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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	May 21, 2015
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	206756
Applicant Name:	Boehringer Ingelheim
Date of Submission:	May 22, 2014
PDUFA Goal Date:	May 22, 2015
Proprietary Name:	Stiolto Respimat
Established Name:	Tiotropium bromide and olodaterol
Dosage form:	Inhalation Spray
Strength:	Tiotropium bromide 3.124 mcg (2.5 mcg of tiotropium) and olodaterol 2.5 mcg per spray
Proposed Indications:	Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD)
Action:	Approval

1. Introduction

Boehringer Ingelheim (BI) submitted this 505(b)(1) new drug application for use of Stiolto Respimat (tiotropium 2.5 mcg and olodaterol 2.5 mcg per spray) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD). The proposed dose is two inhalations (tiotropium 5 mcg and olodaterol 5 mcg) once 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 products containing short- and long-acting beta-2 adrenergic agonists and short- and long-acting anticholinergics, combination products containing long-acting beta-2 adrenergic agonists 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 products containing long-acting beta-2 adrenergic agonists (LABA) and inhaled corticosteroids (ICS), and PDE inhibitors. With the exception of methylxanthines and PDE-4 inhibitors, all others are inhalation products.

Stiolto Respimat is a new inhalation product comprised of the long-acting anticholinergic tiotropium and the long- acting beta-2 adrenergic agonist (LABA) olodaterol. Anoro Ellipta, a combination product containing the long-acting anticholinergic umeclidinium and the long-acting beta-2 adrenergic agonist (LABA) vilanterol, is a similar product of the same class, which was approved for marketing in the US in November 2013. During review of this NDA for Stiolto Respimat, NDAs for the single components tiotropium (Spiriva Respimat, NDA 21936) and olodaterol (Striverdi Respimat, NDA 203108) were reviewed and approved for COPD.

In subsequent sections of this review, safety concerns with the anticholinergic tiotropium and the LABA olodaterol are discussed, followed by a discussion of regulatory interaction between the Agency and BI related to this application.

Tiotropium:

Spiriva (tiotropium bromide) Respimat was approved in September 2014 for use in patients with COPD at a dose of 5 mcg (2 inhalations of 2.5 mcg tiotropium per spray). A dry powder formulation of tiotropium, Spiriva HandiHaler, was approved in January 2004, also for use in patients with COPD, at a dose of 18 mcg tiotropium once daily. Although the nominal dose of the two tiotropium containing products are different, systemic exposure and clinical efficacy of the two are similar in patients with COPD. These products have anticholinergic adverse effects, such as dry mouth, constipation, urinary retention, etc. Safety concerns of stroke and cardiovascular death have been raised in the past 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] Nevertheless, it is important to select an appropriate dose and dose regimen for any anticholinergic in COPD program to limit high systemic exposure and potential safety concerns.

Olodaterol:

Striverdi (olodaterol) Respimat was approved in July 2014 for use in patients with COPD at a dose of 5 mcg (2 inhalations of 2.5 mcg per spray). 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 also been discussed at various FDA Advisory

[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.

[4] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.

Committee meetings,[9] and has led to publications expressing concerns on safety,[10, 11, 12] and 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 development of all LABAs, including olodaterol, which was addressed during development of Striverdi Respimat.

Regulatory interaction between the Agency and BI:

The Division and BI had typical milestone meetings for Spiriva Respimat, Striverdi Respimat, and Stiolto Respimat. Many of the developmental issues relevant for Stiolto Respimat were discussed and resolved at the meetings for Spiriva Respimat and Striverdi Respimat. At the End-of-Phase 2 meeting for Stiolto Respimat held in August 2011, the two pivotal clinical studies that would support Stiolto Respimat were discussed. Agreements were reached on the primary endpoint. It was agreed that no placebo comparator would be necessary for the two pivotal studies, and that 24-hour spirometry to define FEV_1 time-profile could be obtained from a subset of patients enrolled in the pivotal studies.

