm

[2] Tashkin DP, Celli B, Senn S. et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Eng J Med 2008; 359: 1543-54.

[3] Wise RA, Anzueto A, Cotton D, et al. Tiotropium Respimat inhaler and the risk of death in COPD. N Eng J Med 2013; 369:1491-501.

Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in a COPD program to limit high systemic exposure and potential safety concerns.

Formoterol Fumarate:

Formoterol fumarate as a single ingredient product and as combination drug product in various inhalation formulations is widely available in the U.S. and worldwide for the treatment of COPD. Other LABAs currently marketed in the United States for the treatment of COPD include salmeterol, formoterol, arformoterol, vilanterol, and olodaterol.

Inhaled beta-2 adrenergic agonists, particularly inhaled LABAs, have a safety concern of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma.[4, 5, 6, 7, 8] This has been discussed at various FDA Advisory Committee meetings,[9] and has led to publications expressing concerns on safety,[10, 11, 12] and the establishment of a safe use strategy outlined by the FDA.[13] To further assess the safety of LABAs in asthma, the FDA has asked all manufacturers of LABAs that are marketed in the United States for asthma, to conduct controlled clinical trials to assess the safety of a regimen of LABAs plus inhaled corticosteroids as compared with inhaled corticosteroids alone.[14] Unlike patients with asthma, patients with COPD do not appear to carry a similar signal of worsening disease. Nevertheless, the selection of an appropriate and safe dose is an important consideration for the development of LABA.

[4] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[5] Lowell FC, Curry JJ, Schiller IW. A clinical and experimental study of isoproteronol in spontaneous and induced asthma. N Eng J Med 1949; 240:45-51.
[6] Grainger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981-1987: a further case-control study. Thorax 1991; 46:105-111.
[7] Spitzer WD, Suissa S, Ernst P, Horwitz RI, Habbick BH, et al., The use of beta-agonist and the risk of death and near death from asthma. N Eng J Med 1992; 326:501-506.
[8] US Product Labels of salmeterol and formoterol containing products.
[9] Pulmonary-Allergy Drugs Advisory Committee Meeting, July 13, 2005; and Pulmonary-Allergy Drugs, Drug Safety and Risk Management, and the Pediatric Advisory Committee Meeting, December 10-11, 2008.
[10] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.
[11] Kramer JM. Balancing the benefits and risks of inhaled long-acting beta-agonists—the influence of values. New Eng J Med 2009; 360:1952-1955.
[12] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[13] Chowdhury BA, DalPan G. The FDA and safe use of long-acting beta-agonists in the treatment of asthma. New Eng J Med 2010; 362:1169-1171.
[14] Chowdhury BA, Seymour SM, Levenson MS. Assessing the safety of adding LABAs to inhaled corticosteroids for treating asthma. New Eng J Med 2011; 364:2473-2475.

Regulatory interaction between the Agency and Pearl:

Pearl and the Division had several meetings and discussions over the course of the development of (b) (4) the combination drug product. Major discussions and agreements during the course of the development of the products included the following: complete characterization of the single ingredient product including dose and dosing regimen, agreement that 18 mcg dose of glycopyrrolate administered twice daily was reasonable, agreement that 9.6 mg dose of formoterol fumarate administered twice daily was reasonable, factorial design studies to show the contribution of each component using FEV_1 as efficacy variable, and various statistical methodologies for handling of missing data and data analyses.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product Bevespi Aerosphere (glycopyrrolate and formoterol fumarate) contains HFA134a as the propellant, and 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 device contains a standard valve and a pressurized metered dose inhaler canister containing 120 actuations, press-and-breathe actuator, and a dose indicator attached to the canister top. 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. 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.

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) All manufacturing and testing facilities have acceptable inspection status. The product has a proposed expiry of 24 months, which is supported by submitted stability data.

4. Nonclinical Pharmacology and Toxicology

Pearl conducted an abbreviated nonclinical program to support this application, relying in part on the previous findings for single ingredient glycopyrrolate and formoterol fumarate. The nonclinical program for the current program was focused on the nonclinical safety assessment of the combination of glycopyrrolate and formoterol fumarate. The toxicology program consisted of glycopyrrolate inhalation studies up to 6 months in rats and dogs, as well as a 3-month inhalation study of the glycopyrrolate and formoterol fumarate combination in dogs to assess for potential toxicological interactions. In 6-month glycopyrrolate 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 nose and larynx were observed in both sexes at 27.5 (mid-dose) and 54.8 (high-dose) mcg/kg/day (pulmonary deposited dose). An increased incidence of inflammation in the prostate was also observed in high-dose males. No treatment-related effects were observed at 6.8 mcg/kg/day (pulmonary deposited dose) in either sex. No drug-related findings were observed in the dog study at doses up to 18.7 mcg/kg/day (pulmonary deposited dose). In the 3-month glycopyrrolate and formoterol fumarate 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.

