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APPLICATION NUMBER:

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SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date:	July 29, 2014
From:	Badrul A. Chowdhury, MD, PhD Director, Division of Pulmonary, Allergy, and Rheumatology Products, CDER, FDA
Subject:	Division Director Summary Review
NDA Number:	203108
Applicant Name:	Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission:	June 2, 2014 (original NDA was submitted on May 14, 2012)
PDUFA Goal Date:	August 2, 2014 (PDUFA due date for the original NDA was March 14, 2013)
Proprietary Name:	Striverdi Respimat
Established Name:	Olodaterol
Dosage form:	Inhalation Spray
Strength:	2.5 mcg olodaterol per actuation
Proposed Indications:	Chronic Obstructive Pulmonary Disease
Action:	Approval

1. Introduction

Boehringer Ingelheim (BI) submitted this 505(b)(1) new drug application for use of Striverdi Respimat (olodaterol inhalation spray) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. The proposed dose is 5 mcg of olodaterol (two actuations of 2.5 mcg per actuation) once-daily, recommended to be taken at the same time each day. 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. The application was not approved in the first review cycle because of outstanding facility inspection, which is now resolved.

2. Background

There are several drug classes available for the relief of airflow obstruction in patients with COPD. These include beta-2 adrenergic agonists, anticholinergic agents, combination products containing beta-2 adrenergic agonists and anticholinergic agents, combination of long-acting beta-2 adrenergic agonists and corticosteroids, and methylxanthines.

Olodaterol is a new molecular entity that belongs to the class called beta-2 adrenergic agonists. Due to its longer duration of action, olodaterol belongs to the subclass called long-acting beta-2 adrenergic agonists (LABAs). Inhaled LABAs are widely used in the United States and worldwide to treat bronchospasm in patients with asthma and COPD. LABAs currently marketed in the United States include salmeterol, formoterol,

arformoterol, and indacaterol. Some of these are marketed as single ingredient products and others as combination products with inhaled corticosteroids. Salmeterol, formoterol, and arformoterol are dosed twice-daily, and indacaterol is dosed once-daily. Olodaterol is proposed to be dosed once daily.

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. Severe asthma exacerbations and asthma-related deaths have been described with short-acting inhaled beta-2 adrenergic agonists over the last 50 years.[1, 2, 3, 4] More recently, inhaled LABAs have also been linked to severe asthma exacerbations and asthma-related deaths.[5] This has been discussed at various FDA Advisory Committee meetings,[6] has led to publications expressing concerns on safety,[7, 8, 9] and establishment of a safe use strategy outlined by the FDA.[10] 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.[11] The mechanisms by which inhaled beta-adrenergic agonists cause severe asthma exacerbations and asthma-related deaths are not known. Controlled studies and epidemiological studies suggest that higher doses of inhaled beta-adrenergic agonists are a contributing factor. In the United States, a higher dose of inhaled formoterol was not approved because the higher dose caused more severe asthma exacerbation compared to the approved lower dose.[12] 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 is proposed to be marketed

[1] Benson RL, Perlman F. Clinical effects of epinephrine by inhalation. J Allergy 1948; 19:129-140.
[2] 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.
[3] 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.
[4] 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.
[5] US Product Labels of salmeterol and formoterol containing products.
[6] 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.
[7] Martinez FD. Safety of long-acting beta-agonists—an urgent need to clear the air. New Eng J Med 2005; 353:2637-2639.
[8] 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.
[9] Drazen JM, O'Byrne PM. Risks of long-acting beta-agonists in achieving asthma control. New Eng J Med 2009; 360:1671-1672.
[10] 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.
[11] 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.
[12] Mann M, Chowdhury B, Sullivan E, Nicklas R, Anthracite R, Meyer RJ. Serious asthma exacerbation in asthmatics treated with high-dose formoterol. Chest 2003; 124:70-74.

for COPD. Most of the U.S. marketed beta-adrenergic agonists carry both asthma and COPD indications, and the dose and dosing frequency in both indications are the same.

The indication claims of short-acting beta-adrenergic agonists, such as albuterol (Proventil HFA Inhalation Aerosol, Ventolin HFA Inhalation Aerosol, ProAir HFA Inhalation Aerosol, Proventil Inhalation solution) are for general bronchodilation ("treatment or prevention of bronchospasm with reversible obstructive airway disease"). The albuterol product labels do not mention a specific disease, such as asthma or COPD, in the indication section. Clinical studies supporting approval of these products were conducted in patients with asthma. Nevertheless, albuterol is used in patients with asthma and COPD. The indication claims of LABAs, such as salmeterol (Serevent Diskus, Serevent Inhalation Aerosol) and formoterol (Foradil Aerolizer) are also for general bronchodilation, but the product labels mention asthma and COPD as specific diseases in the indication section. Clinical trials supporting the dose and dosing frequency for these two long-acting beta agonists were also conducted in patients with asthma, and the same bronchodilatory dose was carried forward to studies in COPD. The regulatory precedence of performing dose ranging and dose regimen studies for bronchodilators in asthma patients has been established in order to demonstrate a large separation between doses, because the range of response is greatest in a bronchoresponsive population, such as patients with asthma. A COPD population, with some degree of fixed obstruction, has a smaller response range to a bronchodilator. The regulatory precedence of performing dose ranging and dose regimen studies in patients with asthma were followed in the development of indacaterol, a LABA that was approved for marketing in the United States in 2011 as a bronchodilator in patients with COPD. [13]

The Agency and BI had milestone meetings typical of development of a new molecular entity and of a first-cycle NDA submission. In the End of Phase 2 meeting, the Agency agreed with BI that the 5 and 10 mcg doses were reasonable to carry forward into definitive COPD phases. The Agency advised BI to conduct studies to establish the dosing interval. In a subsequent meeting, the Agency recommended evaluating dose and dose regimen in patients with asthma. BI conducted these studies that are included in this NDA submission.

3. Chemistry, Manufacturing, and Controls

The product Striverdi Respimat Inhalation Spray is composed of a Striverdi Respimat cartridge and a Striverdi Respimat inhaler. The Striverdi Respimat cartridge is a 4.5 mL plastic container (crimped into an aluminum cylinder) that contains a sterile aqueous solution of olodaterol in the excipients benzalkonium chloride (b) (4) edetate disodium (b) (4) water for injection, and citric acid (b) (4) Striverdi Respimat Inhalation Spray is supplied in a carton containing one Striverdi Respimat cartridge and one Striverdi Respimat inhaler. Prior to first use, the patient or care provider places the Striverdi Respimat cartridge into the Striverdi Respimat inhaler and primes the unit. To actuate the product, the patient turns the bottom of the inhaler

[13] Chowdhury BA, Seymour SM, Michelle TM, Durmowicz AG, Diu D, Rosebrough CJ. The risks and benefits of indacaterol – The FDA review. N Eng J Med 2011; 365:2247-2249.