3. Chemistry, Manufacturing, and Controls

The product Stiolto Respimat Inhalation Spray is composed of a Stiolto Respimat cartridge and a Stiolto Respimat inhaler. The Stiolto Respimat cartridge is a 4.5 mL plastic container (crimped into an aluminum cylinder) that contains a sterile aqueous solution of tiotropium bromide and olodaterol hydrochlorid, as well as the excipients

[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.

benzalkonium chloride [redacted] edetate disodium [redacted] and hydrochloric acid [redacted] Stiolto Respimat Inhalation Spray is supplied in a carton containing one Stiolto Respimat cartridge and one Stiolto Respimat inhaler. Prior to first use, the cartridge containing the formulation is placed into the Respimat Inhaler. To actuate the product, the bottom of the inhaler is turned 180°, which [redacted] create an aerosol cloud that emits gently from the mouthpiece of the product. The product needs to be primed after the cartridge is placed in the Respimat Inhaler. The Respimat cartridge is designed to deliver 60 actuations after priming. Each actuation provides 2.5 mcg of tiotropium and 2.5 mcg of olodaterol. The product has a dose indicator that is visible on the clear base. After the 60 actuations are delivered, a locking mechanism is engaged and no more drug can be dispensed. The Stiolto Inhalation Spray should be discarded after the locking mechanism is engaged or 3 months after first use, whichever comes first.

BI submitted adequate stability data to support an expiry of 36 months for the drug product that consists of the Respimat device and the unassembled cartridge containing the formulation (stored separately), and an in-use period of 3 months after the cartridge is assembled with the Respimat Inhaler.

The steps needed to use the product and the internal mechanisms of the product are rather complex. During review of another Respimat product that contained tiotropium (Spiriva Respimat), a consultation with CDRH was obtained. The CDRH review did not raise any concern with the manufacturing and quality of the product, but raised concerns on performance testing with regards to human factors. BI has previously performed adequate human factor and patient handling studies with a Respimat product. These assessments did not suggest any problems with patient handling, performance, and robustness of the Respimat product. The only issue identified was that some older patients or patients with hand joint problems may need assistance with initial assembly of the cartridge and the Respimat Inhaler.

The drug substance and drug product including the Respimat device are manufactured at a BI facility in Ingelheim am Rhein, Germany. Manufacturing and testing facilities associated with the drug substance and drug product have an acceptable GMP recommendation from Office of Compliance. All DMFs associated with this application were also found to be acceptable.

Two strengths for Stiolto Respimat (1.25 mcg or 2.5 mcg tiotropium plus 2.5 mcg of olodaterol per actuation) were used in pivotal clinical studies. BI has provided CMC documentation for both in the NDA, however only the 2.5 mcg tiotropium plus 2.5 mcg olodaterol is proposed for marketing. The CMC data pertaining to the 1.25 mcg tiotropium plus 2.5 mcg olodaterol were reviewed and are considered adequate to support the comparability of the in vitro dose performance for the two strengths for the purpose of use in clinical studies.

4. Nonclinical Pharmacology and Toxicology

Full nonclinical pharmacology and toxicology programs were conducted by BI for both individual drug substances under NDA 21395 (Spiriva HandiHaler) for tiotropium and under NDA 203108 (Striverdi Respimat) for olodaterol. The nonclinical program for the current program was, therefore, focused on the nonclinical safety assessment of the combination of tiotropium and olodaterol. The program consisted of 4-week inhalation studies in rats and 4- and 13-week inhalation studies in dogs using a range of tiotropium and olodaterol dose ratios. In the 13-week inhalation toxicology study of the combination in dogs, clinical signs consistent with beta-2 agonist and antimuscarinic activity were observed such as tachycardia, mydriasis, and dry mouth. Target organs of toxicity included the heart (decreased organ weights, gross discoloration, and fibrosis/necrosis/mineralization upon microscopic examination) and liver (glycogen depletion/increased storage), however, there were no novel histopathological findings attributed to the combination. Gross and microscopic changes in the heart were attributed to the increased heart rate, and the changes in liver glycogen were considered a class effect for beta-2 agonists. The toxicology studies conducted in rats and dogs with the tiotropium and olodaterol combination did not reveal any novel toxicity, and there was no evidence of any additive or synergistic toxicity between tiotropium and olodaterol beyond observed increases of heart rate. As such, the nonclinical program adequately supports the proposed clinical use of the Stiolto Respimat combination product.