Both glycopyrrolate and formoterol fumarate were negative in genetic toxicology studies. An evaluation for the carcinogenic potential for glycopyrrolate was not required, as no pre-neoplastic or neoplastic lesions were observed in chronic inhalation studies. With regard to formoterol fumarate, carcinogenicity assessment was completed previously for Symbicort. Reproductive and development toxicity were also assessed previously.

5. Clinical Pharmacology and Biopharmaceutics

Pearl conducted a limited clinical pharmacology program relying on known findings for the single ingredient products. There is no pharmacokinetic drug-drug interaction resulting from the concomitant administration of inhaled glycopyrrolate and formoterol fumarate based on steady-state exposure. Therefore, the relevant findings and conclusions for the mono-therapies can be extrapolated to the combination.

6. Clinical Microbiology

The manufacturing process for Bevespi Aerosphere was reviewed by the microbiology team and it was determined that adequate validation data for the (b) (4) manufacturing environment have been provided to demonstrate that the manufacturing process (b) (4)

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in Section 8.

Table 1. Relevant clinical studies with glycopyrrolate and formoterol fumarate combination drug product in COPD

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy variables ¶**	**Regions and Countries //**
Dose-response studies -- Glycopyrrolate – COPD patients					

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Efficacy variables ¶**	**Regions and Countries //**
10801 [04/09 to 08/09	- ≥ 40 yr - COPD - XO - Single dose	GP 18 mcg BID GP 36 mcg BID GP 72 mcg BID GP 144 mcg BID SHH 18 mcg QD Placebo	33	ΔFEV_1 0-12 hr, change from baseline	US
1002 [05/11 to 10/011	- ≥ 40 yr - COPD - XO - 7 day	GP 4 mcg BID GP 6 mcg BID GP 18 mcg BID GP 36 mcg BID Atrovent MDI Placebo	103	ΔFEV_1 0-12 hr, change from baseline to day 7	US
1003 [04/12 to 08/012	- ≥ 40 yr - COPD - XO - 14 day	GP 0.6 mcg BID GP 1.2 mcg BID GP 2.4 mcg BID GP 4.6 mcg BID GP 9 mcg BID SHH 18 mcg QD Placebo	140	ΔFEV_1 0-12 hr, change from baseline to day 14	US
Dose-response studies – Formoterol Fumarate – COPD patients					
5003 [05/11 to 07/11]	- ≥ 40 yr - COPD - XO - Single dose	FF 7.2 mcg BID FF 9.6 mcg BID FF 19.2 mcg BID FA 12 mg BID Placebo	50	ΔFEV_1 0-12 hr, change from baseline	US
50801 [11/08 to 5/09]	- ≥ 40 yr - COPD - XO - Single dose	FF 2.4 mcg BID FF 4.8 mcg BID FF 9.6 mcg BID FA 12 mg BID Placebo	34	ΔFEV_1 0-12 hr, change from baseline	Australia, New Zealand
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
3006 (Trial 1) [06/13 to 02/15]	- ≥ 40 yr - COPD - PG - 24 weeks	GP/FF 18/9.6 BID GP 18 BID FF 9.6 BID SHH Placebo	527 451 452 453 220	ΔFEV_1 trough, change from baseline, at wk 24	US, Australia, New Zealand
3007 (Trial 2) [07/13 to 02/15]	- ≥ 40 yr - COPD - PG - 24 weeks	GP/FF 18/9.6 BID GP 18 BID FF 9.6 BID Placebo	512 440 439 224	ΔFEV_1 trough, change from baseline, at wk 24	US
Supportive Safety -- COPD patients					
3008 [11/13 to 12/14]	- ≥ 40 yr - COPD - PG	GP/FF 18/9.6 BID GP 18 BID FF 9.6 BID SHH	290 219 213 171	Safety	US, Australia, New Zealand