180°, which will cause a small volume of the formulation to be metered into a chamber and compress a spring. The patient then presses a trigger, which will release the spring to provide mechanical energy that propels the formulation through a nozzle with two outlets that form two jets of solution. The two jets converge on each other and create an aerosol cloud that emits gently from the mouthpiece of the product. The assembled Striverdi Respimat Inhalation Spray is designed to deliver 60 metered actuations. The product has a dose indicator that is visible on the clear base. After the 60 metered actuations are delivered, a locking mechanism is engaged and no more drug can be dispensed. The Striverdi 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. The Respimat device is relatively new to the United States market, with one BI product, Combivent Respimat (ipratropium bromide and albuterol) Inhalation Spray, approved for marketing in October 2011. During review of another Respimat Inhaler product of BI that contained tiotropium (Spiriva Respimat), a consultation with CDRH was obtained because of the complexity of the product. (b) (4) BI has performed adequate specific patient handling studies with the Respimat device. In two phase 3 studies conducted for Combivent Respimat and in two phase 3 studies conducted for Spiriva Respimat, patient handling of the device was assessed and representative devices used in clinical studies were tested for *in vitro* performance characteristics. These assessments did not suggest any problems with patient handling, performance, and robustness of the Respimat device. 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 Boehringer Ingelheim 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.

4. Nonclinical Pharmacology and Toxicology

BI submitted results from a full preclinical program to the Agency. The program included studies in which animals were dosed with the drug via inhalation to evaluate local and systemic toxicities. Pivotal inhalation toxicity studies were conducted in rats for up to 26 weeks and in dogs for up to 52 weeks. The target organs of toxicity (with organ-specific findings in parentheses) in rats were skeletal muscle (hypertrophy and single cell

necrosis); heart (increased heart rate, congestion, and ventricular scar formation); trachea (squamous cell metaplasia); pancreas (lobular hypertrophy); and female reproductive tract (increased incidence of ovarian cysts). Target organs of toxicity in dogs (with organ-specific findings in parentheses) were the cardiovascular system (increased heart rates, ventricular premature beats, and fibrosis of the left ventricle of the heart); kidney (mononuclear infiltration); liver (glycogen deposition and hemorrhage); and trachea (epithelial atrophy, infiltration, and mineralization). Many of these findings in rats and dogs (cardiovascular, liver, skeletal muscle, and female rodent reproductive tract) are known class effects of beta-agonist drugs. There were adequate margins of safety for the expected human exposure for findings of concern. Studies addressing genotoxicity, reproductive toxicity, and carcinogenicity were also performed. Olodaterol was negative for genotoxicity in a complete battery of genetic toxicology assays. A reproductive toxicity study in rats did not reveal adverse effects on male and female fertility or reproductive performance. Embryo-fetal development studies in rats and rabbits showed teratogenic effects at the high dose only in rabbit. The pregnancy category was determined to be C, which is the same category for many other beta-2 adrenergic agonists. Carcinogenicity was assessed in a 2 year study in CD-1 mice, and in a 2-year study in Wistar Han rats. These studies showed increased incidences of uterine leiomyomas and malignant leiomyosarcomas in mice and ovarian leiomyomas in rats. These tumors have been observed with other beta-adrenergic agonists. The relevance of these findings to humans is unknown.

5. Clinical Pharmacology and Biopharmaceutics

BI submitted results from a comprehensive clinical pharmacology program. The program addressed the key pharmacokinetic issues, including *in vitro* studies to assess protein binding and metabolism, pharmacokinetics after single and multiple doses, *in vitro* and *in vivo* metabolism, effect of hepatic and renal impairment, QTc prolongation effect, and drug-drug interaction. Clinical pharmacology studies included inhalation, oral, and IV administration to fully characterize the pharmacokinetics of olodaterol. Inhaled olodaterol has approximately 30% bioavailability resulting from pulmonary absorption; oral bioavailability is very low (<1%). Elimination is through both the biliary and renal routes; in a mass balance study, 53% of drug-related radioactivity was recovered in the feces and 38% was excreted in the urine. Following inhalation of a single dose of olodaterol, Cmax values were generally reached within 10 to 20 minutes post-dose, with an elimination half-life of approximately 45 hours. Pharmacokinetics were linear, and steady state was reached after 8 days. Olodaterol is a substrate for the efflux pump P-gp. It is substantially metabolized by direct glucuronidation and by O-demethylation at the methoxy moiety mainly by CYP2C9 followed by conjugation. A renal impairment study showed that olodaterol levels were increased by approximately 40% in subjects with severe renal impairment. Olodaterol exposure was comparable between normal and mild to moderate hepatic impairment patients. Population pharmacokinetic studies showed approximately 2-fold higher systemic exposure in Japanese patients compared to Caucasians. Dose-dependent QTcF prolongation was observed in the QTc prolongation study. The maximum mean (95% upper confidence bound) difference in QTcF from placebo after baseline correction was 3.4 (7.1) ms, 5.9 (9.6) ms, 7.4 (10.9) ms and 8.5

(12.4) ms following doses of 10, 20, 30 and 50 mcg, respectively. The QT IRT team determined that the study did not demonstrate a significant effect of olodaterol on the QTcF.

6. Clinical Microbiology

Not applicable.

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 olodaterol

ID [Year*]	**Study Characteristics** **- Patient age, mean (range)** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups †**	**N ‡**	**Efficacy variables §**	**Countries or Region (% US patients)**
Dose-ranging and dose-regimen studies in asthma patients					
1222.4 [2006]	- 29 (19-53) yrs - Asthma - Crossover, dose ranging - Single dose	Olo 2 mcg Olo 5 mcg Olo 10 mcg Olo 20 mcg Placebo	31	1°: PC 20 FEV_1 at 24 hr 2°: PC 20 FEV_1 at 0.5, 4, 8, 8, and 32 hr	Canada (0% US)
1222.6 [2008]	- 45 (18-91) yrs - Asthma - Parallel arm, dose ranging - 4 weeks	Olo 2 mcg QD Olo 5 mcg QD Olo 10 mcg QD Olo 20 mcg QD Placebo	61 60 60 61 54	1°: ΔFEV_1 trough at wk 4 2°: PEFR at wk 4	USA, Canada, Europe (21% US)
1222.27 [2011]	- 45 (18-70) yrs - Asthma - Crossover, dose ranging - 4 weeks	Olo 2 mcg QD Olo 5 mcg QD Olo 10 mcg QD Olo 20 mcg QD For 12 mcg BID Placebo	198	1°: ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 4 2°: ΔFEV_1 trough, ΔFEV_1 $AUC_{0\text{-}12\ hr}$, and ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 4	Europe (0% US)
1222.29 [2011]	- 44 (19-69) yrs - Asthma - Crossover, dose regimen - 3 weeks	Olo 2.5 mcg BID Olo 5 mcg QD Olo 5 mcg BID Olo 10 mcg QD Placebo	206	1°: ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 3 2°: ΔFEV_1 $AUC_{0\text{-}12\ hr}$, and ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 3	USA, Europe (31% US)
Dose-ranging and dose-regimen studies in COPD patients					
1222.3 [2006]	- 65 (45-86) yrs - COPD - Crossover, dose ranging - Single dose	Olo 2 mcg Olo 5 mcg Olo 10 mcg Olo 20 mcg Placebo	36	1°: ΔFEV_1 trough at 24 hr 2°: ΔFEV_1 $AUC_{0\text{-}3\ hr}$, ΔFEV_1 $AUC_{0\text{-}12\ hr}$, ΔFEV_1 $AUC_{0\text{-}24\ hr}$, ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at 24 hr	Netherlands (0% US)
1222.5 [2008]	- 63 (40-86) yrs - COPD - Parallel arm, dose ranging - 4 weeks	Olo 2 mcg QD Olo 5 mcg QD Olo 10 mcg QD Olo 20 mcg QD	81 80 86 79	1°: ΔFEV_1 trough at wk 4 2°: ΔFEV_1 trough, ΔFEV_1 $AUC_{0\text{-}3\ hr}$, at wk 1 and wk 2	USA, Canada, Europe (51% US)