5. Clinical Pharmacology and Biopharmaceutics

The general clinical pharmacology and biopharmaceutics considerations for tiotropium bromide were addressed in the tiotropium (Spiriva HandiHaler and Spiriva Respimat) applications (NDAs 21395 and 21936) approved in January 1994 and July 2014, respectively, and in the olodaterol (Striverdi Respimat) application (NDA 203108) approved in September 2014. The clinical pharmacology aspects of tiotropium and olodaterol as monotherapies, including nominal dose and the once daily dosing regimen have been adequately investigated and supported in the respective monotherapy development programs, and have been reviewed previously (NDA 021936 for tiotropium, and NDA 203108 for olodaterol).

For the current combination product, clinical pharmacology program included a tiotropium and olodaterol drug-drug interaction study to ensure the systemic exposure of the drug components was not impacted by the combination of the two ingredients in one product. In the study, patients with COPD received either the fixed dose combination of tiotropium 5 mcg and olodaterol 10 mcg, olodaterol 10 mcg, or tiotropium 5 mcg, all once daily and all via the Respimat device for 21 days. Steady-state exposure, AUC, and Cmax were assessed as the relevant clinical pharmacology variables. Results of the study demonstrated there was no significant drug-drug interaction in that systemic exposure to tiotropium and olodaterol after inhalation of the combination product was not substantially different to the exposure after inhalation of tiotropium or olodaterol

monotherapies (ratios of the PK parameters between the combination product and olodaterol monotherapy or tiotropium monotherapy were between 90–98%).

There are no outstanding thorough QT studies as these studies were conducted for the tiotropium and olodaterol single ingredient products.

6. Clinical Microbiology

The manufacturing process for Stiolto Respimat was reviewed by the microbiology team and determined that adequate validation data for the (b) (4) manufacturing environment have been provided to demonstrate that the manufacturing process is capable of producing a sterile drug product

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 tiotropium and olodaterol combination product in COPD

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
Tiotropium dose-response in combination with olodaterol					
18 [2/10 to 2/11]	- ≥ 40 yr - COPD, GOLD II, III - XO, tio and olo free combination - 4 weeks	Tio+Olo 1.25/5 mcg Tio+Olo 2.5/5 mcg Tio+Olo 5/5 mcg Tio+Olo 1.25/10 mcg Tio+Olo 2.5/10 mcg Tio+Olo 5/10 mcg Olo 5 mcg Olo 10 mcg	109 113 109 110 119 111 108 117	FEV_1 trough at week 4	Canada (23%), Germany (42%), Netherlands (22%), Sweden (14%)
Olodaterol dose-response in combination with tiotropium					
4 [6/08 to 2/09]	- ≥ 40 yr - COPD, GOLD II, III - PG, tio and olo fixed dose combination - 4 weeks	Tio+Olo 5/2 mcg Tio+Olo 5/5 mcg Tio+Olo 5/10 mcg Tio 5 mcg	89 93 88 90	FEV_1 trough at week 4	US (63%), Canada (20%), Germany (17%)
9 [7/08 to 2/09]	- ≥ 40 yr - COPD, GOLD II, III XO, tio and olo fixed dose combination - 4 weeks	Tio+Olo 5/2 mcg Tio+Olo 5/5 mcg	141 141	FEV_1 trough at week 4	US (24%), Canada (26%), Germany (31%). Belgium (19%)
Pivotal bronchodilator (or lung function) efficacy and safety studies -- COPD patients					
5 [9/11 to 9/13]	- ≥ 40 yr - COPD, GOLD II, III, IV - PG - 52 weeks	Tio/Olo 2.5/5 mcg Tio/Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg	522 522 525 527	1^o: ΔFEV_1 0-3 hr response at wk 24 1^o: ΔFEV_1 trough response at wk 24	N America (18%), W Europe (26%), E Europe (18%), Asia (25%), S America

ID Year*	**Study Characteristics †** **- Patient age** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups ‡**	**N §**	**Primary efficacy variables ¶**	**Regions and Countries //**
		Olo 5 mcg	528		(11%), Other
6 [9/11 to 11/13]	- ≥ 40 yr - COPD, GOLD II, III, IV - PG - 52 weeks	Tio/Olo 2.5/5 mcg Tio/Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg	508 507 507 506 510	1^{o}: ΔFEV_1 0-3 hr response at wk 24 1^{o}: ΔFEV_1 trough response at wk 24	N America (21%), W Europe (28%), E Europe (15%), Asia (25%), Other
Bronchodilator (or lung function) efficacy and safety study -- COPD patients					
20 [3/12 to 8/13]	- ≥ 40 yr - COPD, GOLD II, III, IV - XO - 6 weeks	Tio/Olo 2.5/5 mcg Tio/Olo 5/5 mcg Tio 2.5 mcg Tio 5 mcg Olo 5 mcg Placebo	136 139 137 135 138 138	1^{o}: ΔFEV_1 0-24 hr response at wk 6	N America (23%), W Europe (68%), E Europe (9%)
[redacted]					(b) (4)