* Study ID shown, top to bottom, as Pearl's study number, [redacted] (b) (4) and [month year study started-completed]
† XO=cross over, PG=parallel group
‡ FF= formoterol fumarate Aerosphere; FA= Foradil Aerolizer; GP= glycopyrrolate Aerosphere; SHH= Spiriva HandiHaler; GP/FF= glycopyrrolate and formoterol fumarate Aerosphere
§ Intent to treat
¶ The primary endpoint in all studies were all based on FEV_1.
// Shown as countries

b. Design and conduct of the studies

Dose ranging studies (10801, 1002, 1003, 5003, 50801):

There were 3 dose ranging studies with glycopyrrolate (10801, 1002, and 1003) and 2 dose ranging studies with formoterol fumarate (5003 and 50801). The study design, treatment arms, and primary efficacy variables are shown in Table 1. Dose regimen for all studies was twice daily because previous studies with other formulations of these two single ingredients has established twice daily as the appropriate dose regimen.

Pivotal bronchodilator (or lung function) studies (3006, 3007):

These studies were similar in design other than the inclusion of Spiriva HandiHaler as an open-label active comparator in study 3006 (Table 1, Figure 1). Patients eligible for the studies were required to have a diagnosis of moderate-to-severe COPD with post-bronchodilator FEV_1 of ≤80% predicted, a post-bronchodilator FEV_1/FVC ratio of ≤0.70, and a smoking history of >10 pack-years. These studies allowed background treatment with inhaled corticosteroids, PDE-4 inhibitor, and short-acting anticholinergic or short-acting beta-agonists as needed. Study treatment arms and efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs. Patients who completed these studies were allowed to enroll into open label safety study 3008.

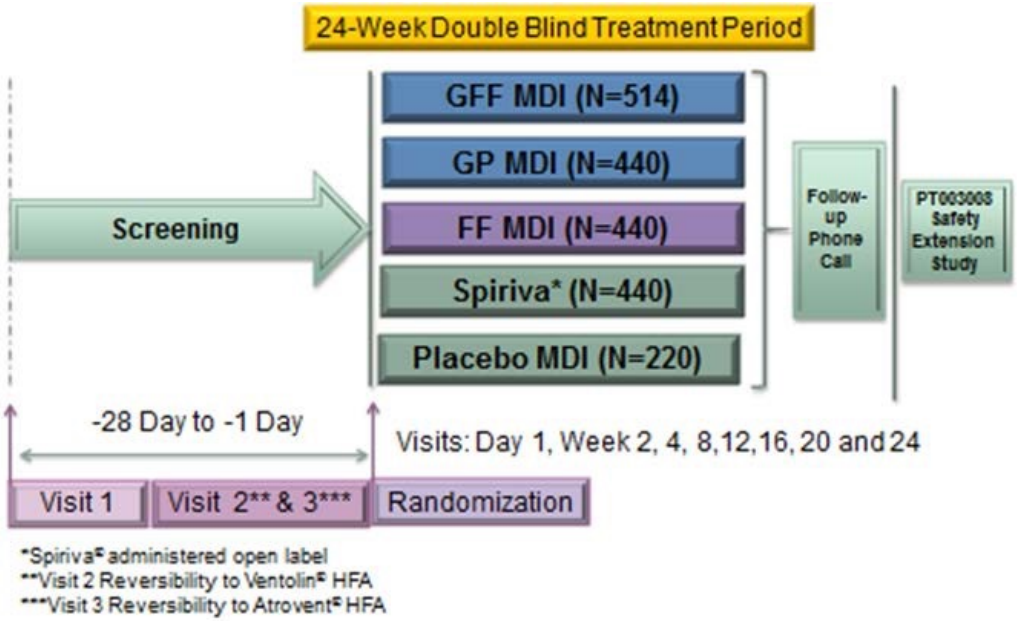

Figure 1. Study flow diagram for Studies 3006 and 3007 (Source: Clinical Efficacy Summary, page 24, NDA)

c. Efficacy findings and conclusions

The clinical program is adequate to support the efficacy of Bevespi Aerosphere at a dose of two inhalations (glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg) twice daily for long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD. The efficacy demonstration builds on the selection of appropriate doses for glycopyrrolate and formoterol fumarate, and then demonstrates the benefit for Bevespi Aerosphere for the claimed benefits of bronchodilation over the single ingredients glycopyrrolate and formoterol fumarate.