ID [Year*]	**Study Characteristics** **- Patient age, mean (range)** **- Patient characteristics** **- Study design, objective** **- Study duration**	**Treatment groups †**	**N ‡**	**Efficacy variables §**	**Countries or Region (% US patients)**
		Placebo	79		
1222.26 [2009]	- 66 (42-78) yrs - COPD - Crossover, dose regimen - 3 weeks	Olo 2 mcg BID Olo 5 mcg QD Olo 5 mcg BID Olo 10 mcg QD	47	1^o: ΔFEV_1 $AUC_{0\text{-}12\ hr}$ and ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 3 2^o: ΔFEV_1 trough, and ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 3	Europe (0% US)
Pivotal COPD studies: 48-week spirometry					
1222.11 Trial 1 [2010]	- 65 (40-87) yrs - COPD - Parallel arm - 48 weeks	Olo 5 mcg QD Olo 10 mcg QD Placebo	208 207 209	1^o: ΔFEV_1 trough at wk 12 ΔFEV_1 $AUC_{0\text{-}3\ hr}$ at wk 12 2^o: Moderate exacerbation ΔFEV_1 $AUC_{0\text{-}12\ hr}$ at wk 12	USA, Asia, Australia & N Zealand (~41% US)
1222.12 Trial 2 [2010]	- 65 (40-84) yrs - COPD - Parallel arm - 48 weeks	Olo 5 mcg QD Olo 10 mcg QD Placebo	209 217 216	1^o: ΔFEV_1 trough at wk 12 ΔFEV_1 $AUC_{0\text{-}3\ hr}$ at wk 12 2^o: Moderate exacerbation ΔFEV_1 $AUC_{0\text{-}12\ hr}$ at wk 12	USA, Asia, Europe (~53% US)
1222.13 Trial 3 [2010]	- 64 (40-89) yrs - COPD - Parallel arm - 48 weeks	Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo	227 225 227 225	1^o: ΔFEV_1 trough at wk 24 ΔFEV_1 $AUC_{0\text{-}3\ hr}$ at wk 24 Mahler TDI focal score 2^o: Moderate exacerbation SGRQ at wk 24	Europe, Asia, Africa (0% US)
1222.14 Trial 4 [2010]	- 64 (40-88) yrs - COPD - Parallel arm - 48 weeks	Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo	232 234 233 235	1^o: ΔFEV_1 trough at wk 24 ΔFEV_1 $AUC_{0\text{-}3\ hr}$ at wk 24 Mahler TDI focal score 2^o: Moderate exacerbation SGRQ at wk 24	Europe, Asia, Africa (0% US)
Profiling studies in COPD patients: 6-week spirometry profile					
1222.24 Trial 5 [2010]	- 62 (43-86) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks	Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo	99	1^o: ΔFEV_1 $AUC_{0\text{-}12}$ hr at wk 6 ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 6 2^o: ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 6	USA (100% US)
1222.25 Trial 6 [2010]	- 64 (45-82) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks	Olo 5 mcg QD Olo 10 mcg QD For 12 mcg BID Placebo	100	1^o: ΔFEV_1 $AUC_{0\text{-}12}$ hr at wk 6 ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 6 2^o: ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 6	USA (100% US)
1222.39 Trial 7 [2010]	- 62 (44-79) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks	Olo 5 mcg QD Olo 10 mcg QD Tio 18 mcg QD Placebo	108	1^o: ΔFEV_1 $AUC_{0\text{-}12}$ hr at wk 6 ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 6 2^o: ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 6	Europe (0% US)
1222.40 Trial 8 [2011]	- 63 (45-79) yrs - COPD - Crossover, 24 hr FEV1 - 6 weeks	Olo 5 mcg QD Olo 10 mcg QD Tio 18 mcg QD Placebo	122	1^o: ΔFEV_1 $AUC_{0\text{-}12}$ hr at wk 6 ΔFEV_1 $AUC_{12\text{-}24\ hr}$ at wk 6 2^o: ΔFEV_1 $AUC_{0\text{-}24\ hr}$ at wk 6	Europe (0% US)
Profiling studies in COPD patients: 6-week exercise endurance					
1222.37 Trial 9 [2011]	- 61 (41-74) yrs - COPD - Crossover, Exercise - 6 weeks	Olo 5 mcg QD Olo 10 mcg QD Placebo	151	1^o: Endurance time at wk 6 2^o: Breathing discomfort intensity at isotime FRC and IC at isotime	Europe, Canada, Australia (0% US)
1222.38 Trial 10 [2011]	- 61 (41-75) yrs - COPD - Crossover, Exercise - 6 weeks	Olo 5 mcg QD Olo 10 mcg QD Placebo	151	1^o: Endurance time at wk 6 2^o: Intensity of breathing discomfort at isotme FRC and IC at isotime	Europe, Canada (0% US)

***** Study ID shown (top to bottom) as BI's study number, as referenced in the proposed olodaterol product label, and [year study subject enrollment ended]

† Olo = Olodaterol inhalation spray; For = Foradil Aerolizer (formoterol fumarate inhalation powder); Tio = Spiriva Handihaler (tiotropium bromide inhalation powder);

ID [Year*]	Study Characteristics - Patient age, mean (range) - Patient characteristics - Study design, objective - Study duration	Treatment groups †	N ‡	Efficacy variables §	Countries or Region (% US patients)
‡ Number randomized and received at least one dose § Primary efficacy variables and selected secondary efficacy variables are shown. The efficacy analysis for the pivotal 48 week studies and profiling 6 week studies were mixed model for repeated measure (MMRM).					

b. Design and conduct of the studies

Dose ranging (1222.4, 1222.6, and 1222.27) and dose regimen (1222.29) studies in patients with asthma:

Study 1222.4 was a crossover, single dose, dose-ranging trial in patients with intermittent asthma. Patients were randomized to receive a sequence of single doses of various doses of olodaterol and placebo (Table 1). Following administration of study medication patients received a series of methacholine challenges. The primary endpoint was the provocative concentration of methacholine required to cause a 20% fall in FEV1 from baseline [Log_2(PC20 FEV1)] at 24 hours following treatment. This is not an acceptable method of dose-ranging study; therefore, this study will not be discussed further in this review.

Study 1222.6 was a parallel arm, multiple dose, dose-ranging study in patients with asthma (FEV1≥60% and <90% predicted). Study 1222.27 was a crossover, multiple dose, dose-ranging study in patients with asthma who were on ICS and were still symptomatic. Study 1222.29 was a crossover, multiple dose, dose-regimen study in patients with moderate to severe persistent asthma. Various treatment arms and primary and secondary efficacy variables for the studies are shown in Table 1.