* Study ID shown (top to bottom) as BI's study number, and [month year study started-completed]
† XO=cross over, PG=parallel group
‡ Tio=tiotropium in Respimat device; Olo=olodaterol in Respimat device;
§ Intent to treat
¶ FEV_1 AUC 0-3 hr was calculated as the area under the FEV1 time curve from 0 to 3 hours post-dose using the trapezoidal rule, divided by the duration (3 hours) reported in Liters. FEV_1 AUC 0-3 hr response is change from pre-treatment baseline. CWRCE = constant work rate cycle ergometry.
// Dose ranging studies are shown as countries, other studies are shown as regions because of large number of countries involved. Countries and regions contributing approximately 10% of the patients are shown.

b. Design and conduct of the studies

Dose ranging studies (18, 4, 9):

Dose-ranging studies were designed to characterize the dose-response for tiotropium in combination with olodaterol and compare to olodaterol monotherapy (study 18), and to characterize the dose-response for olodaterol in combination with tiotropium and compare to tiotropium monotherapy (studies 4 and 9). The study treatment arms and primary efficacy variable are shown in Table 1.

Pivotal bronchodilator (or lung function) studies (5, 6):

These studies were identical in design (Table 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. Eligible patients entered a 2-week single-blind placebo run-in period, and the patients who remained eligible entered the 52-week double-blind treatment period. These studies allowed background treatment with short-acting beta-agonists, inhaled corticosteroids, oral corticosteroids, and methylxanthines, however, inhaled long-acting beta-agonists or inhaled long-acting anticholinergics were not permitted. Study treatment arms and primary efficacy variables are shown in Table 1. Relevant secondary endpoints included pooled analyses for the two studies for SGRQ and COPD exacerbation. COPD exacerbation was defined by acceptable criteria. [15] Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

c. Efficacy findings and conclusions

The clinical program is adequate to support the efficacy of Stiolto Respimat (tiotropium 2.5 mcg and olodaterol 2.5 mcg per spray) for maintenance bronchodilator treatment of airflow obstruction in patients with COPD at a dose of two inhalations (tiotropium 5 mcg and olodaterol 5 mcg) once daily. The efficacy demonstration builds on the selection of appropriate dose and dosing regimens for tiotropium and olodaterol, and then demonstrates the benefit for Stiolto Respimat for the claimed benefits of bronchodilation over the single ingredients tiotropium and olodaterol.

[15] COPD exacerbation defined as a complex of lower respiratory events or symptoms (increase or new onset shortness of breath, sputum production, purulent sputum, cough, wheezing, chest tightness) related to underlying COPD, with a duration of 3 days or more, and requiring a change in treatment. COPD exacerbation were classified as mild (bronchodilator only), moderate (antibiotics or systemic steroids or both, without hospitalization), and severe (hospitalization).

Dose ranging for tiotropium and olodaterol:

Dose selection for Stiolto Respimat was primarily based on studies for the individual components, Spiriva (tiotropium) Respimat and Striverdi (olodaterol) Respimat, both of which are approved for COPD at 5 mcg once-daily doses. Further dose-ranging studies, where increasing doses of one of the component with fixed dose of the other component (results shown in Figure 1 and Figure 2), supports BIs decision to carry two doses - tiotropium 2.5 mcg plus olodaterol 5 mcg, and tiotropium 5 mcg plus olodaterol 5 mg - to the confirmatory studies.