Dose selection for glycopyrrolate and formoterol fumarate:

Glycopyrrolate dose selection was based on three studies, 10801, 1002, and 1003 (Table 1). Results of the Study 1003 showed dose ordering, with the glycopyrrolate 18 mcg demonstrating larger improvement in FEV_1 over 12 hours compared with lower doses (Figure 2). The difference from placebo in change from baseline in trough FEV_1 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 studies 10801 and 1002 in patients with COPD had demonstrated minimal additional benefit at doses above 18 mcg twice daily. These results support the selection of glycopyrrolate 18 mcg twice daily for the confirmatory COPD studies.

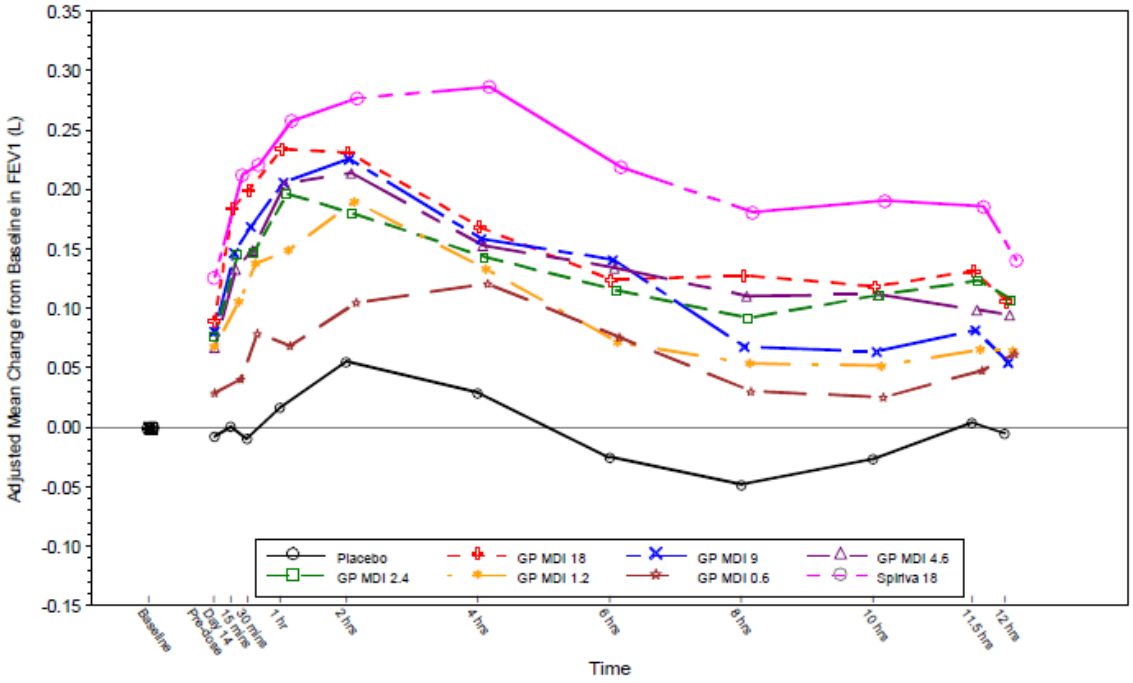

Figure 2. Adjusted mean change from baseline in FEV_1 over time on day 14 (MITT) (Study 1003)

Formoterol fumarate dose selection was based on two studies, 5003 and 50801 (Table 1). Results of Study 50801 showed dose ordering, with the formoterol fumarate 9.6 mcg dose demonstrating larger improvement in FEV_1 compared with lower doses and a similar FEV_1 improvement compared to the approved dose of Foradil Aerolizer (Figure 3). The PK of formoterol fumarate 9.6 mcg was lower than that for Foradil Aerolizer. These results support the selection of formoterol fumarate 9.6 mcg twice daily for the confirmatory COPD studies.