Dose ranging (1222.3, and 1222.5) and dose regimen (1222.26) studies in patients with COPD:

Study 1222.3 was a crossover, single dose, dose-ranging study in patients with COPD. For inclusion in the trial, patients were required to have an FEV1 ≤60% predicted and demonstrate airway reversibility following albuterol administration (≥12% improvement). Study 1222.5 was a parallel arm, multiple-dose, dose-ranging study in patients with COPD. Patients were required to have an FEV1 ≥30% and <80% predicted. Study 1222.26 was a crossover, multiple-dose, dose regimen study in patients with moderate to severe stable COPD. Various treatment arms and primary and secondary efficacy variables for the studies are shown in Table 1.

Pivotal 48-week studies in patients with COPD (1222.11, 1222.12, 1222.13, and 1222.14):

Studies 1222.11 and 1222.12 were identical in design. These were parallel group studies conducted in patients with COPD with FEV1 of <80% predicted, FEV1/FVC ratio of <70% predicted, and with at least a 10 pack year smoking history. Patients with asthma were excluded. These studies allowed standard of care background therapy with short-

acting beta-agonists, inhaled corticosteroids, oral corticosteroids, anticholinergics (including tiotropium), and methylxanthines in all treatment groups. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, ECGs, and Holter monitoring in a subset of patients.

Studies 1222.13 and 1222.14 were also identical in design. The studies were similar in design to 1222.11 and 1222.12 except for the addition of an active comparator arm of formoterol and inclusion of additional endpoints related to dyspnea and quality of life. These studies also allowed standard of care background therapy. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. Safety assessments included adverse event recording, vital signs, physical examination, clinical laboratory and hematology measures, and ECGs.

Spirometry profiling 6-week studies in patients with COPD (1222.24, 1222.25, 1222.39, and 1222.40):

Studies 1222.24 and 1222.25 were identical studies conducted to characterize the 24-hour FEV time profile of olodaterol. These were cross-over studies conducted in patients with COPD with FEV1≤80% predicted. The studies included formoterol as an active comparator. Studies 1222.39 and 1222.40 were similar to studies 1222.24 and 1222.25 except that they included tiotropium as active comparator. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. In studies 1222.24 and 1222.25, patients were permitted to continue long-acting muscarinic antagonists (LAMAs); however, LABAs were prohibited. In studies 1222.39 and 1222.40, both LABAs and LAMAs were prohibited.

Exercise endurance 6-week studies in patients with COPD (1222.37 and 1222.38):

Studies 1222.37 and 1222.38 were identical in design conducted to assess exercise endurance response of olodaterol. These were crossover studies conducted in patients with moderate to severe COPD with an exercise endurance time of at least 25 minutes at baseline. Patients were allowed to take ICS, methylxanthines, and short acting anticholinergics during the trial. However, LABAs and tiotropium were not permitted. Study treatment arms and primary and secondary efficacy variables are shown in Table 1. Endurance time was assessed by constant rate cycle ergometry to symptom limitation at 75% maximal work capacity. Isotime was defined as the endurance time of constant work rate exercise of shortest duration at 75% maximal work capacity. Intensity of breathing discomfort as measured by the Borg Scale at isotime.

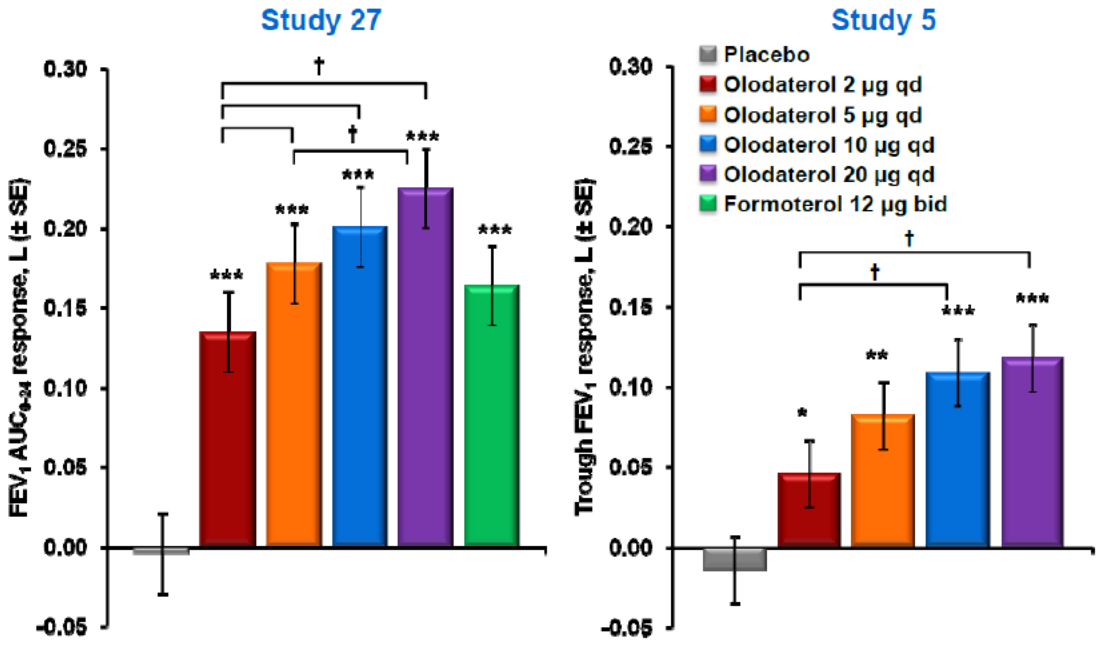
c. Efficacy findings and conclusions

The clinical program showed that olodaterol 5 mcg and 10 mcg once-daily doses (two actuations of 2.5 mcg per actuation) provided a statistically significant bronchodilatory effect compared to placebo in patients with COPD, with replicate findings for both doses.

There were no statistically significant differences between the olodaterol 5 mcg and 10 mcg doses. The olodaterol 5 mcg and 10 mcg once-daily doses also demonstrated a statistically significant difference in exercise endurance measures compared to placebo in patients with COPD; however, the effect sizes were small and the effect was only assessed at peak bronchodilatory effect time point and at 6 weeks. The submitted data support approval of BI's proposed dose of olodaterol 5 mcg once-daily as a bronchodilator treatment in patients with COPD, but do not support an exercise endurance claim for olodaterol.

Dose ranging and dose regimen:

As discussed in section 2 above, selection of appropriate dose and dosing regimen is an important consideration for development of LABAs, and these studies need to be conducted in patients with asthma in addition to COPD because the bronchodilator response is greater in bronchoresponsive patients, such as patients with asthma who can show larger separation between doses. BI conducted adequate exploration of dose ranges and dose regimens in patients with asthma and COPD (Table 1). In dose ranging studies conducted, olodaterol doses from 2 mcg to 20 mcg were explored, both in patients with asthma and COPD. In these studies olodaterol 5 mcg and 10 mcg doses produced adequate bronchodilator response, the 20 mcg dose did not appear to produce further benefit, and the 2 mcg dose appeared to be suboptimal (results from two representative studies are shown in Figure 1). In dose regimen studies olodaterol 5 mcg and 10 mcg once daily doses were compared to similar total daily nominal doses given twice daily, both in patients with asthma and in COPD. In the asthma study, a small numerical benefit of twice daily dose over once daily dose was seen, but the benefit was small and seen in the second half of the 24-hour dosing interval, which was not sufficient to favor a twice daily dosing for olodaterol (data not shown in this review). The COPD study did not show benefit of twice daily dose over once daily dose (Figure 2). These data support once daily dosing regimen for olodaterol. Based on these studies, and with Agency concurrence, BI selected olodaterol 5 mcg and 10 mcg once daily doses for further evaluation in confirmatory COPD studies. Inclusion of two doses in confirmatory COPD studies provides additional dose response information for both efficacy and safety and further informs dose selection.