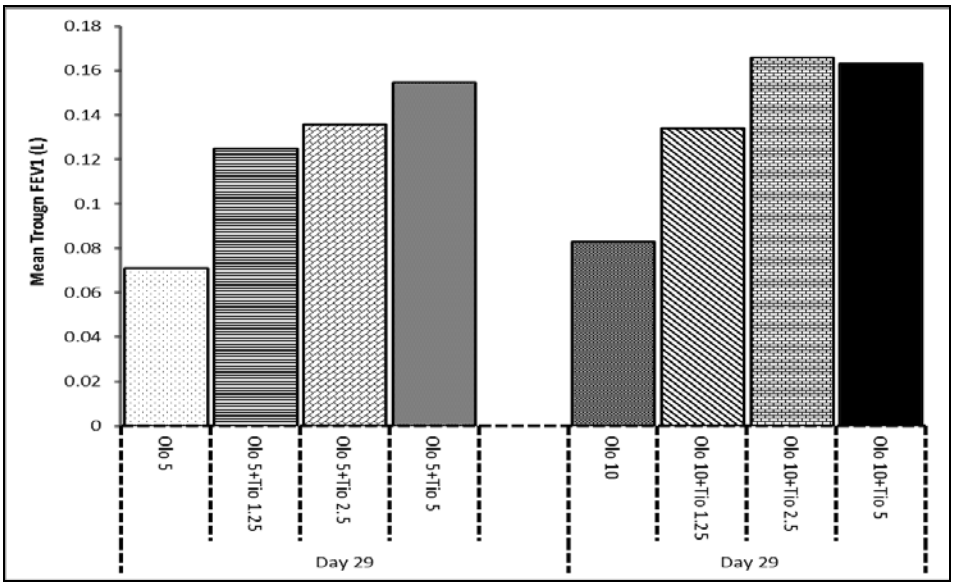

Figure 1. Trough FEV1 at day 29, Study 18 (tiotropium dose ranging in presence of olodaterol)

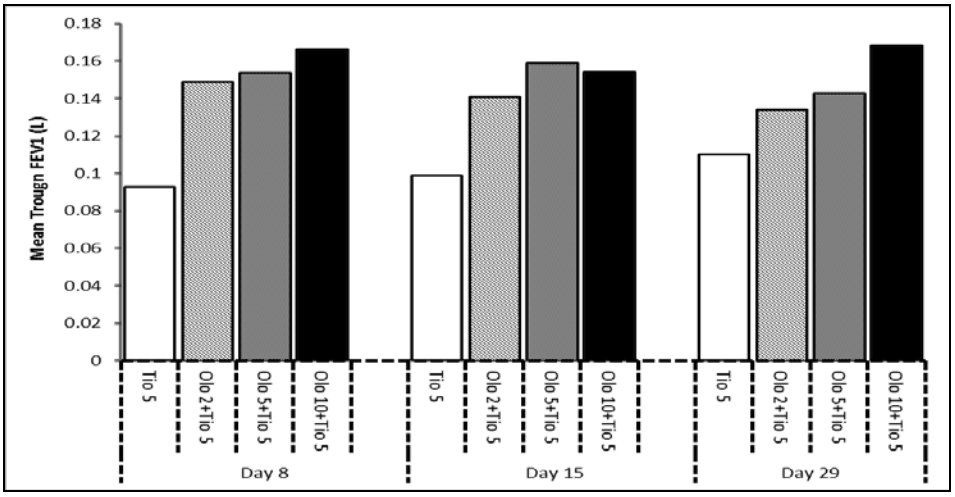

Figure 2. Trough FEV1 at days 8, 15, and 29, Study 4 (olodaterol dose ranging in presence of tiotropium)

Stiolto Respimat, bronchodilator effects:

Studies conducted to support combination 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 product by patients. Studies 5 and 6 compared Stiolto Respimat at two doses to the respective doses of the single ingredient products (Table 1). Results of efficacy variables of mean FEV_1 0-3 hours and FEV_1 trough for the studies 5 and 6 are shown in Table 2 and Table 3. Inflation of the type I error rate due to multiplicity was controlled by pre-specified hierarchical ordering of the comparisons. The differences between Stiolto Respimat to the two active ingredients at the corresponding doses were statistically significant, and the difference between the two doses of Stiolto Respimat showed consistent higher numerical response for the higher dose (Table 2 and Table 3). These efficacy conclusions were the same in a sensitivity utility analysis that considered the 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, and inhaled anticholinergic use at baseline.