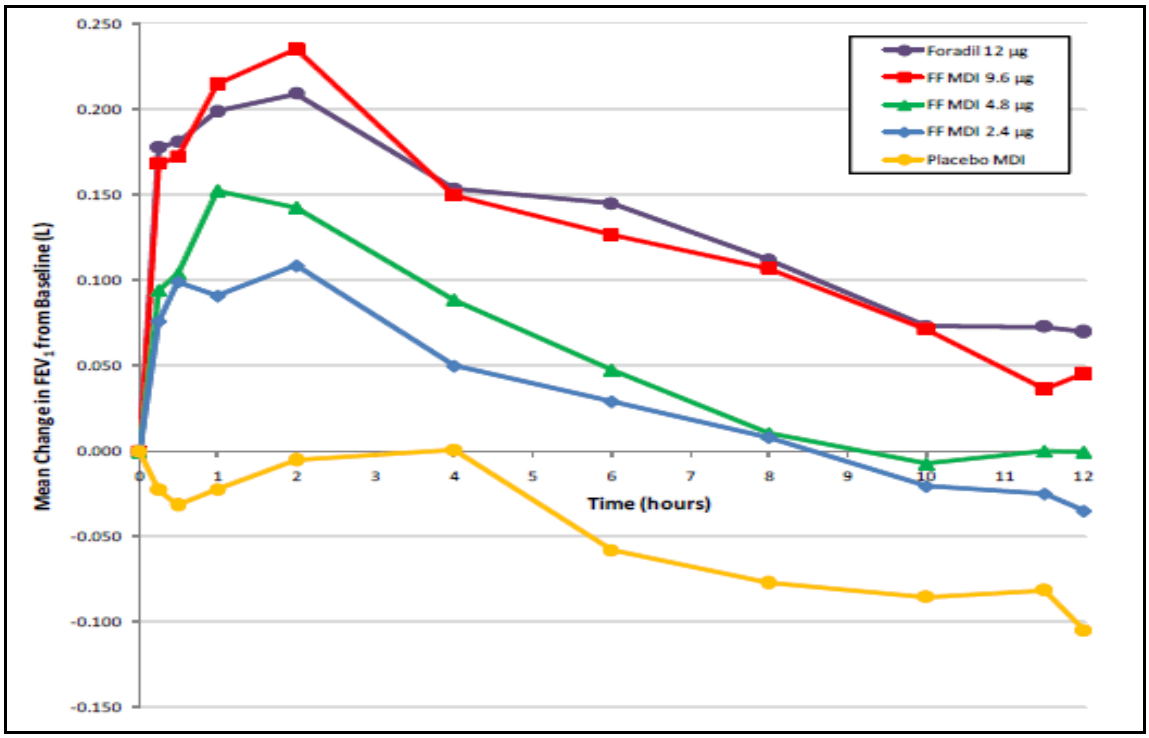

Figure 3. Adjusted mean change from baseline in FEV_1 over time on day 1 (Study 50801)

Bevespi Aerosphere, bronchodilator effects:

Studies conducted to support combination drug products typically compare the combination to each active component to show the contribution of each component present in the combination, and also to show that the combination provides clinically meaningful benefit over each single ingredient present in the combination that would justify the use of the combination drug product by patients. Studies 3006 and 3007 compared Bevespi Aerosphere (glycopyrrolate and formoterol fumarate) to the respective doses of the single ingredient products (Table 1). Results of efficacy variables mean change from baseline of trough FEV_1 for Studies 3006 and 3007 are shown in Table 4, Figure 4, and Figure 5. The differences between Bevespi Aerosphere and the two active ingredients at the corresponding doses were statistically significant (Table 4). Glycopyrrolate and formoterol fumarate were both effective in these studies as both were

also statistically significant over placebo (Table 4). These efficacy conclusions were the same in a sensitivity analysis that considered that study therapy failed for patients who had missing data. Efficacy was consistent across demographic subgroups including gender, race, geographical region, smoking status, BMI, inhaled ICS use at baseline, inhaled SABA use at baseline, etc.

FEV_1 time profile curves for Studies 3006 and 3007 also showed consistent efficacy over time with the Bevespi Aerosphere over the single ingredient products, and the single ingredient products also showed consistent efficacy over placebo (Figure 4, Figure 5).

Table 2. Change from baseline in trough FEV_1 in mL at week 24, Study 3006 and Study 3007

Treatment *	N †	Change	Difference from Pbo (95% CI)	Difference from GP (95% CI)	Difference from FF (95% CI)
Study 3006					
GP/FF 18/9.6 BID	429	126	150 (114, 186)	59 (31, 88)	64 (36, 92)
GP 18 BID	344	66	91 (53, 128)	-	-
FF 9.6 BID	367	62	86 (49, 123)	-5 (-34, 25)	-
SHH	390	105	129 (92, 166)	38 (9, 67)	-
Placebo	161	-24	-	-	-
Study 3007					
GP/FF 18/9.6 BID	433	116	103 (67, 140)	54 (25, 83)	56 (27, 85)
GP 18 BID	367	63	49 (12, 87	-	-
FF 9.6 BID	350	61	47 (10, 85)	-2 (-32, 28)	-
Placebo	170	13	-	-	-

* GP= glycopyrrolate Aerosphere; SHH= Spiriva HandiHaler; GP/FF= glycopyrrolate and formoterol fumarate Aerosphere
† N=number of observations used in the analysis; all randomized patients who received at least one dose of study drug.