Difference from placebo: *$p < 0.05$; ** $p < 0.001$; *** $p < 0.0001$; difference between treatments: † $p < 0.05$.
Analysis with imputation (FAS).

Figure 1. Dose ranging studies in asthma (1222.27) and COPD (1222.5); mean (SE) ΔFEV_1 $AUC_{0\text{-}24\ hr}$ response at week 4 (Source: BI presentation at PADAC held on January 29, 2013).

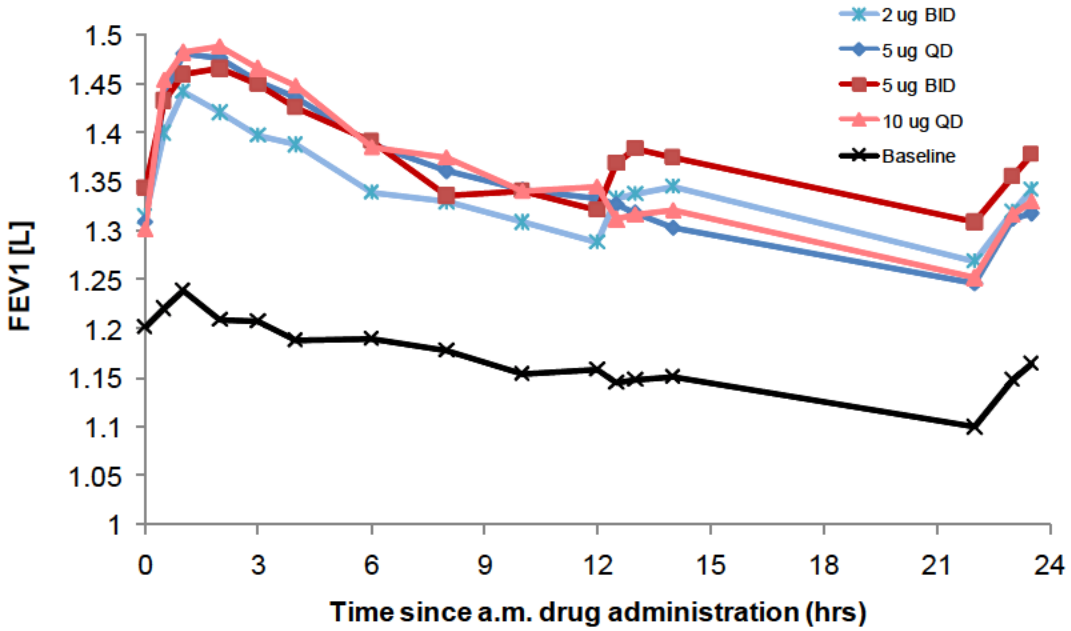


Figure 2. COPD dose regimen study 1222.26; FEV1 time profile for 24 hour after olodaterol administered QD (5 mcg and 10 mcg) and BID (2 mcg and 5 mcg). Horizontal axis is time since olodaterol administration in hours and vertical axis is FEV1 in liters.

Bronchodilator effects:

The results for the primary efficacy variables for the 48-week COPD studies are shown in Table 2. For ease of comparison, data from week 12 are shown for all studies, although the primary efficacy endpoints for studies 1222.13 and 1222.14 were at week 24. The results show that olodaterol 5 mcg once daily and 10 mcg once daily doses were statistically significantly superior to placebo for the primary endpoints with the exception of study 1222.12 in which the 5 mcg olodaterol group was not significant for trough FEV1. Results at weeks 24 and 48 were generally comparable to results at week 12. Comparison of the two doses of olodaterol shows that the 5 mcg and 10 mcg were generally similar (Table 2, Figure 3). Olodaterol had a fairly rapid onset of bronchodilator effect after first dose, and the bronchodilator effect was sustained over 12 weeks, with a numerical trend of a blunted peak effect at week 12 that may be due to tachyphylaxis often seen with beta-agonists (Figure 4). In Figure 4 the box on the top panel shows the onset of effect after first dose, and the box on the bottom panel shows shift of baseline after 12 weeks of treatment that possibly reflects the bronchodilator effect from the previous dose. The 6-week studies, which profiled FEV1 over 24 hours, showed a bronchodilator effect of olodaterol over the 24-hour dosing interval, and responses were comparable with two active comparators (Figure 5). Based on these data, along with dose ranging data, BI proposed a 5 mcg once daily dose for marketing approval, which is reasonable.

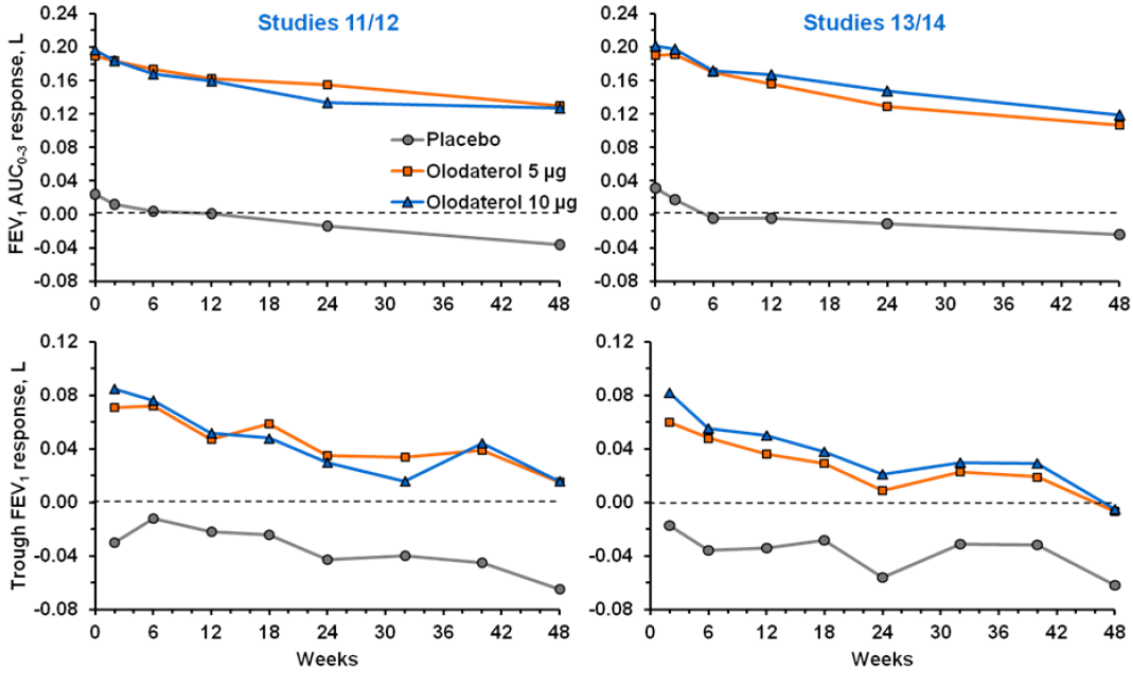
The observed effect size for olodaterol across studies appeared to be smaller than that observed in previous registration trials for other LABAs for COPD. The mean treatment effect across trials for trough FEV1 was 65 mL. For FEV1 $AUC_{0\text{-}3hr}$ the mean treatment effect across trials was 155mL. The smaller treatment effects were possibly due to the olodaterol study design that allowed for patients to continue COPD background treatments, except for LABAs, which was not the case in previous COPD development programs. In studies where formoterol was included as an active comparator, the treatment effect of olodaterol was generally comparable to the observed treatment effect of formoterol (Table 2, Figure 5).