FEV_1 time profile curve for studies 5 and 6 at week 24 also showed consistent efficacy over time with the Stiolto Respimat response higher than the single ingredient products, and a higher response for the Stiolto Respimat higher dose compared to the lower dose (Figure 3). FEV_1 time profile curve for study 20 (6 week cross-over study) also showed similar findings where the curves for the two Stiolto Respimat doses were higher than the single ingredient products, and the combination and single ingredient products were higher compared to placebo (Figure 4).

Table 2. Summary of lung function efficacy results from confirmatory studies at week 24, comparison of tiotropium plus olodaterol to olodaterol to show contribution of tiotropium

Study ID *	Treatment in mg †	n	FEV_1 0-3 hr at wk 24, in L			FEV_1 trough at wk 24, in L		
			Δ from baseline	Diff from olo		Δ from baseline	Diff from olo	
				Mean	95% CI		Mean	95% CI
5	Tio/Olo 2.5/5 mg	522	0.241	0.109	0.09, 0.13	0.111	0.058	0.03, 0.08
	Tio/Olo 5/5 mg	522	0.256	0.123	0.10, 0.15	0.136	0.082	0.06, 0.11
	Tio 2.5 g	525	0.148			0.083		
	Tio 5 mg	527	0.139			0.065		
	Olo 5 mg	528	0.133			0.054		
6	Tio/Olo 2.5/5 mg	508	0.256	0.121	0.10, 0.15	0.125	0.067	0.04, 0.10
	Tio/Olo 5/5 mg	507	0.268	0.132	0.11, 0.16	0.145	0.088	0.06, 0.11
	Tio 2.5 g	507	0.125			0.062		
	Tio 5 mg	506	0.165			0.096		
	Olo 5 mg	510	0.136			0.057		

* Study ID shown as BI study number
† Tio=tiotropium in Respimat device; Olo=olodaterol in Respimat device

Table 3. Summary of lung function efficacy results from confirmatory studies at week 24, comparison of tiotropium plus olodaterol to tiotropium to show contribution of olodaterol

Study ID *	Treatment in mg †	n	FEV_1 0-3 hr at wk 24, in L			FEV_1 trough at wk 24, in L		
			Δ from baseline	Diff from tio		Δ from baseline	Diff from tio	
				Mean	95% CI		Mean	95% CI
5	Tio/Olo 2.5/5 mg	522	0.241	0.093	0.07, 0.12	0.111	0.029	0.01, 0.05
	Tio/Olo 5/5 mg	522	0.256	0.117	0.09, 0.14	0.136	0.071	0.05, 0.09
	Tio 2.5 g	525	0.148			0.083		
	Tio 5 mg	527	0.139			0.065		
	Olo 5 mg	528	0.133			0.054		
6	Tio/Olo 2.5/5 mg	508	0.256	0.131	0.11, 0.15	0.125	0.062	0.04, 0.09
	Tio/Olo 5/5 mg	507	0.268	0.103	0.08, 0.13	0.145	0.050	0.02, 0.08
	Tio 2.5 g	507	0.125			0.062		
	Tio 5 mg	506	0.165			0.096		
	Olo 5 mg	510	0.136			0.057		

* Study ID shown as BI study number
† Tio=tiotropium in Respimat device; Olo=olodaterol in Respimat device