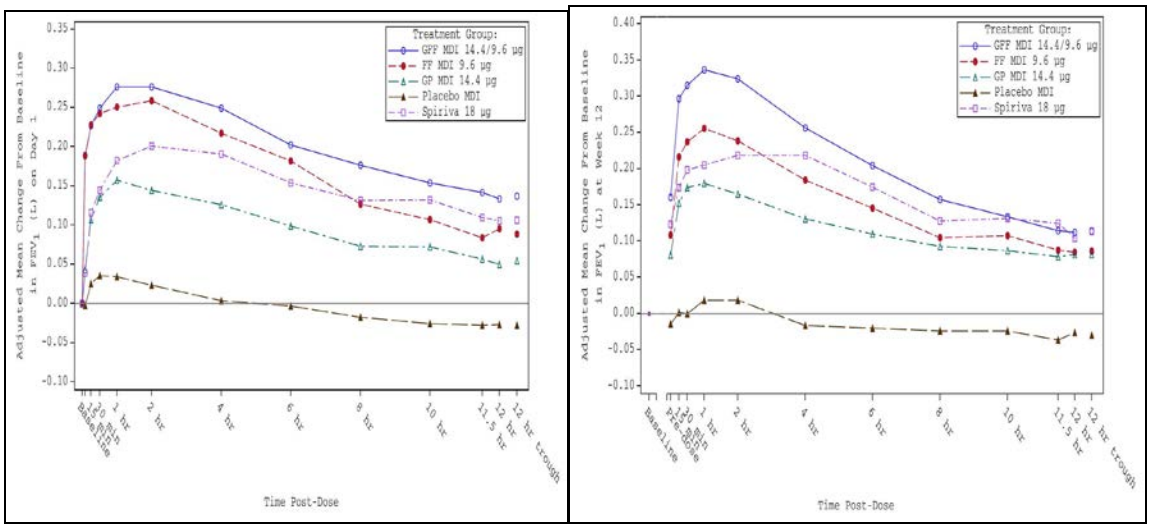

Figure 4. Adjusted mean change from baseline in FEV_1 in liters over 12 hours on day 1 (left panel) and week 12 (right panel), Study 3006

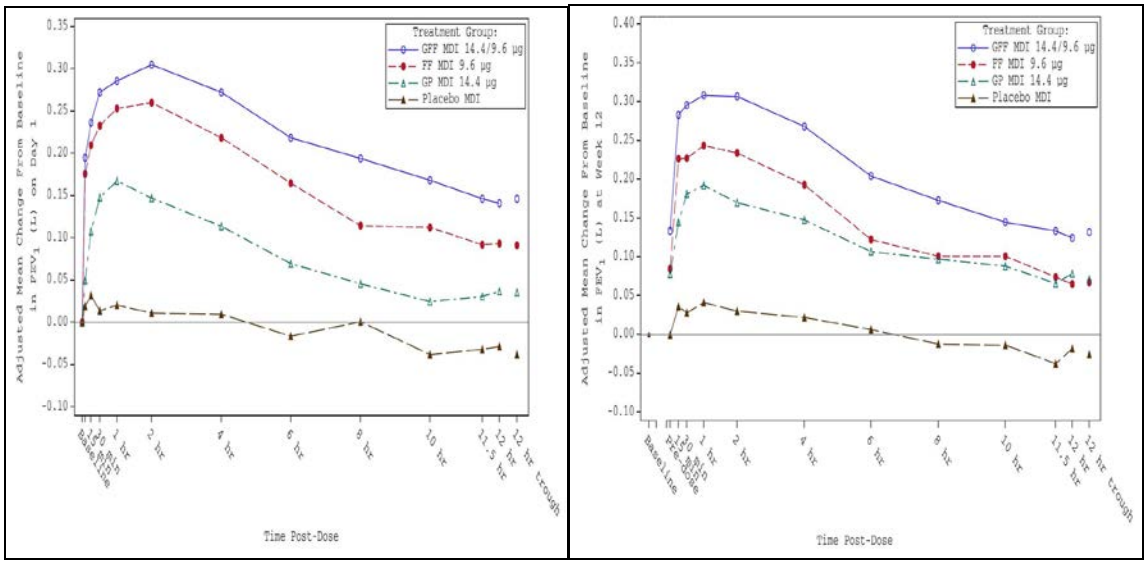

Figure 5. Adjusted mean change from baseline in FEV_1 in liters over 12 hours on day 1 (left panel) and week 12 (right panel), Study 3007