Olodaterol 5 mcg demonstrated a bronchodilatory treatment effect at 5 minutes after the first dose with a mean increase in FEV1 compared to placebo f 110 mL (range 100 to 120 mL).

Table 2. 48-week COPD studies; ΔFEV_1 trough and ΔFEV_1 $AUC_{0\text{-}3\ hr}$ at week 12 (co-primary efficacy end point)

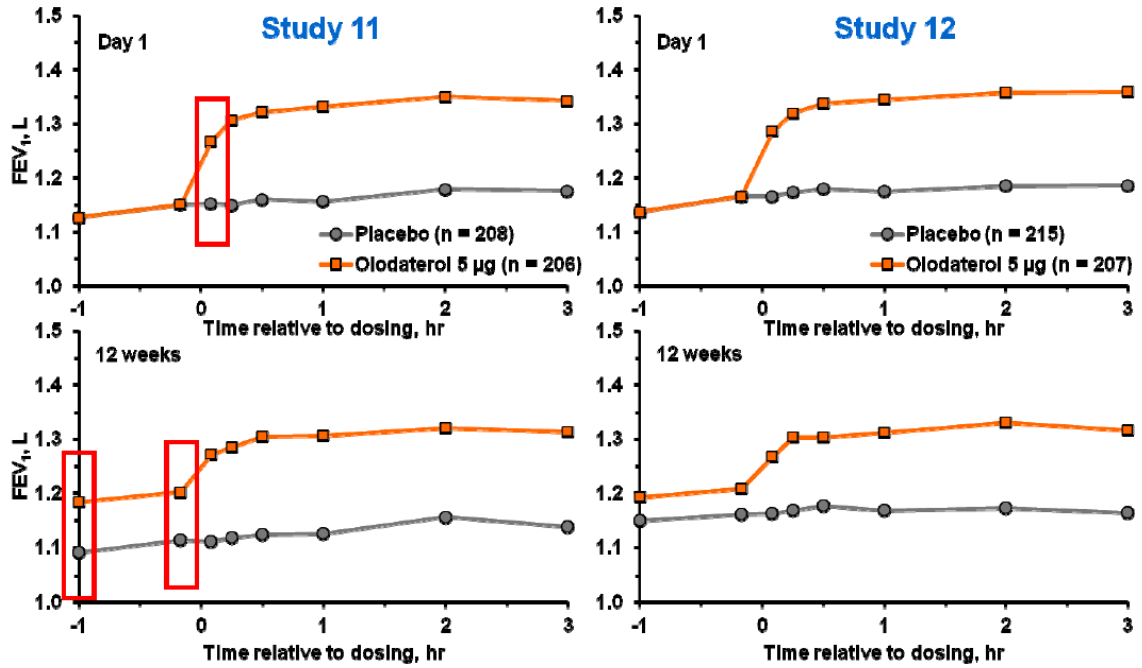
Study	Treatment	N	Trough FEV_1 Response		FEV_1 $AUC_{0\text{-}3\ hr}$ Response	
			Mean	Change (95% CI)	Mean	Change (95% CI)
1222.11	Placebo	188	-0.032		0.002	
	Olo 5 mcg QD	192	0.052	0.084 (0.040, 0.129)	0.167	0.164 (0.120, 0.209)
	Olo 10 mcg QD	192	0.048	0.080 (0.037, 0.124)	0.157	0.155 (0.111, 0.199)

Study	Treatment	N	Trough FEV_1 Response		FEV_1 $AUC_{0\text{-}3\ hr}$ Response	
			Mean	Change (95% CI)	Mean	Change (95% CI)
1222.12	Placebo	197	0.005		0.021	
	Olo 5 mcg QD	196	0.038	0.033 (-0.013, 0.080)	0.155	0.134 (0.090, 0.177)
	Olo 10 mcg QD	201	0.049	0.045 (-0.001, 0.090)	0.151	0.130 (0.087, 0.172)
1222.13	Placebo	187	-0.027		-0.003	
	Olo 5 mcg QD	208	0.056	0.083 (0.043, 0.123)	0.176	0.178 (0.137, 0.219)
	Olo 10 mcg QD	207	0.048	0.075 (0.035, 0.114)	0.167	0.170 (0.129, 0.211)
	For 12 mcg BD	200	0.033	0.059 (0.019, 0.100)	0.182	0.185 (0.144, 0.226)
1222.14	Placebo	212	-0.041		-0.008	
	Olo 5 mcg QD	220	0.018	0.059 (0.022, 0.095)	0.138	0.145 (0.108, 0.182)
	Olo 10 mcg QD	219	0.052	0.093 (0.057, 0.130)	0.167	0.175 (0.138, 0.212)
	For 12 mcg BD	217	0.024	0.065 (0.028, 0.101)	0.163	0.170 (0.133, 0.208)



Common baseline mean (SE): Studies 11/12: 1.145 (0.014); Studies 13/14: 1.208 (0.011). Analysis with imputation (FAS).

Figure 3. Mean FEV1 AUC0-3 and trough FEV_1 response over 48 weeks in COPD studies 1222.11 and 1222.12 (Source: BI presentation at PADAC held on January 29, 2013).



Common baseline mean (SE): Study 11, 1.139 (0.019); Study 12, 1.151 (0.020).
Analysis with imputation (FAS); $p < 0.05$ vs placebo at all time points.

Figure 4. Adjusted mean FEV_1 response after dosing on treatment day 1 and after 12 weeks in COPD studies 1222.11 and 1222.12 (Source: BI presentation at PADAC held on January 29, 2013).