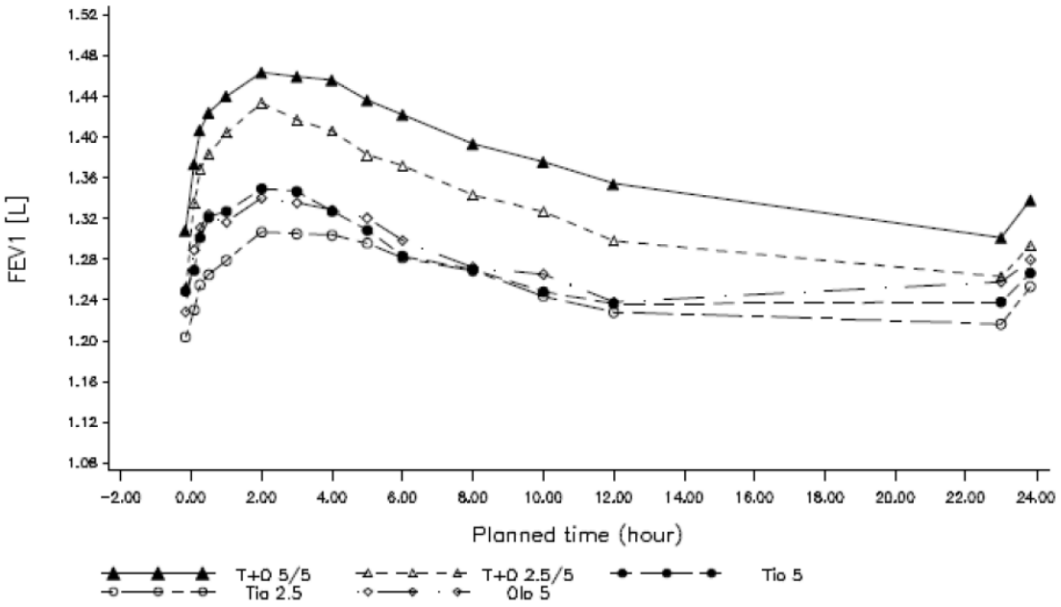

Figure 3. Serial mean FEV1 over 24 hours after 24 weeks, studies 5 and 6 combined

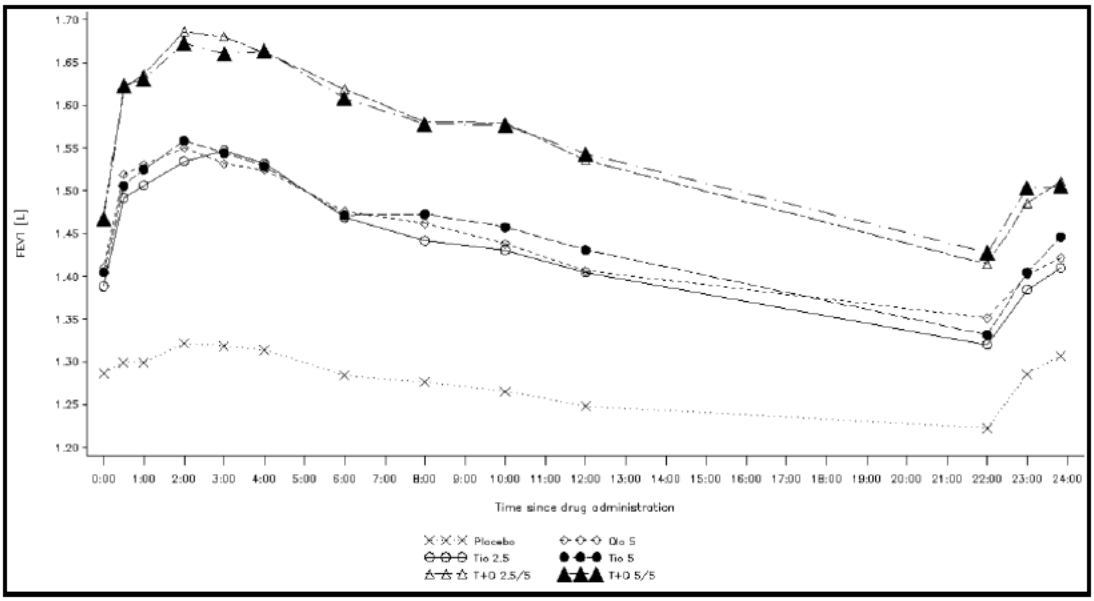

Figure 4. Serial mean FEV1 over 24 hours after 6 weeks, studies 20

Stiolto Respimat, Exacerbation:

Pivotal studies 5 and 6 were not designed for confirmatory evaluation of COPD exacerbation. COPD exacerbation related endpoints were analyzed for the pooled studies 5 and 6 data set. These endpoints included time to first exacerbation, time to first moderate to severe exacerbation, number of exacerbations per patient year, and number of moderate to severe exacerbations. For these exacerbation endpoints, there were no statistical differences when comparing Stiolto Respimat to their monocomponents; the numerical differences were in favor of Stiolto Respimat treatment arms. In the combined dataset from studies 5 and 6, the percentage of patients with at least one moderate-to-severe COPD exacerbation was 27.7 for Stiolto 5/5 mcg, 25.8 for Stiolto 2.5/5 mcg, 28.8 for tiotropium 5 mcg, 29.6 for tiotropium 2.5 mcg, and 31.9 for olodaterol 5 mcg. These data (b) (4) supports the bronchodilator effects of Stiolto Respimat described above.