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Bevespi Aerosphere, COPD Exacerbation

The two pivotal studies were not enriched or powered to demonstrate an effect of Bevespi Aerosphere on COPD exacerbation. Nevertheless, it is expected that the assessment of COPD exacerbation data would trend in the positive direction (i.e., fewer COPD exacerbations). The rates of COPD exacerbation were low in both studies. Integrated data of the two studies (Studies 3006 and 3007) showed that all treatment arms had numerically lower rates of moderate or severe COPD exacerbation over 24 weeks compared to placebo and the combination drug product had numerically lower rates compared to the single ingredient products. The rate ratios for moderate or severe COPD exacerbation compared to placebo were as follows: Bevespi Aerosphere 0.79 [0.60, 1.04], 21% reduction; glycopyrrolate 0.91 [0.69, 1.20], 9% reduction; and formoterol fumarate 0.88 [0.66, 1.16] 12% reduction.

Bevespi Aerosphere, St. George's Respiratory Questionnaire (SGRQ)

SGRQ is designed to measure impact on overall health, daily life, and perceived well-being in patients with obstructive airway disease.[15] SGRQ is designed to measure health impairment in patients with asthma and COPD.[16]

[15] St. George's Respiratory Questionnaire (SGRQ), at ATS website: http://www.thoracic.org/members/assemblies/assemblies/srn/questionaires/sgrq.php
[16] St George's Respiratory Questionnaire Manual, at: http://www.healthstatus.sgul.ac.uk/SGRQ_download/SGRQ%20Manual%20June%202009.pdf

SGRQ was assessed in Studies 3006 and 3007. Results are shown in Table 5. In one study, the proportion of patients with benefits in SGRQ larger than the Minimal Clinical Important Difference or MCID of 4 was statistically significantly greater in Bevespi Aerosphere treatment arm than placebo. Bevespi Aerosphere tended to have numerically greater response compared to the single ingredient products, some of the differences reached nominal statistical significance.

Table 3. Responder (proportion of patients with an improvement of at least 4 units in the SGRQ total score) analysis at week 24, Study 3006 and Study 3007

Treatment *	N †	Responder %	Odds Ratio to Pbo (95% CI)	Odds Ratio to GP (95% CI)	Odds Ratio to FF (95% CI)
Study 3006					
GP/FF 18/9.6 BID	526	37%	1.5 (1.1, 2.1)	1.4 (1.1, 1.8)	1.1 (0.9, 1.5)
GP 18 BID	451	30%	1.1 (0.8, 1.5)	-	-
FF 9.6 BID	449	35%	1.3 (0.9, 1.9)	-	-
SHH	451	39%	1.6 (1.1, 2.3)	-	-
Placebo	219	28%	-	-	-
Study 3007					
GP/FF 18/9.6 BID	510	40%	1.3 (0.9, 1.8)	1.2 (0.9, 1.6)	1.3 (1.0, 1.7)
GP 18 BID	439	35%	1.1 (0.8, 1.5)	-	-
FF 9.6 BID	437	34%	1.0 (0.7, 1.4)	-	-
Placebo	223	34%	-	-	-

* GP= glycopyrrolate Aerosphere; SHH= Spiriva HandiHaler; GP/FF= glycopyrrolate and formoterol fumarate Aerosphere
† N=number of observations used in the analysis; all randomized patients who received at least one dose of study drug.

8. Safety

a. Safety database

The safety assessment of Bevespi Aerosphere is based on the studies shown in Table 1, supported by known safety data for the single ingredient products approved for use in patients with COPD. The safety database for Bevespi Aerosphere was adequate.

b. Safety findings and conclusion

The submitted data support the safety of Bevespi Aerosphere for use as maintenance treatment of airflow obstruction in patients with COPD.

Pearl conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[17]), common adverse events (AEs), and assessment for areas of interest such as cardiovascular safety, anticholinergic and adrenergic effects.