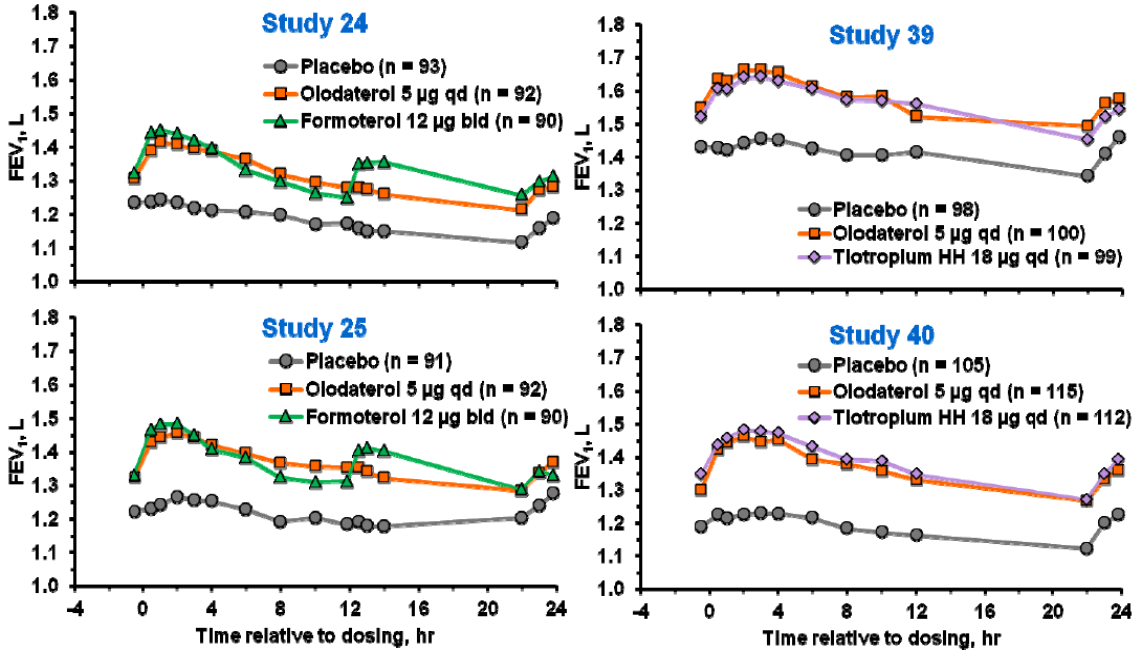


Figure 5. Adjusted mean FEV_1 response over 24 hours after 6 weeks of treatment in COPD studies 1222.24, 1222.25, 1222.39, and 1222.40 (Source: BI presentation at PADAC held on January 29, 2013).

SGRQ:

BI initially proposed to include SGRQ claims in the proposed label based on results from studies 1222.13 and 1222.14, but later in the review cycle submitted a revised label removing SGRQ claims. In one of the two studies, a statistically significant difference of 3.15 in mean total SGRQ scores was observed between olodaterol 5 mcg and placebo, which is below the threshold of the minimally important difference (MID) of -4 units or more for the SGRQ total score. The MCID of -4 for SGRQ has support in the literature.[14, 15]

Exercise endurance:

BI proposes to include exercise endurance claims in the proposed label based on results of improvement in exercise endurance time, and reduced lung hyperinflation (decreased in functional residual capacity or FRC) resulting in increased inspiratory capacity (IC) from two 6-week studies (Table 1). Results of the two studies show statistically significant differences between olodaterol and placebo for these measures (Table 3); however, clinical interpretation of statistical significance is not straightforward for variety of reasons. First, the minimal clinically important difference (MCID) for exercise endurance in drug trials in patients with COPD is unknown. Clinical studies evaluating effects of pulmonary rehabilitation suggest that the MCID may be around a101-153 second improvement from baseline (34%)[16,17]. However, these results are not universally accepted or validated, and it is unclear if the results in pulmonary rehabilitation would also pertain to drug trials. For inspiratory capacity, the MCID is likewise unknown. Second, the relationship between a magnitude of effect demonstrated in the olodaterol studies to any activity of daily living that relates to exercise in COPD patients is not known. Third, exercise testing was performed approximately 2 hours post-dose, which correspond to the time at which the bronchodilator effect of olodaterol has reached its peak. It is not known if the benefit with olodaterol would persist later in the dosing period. Fourth, studies lasting for 6 weeks are not adequate to show sustainability of effect. For comparison, studies to show bronchodilator efficacy are at least 12 weeks in duration, and studies to show exacerbation efficacy are 6 to 12 months in duration. Finally, no other bronchodilator drugs approved for COPD in the Unites States has an exercise endurance claim, and these products potentially could show similar numerical changes if studied. The pharmacological effect of olodaterol is likely to be similar to other beta-agonists.

[14] Jones PW. Interpreting thresholds for a clinically significant change in health status in asthma and COPD. Eur Respir J 2002; 19:398-404.
[15] Jones PW. St. George's Respiratory Questionnaire: MCID. J of COPD 2005; 2:75-79.
[16] Laviolette L, Bourbeau J, Bernard S, et al. Assessing the impact of pulmonary rehabilitation on functional status in COPD. Thorax. 2008 Feb;63(2):115-21.
[17] Puente-Maestu L, Villar F, et al. Clinical relevance of constant power exercise duration changes in COPD. Eur Respir J. 2009 Aug:34(2):340-5.

The proposed wordings for inclusion of an exercise claim in the Clinical Trials section of olodaterol product label are not supported by the submitted data. To support such labeling claim, reasonable expectation would be that olodaterol treatment demonstrates a benefit in some exercise related activity of daily living in COPD patients, or a benefit in exercise endurance test based measures with effect sizes that cross accepted MCIDs. In either scenario, the benefit will need to be demonstrated at various relevant time points of the day after dosing, and over at least 6 months of treatment. Lack of accepted MCIDs for exercise endurance test based measures makes studies challenging. Development of MCIDs for such measure will likely need linking the measures to some exercise related activity of daily living in COPD patients.

Table 3. 6-week COPD studies; Exercise endurance time in seconds and inspiratory capacity in liters at week 6

Study	Treatment	Endurance Time (sec)		Inspiratory Capacity (L)	
		Mean	Change (95% CI)	Mean	Change (95% CI)
1222.37	Placebo	369.8		1.887	
	Olo 5 mcg QD	421.6	1.14 (1.065, 1.221)	2.067	0.180 (0.107, 0.252)
	Olo 10 mcg QD	420.7	1.14 (1.062, 1.219)	2.024	0.137 (0.064, 0.210)
1222.38	Placebo	354.3		2.158	
	Olo 5 mcg QD	396.3	1.12 (1.043, 1.199)	2.236	0.078 (0.010, 0.146)
	Olo 10 mcg QD	391.5	1.10 (1.030, 1.184)	2.330	0.172 (0.105, 0.240)

8. Safety

a. Safety database

The safety assessment of olodaterol is based primarily on studies shown in Table 1. A total of 3353 patients with COPD and a total of 731 patients with asthma were exposed to olodaterol in various studies. Of the COPD patients, 3142 were exposed to olodaterol 5 mcg or 10 mcg in parallel group or cross-over studies. The 48-week parallel group studies included a total of 3104 patients, of whom 1759 patients were exposed to olodaterol 5 mcg or 10 mcg. The safety database for olodaterol was reasonable. Given that the 5 mcg dose is proposed for marketing, the 10 mcg dose provides important supporting safety data.

b. Safety findings and conclusion

The submitted data support safety of olodaterol for use as a maintenance bronchodilator treatment of airflow obstruction in patients with COPD at a dose of 5 mcg once daily.

A major safety concern with LABAs is linked to selection of an appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators, including olodaterol, which is proposed to be marketed for COPD. Marketing an unnecessary and unreasonably high dose has safety concerns. BI conduced adequate dose ranging and dose regimen studies and selected 5 mcg and 10 mcg once daily doses for pivotal confirmatory studies. Of the two doses, BI is proposing

to market the lower 5 mcg dose because there was no separation between the two doses. This is a very reasonable strategy from a safety perspective. Safety data from the asthma program, though limited, did not show a signal of severe asthma exacerbation. The safety findings noted in the COPD program were not concerning and typical of beta-agonist bronchodilators.