Stiolto Respimat, St. George's Respiratory Questionnaire (SGRQ)

SGRQ is a health status assessment instrument commonly used in COPD studies. SGRQ data were analyzed for the pooled studies 5 and 6. At the specified time point of day 169, Stiolto Respimat did not demonstrate a difference grater than the MCID of -4 compared to either tiotropium or to olodaterol, although for the Stiolto Respimat (tio5 mcg/olo 5 mcg,) the difference when compared to tiotropium 5 mcg and olodaterol 5 mcg was statistically significant (-1.2 points p=0.0252, and -1.7 points, p=0.0022, respectively, for combined dataset for studies 5 and 6). The data (b) (4) supports the bronchodilator effects of Stiolto Respimat described above.

8. Safety

a. Safety database

The safety assessment of Stiolto Respimat is based on studies shown in Table 1, and safety of single ingredient tiotropium and olodaterol. The safety database for Stiolto Respimat was large and adequate.

b. Safety findings and conclusion

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

BI conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[16]), common adverse events (AEs), and assessment for areas of interest such as cardiovascular safety, anticholinergic and adrenergic effects.

A total of 75 deaths were reported in the COPD program. All deaths were reviewed and adjudicated. The number and causes of deaths were balanced among the treatment groups. Common causes of deaths included COPD exacerbation, respiratory failure,

[16] 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.

myocardial infarction, and cancers, which are expected causes of death in older COPD patients. Reporting of SAEs was fairly common across treatment arms, as was discontinuation from the studies. These were also balanced among the treatment arms, and the events were typical and expected in COPD patients. Common adverse events included pharyngitis, gastrointestinal disorder, anticholinergic effects, effects related to adrenergic stimulation, and lower respiratory tract infections. The patterns of SAEs and adverse events did not indicate a specific safety concern.

Cardiovascular safety events were of interest because of historical safety concerns with anticholinergics and LABA as discussed in section 2 above. BI included several pre-specified evaluations to assess cardiovascular safety that included adjudication of deaths and SAEs, and analysis of Major Adverse Cardiac Events (MACE). These analyses did not show any concerns attributable to Stiolto Respimat.

Respiratory safety events were also of interest because of the patient population and underlying COPD. Analyses of respiratory safety events did not show any concerning findings attributable to Stiolto Respimat.

Clinical laboratory evaluation did not identify and specific safety concerns for Stiolto Respimat.

c. REMS/RiskMAP

(b) (4)

A REMS is not necessary for Stiolto Respimat. 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 anticholinergic and inhaled LABA as single ingredient products and as combination products are well understood. There were no unique findings in the Stiolto Respimat program that would warrant a discussion at an Advisory Committee meeting.

10. Pediatric

BI is requesting a claim for Stiolto Respimat 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

A DSI audit was not necessary and not conducted for this application as both single ingredient tiotropium and olodaterol in Respimat device is approved, and the data from the Stiolto Respimat program were consistent with what is expected of products of this class in COPD. During review of this application, the review team did not identify any irregularities that would raise concerns regarding data integrity. All studies were conducted in accordance with accepted ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. Five investigators had significant financial interest in BI. 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

BI submitted Stiolto Respimat as the proposed proprietary name, which was accepted by DMEPA.

b. Physician Labeling

BI 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), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and to better communicate the findings to healthcare providers. The Division and BI 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

Stiolto Respimat 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

BI has submitted adequate data to support approval of Stiolto Respimat (tiotropium 2.5 mcg and olodaterol 2.5 mcg per spray) for maintenance bronchodilator treatment of

airflow obstruction in patients with COPD at a dose of two inhalations (tiotropium 5 mcg and olodaterol 5 mcg) once daily. The regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of Stiolto Respimat (tiotropium 2.5 mcg and olodaterol 2.5 mcg per spray) for maintenance bronchodilator treatment of airflow obstruction in patients with COPD at a dose of two inhalations once daily. 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 Stiolto Respimat combination product. The efficacy findings showed that the Stiolto Respimat at the daily dose of tiotropium 5 mcg and olodaterol 5 mcg provided a statistically significant bronchodilator effect that was superior to the single ingredient tiotropium and olodaterol products at the corresponding doses.

c. Post-marketing Risk Management Activities

Stiolto Respimat 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
05/21/2015