[17] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

A total of 12 deaths were reported in the two pivotal COPD controlled studies with 6 in the Bevespi Aerosphere treatment group. The causes of death (small bowel obstruction, cardiac arrest, myocardial infarction, gun-shot wound, neoplasm, and bladder cyst) do not raise any specific concerns. There were two additional deaths (cardiac arrest, myocardial infarction) in the safety extension period, one in the Spiriva HandiHaler treatment group and the other in the formoterol fumarate treatment group. Reporting of SAEs was infrequent in the clinical program, and balanced in the treatment groups (7% for Bevespi Aerosphere, 8% for glycopyrrolate, 7% for formoterol fumarate, and 7% for placebo. The events reported as SAEs were typical and expected in COPD patients. COPD exacerbation and pneumonia were commonly reported as SAE. AEs leading to discontinuations were also infrequent. Common adverse events were typical of LABAs and anticholinergic classes of medications. There were no clinically meaningful changes in laboratory parameters, vital signs, and or ECGs.

Cardiovascular safety events were of interest because of historical safety concerns with anticholinergics and LABA as discussed in section 2 above. 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%).

c. REMS/RiskMAP

Pearl submitted a Risk Management Plan for Bevespi Aerosphere, which consists of routine pharmacovigilance practices. A REMS is not necessary for Bevespi Aerosphere. The product will have a Medication Guide to inform patients about the risk of asthma-related deaths with LABAs.

9. Advisory Committee Meeting

An Advisory Committee meeting was not held to discuss this application because the safety and efficacy for inhaled anticholinergics and inhaled LABAs as single ingredient products and as combination drug products are well understood. There were no unique findings in the Bevespi Aerosphere program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatric

Pearl is requesting a claim for Bevespi Aerosphere for COPD only. Since COPD is a disease that occurs only in adults, specific pediatric studies would not be required related to this action specific to COPD. PeRC had previously agreed that for such COPD applications a full waiver should be granted because studies would be impossible or highly impracticable since the disease does not exist in pediatric patients.

11. Other Relevant Regulatory Issues

a. DSI Audits

The review team requested that DSI audit three clinical sites on the basis of relatively large number of patients enrolled at these sites. Audit of these sites did not show any major irregularities. Review of the application did not identify any irregularities that would raise concerns regarding data integrity. No ethical issues were present. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

Pearl submitted acceptable financial disclosure statements. A total of 16 investigators (out of a total of 310) had disclosable financial interest. The number of subjects enrolled in the investigator site was not large enough to alter the outcome of any study. Furthermore, the multi-center nature of the studies makes it unlikely that the financial interest could have influenced or biased the results of these studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

Pearl submitted Bevespi Aerosphere as the proposed proprietary name, which was accepted by DMEPA.

b. Physician Labeling

Pearl submitted a label in the Physician Labeling Rule format. The label was reviewed by various disciplines of this Division, the Division of Medical Policy Programs (DMPP), DMEPA, and by OPDP. Revisions were made to various sections of the label to reflect the data accurately and to better communicate the findings to healthcare providers. The Division and Pearl have agreed on the final label language.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Bevespi Aersphere will carry safety warnings typical of this class that will be part of the Medication Guide.

13. Action and Risk Benefit Assessment

a. Regulatory Action

Pearl has submitted adequate data to support approval of Bevespi Aerosphere at a dose of two inhalations (glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg) twice-daily for long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD. The regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Bevespi Aerosphere at a dose of two inhalations (glycopyrrolate 18 mcg and formoterol fumarate 9.6 mcg) twice-daily for long-term maintenance bronchodilator treatment of airflow obstruction in patients with COPD. The safety findings seen in the clinical program were consistent with that seen for similar products of the anticholinergic and LABA classes, and there were no unique safety signals seen for Bevespi Aerosphere combination drug product. The efficacy findings showed that Bevespi Aerosphere provided a statistically significant bronchodilator effect that was superior to the single ingredient glycopyrrolate and formoterol products at the corresponding doses. There was also a numerical benefit in SGRQ score with Bevespi Aerosphere over single ingredient glycopyrrolate and formoterol and over placebo that places the bronchodilatory effect in context.

c. Post-marketing Risk Management Activities

Bevespi Aerosphere will carry safety warnings typical of the class that will be part of the Medication Guide. No other post-marketing risk management activities are required.

d. Post-marketing Study Commitments

None.

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/s/

BADRUL A CHOWDHURY
04/25/2016