BI conducted a comprehensive safety analysis of the available data. Safety analysis included evaluation of deaths, serious adverse events (SAEs[18]), adverse events (AEs), and also specific analyses of Major Adverse Cardiac Events (MACE) endpoints and respiratory adverse events. All deaths and SAEs were adjudicated by independent committees. BI also collected vital status information out to 337 + 14 days (50 weeks) for patients who discontinued from the studies. Overall, vital status data are available for 98% of all patients randomized in the 48-week trials. Safety data from the 48-week studies were most informative.

A total of 53 on-treatment deaths were reported in the 48-week studies. These were balanced among the treatment groups. Common causes of deaths included COPD exacerbation, respiratory failure, and pneumonia, which are expected causes of death in older COPD patients. A total of 499 patients with SAEs (fatal and non-fatal) were reported in the 48-week studies. There were also balanced among the treatment causes, and the events were typical and expected in COPD patients. The number of deaths and SAEs in other studies was also balanced and did not raise any concerns.

There was a small imbalance in the olodaterol 10 mcg group compared to placebo for neoplasms, primarily lung-related malignancies. Overall, there were 9 (1.0%), 14 (1.6%), 19 (2.2%), and 8 (1.7%) neoplasms in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. The rate per 100 patient years is 1.94, 2.89, 4.24, and 2.84 in the placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. There were 2, 3, 6, and 4 malignant lung neoplasms in placebo, olodaterol 5 mcg, olodaterol 10 mcg, and formoterol groups, respectively. There were 4 cases of small cell lung carcinoma, all in the olodaterol 10 mcg group. Approximately half of the total malignant lung neoplasms, including 2 of the small cell lung carcinomas, were diagnosed within 5 months of beginning of randomized treatment. Given the small number of neoplasms, short lead-time to the diagnosis of neoplasms, and lack of similar findings in animal carcinogenicity studies, it is not likely that this is a safety signal.

Cardiovascular adverse events are a specific safety event of interest for beta-adrenergic agonist drugs because of their known pharmacologic effects. An adjudicated analysis of MACE did not reveal any concerns. Fatal MACE events occurred in 8 (0.9%), 3 (0.3%), 3 (0.3%), and 6 (1.3%) of patients in the placebo, olodaterol 5 mcg, olodaterol 10 mcg,

[18] 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.

and formoterol groups, respectively. Likewise, nonfatal MACE events were generally balanced.

Other safety assessments, such as ECGs, Holter monitoring and a thorough QT study, did not show any cardiac safety signals. Analysis of common adverse events and laboratory parameters and common adverse events also did not show any specific findings of concern.

c. REMS/RiskMAP

BI submitted a REMS for olodaterol consisting of a Medication Guide and a communication plan regarding LABA safety of asthma related death. The communication plans included a Health Care Professional Letter, information posted on a website, and notification of professional societies.

Per the February 2011, Draft Guidance for Industry: Medication Guides – Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS), in most cases FDA expects to include a Medication Guide as part of a REMS only when the REMS includes elements to assure safe use. The information regarding LABA safety and asthma-related death has been widely distributed to health care providers with demonstrated uptake of the information into clinical practice; the communication plan REMS requirements for other LABAs are currently being removed. Thus, while a Medication Guide is required to communicate the potential risks of olodaterol, a Medication Guide as part of REMS is not necessary.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) was held on January 29, 2013, to discuss this application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indication, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for olodaterol 5 mcg once daily for its proposed indication. In general, the panel members concluded that there were sufficient data to support the efficacy of olodaterol for the proposed indication. On voting questions, the Committee voted favorably regarding whether there was substantial evidence of efficacy (15 yes, 1 no, and 1 abstain), and also voted favorably on the safety of olodaterol (15 yes, 1 no, and 1 abstain). Regarding the approvability question, which is essentially the sum of the demonstration of efficacy and safety, the results were in favor of approval (15 yes, 1 no, and 1 abstain). Overall, members felt that BI had conducted a rigorous, well-designed program that was strengthened by the inclusion of usual care background therapy. The only safety issue of concern was the occurrence of 4 cases of small cell lung carcinoma, all in the olodaterol 10 mcg group. Members noted that while this may have been a random occurrence, appropriate post-marketing surveillance is warranted.

The committee was asked to discuss the finding of the exercise endurance studies. There was no voting question on exercise endurance because this was not an indication that BI was seeking and for complexity of the data discussed in section 7 above. The committee

observed that exercise tolerance is an important endpoint for patients, and many members expressed support for inclusion of exercise endpoints in pharmaceutical trials in COPD. However, members noted that more information is needed to understand the optimal design of exercise trials for COPD and MCID of exercise endpoints. Several members recommended that FDA hold a scientific meeting to discuss exercise. With regard to the BI studies, members requested additional data at later time-points after administration of the drug as well as longer duration trials. One member also wanted to see correlation of exercise endpoints with symptoms and activities of daily living.

10. Pediatric

BI is requesting a claim for olodaterol for COPD only and is not requesting a claim for asthma. 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 previous 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

DSI audited three clinic sites that enrolled patients in the pivotal 48-week studies and the BI site. The clinical review team recommended the clinic sites because these sites enrolled larger number of patients compared to other sites. No irregularities were identified that would impact data integrity. 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. One investigator 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 (formerly known as DDMAC), DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

BI initially submitted (b) (4) as the proposed proprietary name. The DMEPA rejected this proposed name (b) (4) BI subsequently submitted Striverdi Respimat as the proposed proprietary name, which was accepted by the 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 Office of Medical Policy Programs (OMPP), DRISK, DMEPA, and by OPDP. Various changes to different sections of the label were done to reflect the data accurately and better communicate the findings to healthcare providers. The labeling language in the Clinical Trials section related to exercise endurance was not allowed due to reasons discussed in section 7 above. Asthma-related safety warnings are described in the label, including in a Boxed Warning, which are present in all LABAs. 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

Olodaterol will carry an asthma-related safety warning 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 Striverdi Respimat (olodaterol inhalation spray) for long-term once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, at a dose of 5 mcg once daily. The recommended regulatory action on this application is Approval.

b. Risk-Benefit Assessment

The overall risk-benefit assessment supports approval of olodaterol inhalation spray at a dose of 5 mcg once daily for long-term once daily maintenance bronchodilator treatment of airflow obstruction in patients with COPD, including bronchitis and emphysema.

A major safety concern with olodaterol is linked to selection of appropriate dose, because beta-2 adrenergic bronchodilators, particularly at high doses, have the safety concerns of severe asthma exacerbations and asthma-related deaths in patients who use these drugs to treat the symptoms of asthma. Although such a risk of worsening disease has not been shown in COPD, it is nevertheless important to select an appropriate and safe dose for all bronchodilators. BI conducted a comprehensive program, including dose ranging through pivotal confirmatory studies, to select the 5 mcg once daily dose. The submitted safety data do not show safety findings of unique concerns with olodaterol. From an efficacy standpoint, the clinical program showed that olodaterol at 5 mcg once-daily dose provided statistically significant replicate bronchodilator effect with effect. Although the observed effect size for olodaterol across studies appeared to be somewhat lower than that observed in previous registration trials for other LABAs for COPD, the effect sizes were comparable to other marketed bronchodilators when they were compared in the olodaterol program where the background therapy across treatment groups were similar.

c. Post-marketing Risk Management Activities

Olodaterol will carry an asthma-related safety warning 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
07/29/2014